CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	200-533
Priority or Standard	Resubmission (Complete Response)
Submit Date(s)	February 28, 2011
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PDUFA Goal Date	August 28, 2011
Division / Office	DAAAP/OND
Reviewer Name(s)	Elizabeth Kilgore, M.D.
Review Completion Date	July 29, 2011
Established Name	Tapentadol Extended-Release (ER)
(Proposed) Trade Name	Nucynta ER
Therapeutic Class	Opioid analgesic
Applicant	Johnson and Johnson
Formulation(s)	Oral tablets
Dosing Regimen	50, 100, 150, 200 and 250 mg
Indication(s)	Management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
Intended Population(s)	Adult, chronic pain

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Original NDA 200-533, Nucynta ER (Tapentadol extended-release) was submitted by the Applicant on December 1, 2009 under section 505(b)(1). The Agency could not approve the product, with the primary deficiency being that the Applicant's proposed in vitro in vivo correlation (IVIVC) models did not support the bridging of the clinical study batches (PR2) to the to-be-marketed tamper resistant formulation (TRF). The Agency issued a Complete Response on October 1, 2010. The Applicant submitted the response to the Complete Response which serves as the basis for this review.

Approval is recommended for Nucynta ER, 50, 100, 150, 200 and 250mg oral tablets for the indication of management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The Applicant's response to the Agency's Complete Response is acceptable to support approvability based upon the following determinants:

Efficacy: Efficacy was established in the original NDA review cycle and no new efficacy studies were submitted in the Applicant's Complete Response (CR) resubmission. Based upon the Clinical Review of Dr. Eric Brodsky, dated 8/19/10, the efficacy of Tapentadol ER in the treatment of chronic pain was established from two positive adequate and well-controlled trials (Studies 11 and 15) with supportive evidence from Study 8. The two positive trials had different designs (i.e., induction and an enriched randomized withdrawal design), different populations (low back pain [LBP] and painful diabetic peripheral neuropathy [DPN]), and different types of pain (nociceptive and neuropathic), thereby providing heterogeneous designs and populations for study of Tapentadol ER. The number and type of positive trials to support an efficacy claim for a long-acting opioid for chronic pain is consistent with the review division's statements to the sponsor during pre-NDA meetings.

There were no new findings in the CR resubmission which changed the Division's prior efficacy determination.

Safety: The Applicant's safety data in the CR resubmission were, overall, consistent with the safety findings identified in the first cycle review.

As determined in the first review cycle, the safety profile of Tapentadol ER in the treatment of chronic pain appears to be consistent with the safety profile of approved long-acting opioid products. The Tapentadol ER labeling should be consistent with current labeling of approved long-acting opioids and contain Contraindications (in

unmonitored patients with severely impaired pulmonary function and in patients receiving MAO inhibitors), Boxed Warnings (in patients at increased risk of abuse or diversion); Warnings and Precautions (respiratory and CNS depression, increased intracranial pressure, driving and operating machinery, and drug withdrawal). Consistent with the Tapentadol IR label, the Tapentadol ER label should contain additional Warnings and Precautions for seizures and serotonin syndrome given the biologic plausibility and the post-marketing cases of these events in patients who received Tapentadol IR.

The dosing recommendations are acceptable based upon the data from the first cycle.

Risk Mitigation: The Applicant's CR resubmission included an updated Risk Evaluation and Mitigation Strategy (REMS) to manage the risks (including overdose, misuse and abuse) associated with this drug. The REMS is currently under review by the Agency. Ultimately this product will be part of the class-wide, long-acting opioid REMS.

1.2 Risk Benefit Assessment

Tapentadol ER is a Controlled Substance Act (CSA) Schedule II drug, with risk of abuse and misuse.

All opioids carry the risk of abuse and misuse. Based upon the first cycle review by Dr. Brodsky, "overall, the results support an adequately favorable risk-benefit profile for Tapentadol ER within the proposed therapeutic range (100 to 250 mg BID) for the proposed indication of treatment of chronic pain".

The reader is referred to the review of Dr. Alicja Lerner of the Agency's Controlled Substance Staff (CSS) for further discussion regarding abuse and misuse potential of this product. Dr. Lerner's conclusions and recommendations are discussed below:

CSS Conclusions:

- The controlled release properties of the TRF formulation can be readily overcome by multiple simple physiochemical manipulations.
- The TRF formulation, in particular the dose of >150 mg, appears to exhibit an increased frequency of adverse events (e.g. euphoria) signaling abuse potential.
- A high incidence of euphoria and feeling drunk occurred in Phase 1 studies in subjects who received tapentadol TRF as compared to those who received "all tapentadol ER formulations." Euphoria was reported in 50% of subjects who received tapentadol TRF 250 mg with water in Study R331333-PAI-1028 (HP5503/44).
- Review of the current post-CR bioequivalence studies with the TRF formulation indicates a possible gender effect, in that the majority of AEs were reported to occur in females, in particular for nervous, gastrointestinal disorders, and

psychiatric AEs, such as euphoria. They occurred in females in the ratio of 8F:1M. Additionally, almost all discontinuations which were caused by vomiting occurred again mainly in females, 12:5.

- Withdrawal symptoms, including insomnia, depressed mood, depression, suicidal ideation, disturbance in attention and restless leg syndrome, occurred after Nucynta ER administration was stopped. The occurrence of withdrawal symptoms indicates development of dependency and a need to slowly taper discontinuation of drug.

CSS Recommendations

- Include appropriate warning language in the label about susceptibility of females to develop majority of AEs, sometimes of a severity that leads to discontinuation of the drug. The extent of the relation of gender differences to safe use of the drug should be further examined. One of possibilities would be to provide the data on withdrawal, and discontinuation due to AEs with respect to gender, and relationship to the dose.
- All planned clinical trials and all ongoing clinical trials (where possible) should include prospective assessment of suicidality, due to appearance of suicidality in the post-marketing phase of Nucynta.

The CSS recommendations are under further discussion within the Agency at the time of this review.

The risks associated with this extended-release opioid appear similar to other opioids in this class. These risks, however, appear to be manageable with appropriate risk-management strategies, including a REMS, and should not preclude approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant's Risk Evaluation and Mitigation Strategy (REMS) proposal is under review by the Agency's Division of Risk Management (DRISK).

It is expected that the approved REMS for Nucynta ER will be consistent with the interim REMS already approved for other long-acting opioids. This product will adopt the class-wide, long-acting opioid REMS when it is ready for approval.

1.4 Recommendations for Postmarket Requirements and Commitments

There are two Postmarketing Requirements for this product as follows:

1) Pediatric Research Equity Act (PREA): In order to comply with the Pediatric Research Equity Act, the Applicant submitted a pediatric plan.

In the pediatric plan, the Applicant requested and was granted a waiver in the pediatric age group birth to <7 years of age due to the fact that chronic pain studies are impossible or highly impractical in this age group due to the small number of pediatric patients in this category.

Pediatric study requirements for Tapentadol ER include pharmacokinetics, safety and efficacy in pediatric patients ages 7 to <17 years.

As per the current Division policy, efficacy findings from adults may be extrapolated to pediatric patients over the age of two years for the opioid drug class, as the mechanism of action is well understood and is similar in both adults and pediatric patients. Tapentadol is a drug product whose mechanism of action includes both a mu-opioid receptor agonism and an inhibition of norepinephrine uptake, and is not as clearly understood, even in adults. Therefore, the efficacy of this drug cannot be extrapolated from adults to the pediatric population.

A deferral for the conduct of pediatric studies was granted for pediatric patients aged 7 to <17 years, as the Applicant is awaiting pharmacokinetic results in pediatric patients for immediate-release Tapentadol (Tapentadol IR) in order to better determine dosing of the ER formulation.

The Applicant's proposed pediatric plan is shown below in Table 1.

Table 1. Timeline for Proposed Pediatric Study with Tapentadol ER

Study Title	Submission of Final Protocol to IND	First Subject Consented By	First Subject Dosed By	Study Completion	Study Report Available By
Randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety of multiple doses of tapentadol ER in subjects 7 to < 17 years of age experiencing chronic pain	28 May 2014	31 July 2014	14 August 2014	31 October 2017	26 March 2018

(Source: Applicant's submission, p. 1, Pediatric Correspondence, Response to 6/11/11 Request for Information)

The proposed pediatric plan was presented to the Agency's Pediatric Review Committee (PeRC) on 7/6/11 and was found to be acceptable.

2) Enhanced Pharmacovigilance for AEs of Interest: Although no specific safety signal was identified in the Applicant's clinical trials for the AEs of interest that include choking, sticking, or GI obstruction, the Agency had concerns for the potential risk of such events with the Tapentadol ER tamper resistant formulation (TRF) because the product contains (b) (4) polyethylene oxide, which has been associated with stickiness of other drug products and subsequent adverse events such as choking and GI obstruction in patients with abnormal GI tracts. As such, the Applicant will be required to perform postmarketing enhanced pharmacovigilance for the detection of these adverse events of interest. The Applicant's CR resubmission included a revised Safety Surveillance Plan (SSP) to reflect this requirement. The details of the SSP relevant to the choking, sticking and GI obstruction are discussed in Section 7.3.5 of this review (Submission Specific Primary Safety Concerns).

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient of this product, Tapentadol, is a centrally acting analgesic with a dual mode of action being both a mu-opioid receptor agonist and an inhibitor of norepinephrine uptake. The Applicant purports that preclinical data suggest that both mechanisms are likely to contribute to the analgesic effects. Tapentadol is a pure enantiomer that acts directly on the central nervous system (CNS).

The Nucynta ER product characteristics are summarized as follows:

- **Trade Name (established name):** NUCYNTA™ ER (tapentadol extended-release) oral tablets
- **Indication:** For "the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."
- **Age Group:** Adult patients 18 years or older
- **Dose Regimen:** The recommended oral daily dose is 100 to 250 mg BID.
    - For patients currently not taking opioid analgesics, begin with 50 mg BID and then titrate to an optimal dose within 100 to 250 mg BID range.
    - For patients switching from Tapentadol IR to Tapentadol ER, the total daily dose of Tapentadol IR (given 4 to 6 times per day) can be converted to the equivalent total daily dose of Tapentadol ER (given twice a day). The maximum total daily dose of Tapentadol ER is 500 mg per day.

(b) (4)

    - The dosing regimen should be individualized according to the severity of pain, supplemental opioid utilization, previous experience with opioid analgesics, the patient's ability to tolerate Tapentadol ER, the ability for patients to follow-up, and the ability of providers to provide oversight of treatment. Total daily doses greater than 500 mg of Tapentadol ER have not been studied and, therefore, are not recommended.
- **Pharmacologic Class:** Opioid analgesic
- **How supplied:** 50, 100, 150, 200, and 250 mg extended-release tablets

2.2 Tables of Currently Available Treatments for Proposed Indications

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

The proposed indication is the "management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."

Table 2 below summarizes the long-acting opioid products that are approved for the treatment of moderate to severe chronic pain in opioid tolerant and/or opioid-naive patients in the United States.

Table 2. Approved Long-Acting Opioid Products for the Treatment of Chronic Pain

Product	Approval Year	NDA	Sponsor
For Opioid-Tolerant or Opioid-Naive Patients[1]			
Oxycodone Products			
OYYCONTIN tablets	2010 1995	22-272 20-553	Purdue
Morphine Products			
EMBEDA (morphine sulfate & naltrexone HCl) capsules	2009	22-321	Alpharma
AVINZA capsules	2002	21-260	King
KADIAN capsules	1996	20-616	Alpharma
ORAMORPH SR tablets	1991	19-977	Xanodyne
MS CONTIN tablets	1987	19-516	Purdue
Tramadol Products			
RYZOLT tablets	2008	21-745	Purdue
ULTRAM ER tablets	2005	21-692	J & J
Oxymorphone Products			
OPANA ER tablets	2006	21-610	Endo
Methadone Products			
DOLPHINE HCl tablets	1947	6-134	Roxane
For Opioid-Tolerant Patients Only			
Fentanyl Products			
DURAGESIC (fentanyl transdermal system) patch	1990	19-813	J & J
Hydromorphone Products			
EXALGO tablets	2010	21-217	Alza

1 Some of these products are only approved in opioid-tolerant patients at higher doses
Reference: FDA approved labels

(Source: Dr. Eric Brodsky's Nucynta ER Clinical Review, p. 11)

2.3 Availability of Proposed Active Ingredient in the United States

An immediate-release (IR) formulation of Tapentadol (Nucynta) was approved in the United States under NDA 22-304 in November, 2008 "for the relief of moderate to severe acute pain in patients 18 years of age or older". Since Tapentadol IR was not scheduled under the Controlled Substance Act at the time of its approval, it was not allowed to be marketed in the United States. On June 22, 2009, Tapentadol IR was scheduled as a Schedule II drug. The Tapentadol IR label was updated to include the scheduling information, and Tapentadol IR was initially marketed in the United States at that time.

2.4 Important Safety Issues with Consideration to Related Drugs

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

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

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

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

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

Drug abuse, dependence, overdosage and withdrawal are important safety concerns associated with Tramadol and other Schedule II opioid analgesics. Post-Marketing Reports associated with Tapentadol IR from the first review cycle identified the AEs of

hallucination, seizures, serotonin syndrome and suicide as safety issues of interest. The Agency has subsequently conducted an internal review of these safety events. The reader is referred to Section 8 of this review, Postmarketing Experience, for further discussion.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Throughout the original NDA submission review cycle, post-action period for 1st cycle, and CR resubmission there were face-to-face meetings, teleconferences and email exchanges between the Applicant and the Agency. The key correspondences related to regulatory activity are summarized below:

- 11/30/09:
  - NDA 200533 for Nucynta ER (Tapentadol) Extended-Release Tablets 50, 100, 150, 200 and 250mg initially submitted to the Agency by J&J
- 12/1/09:
  - Agency received the submission
- 10/1/10:
  - The Agency issued a Complete Response Letter, on the basis of the following key deficiency:
    - In vitro in vivo correlation (IVIVC) was not supportive of the bridging of the clinical study batches of the Prolonged-Release 2 (PR2) clinical formulation to the to- be-marketed tamper resistant formulation (TRF)
- 11/9/10:
  - Type A Meeting between Agency and Applicant to discuss the results of the 5 Phase 1 pivotal bioequivalence (BE) studies comparing the Tapentadol TRF with the PR2 clinical formulation used in the Phase 3 clinical studies, the proposed content and format of the submission in response to the CR letter, and agreement upon a path forward for regulatory requirements for a complete submission. The Agency required the Applicant to submit the following in the response to Complete Response:
    - Data to support the bioequivalence (BE) of the TRF to PR2 formulation
    - Data to support the interchangeability (switchability) of Tapentadol ER tablets of different dosage strengths to achieve a particular total dose
    - Safety data concerning the question of whether TRF tablets become sticky and expand upon getting moist and the related potential to cause difficulty swallowing and becoming a potential choking hazard

- Division of Scientific Investigations (DSI) Inspection summaries from selected sites
- Safety update and a revised proposed Risk Evaluation and Mitigation Strategy (REMS)

2.6 Other Relevant Background Information

Tapentadol HCl was developed in an extended release (ER) tablet formulation for the indication of 'management of moderate to severe chronic pain'. Prior to this formulation, two ER formulations, referred to as "PR1" and "PR2" were investigated in Phase 1, 2, and 3 studies during the course of Applicant's clinical development. The PR2 formulation replaced the earlier PR1 formulation that had a similar composition but could not accommodate the higher drug load required for the higher doses being studied. The Phase 3 safety and efficacy studies employed the PR2 formulation only.

Another extended release oral tablet formulation, described as a "tamper resistant formulation" (TRF), was developed primarily for the US market. Throughout this review, the formulation used in the studies is so designated when appropriate.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic submission appeared to be of good quality, was well organized and easily navigated. The Applicant responded in a timely manner and complied with all information requests with no substantive outstanding requests at the time of this review.

3.2 Compliance with Good Clinical Practices

As per the Applicant, all studies in the Tapentadol clinical development program were performed according to the principles of Good Clinical Practices.

Division of Scientific Investigation (DSI) inspections were ongoing at four clinical sites (shown below in Table 3) at the time of the 1st cycle review and results of the DSI findings could not be included in that review.

Table 3. U.S. Sites Audited in Studies 11 and 15[1]

Site #	Principle Investigator Contact Information	Number of Patients		
		Randomized[2]	Treated with Tapentadol ER	Treated with Placebo
Study 11 (Pain due to Chronic LBP)				
1477	Bret Wittmer, M.D. Commonwealth Biomedical Research LLC 240 East Ayr Parkway, Madisonville, KY 42431, USA	27	11	9
1460	Allan Soo, M.D. Premiere Pharmaceutical Research, LLC 3316 S. McClintock Drive, Tempe, AZ 85282, USA	32	9	9
1478[3]	Daniel Whittington Dolby Research, LLC 8150 Jefferson Highway, Suite B, Baton Rouge, LA 70809	30	0	10
Study 15 (Pain due to Chronic DPN)				
49	Pamela Amador, M.D., Gables Research 85 Grand Canal Drive, # 400, Miami, FL 33144, USA	16	7	9

1 Studies 11 and 15 are Studies R331333-PAI-3011 (KF5503/23) and R331333-PAI-3015 (KF5503/36), respectively.
2 Randomized patients included patients treated with tapentadol ER, placebo, or the active control (i.e., oxycodone CR) and patients not treated with study medication.
3 This site was selected after J & J informed the Agency that there may have been potential misconduct in Study 11.

(Dr. Brodksy's Nucynta ER Clinical Review, p. 18)

The DSI inspections have now been completed. As taken from the DSI Summary Review and Review addendum by Dr. Susan Leibenhaut, primary DSI reviewer, the final recommendations and conclusions of the DSI inspections are as follow:

- Verification of electronically captured primary efficacy source data was performed by inspection of the Contract Research Organization (CRO) (b) (4) No significant regulatory violations were identified during inspection of (b) (4) and the primary efficacy data were verified to be consistent with the NDA data listings. The data is considered reliable.
- Upon further receipt and review of the EIR for Dr. Soo, as well as taking into account the results of the inspection of (b) (4) and the fact that the data from eDiary was verified, it is unlikely that the identified regulatory violations at Dr. Soo's site would significantly impact overall data reliability. Further, the impact that the regulatory violations identified at Dr. Soo's site may have on overall efficacy conclusions reached in review of the NDA may be mitigated by the randomized, double-blind superiority design of the study allowing the data generated by this site to be used in support of the respective indication.
- There was no evidence of under-reporting of adverse events found during the inspection of Dr. Soo's site. The primary endpoint data contained on the CD agreed with the data found at (b) (4).

- It is deferred to the review Division to evaluate the impact, if any, of six subjects that were transitioned to the Maintenance Phase, even though subjects reported in the eDiary that they continued to take rescue medication within the last three days of the Titration Period.

With regards to the last bullet above, the Division's Clinical team requested a statistical reanalysis of the efficacy data excluding the six subjects referenced and excluding all 32 subjects randomized in Dr. Soo's site. Dr. Yan Zhou of the Agency's Division of Biometrics performed the statistical reanalysis and found that there was essentially no change in the overall treatment effect of Tapentadol ER compared to placebo when excluding the six subjects noted above as well as all subjects from the site.

The clinical site inspection for the BE studies submitted in the Applicant's Complete Response resubmission has been completed but the results are pending at the time of this review. According to DSI, the analytical site inspection at (b) (4) is underway at the time of this review.

3.3 Financial Disclosures

There were no new key efficacy studies submitted with the CR resubmission.

As stated in Dr. Brodsky's review, there was no clear evidence that the financial interest of Investigators changed the overall result of Tapentadol ER in the treatment of chronic pain.

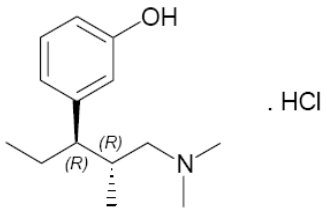
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Certain sub-sections of Section 4 are not included in this review as they did not have relevance to the resubmission. Pertinent sub-sections are shown.

4.1 Chemistry Manufacturing and Controls

The chemical name for Tapentadol ER is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride, the molecular formula is C14H23NO•HCl, and the structural formula is shown below in Figure 1.

Figure 1. Tapentadol ER Structural Formula



(Source: Applicant's submission, Module 2.2, p. 1)

4.4 Clinical Pharmacology

In the first review cycle, Dr. Sandra Suarez, the biopharmaceutics reviewer in the Office of New Drug Quality Assessment (ONDQA), reviewed the sponsor's proposed in vivo in vitro correlation (IVIVC) models which were submitted to support marketing of the 5 dose strengths of the to-be-marketed (TBM) tamper resistant formulation (TRF) manufactured in Gurabo, Puerto Rico. Since the important clinical trials were performed using a different formulation (i.e., PR2), the Agency determined that the Applicant needed to bridge the PR2 formulation to the TBM TRF.

The Applicant proposed that IVIVC models would bridge the formulations (*in vitro* dissolution of the TBM TRF would be comparable to bioavailability of the PR2 formulation). However, Dr. Suarez found that the IVIVC models were not acceptable because the Applicant used an unjustified mathematical term and mean values in the models instead of individual subject values. Based upon these Agency findings, the Applicant submitted amended IVIVC models (i.e., using individual subject values instead of mean values). However, Dr. Suarez again found that the amended models were inadequate because the unjustified mathematical term was retained.

Given the deficiencies of the IVIVC models, Dr. Suarez determined that the marketing of all 5 dose strengths of the TBM TRF was not supported and the Agency recommended that the Tapentadol ER NDA not be approved for this reason.

In the first cycle review, Dr. Suarez stated that the Applicant would need to submit the results of the following to resolve the deficiencies:

- *In vivo* bioequivalence (BE) studies (TBM TRF to Phase 3 PR2) of the 50 and 250 mg strengths under fasting conditions, and
- Dissolution profile comparisons with similarity f2 testing using the approved dissolution method for the strengths not tested in the *in vivo* BE studies (i.e., 50 vs. 100 mg; 250 vs. 150 mg; and 250 vs. 200 mg).

The Applicant submitted the information to the resolve the deficiencies noted above in the Complete Response and, as taken, from Dr. Suarez's review dated 7/8/11:

> *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. It 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 Tapentadol 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*

The reader is referred to Dr. Suarez's review for further details and discussion.

4.4.1 Mechanism of Action

Although its exact mechanism is unknown, analgesic efficacy of Tapentadol is thought to be due to mu opioid agonist activity and the inhibition of norepinephrine reuptake.

4.4.2 Pharmacodynamics

See 1st cycle review

4.4.3 Pharmacokinetics

As per Dr. David Lee's reviews, 1st and 2nd cycles, the following are the pharmacokinetic (PK) highlights of Tapentadol ER:

- Mean absolute bioavailability after single-dose administration of Tapentadol was approximately 32% due to extensive first-pass metabolism.
- Median maximum serum concentrations of Tapentadol were observed about 5 hours after administration of Tapentadol ER.
- There was minimal accumulation of tapentadol following administration of Tapentadol ER.

- Food Effect: The AUC and Cmax increased by 6% and 17%, respectively, when tapentadol ER was administered after a high-fat meal. Dr. Lee agrees with the sponsor that Tapentadol ER can be taken with or without food.
- Geriatric Patients: No new information was submitted to characterize the Tapentadol ER formulation. For administration of Tapentadol as IR formulation, the AUC was similar in geriatric patients compared to younger patients and the Cmax was 16% lower in geriatric patients compared to younger patients.
- Patients with Renal Impairment: No new information was submitted to characterize the Tapentadol ER formulation. For administration of Tapentadol as IR formulation, the AUC and Cmax were comparable in patients with mild and moderate renal function compared to subjects with normal renal function.
- Patients with Hepatic Impairment: No new information was submitted to characterize the Tapentadol ER formulation. Administration of Tapentadol, as IR formulation, resulted in higher AUC and Cmax in patients with impaired hepatic function compared to subjects with normal hepatic function. The ratios of the Tapentadol AUC for the mild and moderate hepatic impairment groups in comparison to the AUC in the normal hepatic function group were 1.7 and 4.2, respectively.
- Co-administration with Alcohol: An *in vivo* PK study in healthy subjects of single-doses of tapentadol ER (100 and 250 mg) with and without 40% ethanol was conducted. No significant "dose dumping" was detected with both 100 and 250 mg. Following coadministration with alcohol, the mean Cmax was increased by 48% and 28% in the 100 and 250 mg groups relative to control, respectively (the individual change in Cmax ranged from 1 to 4 fold and 1 to 3 fold, respectively). There was no significant change in the AUC after coadministration with alcohol.

See Dr. Lee's review for discussion of the Clinical Pharmacology of the BE studies included in the CR resubmission.

From the clinical pharmacology perspective, there were no approvability issues.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This review will address the studies in the Complete Response resubmission which includes updated safety data (cut-off of 9/13/10) from studies which were ongoing at the time of the 1st cycle safety review and 4-month safety update cut-off (9/30/09).

The CR Safety Update included safety data from a total of 22 studies (11 completed and 11 ongoing). Of the 11 completed studies, 9 (eight Phase 1, single-dose BE

studies and one Phase 3 study KF5503/44) were new (i.e. not previously reviewed in the first cycle as either completed or ongoing studies). Of the 11 ongoing studies submitted, 7 were new. A brief description of the completed and ongoing studies included in the CR Safety Update follows:

- 11 Completed Studies:
  - 8 Phase 1 studies
    - Seven of these studies (PAI-1052/HP51, PAI-1053/HP64, PAI-1057/HP80, PAI-1058/HP81, PAI-1059/HP82, PAI-1060/HP83, and PAI-1061/HP84) evaluated the bioequivalence, food effect, or relative bioavailability of the tapentadol TRF formulation in healthy volunteers
    - One study (HP69) evaluated the bioequivalence of the tapentadol PR and PR2small formulations in healthy volunteers
  - 1 Phase 2 study
    - Open-label study (JNS024 PR-JPN-C01), with duration of up to 3 weeks, evaluated the use of Tapentadol ER (PR1) in Japanese subjects with moderate-to severe cancer pain. This study was ongoing at the 9/30/09 cut-off for the 4-Month Safety Update but had been completed before the 9/13/10 cut-off for the Complete Response Safety Update.
  - 2 Phase 3 studies
    - A long-term (1-year), open-label extension study with Tapentadol ER (PR2) (PAI-3010/KF18) in subjects with chronic pain. This study was included as an ongoing study in the tapentadol ER 4-Month Safety Update (9/30/09 cut off date) but was completed (database lock) before the 9/13/10 cut-off for the Complete Response Safety Update.
    - A 12-week, open-label, add-on study with tapentadol ER (PR2) added to World Health Organization (WHO) Step I analgesic therapy and tapentadol immediate-release (IR) as rescue medication (KF44) in subjects with uncontrolled, severe, chronic nociceptive, mixed or neuropathic, low back pain.

11 Ongoing Studies

- Two Phase 2 studies
  - JPN-N21: A randomized, double-blind, placebo-controlled study in Japanese patients with moderate to severe chronic pain due to osteoarthritis (OA) of the knee or low back pain (LBP)
  - JPN-N22: Same design as above but in patients with moderate to severe chronic pain due to diabetic neuropathy (DPN) or postherpetic neuralgia (PHN).
- Nine Phase 3 studies

- KF 56: Randomized-withdrawal, placebo-controlled, multicenter study in patients with diabetic peripheral neuropathy (DPN)
- KF57: Open-label, randomized study with Tapentadol ER and Oxycodone CR in DPN
- KAJ-C02: Double-blind study in cancer pain
- JPN-C03: Open-label study in cancer pain
- KF15: Randomized withdrawal, active (Morphine CR) and placebo-controlled, double-blind study in patients with cancer pain
- KF42: Open-label, multicenter study with Tapentadol ER and Tapentadol IR in patients with uncontrolled severe chronic pain due to knee OA and using WHO Step I or Step II analgesics or no analgesics
- KF43: Same study design as above and same population using WHO Step III analgesics or no regular analgesics
- KF45: Open-label study to evaluate Tapentadol PR and Tapentadol IR in patients with severe chronic nociceptive, mixed or neuropathic low back pain who are taking WHO Step III analgesics but show lack of tolerability
- KF53: Open label study to evaluate the cognitive and psychomotor performance as surrogate parameters for driving ability under stable long-term treatment with Tapentadol ER in patients with chronic low back pain or knee osteoarthritis

The 22 studies that provided safety data included in the resubmission are summarized below in Tables 4 through 6 categorized by Phase and status (completed or ongoing). Tapentadol ER refers to any formulation used. Tapentadol usage by formulation is discussed in Safety Section 7.1.

Table 4. Description of Phase 1 Single-Dose Tapentadol ER Completed Studies

GRT/J&JPRD Study No.	Description of Study
HP5503/69 (GRT)	A single-dose, open label, randomized, 2 period crossover study to assess the bioequivalence of 2 tapentadol ER (PR) 25-mg tablets and a tapentadol ER (PR2small) 50-mg tablet in healthy subjects under fasted conditions. In addition, safety and tolerability of the formulations were assessed. Number of Subjects Evaluable for Safety: 32 Administered tapentadol PR 25 mg: 32 Administered tapentadol PR2small 50 mg: 32
HP5503/51 (GRT) R331333-PAI-1052 (J&JPRD)	A single-dose, open label, randomized, 2 period crossover study to evaluate the effect of food (standard Japanese meal) on the pharmacokinetics of tapentadol TRF in healthy Japanese men. In addition, safety and tolerability of the formulation were assessed. Number of Subjects Evaluable for Safety: 16 Administered tapentadol TRF 100 mg (fed): 15 Administered tapentadol TRF 100 mg (fasted): 13
HP5503/64 (GRT) R331333-PAI-1053 (J&JPRD)	A single-dose, open label, randomized, 2 period crossover study to evaluate the relative bioavailability of the tapentadol TRF tablet formulation to the tapentadol PR1 tablet formulation in Japanese healthy subjects under fasted conditions. In addition, safety and tolerability of the formulations were assessed. Number of Subjects Evaluable for Safety: 16 Administered tapentadol TRF 100 mg: 14 Administered tapentadol PR1 100 mg: 15
HP5503/80 (GRT) R331333-PAI-1057 (J&JPRD)	A single-dose, open-label, randomized, 2-way crossover pivotal study to assess bioequivalence of a new tapentadol extended-release (TRF) 150-mg tablet with respect to a tapentadol extended-release (PR2) 150-mg tablet under fasted conditions in healthy subjects. In addition, safety and tolerability of the formulations were assessed. Number of Subjects Evaluable for Safety: 64 Administered tapentadol TRF 150 mg: 64 Administered tapentadol PR2 150 mg: 63
HP5503/81 (GRT) R331333-PAI-1058 (J&JPRD)	A single-dose, open-label, randomized, 2-way crossover pivotal study to assess bioequivalence of a new tapentadol extended-release (TRF) 200-mg tablet with respect to a tapentadol extended-release (PR2) 200-mg tablet under fasted conditions in healthy subjects. In addition, safety and tolerability of the formulations were assessed. Number of Subjects Evaluable for Safety: 64 Administered tapentadol TRF 200 mg: 61 Administered tapentadol PR2 200 mg: 61
HP5503/82 (GRT) R331333-PAI-1059 (J&JPRD)	A single-dose, open-label, randomized, 2-way crossover pivotal study to assess bioequivalence of a new tapentadol extended-release (TRF) 50-mg tablet with respect to a tapentadol extended-release (PR2) 50-mg tablet under fasted conditions in healthy subjects. In addition, safety and tolerability of the formulations were assessed. Number of Subjects Evaluable for Safety: 64 Administered tapentadol TRF 50 mg: 62 Administered tapentadol PR2 50 mg: 62

HP5503/83 (GRT) R331333-PAI-1060 (J&JPRD)	A single-dose, open-label, randomized, 2-way crossover pivotal study to assess bioequivalence of a new tapentadol extended-release (TRF) 100-mg tablet with respect to a tapentadol extended-release (PR2) 100-mg tablet under fasted conditions in healthy subjects. In addition, safety and tolerability of the formulations were assessed. Number of Subjects Evaluable for Safety: 64 Administered tapentadol TRF 100 mg: 63 Administered tapentadol PR2 100 mg: 63
HP5503/84 (GRT) R331333-PAI-1061 (J&JPRD)	A single-dose, open-label, randomized, 2-way crossover pivotal study to assess bioequivalence of a new tapentadol extended-release (TRF) 250-mg tablet with respect to a tapentadol extended-release (PR2) 250-mg tablet under fasted conditions in healthy subjects. In addition, safety and tolerability of the formulations were assessed. Number of Subjects Evaluable for Safety: 64 Administered tapentadol TRF 250 mg: 59 Administered tapentadol PR2 250 mg: 60

In this table clinical studies are identified using 2 protocol numbers, 1 assigned by GRT (HP5503/xx) and 1 assigned by J&JPRD (R331333-PAI-xxxx).

(Source: Applicant's Table, CR Safety Update, pgs. 27-28)

Table 5. Description of Phase 2 and 3 Tapentadol ER Completed Studies

GRT/J&JPRD Study No.	Description of Study
Phase2 Open-Label	
JNS024PR-JPN-C01 (JPKK)	An open-label, multicenter, non-controlled, optional dose-titration Phase 2 study to assess the efficacy, safety, and pharmacokinetics of tapentadol ER administered to patients with moderate to severe cancer pain. Number of Subjects Evaluable for Safety: 78 Administered tapentadol ER: 78
Phase3 Open-Label	
KF5503/18 (GRT) R331333-PAI-3010 (J&JPRD)	An open-label extension, single-arm, controlled dose adjustment, multicenter Phase 3 study with tapentadol ER in subjects with moderate to severe chronic pain due to osteoarthritis (OA)in the knee or hip, or low back pain (LBP). The study included subjects from a 1-year, open-label safety study (PAI-3007/KF24), an IR/ER switch study (PAI-3019/KF39), and 15-week double-blind studies (PAI-3008/KF11 [osteoarthritis] and PAI-3011/KF23 [low back pain]). Number of Subjects Evaluable for Safety: 1,154 Administered tapentadol ER: 1,154
KF5503/44 (GRT)	An open-label, multicenter Phase 3B study to assess safety and efficacy of oral tapentadol ER added to WHO Step 1 analgesic therapy in subjects with uncontrolled severe chronic nociceptive, mixed or neuropathic low back pain. Number of Subjects Evaluable for Safety: 176[a] Administered tapentadol ER: 176[a]

In this table clinical studies are identified using 3 protocol numbers, 1 assigned by GRT (KF5503/xx), 1 assigned by J&JPRD (R331333-PAI-xxxx), and 1 assigned by JPKK (JNS024PR-JPN-xxx).

[a] There were 12 additional subjects enrolled at site FR002 in study KF44. The safety information for these subjects is presented separately.

(Source: Applicant's Table, CR Safety Update, p. 29)

Table 6. Description of Phase 2 and 3 Tapentadol ER Ongoing Studies

GRT/J&JPRD Study No.	Description of Study
Phase 2 Double-Blind	
JNS024ER-JPN-N21 (JPKK)	A randomized, double-blind, placebo-controlled multicenter Phase 2 study to assess the efficacy, safety, and pharmacokinetics of tapentadol ER administered to subjects with moderate to severe chronic pain due to osteoarthritis (OA) of the knee or low back pain (LBP).
JNS024ER-JPN-N22 (JPKK)	A randomized, double-blind, placebo-controlled multicenter Phase 2 study to assess the efficacy, safety, and pharmacokinetics of tapentadol ER administered to subjects with moderate to severe chronic pain due to diabetic neuropathy (DPN) or postherpetic neuralgia (PHN).
Phase 3 Open-Label	
KF5503/57 (GRT) R331333-PAI-3028 (J&JPRD)	An open-label randomized, controlled dose adjustment, multicenter Phase 3 study with tapentadol ER and oxycodone CR in subjects with chronic, painful diabetic peripheral neuropathy (DPN)
JNS024ER-JPN-C03 (JPKK)	A randomized, open-label, parallel-arm, optimal dose-titration, multicenter Phase 3 study to evaluate the safety and efficacy of tapentadol ER in subjects with severe chronic malignant tumor related cancer pain.
Phase 3 Double-Blind	
KF5503/15 (GRT) R331333-PAI-3013 (J&JPRD)	A randomized withdrawal, active- (morphine CR) and placebo-controlled, double-blind, multicenter Phase 3 study to assess safety and efficacy of oral tapentadol ER in subjects with moderate to severe chronic malignant tumor-related pain
KF5503/56 (GRT) R331333-PAI-3027 (J&JPRD)	A randomized-withdrawal, placebo-controlled, multicenter Phase 3 study evaluating the efficacy, safety, and tolerability of tapentadol ER in subjects with chronic, painful diabetic peripheral neuropathy (DPN)
JNS024ER-KAJ-C02 (JPKK)	A randomized, double-blind, active controlled, optimal dose titration, multicenter, Phase 3 study to evaluate the safety and efficacy of oral tapentadol ER in subjects with moderate to severe chronic malignant tumor related cancer pain.
Phase 3B Open-Label	
KF5503/42 (GRT)	An open-label, multicenter Phase 3B study with tapentadol ER and tapentadol IR in subjects with uncontrolled severe chronic pain due to OA of the knee taking either World Health Organization Step I or Step II analgesics or no regular analgesics.
KF5503/43 (GRT)	An open-label, multicenter Phase 3B study to evaluate the effectiveness and tolerability of tapentadol ER, and tapentadol IR on demand, in subjects with severe chronic pain due to osteoarthritis of the knee taking World Health Organization Step III analgesics but showing a lack of tolerability.
KF5503/45 (GRT)	An open-label, multicenter Phase 3B study to evaluate the effectiveness and tolerability of tapentadol ER, and tapentadol IR on demand, in subjects with severe chronic nociceptive, mixed or neuropathic low back pain taking World Health Organization Step III analgesics but showing a lack of tolerability.
KF5503/53 (GRT)	An open-label, multicenter Phase 3B study to evaluate the cognitive and psychomotor performance as surrogate parameters for driving ability in subjects with chronic non-malignant pain under stable treatment with tapentadol ER.

In this table clinical studies are identified using 3 protocol numbers, 1 assigned by GRT (KF5503/xx), 1 assigned by J&JPRD (R331333-PAI-xxxx), and 1 assigned by JPKK (JNS024ER-JPN/KAJ-xxx).

(Source: Applicant's Table, CR Safety Update, p. 30)

5.2 Review Strategy

The following were the primary data sources for this review:

- Applicant's response to the Agency's Complete Response Letter
- Applicant's Complete Response Safety Update
- Pertinent sections of the Applicant's original NDA 200-533 submission (specifically the Summary of Clinical Safety and 4-month Safety Update)
- Dr. Eric Brodsky's Clinical Review for the original NDA submission, dated 8/19/10
- Dr. Sara Okada's Cross Discipline Team Leader (CDTL) Review for the original NDA submission, dated 9/20/10
- Other discipline reviews from the current review cycle

5.3 Discussion of Individual Studies/Clinical Trials

Efficacy was established in the first review cycle. See Dr. Brodsky's review for discussion of Individual Studies/Clinical Trials.

6 Review of Efficacy

Efficacy Summary

No efficacy studies were submitted as part of the complete response.

Efficacy sub-sections 6.1 through 6.1.10 of the review template have been omitted as they are not applicable to the CR resubmission.

7 Review of Safety

The key safety data, as summarized from Dr. Brodsky's review:

- In the 40 submitted studies of Tapentadol ER in patients with non-malignant pain there were no deaths in Tapentadol ER-treated patients.
- Tapentadol ER-treated patients had a greater incidence of non-fatal SAEs, AEs leading to discontinuation (DAEs), and AEs than placebo-treated patients and the differences in the incidences of DAEs and AEs between these groups were mostly due to known opioid-related toxicities (e.g., nausea, vomiting, dizziness, constipation, somnolence, fatigue).

The safety findings in the CR Safety Update are generally consistent with those presented in the first cycle.

7.1 Methods

The CR Safety Update included safety data on the completed Phase 1 BE studies, completed Phase 2 and Phase 3 studies, and ongoing Phase 2 and 3 studies. As per agreements made between the Agency and Sponsor during the November, 2010 post-action meeting, the Agency accepted the Applicant's proposal that patient profiles and analysis datasets for only completed Phase 3 Study PAI-3010/KF18 would be included in the CR Safety Update as that was the only Phase 3 study whose safety data was not included in the first cycle NDA review (the study was ongoing at the time of cutoff for 4-month Safety Update). Study PAI-3010/KF 18 used the PR2 formulation.

The tapentadol ER formulations used in the studies included in the CR Safety Update included the following:

- First-generation ER formulation (PR1)
- Second-generation ER formulation (PR2) used in Phase 3 clinical research studies
- To-be-marketed tapentadol tamper-resistant formulation (TRF) and
- Other (PR and PR2small) clinical research formulations.

Throughout the remainder of this review, any formulation of Tapentadol ER may be referred to as Tapentadol ER or by the specific formulation (shown below in Tables 7 and 8), when applicable.

Table 7. Safety Data by Tapentadol Formulation: Completed Studies

Studies	Formulation				
Phase 1 Studies					
	TRF	**PR2**	**PR1**	**PR**	**PR2 small**
HP51	X				
HP64	X		X		
HP69				X	X
HP80	X	X			
HP81	X	X			
HP82	X	X			
HP83	X	X			
HP84	X	X			
Phase 2 Studies					
JPN-C01			X		
Phase 3 Studies					
KF18		X			
KF44		X			

(Source: Reviewer)

The ongoing studies used only the TRF or PR2 formulations as shown in Table 8 below.

Table 8. Safety Data by Tapentadol Formulation: Ongoing Studies

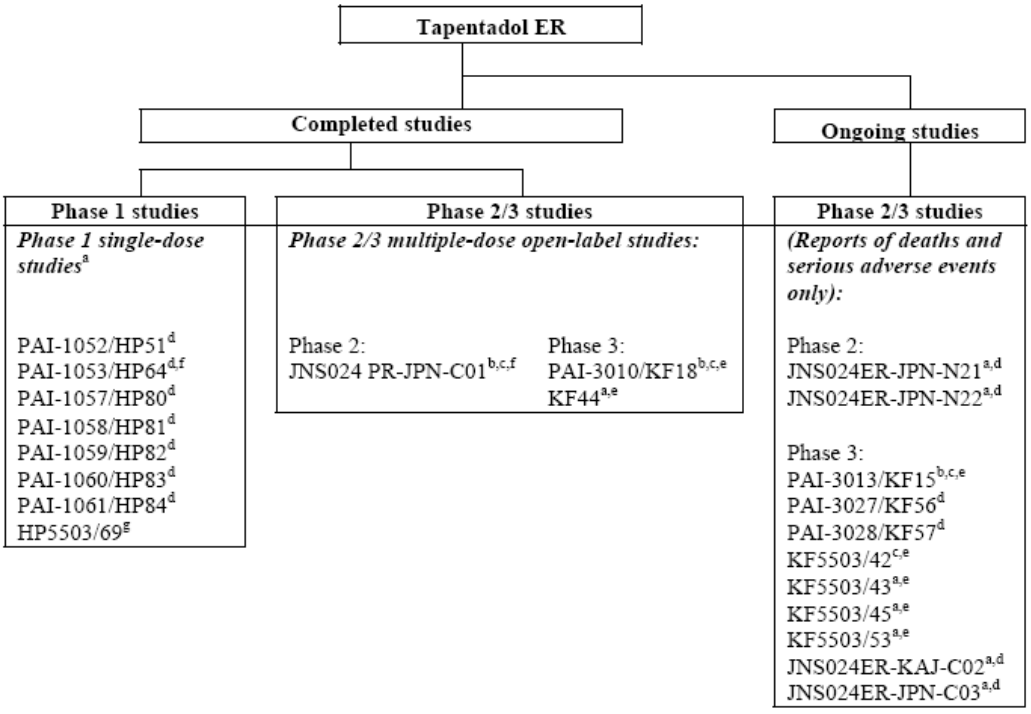
Studies	Formulation	
	Phase 2	
	TRF	PR2
JPN-N21	X	
JPN-N22	X	
	Phase 3	
KF15		X
KF56	X	
KF57	X	
KF42		X
KF43		X
KF53		X
KAJ-C02	X	
JPN-C03	X	

(Source: Reviewer)

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In the Complete Response Safety Update, the following studies, as shown in Figure 2 below, were included in the Applicant's submitted safety data.

Figure 2. Complete Response Safety Update Tapentadol ER Studies



[a] Studies not included in the SCS of NDA 200533 or the 4-Month Safety Update
[b] Completed studies that were ongoing at the time of the cut-off date of the SCS of NDA 200533
[c] Completed studies that were ongoing at the time of the cut-off date of the 4-Month Safety Update
[d] Clinical studies with the tapentadol ER (TRF) formulation
[e] Clinical studies with the tapentadol ER (PR2) clinical research formulation
[f] Clinical studies with the tapentadol ER (PR1) clinical research formulation
[g] Clinical studies with other tapentadol ER (PR and PR2small) clinical research formulations

(Source: Applicant's Table, Complete Response Safety Update, p. 25

See Section 5.1 for descriptions of the studies.

As per agreement with the Agency, the Applicant was required to submit narrative data on deaths, SAEs and AEs leading to discontinuations for completed studies only. Safety information for ongoing studies in the CR Safety Update was limited to reports of deaths, serious adverse events, and pregnancies. The Applicant submitted CIOMS

(Council for International Organizations of Medical Sciences) Reports and Line Listings for deaths and SAEs in the ongoing studies.

In Study KF44, the Applicant reported that irregularities were detected at the French site FR002. The Investigator had falsified study medication dispensation for a subject who had not received the required amount of study drug and other study visit information for another subject. Upon detection of these irregularities, no further enrollment was permitted at site FR002 or its satellite sites at which 12 subjects had enrolled. The safety information for study KF44 was therefore summarized excluding data from site FR002 and its satellite sites. The Applicant submitted separate summaries for site FR002 and its satellite sites.

7.1.2 Categorization of Adverse Events

According to the Applicant, adverse events for the completed Phase 1 studies were summarized using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1 (PAI-1057/HP80, PAI-1058/HP81, PAI-1059/HP82, PAI-1060/HP83, and PAI-1061/HP84), version 11.0 (PAI-1052/HP51 and PAI-1053/HP64), and version 13.0 (HP69). For the Phase 2 and 3 studies, version 11.0 was used for the Phase 3 open-label extension study (PAI-3010/KF18), version 13.0 for the Phase 3B study KF44, and version 12.0 of MedDRA/J (Japanese MedDRA version) for the Phase 2 study JPN-C01.

The Applicant's categorization of adverse events appeared acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

With exception of the pooled analysis of the PAI-3007/KF24 (long-term safety) and PAI-3010/KF18 (open-label extension) studies, the results for individual studies were presented separately by the Applicant due to differences in study design and treatments administered.

7.2 Adequacy of Safety Assessment

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

According to the Applicant, the Summary of Clinical Safety (SCS) in the original NDA, submitted 11/30/09, included safety data for ~4000 subjects who received Tapentadol

ER in 38 clinical studies (28 Phase 1 studies and 10 Phase 2 and 3 studies) completed as of the cut-off date of 6/30/09. The 4-month Safety Update submitted 3/30/10, included an additional 350 subjects who received Tapentadol ER in 32 clinical studies (30 Phase 1 studies and two additional Phase 3 studies) completed between 7/1/09 and 9/30/09.

The Complete Response Safety Update included safety data from over 1,700 subjects who received Tapentadol ER in 11 additional studies (8 Phase 1 studies, one Phase 2 study, and two Phase 3 studies) completed between 10/1/09 and 9/13/10.

According to the Applicant, 845 subjects have been exposed to at least one dose of Tapentadol Tamper Resistant Formulation (TRF) as follows:

- 351 subjects in the Phase 1 studies
- 459 subjects in the ongoing Phase 3, diabetic peripheral neuropathy (DPN) study PAI-3027/KF56
- 35 subjects in the early terminated DPN safety study PAI-3028/KF57 (Terminated by Sponsor when Agency determined that a long-term safety study in support of the planned DPN sNDA was not necessary).

A total of 249 subjects received Tapentadol ER, PR2 formulation, in study KF24 and it's extension study KF18. The median duration of the Tapentadol ER treatment was 700 days (1.9 years). A total of 218 subjects (~88%) took study drug for at least 18 months, and, of those, 20 subjects (8%) took study drug for at least 2 years. Subjects from Study KF24 rolled over into he OL, Phase 3 Study PAI-3010/KF18, which consisted of 1,154 subjects with chronic pain due to osteoarthritis and low back pain treated with Tapentadol ER (PR2) and who enrolled from 4 other studies (PAI-3007/KF24 tapentadol ER or oxycodone CR for 1 year), PAI-3019/KF39 (Tapentadol IR/Tapentadol ER switch study) as well as PAI-3008/KF11 and PAI-3011/KF23 (both placebo, tapentadol ER, or oxycodone CR for 15 weeks).

7.3 Major Safety Results

7.3.1 Deaths

Completed Studies: There were no new deaths reported in the CR Safety Update for the completed studies.

Ongoing Studies: There were 4 deaths reported in the ongoing Phase 3, double-blind study KF15 performed in cancer patients. The CIOMS Reports and Line listings of these deaths were reviewed. There is insufficient information to assign causality to study drug at this time as the studies remain blinded.

The summary of deaths in ongoing Tapentadol ER studies is shown below in Table 9.

Table 9. Summary of Deaths in Ongoing Tapentadol ER Studies

Study Number	Mfr. Control Number/ Subject Number	Age (years) Sex	Treatment Group	Reaction description	Relationship to Study Drug[a]
Phase 2 Double-Blind Studies					
No deaths between 1 October 2009 to 13 September 2010 for JPN-N21 (OA or LBP)					
No deaths between 1 October 2009 to 13 September 2010 for JPN-N22 (DPN or PHN)					
Phase 3 Double-Blind Studies					
PAI-3013/KF15 (cancer pain)	ES-JNJFOC-20100201445/ 130345	66 Female	Blinded	General physical health deterioration	Doubtful
PAI-3013/KF15 (cancer pain)	RO-JNJFOC-20091202896/ 130347	67 Male	Blinded	Cardiopulmonary failure	Not related
PAI-3013/KF15 (cancer pain)	RS-JNJFOC-20100101428/ 130346	49 Female	Blinded	Malignant neoplasm progression	Not related
PAI-3013/KF15 (cancer pain)	RS-JNJFOC-20100601300/ 130390	61 Male	Blinded	Lung neoplasm malignant	Not related/ doubtful[b]
No deaths between 1 October 2009 to 13 September 2010 for KAJ-C02 (cancer pain)					
No deaths between 1 October 2009 to 13 September 2010 for PAI-3027/KF56 (DPN)					
Phase 3 Open-Label Studies					
No deaths between 1 October 2009 to 13 September 2010 for PAI-3028/KF57 (DPN)					
No deaths between 1 October 2009 to 13 September 2010 for JPN-C03 (cancer pain)					
Phase 3B Open-Label Studies					
No deaths between 1 October 2009 to 13 September 2010 for KF42 (OA)					
No deaths between 1 October 2009 to 13 September 2010 for KF43 (OA)					
No deaths between 1 October 2009 to 13 September 2010 for KF45 (mixed back pain)					
No deaths between 1 October 2009 to 13 September 2010 for KF53 (OA or LBP)					

[a] Relationship to study drug was provided by both the investigator and sponsor.
[b] Relationship to study drug was assessed as not related by the investigator and as doubtful by the sponsor.

(Source: Applicant's Table, CR Update, p. 62)

No trends, patterns or new safety findings related to deaths were identified in the Applicant's CR Safety Update.

7.3.2 Nonfatal Serious Adverse Events

The completed Phase 2 and Phase 3 studies in the CR Safety Update were open-label with no placebo controls. Additionally, the completed Phase 2 study used the PR1 formulation. The completed Phase 3 studies (KF18 and KF44) used the PR2 formulation.

Completed Studies
There were no SAEs in the Phase 1 studies.

In the Phase 2 open-label, cancer pain study JPN-C01, using the PR1 formulation, nine subjects reported serious adverse events during the study which included 12 SAEs of

pancreatic carcinoma, lung neoplasm malignant, gastric neoplasm, anemia, drug hypersensitivity, malnutrition, altered state of consciousness, bradyarrhythmia, interstitial lung disease, respiratory arrest, respiratory depression, and gastric ulcer. The narratives for these subjects were reviewed. All events were confounded by underlying malignancy and multiple comorbid conditions, therefore causality to study drug was indeterminate by this reviewer in all cases.

In the Phase 3 open-label, long-term (1-year) safety study PAI-3010/KF18 using PR2 formulation, there were 84 (~7%) of 1,154 subjects who experienced SAEs in the study. The most frequently reported SAE was osteoarthritis, which was reported in 7 subjects (0.6%). The next most common SAE was falls, which occurred in 3 subjects. SAEs occurring in at least two subjects included acute MI, atrial fibrillation, congestive heart failure, MI, abdominal pain, vomiting, chest pain, non-cardiac chest pain, gastroenteritis viral, dehydration, coma, syncope, suicide ideation, and withdrawal syndrome. Each of the 11 subjects with cardiac disorder SAEs had a medical history of cardiovascular disease except for Subject 105601 who experienced an acute myocardial infarction. There were no highly unusual or unexpected SAEs that could be determined to be definitely or probably causally related to study drug.

In the Phase 3 open-label study KF44 using PR2 formulation, seven (4%) of 176 subjects experienced SAEs which included sepsis, confusional state, renal cell carcinoma, cholecystitis acute, renal colic, blood insulin abnormal, and type 2 diabetes mellitus. This patient population also had multiple confounders making causality assignment indeterminate.

In studies where patients took Tapentadol ER for up to 2 years (studies PAI-3007/KF24 and its extension study PAI-3010/KF18), there were 23/249 (~9%) of subjects who experienced serious adverse events. The most frequently reported SAEs that occurred in more than one subject were osteoarthritis, fall, and syncope.

All narratives were reviewed for the SAEs reported in the completed studies. There were no SAEs that occurred with frequency or with definite or probable causality related to study drug to the extent that a change in labeling or other safety information is warranted.

An overview of SAEs in the completed studies is provided in Table 10.

Table 10. Summary of SAEs in Completed Studies in CR Safety Update

Study	# Subjects w/SAEs (%)	Comments (Phase 2 and 3 Studies were OL)
Phase 1 Studies	0	Healthy volunteers
Phase 2 (C01)	9/78 (11.5%)	Cancer patients with multiple concomitant medications. Causality can not be assigned due to confounders.
Phase 3 (KF18)	84/1,154 (7.3%)	No highly unusual SAEs; generally consistent with SAE types previously reported
Phase 3 (KF44)	7/176 (4.0%)	Most patients had multiple comorbid conditions and concomitant medication use; confounders to assigning causality
Phase 3 Pooled (KF24 and KF18)	23/249 (9.2%)	No highly unusual SAEs; generally consistent with SAE types previously reported

(Source: Table, reviewer)

Ongoing Studies: There were no definite patterns or highly unusual SAEs reported in the ongoing studies. No definitive conclusions can be drawn regarding the SAEs in the ongoing studies as full narratives were not required to be provided. The key findings are bulleted below:

- Phase 2 DB study (JPN22): Four patients experienced four SAEs. No SAE occurred more than once.
- Phase 3 DB studies: 30 patients experienced 62 SAEs. Most of the SAEs occurred in the cancer population.
- Phase 3 OL studies: 19 patients experienced 28 SAEs. No patterns were identified.

7.3.3 Dropouts and/or Discontinuations

In the Applicant's resubmission, the discontinuations due to AEs (DAEs) were generally consistent with those reported in the 1st cycle, which were nausea, vomiting, dizziness, constipation, and somnolence. Selected narratives for the DAEs of interest were reviewed.

There were other isolated DAEs which did not occur with frequency or severity to warrant additions to the final approved label.

7.3.4 Significant Adverse Events

The AEs of pregnancy, seizures, serotonin syndrome and suicide ideation were reviewed by this reviewer as AEs of potential clinical importance. The Applicant reported that there were no new reports of pregnancy or serotonin syndrome in the safety data submitted with the CR Safety Update.

Open-label, long-term Study KF18 was ongoing at the time of the first review. In the Applicant's CR Safety Update, it was reported that there were 4 (0.3) subjects who presented with suicidal ideation or related behavior; 2 (0.2%) subjects with suicidal ideation, 1 (0.1%) subject with suicidal behavior (suicidal gesture), and 1 (0.1%) subject who committed suicide (Subject 105590). The subject who committed suicide was previously listed and discussed in Dr. Brodsky's review.

The final approved label for Nucynta ER will include labeling that addresses the AEs of clinical importance discussed above.

7.3.5 Submission Specific Primary Safety Concerns

This section of the review will address the submission specific primary safety concerns related to the Complete Response.

<u>Safety Issues Specific to the Tapentadol 50mg TR</u>
At the Post-action November, 2010 meeting, the Agency identified three safety concerns which required the Applicant to provide additional supportive data.

The Agency's safety issues are bolded below, immediately followed by the Applicant's submitted rationale and data.

Safety Issue 1: The Agency agreed with the Applicant that formal bioequivalence criteria for approvability were met for all proposed dosage strengths except for the 50 mg TRF. The Applicant was required to submit Safety and PK information for the Tapentadol 50 mg TRF tablet.

Applicant's response:

- The 50-mg TRF tablet is intended to be used only during initial dose titration. The safety profile and pharmacokinetic data from the Phase 1 studies and the Phase 3 DPN study PAI-3027/KF56 were submitted to support the use of the 50-mg TRF tablet for dose titration.

- Serum Tapentadol concentrations achieved with the 50mg titration dose do not exceed the concentrations achieved with therapeutic doses (100 to 250mg) of the Tapentadol TRF. A cross-study comparison demonstrated that the Tapentadol TRF exhibits linear and predictable pharmacokinetics across the entire dose range (50 to 250mg). (see Dr. Lee's Clinical Pharmacology Review for discussion).

The Applicant submitted five BE studies which compared the PR2 formulation to the TRF formulation in the 50, 100, 150, 200 and 250 mg tablets. The BE studies are listed below in Table 11:

Table 11. Phase 1 Pivotal Bioequivalence Studies which Compared Tapentadol Formulations PR2 to TRF (Dose Range 50-250mg)

Study Number	Study Description
PAI-1059/HP82	Bioequivalence of TRF and PR2 50-mg tablets
PAI-1060/HP83	Bioequivalence of TRF and PR2 100-mg tablets
PAI-1057/HP80	Bioequivalence of TRF and PR2 150-mg tablets
PAI-1058/HP81	Bioequivalence of TRF and PR2 200-mg tablets
PAI-1061/HP84	Bioequivalence of TRF and PR2 250-mg tablets

(Source: Applicant's table, CR Submission, p. 6)

To specifically support the TRF 50mg dose, the Applicant relied upon safety data from the following studies:

Table 12. Studies Supporting Tapentadol 50mg TRF

Study	Design
HP 82 Healthy vol. N=64; US	Phase 1, OL, randomized single-center, single-dose, 2-way crossover BE study of TRF 50mg and PR2 50 mg Completed study.
KF56 DPN N=300; US	Phase 3, Randomized withdrawal, DB, Placebo controlled 3 weeks OL flexible dose titration followed by 12 weeks fixed dose maintenance. No active control. 50-250mg TRF. Study Ongoing; 1st 3 weeks OL period reported for 50 mg TRF
KF 57 DPN N=35; US	Phase 3, Randomized, multicenter, OL, active control, parallel-group to evaluate TRF over long-term exposure up to 1 year. TRF 50-250mg compared to Oxycodone CR 10-50mg. Study Early terminated; 1st 3 weeks OL period reported for 50 mg TRF
KF 36 DPN N=35; US	Phase 3, Randomized withdrawal, DB, PC, multicenter 3 weeks OL flexible dose titration followed by 12 weeks fixed dose maintenance. No active control. 50-250mg TRF. Study Completed ; 1st 3 weeks OL period reported for 50 mg TRF

OL=Open label; DB=Double blind; TRF= Tapentadol Tamper Resistant Formulation
(Source: Table by reviewer)

Phase 1 Studies: In addition to the above-listed Phase 1 study (HP82), summarized data from two additional Phase 1 studies (PAI-1022/HP41 and PAI 1034/HP42) were also submitted to support the safety of the TRF 50mg. These studies were previously submitted in the original NDA but the Applicant maintained that safety data from these studies could be used to support the safety findings of 50mg TRF since the TRF used in these two studies was compositionally similar to the to-be-marketed Tapentadol TRF. In these studies, a total of 107 subjects received a single dose of Tapentadol PR2 and some formulation of Tapentadol TRF. Although the findings from those studies were reviewed, this reviewer has determined that the data can not be used to support the safety comparability of Tapentadol 50mg PR2 to Tapentadol 50mg TRF because the TRF formulations used in the studies, although compositionally similar to the TBM formulation were not the exact formulation of the TBM Tapentadol TRF.

Phase 3 Studies: Safety data from the first three weeks of Studies KF56 and KF57 were used to support the safety of the Tapentadol 50mg TRF. Although Study KF57 is listed as an ongoing study, the study was terminated early. (Terminated by Sponsor when Agency determined that a long-term safety study in support of the planned DPN sNDA was not necessary).

Phase 1 Safety Findings: The percentage of subjects who experienced a treatment-emergent AE (TEAE) was slightly higher in the Tapentadol 50mg TRF than the PR2 formulation, being 23% and 18%, respectively. However, the types of AEs were similar, with the most frequent (>10%) AE being headache in both treatment groups. Dizziness and fatigue was seen with greater frequency in the TRF group compared to the PR2 group. All AEs were mild. The AEs of the two treatment arms are shown below in Table 13.

Table 13. TEAE Phase 1 Study HP5503/82 – Tapentadol 50mg TRF vs 50mg PR2

Treatment-Emergent Adverse Events by Body System or Organ Class and Dictionary-Derived Term
(Study R331333-PAI-1059; HP5503/82: Safety Analysis Set)

	Tapentadol TRF 50 mg	Tapentadol PR2 50 mg	Total
System Organ Class	(N=62)	(N=62)	(N=64)
Dictionary-derived Term	n (%)	n (%)	n (%)
Total no. subjects with adverse events	14 (23)	11 (18)	18 (28)
Nervous System Disorders	12 (19)	7 (11)	14 (22)
Headache	7 (11)	6 (10)	9 (14)
Dizziness	4 (6)	1 (2)	4 (6)
Somnolence	2 (3)	1 (2)	3 (5)
General Disorders and Administration Site Conditions	4 (6)	1 (2)	5 (8)
Fatigue	4 (6)	1 (2)	5 (8)
Feeling Hot	1 (2)	0	1 (2)
Gastrointestinal Disorders	3 (5)	1 (2)	4 (6)
Nausea	3 (5)	1 (2)	4 (6)
Vomiting	1 (2)	0	1 (2)
Musculoskeletal and Connective Tissue Disorders	1 (2)	2 (3)	3 (5)
Arthralgia	0	2 (3)	2 (3)
Back Pain	1 (2)	0	1 (2)
Metabolism and Nutrition Disorders	1 (2)	0	1 (2)
Decreased Appetite	1 (2)	0	1 (2)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (2)	1 (2)
Nasal Discomfort	0	1 (2)	1 (2)
Skin and Subcutaneous Tissue Disorders	1 (2)	0	1 (2)
Pruritus Generalised	1 (2)	0	1 (2)

Note: Percentages calculated with the number of subjects in each group as denominator.
PR2=prolonged-release 2 clinical formulation; TRF=tamper-resistant formulation

(Source: Applicant's table, CR, Attachment 1.3, p. 43)

Phase 3 Safety Findings: Study PAI-3015/KF36 was chosen by the Applicant as the comparator study for AEs of Tapentadol 50mg TRF because it is a Phase 3 completed study which used the Tapentadol ER (PR2) formulation and had an almost identical study design and study population to ongoing Phase 3 Study KF56, in which Tapentadol 50mg TRF was used. In both studies, patients received Tapentadol ER 50mg twice daily for the first three days of the open-label titration period. Thereafter, the dose was

titrated to an optimal individual dose (not to exceed 250mg twice daily over a three-week period and not to fall below 100 mg twice daily) using combinations of 50- and 100mg Tapentadol ER.

A total of 588 and 459 patients were enrolled in studies KF36 and KF56, respectively. Most (~58%) were male; Caucasian (>70%) and less than 65 years old (~65%). As shown in Table 14 below, although the overall percentage of patients with TEAEs was slightly higher in the TRF group (75%) compared to the PR2 group (71%), the frequency and types of AEs were almost identical between the two treatment groups.

Table 14. AEs ≥10% Study KF36 (50mg PR2) and KF56 (50mg TRF)

MedDRA System Organ Class Preferred Term	**Study KF36** **N=588; N(%)**	**Study KF56** **N=459; N(%)**
Total N with AEs	417 (71)	346 (75)
GI disorders	219 (37)	208 (45)
Nausea	126 (21)	112 (24)
Constipation	63 (11)	54 (12)
Vomiting	47 (8)	47 (10)
Nervous System Disorders	228 (39)	180 (39)
Dizziness	93 (16)	78 (17)
Headache	46 (8)	44 (10)
Somnolence	89 (15)	49 (11)
General Disorders and Administration Site Conditions	83 (14)	75 (16)
Psychiatric Disorders	57 (10)	53 (12)
Skin and Subcutaneous Tissue Disorders	68 (12)	56 (12)

(Source: Table by reviewer, adapted from Applicant's tables, CR Attachment 3.1)

The Applicant also analyzed data between the two treatment groups based on the first three days of titration, time to discontinuation during the OL titration period due to any treatment-emergent adverse event, and time to onset of AE. In all instances, the findings between the two groups appeared similar.

Study KF57 is an ongoing Phase 3 study which used Tapentadol TRF during the three-week, OL titration period in 35 diabetic peripheral neuropathy (DPN) patients. The demographics in this study were similar to prior studies KF36 and 56 with the majority of patients being male (~57%), Caucasian (~83%) and younger than 65 years of age (~74%). The safety findings of the 50mg TRF in Study 57 are similar to the 50mg TRF

findings in Study 56 with the most common AE being nausea (20%), as seen in Table 15.

Table 15. Incidence of TEAEs in at Least 5% of Subjects in Any Treatment Group (TRF or Oxycodone CR)

Incidence of Treatment Emergent Adverse Events in at Least 5% of Subjects in any Treatment Group
(Study R331333-PAI-3028; KF5503/57: Safety Analysis Set)

System Organ Class Dictionary-Derived Term	Tapentadol TRF (N=35) n (%)	Oxycodone CR (N=12) n (%)
Total no. subjects with adverse events	23 (65.7)	11 (91.7)
Gastrointestinal disorders	10 (28.6)	10 (83.3)
Nausea	7 (20.0)	6 (50.0)
Dry mouth	3 (8.6)	1 (8.3)
Constipation	2 (5.7)	3 (25.0)
Diarrhoea	2 (5.7)	0
Vomiting	1 (2.9)	2 (16.7)
Abdominal pain	0	2 (16.7)
Nervous system disorders	6 (17.1)	6 (50.0)
Somnolence	3 (8.6)	3 (25.0)
Dizziness	1 (2.9)	1 (8.3)
Headache	1 (2.9)	3 (25.0)
Psychiatric disorders	6 (17.1)	4 (33.3)
Anxiety	2 (5.7)	1 (8.3)
Confusional state	2 (5.7)	0
Insomnia	2 (5.7)	0
Abnormal dreams	0	1 (8.3)
Depression	0	1 (8.3)
Euphoric mood	0	1 (8.3)
Mood swings	0	1 (8.3)
General disorders and administration site conditions	4 (11.4)	2 (16.7)
Fatigue	3 (8.6)	2 (16.7)
Asthenia	0	1 (8.3)
Infections and infestations	4 (11.4)	0
Upper respiratory tract infection	2 (5.7)	0
Skin and subcutaneous tissue disorders	4 (11.4)	4 (33.3)
Pruritus	2 (5.7)	3 (25.0)
Hyperhidrosis	1 (2.9)	1 (8.3)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Percentages calculated with the number of subjects in each group as denominator.

(Source: Applicant's Table, CR Attachment 3.15, p. 79)

Safety Issue 2: **Interchangeability (switchability) of Tapentadol ER tablets of different dosage strengths to achieve a particular total dose (i.e, taking two or more lower dose tablets to achieve a higher total dose).**

The Applicant submitted data from the open-label titration period of studies KF56 and KF57 which used Tapentadol 50mg TRF and compared those findings to study PAI-36 (50mg PR2) as this group of patients represented a subset of patients who took the 50mg TRF tablet as part of a combination of tablets (during the titration phase) to achieve doses that are available as single tablets.

In studies KF36 and KF56, study drug blister cards for the OL titration period were designed to facilitate a titration from a starting dose of 50mg twice daily to 1 of 4 possible maintenance dose levels (twice daily 100, 150, 200 or 250mg). Similar combinations of 50mg and 100mg tablets to achieve the required dose were supplied for both studies. The exact combinations of tablets were recorded in the database for Study KF56 as shown in Table 16:

Table 16. Doses and Tablets Strengths for a Single Intake for the Open-Label Period (Study KF56)

Days	Protocol-allowed Doses (taken twice daily)	Available Tablet Strengths for a Single Intake
1-3	50 mg	1 x 50 mg
4-6	100 mg	1 x 100 mg
7-9	100 mg or 150 mg	1 x 50 mg, 1 x 100 mg
10-12	100 mg, 150 mg, or 200 mg	2 x 50 mg, 1 x 100 mg
13-end of OL period	100 mg, 150 mg, 200 mg, or 250 mg	1 x 50 mg, 2 x 100 mg

OL=open-label

(Source: Applicant's table, CR, p. 28)

When analyzing the data from these patients during the 3-week, OL titration period in studies 36 (PR2) and 56 (TRF), the AE profile appeared similar between the two groups (previously discussed above).

The mean duration of exposure to Tapentadol in both studies during the OL titration period was approximately 20 days, with most (>80%) of the patients exposed for at least 15 days with a dose range being comparable to 100 to 250mg twice daily. The Applicant analyzed the data from the perspective of AEs, dose proportionality across the dose range (50-250mg), mean serum Tapentadol concentrations and pain intensity during the OL period. The Applicant reported that there were no major differences found during this period between Studies KF36 (PR2) and Studies 56 and 57 (TRF) in the data analyzed. The safety data during this period has been discussed above (Issue 1). The reader is referred to the review of Dr. David Lee, Clinical

Pharmacology, regarding the Agency's analysis of the dose proportionality and serum Tapentadol concentrations during the OL titration period.

Safety Issue 3: Potential for the tablet to become sticky and expand when moist causing difficulty swallowing. The Applicant was required to perform a safety analysis of any reports of difficulty swallowing during the studies using the TRF and provide the information in the submission.

The Applicant reported that a review of Product Quality Complaints (PQCs) from sites participating in the completed Phase 1 studies, the ongoing Phase 3 DPN study (KF56) and the terminated DPN study (KF57), was conducted searching for any comments related to difficulty swallowing. They found that there were no submitted PQCs which would suggest a potential for choking or difficulty swallowing the TRF formulation.

Additionally, the Applicant conducted a manual review of AEs related to difficulty swallowing (terms gagging, choking, stuck in throat) for TRF studies.

According to the Applicant, there were no treatment-emergent adverse events that would suggest difficulty swallowing the Tapentadol TRF tablet in the 845 subjects who took Tapentadol TRF in the Phase 1 and Phase 3 studies. Two subjects were identified as having experienced AEs possibly related to difficulty swallowing. Upon review of the narratives, these events do not appear to be causally related to choking on the drug, given the fact that the events occurred 10 hours after dosing in one subject, and in one subject who reportedly took more tablets than recommended. The brief narratives are summarized below.

- Patient 1: 41 yo female, completed Phase 1 BE study HP83 (100 mg TRF) reported mild choking ~10 hours after ingestion of tablet. The event occurred at dinnertime related to food ingestion; required Heimlich maneuver. Event resolved same day.
- Patient 2: 70 yo male, Phase 3 DPN study KF56 reported "feeling of tightness in throat" with onset 14 days after start of study drug while taking a total daily dose of 250 mg TRF in a combination of one 50mg tablet and two 100 mg tablets. There were associated symptoms of chest tightness and hypertension. The symptoms resolved and the subject was withdrawn from the study on Day 14. It was reportedly later learned that the patient had taken 6 doses of the tablet combination 50-50-100mg and 3 doses of the 50-100-100mg starting on Day 13 of OL titration.

<u>Summary Submission Specific Primary Safety Concerns:</u>

- Bioequivalence of the to-be-marketed (TBM) Tapentadol 50mg to Tapentadol PR2 50mg:

  - Safety: In the BE studies, all dosage strengths were found to be bioequivalent except Tapentadol TRF 50mg (where the observed maximum serum concentration [Cmax] 90% confidence interval [CI]:123% to 135% compared to the Phase 3 PR2 clinical formulation). The Agency determined that since the 50mg TRF will only be used for titration and since the safety profile of the to-be-marketed (TBM) Tapentadol 50mg appears clinically similar to that of the Tapentadol PR2 50mg used in some of the Phase 3 research trials, this difference in Cmax was clinically acceptable. This difference in Cmax is also in the range that would be expected if a patient took an immediate-release Tapentadol dose as rescue, which would not likely pose clinically important safety concerns.
  - Biowaiver: The Agency concurred with the Applicant that a biowaiver request for the Tapentadol ER intermediate strengths (100, 150, and 200mg) was not needed as bioequivalence studies have been conducted with the intermediate strengths and the study reports for these BE studies were included in the CR submission.
  - PK: See Dr. David Lee's Clinical Pharmacology review for discussion of the PK analysis included in the CR resubmission.

- Interchangeability
  - The Applicant's submitted data appeared to show no specific safety issues related to the interchangeability of the use of multiple 50mg TRF to achieve a single dose of Tapentadol ER tamper resistant formulation (TRF)

- Question of potential choking risk with the TRF
  - The safety data submitted by the Applicant identified no cases of choking or swallowing difficulties determined to be causally related to study drug
  - The label will include instructions for use for patients to take the tablets with adequate water to ensure swallowing.
  - The proposed methodology for enhanced pharmacovigilance in the revised Safety Surveillance Plan (SSP) submitted in the Applicant's CR is as follows:
    - Development and use of a pre-defined set of MedDRA preferred terms (PTs) to identify cases reporting events suggestive of choking, sticking, and esophageal obstruction
    - Development and use of a guided questionnaire at case intake and follow-up for cases reporting any of the defined PTs. This questionnaire will provide guidance to gather information on cases suggestive of choking, sticking, and esophageal obstruction, including how to identify reports of the events of interest and how to subsequently collect relevant information such as:
      - How many tablets were taken at once

    - How they were taken (sitting or standing, with or without liquid, etc)
    - What the reporter did and felt following the event.
    - The questionnaire will also prompt questions on medical history and concurrent medical conditions, and on the concomitant medications taken by the patient, which may be relevant to the currently reported event.
- Quarterly review of cases reporting any of the defined PTs. In addition to the number of cases reported during the period, the indications, medical histories and concurrent medical conditions, doses, and concomitant medications reported among the cases will be tabulated and reviewed.
- The results of the quarterly reviews will be summarized in the section of the Periodic Adverse Drug Experience Report (PADER) that presents SSP events of interest, and in the semi-annual progress report. In addition to the review of cases received during the PADER and progress report period, respectively, the progress report will also include a summary of the cumulative number of cases reporting events suggestive of choking, sticking, and esophageal obstruction, as is done for other SSP events of interest.
- This review schedule will be in place for the first 2 years after tapentadol ER launch, at which point the methodology, periodicity, and need for this analysis will be reassessed.
- The SSP, which was submitted in NDA 200533, has been revised to reflect the information provided in this response regarding the proposal for enhanced NDA 200533 Enhanced Pharmacovigilance Proposal pharmacovigilance for events suggestive of choking, sticking, and esophageal obstruction. These changes are marked as underlined text in the revised SSP.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Because the studies in the CR Safety Update could not be pooled, the most common AEs were presented by individual study. The completed Phase 2 and 3 studies in the CR Safety Update were open label.

Table 17 below summarizes the most common AEs from the 1st cycle review.

Table 17. Common AEs Tapentadol ER First Cycle Review

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
AEs	**858 (86%)**	**715 (73%)**	**583 (59%)**	**202 (91%)**	**766 (86%)**
Nausea	36%	21%	7%	33%	18%
Constipation	33%	17%	7%	39%	23%
Dizziness	21%	17%	6%	19%	15%
Vomiting	21%	8%	3%	14%	7%
Somnolence	17%	12%	4%	11%	15%
Headache	13%	15%	13%	8%	13%
Pruritus	13%	5%	2%	10%	5%
Fatigue	9%	9%	4%	10%	10%
Hyperhidrosis	6%	5%	1%	4%	5%
Diarrhea	5%	5%	6%	5%	8%
Insomnia	5%	4%	2%	4%	7%
Dry mouth	4%	7%	2%	5%	9%
Nasopharyngitis	2%	3%	4%	3%	6%
Sinusitis	1%	1%	1%	6%	4%

1 AEs that occurred ≥ 5% in any treatment group are listed. Incidence is based on the number of patients who experienced at least 1 AE (not the number of AEs)

(Source: Dr. Brodsky's review, p. 64)

Common AEs reported in the safety update were similar in frequency, type and severity to those noted during the first cycle review. In the CR Safety Update, the common AEs in the completed studies are discussed below by study:

- Phase 1 Studies: The most common AEs were expected opioid-related AEs. All of the studies were single-dose studies performed in healthy volunteers under fasted conditions (except study HP51). The common AEs appeared dose-related, with the highest percentage of reports occurring in the higher doses of 200 and 250mg Tapentadol ER.

- Phase 2 Study (Study JPN-C 01): The percentage of subjects with at least one TEAE was 79.5% among the 78 Tapentadol ER-treated subjects. The most frequently reported (≥10%) were nausea, vomiting, constipation and somnolence. The incidence of TEAEs was higher in opioid-naïve patients compared to opioid-switching patients (69% to 92%), respectively.

- Phase 3 Study (PAI-3010/KF18): The percentage of subjects with at least one TEAE was 78.6% among 1154 Tapentadol ER-treated subjects. The most frequently TEAEs (≥10%) were headache (13.1%), nausea (11.8%), and constipation (11.1%). Subjects who received placebo before entering the current open-label extension study reported higher incidences of TEAEs (84.5%) than those who were treated with active treatment during the parent study (75.1% to 77.7%).

- Phase 3 Study (KF44): The overall percentage of subjects with at least 1 TEAE was 84.7% among 176 Tapentadol ER treated subjects. The most frequently reported, in addition to nausea and dizziness and headache were dry mouth (~15%) and fatigue (~10%) in the titration phase. The most frequently (≥5%) reported TEAEs in the maintenance period were diarrhea (~6%) and nasopharyngitis (~5%).

- Phase 3 OL, Long-Term Pooled Studies (KF24 and KF18): There were 249 subjects treated with Tapentadol ER. For subjects who took tapentadol ER for up to 2 years in studies PAI-3007/KF24 and PAI-3010/KF18, the percentage of subjects with at least 1 TEAE was 97.2%. The most frequently reported TEAEs (≥10%) were constipation (29.3%), nausea (20.5%), headache (20.5%), dizziness (15.7%), dry mouth (14.1%), insomnia (14.1%), nasopharyngitis (14.1%), somnolence (13.7%), diarrhea (13.7%), influenza (12.9%), upper respiratory tract infection (12.0%), hypertension (10.8%), and vomiting (10.4%).

7.4.2 Laboratory Findings

There were potentially clinically important (PCI) abnormal values in many of the studies, but only one laboratory abnormality of Type 2 diabetes mellitus in Study KF44 was determined by the Investigators to result in a serious adverse event.

TEAEs of hypomagnesemia, hypocalcemia and liver function test abnormal resulted in study discontinuation in the pooled KF24 and KF18 study.

In the long-term study KF18, 83/1154 (7.2%) of subjects in the Tapentadol ER group had TEAEs related to clinical laboratory findings. For 79 of those subjects, the TEAES related to a laboratory finding that the Investigators did not qualify as PCI abnormalities. In four subjects, the PCI abnormalities were hypertriglyceridemia, lipase increased (2 subjects) and lipase abnormal. For three subjects, the TEAEs related to clinically abnormal labs of platelet count decreased, increased blood lipase, hypocalcemia/hypomagnesemia were determined to be serious and in some cases led to study discontinuation (hypocalcemia/hypomagnesemia, ALT increased, hyperlipedima/liver function test abnormal, liver function test abnormal).

7.4.3 Vital Signs

There were a small number of subjects who experienced Potentially Clinically Important (PCI) vital sign changes in most of the completed studies included in the Applicant's CR resubmission. These changes included blood pressure increased, blood pressure decreased, heart rate increased and hyperventilation.

In the completed Phase 1 and Phase 2/3 studies, only one subject experienced an SAE related to vital signs. This subject (Subject 22-05) in Study JPN-C01 had both bradyarrhythmia and respiratory depression. The narrative of this subject revealed extensive lymphangiosis carcinomatosa (cancer). The subject was subsequently discontinued from the study.

In the OL, pooled Phase 3 studies (KF24 and KF18) TEAEs related to vital sign findings included most frequently reported hypertension (10.8%) as well as hypotension, heart rate decreased, blood pressure increased and blood pressure decreased (each 0.8%) and diastolic hypertension (0.4%). None of these TEAEs were deemed serious by the Investigator. One TEAE of hypertension resulted in study discontinuation.

Approved labeling reflects the types of vital sign events noted.

7.4.4 Electrocardiograms (ECGs)

As taken from Dr. Brodsky's review: there appeared to be no evidence of Tapentadol ER-associated pro-arrhythmic effect in the tapentadol ER clinical database at anticipated doses. There were no concerning clinical events that could indicate a proarrhythmic effect of tapentadol ER and the thorough QT study of tapentadol IR was negative (using doses that produced similar tapentadol exposure as the maximum proposed tapentadol ER dose regimen of 250 mg BID).

In the updated safety submission, there were no reports of clinically significant abnormal ECGs in the Phase 1 studies. In Phase 2 study JPN-C01, there were 15 (~19%) who experienced abnormal ECG findings following study drug administration which included 4 (5%) with one report each of extrasystole, sinus bradycardia, ventricular extrasystoles, and bradyarrhythmia.

ECG parameters were not collected for Study KF44.

Four subjects in Study KF18 experienced a QTc interval prolongation to at least 500ms while on Tapentadol ER.

In the pooled Phase 3 studies (KF24 and KF18), treatment-emergent adverse events related to ECG findings consisted of atrial fibrillation and bradycardia (each 1.2%), heart rate irregular, atrial flutter, bundle branch block right, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, tachycardia, and ventricular tachycardia (each 0.4%). The TEAEs of atrial fibrillation and atrial flutter (both 0.4%) were determined to be serious by the investigator and the TEAE of atrial flutter (0.4%) resulted in study discontinuation.

7.5 Other Safety Explorations

7.5.3 Drug-Demographic Interactions

Of the eight Phase 1 studies included in the CR resubmission, four analyzed data by gender (Studies HP82, HP80, HP81 and HP84). Studies HP51, HP64, and HP69 included only male subjects. Study HP83 AE data was not analyzed by sex.

The Phase 1 studies enrolled almost identical numbers of females and males. The most common AEs were nausea, vomiting, dizziness, headache, somnolence and fatigue. As shown in the Table 18 below, there does appear to be a female predominance for certain AEs in these Phase 1 studies. However, the numbers of subjects are small (~13-16 males or females in each treatment arm) making interpretation of these findings limited. The generalizability and clinical implications, therefore, are unclear.

Table 18. Phase 1 Studies: Gender Differences in TEAEs (Tapentadol TRF and PR2)

		Tapentadol Formulation	
		TRF	PR2
Study (Dosage)	**MedDRA Preferred Term**	**Female : Male**	**Female : Male**
HP82	Headache	7:0	4:2
(50mg)	Dizziness	2:2	0:1
	Nausea	2:1	1:0
Total N=62	Vomiting	1:0	0:0
HP80	Headache	7:0	3:0
(150mg)	Dizziness	8:1	7:2
	Nausea	4:5	3:3
	Vomiting	2:1	0:1
Total N=64	Somnolence	4:0	2:0
HP81	Headache	3:2	3:2
(200mg)	Dizziness	10:5	12:5
	Nausea	8:3	7:5
Total N=61	Vomiting	4:2	3:2
	Somnolence	4:3	1:3
HP84	Headache	8:1	4:1
(250mg)	Dizziness	12:6	15:5
	Nausea	6:2	10:3
Total N=59	Vomiting	3:1	6:1
	Somnolence	2:0	1:1

(Source: Table prepared by Reviewer)

In the Phase 3 open-label study PAI-3010/KF18, the overall incidence of TEAEs among all treated subjects was similar among men (76.5%) and women (80.1%). A higher percentage of women experienced TEAEs of nausea, vomiting, and diarrhea compared with men among all treated subjects regardless of prior study drug treatment. The incidence of TEAEs in the other System Organ Classification (SOC) did not differ by sex.

For the pooled analysis of subjects who participated in the long-term, open-label studies PAI-3007/KF24 and its extension PAI-3010/KF18, the overall incidence of TEAEs among all treated subjects was similar among men (98.1%) and women (96.5%). A higher percentage of women experienced TEAEs of nausea, vomiting, and diarrhea compared with men. The incidence of TEAEs in the other System Organ Classification (SOC) did not differ by sex.

7.6 Additional Safety Evaluations

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

As per the Applicant, the following summarizes data pertaining to overdose, drug abuse potential, withdrawal and rebound in the CR submission:

Overdose: There was one case of accidental Tapentadol overdose in the Phase 3 DB Tapentadol IR study (KF40) which was previously reported in the 4-month Safety Update while the study was ongoing. The study has now been unblinded and the drug was identified as Tapentadol IR. The subject reportedly took 8475 mg of Tapentadol IR over 11 days of treatment. There was no report of an adverse reaction.

Abuse: The Applicant reported no new cases of abuse not previously included in the Summary of Clinical Safety or 4-month Safety Update

Withdrawal

- There were no reported TEAEs of withdrawal or drug withdrawal syndrome in the Phase 2 open-label study JPN-C01.
- In the Phase 3 long-term, open-label safety study PAI-3010/KF18, 34 subjects (2.9%) had a TEAE of withdrawal syndrome under the system organ class of psychiatric disorders. The reported TEAE of withdrawal syndrome was generally unspecified, sometimes reported by the investigator as ‘withdrawal symptoms’, ‘withdrawal’, ‘narcotic withdrawal’, or ‘withdrawal-like symptoms’, but was occasionally reported as related unspecific symptoms, such as anxiety, nausea, agitation, diarrhea, rapid respiration, or runny nose. Eighteen additional subjects

experienced an adverse event coded as 'drug withdrawal syndrome' under the system organ class of general disorders and administration site conditions.

- In the Phase 3B open-label study KF44, 2 subjects (1.1%) had a TEAE of withdrawal syndrome under the system organ class of psychiatric disorders. Another subject experienced an adverse event coded as 'drug withdrawal syndrome' under the system organ class of general disorders and administration site conditions. These events occurred during the titration period (Weeks 1-5) of the study.
- For subjects who completed both long-term studies PAI-3007/KF24 and PAI-3010/KF18, 2 subjects (0.8%) had a TEAE of withdrawal syndrome under the system organ class of psychiatric disorders. Five (2.0%) subjects experienced an adverse event coded as 'drug withdrawal syndrome' under the system organ class of general disorders and administration site conditions.

7.7 Additional Submissions / Safety Issues

Other Tapentadol Formulations: In the CR Safety Update, safety data from other formulations of Tapentadol (immediate release [IR], Tapentadol injectable, and Tapentadol oral solution) was summarized by the Applicant and provided for the following:

- *Completed Studies*: 5 completed studies with other Tapentadol formulations:
  - PAI-1030/HP50 (Tapentadol IR)
  - PAI-1044/HP59 (Tapentadol Oral Solution and IR)
  - HP65 (Tapentadol Injectable Solution)
  - PAI-3021/KF40 (Tapentadol IR)
  - PAI-3022/KF49 (Tapentadol IR)
- *Ongoing Studies:* 2 ongoing studies with other Tapentadol formulations:
  - HP49 (Tapentadol IR)
  - PAI-3025/KF51 (Tapentadol IR)

The safety findings from these studies were consistent with what is known about Tapentadol IR and no new safety findings were identified from these summarized safety data.

8 Postmarket Experience

Tapentadol IR (NUCYNTA®) was approved for use in the US on 11/20/08 and marketed on 11/22/09. The Applicant reported that there were additional approvals for tapentadol IR and PR (PALEXIA®) in other countries but no patient exposure outside of the US before the cut-off date of 9/13/10 for the Complete Response Safety Update.

The Applicant reported that post-marketing safety data review for postmarketing data received from 6/22/09 through 6/30/09 were included in original NDA 200533 Summary of Clinical Safety and postmarketing data received from 7/1/09 through 9/30/09 were included in the 4-Month Safety Update of the 1st cycle review. The Applicant's postmarketing data submitted with the CR resubmission covered the period from 10/1/09 to 9/13/10.

The Applicant identified a total of 631 spontaneous, medically confirmed cases reporting Tapentadol IR either as the suspect, cosuspect, or suspect-interacting drug:

- Deaths -10 cases
  - 9 cases the preferred term *Death* was reported with no other AEs and did not describe the circumstances surrounding the patient's death.
  - 1 case reported the preferred terms *Drug toxicity, Disturbance in social behavior,* and *Unresponsive to stimuli*. Per Applicant's data, the cause of death was combined drug toxicity with Tapentadol IR, methadone, bupropion and fluoxetin HC.
- SAEs - 160 cases
- Non serious: 461 cases

Overall, the most frequently reported preferred terms were (in descending order of frequency) nausea, drug ineffective, and hallucination. Case level review of the events of interest (ie, cases with a fatal outcome, drug abuse, drug interactions, medication errors, overdose, serotonin syndrome, seizures, and suicidal ideation and behaviors) did not identify any new safety signal. A review of serious unlisted events also did not identify any new safety signal.

As a result of the postmarketing review, the following changes have been made in the USPI Tapentadol IR label:

- Hallucination was added to the March, 2010 version of the USPI (IR label).
- Headache was added to the June, 2010 version of the USPI (IR label).
- [redacted] (b) (4)

- Diarrhea was identified as a potential signal during routine quarterly surveillance for tapentadol IR (covering the third quarter of 2010), and is under further evaluation

The Agency's Office of Surveillance and Epidemiology (OSE) and the Division also performed an internal postmarketing review of Tapentadol IR on 11/22/10 (915 Postmarketing safety review). The AEs of hallucinations, suicidal ideation, serotonin syndrome, palpitations, headache, seizure and angioedema were identified as potential safety issues.

Upon full review by OSE, the following conclusions and recommendations were made by the Agency:

- Hallucination and seizure are adequately described in revised labeling of 11/1/10.
- Headache likely confounded by underlying medical conditions. Continue routine postmarket surveillance for these events.
- Serotonin syndrome, suicidal ideation, angioedema and palpitations are being added to the IR and ER labels as postmarketing events.

9 Appendices

9.1 Literature Review/References

The Applicant provided literature references related to the Clinical Summary for Biopharmaceutical studies, Clinical Pharmacology, Clinical Efficacy and Clinical Safety with electronic hyperlinks to the articles.

Selected literature references were read as appropriate for this review.

9.2 Labeling Recommendations

The label is currently under review. Major labeling issues include:

- Box Warning similar to those found in other extended-release opioid products.
- Warnings regarding serotonin syndrome similar to the IR Nucynta label and tramadol products
- Language to ensure that patients swallow the tablets with adequate water (since Nucynta ER contains polyethylene oxide)
- Medication Guide, similar to other extended-release opioids.

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting held for this resubmission.

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

/s/

ELIZABETH M KILGORE
07/29/2011

ELLEN W FIELDS
07/29/2011

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia and Analgesia Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	October 1, 2010
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA No.	200533
Applicant Name	Ortho-McNeil-Janssen Pharmaceuticals, Inc., c/o Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Date of Submission	December 1, 2009
PDUFA Goal Date	October 1, 2010
Proprietary Name / Established (USAN) Name	Nucynta ER / Tapentadol Extended Release
Dosage Forms / Strength	50, 100, 150, 200, and 250 mg tapentadol (as free base)/ tablet
Proposed Indication(s)	For the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Eric Brodsky, M.D.
CDTL Review	Sarah Okada, M.D.
Statistical Review	Yan Zhou, Ph.D. / Dionne Price, Ph.D.
Pharmacology Toxicology Review	Armaghan Emami, Ph.D. / Adam Wasserman, Ph.D.
CMC Review	Craig Bertha, Ph.D. / Prasad Peri, Ph.D.
Clinical Pharmacology Review	David Lee, Ph.D. / Suresh Doddapaneni, Ph.D.
ONDQA Biopharmaceutics Review	Sandra Suarez-Sharp, Ph.D. / Patrick Marroum, Ph.D.
DSI	Susan Leibenhaut, M.D. / Tejashri Purohit-Sheth, M.D.
OSE/DRISK	Steve Morin / Marcia Britt, Ph.D. / Jodi Duckhorn, MA / Cynthia LaCivita, Pharm.D. / Gita Toyserkani, Pharm.D. MBA / Claudia Karwoski, Pharm.D.
Controlled Substances Staff	Alicja Lerner, M.D., Ph.D. / Lori A. Love, M.D., Ph.D. / Michael Klein, Ph.D.

CDTL = Cross-Discipline Team Leader
DRISK = Division of Risk Management
DSI = Division of Scientific Investigations
OND = Office of New Drugs
ONDQA = Office of New Drug Quality Assesment
OSE = Office of Surveillance and Epidemiology

1. Introduction

The Applicant, Ortho-McNeil-Janssen Pharmaceuticals, Inc. (c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.), submitted an application on December 1, 2009, for a new formulation of Nucynta (tapentadol). The new formulation is an extended release tablet, in the following dosage strengths: 50, 100, 150, 200, and 250 mg. The Applicant seeks the following indication: management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

In support of this application, the Applicant has submitted data from three randomized induction trials (two in patients with knee osteoarthritis, and one in patients with chronic low back pain) and one randomized withdrawal trial in patients with diabetic peripheral neuropathy. In addition, data from a one-year, open-label safety study as well as data from multiple Phase 1 and Phase 2 trials have been submitted in support of the application.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

Tapentadol is a centrally active antinociceptive drug, with nonclinical data supporting a dual mechanism of action – as a μ-opioid receptor agonist and a norepinephrine re-uptake inhibitor. The Applicant had previously developed an immediate-release formulation of tapentadol, receiving approval for marketing for the relief of moderate to severe acute pain in patients 18 years or older (NDA 022304, approved November 20, 2008)

As noted in Dr. Okada's review, because tapentadol is a μ-opioid receptor, the extended-release formulation will require a Risk Evaluation and Mitigation Strategy (REMS). Until the REMS intended for opioids that are indicated for chronic use is finalized, the REMS for this extended-release formulation will be closely modeled on the recently approved REMS for Embeda and OxyContin CR.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

As noted in Dr. Bertha's review, the formulation consists of tapentadol hydrochloride (b) (4) polyethylene oxide (b) (4), hypromellose (b) (4) and polyethylene glycol (b) (4). The formulation also contains a small amount of Vitamin E (b) (4). The formulations are not compositionally proportional with respect to the active and excipient components.

(b) (4)

(b) (4)

The tablet cores are coated with proprietary coatings of different colors denoting the particular strength of the tablet, and each is also imprinted with a unique alphanumeric code.

The drug product is packaged in high-density polyethylene bottles fitted with child-resistant closures, each containing 60 tablets (for all strengths). Each strength is also packaged in cartons, intended for hospital use only, that contain ten blister cards each containing ten tablets (100 count).

The Applicant changed the formulation of the product three times during the course of the drug development. This has resulted in the situation where the clinical trials were conducted with a formulation that is different than the to-be-marketed formulation. Subsequently, the Applicant needed to provide data to "bridge" the two formulations; this will be discussed in further detail below, in Section 5 of this review.

The Applicant has attempted to give the formulation tamper-resistant properties, which are intended to address tampering by accidental misuse (b) (4)
tampering by the recreational abuser (b) (4)
(b) (4)
tampering by experienced abusers (b) (4)
tampering by persons identified as the "kitchen chemist"
The design, conduct, and results of these studies will be discussed at an advisory committee meeting during the second review cycle.

Facilities Review/Inspections
The Office of Compliance completed the manufacturing facilities site inspections and issued an overall recommendation of acceptable on September 15, 2010.

Outstanding or Unresolved Issues
I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry period of 24 months for both, the bottled and the blister-packaged product.

The "tamper-resistance" aspects of the formulation will be addressed within the context of an advisory committee meeting.

4. Nonclinical Pharmacology/Toxicology

General Considerations
The Applicant cross-referenced their INDs and the NDA for the immediate-release formulation of tapentadol (INDs 061345 and 105766, and NDA 022304). No new nonclinical data were submitted in support of this application.

As noted in Dr. Emami's review, the major toxicity findings were consistent with tapentadol's μ-opioid receptor agonist activity, affecting the respiratory, cardiovascular, gastrointestinal, and central nervous systems. Upon re-evaluation of the nonclinical toxicology package, she

noted that the safety margin for the extended-release tablet (and the immediate-release tablet) is not supported by the data in the application in terms of the clinical systemic exposure (measured as area under the curve, $AUC_{0\text{-}24\ hr}$) at the maximum recommended human dose (MRHD). This is summarized in the table below, adapted from Dr. Emami's review.

	Dose (mg/kg/d)	C_{max} (ng/ml)		$AUC_{0\text{-}24}$ (ng•hr/ml)		Human SM Based on C_{max}		Human SM Based on AUC	
Human **ER** MRHD		parent	metabolite	parent	metabolite	parent	metabolite	parent	metabolite
250 mg Twice a day	8.3	132	5714	2288 (1144x2)	96492 (48246x2)				
Rat 26 wk									
NOAEL	75	386	~24227	624	~156905	3X	4.2X	0.3X	1.6X
	150	479	~30419	1260	~295075	3.6X	5.3X	0.5X	3X
	300	1181	~45066	2537	~491457	8.9X	7.9X	1.1X	5X
Dog 52 wk									
NOAEL	10	6.5	7563	20	28091	0.05X	1.3X	0.01X	0.3X
	30	40	26003	101	86308	0.30X	4.5X	0.04X	0.5X
	80	183	47424	355	227917	1.4X	8.3X	0.15X	2.4X

Dr. Wasserman notes in his review that the type of toxicity observed in nonclinical studies was principally CNS-related, and that this typically correlates better with plasma levels (i.e., C_{max} or C_{ss}). He notes that clinical C_{max} was covered by the rat, although the C_{max} values in the dog were below the human, except for the highest dose tested (1.4X). Dr. Wasserman further notes that the majority of the parent drug is directly glucuronidated, rendering it inactive in analgesic assays, and that this metabolite forms the major human metabolite, circulating at levels greater than 40 times higher than tapentadol, based on C_{max} and AUC. This pattern holds in nonclinical models as well, though metabolism is even more extensive. He concludes that although the NOAEL dose in the dog study does not provide support for the exposure to the glucuronidated metabolite, the highest dose used does cover this exposure and he notes that the rat NOAEL is 1.6 times the exposure at the MRHD.

Dr. Wasserman's final assessment of this issue is that, although he recognizes Dr. Emami's evaluation that the nonclinical data does not technically support the systemic exposure at the MRHD for the extended-release tablet, the toxicities observed are largely confined to the central nervous system and are common to opioid and/or norepinephrine reuptake inhibitors. He notes as reassuring the significant body of clinical safety data available, which has not, to this point, revealed unusual toxicity for tapentadol relative to its class.

Carcinogenicity

As noted in Dr. Emami's review, tapentadol was negative for carcinogenicity in 104-week oral administration studies in mice treated by gavage, and in rats given tapentadol by dietary admixture.

Genotoxicity

As noted in the review of the immediate-release formulation by Dr. Kathy Young, and captured in Dr. Emami's review, tapentadol was evaluated in a standard battery of genetic toxicity studies and is considered to be equivocal for clastogenicity. A positive response was found in one of two in vitro Chromosome Aberration studies in Chinese hamster V79 cells, showing increased incidence of structural chromosome aberrations at concentrations greater

than 1000 mcg/ml in the presence of metabolic activation with S9. No evidence of genetic toxicity by tapentadol was found in the Ames test, the in vivo assay for clastogenicity in rat bone marrow cells, or in rat hepatocytes in the Unscheduled DNA Synthesis assay. As noted above, a two-year carcinogenicity study was negative.

Reproductive Toxicology

Dr. Rappaport noted in his summary review of the immediate-release formulation that, while some fetal malformations were noted in the Segment II (Embryofetal Development) Study, Drs. Young and Wasserman concurred with the sponsor that these abnormalities were due to maternal toxicity and not to a direct teratogenic effect of tapentadol. No other significant abnormalities were documented in the reproductive toxicology studies.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Emami and Wasserman that, based on measures of systemic exposure, the data from the nonclinical studies do not support the maximum recommended human dose in the application. I also concur with Dr. Wasserman that additional nonclinical data is not necessary in this case, due to the observation that the toxicities observed in the nonclinical studies are largely confined to the central nervous system and were similar to what has been seen with other opioid and/or norepinephrine reuptake inhibitors, and the significant amount of clinical safety data that is currently available for this product.

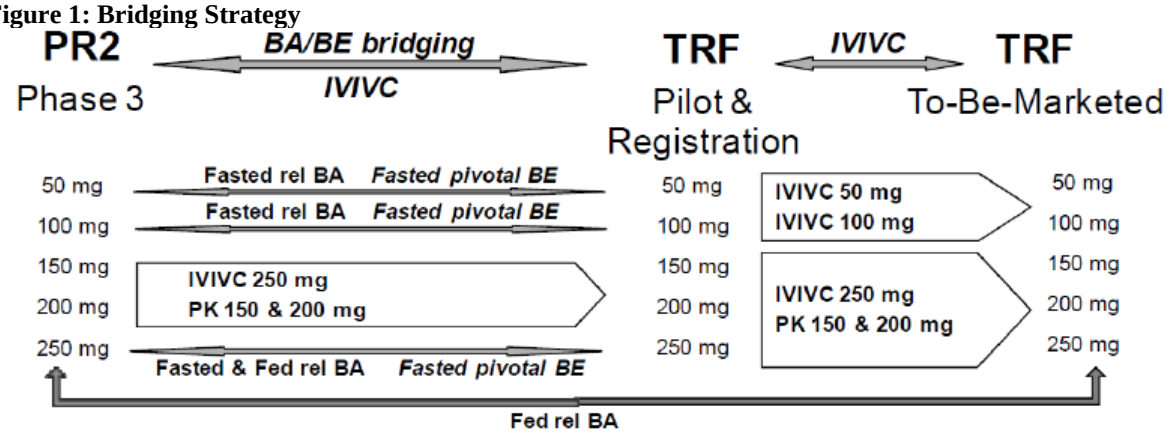
5. Clinical Pharmacology/Biopharmaceutics

General Considerations

As was noted above, the formulation for the extended-release tablet has been modified during the course of the drug product's development. Phase 1 and 2 clinical trials were conducted with (b) (4) formulations, designated PR1. Phase 3 clinical trials, as well as additional Phase 1 studies during that period, were conducted with what the Applicant designated as the PR2 formulation, which was similar in ingredients and dissolution to the PR1 tablets, but developed to accommodate the higher doses required for Phase 3 clinical trials. The tamper-resistant formulations (TRF) were subsequently developed to offer "tamper-resistant" properties while maintaining a similar dissolution profile to the Phase 3 PR2 formulations. There are three TRF formulations, namely, pilot, registration and the to-be-marketed (TBM) formulations.

The Applicant did not submit bioequivalence information bridging the PR2 Phase 3 clinical and the TBM formulations, opting instead to bridge the formulations with a combination of In-Vivo-In-Vitro Correlation (IVIVC) models and bioavailability/bioequivalence (BA/BE) bridging. Dr. Lee also noted in his review that this 2-part strategy was discussed and agreed upon during a Type C Meeting (September 5, 2008) and the pre-NDA meeting (January 23, 2009). This bridging strategy is illustrated in the diagram below, which was provided in the Applicant's submission.

Figure 1: Bridging Strategy



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

As noted in Dr. Lee's review, two bridging strategies were 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 models to bridge between the pilot batches (manufactured in Aachen, Germany) and registration batches of the TRF formulation (manufactured in Beerse, Belgium), and the TBM TRF formulation (manufactured in Gurabo, Puerto Rico); the IVIVC models were also used to bridge between the PR2 Phase 3 formulation and the TRF formulation.

During the review of this submission, the biopharmaceutics team found the proposed IVIVC models unacceptable. The deficiencies in the models were conveyed to the Applicant via teleconference on April 21, 2010, at which time the Agency advised the Applicant to reconstruct the models using individual plasma concentration values and to eliminate a mathematical term being used in the models (b) (4)

In a submission dated June 6, 2010 the Applicant decided not to reconstruct the IVIVC 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 (i.e., 150 mg and 200 mg doses). The Applicant proposed to submit the reports of these studies in August, prior to the end of the 10-month review cycle. However, 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 advised the Applicant to conduct BE studies with the highest (250 mg) and lowest (50 mg) strengths instead.

Further, although the proposed dissolution method to characterize the drug release of tapentadol TRF tablets was found to be acceptable, the proposed dissolution specifications were not acceptable because they were based on the IVIVC models that were determined to be unacceptable. The review team's recommendations regarding the acceptance criteria will need

to be finalized once the results of the proposed BE studies bridging the to-be-marketed formulation to the clinical trials formulation and the dissolution profile comparisons data are submitted.

Pharmacokinetics of the extended-release formulation

The absolute oral bioavailability of tapentadol from the PR1 tablets was 32% in the fasted state. The C_{max} 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 C_{max} of approximately 60% and a higher median value for t_{max} 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. C_{max} increased with dose, but did not fulfill the criteria for dose proportionality. Graphical exploration of the data, however, suggested approximate linearity between C_{max} and dose in the dose range of 50 to 250 mg.

Study 38, an open-label, single-center, single- and multiple-dose study using registration "TRF" 250 mg tablets, indicated that the estimated mean $T_{1/2}$ for tapentadol in this formulation was similar after single- and multiple doses (4.4 hours vs. 5.2 hours respectively). There is minimal accumulation after multiple-doses. The C_{max} is approximately 88 ng/mL after a single 250 mg dose, and 132 ng/mL after multiple doses. AUC is approximately 1070 ng•h/mL after a single dose, and 1144 ng•h/mL after multiple doses. As previously mentioned, PK parameters for the TBM TRF are not currently available.

Critical Intrinsic Factors

The Applicant did not submit any data in pediatric patients, elderly patients, or patients with hepatic or renal impairment with this NDA. Analysis of the pharmacokinetic data by gender indicated that women had approximately 20% higher C_{max} and AUC values compared to men, but most of this difference was accounted for by differences in body weight (men had approximately 20% higher body weight on average). The package insert for the extended-release tapentadol formulation will mirror the language in the immediate release tapentadol label with respect to intrinsic factors.

Thorough QT Study

As noted in Dr. Okada's review, the Applicant submitted a QT study (HP5503/10) conducted in March, 2003. This study used 100 mg and 200 mg extended-release twice daily dosing. The total daily dose from this extended-release formulation study was less than that of the total daily dose used in the TQT study (HP5503/25) with the immediate-release product previously submitted and reviewed in NDA 22-304. The previously submitted information (for the immediate-release formulation of Nucynta, NDA 22304) indicated that tapentadol did not have any significant QT prolongation effect.

Since the total extended-release daily dose used in HP5503/10 was less than the total immediate-release daily dose used in HP5503/25, and the study did not show any significant effect, the Agency's QT review team was not consulted. The labeling for this extended-release

formulation will continue to reflect that no significant QT prolongation effect of tapentadol was detected.

Drug-drug Interactions
In vitro data indicate that tapentadol is not an inhibitor of CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4, nor an inducer of CYP450 1A2, 2C9 or 3A4. No new information was submitted with this NDA to characterize drug-drug interactions further.

Studies intended to assess the effect of alcohol on the TRF formulation did not reveal any dose-dumping characteristics.

Outstanding or Unresolved Issues
I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that the lack of adequate bridging of the Phase 3 clinical formulations ("PR2") and the to-be-marketed (TBM) formulation will preclude approval of this application during this review cycle.

6. Clinical Microbiology

Tapentadol is not a therapeutic antimicrobial, therefore clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

The clinical development program for the extended-release formulation included three 15-week, Phase 3 induction trials: two in patients with chronic pain due to osteoarthritis (OA), and one in patients with chronic low back pain (LBP) and one 15-week randomized-withdrawal Phase 3 trial in diabetic patients with chronic pain due to diabetic peripheral neuropathy (DPN).

The three trials with an induction design were:

- Study 3008, 1023 patients with chronic pain due to knee OA received study medication at 112 sites in the United States, Canada, New Zealand, and Australia.
- Study 3009, 987 patients with chronic pain due to knee OA were treated at 79 sites in 12 European countries.
- Study 3011, 965 patients with chronic non-malignant LBP were treated at 97 sites in United States, Canada, and Australia.

The fourth trial, Study 3015, was a 15-week double-blind, parallel-group, multicenter, randomized-withdrawal Phase 3 trial of extended-release tapentadol in diabetic patients with chronic pain (defined as ≥ 6 months) from diabetic peripheral neuropathy. After a Washout Period where all analgesics were discontinued, patients received open-label tapentadol in the 3-week Titration Period. If patients responded to open-label extended-release tapentadol (i.e., ≥ 1 point improvement in the average pain intensity score from open-label baseline), they entered the double-blind Randomized Withdrawal Period and were randomized 1:1 to continue treatment with extended release tapentadol (at the current dose between 100 to 250 mg BID) or placebo. A total of 588 patients with chronic diabetic peripheral neuropathy were treated with

open-label tapentadol at 88 sites in the United States and Canada (389 patients were treated in the double-blind Randomized Withdrawal Period).

Endpoints:
The three induction Phase 3 trials were 15-week, randomized, double-blind, placebo-controlled and active-controlled, parallel-group, multi-center, 3-arm trials of controlled adjustment of extended-release tapentadol (100 to 250 mg BID) in patients with moderate to severe chronic pain (≥ 3 months). After a Washout Period where all analgesics were discontinued, patients were randomized 1:1:1 to extended-release tapentadol 50 mg BID, oxycodone CR 10 mg BID, or placebo BID. After 3 days, the tapentadol and oxycodone CR doses were increased to 100 mg BID and 20 mg BID, respectively. Following the Titration Period, patients entered the 12-week Maintenance Period where dose adjustment was discouraged; however, up or down titration was permitted if needed. The primary efficacy endpoint in all three induction trials was the change from baseline of the average pain intensity using an 11-point numerical rating scale over the last week of the trial (i.e., Week 15).

The primary efficacy endpoint in Study 3015 was the change from double-blind baseline of the average pain intensity using an 11-point numerical rating scale at the last week of the Randomized Withdrawal Period (i.e., Week 15).

Summary of Efficacy Findings**:**
As noted in the clinical and statistical reviews, the results from the trial in patients with chronic low back pain and the trial in patients with diabetic peripheral neuropathy were in favor of the extended-release tapentadol, regardless of the imputation strategy utilized to account for missing data. These results are summarized in the table below, reproduced from Dr. Okada's review.

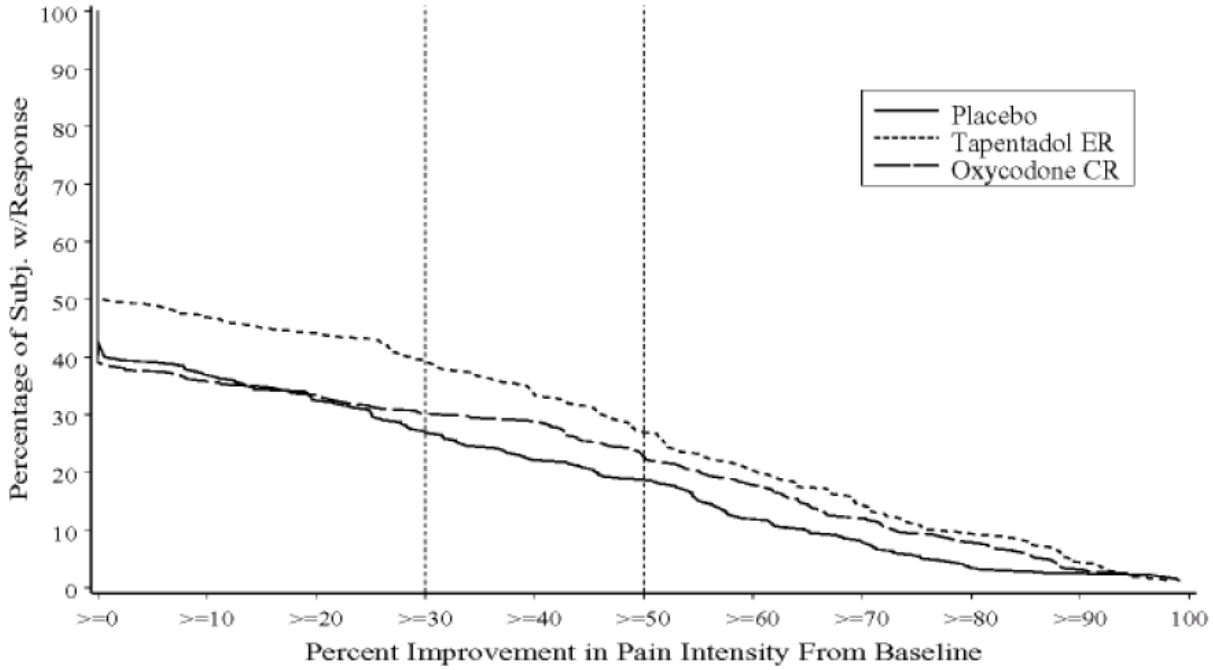
Efficacy Results for Successful Studies in Low Back Pain (LBP) and Diabetic Peripheral Neuropathy (DPN)

	Imputation	Tapentadol ER	Oxycodone CR	Placebo
Study 3011 (LBP) Primary Endpoint: **Change in Average Pain Intensity from Baseline to Last Week of Maintenance**				
Applicant's results		**n = 312**	**n = 323**	**n = 316**
LS means	LOCF	-2.9	-2.9	-2.1
p-value vs. placebo		<0.001	<0.001	
FDA Statistician results				
LS means (SE)	BOCF	-1.8 (0.1)	-1.5 (0.1)	-1.3 (0.1)
p-value vs. placebo		0.002	0.213	
LS means (SE)	WOCF	-1.4 (0.2)	-1.1 (0.2)	-0.8 (0.2)
p-value vs. placebo		0.004	0.149	
Study 3015 (DPN) Primary Endpoint: **Change in Average Pain Intensity from Double Blind Baseline to Last Week of Randomized Withdrawal Period**				
Applicant's results		**n = 196**		**n = 192**
LS means	LOCF	0.0		1.4
p-value vs. placebo		<0.001		
FDA statistician results		**n=179[a]**		**n=188[a]**
LS means (SE)	Screening BOCF	2.0 (0.4)		2.6 (0.4)
p-value vs. placebo		0.015		
LS means (SE)	WOCF, including screening baseline	2.1 (0.4)		2.8 (0.4)
p-value vs. placebo		0.004		

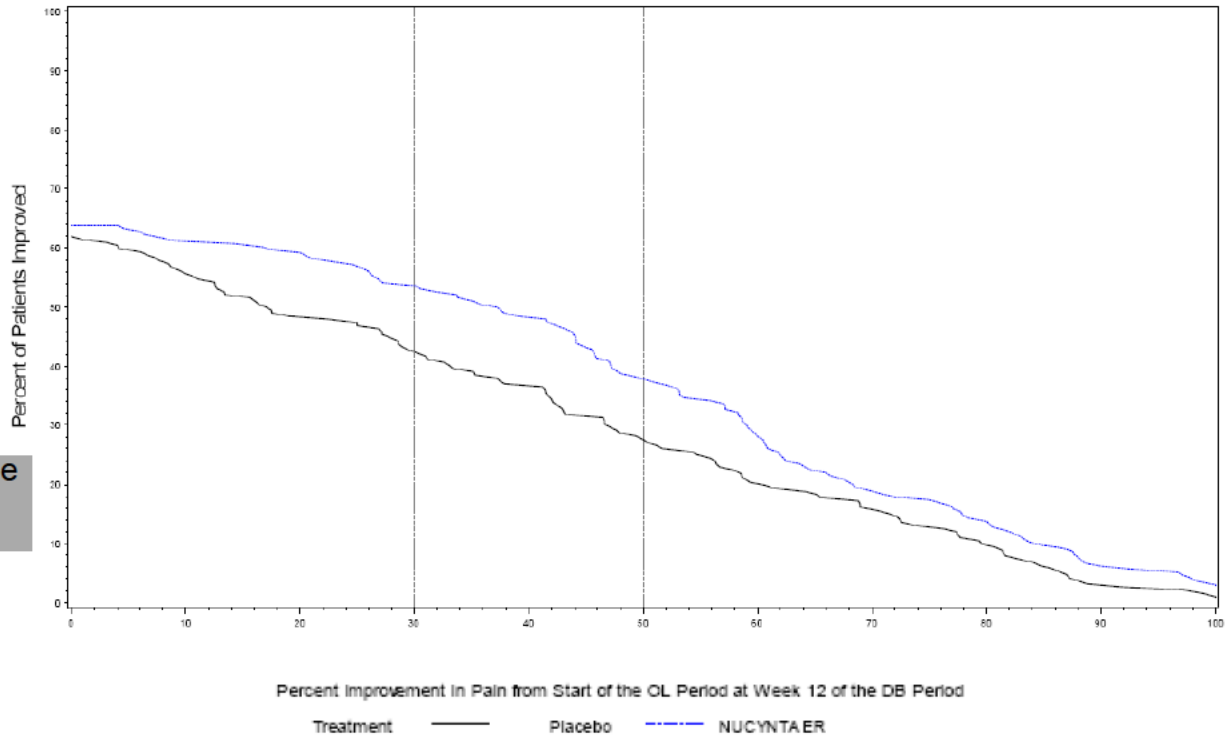
[a]does not include the 21 patients who were randomized but did not achieve an improvement in the change in pain intensity of 1 or more during the 3-week open label titration period
Sources: CSR Tables 18 and 26 and Dr. Yan Zhou's analyses

The Applicant's pre-specified imputation method for missing date was last-observation-carried-forward (LOCF), which had efficacy results with the lowest p-value (compared to placebo). The review team's statistician, Dr. Yan Zhou, performed additional sensitivity analyses using more conservative imputation methods for missing data, such as baseline-observation-carried forward (BOCF) and worst-observation carried forward (WOCF). Even with the use of these imputation methods, the results for Study 3011 and Study 3015, remained statistically significant in favor of the extended-release tapentadol.

The Applicant also performed an analysis of the cumulative proportion of responders. For Study 3011, there was a clear separation between the extended-release tapentadol and placebo curves across most of the response range. The difference between the two curves was found to be statistically significant. This is illustrated in the figure below, reproduced from the submission.



As noted by Dr. Okada, for Study 3015, twenty-one patients were misclassified as having met criteria for entry into the randomized withdrawal period, when, in fact, they did not meet minimum response criteria. Dr. Zhou performed a cumulative proportion of responders analysis which included these patients, and one which did not. In both analyses, the placebo and tapentadol curves remained similar and separated, which was interpreted as suggesting that these twenty-one patients did not affect the overall efficacy outcome conclusions. Statistical testing of the difference between curves demonstrated a statistically significant difference in each scenario. The figure below demonstrates the results of the analysis which includes the twenty-one patients (the more conservative of the two results).



In Study 3008, in patients with osteoarthritis, the Applicant's pre-specified imputation method for missing data was LOCF, and the results were statistically significant in favor of tapentadol. The Agency had previously advised the Applicant at the End-of-Phase 2 meeting on August 24, 2006, that LOCF was not considered an appropriate imputation method for these trials.

The review team used the more conservative imputation methods of BOCF and WOCF in their review of the trial, at which point the treatment difference lost its statistical significance. Therefore, although the trial was technically successful, based on the Applicant's pre-specified imputation method, the clinical and statistical reviewers concluded that Study 3008 did not provide convincing evidence of a treatment benefit for tapentadol. Furthermore, Study 3009, which was a similarly designed trial in patients with knee OA study, failed to show a statistically significant difference between tapentadol and placebo, regardless of which imputation method was used.

Nevertheless, as noted in Dr. Okada's review, although the two trials in patients with knee osteoarthritis did not meet the evidentiary standard to conclude effectiveness, the trials in patients with chronic low back pain and in patients with diabetic peripheral neuropathy do provide substantial evidence of effectiveness. Therefore, I concur with the clinical and statistical reviewers that the Applicant has provided sufficient data to demonstrate the effectiveness of the extended-release formulation of tapentadol.

8. Safety

The primary safety database is comprised of 4407 subjects who received at least one dose of the extended-release formulation of tapentadol: 3694 patients in Phase 2 and 3 trials, 79

healthy subjects in multiple-dose Phase 1 studies, and 634 healthy subjects in single-dose Phase 1 studies. A total of 1874 patients were exposed to tapentadol in the three Phase 3 randomized controlled induction trials and the 1-year open-label safety study, with 492 being exposed for over 24 weeks, and 227 patients exposed for 12 months or longer. The mean exposure in these studies was 139 days, with a mean total daily dose of 310 mg.

Deaths
In the controlled periods of the extended-release tapentadol trials, there were no deaths in the extended-release tapentadol treated patients. In the ongoing studies of extended-release tapentadol in patients with chronic non-cancer pain there were 3 (0.2%) deaths in 1513 tapentadol-treated patients. Two (Patient 105139 and Patient 105689) of the three deaths occurred in patients with known coronary artery disease and both of these deaths were likely due to cardiovascular events. The third death (Patient 105590) was a completed suicide in a 65 year old male with a history of depression, anxiety disorder, and panic disorder.

Serious Adverse Events
Extended-release tapentadol-treated patients had a greater incidence of non-fatal serious adverse events (SAEs), AEs leading to discontinuation (DAEs), and common AEs than placebo-treated patients. The differences in the incidences of DAEs and AEs between these groups were mostly due to known opioid-related toxicities (e.g., nausea, vomiting, dizziness, constipation, somnolence, fatigue). Although higher than in the placebo-treatment groups, frequencies were generally lower than in the oxycodone CR treatment groups in the studies. With respect to specific safety concerns, such as abuse potential, dependence, withdrawal and neuropsychiatric adverse events, the safety profile of extended-release tapentadol appeared to be consistent with other products with similar pharmacologic properties. There is suggestion that extended-release tapentadol may have abuse potential and dependence/withdrawal characteristics similar to long acting opioids. It also may be associated with some of the neuropsychiatric adverse effects noted with immediate-release tapentadol and tramadol.

Common Adverse Events
The most commonly observed adverse events were the type of events typically seen with products of this class: nausea, vomiting, dizziness, constipation, and somnolence. There were no new signals of concern noted in the safety database.

Risk Evaluation and Mitigation Strategy (REMS)
As a centrally-acting opioid analgesic with an extended-release formulation, this product will need a REMS to address the risks of abuse, misuse, and overdose. The Applicant is aware of the need for the REMS and has submitted a proposed REMS to their application. The Division of Risk Management has made a preliminary evaluation of the proposal, and their comments have been conveyed to the Applicant. Final evaluation of the proposed REMS will occur in the next review cycle.

Outstanding or Unresolved Issues
I concur with the review team's conclusion that the safety profile of the extended-release formulation is consistent with the safety profile of other approved long-acting opioid products, and the labeling should be consistent with current labeling of approved long-acting opioids and the immediate-release formulation of tapentadol.

I also concur with the assessment that this product will need to have a REMS similar to the REMS that is being instituted for other opioids indicated for the treatment of chronic pain.

(b) (4)

10. Pediatrics

The Applicant submitted a waiver for pediatric patients (b) (4)

(b) (4)

11. Other Relevant Regulatory Issues

Division of Scientific Investigations Audits

The Division of Scientific Investigations (DSI) conducted inspections of four clinical investigator sites and a sponsor inspection in the course of the evaluation of this application. Three sites were initially identified by the review team for routine inspection for the two studies considered to provide the basis of the efficacy evidence: two sites from Study 3011 and one site from Study 3015. The sites were selected based on the number of treated patients or wider treatment margins observed in favor of the extended-release tapentadol.

As noted in Dr. Okada's review, after the Applicant was informed of the planned site inspections, they conducted a review of the sites and informed the Agency that they had

uncovered potential misconduct at Site # 1460 in Study 3011 (Dr. Allan Soo). Potential issues related to minimal/limited source documentation, poor documentation (e.g., backdating, adverse events may have not been fully reported), dose escalations may have been compromised, and the use of potentially unqualified staff. Given this information, the DSI added one additional site in Study 3011 for inspection.

The overall assessment and recommendations by the DSI after the inspections were that the data from Dr. Soo's site should be considered unreliable and removed from the efficacy analysis. In general, no pervasive issues were identified in the inspections of the three remaining clinical sites which would significantly impact the reliability of the data. It is noted that, due to the number of clinical sites involved in the trials, the review team did not identify any single site which would have changed the overall efficacy results.

In addition, data pertaining to patient eligibility, primary endpoint, and rescue medication use were directly submitted by patient via electronic diaries (eDiaries) to eTrials, the contract research organization (CRO) responsible for this electronic data capture. The clinical investigator sites did not maintain independent source documentation of the data that was transmitted directly to eTrials via eDiaries; therefore, verification of the electronically captured primary efficacy source data could not be performed at the clinical investigator sites. Verification of source data at the CRO by the DSI, in conjunction with evaluation of findings from other completed inspections, is required before the DSI can render their final recommendation regarding the approvability of this application.

Financial Disclosure

The Applicant certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that the clinical investigators were required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant, as defined in 21 CFR 54.2(b), and that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f).

Consult from the Controlled Substances Staff

The Controlled Substances Staff was consulted to address abuse-related safety issues, such as the potential for overdose, withdrawal, misuse and abuse with the proposed formulation. Their conclusions are summarized below.

1. The controlled-release properties of the purported tamper-resistant formulation can be readily overcome by multiple simple physiochemical manipulations.
2. The to-be-marketed formulation exhibits an increased frequency of abuse-related adverse events.
3. Withdrawal symptoms, including insomnia, depressed mood, depression, suicidal ideation, and disturbance in attention, occurred after the extended-release formulation tapentadol was stopped. They noted

that such withdrawal symptoms are typical of all μ-opioid receptor agonists.

Their recommendations were as follows:

1. The sponsor must provide information and explanations of the pharmacokinetic and adverse event differences noted in the clinical trials using the tamper-resistant formulation and other extended-release formulations, because of pooled data that encompasses all formulations that were investigated. Linkage of the pharmacokinetic/pharmacodynamic data for the various formulations is needed.
2. Because the drug product at the 250 mg dose level appears to result in a high percentage of euphoria and other opioid-like adverse events, the sponsor must provide an adequate rationale for marketing the dose, so that the benefits continue to outweigh the risks.
3. Upon approval and marketing, the drug product should continue to be monitored for abuse, misuse, overdose, and withdrawal.

Outstanding or Unresolved Issues

I concur that verification of the source data at the CRO, in conjunction with evaluation of findings from other completed inspections, is required before this application may be approved. In addition, the recommendations from the Controlled Substances Staff will be discussed internally and conveyed to the Applicant as appropriate in a subsequent review cycle.

12. Labeling

The review team has reviewed the label proposed by the Applicant and had made substantial revisions. A final label will require further discussions with the Applicant; since it will not be possible to approve the application at this time, these discussions will be undertaken during the subsequent review cycle.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Complete Response.

Risk:Benefit Assessment

Although the Applicant has submitted sufficient data to support the efficacy and safety for the proposed indication, the approval of this application is not possible during this review cycle due to the lack of adequate bridging of the Phase 3 clinical formulations ("PR2") and the to-be-marketed (TBM) formulation.

Furthermore, verification of source data at the CRO, in conjunction with evaluation of findings from the other completed inspections, is required before this application may be approved.

Recommendation for Postmarketing Risk Management Activities

As a centrally-opioid analgesic with an extended-release pharmacokinetic profile, this product will need a REMS to address the risks of abuse, misuse, and overdose. The final assessment and evaluation of the Applicant's proposal for their REMS will be undertaken in the next review cycle.

Recommendation for other Postmarketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
10/01/2010

Cross-Discipline Team Leader Review

Date	September 20, 2010
From	Sarah Okada, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA # 200533
Applicant	Johnson & Johnson/Grunenthal
Date of Submission	December 1, 2009
PDUFA Goal Date	October 1, 2010
Proprietary Name / Established (USAN) names	Nucynta ER/ Tapentadol ER
Dosage forms / Strength	50, 100, 150, 200, 250 mg Extended-Release Tablets
Proposed Indication(s)	1. For the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
Recommended:	*Complete Response*

1. Introduction

Tapentadol is a centrally-acting analgesic compound that is being developed in an extended-release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older in a global development program. Tapentadol offers a dual mechanism of action, involving both mu-opioid agonism and norepinephrine reuptake inhibition. Non-clinical data indicate that both mechanisms are likely to contribute to the analgesic effects. A tapentadol immediate release (IR) tablet formulation has been developed and subsequently received FDA approval 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 pure stereoisomer that acts directly on the central nervous system; no metabolites with analgesic activity are known. Of the many long-acting opioids that have been approved, tapentadol is most similar to tramadol, which also has agonist activity on the mu opioid receptor and inhibits the reuptake of norepinephrine, but also of serotonin. Therefore, in addition to typical opioid effects, tapentadol, like tramadol, could be associated with an increased risk of seizures and serotonin syndrome, particularly in combination with monoamine oxidase inhibitors.

The tapentadol ER Phase 3 program was designed in accordance with Agency expectations expressed in an End-of-Phase 2 (EOP2) meeting of 24 August 2006 (see Dr. Brodsky's review, Table 2.5, for further details).

2. Background

Approximately 3.8 million patients annually receive prescriptions for long-acting opioids in the outpatient setting (Governale FDA presentation July 22, 2010 Opioid REMS AC Meeting). Data from the Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network (DAWN) show that emergency department visits involving nonmedical use of prescription opioids increased 111% between 2004 and 2008, with the estimated number of visits rising from 144 644 to 305 885 per year (MMWR Morb Mortal Wkly Rep. 2010;59[23]:705-709).

In response to this growing problem, FDA has been developing an approach to a Risk Evaluation and Mitigation Strategy (REMS) with input from all stakeholders including the pharmaceutical industry, academia, professional organizations and patient advocacy groups. The most recent proposal, put forward at the July 2010 AC meeting, was described as follows [B Kuehn, JAMA Volume 304(8), 25 August 2010, p 845]:

Because tapentadol is a mu receptor agonist, tapentadol ER falls under the rubric of the chronic opioid REMS. Because the chronic opioid REMS is still being finalized, the tapentadol ER REMS will be closely modeled on the recently approved chronic opioids that have preceded it, such as Embeda and Oxycontin CR.

The basis for this NDA are 3 randomized controlled induction trials (2 in knee osteoarthritis and 1 in chronic low back pain) and 1 randomized withdrawal trial in diabetic peripheral neuropathy. Additional open-label data are submitted from a one-year safety study of chronic patients taking Tapentadol ER or Oxycodone CR. However an additional 35 studies were also submitted with the NDA, including 5 randomized 4-5 week Phase 2 trials in chronic pain, 3 multiple-dose Phase 1 studies in healthy subjects (including a QT study), and 27 single-dose Phase 1 studies in healthy subjects. As will be discussed further in Section 7 below, two of the 4 efficacy trials convincingly demonstrated a treatment benefit in favor of tapentadol ER, whereas the two did not (the knee osteoarthritis trials). Considering the difficulty of demonstrating efficacy in osteoarthritis (OA), the failure of the two knee OA trials is not unexpected. The safety of tapentadol ER (see Section 8 below) appears to be consistent with other extended release opioids and norepinephrine reuptake inhibitors.

However, the clinical data provided in this submission are not adequately bridged to the to-be-marketed (TBM) formulations, as the clinical trials were done with earlier extended-release formulations (designated "PR2"). This is the crux of the issue precluding approval of the NDA.

3. CMC/Device

Primary CMC Reviewer: Craig Bertha, Ph.D.
CMC Team Leader: Prasad Peri, Ph.D.

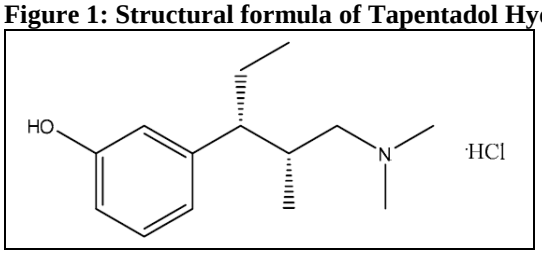
- **General product quality considerations**

The drug product, Nucynta ER (tapentadol) Extended Release Tablets is a solid dosage form with strengths of 50, 100, 150, 200, and 250 mg (as tapentadol freebase), intended for oral administration. It is packaged in high-density polyethylene bottles fitted with child resistant closures, each containing 60 tablets (for all strengths). Each strength is also packaged in cartons, said to be for hospital use only, that contain ten blister cards each containing ten tablets (100 count). The drug product formulation consists of tapentadol hydrochloride (b) (4) polyethylene oxide (b) (4) hypromellose (b) (4) and polyethylene glycol (b) (4) The formulation also contains a small amount (b) (4) of Vitamin E (b) (4) The formulations are not compositionally proportional with respect to the active and excipient components. (b) (4) The tablet cores are coated with proprietary coatings of different colors for each strength and each is also imprinted with a unique alphanumeric code. Whether these properties actually result in tamper-resistance in the marketed setting, in the hands of experienced abusers, is an issue that requires further discussion (see Notable Issues Section below).

As previously noted, the commercial products (referred to as "tamper-resistant formulations", TRF), differ from the formulations studied in the phase 3 clinical trials (PR2 formulations). The adequacy of what the applicant has proposed to link the clinical trial lots to the to-be-marketed (TBM) formulation is discussed further in the Biopharmaceutics section below.

The drug substance, tapentadol hydrochloride (chemical name 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride; molecular formula $C_{14}H_{23}NO \cdot HCl$), has already been approved as an immediate release formulation (NDA 22304, November 2008). It is a chiral opioid compound (b) (4)

Figure 1: Structural formula of Tapentadol Hydrochloride



A review of the 12 months of long term and 6 months of accelerated stability data for the registration stability batches and the data for the batches of drug product prepared at the planned commercial site was found to be supportive of the 24 month expiry period that had been proposed by the applicant for the HDPE bottled and the (b) (4) blister packaged drug product (see CMC reviews #1 and #2). In the 30-APR-2010 amendment, the applicant has provided the 18 month time-point data for the long term storage of the registration stability batches at 25°C/60%RH as well as that for the conditions of 30°C/75%RH. No extension of the expiry is proposed beyond the original 24 months. Updated plots of the 18 month long term stability data (25°C/60%RH) for the assay, vitamin E assay, (b) (4), and dissolution parameters have been prepared. The assay data for both the bottled and blister packaged drug product show little if any stability trend up to the 18 month time-point and are still supportive of the proposed 24 month expiry relative to the specification acceptance criteria of (b) (4) of label claims.

- **Facilities review/inspection**

Table 1 Proposed Commercial Manufacturing Sites for Tapentadol Extended Release Tablets

Facility	Responsibility of the Facility
Janssen Ortho, LLC State Road 933, KM 0.1 Gurabo, PR 00778 FDA Drug Establishment Number: 2650104	Manufacturing Packaging Labeling Release testing Release
Ortho-McNeil Janssen Pharmaceuticals, Inc. 1125 Trenton-Harbourton Road Titusville, NJ 08560 FDA Drug Establishment Number: 2242843	Marketed drug product stability testing

The Office of Compliance has issued an overall recommendation of acceptable for the manufacturing facilities on September 15, 2010.

- **Other notable issues (resolved or outstanding)**

Tamper Resistant Formulation

Because ER versions of opioid products are often subject to abuse, the Applicant has attempted to give the formulations tamper resistant properties (b) (4)

(b) (4) These "tamper-resistant formulations" (TRF) were developed after the performance of the Phase 3 clinical trials with earlier PR2 formulations. The TRF formulations consist of (b) (4) The Applicant states that they "fine-tuned" the TRF formulations to match the release profile of the phase 3 PR2 formulations of corresponding strength. (b) (4)

The applicant performed a number of tests intended to simulate accidental misuse, tampering by the recreational abuser, tampering by experienced abusers, and tampering by "kitchen chemists."

- Accidental Misuse:

(b) (4)

- Recreational Abuser:

(b) (4)

(b) (4)

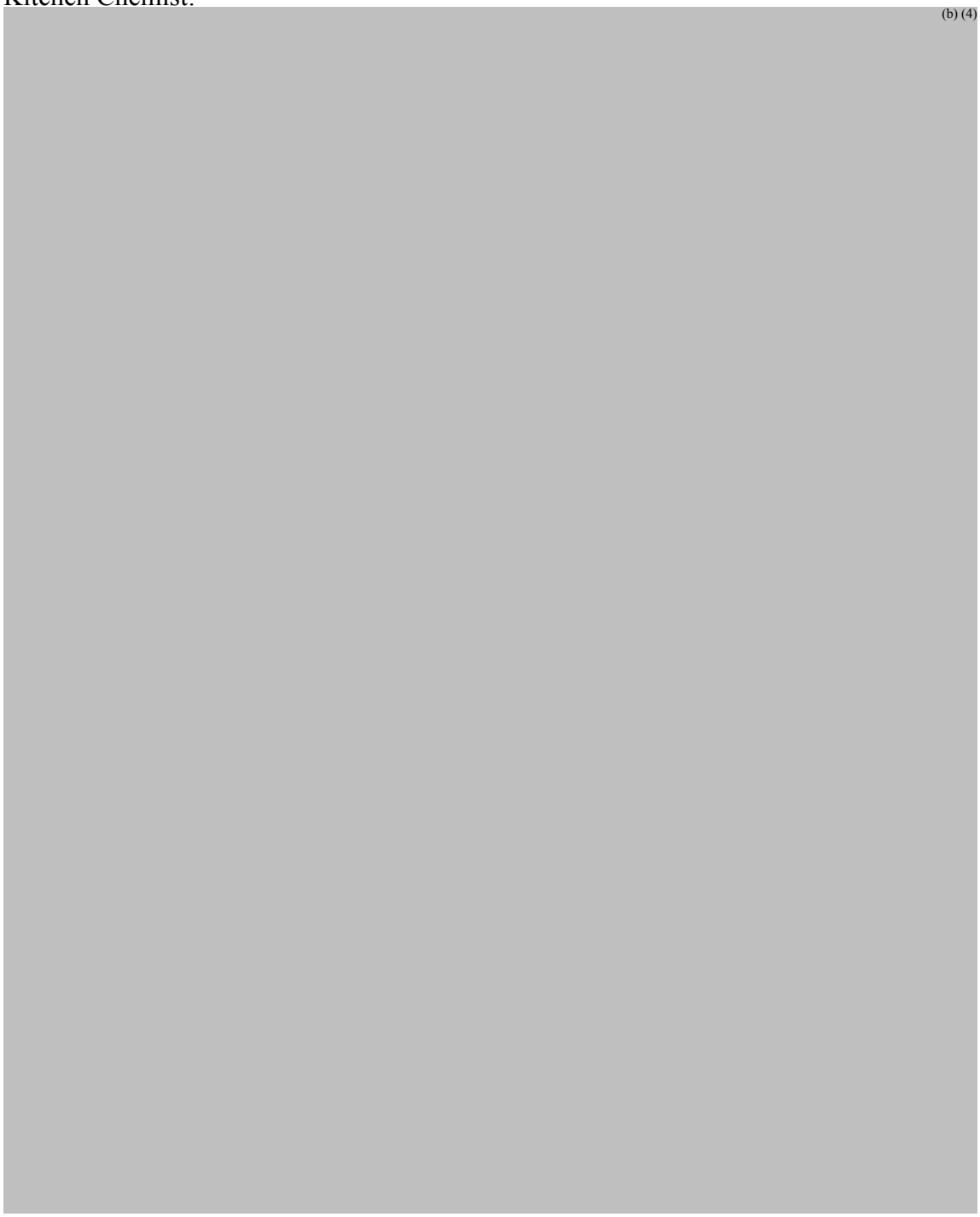
- Experienced Abuser:

(b) (4)

(b) (4)

- Kitchen Chemist:

(b) (4)



(b) (4)

(b) (4)

Dr. Bertha and Dr. Peri agree that NDA 200533 is approvable, pending resolution of the issue regarding appropriate bridging of the PR2 formulations to the TBM formulations, and successful facility inspections.

4. Nonclinical Pharmacology/Toxicology

Primary Pharmacology/Toxicology Reviewer: Armaghan Emami, Ph.D.
Pharmacology/Toxicology Supervisor: Adam Wasserman, Ph.D.

- **General nonclinical pharmacology/toxicology considerations**

A tapentadol immediate release (IR) tablet formulation received FDA approval for the relief of moderate to severe acute pain in patients 18 years of age or older (NDA 22-304, approved 20 November 2008). The Sponsor (J&JPRD on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc.) is cross-referencing to the INDs (#61,345, 105,766) and NDA 22-304 for nonclinical support of the safety of Tapentadol ER formulation. No new nonclinical studies for tapentadol were submitted with this NDA.

Tapentadol IR is administered up to 100 mg 6 times per day (700 mg on the first day and 600 mg/day thereafter) while the proposed ER formulation is up to 250 mg twice a day. While the ER AUC_{0-24} is approximately 40% lower than IR AUC_{0-24}, the ER Cmax is approximately 30% greater than the IR Cmax at the maximum human recommended dose (MHRD). Tapentadol has been evaluated in a comprehensive preclinical program including pharmacological characterization, preclinical safety (safety pharmacology and toxicology), pharmacokinetics, and ADME. Non-clinical studies were reviewed by Dr. Kathy Young under NDA 22-304.

The major toxicity findings of tapentadol were consistent with its mu-opioid receptor agonist activity (ie, effects on the gastrointestinal, central nervous, respiratory, and cardiovascular systems). At high doses of tapentadol, transient, dose dependent and predominantly CNS-related findings, e.g. fearfulness, sedation or excited behavior, recumbency and hunched posture, impaired respiratory function, rarely convulsions, were observed. In dogs, salivation, vomiting and retching were additionally observed. Tapentadol was shown to have pro-convulsant activity in rats, and induced convulsions in rats, mice, and dogs at high doses. The tapentadol-O-glucuronide metabolite may contribute to this effect. Changes of the liver and cardiovascular system (e.g. QT prolongation) were seen in rats and dogs respectively. Of note, toxicities observed in non-clinical (rats and dogs) studies were associated with exposure levels that do not support human exposures.

Dr. Emami's overall conclusions are that the non-clinical studies of tapentadol are not sufficient to support the maximum human exposure to tapentadol in either the Tapentadol ER or IR product. In addition to the lack of supportive NOAEL exposures, the highest dose used in the chronic toxicology study in the dog was unable to reach the human exposure associated with the MRHD for the ER product, and neither chronic toxicology study reached AUC levels that support the MRHD exposure for the IR product.

- **Carcinogenicity**

From Dr. Kathleen Young's Review, NDA 22-304, studies on the active moiety showed that tapentadol was negative for carcinogenicity in 104-week oral administration studies in mice treated by gavage, and in rats given tapentadol by dietary admixture.

- **Reproductive toxicology**

From Dr. Kathleen Young's Review, NDA 22-304
There was no evidence of adverse effects on fertility and reproductive performance, embryo-fetal malformations and pre- and post-natal development in rats. The results of an embryo-fetal study in Himalayan rabbits given subcutaneous tapentadol showed dose related increases in the incidence of runts and multiple malformations, including thoracogastroschisis, prolapsed organs, amelia, phocomelia, encephalocele, spina bifida, cleft palate, ablepharia, and skeletal malformations. The malformations were observed in fetuses from dams showing severe maternal toxicity, although not all dams showing treatment-related toxicity had malformed fetuses. The incidences of malformations in the rabbits were within the upper limit of historical control range for the laboratory provided by the Sponsor, except for ablepharia, which slightly exceeded the upper historical control range. Tapentadol was found negative for external and skeletal malformations, variations, and retardations in another, intravenous study in rabbits. However, a relationship of the dose-related increased incidences of malformations to tapentadol treatment in the subcutaneous study in rabbits cannot be rejected unequivocally.

- **Other notable issues (resolved or outstanding)**

The Division's pharmacology/toxicology review team believes that the nonclinical data contained in the cross-referenced NDA 22-304 submission (Tapentadol IR) are not sufficient

to support the maximum human exposure to tapentadol in Tapentadol ER as proposed under NDA 200533. However, they also believe that due to animal intolerance to use of higher doses in non-clinical studies, additional non clinical studies would likely not be informative. Dr. Wasserman also points out in his review that the toxicities observed in the tapentadol nonclinical studies are largely confined to the CNS and are common to opioid and/or norepinephrine reuptake inhibitors, and that a relatively large body of clinical safety data has not demonstrated any unusual toxicity for this drug relative to its class. This, in addition to the fact that the systemic exposures with the ER tablet are similar to the IR tablet, leads Dr. Wasserman to conclude that Nucynta ER tablets may be approved. Although the ER product has approximately 30% more exposure based on the Cmax parameter, an increase in this parameter would most likely only be associated with a possible increased incidence of CNS type symptoms.

5. Clinical Pharmacology/Biopharmaceutics

ONDQA Biopharmaceutics Review: Sandra Suarez-Sharp, Ph.D.
ONDQA Biopharmaceutics Supervisor: Patrick Marroum, Ph.D.
Clinical Pharmacology Reviewer: David Lee, Ph.D.
Clinical Pharmacology Supervisor: Suresh Doddapaneni, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

Phase 1 and 2 clinical trials were conducted with (b) (4) formulations of the tapentadol ER tablets, designated PR1. Phase 3 clinical trials, as well as additional Phase 1 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 Phase 3 clinical trials. The tamper-resistant formulations (TRF) were subsequently developed to offer "tamper-resistant" properties with similar dissolution profile to the Phase 3 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. The Applicant did not submit bioequivalence information bridging the PR2 Phase 3 clinical and the TBM formulations (See Notable Issues section below).

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.

Based on Study 38, which was an open-label, single-center, single- and multiple-dose study using registration "TRF" 250 mg tablets, the estimated mean T1/2 for tapentadol in this formulation was similar after single- and multiple doses (4.4 hours vs. 5.2 hours respectively). There is minimal accumulation after multiple-doses of tapentadol ER tablets. Cmax is approximately 88 ng/mL after a single 250 mg dose, and 132 ng/mL after multiple doses. AUC is approximately 1070 ng•h/mL after a single dose, and 1144 ng•h/mL after multiple doses. As previously mentioned, PK parameters for the TBM TRF are not currently available.

- **Drug-drug interactions**

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. No new information was submitted with this NDA to characterize drug-drug interactions further. The effect of alcohol on the TRF formulation was discussed in Section 3 above. No dose-dumping characteristics were noted.

- **Pathway of elimination**

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. 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.

- **Intrinsic factors: age, gender, hepatic insufficiency and renal impairment**

No data in pediatric patients, elderly patients, or patients with hepatic or renal impairment were submitted with this NDA. Evaluation by gender showed that women had approximately 20% higher Cmax and AUC values compared to men, but most of this difference was accounted for by differences in body weight (men had approximately 20% higher body weight on average). The package insert for the tapentadol ER formulation will mirror the language in the tapentadol IR label with respect to intrinsic factors.

- **Demographic interactions/special populations**

No 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 compared to non-Japanese subjects.

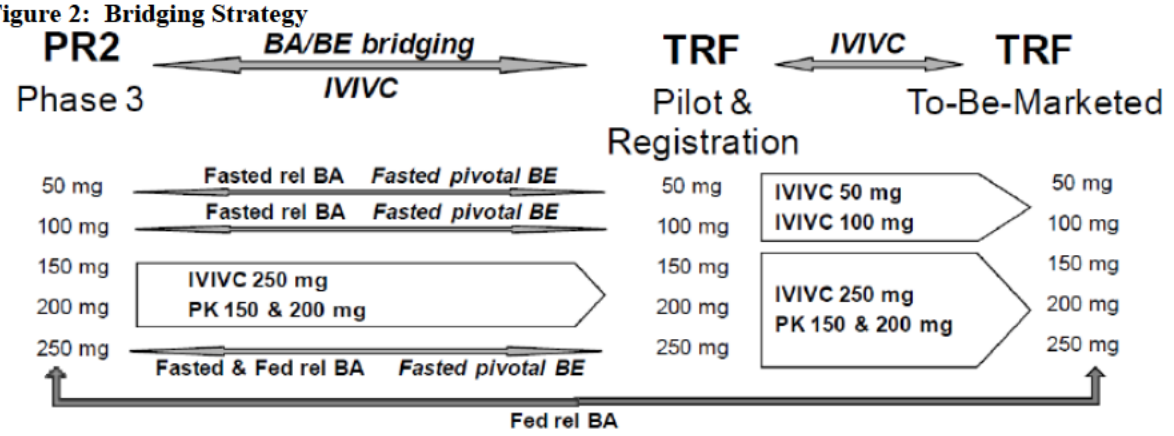
- **Thorough QT study or other QT assessment**

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, the Agency's QT review team 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.

- **Other notable issues (resolved or outstanding)**

The primary issue precluding approval is the lack of adequate bridging of the Phase 3 clinical formulations ("PR2") and the To-Be-Marketed (TBM) formulation. The Applicant's proposed bridging strategy is summarized in Figure 2, below.

Figure 2: Bridging Strategy



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

The sponsor proposed the use of two In-Vivo-In-Vitro Correlation (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. This was communicated to the Applicant via teleconference on April 21, 2010, at which time the Agency advised the Applicant to reconstruct the model 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 Applicant decided not to reconstruct the IVIVC 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 (i.e., 150 mg and 200 mg doses). The Applicant proposed to submit the reports of these studies prior to the end of the 10-month review cycle in August. However, 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 advised the Applicant to conduct BE studies with the highest (250 mg) and lowest (50 mg) strengths instead (Biopharmaceutics review dated June 14, 2010).

The dissolution method to characterize the drug release of tapentadol 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. ONDQA Biopharmaceutics team believes the proposed dissolution method is acceptable. However, the proposed dissolution specifications are not acceptable because these were based on the IVIVC models that were determined to be unacceptable. The acceptance criteria recommendations will need to 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.

The Applicant is currently working on the required BE studies and revised dissolution specification acceptance criteria. They are proposing to attempt to submit these before the October 1, 2010 due date and request an extension of the review cycle (90 days for a major amendment). However, at this time it appears unlikely that required inspections for these pivotal BE studies could be accomplished in a 90-day timeframe, as the site performing study sample analyses is foreign (b) (4) The clinical study site is Celerion, Inc. in Lincoln, Nebraska. Thus it does not appear that a 90-day extension of the review clock would be useful, as an approval action is not likely to be feasible in that timeframe.

6. Clinical Microbiology – not applicable

7. Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Eric Brodsky, M.D.
Primary Statistical Reviewer: Yan Zhou, Ph.D.
Statistical Team Leader: Dionne Price, Ph.D.

The studies forming the basis for the efficacy evaluation include three 15-week, Phase 3 induction trials—two in patients with chronic pain due to osteoarthritis (OA), and one in patients with chronic low back pain (LBP)—and one 15-week randomized-withdrawal Phase 3 trial in diabetic patients with chronic pain due to diabetic peripheral neuropathy (DPN). These studies, along with a 1-year, safety study of tapentadol ER in patients with non-malignant chronic pain served as the primary basis to support the safety of tapentadol ER for the chronic treatment of pain.

The 3 induction Phase 3 trials were 15-week, randomized, double-blind (DB), placebo-controlled (PC) and active-controlled, parallel-group, multi-center (MC), 3-arm trials of controlled adjustment of tapentadol ER (100 to 250 mg BID) in patients with moderate to severe chronic pain (≥ 3 months). After a Washout Period where all analgesics were discontinued, patients were randomized 1:1:1 to tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID and then after 3 days the tapentadol ER and oxycodone CR doses were increased to 100 mg BID and 20 mg BID, respectively. Following the Titration Period, patients entered the 12-week Maintenance Period where dose adjustment was discouraged; however, up or down titration was permitted if needed. The primary efficacy endpoint in all 3 induction trials was the change from baseline of the average pain intensity using an 11-point numerical rating scale over the last week of the trial (i.e., Week 15).

The three trials with an induction design included:

- Study 3008, 1023 patients with chronic pain due to knee OA received study medication at 112 sites in the U.S., Canada, New Zealand, and Australia.
- Study 3009, 987 patients with chronic pain due to knee OA were treated at 79 sites in 12 European countries.
- Study 3011, 965 patients with chronic non-malignant LBP were treated at 97 sites in United States, Canada, and Australia.

Study 3015 was a 15-week DB, parallel-group, MC, randomized-withdrawal Phase 3 trial of tapentadol ER in diabetic patients with chronic pain (≥ 6 months) from DPN. After a Washout Period where all analgesics were discontinued, patients received OL tapentadol ER in the 3-week Titration Period. If patients responded to OL tapentadol ER (i.e., ≥ 1 point improvement in the average pain intensity score from OL baseline), they entered the DB Randomized Withdrawal Period and were randomized 1:1 to continue treatment with tapentadol ER (at the current dose between 100 to 250 mg BID) or placebo. The primary efficacy endpoint in Study 3015 was the change from DB baseline of the average pain intensity using an 11-point numerical rating scale at the last week of the Randomized Withdrawal Period (i.e., Week 15). In Study 3015, 588 patients with chronic DPN were treated with OL tapentadol at 88 sites in the United States and Canada (389 patients were treated in the DB Randomized Withdrawal Period).

Two of the studies, Study 3011 in LBP and Study 3015 in DPN, convincingly achieved their primary endpoint, with results in favor of Tapentadol ER (Nucynta) regardless of imputation method, as shown in Table 2 below.

Table 2 Efficacy Results for Study 3011 (LBP) and Study 3015 (DPN)

Efficacy Results for Successful Studies in Low Back Pain (LBP) and Diabetic Peripheral Neuropathy (DPN)				
	Imputation	**Tapentadol ER**	**Oxycodone CR**	**Placebo**
Study 3011 (LBP) Primary Endpoint: **Change in Average Pain Intensity from Baseline to Last Week of Maintenance**				
		n = 312	**n = 323**	**n = 316**
Applicant's results				
LS means	LOCF	-2.9	-2.9	-2.1
p-value vs. placebo		<0.001	<0.001	
FDA Statistician results				
LS means (SE)	BOCF	-1.8 (0.1)	-1.5 (0.1)	-1.3 (0.1)
p-value vs. placebo		0.002	0.213	
LS means (SE)	WOCF	-1.4 (0.2)	-1.1 (0.2)	-0.8 (0.2)
p-value vs. placebo		0.004	0.149	
Study 3015 (DPN) Primary Endpoint: **Change in Average Pain Intensity from Double Blind Baseline to Last Week of Randomized Withdrawal Period**				
Applicant's results		**n = 196**		**n = 192**
LS means	LOCF	0.0		1.4
p-value vs. placebo		<0.001		
FDA statistician results		**n=179[a]**		**n=188[a]**
LS means (SE)	Screening BOCF	2.0 (0.4)		2.6 (0.4)
p-value vs. placebo		0.015		
LS means (SE)	WOCF, including screening baseline	2.1 (0.4)		2.8 (0.4)
p-value vs. placebo		0.004		

[a]does not include the 21 patients who were randomized but did not achieve an improvement in the change in pain intensity of 1 or more during the 3-week open label titration period
Sources: CSR Tables 18 and 26 and Dr. Yan Zhou's analyses

The Applicant's pre-specified imputation method was last-observation-carried-forward (LOCF), which provided for results with lowest p-value compared with placebo. FDA statistician, Dr. Yan Zhou, performed additional analyses using more conservative imputation methods, such as baseline-observation-carried forward (BOCF) and worst-observation-carried-forward (WOCF). For studies 3011 and 3015, even with the use of these imputation methods for missing data treatment differences in favor of tapentadol ER remained statistically significant.

In contrast, in Study 3008 in OA, the Applicant's imputation method of LOCF resulted in statistically significant treatment difference in favor of tapentadol, but using the more conservative imputation methods of BOCF and WOCF, this difference is not statistically significant (see Table 3, below). The Agency had already advised the Applicant at an End-of-Phase 2 (EOP2) meeting on August 24, 2006 that LOCF was not considered an appropriate imputation method for these trials, as patients dropping out due to adverse effects (which in fact is the most common reason for drop-outs—see Table 6.4 of Dr. Brodsky's review) could be ascribed a beneficial outcome with respect to change in pain intensity. Therefore, although the trial was technically successful based on the pre-specified imputation method, Agency clinical and statistical reviewers do not believe Study 3008 provides convincing evidence of a treatment benefit for tapentadol ER. Furthermore, Study 3009, which is a similarly designed knee OA study conducted primarily in Europe, failed to show a statistically significant difference between tapentadol ER and placebo, regardless of imputation method, including LOCF.

Table 3 Efficacy Results for Study 3008 and Study 3009 in Knee Osteoarthritis

Efficacy Results for Unsuccessful Studies in Osteoarthritis (OA)				
	Imputation	**Tapentadol ER**	**Oxycodone CR**	**Placebo**
Study 3008 (OA) Primary Endpoint: Change in Average Pain Intensity from Baseline to Last Week of Maintenance				
Applicant's results		**n = 344**	**n = 342**	**n = 336**
LS means	LOCF	-2.9	-2.6	-2.3
p-value vs. placebo		**<0.001**	0.069	
FDA Statistician results				
LS means (SE)	BOCF	-2.0 (0.1)	-1.2 (0.1)	-1.7 (0.1)
p-value vs. placebo		0.082	0.002	
LS means (SE)	WOCF	-1.5 (0.2)	-0.7 (0.1)	-1.3 (0.1)
p-value vs. placebo		0.191	0.002	
Study 3009 (OA) Primary Endpoint: Change in Average Pain Intensity from Baseline to Last Week of Maintenance				
Applicant's results		**n = 319**	**331**	**n = 336**
LS means	LOCF	-2.6	-2.2	-2.4
p-value vs. placebo		0.152	0.279	
LS means (SE)	BOCF	-1.7	-1.1	-1.7
p-value vs. placebo		0.953	<0.001	
LS means (SE)	WOCF	-1.5	-0.7	-1.5
p-value vs. placebo		0.997	<0.001	

Sources: CSR Table 26 and Dr. Yan Zhou's analyses, Study 3009 CSR Tables 27, 28, 29

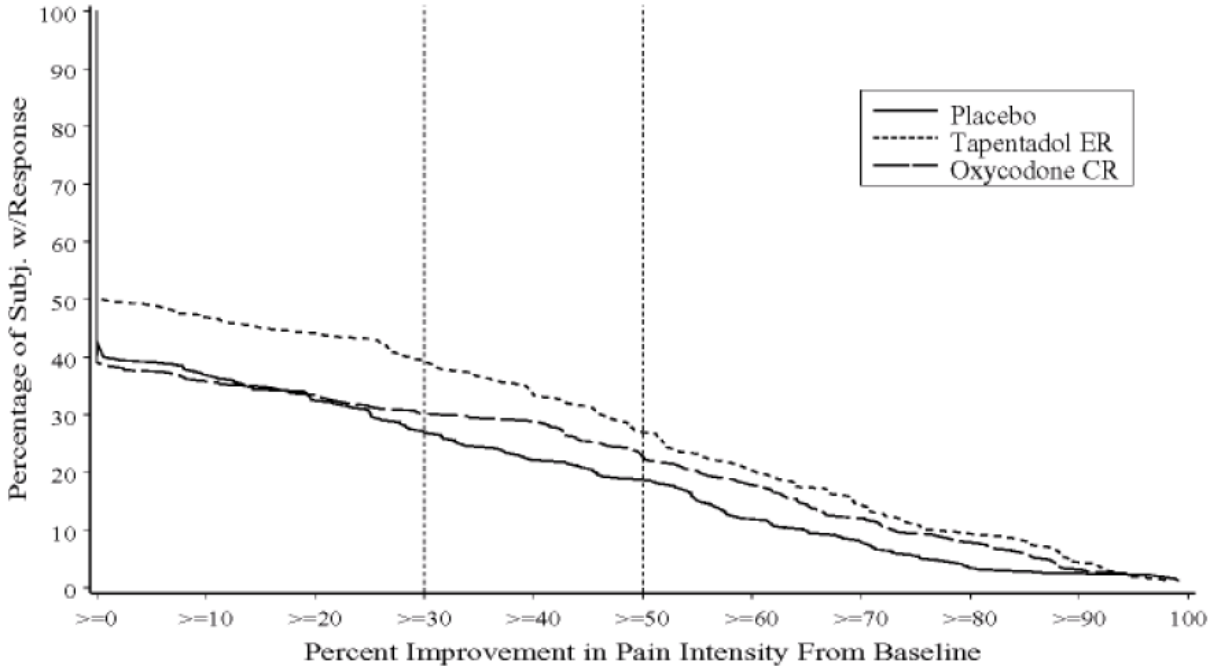
It is worth noting, however, that Oxycodone CR, an approved and known potent analgesic, was also not able to demonstrate a consistent statistically significant improvement using all imputation methods in these trials. Thus the failure of tapentadol ER to demonstrate a statistically significant difference in these OA trials does not preclude a conclusion of efficacy of tapentadol based on the other trials submitted in this NDA.

Cumulative Proportion of Responders Analyses (CPRA)

It can be difficult to interpret results of analgesic trials, as pain is a subjective experience that varies from person to person and the degree of improvement required for a person to report that their pain is "better" varies from person to person and can be different on the different parts of typical pain scales. This variability in the intrinsic meaning of pain scales can make it difficult to interpret the clinical or scientific importance of differences between groups using summary statistics that report the central tendency (i.e., mean or median). To address this difficulty, Farrar and colleagues proposed the use of Cumulative Proportion of Responders Analyses (CPRA) [J Pain Symptom Manage 2006; 31:369-377]. The advantages of the CPRA include the ability to display information over the full range of potential response levels and the ability to assess data on the group response at one or more cut-off points (e.g., 50% improvement or 70% improvement) that a clinician may find most appropriate or clinically relevant for his/her own patients.

CPRA for Study 3011 (LBP) and Study 3015 (DPN) are shown in Figures 3 and 4 below. In both figures the tapentadol ER curve clearly separates from the placebo curve across most of the response range. The difference between curves in both studies was statistically significant using a Kolmogorov-Smirnov test.

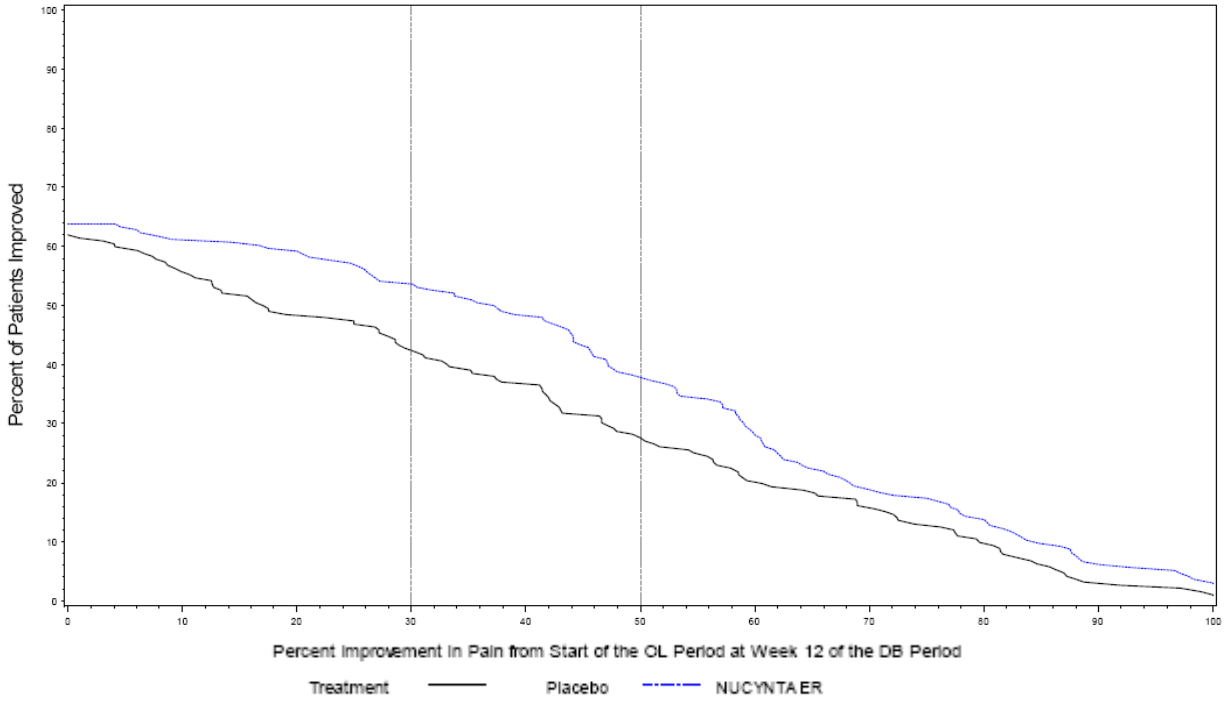
Figure 3: Cumulative Proportion of Responders Analysis of Study 3011 (LBP)



Source: Study 3011 CSR, Figure 15

Twenty-one patients were misclassified as having met criteria for entry into the randomized withdrawal period of Study 3015 when in fact they did not meet minimum response criteria. Dr. Zhou performed a CPRA including these patients and excluding these patients—the placebo and tapentadol ER curves remained similar and separated, suggesting that these 21 patients did not affect the overall efficacy outcome conclusions. Statistical testing of the difference between curves showed a statistically significant difference for analyses including or excluding these 21 patients. The CPRA shown in Figure 4 includes the 21 patients—the more conservative of the two results.

Figure 4: Cumulative Proportion of Responders Analysis of Study 3015 (DPN Randomized Withdrawal Study)



Source: Dr. Yan Zhou's statistical review, Figure 3

- **Statistical and clinical conclusions**

The statistical and clinical review teams concur that Study 3011 (in low back pain) and Study 3015 (in diabetic peripheral neuropathy) provide substantial evidence of the effectiveness of tapentadol ER for the treatment of chronic pain. Both teams also concur that the results of Study 3008 and Study 3009, in knee osteoarthritis, did not meet the evidentiary standard to conclude effectiveness, but also that those results do not preclude an overall conclusion of efficacy for the product based on the evidence provided by Studies 3011 and 3015.

- **Notable efficacy issues**

See discussion of Study 3008 above.

8. Safety

- **Discuss the adequacy of the database, major findings/signals**

The safety database included 4407 subjects who received at least one dose of tapentadol ER—3694 patients in Phase 2 and 3 trials, 79 healthy subjects in multiple-dose Phase 1 studies, and 634 healthy subjects in single-dose Phase 1 studies. In the three Phase 3 randomized-controlled induction trials and the 1 year open-label safety study, 1874 patients were exposed

to tapentadol ER in total, with 492 being exposed for over 24 weeks, and 227 patients exposed for 12 months or longer. The mean exposure in these studies was 139 days, with a mean total daily dose of 310 mg. Dr. Brodsky did not include the results of Study 3015 in the pooled safety analyses, as this study was a randomized withdrawal design with a 3-week open-label titration period where all 389 patients were exposed to tapentadol ER, confounding the ability to attribute adverse reactions in the control group (193 patients) when they were withdrawn to placebo for the 12-week withdrawal period. Approximately 196 patients remained on tapentadol ER. The safety findings in Study 3015 were consistent with the other studies and therefore to facilitate the comparison between treatment groups in the controlled trials, this study was not included.

In the controlled periods of the tapentadol ER trials, there were no deaths in tapentadol ER-treated patients. Tapentadol ER-treated patients had a greater incidence of non-fatal serious adverse events (SAEs), AEs leading to discontinuation (DAEs), and common AEs than placebo-treated patients. The differences in the incidences of DAEs and AEs between these groups were mostly due to known opioid-related toxicities (e.g., nausea, vomiting, dizziness, constipation, somnolence, fatigue). Although higher than in the placebo-treatment groups, frequencies were generally lower than in the oxycodone CR treatment groups in the studies.

With respect to specific safety concerns, such as abuse potential/dependence or withdrawal and neuropsychiatric adverse events, the safety profile of Tapentadol ER appeared to be consistent with other products with similar pharmacologic properties. There is suggestion that tapentadol ER may have abuse potential and dependence/withdrawal characteristics similar to long acting opioids. It also may be associated with some of the neuropsychiatric adverse effects noted with tapentadol IR and tramadol.

- **Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Deaths

As mentioned above, there were no deaths in tapentadol ER-treated patients in the controlled periods of the Phase 3 studies (excluding studies in cancer indications). There were 3 deaths (out of 1154 patients) during Study 3010, a one-year open-label extension study for patients who completed studies 3007, 3008, 1011, or 3019 (patients with moderate to severe chronic pain due to knee or hip OA or LBP). The deaths did not appear to be likely to be related to tapentadol ER (see Table 7.3 in Dr. Brodsky's review).

Serious Adverse Events (SAEs)

As noted in Table 4 below, the incidence of serious adverse events with tapentadol ER was similar to that seen in the placebo treatment group in the controlled studies (1% for each), and lower than the incidence observed in the oxycodone CR treatment group (3%). In 1-year open-label safety follow up, the incidence of SAE for patients treated with oxycodone CR or tapentadol ER was similar (approximately 4%). SAEs were scattered single events, except for the preferred terms listed in Table 4. Overall the SAEs were consistent with the underlying

patient population, and there was no pattern of events that suggested heretofore unidentified toxicities of tapentadol ER.

Table 4: SAE Preferred Terms Reported 2 or More Times in Any Treatment Group

	Pooled DB 15-Week Trials[2]			1-Year OL Safety Study[3]	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
SAEs	**32 (3.2%)**	**11 (1.1%)**	**10 (1.0%)**	**8 (3.6%)**	**38 (4.3%)**
Constipation	2 (0.2%)	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)
Dizziness	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Angina pectoris	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Myocardial infarction	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Anemia	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal failure acute	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dehydration	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)
Atrial Fibrillation	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	3 (0.3%)
Abdominal Pain	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	2 (0.2%)
Syncope	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	2 (0.2%)
Intestinal Obstruction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)
COPD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)

COPD = Chronic obstructive pulmonary disease
1 Number of patients with at least one SAE during treatment until 3 days after the last dose of study medication (SAEs that occurred 2 or more times in any treatment group are listed).
2 Studies 8, 9, and 11
3 Study 7
Reference: ISS, Appendix 4.3.3.2, Page 18009-18018
Source: Table 7.5 of Dr. Brodsky's review

Discontinuations due to Adverse Events (DAEs) and Common Adverse Events (AEs)

Adverse events leading to discontinuation were basically the same type of adverse events observed commonly (note overlapping preferred terms in Tables 5 and 6 below). The types of preferred terms reported were symptoms typically observed with opioid therapy. Thus it is not surprising that the incidence of these AEs was typically highest in the oxycodone CR group, and was also increased in the tapentadol ER group compared to the placebo group.

Table 5: Discontinuations due to Adverse Events (DAEs) by Preferred Term and Treatment Group

	Pooled DB 15-Week Trials[2]			1-Year OL Safety Study[3]	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
DAEs[2]	**390 (39%)**	**179 (18%)**	**63 (6%)**	**82 (37%)**	**198 (22%)**
Nausea	14%	4%	<1%	12%	3%
Vomiting	10%	3%	<1%	7%	3%
Dizziness	9%	4%	<1%	7%	3%
Constipation	7%	2%	<1%	7%	2%
Somnolence	6%	2%	<1%	4%	3%
Fatigue	3%	2%	<1%	5%	2%
Pruritus	3%	<1%	<1%	3%	1%
Headache	2%	<1%	<1%	1%	1%
Hyperhidrosis	2%	<1%	<1%	1%	<1%
Insomnia	1%	<1%	<1%	<1%	<1%
Vertigo	1%	<1%	<1%	1%	<1%
Dry mouth	1%	<1%	<1%	1%	1%
Lethargy	<1%	<1%	0%	1%	<1%

COPD = Chronic obstructive pulmonary disease
1 DAEs that occurred ≥ 1% in any treatment group are listed.
2 Incidence is based on the number of patients who experienced at least 1 DAE (not the number of DAEs)
Reference: ISS, Appendix 4.4.5.1, Pages 20387-20394; CSR of Study 7, Attachment 3.5.3, Pages 1721-1726.
Source: Table 7.6 of Dr. Brodsky's review

Table 6: Most Common Adverse Events by Preferred Term and Treatment Group

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
AEs	**858 (86%)**	**715 (73%)**	**583 (59%)**	**202 (91%)**	**766 (86%)**
Nausea	36%	21%	7%	33%	18%
Constipation	33%	17%	7%	39%	23%
Dizziness	21%	17%	6%	19%	15%
Vomiting	21%	8%	3%	14%	7%
Somnolence	17%	12%	4%	11%	15%
Headache	13%	15%	13%	8%	13%
Pruritus	13%	5%	2%	10%	5%
Fatigue	9%	9%	4%	10%	10%
Hyperhidrosis	6%	5%	1%	4%	5%
Diarrhea	5%	5%	6%	5%	8%
Insomnia	5%	4%	2%	4%	7%
Dry mouth	4%	7%	2%	5%	9%
Nasopharyngitis	2%	3%	4%	3%	6%
Sinusitis	1%	1%	1%	6%	4%

1 AEs that occurred ≥ 5% in any treatment group are listed. Incidence is based on the number of patients who experienced at least 1 AE (not the number of AEs)
Reference: ISS, Table 24, Page 143, Table 25, page 144; Appendix 4.1.4.2, Pages 14693-14746; CSR of Study 7, Attachment 3.1.2, Pages 933-952
Source: Table 7.7 of Dr. Brodsky's review

There were no consistent laboratory abnormalities observed with tapentadol ER treatment (see Tables 7.17 and 7.18 in Dr. Brodsky's clinical review).

- **Immunogenicity**

Tapentadol ER is a chemical entity, not a protein, thus would not be expected to be immunogenic. No specific immunogenicity testing was required for this product.

- **Special safety concerns**

Abuse Potential and Dependence/Withdrawal

Per the Controlled Substance Staff (CSS) consult, there was evidence of reactions indicative of abuse potential in the tapentadol ER clinical development program. They state that in the Phase 1 study in 80 healthy subjects (R331333-PAI-1028) evaluating the effect of ingestion with alcohol of the 100 mg and 250 mg TRF tapentadol ER formulations, 50% of the subjects exhibited euphoria at 250 mg. In the pooled AE analysis of the 27 Phase 1 single-dose studies in healthy subjects (1917 subjects, 1907 were on some version or dose of tapentadol), 5.5% of subjects taking the tapentadol TRF formulation (n = 529) exhibited euphoria, and 8.1% subjects reported "feeling drunk" as compared to 1% or less of subjects taking other ER formulations, respectively. The pooled analysis also contains the 80 patients in the alcohol co-ingestion study.

A similar proportion of patients in the oxycodone CR and tapentadol ER treatment groups of the Phase 2 and 3 studies exceeded the maximum allowed daily dose of their assigned treatment (approximately 3% in each treatment group). One tapentadol-ER treated patient, with a history of substance abuse and depression took 3 times the maximum recommended daily dose over 10 days (57 tablets instead of 20 tablets). The patient did report visual disturbance and euphoria related to these high doses (resolved after 15 days). In a drug accountability analysis, a similarly low proportion of dispensed pills were missing in the tapentadol ER, oxycodone CR, and placebo groups of the studies (approximately 1%). Patients reporting study medication loss were similarly low among the treatment groups: 1/980 (0.1%) for tapentadol ER, 1/993 (0.1%) for placebo, and 4/1001 (0.4%) for oxycodone CR.

CSS utilizes a basket of approximately 130 MedDRA terms that they believe may indicate abuse potential. Using these terms, it appears that the highest proportion of patients with these AEs were receiving oxycodone CR treatment. A higher proportion of patients in the tapentadol ER groups reported these AEs than did patients receiving placebo, but proportions were lower than with oxycodone CR (see Table 7.27 of Dr. Brodsky's review).

An analysis of AEs that occurred during the 5 days after study medication discontinuation was performed to assess for symptoms suggestive of opioid withdrawal. As shown in Table 7, below, a higher proportion of patients in the oxycodone CR and tapentadol ER groups reported AEs compared with placebo-treated patients. A number of these AEs are symptoms suggestive of opioid withdrawal, such as diarrhea, nausea, anxiety, hyperhidrosis, insomnia, and irritability.

The totality of these data suggests that tapentadol ER likely possesses dependence/withdrawal and abuse potential characteristics, as might be expected from its action on the mu opioid receptor.

Table 7: AEs (Greater than 0.5% Incidence) Occurring within 5 Days from the Last Dose of Study Drug

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Oxycodone CR (n=799)	Tapentadol ER (n=679)	Placebo (n=690)	Oxycodone CR (n=178)	Tapentadol ER (n=645)
Total n (%) of patients with AEs	**141 (18%)**	**93 (14%)**	**56 (8%)**	**15 (8%)**	**93 (14%)**
Diarrhea	3%	2%	< 1%	2%	2%
Nausea	3%	2%	1%	1%	2%
Vomiting	2%	1%	1%	1%	1%
Anxiety	2%	1%	< 1%	1%	1%
Hyperhidrosis	1%	1%	< 1%	1%	1%
Headache	1%	1%	1%	0%	0%
Abdominal pain	1%	< 1%	< 1%	0%	1%
Arthralgia	1%	1%	< 1%	0%	1%
Insomnia	1%	1%	< 1%	0%	1%
Constipation	1%	1%	< 1%	1%	1%
Withdrawal syndrome	1%	< 1%	< 1%	1%	1%
Somnolence	1%	< 1%	0%	0%	< 1%
Chills	1%	1%	0%	0%	1%
Irritability	1%	< 1%	< 1%	0%	1%
Urinary tract infection	1%	< 1%	1%	0%	< 1%
Fatigue	< 1%	< 1%	< 1%	0%	1%

1 Using MedDRA preferred terms, incidence ≥ 0.5% in any one combined treatment group (i.e., all tapentadol ER, all oxycodone CR, placebo).
Reference: Adapted from Amendment #5, Attachment 2.1, Pages 16-25.
Source: Table 7.29 of Dr. Brodsky's review

Neuropsychiatric AEs

Hallucinations: Hallucinations occurred in 5/980 (0.5%) patients in the Tapentadol ER groups of three pooled induction trials vs. 2/1001 (0.2%) of patients on Oxycodone CR and no placebo patients. One additional case was observed in the 1 year open label safety study 3007; this patient was in the tapentadol ER treatment group (see Table 7.8 of Dr. Brodsky's review). There have been 39 cases of hallucinations reported to FDA's Adverse Event Reporting System (AERS) for the tapentadol IR formulation (AERS search from date of approval, November 20, 2008, through May 25, 2010).

Seizures: In the tapentadol ER database (4407 subjects/patients exposed to tapentadol ER), there was 1 case of seizure in a 47 year old male in Study HP10 (thorough QT study) with a history of a seizure disorder uncontrolled on valproic acid (the history of seizure was unknown to the investigator at the time of randomization). He received 2.5 days of 172 mg of tapentadol ER BID (5 doses) and had a tonic clonic seizure requiring hospitalization. His work-up for causes of the seizure showed possible hypoplasia of the temporal lobe on MRI of the brain (his other studies were negative including chemistries, EEG, and CT brain). The clinical studies excluded patients with a history of seizures; recent history of traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm; or metabolic disturbances. Convulsions were observed in tapentadol animal studies at approximate human exposures and seizures have been noted with a related product, tramadol. In addition, there have been 15 post-marketing cases of seizures seen in tapentadol IR-treated patients.

Suicidal ideation: One completed suicide occurred in an ongoing open-label study (Study 10) in a 65 year old male with a history of anxiety and depression and recent situational exacerbation related to the loss of his job. Dr. Brodsky discusses the case further in Table 7.3 of his review. Overall, suicidal ideation appeared to occur infrequently (0.1 to 0.2%), and similarly in all treatment groups (see Table 7.10 of Dr. Brodsky's clinical review). In the postmarketing experience for tapentadol IR, 8 cases of suicidal ideation, one suicide attempt, and one completed suicide have been reported.

Serotonin Syndrome

In the tapentadol ER database, there were no definitively diagnosed cases of serotonin syndrome. The Applicant performed an exploratory analysis using the signs and symptoms associated with serotonin syndrome (although these individual signs and symptoms are nonspecific). These included: sinus tachycardia, tachycardia, mydriasis, diarrhea, hyperthermia, pyrexia, body temperature increased, ataxia, coordination abnormal, dyskinesia, muscle contractions involuntary, myoclonus, psychomotor hyperactivity, tremor, agitation, confusional state, hyperhidrosis, hypertension, and hypertensive crisis. Table 8 below displays the incidence of patients having ≥ 1, ≥ 2, or ≥ 3 AEs that could be associated with serotonin syndrome in the Phase 2 and 3 studies of tapentadol ER in chronic pain. The proportion of patients with 3 or more AEs of this nature was low, and similar in the tapentadol ER and oxycodone CR groups. It should be noted however, that the clinical studies excluded patients taking concomitant SSRIs, SNRIs, tricyclic antidepressants, MAO inhibitors, all of which have been reported to increase the risk for serotonin syndrome. There have been 18 post-marketing cases of serotonin syndrome reported with tapentadol IR.

Table 8: Incidence of Adverse Events that Could be Associated with Serotonin Syndrome in Tapentadol ER Phase 2/3 Chronic Pain Development Program

	Placebo (n=1498)	Tapentadol ER (n=3613)	Oxycodone CR (n=1472)	Tramadol PR (N=249)
≥ 1 AE	135 (9%)	484 (13%)	202 (14%)	45 (18%)
≥ 2 AEs	18 (1%)	80 (2%)	33 (2%)	10 (4%)
≥ 3 AEs	1 (<1%)	10 (<1%)	4 (<1%)	3 (1%)

Reference: ISS, Table 31, Page 188
Source: Table 7.9 of Dr. Brodsky's review

With respect to neuropsychiatric adverse effects, the data submitted do not rule out a potential risk with tapentadol ER, but neither do these data suggest the risk is excessive, or different from approved products with similar mechanisms of action, such as tapentadol IR or tramadol.

- **Discussion of primary reviewer's comments and conclusions**

Dr. Brodsky believes that the safety profile of tapentadol ER in the chronic treatment of pain appears to be consistent with the safety profile of approved long-acting opioid products and that tapentadol ER labeling should be consistent with current labeling of approved long-acting opioids and tapentadol IR.

- **Conclusions**

The safety database submitted in support of this NDA appears to be adequate to characterize the overall safety profile of tapentadol ER. I concur with Dr. Brodsky that the safety profile of tapentadol ER appears to be consistent with the profile of tapentadol IR, other chronic opioids, and tramadol. No safety issues were identified that would preclude approval. Tapentadol ER will be labeled similarly to tapentadol IR, chronic opioids, and tapentadol, and will also be required to have a risk evaluation and mitigation strategy (REMS) consistent with other chronic opioids.

- **Notable safety issues (resolved or outstanding)**

1) REMS:
The Agency has been considering a class REMS for long-acting and extended release opioid products, to address the risks of abuse, misuse, and overdose. Until the Agency has determined the elements of the class opioid REMS, the Division of Anesthesia and Analgesia Products (DAAP) with input from OSE, has decided that an interim REMS for these opioids will be required as these products are approved.

The original proposed REMS submitted by the Applicant consisted of a Medication Guide, communication plan, and a timetable for assessment of the proposed REMS. On April 22, 2010 DAAP notified the sponsor that the proposed REMS must include elements to assure safe use, specifically training for healthcare providers as described under 505-1(f)(3)(A), to ensure that the benefits of the drug outweigh the risks of: abuse, misuse, and overdose, use of Nucynta ER in non-opioid tolerant individuals, and to prevent the occurrence of serious adverse events associated with those risks. The amended proposed REMS and amended REMS supporting document was submitted on June 21, 2010. DRISK preliminary comments on the amended proposed REMS and supporting document were relayed to the Applicant, but final review and comment will be performed on resubmission of the documents with the final review cycle.

2) Tamper-Resistant Formulation
Because tapentadol ER is an agonist of the mu opioid receptor, in addition to having opioid-like toxicities, there exists a possibility that tapentadol ER could become a drug of abuse and diversion. As mentioned in section 3, the Applicant has formulated the product to purportedly be resistant to tampering. Similar to other products that have been formulated for this purpose, it is likely that these properties are inadequate to meet the intended purpose. (b) (4)

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held during this review cycle, (b) (4)

(b) (4)

10. Pediatrics

- **A brief documentation of the scientific data supporting extrapolation if extrapolation from one population to anther is used to support efficacy**
- **Peds exclusivity board review - PPSR/WR**
- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**
- **Consults**

The Applicant submitted a waiver for pediatric patients (b) (4)

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted.
- **Exclusivity or patent issues of concern**
- **Financial disclosures**—Submitted, no major issues.
- **Other GCP issues**—No major issues.
- **DSI audits**

The Division of Scientific Investigations (DSI) was consulted to perform routine audits of clinical sites for the two studies considered to provide the basis of the efficacy evidence—Studies 3011 and 3015. Three sites for Study 3011 and one site for Study 3015 were selected because of having a large number of treated patients or wider treatment margins in favor of tapentadol ER. No single site was identified which would have changed the overall efficacy results. After the Agency informed J & J of the 3 site inspections, J & J conducted a review of all three sites and informed the Agency that they uncovered potential misconduct at Site # 1460 in Study 11 (Dr. Allan Soo). Potential issues related to minimal/limited source documentation, poor documentation (e.g., backdating, adverse events may have not been fully reported), dose escalations may have been compromised, and the staff may not have been

qualified. Given these issues at this site, DSI inspected one additional site in Study 11. At the time of the completion of this review, final inspection results are still pending.

12. Labeling

- **Proprietary name**—The proprietary name Nucynta has already been reviewed and approved with the NDA for tapentadol IR.
- **DDMAC and OSE Division comments**—Preliminary input was received from DDMAC and OSE regarding the label. The initial proposed REMS was also evaluated by OSE with comments relayed to the Applicant and a revised REMS resubmitted. The reader is referred to DRISK's August 6, 2010 consult review of the revised REMS for further details. Additional revisions are being recommended by DRISK for the REMS and these will be relayed to the Applicant.
- **Physician labeling**—Labeling was preliminarily revised by Dr. Brodsky to be consistent with other chronic opioid labels. No final agreement has yet been reached on the label, as a complete response action is anticipated for this review cycle.
- **Carton and immediate container labels (if problems are noted)—**no issues identified.
- **Patient labeling/Medication guide (if considered or required)—**Medication Guide review has been deferred pending agreement on final labeling (which will occur in the next review cycle).

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend a complete response action for this NDA in light of the lack of bridging data from the clinical trial lots to the to-be-marketed formulation.

- **Risk Benefit Assessment**

Like the immediate release formulation already approved, tapentadol ER appears to be effective, based on the results of two adequate and well controlled trials in low back pain and diabetic peripheral neuropathy. Although tapentadol ER results from the knee osteoarthritis trials did not demonstrate a statistically significant difference compared to placebo, neither were oxycodone CR results consistently statistically different. Therefore, the results of the knee osteoarthritis studies do not preclude an overall conclusion of efficacy based the low back pain and diabetic peripheral neuropathy trials.

The safety profile of tapentadol ER appears to be consistent with other products with similar pharmacologic properties. There is suggestion that tapentadol ER may have abuse potential and dependence/withdrawal characteristics similar to long acting opioids. It also may be

associated with some of the neuropsychiatric adverse effects noted with tapentadol IR and tramadol.

Overall, the risk:benefit balance of tapentadol ER appears to be acceptable, and consistent with other approved products of similar type.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

The REMS for tapentadol ER should follow the interim REMS for chronic opioids. Thus the REMS should contain a medication guide, communication plan, and elements to assure safe use, specifically training for healthcare providers as described under 505-1(f)(3)(A), to ensure that the benefits of the drug outweigh the risks of: abuse, misuse, and overdose, use of Nucynta ER in non-opioid tolerant individuals, and to prevent the occurrence of serious adverse events associated with those risks.

- **Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments were recommended by the current NDA review team.

- **Recommended Comments to Applicant**

Deficiencies regarding the IVIVC model were previously conveyed to the Applicant via information requests and a biopharmaceutics discipline review letter. The Applicant is aware that fasting bioequivalence studies are expected using the 50 mg and 250 mg doses to bridge the PR2 and to-be-marketed formulations.

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

/s/

SARAH K OKADA
09/20/2010

Clinical Review of Nucynta ER (tapentadol extended-release)

Application Type	NDA
Application Number	200533
Priority or Standard	Standard
Submit Date	November 30, 2009
Received Date	December 1, 2009
PDUFA Goal Date	October 1, 2010
Division/Office	DAAP/OND
Reviewer Name	Eric Brodsky, M.D.
Review Completion Date	August 19, 2010
Established Name	Tapentadol Extended-Release (ER)
Proposed Trade Name	Nucynta™ ER
Therapeutic Class	Opioid analgesic
Applicant	Johnson and Johnson
Formulations	50, 100, 150, 200, and 150 mg tablets
Proposed Dosing Regimen	The proposed recommended dose is 100 to 250 mg BID. The dosing regimen should be individualized (e.g., according to pain severity, prior opioids experience). For patients currently not taking opioids, start at 50 mg BID, then increase dose to 100 mg BID (may titrate up to a maximum of 250 mg BID). For switching from opioids to tapentadol ER the initial tapentadol ER dose should be based on the total daily opioid dose and the conversion ratio.
Proposed Indication	"For the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend **approval** of Nucynta ER (tapentadol extended-release), under New Drug Application (NDA) 200533, for the chronic treatment of moderate to severe pain in opioid-naive and opioid-experienced adult patients **contingent upon resolution** of the following issues: support for bridging of the clinical trial formulations to the to-be-marketed formulations; approval of Risk Evaluation and Mitigation Strategies (REMS) to reduce the risks of abuse, misuse, overdose, and addiction associated with long-acting opioid products; successful inspection of the commercial manufacturing site in Puerto Rico; completion of the Division of Scientifics' review of data integrity at 4 clinical trial sites; and revisions to the label.

1.2 Risk Benefit Assessment

Overview of Clinical Program

Johnson and Johnson (J & J) submitted NDA 200533 in November 2009 to support the approval of Nucynta ER (tapentadol extended-release), a mu-opioid agonist and a selective norepinephrine reuptake inhibitor (SNRI), for the chronic treatment of moderate to severe pain in adult patients. J & J proposes a daily dose of 100 to 250 mg BID (i.e., 200 to 500 mg per day). For patients not currently taking opioids, J & J proposes that tapentadol ER be started at 50 mg BID and then be titrated to an optimal dose within the 100 to 250 mg BID range. J & J proposes that patients can be switched from immediate-release tapentadol (tapentadol IR) to tapentadol ER using an equivalent total daily dose up to a maximum of 500 mg/day. (b) (4) [redacted]

Results from three 15-week, Phase 3 induction trials [2 in patients with chronic pain due to osteoarthritis (OA), i.e., Studies 8 and 9, and 1 in patients with chronic low back pain (LBP), i.e., Study 11] and one 15-week randomized-withdrawal Phase 3 trial in diabetic patients with chronic pain due to diabetic peripheral neuropathy (DPN), i.e., Study 15, served as the primary basis to support the efficacy of tapentadol ER in the chronic treatment of pain. Results from the 3 induction trials and a 1-year, safety study of tapentadol ER in patients with non-malignant chronic pain (Study 7) served as the primary basis to support the safety of tapentadol ER for the chronic treatment of pain. See Table 5.1 in Section 5.1 (Tables of Clinical Studies) and Section 5.3 (Discussion of Individual Studies) for details on the design of the important studies. Results from an additional 5 Phase 2 studies in patients with chronic pain and 30 Phase 1 studies in healthy subjects were also submitted as supportive evidence of efficacy, safety, pharmacokinetics, and/or bridging different tapentadol ER formulations.

The 3 induction Phase 3 trials were 15-week, randomized, double-blind (DB), placebo-controlled (PC) and oxycodone CR-controlled, parallel-group, multi-center (MC), 3-arm trials of controlled adjustment of tapentadol ER (100 to 250 mg BID) in patients with moderate to severe chronic pain (≥ 3 months). After a Washout Period where all analgesics were discontinued, patients were randomized 1:1:1 to tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID and then after 3 days the tapentadol ER and

oxycodone doses were increased to 100 mg BID and 20 mg BID, respectively. Following the Titration Period, patients entered the 12-week Maintenance Period where dose adjustment was discouraged; however, up or down titration was permitted if needed. The primary efficacy endpoint in all 3 induction trials was the change from baseline of the average pain intensity using an 11-point numerical rating scale over the last week of the trial (i.e., Week 15). The following is a summary of the populations in the 3 induction trials:

1. In **Study 8**, **1023 patients** with chronic pain due to **knee OA** received study medication at 112 sites in the U.S., Canada, New Zealand, and Australia.
2. In **Study 9**, **987 patients** with chronic pain due to **knee OA** were treated at 79 sites in 12 European countries.
3. In **Study 11**, **965 patients** with chronic non-malignant **LBP** were treated at 97 sites in United States, Canada, and Australia.

Study 15 was a 15-week DB, parallel-group, MC, randomized-withdrawal Phase 3 trial of tapentadol ER in diabetic patients with chronic pain (≥ 6 months) from DPN. After a Washout Period where all analgesics were discontinued, patients received OL tapentadol ER in the 3-week Titration Period. If patients responded to OL tapentadol ER (i.e., ≥ 1 point improvement in the average pain intensity score from OL baseline), they entered the DB Randomized Withdrawal Period and were randomized 1:1 to continue treatment with tapentadol ER (at the current dose between 100 to 250 mg BID) or placebo. The primary efficacy endpoint in Study 15 was the change from DB baseline of the average pain intensity using an 11-point numerical rating scale at the last week of the Randomized Withdrawal Period (i.e., Week 15). In **Study 15**, **588 patients** with chronic **DPN** were treated with OL tapentadol at 88 sites in the United States and Canada (389 patients were treated in the DB Randomized Withdrawal Period).

Study 7 was a 1-year, OL, randomized, oxycodone CR-controlled, parallel group, MC, Phase 3 safety study of controlled adjustment of tapentadol ER (100 to 250 mg BID) in patients with chronic pain (≥ 3 months) from knee OA, hip OA, or non-malignant LBP. After completion of the Washout Period where all analgesics were discontinued, patients entered a 1-week Titration Period and were randomized 4:1 to tapentadol ER 50 mg BID or oxycodone CR 10 mg BID and then after 3 days the dose was increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID, respectively. In the 51-week Maintenance Period, upward or downward titration was allowed to optimize the patients' analgesic needs and tolerability. There was no primary efficacy endpoint in Study 7 because it was a primary safety study. In **Study 7**, **1117 patients** with chronic pain from knee **OA, hip OA, or LBP** were treated at 89 sites in the United States, Canada, and Europe.

In the entire safety database of the 40 completed studies of tapentadol ER, 4407 subjects/patients received at least one dose of tapentadol ER (3694 patients received tapentadol ER in the Phase 2 and 3 trials, 79 healthy subjects received multiple-doses of tapentadol ER in Phase 1 studies, and 634 healthy subjects received single-doses in Phase 1 studies). In the 4 pooled studies that served as the primary support for the safety of tapentadol ER (i.e., Studies 7, 8, 9, and 11), 2092, 481, and 227 patients received at least 4, 24, and 52 weeks of tapentadol ER, respectively (patients may have been counted more than once). The median tapentadol ER daily dose in pooled Studies 7, 8, 9, and 11 was 297 mg.

Summary of Efficacy

In 1 of the 3 induction trials (Study 11, LBP), tapentadol ER had a statistically significant improvement from baseline in pain intensity at Week 15 compared to placebo, using conservative imputation, i.e., baseline observation carried forward (BOCF). Using BOCF imputation, the treatment margin of the tapentadol ER group compared to placebo was small in Study 11 (0.6 LS mean difference on an 11-point scale). However, this treatment margin is consistent with the treatment margins of other opioid analgesics in PC, induction trials in chronic pain. In Study 8 (OA), the tapentadol ER group had a numerical improvement from baseline in pain intensity at Week 15 compared to placebo (using BOCF imputation); although this difference was not statistically significant. In Study 9 (OA), tapentadol ER did not have a numerical improvement from baseline in pain intensity at Week 15 compared to placebo (using BOCF imputation). In all 3 induction trials, the tapentadol ER group had a numerical improvement from baseline in pain intensity at Week 15 compared to oxycodone CR, using BOCF imputation. This assay sensitivity is supportive of the efficacy of tapentadol ER in the chronic treatment of pain; however, no comparative claims should be made because these were exploratory analyses.

In Study 15 (DPN), tapentadol ER compared to placebo had less worsening in the pain intensity from the DB baseline at Week 15, using very conservative imputation, i.e., OL BOCF. These results were statistically significant. The treatment margin in Study 15 (1.1 LS mean difference on an 11-point scale) was consistent with the results of other randomized withdrawal, PC, chronic pain trials of long-acting opioids (e.g., Exalgo, Embeda).

In summary, the efficacy of tapentadol ER in the chronic treatment of pain was established from 2 positive adequate and well-controlled trials (Studies 11 and 15) with supportive evidence from Study 8 (Study 9 was a negative trial). The heterogeneous designs/populations of the 2 positive trials supports the efficacy of tapentadol: the two positive trials had different designs (i.e., induction and an enriched randomized withdrawal design), different populations (LBP and DPN), and different types of pain (nociceptive and neuropathic pain). Finally, the number and type of positive trials to support an efficacy claim for a long-acting opioid for chronic pain is consistent with the review division's statements to the sponsor during pre-NDA meetings.

Summary of Safety

In the 40 submitted studies of tapentadol ER in patients with non-malignant pain there were no deaths in tapentadol ER-treated patients. Tapentadol ER-treated patients had a greater incidence of non-fatal SAEs, AEs leading to discontinuation (DAEs), and AEs than placebo-treated patients and the differences in the incidences of DAEs and AEs between these groups were mostly due to known opioid-related toxicities (e.g., nausea, vomiting, dizziness, constipation, somnolence, fatigue). Tapentadol ER-treated patients had a lower incidence of non-fatal SAEs, DAEs, and AEs than oxycodone CR-treated patients and these differences were mostly due to known opioid-related toxicities.

Tapentadol ER-treated patients did not have evidence of greater misuse or abuse than the oxycodone CR-treated patients: tapentadol ER-treated patients had a lower proportion of possible abuse-related AEs and lower incidence of reports of study medication loss than oxycodone CR-treated patients (0.1% vs. 0.4%).

Although tapentadol ER-treated patients compared to oxycodone CR-treated patients had a slightly lower incidence of AEs within 5 days of study medication discontinuation (no taper), tapentadol ER-treated

patients experienced a slightly greater proportion of AEs compared to placebo-treated patients within the same timeframe. This imbalance was due to several AEs associated with opioid withdrawal (e.g., diarrhea, nausea, anxiety, hyperhidrosis, insomnia, irritability).

There appeared to be no evidence of tapentadol ER-associated hepatotoxicity in the tapentadol ER clinical database: in the controlled and uncontrolled portions of the tapentadol ER studies, there were no cases of acute liver failure or Hy's Law and there was no difference in the proportion of tapentadol ER-treated patients and control-treated patients who had liver enzyme test elevations.

There appeared to be no evidence of tapentadol ER-associated pro-arrhythmic effect in the tapentadol ER clinical database at anticipated doses: there were no concerning clinical events that could indicate a pro-arrhythmic effect of tapentadol ER and the thorough QT study of tapentadol IR was negative (using doses that produced similar tapentadol exposure as the maximum proposed tapentadol ER dose regimen ─ 250 mg BID). Since this QT study did not assess the QT interval at higher than anticipated exposures due to dose-limited toxicities (e.g., dizziness, vomiting, nausea), the effects of tapentadol on the QT interval at substantial multiples of the maximum therapeutic exposure are not known.

There were no significant differences in the incidence of AEs in tapentadol ER-treated patients by demographics (i.e., age, gender, race, or weight), by dose, and by duration.

In the tapentadol ER database, there was no evidence of serotonin syndrome: there were no cases of serotonin syndrome and the tapentadol ER group had a similar incidence of signs and symptoms of serotonin syndrome as the oxycodone CR and placebo groups. However, there have been 18 post-marketing cases of serotonin syndrome associated with tapentadol IR use. Given these cases and the biologic plausibility (SNRIs have been associated with serotonin syndrome), serotonin syndrome should be included in the Warnings and Precautions of the tapentadol ER label.

In the tapentadol ER database, there was no clear evidence of a seizure signal. There have been 15 post-marketing cases of seizures associated with tapentadol IR use. Given these cases and biologic plausibility [convulsions seen in animals at approximate human tapentadol exposures and seizures seen in a related product in humans (tramadol)], seizure should be included in the Warnings and Precautions of the tapentadol ER label.

In summary, the safety profile of tapentadol ER in the chronic treatment of pain appears to be consistent with the safety profile of approved long-acting opioid products. The tapentadol ER labeling should be consistent with current labeling of approved long-acting opioids and contain Contraindications (in unmonitored patients with severely impaired pulmonary function and in patients receiving MAO inhibitors), Boxed Warnings (in patients at increased risk of abuse or diversion); Warnings and Precautions (respiratory and CNS depression, increased intracranial pressure, driving and operating machinery, and drug withdrawal). Consistent with the tapentadol IR label, the tapentadol ER label should contain additional Warnings and Precautions for seizures and serotonin syndrome given the biologic plausibility and the post-marketing cases of these events in patients who received tapentadol IR.

Risk Benefit Assessment

Overall, the results support an adequately favorable risk-benefit profile for tapentadol ER within the proposed therapeutic range (100 to 250 mg BID) for the proposed indication of treatment of chronic pain.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) that consists of elements to assure safe use that includes healthcare provider training, a Medication Guide, and a timetable for submission of assessments is recommended. The REMS should be consistent with the REMS for the long-acting opioids approved for chronic pain (e.g., Oxycontin, Embeda) and should address the risks of abuse, misuse, overdose, and addiction associated with these products. The sponsor's proposed REMS for tapentadol ER is under review by the Division of Risk Management (DRISK).

1.4 Recommendations for Postmarketing Requirements and Commitments

Studies to achieve compliance with Pediatric Research Equity Act (PREA)

(b) (4)

At present, PREA-required pediatric studies of tapentadol ER will be deferred pending further evaluation of this potential safety signal.

2 Introduction and Regulatory Background

2.1 Product Information

Proposed Trade Name (established name): NUCYNTA™ ER (tapentadol extended-release) oral tablets

Proposed Indication: For "the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."

Proposed Age Group: Adult patients 18 years or older

Proposed Dose Regimen: The recommended daily dose is 100 to 250 mg BID.

- For patients currently not taking opioid analgesics, begin with 50 mg BID and then titrate to an optimal dose within 100 to 250 mg BID range.
- For patients switching from tapentadol IR to tapentadol ER, the total daily dose of tapentadol IR (given 4 to 6 times per day) can be converted to the equivalent total daily dose of tapentadol ER (given twice a day). The maximum total daily dose of tapentadol ER is 500 mg per day.
- (b) (4)
-

The dosing regimen should be individualized according to the severity of pain, supplemental opioid utilization, previous experience with opioid analgesics, the patient's ability to tolerate tapentadol ER, the ability for patients to follow-up, and the ability of providers to provide oversight of treatment. Total daily doses greater than 500 mg of tapentadol ER have not been studied and, therefore, are not recommended.

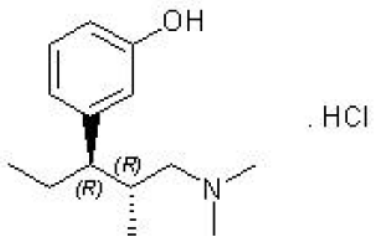
Pharmacologic Class: Opioid analgesic

Chemical Class: Type III (New Dosage Form) - A new dosage form of an active ingredient that has been approved or marketed in the United States by the same applicant but in a different dosage form.

Legal Basis for Submission: 505(b)(1)

Description: The chemical name of tapentadol is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride and the molecular formula is $C_{14}H_{23}NO•HCl$ (see Figure 2.1 for the structural formula).

Figure 2.1: Structural formula of tapentadol ER



How supplied: 50, 100, 150, 200, and 250 mg extended-release tablets

2.2 Tables of Currently Available Treatments for Proposed Indication

J & J proposes the following indication for tapentadol ER: "for the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." There are multiple long-acting opioid products (e.g., oxycodone, morphine, tramadol, oxymorphone, methadone, fentanyl, and hydromorphone containing products) that are approved for the treatment of chronic treatment of moderate to severe pain in opioid tolerant and/or opioid-naive patients in the United States (see Table 2.2). J & J's clinical program for tapentadol ER was not designed to demonstrate superior efficacy or safety to any of the long-acting opioid products approved for the chronic treatment of moderate to severe pain.

Table 2.2: Approved long-acting opioid products for the chronic treatment of pain

Product	Approval Year	NDA	Sponsor
For Opioid-Tolerant or Opioid-Naive Patients[1]			
Oxycodone Products			
OYYCONTIN tablets	2010 1995	22-272 20-553	Purdue
Morphine Products			
EMBEDA (morphine sulfate & naltrexone HCl) capsules	2009	22-321	Alpharma
AVINZA capsules	2002	21-260	King
KADIAN capsules	1996	20-616	Alpharma
ORAMORPH SR tablets	1991	19-977	Xanodyne
MS CONTIN tablets	1987	19-516	Purdue
Tramadol Products			
RYZOLT tablets	2008	21-745	Purdue
ULTRAM ER tablets	2005	21-692	J & J
Oxymorphone Products			
OPANA ER tablets	2006	21-610	Endo
Methadone Products			
DOLPHINE HCl tablets	1947	6-134	Roxane
For Opioid-Tolerant Patients Only			
Fentanyl Products			
DURAGESIC (fentanyl transdermal system) patch	1990	19-813	J & J
Hydromorphone Products			
EXALGO tablets	2010	21-217	Alza

1 Some of these products are only approved in opioid-tolerant patients at higher doses
Reference: FDA approved labels

2.3 Availability of Tapentadol in the United States

An immediate-release (IR) formulation of tapentadol (Nucynta) was approved in the United States in November 2008 "for the relief of moderate to severe acute pain in patients 18 years of age or older" (under NDA 22,304). Since tapentadol IR was not scheduled under the Controlled Substance Act at the time of its approval in November 2008, it was not allowed to be marketed in the United States. On June 22, 2009, tapentadol IR was scheduled (Schedule II), the tapentadol IR label was updated to include the scheduling information, and tapentadol IR was initially marketed in the United States.

Post-Marketing Reports Associated with Tapentadol IR: According to J & J, from June 2009 (initial marketing) until April 2010, there were (b) (4) prescriptions for tapentadol IR (over 99.5% of the prescriptions were in adult patients). According to J & J, within a similar reporting period (i.e., June 2009 to May 19, 2010), there were reports of the following serious adverse events associated with the use of tapentadol IR: hallucination (35), serotonin syndrome (18), seizure (15), suicidal ideation (6), and suicidal attempt (1).

Hallucination: Hallucination has been associated with the use of opioids and several opioid labels include hallucination in the Adverse Reactions section (e.g., oxycodone, tramadol, hydromorphone, and fentanyl). Of the 35 cases of tapentadol ER-associated hallucination, at least 3 demonstrated

dechallenge. Given the hallucination cases and biologic plausibility of hallucinations in opioid products, J & J stated that hallucination was an adverse drug reaction of tapentadol IR and J & J included hallucinations in the Post-Marketing Experience section of the Adverse Reactions section of the tapentadol IR label.

Seizures: There is biologic plausibility in a possible causal relationship between tapentadol and seizures. Tramadol, a related compound with opioid agonist, SNRI, and SSRI activity, has been associated with seizures in humans and animal toxicology studies.

In a 26-week dog toxicology study of tapentadol, convulsions occurred at the mid and high tapentadol doses ─ at exposures similar to the therapeutic exposures in humans [for more details see Dr. Kathy Young's (pharmacology/toxicology) review of the tapentadol IR NDA].

Of the 15 post-marketing cases of seizures associated with tapentadol IR, at least 3 occurred in patients with a history of seizure disorder who were taking anti-seizure medication.

Serotonin Syndrome: Serotonin syndrome has been reported in patients taking serotonergic products including SNRIs, SSRIs, tripans, MAO inhibitors, and tricyclic antidepressants. Of the 18 post-marketing cases of serotonin syndrome, at least 8 patients were taking concomitant SSRIs, SNRIs, and/or tricyclic antidepressants.

Suicide: Of the 7 cases of suicidal attempt or suicidal ideation, at least 3 patients had a history of depression.

For evaluation of potential signals of these adverse events in the tapentadol ER clinical program see Section 7.3.5 (Potentially Significant Adverse Events).

2.4 Important Safety Issues With Consideration to Related Drugs

Opioid analgesics are associated with serious toxicities including some that have lead to death. Table 2.3 displays toxicities included in the Contraindications, Boxed Warnings, Warnings and Precautions, Adverse Reactions, Drug Abuse and Dependence, and Overdosage sections of long-acting opioid analgesic labels for the treatment of chronic pain.

Table 2.3: Labeled toxicities of long-acting opioid analgesics for chronic treatment of pain[1]

Contraindications	
1.	Not to be used in patients with significant respiratory depression (hypoventilation) in unmonitored settings or in the absence of resuscitative equipment. Opioids can worsen hypoventilation in patients with baseline hypoventilation.
2.	Not to be used in patients with acute or severe asthma in unmonitored settings or in the absence of resuscitative equipment. Opioids can stimulate histamine release which may cause an asthma exacerbation.
3.	Not to be used in patients with a paralytic ileus.[2]
Boxed Warnings	
1.	Opioids are controlled substance and can be abused. Risk of misuse, abuse, or diversion. Swallow pills whole. Taking broken, chewed, dissolved, or crushed pills could lead to rapid release and absorption of a potentially fatal dose.
2.	Not indicated for use in the treatment of acute pain or for prn (as needed) use
3.	Accidental consumption, especially in children, could result in a fatal overdose
4.	Concomitant use with alcohol may result in increased plasma levels and a potential fatal overdose
Warnings and Precautions[3]	
1.	CNS depression [respiratory depression, bradycardia, decreased consciousness (including coma), dizziness, alterations in judgment]
2.	Should not be used in patients with increased CSF pressure (e.g., head injury) because opioids can raise CSF fluid pressure (by increasing carbon dioxide retention) and may obscure the clinical course of patients with head injury.
3.	May impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery
4.	Concomitant use with other CNS depressants (e.g., alcohol, other opioids, general anesthetics, benzodiazepines, phenothiazines, tricyclic antidepressants) may result in additive CNS depression and/or respiratory depression.
5.	Prescribe with caution in patients with a history of seizures or patients at risk for a seizure disorder.
6.	Withdrawal symptoms (restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate) can occur if discontinued.
7.	Can cause spasm of the sphincter of Oddi; therefore, use with caution in patients with biliary tract disease including acute pancreatitis.
8.	Individuals should not use the product if they were not prescribed the product.
9.	Hypotension due to vasodilation. Patients with hypovolemia are at higher risk.
10.	Can obscure the diagnosis of clinical course in patients with acute abdominal conditions.
11.	Tolerance to opioids is demonstrated by the need for increasing doses to maintain adequate analgesic effect (in the absence of disease progression or other external factors).
Adverse Reactions	
Common adverse reactions are constipation, nausea, somnolence, dizziness, pruritus, vomiting, headache, and fatigue.	
Drug Abuse and Dependence	
1.	Subject to diversion (distribution outside legitimate channels)
2.	With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.
3.	Drug addiction is characterized by compulsive abuse, repeated use for non-medical purposes, loss of control over intake, craving of psychic effects and continued abuse despite harm or risk of harm in medical, social, legal or occupational domains.
4.	Physical dependence to an opioid is manifested by characteristic withdrawal signs and symptoms after abrupt discontinuation of a drug, significant dose reduction or upon administration of an antagonist. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms.
Overdosage	
Overdosage can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death.	

1 Not all the opioids are labeled for all of these contraindications, warnings and precautions, and adverse reactions.

2 Although, opioids are labeled with a contraindication for use in patients with a paralytic ileus, clinically opioids are used in the setting of paralytic ileus (e.g., post-operative ileus, for severe pain control in patients with paralytic ileus). Since there are few options for pain control in some patients with paralytic ileus, this is a relative contraindication and therefore, paralytic ileus should be moved from the Contraindications to the Warnings and Precautions section.

3. Warnings and Precautions that are Boxed Warnings or Contraindications are not repeated in this table.

In addition to mu-opioid agonist activity, tapentadol ER inhibits norepinephrine reuptake (tapentadol inhibited norepinephrine reuptake in rat brains resulting in increased blood norepinephrine concentrations). The tapentadol IR label includes the following possible toxicities due to inhibition of norepinephrine reuptake:

- Contraindication: The use of tapentadol is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken MAO inhibitors within the last 14 days due to potential additive effects on norepinephrine levels which may increase the chance of a hypertensive crisis.
- Warnings and Precautions: The use of SNRIs including tapentadol is associated with an increased risk of serotonin syndrome. Serotonin syndrome, which can be life-threatening, may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The risk of serotonin syndrome is greater with the concomitant use of other SNRIs, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), triptans, and with drugs that impair metabolism of serotonin (including MAOIs).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

See Tables 2.4 and 2.5 for the important Pre-NDA submission interactions between the FDA and the original tapentadol ER sponsor (Grünenthal) and the current tapentadol ER sponsor (J & J), respectively.

Tapentadol IR was not approved at the time of the clinical development meetings in 2003 and 2005 and at the end-of-phase-II meeting in 2006; therefore, Agency responses during these meetings were based on the assumption that tapentadol ER would be a new molecular entity (NME). Tapentadol IR was approved at the time of the 2009 Pre-NDA meeting; therefore, responses during this meeting were based on the knowledge that tapentadol ER would not be a NME.

Table 2.4: Pre-NDA submission interactions between the FDA and the original sponsor of tapentadol ER about the clinical development of tapentadol ER for chronic pain

Meetings with the Original Tapentadol ER Sponsor (Grünenthal)
Clinical Development Meeting (Type C) on 11/13/03 (minutes sent on 12/11/03)
1. If the 50 mg BID titration dose is used in the clinical studies but not shown to be effective, it will be labeled as a titration dose. **2. Phase 3 trials in non-malignant pain should contain a 12-week fixed dosing period (not including the Titration Period).** **3. A general indication for chronic pain does not require replication in each type of pain, but rather a replicated demonstration of efficacy.** **4. Inclusion of an active comparator is not necessary if the drug is superior to placebo. Inclusion of a comparator is useful if the drug and the comparator is not superior to placebo. This could demonstrate that the study was flawed; not the drug.** **5. The safety database would require 1500 patients exposed to the drug with the most exposed at the higher doses.**
Clinical Development Meeting (Type C) on 12/16/05 (minutes sent on 1/13/06)
1. One of two trials to support a chronic pain indication must not be an enriched design. One of two trials could be an enriched design (e.g., randomized withdrawal). Two studies in cancer patients would not support a general pain indication. For an NME, efficacy in more than one patient population (e.g., OA, LBP, DPN, cancer) is necessary to support a general chronic pain indication. So 1 study in cancer pain and 1 study in non-cancer pain would be acceptable for a general chronic pain indication claim (1 of the studies must not be an enriched design). The Agency encouraged the sponsor to evaluate other populations so that they may gather more information regarding neuropathic or visceral pain. **2. For randomized withdrawal trials, the primary endpoint should be a measure of change in pain intensity. The primary endpoints of time to rescue medication administration or time to inadequate analgesia are suboptimal because the use of rescue medication or inadequate analgesia could be due to withdrawal; rather than improved pain control of tapentadol ER compared to placebo. However, the Agency stated that the sponsor could propose these endpoints; however, it would be necessary to provide evidence that withdrawal symptoms did not interfere with pain intensity assessments. The Agency stated that the sponsor could explore what happens when patients are withdrawn from tapentadol ER using different tapers and that the pain is not related to drug withdrawal.** **3. For randomized withdrawal trials, precautions should be taken to prevent un-blinding (e.g., slow taper for patients randomized to placebo).** **4. Phase 3 trials in non-malignant pain should include 12 weeks of DB dosing; however, Phase 3 trials in malignant pain could be 4 weeks because of the difficulty in studying cancer patients.** **5. LOCF is not an acceptable imputation method; conservative methods should be used (e.g., BOCF, imputing the mean of the comparator group).** **6. COWS and SOWS should be assessed during opioid tapering** **7. An *in vitro* alcohol interaction study is required.**

Reference: Adapted from the official meeting minutes for these meetings.

Table 2.5: Pre-NDA submission interactions between the FDA and J & J (the current sponsor) of tapentadol ER about the clinical development of tapentadol ER for chronic pain

Meetings with the Current Tapentadol ER Sponsor (J & J)
EOPII Meeting on 8/24/06 (minutes sent on 9/22/06)[1]
General **1. Since tapentadol ER was a NME[1] two positive trials are needed and only one may be in an enriched population.** **2.** (b) (4) **3. The Agency agreed with J & J that one 15-week parallel group trial in LBP, one 15-week parallel group trial in OA, and one 6-week randomized withdrawal study in cancer (2 weeks Titration and 4 weeks randomized withdrawal) would be representative to support a chronic pain indication.** **4. The safety database should include a substantial number of patients treated at the highest tapentadol ER dose (i.e., 250 mg BID).** **Randomized Withdrawal Trials** **1. In randomized withdrawal studies of tapentadol ER, patients randomized to the placebo group should have slow taper (abrupt withdrawal of an opioid is not acceptable in opioid-tolerant patients). J & J agreed to a stepwise taper over several days in the randomized withdrawal trials.** **2. The Agency recommended the use of COWS and SOWS after tapentadol ER is discontinued during the randomized withdrawal portion.** **3. The Agency agreed with J & J's proposal to limit the use of SOWS to English speaking countries.** **15-Week Parallel Group Trials** **4. J & J proposed a 15-week parallel group trial with a 3-week Titration Period followed by a 12-week Maintenance Period. In both periods, the tapentadol ER dose could be up or down titrated within 100 to 250 mg BID. The Agency agreed with the flexible dosing in the Titration Period, but expressed concern that the problem of flexible dosing in the Maintenance Period is that patients may cluster in the mid tapentadol ER doses and there may be insufficient information on the dose response of the low and high tapentadol ER doses to approve these doses. The Agency stated that it also difficult to assess the relationship between AEs and dose with a flexible dose design.** **2. LOCF imputation method is inappropriate to handle missing data (good scores cannot be given to patients who drop out doe to AEs). The Agency did state that J & J may choose any imputation method, but the Agency will reanalyze the data using BOCF.** **3.** (b) (4) **4. Financial disclosure documents are required for any study used to support the efficacy of tapentadol ER.**
Pre-NDA Meeting on 1/23/09 (minutes sent on 1/21/09)[2]
1. Phase 3 studies 8, 11, and 15 are sufficient to support the filing of an NDA for tapentadol ER. **2. Comparative efficacy or safety claims of tapentadol ER to oxycodone CR can only be done when equianalgesic doses of the opioids are used in two replicative trials with pre-specified statistical methods.** **3. Case report forms (CRFs) and narratives for all patients who died, had a SAE, or a DAE was acceptable. CRFs and narratives should be provided for all events of abuse, overuse, intentional or unintentional overdose, or drug that is lost, stolen, missing, or unaccounted for in all completed Phase 2 and Phase 3 studies. CRFs and narratives should be provided for patients that drop out due to "protocol violation", "lack of efficacy", "lost to follow up", "non-compliance to study medication or procedures," "over compliance", or for "other" in all completed Phase 2 and Phase 3 studies.** **4. Provide information on how aberrant drug behavior was defined, identified, collected, and evaluated.**

EOPII = end of phase II meeting; TRF is tamper resistant formulation

1 In 2006, no tapentadol formulation was approved, so tapentadol ER was a new molecular entity (NME).

2 The January 23, 2009 meeting was canceled by J & J because J & J found the Agency's January 21, 2009 responses to the questions satisfactory.

Reference: Adapted from the official meeting minutes for these meetings.

2.6 Other Relevant Background Information

At the time of the original tapentadol ER NDA submission (November 2009), tapentadol ER was not approved or marketed in any foreign country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic common technical document (CTD) NDA submission was well-organized and complete and there were no major amendments.

3.2 Compliance with Good Clinical Practices

According to J & J, the 5 Phase 3 trials were conducted in compliance with the ethical principles in the Declaration of Helsinki that are consistent with Good Clinical Practices and applicable regulatory requirements including IND regulations (CFR Part 312). Subjects or their legally acceptable representatives provided their written informed consent to participate in each of the Phase 3 trials and IRB approval was obtained by the investigators.

The Division of Scientific Investigations (DSI) was requested to perform routine audits of clinical sites (see Table 3.1). Initially, 3 individual sites (Sites 1477 and 1460 in Study 11 and Site 49 in Study 15) were chosen because each of these sites included a large number of treated patients and the treatment margins (tapentadol ER minus placebo) were greater at these sites than the overall treatment margin in the studies. If the efficacy data from Sites 1477 or 1460 in Study 11 were disregarded, there would be no change in the overall treatment effect of tapentadol ER compared to placebo. The sites in Study 11 were also chosen because these investigators performed multiple clinical studies under INDs but have not been inspected by the FDA. If the efficacy data from Site 49 in Study 15 were disregarded, tapentadol ER would still demonstrate significant treatment effects over placebo, although the overall treatment effect of tapentadol ER compared to placebo would be reduced. In the pivotal trials of tapentadol ER, no investigator who enrolled patients had a potential conflict of interest.

After the Agency informed J & J of the 3 site inspections, J & J conducted a review of all three sites and informed the Agency that they uncovered potential misconduct at Site # 1460 in Study 11 (Dr. Allan Soo). Potential issues related to minimal/limited source documentation, poor documentation (e.g., back-dating, adverse events may have not been fully reported), dose escalations may have been compromised, and the staff may not have been qualified. Given these issues at this site, DSI inspected one additional site in Study 11 (i.e., Site 1478 ─ see green highlights in Table 3.1). This site was selected because it included a large number of treated patients and the treatment margin (tapentadol ER minus placebo) was greater than the overall treatment margin in Study 11. If the efficacy data from Site 1478 were disregarded, there would be no change in the overall treatment effect of tapentadol ER compared to placebo.

At the time of this NDA review, the DSI review of the validity of the data from these 4 sites is ongoing according to Dr. Susan Leibenhaut, the DSI clinical reviewer.

Table 3.1: U.S. sites audited in Studies 11 and 15[1]

Site #	Principle Investigator Contact Information	Number of Patients		
		Randomized[2]	Treated with Tapentadol ER	Treated with Placebo
Study 11 (Pain due to Chronic LBP)				
1477	Bret Wittmer, M.D. Commonwealth Biomedical Research LLC 240 East Ayr Parkway, Madisonville, KY 42431, USA	27	11	9
1460	Allan Soo, M.D. Premiere Pharmaceutical Research, LLC 3316 S. McClintock Drive, Tempe, AZ 85282, USA	32	9	9
1478[3]	Daniel Whittington Dolby Research, LLC 8150 Jefferson Highway, Suite B, Baton Rouge, LA 70809	30	0	10
Study 15 (Pain due to Chronic DPN)				
49	Pamela Amador, M.D., Gables Research 85 Grand Canal Drive, # 400, Miami, FL 33144, USA	16	7	9

1 Studies 11 and 15 are Studies R331333-PAI-3011 (KF5503/23) and R331333-PAI-3015 (KF5503/36), respectively.
2 Randomized patients included patients treated with tapentadol ER, placebo, or the active control (i.e., oxycodone CR) and patients not treated with study medication.
3 This site was selected after J & J informed the Agency that there may have been potential misconduct in Study 11.
Reference: CSR in Study 11 and CSR in Study 15. Amendment #4 to NDA 200533, Correspondence Regarding Meetings, Pages 1-2.

3.3 Financial Disclosures

J & J submitted FDA Form 3454 certifying that J & J did not enter into "any financial arrangement" with any investigator (except the two exceptions noted below) in the 4 important trials that served as the primary support for the efficacy of tapentadol ER. All of these investigators did not receive compensation that could be affected by the outcome of the study as defined in 21 CRF 54.2(a). In addition, J & J certified that all of these investigators disclosed that they did not have a proprietary interest in tapentadol ER or a significant equity interest in J & J as defined in 21 CRF 52.2(b). Finally, J & J certified that none of these investigators was a recipient of significant payments as defined in 21 CRF 54.2(f).

Only 1 investigator in these 4 important trials had reported that he participated in financial arrangements or held financial interests that were required to be disclosed. [redacted] (b) (6) a principal investigator in a U.S. site, reported significant honoraria payments in excess of $25,000 on Form 3455. Since [redacted] (b) (6) did not enroll any patients in Study 11, the overall results and conclusions from Study 11 are unchanged. J & J certified that only 1 investigator [redacted] (b) (6) in these 4 important trials did not respond to their numerous requests for financial disclosure information. Since this site did not enroll any patients in Study, the overall results and conclusions from Study 8 are unchanged.

In summary, there is no clear evidence that the financial interest of investigators changed the overall results of tapentadol ER in the chronic treatment of pain.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

According to Dr. Craig Bertha (the chemistry, manufacturing, and controls reviewer), there are no concerning issues with the submitted purity, stability, and manufacturing data that would prevent the approval of the tapentadol ER NDA. However, the Office of Compliance inspection of the proposed manufacturing site for tapentadol ER in Gurabo, Puerto Rico is pending at this time.

Dr. Sandra Suarez, the biopharmaceutics reviewer in the Office of New Drug Quality Assessment (ONDQA) reviewed the sponsor's proposed in vivo in vitro correlation (IVIVC) models to support marketing of the 5 dose strengths of the to-be-marketed (TBM) tamper resistant formulation (TRF) manufactured in Gurabo, Puerto Rico. Since the important clinical trials were performed using a different formulation (i.e., PR2) than the proposed TBM TRF, J & J needed to bridge the PR2 formulation to the TBM TRF. J & J proposed that IVIVC models would bridge the formulations (*in vitro* dissolution of the TBM TRF would be comparable to bioavailability of the PR2 formulation). However, Dr. Suarez stated that the IVIVC models were not acceptable because they used an unjustified mathematical term and they used mean values instead of individual subject values. J & J submitted new IVIVC models (i.e., using individual subject values instead of mean values), after Dr. Suarez communicated these deficiencies to J & J. However, Dr. Suarez stated that the amended models were inadequate because they retained the unjustified mathematical term.

Given the deficiencies of the IVIVC models, Dr. Suarez stated that the marketing of all 5 dose strengths of the TBM TRF was not supported and she recommended that the tapentadol ER NDA not be approved. Dr. Suarez stated that J & J needs to submit the results of the following to resolve the deficiencies:

- *In vivo* bioequivalence (BE) studies (TBM TRF to Phase 3 PR2) of the 50 and 250 mg strengths under fasting conditions, and
- Dissolution profile comparisons with similarity f2 testing using the approved dissolution method for the strengths not tested in the *in vivo* BE studies (i.e., 50 vs. 100 mg; 250 vs. 150 mg; and 250 vs. 200 mg).

4.2 Clinical Microbiology

Tapentadol ER is not an anti-microbial product. There are no clinical microbiology issues that would prevent approval of tapentadol ER.

4.3 Preclinical Pharmacology/Toxicology

According to Dr. Armaghan Emami, the pharmacology/toxicology reviewer, no new non-clinical studies of tapentadol were submitted to the tapentadol ER NDA. Eight non-clinical studies that were submitted after the approval of the tapentadol IR NDA were not considered to provide significant new information for the tapentadol ER NDA. Therefore, the non-clinical data to support the tapentadol ER NDA was from the data used to support the tapentadol IR NDA.

According to Dr. Emami, there were 2 important toxicology studies (26-week rat study and a 52-week dog study). In the rat study, the NOAEL was at the low dose because the following toxicities were found at the mid and high doses: death likely due to respiratory depression, CNS toxicity (excitability, recumbency, and hunched posture) and hepatotoxicity (liver enzyme elevations, increased liver weights and hepatocellular hypertrophy). In the dog study, the NOAEL was at the low dose because the following toxicities were found at the mid and high doses: CNS toxicity (seizures, paddling movements, muscle twitching, recumbency, tremor, and decreased activity and gliosis with perivascular mononuclear cell infiltration in the medulla oblongata and/or pons) and cardiovascular toxicity (prolonged QT).

Table 4.1, adapted from Dr. Emami's review, compares the exposures (Cmax and AUC) in these toxicology studies to the exposures of the maximum recommended human proposed dose (MRHD) of tapentadol ER in human studies (250 mg BID). According to Dr. Emami, the NOAEL in the rat toxicology study was associated with an AUC below the daily AUC associated with the MHRD. The NOAEL in the dog toxicology study was associated with an AUC and Cmax below both the AUC and Cmax associated with the MHRD. Based solely on the non-clinical data, Dr. Emami recommended that the tapentadol ER NDA should not be approved. However, Dr. Adam Wasserman, the non-clinical supervisor, recommended approval of the tapentadol ER NDA because of the safety data in the clinical database and the known toxicological effects of opioids. Dr. Wasserman also recommended approval, since there was a sufficient safety margin at the highest doses in the rats and dogs based on the Cmax (the toxicokinetic parameter of importance), and the findings in the rats and dogs were reversible. Dr. Wasserman also noted that although a related opioid analgesic (i.e., tramadol) had similar non-clinical toxicities without sufficient exposure to cover MRHD, tramadol was approved.

Table 4.1: Safety margins of 500 mg of tapentadol ER (the maximum recommended human daily dose) derived from the 26-week rat and the 52-week dog toxicology studies[1]

Dose (mg/kg/day)	HED (mg/kg/day)	Cmax (ng/mL)	AUC_{0-24} (ng•hour/mL)	Human Safety Margin Based on Cmax	Human Safety Margin Based on AUC
Human Studies of Tapentadol ER 250 mg BID (500 mg/day)					
8	—	132	2288	—	—
26-Week Rat Toxicology Study					
75[2]	12	386	624	3x	0.3x
150	24	479	1260	3.6x	0.5x
300	48	1181	2537	8.9x	1.1x
52-Week Dog Toxicology Study					
10[2]	6	7	20	0.1x	<0.1x
30	17	40	101	0.3x	<0.1x
80	44	183	355	1.4x	0.2x

1 Safety margins of the parent compound (tapentadol) are presented in this table. The green highlights in this table represent lack of a safety margin.
2 NOAELs in the rat and dog toxicology studies.
Reference: Adapted from Dr. Emami's review of the tapentadol ER NDA

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Although its exact mechanism is unknown, analgesic efficacy of tapentadol is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake.

4.4.2 Pharmacodynamics

See Section 7.4.3 (Assessment of Pro-arrhythmic Effects and Electrocardiograms) for a review of the thorough QT studies of tapentadol.

4.4.3 Pharmacokinetics

According to Dr. David Lee, the clinical pharmacology reviewer, the following are the pharmacokinetic (PK) highlights of tapentadol ER:

- Mean absolute bioavailability after single-dose administration of tapentadol was approximately 32% due to extensive first-pass metabolism.
- Median maximum serum concentrations of tapentadol were observed about 5 hours after administration of tapentadol ER.
- There was minimal accumulation of tapentadol following administration of tapentadol ER.
- Food Effect: The AUC and Cmax increased by 6% and 17%, respectively, when tapentadol ER was administered after a high-fat meal. Dr. Lee agrees with the sponsor that tapentadol ER can be taken with or without food.
- Geriatric Patients: The AUC was similar in geriatric patients compared to younger patients and the Cmax was 16% lower in geriatric patients compared to younger patients.
- Patients with Renal Impairment: The AUC and Cmax were comparable in patients with varying degrees of renal function to subjects with normal renal function.
- Patients with Hepatic Impairment: Administration of tapentadol resulted in higher AUC and Cmax in patients with impaired hepatic function compared to subjects with normal hepatic function. The ratios of the tapentadol AUC for the mild and moderate hepatic impairment groups in comparison to the AUC in the normal hepatic function group were 1.7 and 4.2, respectively. The ratios of the tapentadol Cmax for the mild and moderate hepatic impairment groups in comparison to the Cmax in the normal hepatic function group were 1.4 and 2.5, respectively. Dr. Lee agrees with the sponsor's recommendation that tapentadol ER should not be used in patients with severe hepatic impairment and tapentadol ER should be dosed only once daily (starting at 50 mg once daily) in patients with moderate hepatic impairment.
- Co-administration with Alcohol: An *in vivo* PK study in healthy subjects of single-doses of tapentadol ER (100 and 250 mg) with and without 40% ethanol was conducted. Following co-administration with alcohol, the mean Cmax was increased by 48% and 28% in the 100 and 250 mg groups relative to control, respectively (the individual change in Cmax ranged from 1 to 4 fold and 1 to 3 fold, respectively). There was no significant change in the AUC after co-administration with alcohol.

Dr. Lee agrees with Dr. Suarez' recommendations — there is no adequate support for the 5 dose strengths of the TBM TRF — and recommends that the tapentadol ER NDA should not be approved.

5 Sources of Clinical Data

5.1 Tables of Studies

J & J submitted final study reports of **40 completed studies** of tapentadol ER in their NDA to support approval of tapentadol ER for the chronic treatment of moderate to severe pain:

1. **5 randomized Phase 3 studies of tapentadol ER in patients with moderate to severe chronic pain:** Three 15-week parallel-group, DB, PC and oxycodone-controlled trials (Studies 8, 9, and 11); one 15-week randomized withdrawal trial (Study 15), and one, 1-year, OL, oxycodone-CR-controlled safety study (Study 7) — see Table 5.1.
2. **5 randomized, DB, 4-5 week Phase 2 trials of tapentadol ER in patients with chronic pain:** Studies 1, 2, 19, KF09, and KF10 (see Table 5.2).
3. **3 multiple-dose, Phase 1 studies of tapentadol ER in healthy subjects:** including the thorough QT study of tapentadol ER (Study HP10) — (see Table 5.3)
4. **27 randomized, single-dose, Phase 1 studies of tapentadol ER in healthy subjects:** see Table 5.4).

Table 5.1: Five randomized Phase 3 studies of tapentadol ER in patients with moderate to severe chronic pain[1]

Study[2]	Population	Sites[3]	Treatment Groups	Primary Efficacy Endpoint
Parallel-Group, DB, PC and Oxycodone-CR-Controlled Trials (3 weeks titration followed by 12 weeks of maintenance)				
8	Knee OA	112 Sites: U.S., Australia, Canada, New Zealand	Tapentadol ER (n=344) Oxycodone CR (n=342) Placebo (n=337)	Individual Studies 8, 9, and 11 had the following identical primary endpoint: Change from baseline in the mean pain intensity (based on an 11-point NRS) over the last week of the Maintenance Period between the tapentadol ER and placebo groups.
9	Knee OA	79 Sites: Austria, Croatia, Germany, Hungary, Latvia, Poland, Portugal, Romania, Slovakia, Spain, Netherlands, United Kingdom	Tapentadol ER (n=319) Oxycodone CR (n=331) Placebo (n=337)	
11	Chronic LBP	97 Sites: U.S., Canada, Australia	Tapentadol ER (n=318) Oxycodone CR (n=328) Placebo (n=319)	
Randomized Withdrawal Trial (3 week OL titration then 12 week randomized, DB withdrawal)				
15	Diabetic Peripheral Neuropathy	88 Sites: U.S., Canada	Tapentadol ER (n=196) Placebo (n=193)	Change from baseline (start of the DB period) in mean pain intensity (11-point NRS) over the last week of Randomized Withdrawal Period.
One-Year, OL, Oxycodone-CR-Controlled, Safety Study				
7	Knee OA, Hip OA, or Low Back Pain	89 Sites: Austria, Belgium, Canada, France, Ireland, Netherlands, Slovakia, Spain, U.S.	Tapentadol ER (n=894) Oxycodone CR (n=223)	There was no primary endpoint in this primary safety study

NRS is numerical rating scale

1 Studies 8, 9, 11, and 15 served as the primary support for efficacy of tapentadol ER. Studies 7, 8, 9, and 11 served as the primary support for safety. Tapentadol ER and oxycodone CR were dosed BID.

2 Studies 7, 8, 9, 11, and 15 are abbreviations for Studies R331333-PAI-3007 (KF5503/24), R331333-PAI-3008 (KF5503/11), R331333-PAI-3009 (KF5503/12), R331333-PAI-3011 (KF5503/23), and R331333-PAI-3015 (KF5503/36), respectively. Note each study has two numbers (the first number represents J & J's designation and the second number represents Grünenthal GmbH's designation). Grünenthal GmbH is a German pharmaceutical company that has a license agreement with J & J for tapentadol ER.

3 The number of sites is based on sites that treated patients with study medication.

Table 5.2: Five randomized, DB, MC, Phase 2 trials of tapentadol ER in patients with chronic pain[1]

Trial[2]	Population[3]	Sites	Treatment Groups
Crossover Trial to Establish the Conversion Ratio between Tapentadol IR and ER			
19	Low Back Pain	U.S.	Part 1: OL 3-week titration to effect Tapentadol IR 50 QID start, increased to effect up to a maximum of 500 mg/day (dosing is every 4 to 6 hours) Part 2: DB period (14 days) fixed dose (equivalent daily dose as in Part 1) Tapentadol IR every 4 to 6 hours (n=81) Tapentadol ER BID (n=84)
One-Month, PC and Active-Controlled, Parallel-Group, Fixed Dose Trials			
KF09	Hip or Knee OA	U.S.	Tapentadol ER 21.5 mg BID (n=78) Tapentadol ER 43 mg BID (n=77) Tapentadol ER 86 mg BID (n=73) Oxycodone CR 20 mg BID (n=79) Placebo (n=77)
KF10	Low Back Pain	Austria, Belgium, France, Germany, Hungary, Spain, Netherlands, Poland, Portugal, UK	Tapentadol ER 21.5 mg BID (n=91) Tapentadol ER 43 mg BID (n=77) Tapentadol ER 86 mg BID (n=73) Tramadol prolonged release 100 mg BID (n=90) Placebo (n=93)
One-Month, PC & Active-Controlled, Forced-Titration then Fixed-Dose Trials[4]			
1	Knee OA	U.S.	Tapentadol ER 25 to 50 to 100 mg BID (n=162) Tapentadol ER 100 to 150 to 200 mg BID (n=167) Oxycodone CR 10 to 10 to 20 mg BID (n=169) Placebo (n=167)
2	Low Back Pain	Austria, Belgium, Croatia, France, Germany, Spain, Netherlands, Poland, Portugal, Switzerland	Tapentadol ER 25 to 50 to 100 mg BID (n=175) Tapentadol ER 100 to 150 to 200 mg BID (n=171) Tramadol prolonged release 100 to 150 to 200 mg BID (n=172) Placebo (n=175)

1 These trials required patients to have at least 3 months of pain, except Study 1 (patients had to have pain for at least 30 days). Patients had have been treated with opioid or non-opioid analgesics at baseline. In Studies 1, 2, and 19, patients needed to be dissatisfied with there baseline analgesic medication due to intolerability or due to lack of efficacy.

2 Study 19 is the abbreviation for Study R331333-PAI-3019 (J & J's designation) and Study KF5503/39 (Grünenthal's designation); Study KF10 is the abbreviation for Study KF5503/10; Study KF9 is the abbreviation for Study KF5503/09; Study 1 is the abbreviation for Study R331333-PAI-2001 (J & J's designation) and Study KF5503/19 (Grünenthal's designation); Study 2 is the abbreviation for Study R331333-PAI-2002 (J & J's designation) and Study KF5503/20 (Grünenthal GmbH's designation).

3 In the OA trials, patients had to be at least 40 years old; whereas, in the LBP trials, patients had to be at least 18 years old

4 During the 14-day forced titration period, up-titration was mandatory except for dose intolerance. During the 14-day fixed-dose period the patient had to stay on the last titration dose (except for dose intolerance).

Reference: Protocols for Studies 19, KF09, KF10, 1, and 2.

Table 5.3: Three multiple-dose, Phase 1 studies of tapentadol ER in healthy subjects

Study	J & J's Designation	Grünenthal's designation	Treatments
Thorough QT Study (Randomized, Crossover, DB, PC, Moxifloxacin-Controlled)			
HP10	None	HP5503/10	Tapentadol ER 86 mg BID for 2.5 days (n=35) Tapentadol ER 172 mg BID for 2.5 days (n=36) Moxifloxacin 800 mg single dose (n=34) Placebo (n=37)
Randomized, Crossover, OL, Study			
HP54	None	HP5503/54	Tapentadol PR2 150 mg BID x 3.5 days (n=24) Tapentadol PR2 small 150 mg BID x 3.5 days (n=22)
Single-Dose and Multiple-Dose, OL, Uncontrolled PK Study			
36	R331333-PAI-1036	HP5503/38	Tapentadol TRF 250 mg initial dose then after 3 days 250 mg BID x 2.5 days (n=18)

Reference: Tabular listing of clinical studies, Pages 1-42

Table 5.4: Twenty-seven randomized, single-dose, Phase 1 studies of tapentadol ER in healthy subjects

Study	J & J's Designation	Grünenthal's designation	Treatments
Crossover, OL, Bioavailability Studies			
47	R331333-PAI-1047	HP5503/62	Tapentadol TRF 100 mg (n=24)[1] Tapentadol IR 100 mg (n=24)
HP07	None	HP5503/07	Tapentadol IR 21.5 mg (n=16) Tapentadol IR 86 mg (n=16) Tapentadol PR1 86 mg (n=16) Tapentadol PR1 172 mg (n=16)
4	R331333-PAI-1004	HP5503/18	Tapentadol PR1 200 mg (n=24) Tapentadol PR2 200 mg (n=24)
33	R331333-PAI-1033	HP5503/31	Tapentadol oral solution 75 mg (n=28) Tapentadol PR2 250 mg (n=24) Tapentadol TRF 250 mg (n=25)
34	R331333-PAI-1034	HP5503/42	Tapentadol oral solution 21.5 mg (n=24) Tapentadol ER 50 mg (n=21) Tapentadol TRF 50 mg (n=20)
22	R331333-PAI-1022	HP5503/41	Tapentadol PR2 50 mg (n=24) Tapentadol TRF 50 mg (n=24)
23	R331333-PAI-1023	HP5503/36	Tapentadol PR2 100 mg (n=24) Tapentadol TRF 100 mg (n=24)
HP33	None	HP5503/33	Tapentadol PR2 150 mg fast (n=24) Tapentadol PR2(small) 150 mg fast (n=24)
HP52	None	HP5503/52	Tapentadol PR2 150 mg fed (n=24) Tapentadol PR2 small 150 mg fed (n=24)
HP53	None	HP5503/53	Tapentadol PR2 50 mg (n=21) Tapentadol PR2 small 50 mg (n=22)
37	R331333-PAI-1037	HP5503/57	Tapentadol oral solution 75 mg (n=16) Tapentadol TRF 150 mg (n=15) Tapentadol TRF 200 mg (n=15)
24	R331333-PAI-1024	HP5503/35	Tapentadol PR2 250 mg fed (n=32) Tapentadol TRF 250 mg fed (n=31)
46	R331333-PAI-1046	HP5503/61	Tapentadol PR2 100 mg fast (n=74) Tapentadol TRF 100 mg fast (n=74)
49	R331333-PAI-1049	HP5503/60	Tapentadol PR2 50 mg (commercial site), n=32 Tapentadol PR2 50 mg (clinical site), n=31
51	R331333-PAI-1051	HP5503/63	Tapentadol PR2 150 mg (commercial site), n=29 Tapentadol PR2 150 mg (clinical site), n=33
Crossover, OL, Food Effect, Bioavailability Studies			
55	R331333-PAI-1055	HP5503/67	Tapentadol PR2 250 mg fed (n=52) Tapentadol TRF 250 mg fed (n=52) Tapentadol TRF 250 mg fast (n=54)

Study	J & J's Designation	Grünenthal's designation	Treatments
HP08	None	HP5503/08	Tapentadol PR1 21.5 mg fast (n=19) Tapentadol PR1 86 mg fast (n=18) Tapentadol PR1 86 mg fed (n=19) Tapentadol IV 34 mg fast (n=23)
1020	R331333-PAI-1020	HP5503/28	Tapentadol PR2 250 mg fast (n=33) Tapentadol PR2 250 mg fed (n=40)
3	R331333-PAI-1003	HP5503/17	Tapentadol PR2 300 mg fast (n=35) Tapentadol PR2 300 mg fed (n=38)
HP12	None	HP5503/12	Tapentadol PR1 100 mg fast (n=9) Tapentadol T1 100 mg fed (n=9) Tapentadol T1 100 mg fast (n=9) Tapentadol T2 100 mg fed (n=9) Tapentadol T2 100 mg fast (n=9)
Crossover, OL Studies to Support IVIVC			
[redacted] (b) (4)			
Crossover, OL, DDI Study of Tapentadol ER With and Without Alcohol			
28	R331333-PAI-1028	HP5503/44	Tapentadol TRF 100 mg & ethanol (n=20) Tapentadol TRF 100 mg & water (n=20) Tapentadol TRF 250 mg & ethanol (n=20) Tapentadol TRF 250 mg & water (n=20)
DB, PC, Safety, PK Study			
26	R331333-PAI-1026	HP5503/47	Tapentadol PR1 25 mg (n=9) Tapentadol PR1 50 mg (n=8) Tapentadol PR1 100 mg (n=8) Tapentadol PR1 200 mg (n=7) Placebo (n=10)
Single Ascending Dose, Dose proportionality, Bioavailability Study			
21	R331333-PAI-1021	HP5503/27	Tapentadol IR 50 mg (n=36) Tapentadol PR2 50 mg (n=36) Tapentadol PR2 100 mg (n=36) Tapentadol PR2 200 mg (n=36) Tapentadol PR2 250 mg (n=36)

PR=prolonged release; TRF=tamper-resistant formulation; IVIVC is in vitro/in vivo correlation
1 Bioavailability of TRF after chewing then swallowing
Reference: Tabular listing of clinical studies, Pages 1-42

J & J also submitted deaths and nonfatal SAEs as of the last safety update (i.e., the 120-Day Safety Update) from 9 ongoing multi-centered studies of tapentadol ER in patients with pain due to cancer and pain due to OA, LBP, or DPN:

- 6 studies in patients with non-cancer pain (e.g., chronic pain due to knee OA, hip OA, LBP, and DPN) — see Table 5.5. Note, Study 20 was recently completed and the final study report is in progress.
- 3 studies in patients with cancer pain (see Table 5.6)

Table 5.5: Six ongoing multi-centered studies of tapentadol ER in patients with moderate to severe pain due to OA, LBP, or DPN

Study	J & J's Designation (Grünenthal's designation)	Design	Treatments	N[1]
Chronic Pain due to Knee or Hip OA or LBP				
Moderate to Severe Chronic Pain due to Knee or Hip OA or LBP				
10	R331333-PAI-3010 (KF5503/18)	One-year, OL extension, uncontrolled, single-arm, safety Phase 3 study. Patients must have completed the DB Treatment Period in Studies 7, 8, 11, or 19.	Tapentadol ER BID[2] between 100 to 250 mg BID	1154
Severe Uncontrolled Pain due to Knee OA				
KF42	N/A (KF5503/42)	12-week, OL	Tapentadol ER BID with rescue tapentadol IR	4[3]
Uncontrolled Severe Chronic Nociceptive, Neuropathic, or Mixed LBP				
KF44	N/A (KF5503/44)	12-week, OL	Tapentadol ER BID with rescue tapentadol IR	0[3]
Chronic Pain due to Non-Inflammatory End-Stage Hip or Knee OA (candidates for joint replacement)				
20	R331333-PAI-3020 (KF5503/41)	Randomized, DB, PC and oxycodone CR-controlled, parallel-arm, Phase 3 study. Two DB treatment periods: a 2-week IR treatment period (tapentadol IR, oxycodone IR, and placebo) followed by a 4-week ER treatment period (tapentadol ER, oxycodone CR, and placebo).	Tapentadol IR q 4-6 hours for 2 weeks followed by Tapentadol ER BID for 4 weeks 1. Tapentadol IR 50 mg q 4-6 hours then Tapentadol ER BID (n=151) 2. Tapentadol IR 75 mg q 4-6 hours then Tapentadol ER BID (n=154) 3. Oxycodone IR 10 mg q 4-6 hours then Oxycodone CR BID (n=143) 4. Placebo q 4-6 hours then BID (n=148)	596[4]
Moderate to Severe Chronic Pain due to Diabetic Peripheral Neuropathy				
27	R331333PAI3027 (KF5503/56)	15-week, Randomized Withdrawal, DB, PC (3-week Titration Period with OL tapentadol ER followed by a 12-week DB, randomized withdrawal period)	Tapentadol ER TRF (between 100 – 250 mg BID) Placebo	N/A[3]
28	R331333PAI3028 (KF5503/57)	One-year, randomized, oxycodone CR-controlled, OL, long-term safety study	Tapentadol ER TRF (between 100 – 250 mg BID) Oxycodone CR	N/A[3]

1 Number of patients in the ongoing study as of September 30, 2009 (the cut-off date in the 4-month Safety Update)
2 Patients who received tapentadol ER in Study 7 will continue their current dose of tapentadol ER in Study 10. However, all other patients in Study 10 will initiate tapentadol ER at 50 mg BID and the dose should be increased after the first 3 days to 100 mg BID. Additional increments in dose (50 mg BID) can be made after 3 days. However, patients may have an accelerated titration schedule to return to the level of pain control or to minimize withdrawal symptoms. The range of dosing in Study 10 is between 100 to 250 mg BID.
3 Planned numbers of patients in Studies KF42 and KF44 is 180 in each study. The planned number of patients in Study 27 is 455 (300 for the Randomized Withdrawal Period). The planned number of patients in Study 28 is 800 (600 and 200 patients on tapentadol ER and oxycodone CR, respectively).
4 Study 20 has been completed; however, the final study report is in progress.
Reference: Adapted from the 4-Month Safety Update, tabular listings, Pages 1-10, also adapted from protocols 27 and 28.

Table 5.6: Three ongoing multi-centered studies of tapentadol ER in patients with cancer pain

Study	J & J's Designation (Grünenthal's designation)	Design	Treatments	N[1]
C01	JNS024 PR-JPN-C01 (N/A)	19-day, OL, uncontrolled, dose-titration, PK Phase 2 study in Japanese patients	Tapentadol ER BID	78[2]
13[3]	R331333-PAI-3013 (KF5503/15)	Randomized withdrawal, morphine CR-controlled and PC, DB, Phase 3 study (2 weeks flexible dose titration then 4 weeks fixed dose maintenance)	Tapentadol ER Placebo Morphine CR	270[2]
14[4]	R331333-PAI-3014 (KF5503/16)	Randomized withdrawal, DB, morphine CR-controlled and PC, Phase 3 study (2 weeks flexible dose titration then 4 weeks fixed dose maintenance)	Tapentadol ER Placebo Morphine CR	93

1 Number of patients in the ongoing study as of September 30, 2009 (the cut-off date in the 4-month Safety Update)
2 Planned number of patients in Studies C01 and 13 is 573 and 80, respectively.
3 Study 13 is a non-IND study.
4 Study 14 was terminated early due to feasibility issues. Only 93 patients were enrolled (573 were planned).
Reference: Adapted from the 4-Month Safety Update, tabular listings, Pages 1-10.

5.2 Review Strategy

Efficacy: Studies 8, 9, 11, and 15 served as the critical trials for the **evaluation of efficacy** of tapentadol ER for the chronic treatment of moderate to severe pain. These trials were adequate and well-controlled, had acceptable endpoints, included three different populations [patients with OA (Studies 8 and 9), LBP (study 11), and DPN (Study 15)], included two different types of pain [nociceptive (Studies 8, 9, and 11) and neuropathic pain (Study 15)], and included two different trial designs [non-enriched, parallel-group, randomized, DB, controlled (Studies 8, 9, and 11) and enriched, randomized withdrawal (Study 15)]. For the efficacy evaluation of individual Studies 8, 9, 11, and 15, see Section 6.1.5 (Analysis of Primary Endpoint) and the individual study reports in Sections 9.4.1, 9.4.2, 9.4.3, and 9.4.4.

Safety: The safety results from the following 4 studies served as the critical studies for the **evaluation of safety** of tapentadol ER for the chronic treatment of moderate to severe pain: pooled data from 3 randomized, DB, controlled Phase 3 induction trials (Studies 8, 9, and 11) and 1 one-year long-term, controlled safety study (Study 7). The safety data from Studies 8, 9, and 11 were also pooled because these trials had similar designs, safety evaluations, and populations. See Section 7.3 for the major safety analyses including Section 7.3.6 for the specific safety concerns of opioid analgesics.

Supportive safety data was obtained from 6 Phase 2 and Phase 3 trials (Studies 15, 1, 2, 19, KF09, and KF10) and 30 Phase 1 studies in healthy subjects (3 multiple-dose studies and 27 single-dose studies). The 6 Phase 2 and Phase 3 trials were not included in the most important safety analyses because some of the studies were of short duration, e.g., 4-5 weeks, (Studies 1, 2, 19, KF09, and KF10), included subtherapeutic doses of tapentadol ER which were lower than the proposed doses (Studies KF09 and KF10), and included a cross-over design or a randomized withdrawal design where patients in both treatment groups received tapentadol which could minimize the actual difference in adverse reactions between the groups (Study 15).

5.3 Discussion of Individual Studies/Clinical Trials

Four 15-week Phase 3 trials served as the primary support for the efficacy of tapentadol ER for the treatment of chronic pain (Studies 8, 9, 11, and 15). The safety of tapentadol ER for the treatment of

chronic pain was primarily supported by Studies 8, 9, and 11 and Study 7 (the 1-year long-term safety study). See Sections 9.4.1, 9.4.2, 9.4.3, 9.4.4, and 9.4.5 for the individual study reports for Studies 8, 9, 11, 15, and 7, respectively.

Study 8 [Study R331333-PAI-3008 (J & J's trial designation); Study KF5503/11 (Grünenthal's trial designation)]: Study 8 was a randomized, DB, PC and oxycodone CR-controlled, parallel group, MC, 3-arm, Phase 3 trial of controlled adjustment of tapentadol ER in 1023 patients with moderate to severe chronic pain (≥ 3 months) from knee OA. Patients must have been at least 40 years old, taking analgesic medication for their knee OA ≥ 3 months, and been dissatisfied with their current analgesic medication due to inadequate analgesia or intolerability. In Study 8, 1023 patients with chronic pain due to knee OA received study medication at 112 sites in the U.S., Canada, New Zealand, and Australia.

Prior to randomization and prior to receiving study medication, patients entered a Washout Period where all analgesics (including acetaminophen) were discontinued and new analgesics were not allowed. To be randomized and receive study medication, patients needed to have an average pain intensity score of ≥ 5 on an 11-point numerical rating scale (NRS) during the last 3 days of the Washout Period. After completion of the Washout Period, patients entered the 3-week Titration Period and were randomized 1:1:1 to tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID and then after 3 days the tapentadol ER and oxycodone doses were increased to 100 mg BID and 20 mg BID, respectively. In the Titration Period, upward or downward titration was allowed in increments of tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID (at a minimum of 3-day intervals for upward titration) to provide a meaningful improvement of pain with tolerability to the study medication. Following the Titration Period, patients entered the 12-week Maintenance Period where dose adjustment was discouraged; however, up or down titration was permitted if needed. The allowed dose ranges in the 15-week treatment period (Titration and Maintenance Periods) were tapentadol 100 mg to 250 mg BID, oxycodone CR 20 to 50 mg BID, and placebo BID. All analgesics were not allowed during the Titration and Maintenance Periods of Study 8, except the following medication:

- Study medication
- Stable daily doses of daily aspirin ≤ 325 mg for cardiovascular prophylaxis
- Up to 1000 mg of daily acetaminophen for rescue analgesia during the Titration Period (except for the last 3 days) and up to 1000 mg of acetaminophen per day for ≤ 3 consecutive days for non-trial-relating pain (not pain from knee OA) during the Maintenance Period.

At the end of the Maintenance Period, patients stopped their study medication without a taper and may have been started on appropriate analgesic medication according to local practice standards.

The primary efficacy endpoint was the change from baseline (average during the last 3 days of the Washout Period) of the average pain intensity using an 11-point NRS over the last week of the Maintenance Period. Comparison of the primary efficacy endpoint results between the tapentadol ER and placebo groups was performed using a 2-sided analysis of covariance (ANCOVA) test at the 5% significance level. Treatment effect of tapentadol ER versus placebo was estimated based on least-square means of the difference (LSD). The primary efficacy analysis was performed using the ITT population (all randomized patients who received at least one dose of study medication) and the LOCF imputation method was used for missing values.

Study 9 [Study R331333-PAI-3009 (J & J's trial designation); Study KF5503/12 (Grünenthal's trial designation)]: The design of Study 9 was identical to Study 8 (see the overview of the design of Study 8 above for details). In Study 9, 987 patients with moderate to severe chronic pain (≥ 3 months) from knee OA were treated at 79 sites in 12 European countries.

Study 11 [Study R331333-PAI-3011 (J & J's trial designation); Study KF5503/23 (Grünenthal's trial designation)]: The design of Study 11 was identical to Study 8 (see the overview of the design of Study 8 above for details) except that Study 11 was in patients with chronic (≥ 3 months), non-malignant low back pain who were at least 18 years old; whereas, Study 8 was in patients with chronic knee OA who were at least 40 years old. In Study 11, 965 patients with chronic LBP were treated at 97 sites in United States, Canada, and Australia.

Study 15 [Study R331333-PAI-3015 (J & J's trial designation); Study KF5503/36 (Grünenthal's trial designation)]: Study 15 was DB, parallel-group, MC randomized-withdrawal Phase 3 trial of tapentadol ER in diabetic patients (type I or type II) with chronic pain (≥ 6 months) from diabetic peripheral neuropathy (DPN). Patients must have been taking analgesic medications for their DPN pain ≥ 3 months, and dissatisfied with their current analgesics due inadequate analgesia or intolerability. In Study 15, 588 patients with chronic DPN were treated with OL tapentadol at 88 sites in the United States and Canada (389 patients were treated in the DB Randomized Withdrawal Period).

Prior to receiving study medication, patients entered a Washout Period where all analgesics were discontinued and new analgesics were not allowed (except for 2000 mg of acetaminophen per day). To enter the OL Titration Period (after washout), patients needed to have an average pain intensity score of ≥ 5 on an 11-point NRS during the 3 days before the Titration Period. During the Titration Period, all patients received tapentadol ER 50 mg BID for the first 3 days then 100 mg BID for the next 3 days. In the Titration Period, upward or downward titration of tapentadol ER was allowed in increments of 50 mg BID to optimize the patients' analgesic needs and tolerability. The allowed dose ranges in the Titration Period was between 100 mg to 250 mg of tapentadol ER BID.

If during the last three days of the Titration Period, if patients responded (the change in the average NRS pain score was ≥ 1 point reduction from the average NRS at OL baseline), then patients entered the DB Randomized Withdrawal Period and were randomized 1:1 to continue treatment with tapentadol ER (at the dose used during the last 4 days of the Titration Period) or placebo. Patients who received placebo had their tapentadol ER tapered (100 mg BID for the first 3 days of the Randomized Withdrawal Period and then no tapentadol ER thereafter). Patients who continued their tapentadol ER dose during the Randomized Withdrawal Period had to continue the same dose throughout the 12-week Randomized Withdrawal Period. During the first four days of the Withdrawal Period, patients were allowed to receive 2 doses of 25 mg of tapentadol ER at least 6 hours apart for rescue analgesia, and from Day 5 through the end of Week 12, patients were allowed to receive a single 25 mg tapentadol ER dose every day for rescue analgesia.

At the end of the Randomized Withdrawal Period, patients stopped their study medication without a taper and may have been started on appropriate analgesic medication according to local practice standards.

The primary efficacy endpoint in Study 15 was the change from DB baseline (average score during the last 3 days of the OL Titration Period) of the average pain intensity using an 11-point NRS at Week 12

(the last week of the Randomized Withdrawal Period). Comparison of the primary efficacy endpoint results between the tapentadol ER and placebo groups was performed using a 2-sided analysis of covariance (ANCOVA) test at the 5% significance level. Treatment effect of tapentadol ER versus placebo was estimated based on least-square means of the difference (LSD). The primary efficacy analysis was performed using the ITT population (all randomized patients who received at least one dose of study medication) and the LOCF imputation method was used for missing values.

Study 7 [Study R331333-PAI-3007 (J & J's trial designation); Study KF5503/24 (Grünenthal's trial designation)]: Study 7 was a 1-year, OL, randomized, oxycodone CR-controlled, parallel group, MC, Phase 3 safety study of controlled adjustment of tapentadol ER in patients with chronic pain (≥ 3 months) from knee OA, hip OA, or non-malignant low back pain. Patients must have been at least 18 years old, taking analgesic medications, and dissatisfied with their current analgesics due inadequate analgesia or intolerability. Patients may have received stable doses of tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, mood stabilizers, anti-Parkinsonian drugs, or anticonvulsants or rescue acetaminophen for analgesia during the study. In Study 7, 1117 patients with chronic pain from knee OA, hip OA, or low back pain were treated at 89 sites in the United States, Canada, and Europe.

Prior to receiving study medication and prior to randomization, patients entered a Washout Period where all analgesics were discontinued and new analgesics were not allowed. To be randomized and receive study medication, patients needed to have an average pain intensity score of ≥ 4 on an 11-point NRS during the 24 hours prior to the Titration Period (after washout). After completion of the Washout Period, patients entered the 1-week Titration Period and were randomized 4:1 to tapentadol ER 50 mg BID or oxycodone CR 10 mg BID and then after 3 days the dose was increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID, respectively. Patients remained on tapentadol ER 100 mg BID or oxycodone CR 20 mg BID for the last 4 days of the Titration Period. In the 51-week Maintenance Period, upward or downward titration was allowed in increments of tapentadol ER 50 mg BID or oxycodone CR 10 mg BID (at a minimum of 3-day intervals for upward titration) to optimize the patients' analgesic needs and tolerability. The allowed dose range in the 51-week Maintenance Period were tapentadol 100 mg to 250 mg BID and oxycodone CR 20 to 50 mg BID.

At the end of the Maintenance Period, patients either entered an OL extension study (Study 10) or stopped their study medication without a taper and may have been started on appropriate analgesic medication according to local practice standards.

There was no formal hypothesis testing in Study 7 because it was a primary safety study. All statistical tests were 2-sided at a significance level of 0.05 and were interpreted in an exploratory manner. Summaries of data at the endpoint included imputation by LOCF. Since pain intensity scores were not of primary interest in Study 7 (unlike for Studies 8, 9, 11, and 15), no other imputations or alternative sensitivity analyses for missing data was implemented.

6 Review of Efficacy

Efficacy Summary

In 1 of the 3 induction trials (Study 11, LBP), tapentadol ER had a statistically significant improvement from baseline in pain intensity during the last week of the Treatment Period (i.e., Week 15) compared to placebo, using conservative imputation, i.e., baseline observation carried forward (BOCF). Using BOCF imputation, the treatment margin of the tapentadol ER group compared to placebo was small in Study 11 (0.6 LS mean difference on an 11-point scale). However, this treatment margin is consistent with the treatment margins of other opioid analgesics in PC, induction trials in chronic pain. In Study 8 (OA), the tapentadol ER group had a numerical improvement from baseline in pain intensity during Week 15 compared to placebo (using BOCF imputation); although, this difference was not statistically significant. In Study 9 (OA), tapentadol ER did not have a numerical improvement from baseline in pain intensity during Week 15 compared to placebo (using BOCF imputation). In all 3 induction trials, the tapentadol ER group had a numerical improvement from baseline in pain intensity during Week 15 compared to oxycodone CR, using BOCF imputation. This assay sensitivity is supportive of the efficacy of tapentadol ER in the chronic treatment of pain; however, no comparative claims should be made because these were exploratory analyses.

In Study 15 (DPN), tapentadol ER compared to placebo had less worsening in the pain intensity from the DB baseline during the last week of the Randomized Withdrawal Period, using very conservative imputation, i.e., OL BOCF. These results were statistically significant. The treatment margin in Study 15 (1.1 LS mean difference on an 11-point scale) was consistent with the results of other randomized withdrawal, PC, chronic pain trials of long-acting opioids (e.g., Exalgo, Embeda).

In summary, the efficacy of tapentadol ER in the chronic treatment of pain was established from 2 positive adequate and well-controlled trials (Studies 11 and 15) with supportive evidence from Study 8 (Study 9 was a negative trial). The heterogeneous designs/populations of the 2 positive trials also supports the efficacy of tapentadol: different designs (i.e., induction and enriched randomized withdrawal design), different populations (LBP and DPN), and different types of pain (nociceptive and neuropathic pain). The number and type of positive trials to support an efficacy claim for a long-acting opioid for chronic pain is consistent with the review division's statements to the sponsor during pre-NDA meetings.

6.1 Indication

J & J proposes the following indication for tapentadol ER: "for the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."

6.1.1 Methods

Studies 8, 9, 11, and 15 served as the critical trials for the evaluation of efficacy of tapentadol ER for the chronic treatment of moderate to severe pain. These trials were adequate and well-controlled, had acceptable endpoints, included three different populations [patients with OA (Studies 8 and 9), LBP (study 11), and DPN (Study 15)], included two different types of pain [nociceptive (Studies 8, 9, and 11)

and neuropathic pain (Study 15)], and included two different trial designs [non-enriched, parallel-group, randomized, DB, controlled (Studies 8, 9, and 11) and enriched, randomized withdrawal (Study 15)].

6.1.2 Demographics

Demographics were similar in the treatment groups within each important efficacy trial (Studies 8, 9, 11, and 15). See Tables 9.14, 9.20, 9.27, and 9.34 for the demographic tables in Studies 8, 9, 11, and 15, respectively.

Table 6.1 displays the baseline demographics in the three populations [OA (Studies 8 and 9), LBP (Study 11), and DPN (Study 15)]. Demographics were similar in the two OA trials (Studies 8 and 9) except that the majority of the patients were treated in the U.S. in Study 8; whereas, all of the patients were treated in Europe in Study 9. The differences in racial demographics in Studies 8 and 9 were likely to the differences in nationality in the trials (i.e., greater proportion of Caucasians in Study 9 than in Study 8).

In the 4 trials, the median body mass index (BMI) was in the obese range (ranging from 30 to 34 kg/m^2), which is consistent with BMI in other trials of patients with chronic pain.

Table 6.1: Baseline demographics in Studies 8, 9, 11, and 15[1]

		OA		LBP	DPN
		Study 8 (Knee OA, primarily U.S.) (N=1023)	Study 9 (Knee OA, Europe) (N=987)	Study 11 (LBP) (N=965)	Study 15 (DPN) (N=389)
Age	Mean (SD), years	58 (10)	62 (9)	50 (14)	60 (11)
	< 65 years old	74%	61%	85%	66%
	≥ 65 years old	26%	39%	15%	34%
Sex	Male	40%	28%	42%	60%
	Female	60%	72%	58%	40%
Race	Caucasian	76%	99%	73%	70%
	Black	13%	<1%	17%	12%
	Hispanic	8%	<1%	6%	16%
	Other	4%	<1%	3%	3%
Country	United States	78%	0%	83%	98%
	Canada	17%	0%	16%	2%
	New Zealand	3%	0%	0%	0%
	Australia	2%	0%	1%	0%
	Europe[2]	0%	100%	0%	0%
Weight	Median, kg	94	82	86	99
BMI	Median, kg/m^2	33	30	30	34

1 ITT population: all randomized patients who received at least 1 dose of study medication in Studies 8, 9, and 11 and all randomized patients who received at least 1 dose of study medication in the Randomized Withdrawal Period in Study 15.

2 See Table 9.20 In Section 9.4.2 (the final study report for Study 9) for details about the 12 European countries.

Reference: Adapted from the CSR for Study 8, Table 10, Pages 97-98; adapted from the CSR for Study 9, Table 10, Pages 89-90; adapted from the CSR for Study 11, Table 10, Pages 90-91; adapted from the CSR for Study 15, Table 10, Pages 76-77; JMP KDEMOG datasets for Study 15.

6.1.3 Disease Characteristics

The baseline pain intensity scores and pain severity categories were similar in the treatment groups within each important efficacy trial (Studies 8, 9, 11, and 15). See Tables 9.15, 9.21, 9.28, and 9.35 for the baseline pain intensity scores in Studies 8, 9, 11, and 15, respectively.

As shown, in Table 6.2 the baseline pain intensity scores and severity categories were similar across Studies 8, 9, 11, and 15 and ranged from 7.3 to 7.5 (0 to 10 NRS scale).

Table 6.2: Baseline pain intensity in Studies 8, 9, 11, and 15

		Study 8 (Knee OA, primarily U.S.) (N=1023)[1]	Study 9 (Knee OA, Europe) (N=987)[1]	Study 11 (LBP) (N=965)[1]	Study 15 (DPN)	
					OL Baseline (N=588)	DB Baseline (N=389)
Baseline Pain Intensity Score[2]	Mean (SD)	7.3 (1.3)	7.3 (1.1)	7.5 (1.3)	7.3 (1.4)	3.5 (1.9)
Baseline Pain Intensity Category[3]	Severe	83%	89%	89%	79%	12%
	Moderate	16%	11%	12%	19%	30%
	Mild	<1%	9%	0%	1%	56%
	None	0%	0%	0%	0%	2%

1 For Studies 8, 9, and 11, the number of patients in the ITT population (all randomized patients who received at least 1 dose of study medication). For Study 15, the OL baseline population was all patients who received at least 1 dose of OL tapentadol ER in Study 15 and the DB baseline population was all randomized patients who received at least 1 dose of study medication in the DB Randomized Withdrawal Period.

2 For Studies 8, 9, and 11, baseline pain intensity score is the average pain intensity score, using a 0-10, 11-point NRS, over 72 hours prior to randomization (after the Washout Period). For Study 15, baseline pain intensity prior to the OL baseline and prior to the DB baseline (after 3 weeks of OL tapentadol ER treatment) are displayed.

3 Baseline pain intensity categories of mild, moderate, and severe were defined as scores of 1 to < 4, ≥ 4 to < 6, and ≥ 6, respectively, in Studies 8, 9, and 11. In Study 15, the baseline pain intensity category of none was defined as a score of 0 and the mild category was defined as a score >0 and < 4.

Reference: Adapted from the CSR for Study 8, Table 10, Pages 97-98; adapted from the CSR for Study 9, Table 10, Pages 89-90; adapted from the CSR for Study 11, Table 10, Pages 90-91; adapted from the CSR for Study 15, Table 10, Pages 76-77; Attachment 1.5.1, Pages 188-189

As shown in Table 6.3 almost all patients used analgesics within 3 months prior to initiation of Studies 8, 9, 11, and 15 and almost all patients were dissatisfied with their analgesic medication. The proportion of patients who used opioid analgesics and non-opioid analgesics prior to study treatment was similar in the treatment groups within each important efficacy trial (see Tables 9.16, 9.22, and 9.29 for Studies 8, 9, and 11, respectively (the prior analgesic use for Study 15 is presented in Table 6.3).

The proportion of patients who used non-opioid analgesics prior to treatment was similar across the trials and ranged from 82% to 94%. The proportion of patients who used opioid analgesics prior to treatment ranged from 17% in the European OA trial to 55% in the LBP trial. See Table 6.16 in Section 6.1.8 (Subpopulations) for a subgroup efficacy analysis by prior use of opioid status. The types of opioids and non-opioid analgesics were similar across the U.S. trials (Studies 8, 11, and 15).

Table 6.3: Prior use of analgesic medication in Studies 8, 9, 11, and 15

		Study 8 (Knee OA, primarily U.S.) (N=1023)[1]	Study 9 (Knee OA, Europe) (N=987)[1]	Study 11 (LBP) (N=965)[1]	Study 15 (DPN) OL Baseline (N=588)[2]
Prior Use of Any Analgesic[3]		99%	100%	100%	N/A
Reason for Dissatisfaction With Analgesic	Inadequate analgesia	99%	99%	98%	N/A
	Poor tolerability	1%	1%	2%	
Opioid Analgesics[4]		**35%**	**17%**	**55%**	**22%**
Hydrocodone/acetaminophen		9%	<2%	19%	6%
Codeine/acetaminophen		5%	3%	8%	<2%
Tramadol		4%	5%	4%	2%
Propoxyphene/acetaminophen		4%	<2%	4%	3%
Hydrocodone		3%	<2%	5%	3%
Oxycodone/acetaminophen		3%	<2%	5%	<2%
Tramadol HCl		2%	3%	4%	<2%
Tramadol/acetaminophen		<2%	3%	<2%	<2%
Non-Opioid Analgesics[4]		**87%**	**94%**	**82%**	**83%**
Acetaminophen		29%	23%	26%	32%
Ibuprofen		27%	16%	36%	25%
Aspirin		18%	14%	14%	42%
Celecoxib		12%	<5%	<5%	<5%
Naproxen		8%	<5%	6%	<5%
Meloxicam		7%	<5%	<5%	<5%
Naproxen sodium		6%	<5%	10%	7%
Naproxen/pseudoephedrine		6%	<5%	<5%	<5%
Diclofenac		<5%	25%	<5%	<5%

1 For Studies 8, 9, and 15, the ITT population was all randomized patients who received at least 1 dose of study medication.
2 For Study 15, the OL baseline was all patients who took at least 1 dose of OL tapentadol ER in the OL Titration Period.
3 Prior use was defined as used during the 3 months prior to the Screening Visit
4 Prior use was defined as used prior to the first dose of study medication. Patients may have received more than one analgesic medication prior to the first dose of study medication. For the opioid and non-opioid analgesics, analgesics used in greater than 2% or 5% in the study, respectively, are listed. Note, in Study 9, 9%, 9%, 8%, 7%, and 7% of the patients received meloxicam, ketoprofen, piroxicam, diclofenac sodium, aceclofenac, and/or etoricoxib, respectively.
Reference: Adapted from the CSR for Study 8, Attachment 1.4.1, Page 926; Attachment 1.4.2, Pages 927-928; Attachment 1.4.3, Pages 929-930; adapted from the CSR for Study 9, Attachment 1.4.1, Page 819; Attachment 1.4.2, Page 820; Attachment 1.4.3, Pages 821-823; adapted from the CSR for Study 11, Attachment 1.5.1, Page 260; Attachment 1.5.2, Pages 261-262; Attachment 1.5.3, Pages 263-264; adapted from the CSR for Study 15, Attachment 1.8, Pages 201-202.

6.1.4 Subject Disposition

Table 6.4 displays the disposition of patients by treatment group in the 3 induction Phase 3 trials of tapentadol ER (Studies 8, 9, and 11). Similar to other trials of opioid analgesics in the chronic treatment of pain, there were a large proportion of patients who discontinued study medication over the 15-week Treatment Period. In all 3 trials, the tapentadol ER groups had a lower percentage of patients who discontinued compared to patients in the oxycodone CR groups. In the pooled trials, the

proportion of patients in the tapentadol ER groups that discontinued treatment was similar to the proportion of patients in the placebo groups that discontinued treatment. The majority of discontinuations in the trials occurred during the 3-week Titration Period where patients were forced to increase their study medication (patients randomized to tapentadol ER 50 mg BID automatically increased to 100 mg BID after 3 days and patients randomized to oxycodone CR 10 mg BID automatically increased to 20 mg BID in the beginning of the Titration Period). A lower proportion of patients discontinued study medication during the longer 12-week Maintenance Period where no forced titration occurred.

In all 3 trials, the tapentadol ER group had a lower proportion of AEs leading to discontinuation (DAEs) compared to the oxycodone CR group, but a greater proportion of DAEs compared to the placebo group (see Table 7.6 in Section 7.3.3 for details on the DAEs in these trials). In all 3 trials, the tapentadol ER group had a lower proportion of discontinuations due to a lack of efficacy compared to the placebo group, but had a greater proportion of discontinuations due to a lack of efficacy compared to oxycodone CR. Patients in the 3 treatment groups within each induction Phase 3 trial had similar proportions of patients discontinue due to the following categories: patient choice, other, study medication non-compliant, and lost to follow-up.

Table 6.4: Patient disposition in Studies 8, 9, and 11[1]

	Study 8 (Knee OA)			Study 9 (Knee OA)			Study 11 (LBP)		
	Oxy CR n=342	Tap ER n=344	PL n=337	Oxy CR n=331	Tap ER n=319	PL n=337	Oxy CR n=328	Tap ER n=318	PL n=319
Entire DB Treatment Period (3-week Titration & 12-week Maintenance)									
Completed DB Treatment Period[2]	35%	57%	61%	37%	58%	66%	43%	54%	51%
Discontinued DB Treatment Period	65%	43%	39%	63%	42%	34%	57%	46%	50%
DAE	43%	19%	7%	43%	19%	8%	32%	17%	5%
Patient Choice	10%	11%	8%	15%	11%	8%	11%	10%	9%
Lack of Efficacy	4%	6%	17%	4%	7%	13%	3%	6%	21%
Other	4%	4%	5%	1%	3%	4%	5%	4%	5%
Study Medication Non-compliant	4%	2%	2%	1%	2%	2%	4%	7%	6%
Lost to Follow-up	0%	<1%	<1%	0%	<1%	0%	2%	4%	4%
3-week DB Titration Period									
Discontinuation	49%	23%	25%	45%	24%	17%	39%	26%	34%
12-week DB Maintenance Period									
Discontinuation	15%	20%	14%	19%	18%	17%	17%	20%	16%

DAE is AE leading to discontinuation; Tap ER is tapentadol ER, PL is placebo, and Oxy CR is oxycodone CR.
1 ITT population was randomized patients who received at least 1 dose of study medication. Studies 8 and 11 were primarily conducted in the U.S.; whereas, Study 9 was conducted in Europe.
2 Completion of treatment was defined as completion of the 3-week Titration Period and the 12-Week Maintenance Period.
Reference: Adapted from CSR for Study 8, Table 7, Page 91; adapted from CSR for Study 9, Table 7, Page 83; adapted from CSR for Study 11, Table 7, Page 85.

It is important to make sure that the classification for discontinuations was appropriate because missing data has implications in the interpretation of efficacy in trials of chronic pain because typically the

treatment margins are small and a large proportion of patients do not complete study treatment. Table 6.5 presents cases of probable misclassification of the discontinuation category in the induction trials. Since more placebo-treated patients than tapentadol ER-treated patients in each trial were misclassified as "subject choice", "study medication non-compliant", or "other" reasons and likely discontinued due to lack of efficacy, these misclassifications would not be expected to confound the efficacy results.

In the pooled Studies 8, 9, and 11, 4 oxycodone CR-treated and 3 tapentadol ER-treated patients likely discontinued due to adverse events (DAEs) instead of "subject choice", "study medication non-compliant", or "other" reasons (see Table 6.5). These misclassifications do not change the safety assessment of tapentadol ER because the proportions and types of AEs in these patients were similar to the incidence of DAEs.

Table 6.5: Patients with probable mischaracterization of the discontinuation category in Studies 8, 9, and 11

Treatment Group	Patient #	Study	Original Discontinuation Category	Additional Information
Probable Discontinuation Due to Lack of Efficacy				
Oxycodone CR	803355	8	Patient choice	Receive analgesic medication for knee OA
Oxycodone CR	804785	8	Other	Unsatisfied with pain control
Oxycodone CR	806734	8	Study medication non-compliant	Received analgesic medication for knee OA
Tapentadol ER	805663	8	Other	No Pain relief
Tapentadol ER	806567	8	Subject choice	Patient found medication ineffective
Placebo	803726	8	Other	Lack of efficacy
Placebo	806291	8	Other	Terminated due to lack of efficacy
Placebo	806325	8	Subject choice	Withdrew consent due to lack of efficacy
Placebo	114462	11	Other	Patient received analgesic medication for LBP
Placebo	116090	11	Other	Withdrew due to pain
Probable Discontinuation Due to AE (DAE)				
Oxycodone CR	805711	8	Other	Investigator decision due to unknown AEs
Oxycodone CR	806857	8	Subject Choice	Stopped study medication because of diarrhea, vomiting, and nausea
Oxycodone CR	901046	9	Subject Choice	Discontinued study medication due to HTN, tremor, nausea, palpitations
Oxycodone CR	112933	11	Other	Discontinued due to non-cardiac chest pain (GERD)
Tapentadol ER	806705	8	Other	Knee drainage
Tapentadol ER	806363	8	Study medication non-compliant	Stopped study medication due to AE (influenza like illness)
Tapentadol ER	806580	8	Other	Discontinued due to elevated blood pressure
Tapentadol ER	806700	8	Other	Unable to tolerate study medication

Reference: Subject Discontinuation Listing, Pages 222-453

Table 6.6 displays the patient disposition in the OL and randomized withdrawal periods of Study 15. Of the 588 patients treated with tapentadol ER in the 3-week OL Period, 17% of the patients discontinued due to a DAE (AE leading to discontinuation) and 11% of the patients did not have effective pain control (i.e., 4% discontinued due to lack of efficacy, 4% did not achieve an improvement in the pain intensity of 1 or more and were not randomized, and 4% did not achieve an improvement in pain intensity of 1 or more and were mistakeningly randomized). In the 12-week Randomized Withdrawal Period, a greater

proportion of tapentadol ER-treated patients than placebo-treated patients had a DAE but a lower proportion of tapentadol ER-treated patients than placebo-treated patients discontinued due to lack of efficacy. These findings are consistent with other opioid analgesics in the chronic treatment of pain.

Table 6.6: Patient disposition in Study 15[1]

3-Week OL Treatment Period		
	OL Tapentadol ER (N=588)	
Completed OL Period	390 (66%)	
Discontinued OL Period	198 (34%)	
DAE	17%	
Patient Did Not Fulfill the Criterion for Randomization Into DB[2]	4%	
Patient Choice	4%	
Lack of Efficacy	3%	
Study Medication Non-compliant	3%	
Other	2%	
Lost to Follow-up	1%	
12-week DB Randomized Withdrawal Period[3]		
	Tapentadol ER (n=196)	Placebo (n=193)
Completed DB Randomized Withdrawal Period	137 (70%)	134 (69%)
Discontinued DB Treatment Period	59 (31%)	59 (30%)
DAE	15%	8%
Patient Choice	7%	4%
Lack of Efficacy	4%	14%
Other	2%	3%
Study Medication Non-compliant	2%	1%
Lost to Follow-up	1%	1%

DAE is AE leading to discontinuation.
1 ITT population was randomized patients who received at least 1 dose of study medication.
2 Twenty-one (4%) patients were randomized; although, they did not qualify for randomization (they did not achieve an improvement in pain intensity of at least 1). Therefore, a total of 47 (8%) patients did not fulfill the criterion for randomization in the DB Period.
3 During the first 3 days of the Randomized Withdrawal Period, patients in the placebo group received tapentadol ER 100 mg BID. Patients in both groups were allowed to receive 2 doses of 25 mg of tapentadol ER at least 6 hours apart every day for rescue analgesia during the first four days of the Randomized Withdrawal Period. Also patients were allowed to receive a single 25 mg tapentadol ER dose every day for rescue analgesia from Day 5 through the end of the 12-week Randomized Withdrawal Period.
Reference: Adapted from CSR for Study 15, Table 7, Page 71; Table 8, Page 73.

As in the induction trials, it is important to make sure that the classification for discontinuations was appropriate in the randomized withdrawal trial because missing data has implications in the interpretation of efficacy in trials of chronic pain because typically the treatment margins are small and a large proportion of patients do not complete study treatment. Table 6.7 presents cases of probable misclassification of the discontinuation category in the 3-Week OL Period and the 12-Week Randomized Withdrawal Period in Study 15. Since more placebo-treated patients than tapentadol ER-treated patients were misclassified as "subject choice", "study medication non-compliant", or "other" reasons and likely discontinued due to lack of efficacy in the Randomized Withdrawal Period, these misclassifications would not be expected to confound the efficacy results. Also since an equal number of placebo-treated patients

and tapentadol ER-treated patients were misclassified and likely had a DAE, the safety assessment of tapentadol-ER is not changed by these mischaracterizations.

Table 6.7: Patients with probable mischaracterization of the discontinuation category in Study 15

Treatment Group	Patient #	Original Discontinuation Category	Probable Discontinuation Due to Lack of Efficacy or AE	Additional Information
3-Week OL Period (Tapentadol ER)				
Tapentadol ER	150281	Subject choice	AE	hypoglycemia
Tapentadol ER	150613	Study medication noncompliant	AE	hypoglycemia
Tapentadol ER	151094	Study medication noncompliant	Lack of Efficacy	Study medication not helping
12-Week Randomized DB Withdrawal Period				
Tapentadol ER	150462	Subject choice	AE	Presyncope
Tapentadol ER	150950	Study medication noncompliant	AE	dehydration, urosepsis, inadequate diabetes mellitus control
Placebo	150456	Subject choice	Lack of efficacy and AE	Lack of efficacy and foot ulcer
Placebo	150366	Subject choice	Lack of efficacy	Lack of efficacy
Placebo	151136	Other	Lack of efficacy	Not benefiting from study medication
Placebo	150998	Other	AE	bronchitis

Reference: Subject Discontinuation Listing, Pages 454-524

6.1.5 Analysis of Primary Endpoint

In this section, the analyses of the primary efficacy endpoint results in the 4 DB Phase 3 trials are separated into the induction trials and the randomized withdrawal trial.

Induction Trials: In the 3 induction Phase 3 trials, the primary efficacy endpoint was the change from baseline of the mean pain intensity using an 11-point numerical rating scale (NRS) over the last week of the Maintenance Period (Week 15) for the tapentadol ER and placebo pair-wise comparison. Table 6.8 presents the primary efficacy endpoint using the pre-specified statistical imputation method [last observation carried forward (LOCF)]. Note, that the pair-wise comparisons between oxycodone CR and placebo, and tapentadol ER and oxycodone CR were exploratory.

The tapentadol ER group compared to the placebo group had a greater reduction and a statistically significant change from baseline in pain intensity at Week 15 (using LOCF) in 2 of the 3 induction trials (Studies 8 and 11). Although the treatment margins of the tapentadol ER groups compared to placebo were small (0.7 and 0.8 LS mean difference on an 11-point scale in Studies 8 and 11, respectively) these results are consistent with the treatment margins of other opioid analgesics in chronic pain trials.

The tapentadol ER group had similar or greater treatment margins (when compared to placebo) than oxycodone CR groups (when compared to placebo) in the 3 induction trials. This assay sensitivity is

supportive of the efficacy of tapentadol ER in the chronic treatment of pain. However, no comparative efficacy claims of tapentadol ER to oxycodone CR should be made because these were exploratory analyses. In addition, the maximum oxycodone CR dose allowed in the trials (up to 100 mg per day) was lower than the maximum approved oxycodone CR dose in the labeling (there is no maximum oxycodone CR dose).

Table 6.8: Change from baseline in the mean pain intensity scores at Week 15 in Studies 8, 9, and 11, using LOCF imputation[1]

	Placebo	Tapentadol ER	Oxycodone CR
Study 8			
	n=336	n=344	n=342
Baseline, mean (SD)	7.2 (1.3)	7.4 (1.4)	7.2 (1.3)
Week 12 of Maintenance Period, mean (SD)	5.0 (2.6)	4.4 (2.5)	4.7 (2.4)
Change from Baseline at Week 12, LS mean	-2.3	-2.9	-2.6
LS mean difference (SE) vs. placebo	—	-0.7 (0.2)	-0.3 (0.2)
95% CI vs. placebo	—	(-1.0, -0.3)	(-0.7, < 0.1)
P-value vs. placebo	—	<0.001	0.069
Study 9			
	n=336	n=319	n=331
Baseline, mean (SD)	7.3 (1.1)	7.3 (1.1)	7.3 (1.1)
Week 12 of Maintenance Period, mean (SD)	4.8 (2.5)	4.5 (2.5)	5.0 (2.4)
Change from Baseline at Week 12, LS mean	-2.2	-2.4	-2.1
LS mean difference (SE) vs. placebo	—	-0.2 (0.2)	0.1 (0.2)
95% CI vs. placebo	—	(-0.6, 0.1)	(-0.2, 0.4)
P-value vs. placebo	—	0.135	0.421
Study 11			
	n=316	n=312	n=323
Baseline, mean (SD)	7.6 (1.3)	7.5 (1.3)	7.5 (1.2)
Week 12 of Maintenance Period, mean (SD)	5.5 (2.6)	4.6 (2.7)	4.6 (2.6)
Change from Baseline at Week 12, LS mean	-2.1	-2.9	-2.9
LS mean difference (SE) vs. placebo	—	-0.8 (0.2)	-0.9 (0.2)
95% CI vs. placebo	—	(-1.2, -0.5)	(-1.2, -0.5)
P-value vs. placebo	—	<0.001	<0.001

LS = least squared; SE = standard error; SD is standard deviation

1 Based on an 11-point NRS. ITT patients were all randomized patients who received at least one dose of study medication. Imputation was LOCF, the pre-specified primary method of imputation.

Reference: Adapted from the CSR in Study 8, Table 26, Page 140; Table 27, Page 142; also adapted from the CSR in Study 9, Table 27, Page 130; Table 28, Page 132. Also adapted from the CSR in Study 11, Table 26, Page 130; Table 27, Page 131.

It is essential to assess the efficacy of investigational chronic pain products with conservative imputation methods since chronic pain trials typically have a large proportion of DAEs and it would be inappropriate to impute a good score for a patient who had a DAE. Table 6.9 displays the primary efficacy endpoint results in the 3 induction trials using the conservative baseline carried forward (BOCF) imputation. The tapentadol ER group compared to the placebo group had a statistically significant change from baseline in pain intensity at Week 12 (using BOCF) in only 1 of the 3 trials (Study 8). Using BOCF imputation, the treatment margin of the tapentadol ER group compared to placebo was slighter smaller (0.6 LS mean difference on an 11-point scale in Study 11) than the treatment margins using LOCF imputation. In Study 11, the tapentadol ER group had greater treatment margin when compared to placebo than

oxycodone CR group when compared to placebo. This assay sensitivity is supportive of the efficacy of tapentadol ER in the chronic treatment of pain.

Table 6.9: Change from baseline in the mean pain intensity scores at Week 12 in Studies 8, 9, and 11, BOCF imputation[1]

	Placebo	Tapentadol ER	Oxycodone CR
Study 8			
	n=336	n=344	n=342
Baseline, mean (SD)	7.2 (1.3)	7.4 (1.4)	7.2 (1.3)
Change from Baseline at Week 12, LS mean	-1.7	-2.0	-1.2
LS mean difference (SE) vs. placebo	—	-0.3 (0.2)	0.5 (0.2)
95% CI vs. placebo	—	(-0.6, < 0.1)	(0.2, 0.9)
P-value vs. placebo	—	0.084	0.002
Study 9			
	n=336	n=319	n=331
Baseline, mean (SD)	7.3 (1.1)	7.3 (1.1)	7.3 (1.1)
Change from Baseline at Week 12, LS mean	-1.7	-1.7	-1.1
LS mean difference (SE) vs. placebo	—	0 (0.2)	0.6 (0.2)
95% CI vs. placebo	—	(-0.3, 0.3)	(0.3, 0.9)
P-value vs. placebo	—	0.953	<0.001
Study 11			
	n=316	n=312	n=323
Baseline, mean (SD)	7.6 (1.3)	7.5 (1.3)	7.5 (1.2)
Change from Baseline at Week 12, LS mean	-1.3	-1.8	-1.5
LS mean difference (SE) vs. placebo	—	-0.6 (0.2)	-0.2 (0.2)
95% CI vs. placebo	—	(-0.9, -0.2)	(-0.6, 0.1)
P-value vs. placebo	—	0.002	0.216

LS = least squared; SE = standard error; SD is standard deviation

1 Based on an 11-point NRS), ITT patients were all randomized patients who received at least one dose of study medication. Imputation was with BOCF, an exploratory method of imputation requested by the Agency.

Reference: Adapted from the CSR in Study 8, Table 26, Page 140; Table 27, Page 142; also adapted from the CSR in Study 9, Table 27, Page 130; Table 28, Page 132. Also adapted from the CSR in Study 11, Table 26, Page 130; Table 27, Page 131.

Randomized Withdrawal Trial: In Study 15, the primary efficacy endpoint was the change from the DB baseline in the mean pain intensity using an 11-point (0-10) NRS over the last week of the Randomized Withdrawal Period (Week 15). Table 6.10 displays the results of the primary endpoint using the primary statistical imputation (LOCF) and a very conservative statistical imputation (OL BOCF). Note, the LOCF analysis was preformed by J & J and the conservative imputation was performed by Dr. Yan Zhou, the statistical reviewer.

In both analyses, the tapentadol ER group compared to the placebo group achieved a less worsening in the pain intensity at Week 15 and both results were statistically significant. The treatment margin in this randomized withdrawal trial (1.1 LS mean difference between tapentadol ER and placebo, using conservative imputation) was greater than the treatment margin in the positive induction trial (0.6 LS mean difference in Study 11 using conservative imputation). The greater treatment margin was likely due to the enriched design of the randomized withdrawal trial (the selection of patients who had a positive response to tapentadol ER during the 3-week OL Period).

Table 6.10: Change from DB baseline in the mean pain intensity scores at Week 15 in Study 15[1]

LOCF Imputation (Pre-Specified Primary Method of Imputation)[1]		
	Placebo (n=192)	**Tapentadol ER (n=193)**
Baseline, mean (SD)	**3.4 (1.9)**	**3.6 (1.9)**
Week 12 of Maintenance Period, mean (SD)	**4.7 (2.5)**	**3.5 (2.1)**
Change from Baseline at Week 12, LS mean	**1.4**	**0**
LS mean difference (SE) vs. placebo	**—**	**-1.3 (0.2)**
95% CI vs. placebo	**—**	**(-1.7, -0.9)**
P-value vs. placebo	**—**	**<0.001**
OL BOCF Imputation[2]		
	Placebo (n=188)	**Tapentadol ER (n=179)**
Change from Baseline at Week 12, LS mean	**2.1**	**1.0**
LS mean difference (SE) vs. placebo	**—**	**-1.1 (0.2)**
95% CI vs. placebo	**—**	**(-1.5;-0.7)**
P-value vs. placebo	**—**	**<0.001**

LS = least squared; SE = standard error; SD is standard deviation
1 Sponsor's analysis using LOCF. ITT patients were all randomized patients who received at least one dose of study medication in the DB period.
2 Dr. Zhou's conservative analysis using OL BOCF. Dr. Zhou did not include the 21 patients who were randomized but did not achieve an improvement in the change in pain intensity of 1 or more during the 3-week OL Titration Period.
Reference: Adapted from the CSR in Study 15, Table 18, Page 93; Table 19, Page 94.

6.1.6 Analysis of Secondary Endpoints

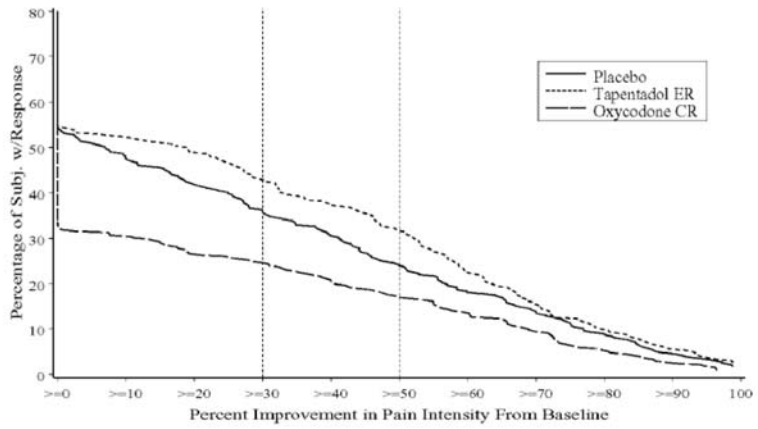
Induction Trials (Studies 8, 9, and 11)

There were multiple pre-specified secondary endpoints in the induction trials (there were approximately 166, 158, and 159 endpoints in Studies 8, 9, and 11, respectively — see the individual study reports in Sections 9.4.1, 9.4.2, and 9.4.3 for more details). Since there was no appropriate statistical gate-keeping for these endpoints, these endpoints will be considered exploratory.

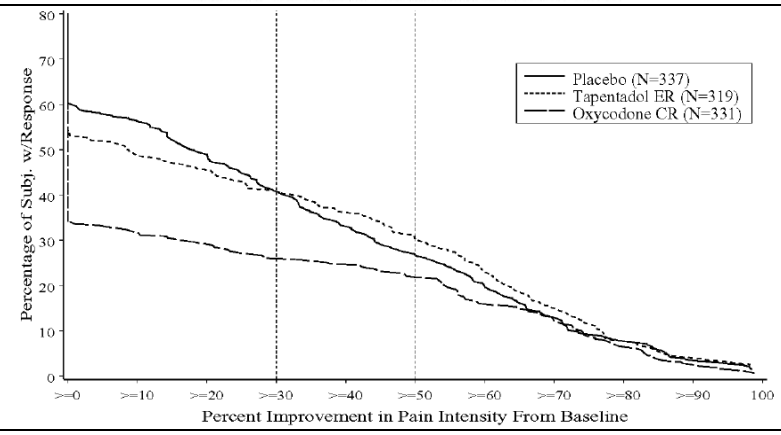
Continuous Responder Analysis: Figure 6.11 displays the distribution of responders (the proportion of patients achieving various levels of improvement in pain intensity based on the percent change from baseline at Week 15) which was a pre-specified endpoint in the 3 induction trials (Studies 8, 9, and 11). [redacted] (b) (4) However, the non-parametric test on the distribution of responder curves for the pairwise comparison of the tapentadol ER and placebo groups in Study 8 was not statistically significant using the Kolmogorov-Smirnov Test according to Dr. Yan Zhou, the statistical reviewer (p value = 0.010). [redacted] (b) (4)

Figure 6.11: Distribution of responder rates (percent change from baseline in pain intensity at Week 15) in Studies 8, 9, and 11

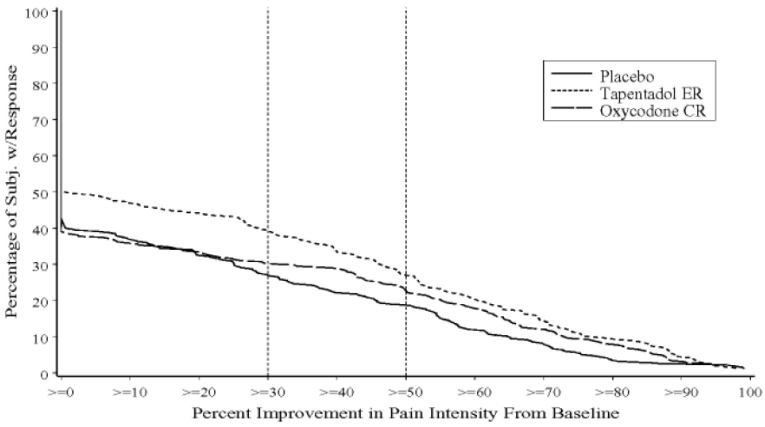
Study 8



Study 9



Study 11



1 Using the ITT population with a non-responder imputation (patients who worsened or prematurely discontinued prior to the end of the Week 15 were assigned a value of 0 and patients with no change were assigned a value close to zero). Responder rates for a given percent improvement value were defined as the proportion of patients equal to and above that threshold value, where threshold values was presented as 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%. The distribution of time to improvement was estimated by the Kaplan-Meier estimate and compared among the treatment groups using the log-rank test.

Reference: Adapted from the CSR of Study 8, Figure 15, Page 150, adapted from the CSR of Study 9, Figure 14, Page 138, and adapted from the CSR of Study 11, Figure 15, Page 137.

Proportion of Patients Who Achieved At Least a 30% or 50% Improvement: Table 6.12 Displays the proportion of patients who achieved at least 30% or at least 50% improvement in the change from baseline in pain intensity at Week 15 (these two analyses, derived from the continuous responder curves, were pre-specified secondary endpoints in the 3 induction trials). In Study 11, the tapentadol ER group compared to the placebo group demonstrated a statistically significant difference in the proportion of patients who achieved a 30% or 50% improvement from baseline. In Study 8, the tapentadol ER group compared to the placebo group demonstrated a 30% significant improvement, but failed to demonstrate a significant difference in the proportion of patients with a 50% improvement. In Study 9, there were no significant differences between the tapentadol ER and placebo groups. These results are consistent with the primary efficacy endpoint results using conservative imputation that Study 11 was a positive trial and Studies 8 and 9 were negative trials.

Table 6.12: Proportion of patients achieving 30% or 50% improvement from baseline in pain intensity at Week 15 in Studies 8, 9, and 11[1]

	Placebo	Tapentadol ER	Oxycodone CR
Study 8			
	n=337	n=344	n=342
> 0% improvement[2]	53%	54%	33%
≥ 30% improvement (p-value vs. placebo)[3]	36% (—)	43% (0.058)	25% (0.002)
≥ 50% improvement (p-value vs. placebo)[3]	24% (—)	32% (0.027)	17% (0.023)
Study 9			
	n=337	n=319	n=331
> 0% improvement[2]	60%	53%	34%
≥ 30% improvement (p-value vs. placebo)[3]	41% (—)	41% (0.976)	26% (<0.001)
≥ 50% improvement (p-value vs. placebo)[3]	27% (—)	31% (0.256)	22% (0.138)
Study 11			
	n=317	n=315	n=326
> 0% improvement[2]	40%	50%	39%
≥ 30% improvement (p-value vs. placebo)[3]	27% (—)	40% (<0.001)	30% (0.365)
≥ 50% improvement (p-value vs. placebo)[3]	19% (—)	27% (0.016)	23% (0.174)

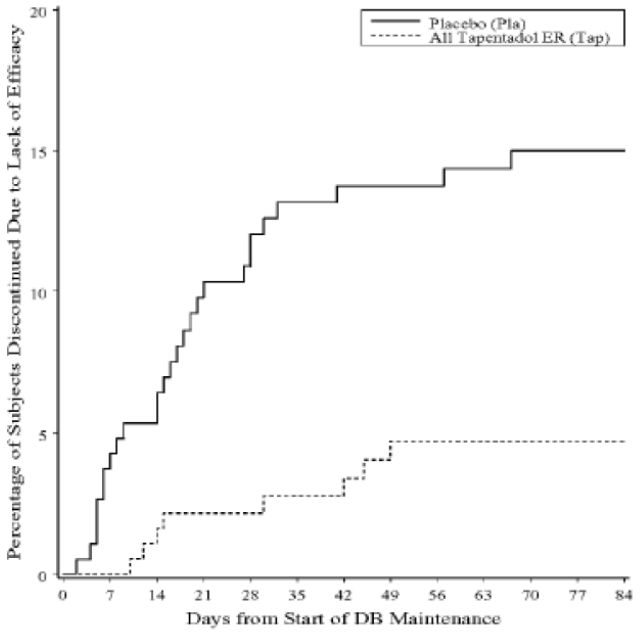
1 Using the ITT population with a non-responder imputation (patients who worsened or prematurely discontinued prior to the end of the Week 15 were assigned a value of 0 and patients with no change were assigned a value close to zero).
2 Responders were patients who had any improvement in pain intensity at Week 15 from baseline (> 0% improvement).
3 Pairwise comparison using the Cochran-Mantel-Haenszel test, using the ITT population.
Reference: Adapted from the CSR in Study 8, Attachment 3.4.2, Page 1276; Table 34, Page 151; adapted from the CSR in Study 9, Attachment 3.4.1, Page 5980; Table 33, Page 139; adapted from the CSR in Study 11, Attachment 3.7.1, Page 606; Table 31, Page 138.

Randomized Withdrawal Trial

In Study 15, the time to treatment discontinuation due to lack of efficacy was calculated in days as the duration from the start of the DB Randomized Withdrawal Period to treatment discontinuation due to

lack of efficacy (see Figure 6.13). This analysis, a pre-specified secondary endpoint in Study 15, is frequently used in randomized withdrawal trials to assess efficacy. In Study 15, 8 (4%) and 27 (14%) of tapentadol ER-treated patients and placebo-treated patients, respectively, discontinued due to lack of efficacy. The percentage of patients who discontinued due to lack of efficacy was statistically significantly lower in the tapentadol ER group than the placebo group.

Figure 6.13: Time to discontinuation due to lack of efficacy in the Randomized Withdrawal Period in Study 15[1]



1 Patients who completed the DB period of the study were censored at the last observation time point. Patients who discontinued from the DB Period for reason other than lack of efficacy were censored at the time of discontinuation. The distribution of the time to treatment discontinuation due to lack of efficacy was estimated by the Kaplan-Meier estimate and compared among the treatment groups using the log-rank test.
Reference: Adapted from the CSR in Study 15, Figure 9, Page 104.

6.1.7 Other Endpoints

Concomitant Analgesic Use During the Treatment Period: Table 6.14 displays the percent of patients who received concomitant analgesic medication and rescue medication during the DB Treatment Periods of Studies 8, 9, and 11. In all 3 induction trials, a greater proportion of placebo-treated patients compared to tapentadol ER-treated patients received concomitant opioid analgesics, concomitant non-opioid analgesic, and received rescue acetaminophen. Also in Studies 8 and 11, placebo-treated patients received acetaminophen for a greater number of days than tapentadol ER-treated patients. Lower utilization of analgesics in the tapentadol ER group compared to the placebo group supports the efficacy of tapentadol ER in the chronic treatment of pain.

Table 6.14: Concomitant analgesic medication and rescue analgesic medication use during the DB Treatment Period in Studies 8, 9, and 11[1]

Study 8	Placebo (n=337)	Tapentadol ER (n=344)	Oxycodone CR (n=342)
Concomitant Medication			
Opioid Analgesics	7%	4%	4%
Non-Opioid Analgesics	34%	28%	29%
Rescue Analgesic Medication (acetaminophen) 15-Week DB Period (Titration and Maintenance Periods)[2]			
% who took rescue acetaminophen	68%	64%	59%
Median # of days of acetaminophen use	7.0	5.0	4.0
Study 9	**Placebo (n=337)**	**Tapentadol ER (n=319)**	**Oxycodone CR (n=331)**
Concomitant Medication			
Opioid Analgesics	4%	3%	4%
Non-Opioid Analgesics	25%	24%	23%
Rescue Analgesic Medication (acetaminophen) 15-Week DB Period (Titration and Maintenance Periods)[2]			
% who took rescue acetaminophen	66%	56%	47%
Median # of days of acetaminophen use	5.0	5.0	3.5
Study 11	**Placebo (n=319)**	**Tapentadol ER (n=318)**	**Oxycodone CR (n=328)**
Concomitant Medication			
Opioid Analgesics	13%	11%	8%
Non-Opioid Analgesics	34%	32%	31%
Rescue Analgesic Medication (acetaminophen) 15-Week DB Period (Titration and Maintenance Periods)[2]			
% who took rescue acetaminophen	73%	69%	60%
Median # of days of acetaminophen use	7.0	5.5	4.0

1 ITT population were all randomized patients who received at least 1 dose of study medication.
2 During the DB Period, acetaminophen up to 1,000 mg/day was allowed for rescue during the Titration Period (except during the last 3 days) and during the Maintenance Period, up to 1000 mg daily for no more than 3 consecutive days for non-study related pain was allowed. The overwhelming majority of rescue medication was taken in the 3-Week Titration Periods.
Reference: Adapted from the CSR for Study 8, Attachment 1.4.5, Pages 948; Attachment 1.4.6, Pages 949-950; Table 14, Page 104; Adapted from the CSR for Study 9, Attachment 1.4.5, Page 839; Attachment 1.4.6, Pages 840-841; Table 14, Page 96; Adapted from the CSR for Study 11, Attachment 1.5.5, Pages 282; Attachment 1.5.6, Pages 283-284; Table 15, Page 97.

Table 6.15 displays the percent of patients who received concomitant analgesic medication and rescue medication during the OL and DB Treatment Periods of Study 15. In the DB, Randomized Withdrawal Period, a slightly lower proportion of tapentadol ER-treated patients compared to placebo-treated patients received non-opioid analgesics and took rescue tapentadol ER; whereas, a slightly higher proportion of tapentadol ER-treated patients received concomitant opioid analgesics than placebo-treated patients.

Table 6.15: Concomitant analgesic medication and rescue analgesic medication use during the OL Titration Period and the DB Randomized Withdrawal Period in Study 15

OL Titration Period[1]		
	OL Tapentadol ER (N=588)	
Opioid Analgesics	**3%**	
Non-Opioid Analgesics	**47%**	
% who took rescue acetaminophen[2]	**39%**	
For patients who took rescue acetaminophen, median # of days of use[2]	**4.0**	
DB Maintenance Period[3]		
	Placebo (n=193)	**Tapentadol ER (n=196)**
Opioid Analgesics	**5%**	**7%**
Non-Opioid Analgesics	**53%**	**47%**
% who took rescue tapentadol ER[4]	**45%**	**39%**
For patients who took rescue tapentadol ER, % of days rescue tapentadol ER taken[4]	**17%**	**10%**

1 All patients who received at least 1 dose of tapentadol ER in the OL Titration Period.
2 Acetaminophen up to 2000 mg/day was allowed during the OL Titration Period except the last 4 days of the Titration Period (acetaminophen was not allowed during the Randomized Withdrawal Period).
3 ITT population was all randomized patients who received at least 1 dose of study medication in the Randomized Withdrawal Period.
4 Tapentadol ER 25 mg was allowed (a maximum of two doses at least 6 hours apart each day) as rescue analgesia during the first 4 days of the DB Randomized Withdrawal period. From Day 5 through the end of the DB Randomized Withdrawal period, patients were allowed a single dose of 25 mg of tapentadol ER every day for rescue.
Reference: Adapted from the CSR for Study 15, Attachment 1.9.1, Page 217; Attachment 1.9.2, Page 232; also adapted from the CSR for Study 15, Attachment 1.10, Page 263, Table 15, Page 86.

6.1.8 Subpopulations

Table 6.16 displays the subgroup efficacy analyses by demographic and baseline characteristics using the pre-specified primary endpoint (change from baseline in mean pain intensity at Week 15) in the induction trials (Studies 8, 9, and 11). In almost all subgroups, the tapentadol ER group had numerical improvements compared to the placebo group in the change in pain intensity. There did not appear to be a subpopulation of patients that responded better to tapentadol ER compared to placebo in all 3 induction trials.

Table 6.16: Change from baseline in mean pain intensity at Week 15 (LS mean) by demographic and baseline characteristics in Studies 8, 9, and 11[1]

		Study 8 (knee OA)		Study 9[2] (Europe, knee OA)		Study 11 (LBP)	
		Tapentadol ER	Placebo	Tapentadol ER	Placebo	Tapentadol ER	Placebo
Entire Study		-2.9 (n=344)	-2.3 (n=336)	-2.4 (n=319)	-2.2 (n=336)	-2.9 (n=312)	-2.1 (n=316)
Prior Opioid Use	No	-3.0 (n=235)	-2.3 (n=223)	-2.9 (n=267)	-2.5 (n=281)	-3.2 (n=136)	-2.2 (n=144)
	Yes	-2.9 (n=109)	-2.0 (n=114)	-2.2 (n=52)	-2.4 (n=55)	-2.6 (n=176)	-2.0 (n=172)
Baseline Pain Intensity Category	Moderate	-2.1 (n=49)	-1.4 (n=61)	-2.5 (n=35)	-1.8 (n=42)	-2.4 (n=35)	-1.1 (n=40)
	Severe	-3.1 (n=293)	-2.4 (n=275)	-2.8 (n=284)	-2.5 (n=294)	-3.0 (n=277)	-2.2 (n=276)
Gender	Male	-2.6 (n=128)	-1.9 (n=137)	-2.9 (n=88)	-2.6 (n=80)	-2.7 (n=122)	-1.9 (n=134)
	Female	-3.2 (n=216)	-2.4 (n=200)	-2.7 (n=231)	-2.4 (n=256)	-3.1 (n=190)	-2.2 (n=182)
Age	< 65	-3.1 (n=249)	-2.3 (n=259)	-2.8 (n=194)	-2.7 (n=193)	-3.0 (n=273)	-2.2 (n=263)
	≥ 65	-2.5 (n=95)	-1.7 (n=77)	-2.7 (n=125)	-2.1 (n=143)	-2.4 (n=39)	-1.6 (n=53)
Race	Caucasian	-2.8 (n=260)	-2.2 (n=266)	—	—	-2.8 (n=226)	-2.0 (n=235)
	Black	-3.8 (n=49)	-2.5 (n=38)	—	—	-3.5 (n=59)	-2.6 (n=49)
	Hispanic	-2.6 (n=21)	-2.2 (n=20)	—	—	-2.5 (n=18)	-2.6 (n=21)
Country	Canada	-2.7 (n=62)	-1.5 (n=58)	—	—	-2.0 (n=53)	-1.8 (n=48)
	U.S.	-3.0 (n=265)	-2.3 (n=258)	—	—	-3.1 (n=256)	-2.1 (n=265)

1 The primary statistical imputation (LOCF) was used. ITT population was all randomized patients who received at least 1 dose of study medication. Only the tapentadol ER and placebo groups are included in this table because these groups were included in the primary statistical comparison (the oxycodone CR group was not included in the primary statistical comparison).

2 There were few non-Caucasian patients in Study 9 (the European study) and these analyses are not displayed in this table.

Reference: Study 8 CSR: Attachment 3.12.2, Pages 1670-1675; Attachment 3.13.1, Pages 1680-1685; Attachment 3.13.2, Pages 1686-1671; Attachment 3.13.3, Pages 1692-1703; Attachment 3.14.1, Pages 1704-1715; Study 9 CSR: Attachment 3.11.2, Pages 6342-6347; Attachment 3.12.3, Pages 6358-6363; Attachment 3.13.1, Pages 6364-6369; Study 11 CSR: Attachment 3.14.2, Pages 697-702; Attachment 3.15.2, Pages 709-714; Attachment 3.17, Pages 725-730; Attachment 3.18, Pages 731-742; Attachment 3.19, Pages 743-751

The tapentadol ER group had numerical improvements compared to the placebo group in the change from DB baseline in the mean pain intensity at Week 15 in the demographic groups and prior opioid status subpopulations in the randomized withdrawal trial (see Table 6.17).

Table 6.17: Change from DB baseline in mean pain intensity at Week 15 (LS mean) by demographic and baseline characteristic subgroups in Study 15[1]

		Tapentadol ER	Placebo
Entire Study		**0.0 (n=193)**	**1.4 (n=192)**
Prior Opioid Use	No	-0.2 (n=127)	1.2 (n=127)
	Yes	0.0 (n=66)	1.4 (n=65)
Baseline Pain Intensity Category	Mild	0.2 (n=103)	1.8 (n=113)
	Moderate	-0.5 (n=65)	0.4 (n=50)
	Severe	-0.6 (n=22)	0.0 (n=24)
Gender	Male	0.1 (n=118)	1.2 (n=115)
	Female	-0.3 (n=75)	1.4 (n=77)
Age	< 65	-0.2 (n=133)	1.2 (n=119)
	≥ 65	0.1 (n=60)	1.5 (n=73)
Race	Caucasian	0.1 (n=135)	1.5 (n=134)
	Black	-0.6 (n=26)	0.3 (n=19)
	Hispanic	-0.1 (n=27)	1.0 (n=34)

1 Using LOCF imputation (primary statistical imputation). ITT population was all randomized patients who received at least 1 dose of study medication). There were too few patients from non-U.S. countries, thus, subgroup efficacy analyses by country were not included in this table.

Reference: Study 8 CSR: Attachment 3.91., Pages 521-526; Attachment 3.9.3, Pages 529-531; Attachment 3.9.4, Pages 532-534; Attachment 3.9.5; pages 535-537; Attachment 3.9.6, Pages 538-542

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

As shown in Tables 6.18 and 6.19, in the induction trials patients taking higher doses of tapentadol ER or oxycodone CR compared to patients taking lower doses had lower responses at Weeks 9 and 12, respectively. Patients taking higher doses of tapentadol ER and oxycodone CR likely represented a more refractory population with more opioid requirements than patients taking lower doses.

Table 6.18: Change from baseline in mean pain intensity at Week 15 (LS mean) of the Maintenance Period by tapentadol ER and oxycodone CR dose category in Studies 8, 9, and 11

	Study 8 (knee OA)		Study 9 (Europe, knee OA)		Study 11 (LBP)	
	Tapentadol ER	Oxycodone CR	Tapentadol ER	Oxycodone CR	Tapentadol ER	Oxycodone CR
Entire Study (Observed Data)[1]	-3.8 (n=191)	-3.5 (n=119)	-3.4 (n=183)	-3.5 (n=119)	—	—
50 to < 100 mg BID: tapentadol ER (10 to < 20 mg BID: oxycodone CR)	-3.5 (n=1)	-1.7 (n=1)	-4.1 (n=1)	—	—	—
100 to < 150 mg BID: tapentadol ER (20 to < 30 mg BID: oxycodone CR)	-4.2 (n=46)	-3.6 (n=27)	-3.7 (n=70)	-3.9 (n=68)	-4.6 (n=30)	-4.5 (n=24)
150 to < 200 mg BID: tapentadol ER (30 to < 40 mg BID: oxycodone CR)	-4.0 (n=30)	-3.8 (n=28)	-3.5 (n=39)	-4.0 (n=22)	-4.0 (n=30)	-4.1 (n=34)
200 to < 250 mg BID: tapentadol ER (40 to < 50 mg BID: oxycodone CR)	-3.9 (n=47)	-3.6 (n=27)	-3.5 (n=42)	-3.4 (n=20)	-3.8 (n=24)	-4.1 (n=33)
≥ 250 mg BID: tapentadol ER (≥ 50 mg BID: oxycodone CR)	-3.7 (n=68)	-3.5 (n=37)	-2.8 (n=34)	-3.2 (n=10)	-3.3 (n=83)	-3.0 (n=45)

1 Observed data. Patients may not have been within the dose category during the entire 12-week Maintenance Period.
Reference: CSR for Study 8; Table 31, Page 144, Attachment 3.15.1, Pages 1986-1995; CSR for Study 9; Table 32, Page 134, Attachment 3.15.1, Pages 6604-6613; CSR for Study 11; Attachment 3.21, Pages 1001-1010

Table 6.19: Change from baseline in mean pain intensity at Week 9 (LS mean) of the Maintenance Period by tapentadol ER and oxycodone CR dose category in Studies 8, 9, and 11

	Study 8 (knee OA)		Study 9 (Europe, knee OA)		Study 11 (LBP)	
	Tapentadol ER	Oxycodone CR	Tapentadol ER	Oxycodone CR	Tapentadol ER	Oxycodone CR
Entire Study (Observed Data)[1]	-3.8 (n=191)	-3.5 (n=119)	-3.4 (n=183)	-3.5 (n=119)	—	—
50 to < 100 mg BID: tapentadol ER (10 to < 20 mg BID: oxycodone CR)	—	—	-3.0 (n=2)	—	—	—
100 to < 150 mg BID: tapentadol ER (20 to < 30 mg BID: oxycodone CR)	-4.1 (n=53)	-3.6 (n=33)	-3.4 (n=83)	-3.4 (n=75)	-4.1 (n=37)	-4.3 (n=33)
150 to < 200 mg BID: tapentadol ER (30 to < 40 mg BID: oxycodone CR)	-3.7 (n=44)	-3.8 (n=27)	-3.1 (n=40)	-3.3 (n=30)	-3.7 (n=31)	-4.4 (n=37)
200 to < 250 mg BID: tapentadol ER (40 to < 50 mg BID: oxycodone CR)	-3.7 (n=49)	-2.8 (n=43)	-2.8 (n=46)	-2.9 (n=26)	-3.7 (n=38)	-3.9 (n=48)
≥ 250 mg BID: tapentadol ER (≥ 50 mg BID: oxycodone CR)	-3.3 (n=66)	-3.7 (n=36)	-3.1 (n=32)	-2.2 (n=7)	-3.2 (n=89)	-3.2 (n=44)

1 Observed data. Patients may not have been within the dose category during the entire 12-week Maintenance Period.
Reference: CSR for Study 8; Table 31, Page 144, Attachment 3.15.1, Pages 1986-1995; CSR for Study 9; Table 32, Page 134, Attachment 3.15.1, Pages 6604-6613; CSR for Study 11; Attachment 3.21, Pages 1001-1010

As shown in Table 6.20, all of the tapentadol ER doses in the randomized withdrawal Period of Study 15 had numerical improvements in the change from DB baseline in pain intensity at Week 15. There was no clear dose-response relationship. This supports the efficacy of higher tapentadol ER doses (200 to 250 mg BID) in the chronic treatment of pain.

Table 6.20: Change from DB baseline in mean pain intensity at Week 15 (LS mean) by tapentadol ER and oxycodone CR dose category in Study 15[1]

	Tapentadol ER	Placebo
Entire Study	**0.1 (n=129)**	**1.1 (n=130)**
Tapentadol ER 100 mg BID	**-0.4 (n=19)**	**—**
Tapentadol ER 150 mg BID	**0.0 (n=24)**	**—**
Tapentadol ER 200 mg BID	**0.0 (n=21)**	**—**
Tapentadol ER 250 mg BID	**-0.3 (n=65)**	**—**

1 Subgroup analyses of observed data using LOCF. In this trial, all patients were maintained on the identical tapentadol ER dose after they responded in the OL Period.

Reference: CSR of Study 15, Table 20, Page 96, Attachment 3.9.10, Pages 551-552.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary efficacy endpoints in the 4 Phase 3 trials (i.e., Studies 8, 9, 11, and 15) were measured during the last week of the trials (i.e., Week 15 of the Maintenance Periods). Therefore, the positive efficacy results using conservative imputation in Studies 11 and 15 support the persistence of efficacy of tapentadol ER for the chronic treatment of pain. See Section 6.1.5 (Analysis of the Primary Endpoint) for more details.

Table 6.21 presents an additional evaluation of the efficacy of tapentadol ER compared to placebo over time in the induction trials (the change in mean pain intensity from baseline). Over the course of the trials, the numerical improvements of tapentadol ER groups compared to the placebo groups either were the same (Study 9) or improved (Studies 8 and 11). One limitation of this analysis is that it does not include patients who discontinued study medication due to lack of efficacy, although a small percentage of tapentadol ER-treated patients discontinued due to lack of efficacy in the Maintenance Period.

Table 6.21: Change from baseline in mean pain intensity (LS mean) over time in Studies 8, 9, and 11[1]

	Study 8		Study 9		Study 11	
	Tapentadol ER	Placebo	Tapentadol ER	Placebo	Tapentadol ER	Placebo
Titration Period						
Week 1	-1.0 (n=342)	-0.7 (n=333)	-0.7 (n=318)	-0.7 (n=336)	-1.0 (n=310)	-0.8 (n=313)
Week 2	-2.1 (n=316)	-1.5 (n=302)	-1.5 (n=300)	-1.4 (n=326)	-1.8 (n=281)	-1.5 (n=284)
Week 3	-2.7 (n=287)	-2.0 (n=283)	-2.0 (n=275)	-1.8 (n=309)	-2.5 (n=253)	-2.0 (n=248)
Maintenance Period						
Week 1	-3.1 (n=267)	-2.4 (n=261)	-2.5 (n=247)	-2.2 (n=282)	-3.0 (n=230)	-2.3 (n=218)
Week 2	-3.4 (n=254)	-2.6 (n=248)	-2.6 (n=233)	-2.3 (n=272)	-3.2 (n=222)	-2.5 (n=195)
Week 3	-3.5 (n=239)	-2.7 (n=244)	-2.8 (n=222)	-2.5 (n=256)	-3.3 (n=211)	-2.7 (n=186)
Week 4	-3.6 (n=232)	-2.8 (n=234)	-2.9 (n=215)	-2.5 (n=250)	-3.4 (n=203)	-2.8 (n=181)
Week 5	-3.7 (n=218)	-2.8 (n=232)	-3.1 (n=208)	-2.7 (n=239)	-3.4 (n=200)	-2.8 (n=177)
Week 6	-3.8 (n=212)	-2.9 (n=228)	-3.1 (n=201)	-2.8 (n=230)	-3.5 (n=196)	-2.9 (n=172)
Week 7	-3.8 (n=208)	-2.9 (n=227)	-3.2 (n=195)	-2.8 (n=228)	-3.6 (n=190)	-2.8 (n=170)
Week 8	-3.8 (n=203)	-3.0 (n=222)	-3.2 (n=192)	-2.9 (n=227)	-3.7 (n=183)	-2.7 (n=167)
Week 9	-3.8 (n=200)	-2.9 (n=216)	-3.2 (n=191)	-3.0 (n=226)	-3.7 (n=182)	-2.7 (n=166)
Week 10	-3.8 (n=196)	-2.8 (n=214)	-3.3 (n=189)	-3.0 (n=226)	-3.7 (n=177)	-2.8 (n=160)
Week 11	-3.9 (n=197)	-2.9 (n=209)	-3.4 (n=185)	-3.1 (n=225)	-3.6 (n=171)	-2.7 (n=159)
Week 12	-3.9 (n=192)	-2.9 (n=206)	-3.4 (n=185)	-3.0 (n=218)	-3.7 (n=167)	-2.8 (n=153)

1 ITT population with observed data

Reference: CSR of Study 8, Attachment 3.1.1, Pages 1205-1206; CSR of Study 9, Attachment 3.1.1, Pages 1136-1137; CSR of Study 11, Pages 538-539

Opioid products have been associated with drug tolerance (i.e., greater doses are required to achieve the same effect with increased duration of therapy). Therefore, it is important to assess for possible drug tolerance with tapentadol ER with increased duration of use. Table 6.22 displays the proportion of patients in the Maintenance Periods of the 3 induction trials that had increases in their dose. One limitation of this analysis is that it does not include patients who discontinued study medication due to lack of efficacy, although a small percentage of tapentadol ER-treated patients discontinued due to lack of efficacy in the Maintenance Period.

In the induction trials a large proportion of tapentadol ER-treated patients had increases in their initial Maintenance Period dose (43% to 57%). The tapentadol ER groups did not appear to have a greater proportion of dose increases compared to the placebo and oxycodone CR groups. From these analyses, it does not appear that tapentadol ER had worse tolerance than oxycodone CR. Since opioid products are known to have drug tolerance and the above analyses have limitations, the tapentadol ER label should contain the standard drug tolerance language for opioid products.

Table 6.22: Proportion of patients with dose increase during the Maintenance Periods of Studies 8, 9, and 11[1]

	Placebo	Tapentadol ER	Oxycodone CR
Study 8			
n[2]	n=254	n=264	n=173
Any dose increase	55%	49%	52%
≥ 3 dose increases	11%	11%	15%
Study 9			
n[2]	n=279	n=242	n=183
Any dose increase	45%	43%	36%
≥ 3 dose increases	6%	5%	3%
Study 11			
n[2]	n=211	n=235	n=199
Any dose increase	59%	57%	59%
≥ 3 dose increases	13%	19%	17%

1 Missed doses were not considered dose changes
2 The number of patients who received study medication during the Maintenance Period.
Reference: CSR of Study 8, Attachment 1.8.3, Page 1133, Attachment 1.8.4, Page 1135; CSR of Study 9, Attachment 1.8.3, Page 1032, Attachment 1.8.4, Page 1034; CSR of Study 11, Attachment 1.9.3, Page 458, Attachment 1.9.4, Page 460

It is also important to assess evidence of drug tachyphylaxis (i.e., decreasing efficacy to a drug following administration of the initial dose) for opioid products. The design of the Phase 3 induction trials did not allow for direct evidence of tapentadol ER tachyphylaxis because the tapentadol ER dose was not constant throughout the Treatment Period — up titration of study medication was allowed if there was evidence of decreased effect. In addition, the design of the Phase 2 trials also did not allow for evaluation of tachyphylaxis because the trials either had flexible dosing (Studies KF09 and KF10) or the fixed dose periods were too short, i.e., 2 weeks, (Studies 1 and 2) to assess tachyphylaxis.

In Study 15 the dose of tapentadol ER was constant in the 12-week Randomized Withdrawal Period. Table 6.23 shows the mean pain intensity over time in the Randomized Withdrawal Period of Study 15. In this trial, the mean pain intensity in the tapentadol ER group did not decrease over time. One limitation of this analysis is that it does not include patients who discontinued study medication due to lack of efficacy; although a small percentage of tapentadol ER-treated patients discontinued due to lack of efficacy in the Randomized Withdrawal Period. There appeared no clear evidence of tachyphylaxis of tapentadol ER in Study 15.

Table 6.23: Mean pain intensity over time in the Randomized-Withdrawal Period of Study 15[1]

	Tapentadol ER	Placebo
Start DB Period	3.6 (n=193)	3.4 (n=192)
Week 4	3.8 (n=196)	4.2 (n=191)
Week 5	3.7 (n=190)	4.5 (n=174)
Week 6	3.5 (n=171)	4.5 (n=168)
Week 7	3.5 (n=163)	4.5 (n=154)
Week 8	3.5 (n=156)	4.4 (n=149)
Week 9	3.4 (n=153)	4.3 (n=145)
Week 10	3.3 (n=148)	4.2 (n=142)
Week 11	3.3 (n=138)	4.2 (n=139)
Week 12	3.3 (n=136)	4.2 (n=137)
Week 13	3.3 (n=135)	4.2 (n=135)
Week 14	3.3 (n=133)	4.3 (n=132)
Week 15	3.3 (n=130)	4.2 (n=130)

1 ITT population (patients randomized in the DB Treatment Period who received at least one dose of study medication) using observed data. The Randomized-Withdrawal Period was from Weeks 4 to 15.
Reference: CSR of Study 15, Attachment 3.1.1, Pages 423-424.

6.1.11 Additional Efficacy Issues/Analyses

J & J recommends that language be placed in the Dosage and Administration section of the tapentadol ER label regarding the conversion from immediate-release tapentadol (tapentadol IR) to tapentadol ER. J & J states that results from Study 19 support these claims in the label.

Study 19 was a randomized, DB, MC, 2-period crossover Phase 2 trial in patients with chronic non-malignant LBP to establish the conversion ratio between tapentadol IR and ER. After washout of analgesic medications, all patients with a mean pain intensity score ≥ 5 on an 11-point NRS received 50 mg of OL tapentadol IR QID (200 mg/day) at the start of the 3-week Titration Period. The dose could be changed to achieve meaningful analgesia within the following range: 200 to 500 mg/day given 4 to 6 times per day. If the dose was stable during the last 3 days of the Titration Period, patients were randomized 1:1 and entered the DB cross-over period. Patients either continued their tapentadol IR dose regimen or switched to tapentadol ER in the first 14-day period, and in the next 14-day period patients crossed over to the other treatment. The tapentadol ER daily dose was administered in two equally divided doses at a total daily dose approximately equivalent to the total daily dose of tapentadol IR. During the OL and DB periods patients were allowed to receive up to 2,000 mg/day of acetaminophen for rescue analgesia.

The primary efficacy endpoint was the mean pain intensity score during the last 3 days of each DB period for the tapentadol IR and tapentadol ER groups. The primary statistical population was the per protocol population (all randomized patients who completed both crossover treatment periods, maintained the dosage schedule, and were compliant with the protocol). The mean of the average pain intensity scores was analyzed with a 2-period crossover analysis of variance (ANOVA) model. If the 95% confidence intervals of the least squares mean difference between ER and IR were within the non-inferior range of (-2, 2) using the Schuirmann's two 1-sided t-test, the formulations was to be considered non-inferior.

Table 6.24 displays the results of the primary endpoint (mean pain intensity during the last 3 days of the DB Period). The mean pain intensity of the tapentadol IR group was non-inferior to the mean pain intensity of the tapentadol ER group. The results of this trial support labeling claims of a 1:1 dose conversion between tapentadol IR and tapentadol ER.

Table 6.24: Mean pain intensity scores during last 3 days of DB Period in Study 19[1]

	Tapentadol ER	Tapentadol IR	Difference (Tapentadol ER – Tapentadol IR)
N[2]	60	60	
OL Baseline Pain Intensity	7.3	7.3	
DB Baseline Pain Intensity	4.2	4.2	
Mean Pain Intensity during last 3 days of DB Period	4.0	3.9	0.1
95% CI	—	—	(-0.09, 0.28)

1 Per protocol population (all randomized patients who completed both crossover treatment periods, maintained the dosage schedule, and were compliant with the protocol).
2 N = the number of patients who received study medication. The same sixty patients received tapentadol ER and tapentadol IR during the DB Period.
Reference: CSR of Study 19, Section 6.2, Table 20, Page 99.

(b) (4)

[redacted]

7 Review of Safety

Safety Summary

In the 40 submitted studies of tapentadol ER in patients with non-malignant pain there were no deaths in tapentadol ER-treated patients. Tapentadol ER-treated patients had a greater incidence of non-fatal SAEs, AEs leading to discontinuation (DAEs), and AEs than placebo-treated patients and the differences in the incidences of DAEs and AEs between these groups were mostly due to known opioid-related toxicities (e.g., nausea, vomiting, dizziness, constipation, somnolence, fatigue). Tapentadol ER-treated patients had a lower incidence of non-fatal SAEs, DAEs, and AEs than oxycodone CR-treated patients and these differences were mostly due to known opioid-related toxicities.

Tapentadol ER-treated patients did not have evidence of greater misuse or abuse than the oxycodone CR-treated patients: tapentadol ER-treated patients had a lower proportion of possible abuse-related AEs and lower incidence of reports of study medication loss than oxycodone CR-treated patients (0.1% vs. 0.4%).

Although tapentadol ER-treated patients compared to oxycodone CR-treated patients had a slightly lower incidence of AEs within 5 days of study medication discontinuation (no taper), tapentadol ER-treated patients experienced a slightly greater proportion of AEs compared to placebo-treated patients within the same timeframe. This imbalance was due to several AEs associated with opioid withdrawal (e.g., diarrhea, nausea, anxiety, hyperhidrosis, insomnia, irritability).

There appeared to be no evidence of tapentadol ER-associated hepatotoxicity in the tapentadol ER clinical database: in the controlled and uncontrolled portions of the tapentadol ER studies, there were no cases of acute liver failure or Hy's Law and there was no difference in the proportion of tapentadol ER-treated patients and control-treated patients who had liver enzyme test elevations.

There appeared to be no evidence of tapentadol ER-associated pro-arrhythmic effect in the tapentadol ER clinical database at anticipated doses: there were no concerning clinical events that could indicate a pro-arrhythmic effect of tapentadol ER and the thorough QT study of tapentadol IR was negative (using doses that produced similar tapentadol exposure as the maximum proposed tapentadol ER dose regimen ─ 250 mg BID). Since this QT study did not assess the QT interval at higher than anticipated exposures due to dose-limited toxicities (e.g., dizziness, vomiting, nausea), the effects of tapentadol on the QT interval at substantial multiples of the maximum therapeutic exposure are not known.

There were no significant differences in the incidence of AEs in tapentadol ER-treated patients by demographics (i.e., age, gender, race, or weight), by dose, and by duration.

In the tapentadol ER database, there was no evidence of serotonin syndrome: there were no cases of serotonin syndrome and the tapentadol ER group had a similar incidence of signs and symptoms of serotonin syndrome as the oxycodone CR and placebo groups. However, there have been 18 post-marketing cases of serotonin syndrome associated with tapentadol IR use. Given these cases and the biologic plausibility (SNRIs have been associated with serotonin syndrome), serotonin syndrome should be included in the Warnings and Precautions of the tapentadol ER label.

In the tapentadol ER database, there was no clear evidence of a seizure signal. There have been 15 post-marketing cases of seizures associated with tapentadol IR use. Given these cases and biologic plausibility [convulsions seen in animals at approximate human tapentadol exposures and seizures seen in a related product in humans (tramadol)], seizure should be included in the Warnings and Precautions of the tapentadol ER label.

In summary, the safety profile of tapentadol ER in the chronic treatment of pain appears to be consistent with the safety profile of approved long-acting opioid products. The tapentadol ER labeling should be consistent with current labeling of approved long-acting opioids and contain Contraindications (in unmonitored patients with severely impaired pulmonary function and in patients receiving MAO inhibitors), Boxed Warnings (in patients at increased risk of abuse or diversion); Warnings and Precautions (respiratory and CNS depression, increased intracranial pressure, driving and operating machinery, and drug withdrawal). Consistent with the tapentadol IR label, the tapentadol ER label should contain additional Warnings and Precautions for seizures and serotonin syndrome given the biologic plausibility and the post-marketing cases of these events in patients who received tapentadol IR.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.2 (Review Strategy) for the safety pool that will be used to evaluate the safety of tapentadol ER for the chronic treatment of pain. See Table 5.1 in Section 5.1 for the study designs of the studies in the primary safety pool (i.e., Studies 7, 8, 9, and 11).

7.1.2 Categorization of Adverse Events

J & J's categorization of AEs with preferred terms are consistent with the investigator's verbatim terms including the most common DAEs (e.g., nausea, vomiting, dizziness, constipation, somnolence, and fatigue).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See Section 5.2 (Review Strategy) for the rationale for pooling data from Studies 7, 8, 9, and 11 to support the major safety analyses of tapentadol ER for the chronic treatment of pain.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses and Durations

In the entire safety database of the 40 completed studies of tapentadol ER, 4407 subjects/patients received at least one dose of tapentadol ER (3694 patients received tapentadol ER in the Phase 2 and 3 trials, 79 healthy subjects received multiple-doses of tapentadol ER in Phase 1 studies, and 634 healthy subjects received single-doses in Phase 1 studies). In the 4 pooled studies that served as the primary support for the safety of tapentadol ER (i.e., Studies 7, 8, 9, and 11), 2092, 481, and 227 patients received

at least 4, 24, and 52 weeks of tapentadol ER, respectively (patients may have been counted more than once). See Table 7.1 for the exposure to tapentadol ER.

The median tapentadol ER dose in pooled studies 7, 8, 9, and 11 was 297 mg. During the first 4 weeks of treatment, the mean total daily dose of tapentadol ER was 256 mg; thereafter, the mean total daily dose remained stable, with the mean total daily dose ranging between 360 and 398 mg (see Figure 7.2 for the mean daily dose over time). The tapentadol ER doses were lower in the first 3 weeks of treatment in these trials, because all patients started dosing at 50 mg BID during the Titration Periods and then were allowed to up titrate to doses as high as 250 mg BID.

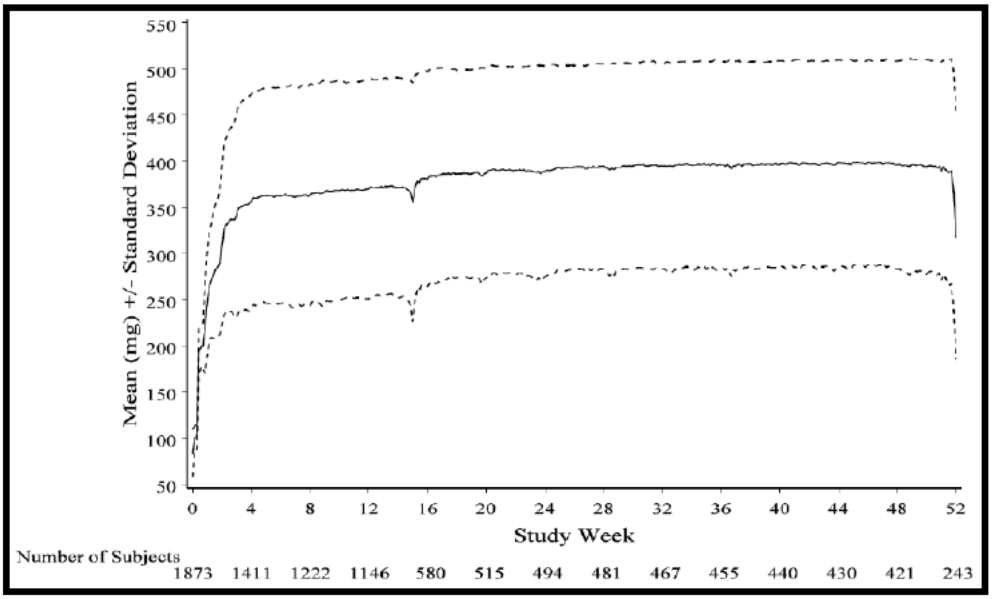
An adequate number of patients were exposed to tapentadol ER to assess its safety. The safety database fulfills the guidelines for an adequate safety database according the 2005 *Premarketing Risk Assessment* Guidance and is consistent with FDA recommendations during the pre-submission meetings regarding the tapentadol ER development program (i.e., a significant number of patients should receive 500 mg/day).

Table 7.1: Exposure of tapentadol ER and oxycodone CR by duration and total daily dose in 4 pooled studies (i.e., Studies 7, 8, 9, and 11)[1]

	Tapentadol ER (n=1874)	Oxycodone CR (n=1224)
Duration of Exposure		
# of patients exposed > 4 weeks	1409	669
# of patients exposed > 24 weeks	492	94
# of patients exposed ≥ 12 months	227	44
Mean (SD) days of exposure	139 (132) days	74 (91) days
Median days of exposure	105 days	42 days
Total Daily Dose[2]		
Mean (SD)	310 (115) mg	49 (23) mg
Median	297 mg	41 mg
Median Maximum Total Daily Dose[3]	400 mg	60 mg
Median Minimum Total Daily Dose[3]	100 mg	20 mg

1 Patients may have been counted more than once.
2 This analysis is the total daily dose for the days patients were taking study medication.
3 Median maximum total daily dose is the median of daily maximum dose for each patient. Median minimum total daily dose is the median of the daily minimum daily dose for each patient.
Reference: ISS, Appendix 2.2.3.1, Pages 1865-1866

Figure 7.2: Mean total daily tapentadol ER dose over time in pooled Studies 7, 8, 9, and 11



Reference: ISS, Appendix 2.2.3.2, Page 1897.

7.2.2 Overall Exposure at Appropriate Demographics of Target Populations

See Section 6.1.2 (Demographics and Baseline Characteristics) and Section 9.4 (individual study reports) for the baseline demographics in the important safety studies. The statistical populations for the primary efficacy and safety analyses were the same, i.e., ITT population (all randomized patients who received at least one dose of study medication). There was adequate tapentadol ER exposure to most demographic subgroups including age (e.g., patients less than 65 years old and geriatric patients), gender (women and men), and Caucasians to perform subgroup safety analyses. Although there were few Black patients in the U.S. trials (13%, 17%, and 12% of the patients in Studies 8, 11, and 15, respectively, were Black), the racial demographics in these trials are consistent with the racial demographics in the United States.

7.2.3 Special Animal and/or In Vitro Testing

According to Dr. Armaghan Emami, the pharmacology and toxicology studies of tapentadol were adequate to explore tapentadol's potential adverse reactions [see Section 4.3 (Preclinical Pharmacology/Toxicology) for more details].

7.2.4 Routine Clinical Testing

The types and frequencies of safety tests used to assess AEs, vital signs, labs, and other tests were adequate to assess the safety of tapentadol ER in the chronic treatment of pain.

7.2.5 Metabolic, Clearance, and Interaction Workup

According to Dr. David Lee, the clinical pharmacology reviewer, the metabolic, clearance, and interaction work-up for tapentadol ER was acceptable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The evaluation for known toxicities of long-acting opioids and SNRIs was acceptable.

7.3 Major Safety Results

7.3.1 Deaths

Non-Cancer Studies: In the 40 submitted studies of tapentadol ER in patients with non-malignant pain there were no deaths in tapentadol ER-treated patients from study medication initiation to 30 days after the last dose of tapentadol ER. In the 10 Phase 2 and 3 studies, 0 (0%) of 3613 tapentadol-ER patients died, 1 (0.1%) of 1498 placebo-treated patients died, 1 (0.1%) of 1472 oxycodone CR-treated patients died, and 0 (0%) of 249 tramadol-treated patients died from study medication initiation to 30 days after the last dose of study medication. See the narratives of the death in a placebo-treated patient and the death in the oxycodone CR-treated patient in Table 7.3. There were no deaths in tapentadol ER-treated subjects the 30 single and multiple-dose Phase 1 studies in healthy subjects (634 subjects received single doses of tapentadol ER and 79 subjects received tapentadol ER doses up to 3.5 days).

In the ongoing studies of tapentadol ER in patients with chronic non-cancer pain (Studies 10, 20, KF44, and KF44), there were 3 (0.2%) deaths in tapentadol ER-treated patients in 1513 tapentadol ER-treated patients. See Table 5.5 in Section 5.1 (Table of Studies) for a description of the ongoing studies in patients with non-cancer pain. Table 7.3 displays the narratives for the 3 tapentadol ER-treated patients who died within 30 days after the last dose of tapentadol ER. Two (Patients 105139 and 105689) of the three deaths occurred in patients with known coronary artery disease and both of these deaths were likely due to cardiovascular events. The last death occurred in a 65 year old male with a history of depression, anxiety disorder, and panic disorder who had a completed suicide. See Section 7.3.6 (Submission Specific Primary Safety Concerns) for a further discussion of the relationship of tapentadol ER and suicide events.

Table 7.3: Deaths in the completed and ongoing tapentadol ER studies in patients with pain due to non-cancer etiologies[1]

Patient # (Study)	Cause of death	Narrative
Deaths in the Controlled Portions of the Tapentadol ER Studies		
Placebo Group		
202072 (Study 1)	Lung cancer	64 year old Caucasian male with a history of knee OA received placebo treatment on Day 1. On Day 13, hospitalized for metastatic small cell lung cancer, study medication was discontinued on Day 17, and died on Day 85.
Oxycodone CR Group		
805900 (Study 8)	MI	64 year old Black female with a history of OA, morbid obesity, HTN, depression, and anemia treated with hydrocodone/acetominophen, hydroclorothiazide, escitalopram oxalate. She received oxycodone CR on Day 1 and on Day 90 became unresponsive, was intubated, and received advance life support but was pronounced dead in the emergency room. The cause of death was a cardiac arrest due to a MI. The patient stopped oxycodone CR treatment on the day of her death (Day 90).
Deaths in the Uncontrolled Portions of the Ongoing Tapentadol ER Studies (Tapentadol ER Treatment)		
Tapentadol ER Group		
105139 (Study 10)	Sudden death	49 year old female with a history of angina, HTN, morbid obesity, GERD, OA, seasonal allergies, constipation, and anemia taking isosorbide mononitrate, lopressor, telmisartan, hydrochlorothiazide, furosemide, potassium chloride, cetirizine, esomeprazole, and lubiprostone. Received tapentadol ER and titrated up to 250 mg BID. On Day 142 arrived in the emergency room with CPR in progress (patient found to be pulseless and in asystole). Patient had some empty pill bottles including percocet in her car.
105689 (Study 10)	Myocardial infarction	70 year old male with a history of hypertensive cardiomyopathy, stroke, HTN, GERD, taking atenolol, aspirin, lisinopril, HCTZ, and formoterol. Started treatment with tapentadol ER and discontinued it on Day 30. Admitted to the hospital for food poisoning and died of an MI on Day 32 (two days after tapentadol ER discontinuation).
105590 (Study 10)	Suicide	65 year old male with a history of depression, panic disorder, anxiety disorder, HTN, hyperlipidemia, and GERD received 1-year of OL oxycodone CR in Study 7 and then entered Study 10 and received OL tapentadol ER. He was taking concomitant clonazepam, lorazepam, sildenafil, ranitidine, atorvastatin, olmesartan, medoximil, and aspirin and died of a completed suicide. On Day 47 of Study 10, patient reported increased anxiety and depression and went to the ER for depression. He received setraline, trazadone, and lithium. On Day 100 of the study, he discontinued from the study. On Day 103 (3 days after the last dose of tapentadol ER) he committed suicide by a gun shot to the head (according to the family he became severely depressed after he lost his job).

1 Includes all deaths during treatment until 30 days after the last dose of study medication as of the September 30, 2009 cut-off date.
Reference: ISS, COMIS reports, Appendix 4.2.2, Page 17324, ISS, Appendix 4.3.8.4, Pages 19449-19451; Pages 19462-19463; Pages 19830-19833.

Cancer Studies: In the ongoing and completed studies of tapentadol ER in patients with cancer pain (Studies 13, 14, and C01 – see Table 5.6 for the design of these studies), there were multiple deaths in the tapentadol ER and morphine CR groups (see Table 7.4). All of these patients who died had baseline metastatic cancer with poor prognosis. The overwhelming majority of patients died from progression of their malignancy and/or infectious complications from immunosuppression. Given the confounding factors (e.g., underlying metastatic cancer, poor prognosis), it is not likely that tapentadol ER played a causative role in these deaths.

Table 7.4: Deaths in the ongoing tapentadol ER studies of patients with pain due to cancer[1]

	Patient	Demographics	Adverse Event preferred term
Study C01 (OL Tapentadol ER)			
1	08-02	70 year old male	Gastric cancer
2	10-01	68 year old male	Respiratory failure
3	22-03	77 year old female	Malignant neoplasm progression
4	17-02	72 year old male	Septic shock
5	08-04	79 year old male	Malignant neoplasm progression
6	24-01	78 year old female	Malignant neoplasm progression
7	22-05	74 year old male	Malignant neoplasm progression
8	08-09	72 year old male	Malignant neoplasm progression
9	06-04	72 year old male	Malignant neoplasm progression
10	11-05	74 year old male	Pneumonia bacterial
11	17-04	80 year old male	Malignant neoplasm progression
12	09-03	61 year old male	Lung neoplasm malignant
13	14-05	82 year old male	Concomitant disease aggravated
Study 14 (Tapentadol ER Group)			
14	140044	64 year old male	Malignant neoplasm progression (lung cancer)
15	140052	46 year old, female	Malignant neoplasm progression (cervical cancer)
16	140066	53 year old female	Malignant neoplasm progression (breast cancer)
17	140067	52 year old female	Malignant neoplasm progression (colon cancer)
18	140072	74 year old male	Malignant neoplasm progression
19	140106	69 year old female	Respiratory failure
20	140058	80 year old female	Malignant neoplasm progression
21	140082	72 year old female	Malignant neoplasm progression
22	140119	35 year old female	Anemia
23	140048	69 year old female	Death
Study 14 (Morphine Sulfate Group)			
24	140069	51 year old male	Malignant neoplasm progression
25	140087	74 year old male	Death
26	140094	43 year old female	Malignant neoplasm progression (cervical cancer)
27	140124	70 year old female	Pneumonia

1 Includes all deaths after the first dose of study drug, during treatment, and until 30 days after the last dose of study medication as of the September 30, 2009 cut-off date. Only deaths that were unblinded are included in this table; there were deaths in Study 13, but the treatment groups remain blinded.
Reference: ISS, Table 28, Pages 155-156; 4-month safety update, Table 9, Page 62, Table 10, Page 63.

7.3.2 Nonfatal Serious Adverse Events

In the tapentadol ER studies, a non-fatal SAE was defined as any AE that was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability and/or incapacity (i.e., a substantial disruption in a person's ability to conduct normal activities of daily living), was a congenital anomaly and/or birth defect, or an important medical event that could have been considered an SAE if it required medical or surgical intervention to prevent one of the outcomes listed above.

Table 7.5 presents the non-fatal SAEs in the 3 pooled DB controlled studies and the long-term OL study that served as the critical studies to support the safety of tapentadol ER. Tapentadol ER-treated patients had a greater incidence of non-fatal SAEs than placebo-treated patients but a lower incidence of non-fatal SAEs than oxycodone-CR-treated patients. The opioid groups had a greater proportion of known opioid-related SAEs (e.g., abdominal pain, constipation, intestinal obstruction, dizziness) than the placebo group.

A slightly greater proportion of tapentadol ER-treated patients compared to the other treatment groups had SAEs of atrial fibrillation, abdominal pain, syncope, and intestinal obstruction [see Section 7.3.5 (Potentially Significant Adverse Events) for discussion of these events].

Table 7.5: Non-fatal SAEs in the 3 pooled, DB Phase 3 trials and 1 OL Phase 3 study of tapentadol ER in chronic pain[1]

	Pooled DB 15-Week Trials[2]			1-Year OL Safety Study[3]	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
SAEs	**32 (3.2%)**	**11 (1.1%)**	**10 (1.0%)**	**8 (3.6%)**	**38 (4.3%)**
Constipation	2 (0.2%)	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)
Dizziness	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Angina pectoris	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Myocardial infarction	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Anemia	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal failure acute	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dehydration	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)
Atrial Fibrillation	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	3 (0.3%)
Abdominal Pain	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	2 (0.2%)
Syncope	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	2 (0.2%)
Intestinal Obstruction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)
COPD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)

COPD = Chronic obstructive pulmonary disease
1 Number of patients with at least one SAE during treatment until 3 days after the last dose of study medication (SAEs that occurred 2 or more times in any treatment group are listed).
2 Studies 8, 9, and 11
3 Study 7
Reference: ISS, Appendix 4.3.3.2, Page 18009-18018

7.3.3 Adverse Events Leading to Discontinuations

Table 7.6 displays the AEs leading to discontinuation (DAEs) in the pooled DB controlled Phase 3 trials (Studies 8, 9, and 11) and the 1-year OL safety study of tapentadol ER in the chronic treatment of pain. See Table 6.3 in Section 6.1.4 (Subject Disposition) for the disposition and reasons for dropouts in Studies 8, 9, and 11.

A lower proportion of tapentadol ER-treated patients compared to oxycodone CR-treated patients had DAEs in the pooled DB trials and the long-term OL study. Tapentadol-ER treated patients had lower proportions of typical opioid associated DAEs (e.g., nausea, vomiting, dizziness, constipation, somnolence, and fatigue).

A greater proportion of tapentadol ER-treated patients compared to placebo-treated patients had DAEs in the pooled DB trials (18% vs. 6%). The differences in DAEs between these treatment groups were due to typical opioid-associated AEs (e.g., nausea, vomiting, dizziness, constipation, somnolence, and fatigue).

Table 7.6: DAEs in the 3 pooled, DB Phase 3 trials and 1 OL Phase 3 study of tapentadol ER in chronic pain[1]

	Pooled DB 15-Week Trials[2]			1-Year OL Safety Study[3]	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
DAEs[2]	**390 (39%)**	**179 (18%)**	**63 (6%)**	**82 (37%)**	**198 (22%)**
Nausea	14%	4%	<1%	12%	3%
Vomiting	10%	3%	<1%	7%	3%
Dizziness	9%	4%	<1%	7%	3%
Constipation	7%	2%	<1%	7%	2%
Somnolence	6%	2%	<1%	4%	3%
Fatigue	3%	2%	<1%	5%	2%
Pruritus	3%	<1%	<1%	3%	1%
Headache	2%	<1%	<1%	1%	1%
Hyperhidrosis	2%	<1%	<1%	1%	<1%
Insomnia	1%	<1%	<1%	<1%	<1%
Vertigo	1%	<1%	<1%	1%	<1%
Dry mouth	1%	<1%	<1%	1%	1%
Lethargy	<1%	<1%	0%	1%	<1%

COPD = Chronic obstructive pulmonary disease
1 DAEs that occurred ≥ 1% in any treatment group are listed.
2 Incidence is based on the number of patients who experienced at least 1 DAE (not the number of DAEs)
Reference: ISS, Appendix 4.4.5.1, Pages 20387-20394; CSR of Study 7, Attachment 3.5.3, Pages 1721-1726.

7.3.4 Common Adverse Events

Table 7.7 displays the most common AEs (≥ 5% in any treatment group) in the pooled DB controlled Phase 3 trials (Studies 8, 9, and 11) and the 1-year OL safety study of tapentadol ER in the chronic treatment of pain. A large proportion of patients experienced AEs in the 15-week trials (59% to 86%) and the 1-year safety study (86% to 91%). The tapentadol ER treated patients had a lower proportion of AEs than the oxycodone CR-treated patients in the pooled DB 15-week trials and in the 1-year safety study, but had a greater proportion of AEs than the placebo-treated patients in the pooled DB 15-week trials. Tapentadol ER-treated patients had a greater proportion of typical opioid-associated AEs than placebo-treated patients (e.g., nausea, constipation, dizziness, vomiting, somnolence, pruritis, fatigue, and hyperhidrosis, and dry mouth).

A greater rate of AEs occurred in the 3-week Titration Period than the 12-week Maintenance Period in the pooled induction trials. In pooled Studies 8, 9, and 11, the proportion of oxycodone CR, tapentadol ER, and placebo treated patients with AEs during the 3-week Titration Period was 78%, 58%, and 42% and during the 12-week Maintenance Period was 66%, 60%, and 48%, respectively. The greater rate of tapentadol-ER associated AEs in the Titration Period compared to the Maintenance Period was likely due to the forced titration (from 50 mg BID to 100 mg BID) in the Titration Period.

Table 7.7: Most common AEs in the 3 pooled, DB Phase 3 trials and 1 OL Phase 3 study of tapentadol ER in chronic pain[1]

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
AEs	**858 (86%)**	**715 (73%)**	**583 (59%)**	**202 (91%)**	**766 (86%)**
Nausea	36%	21%	7%	33%	18%
Constipation	33%	17%	7%	39%	23%
Dizziness	21%	17%	6%	19%	15%
Vomiting	21%	8%	3%	14%	7%
Somnolence	17%	12%	4%	11%	15%
Headache	13%	15%	13%	8%	13%
Pruritus	13%	5%	2%	10%	5%
Fatigue	9%	9%	4%	10%	10%
Hyperhidrosis	6%	5%	1%	4%	5%
Diarrhea	5%	5%	6%	5%	8%
Insomnia	5%	4%	2%	4%	7%
Dry mouth	4%	7%	2%	5%	9%
Nasopharyngitis	2%	3%	4%	3%	6%
Sinusitis	1%	1%	1%	6%	4%

1 AEs that occurred ≥ 5% in any treatment group are listed. Incidence is based on the number of patients who experienced at least 1 AE (not the number of AEs)

Reference: ISS, Table 24, Page 143, Table 25, page 144; Appendix 4.1.4.2, Pages 14693-14746; CSR of Study 7, Attachment 3.1.2, Pages 933-952

7.3.5 Potentially Significant Adverse Events

Evaluation of Hallucination, Serotonin Syndrome, Seizures, and Suicidal Ideation: There have been post-marketing reports of hallucination (35), serotonin syndrome (18), seizures (15), and suicidal ideation (7) associated with tapentadol IR from initial marketing in June 2009 to May 2010 [see Section 2.3 (Availability of Tapentadol in the United States) for more details]. Therefore, it is important to evaluate for the presence of these AEs in the tapentadol ER clinical program.

Hallucination: Table 7.8 displays hallucinations SAEs, DAEs, and AEs in the 3 induction trials and the 1-year safety study. A greater proportion of tapentadol ER-treated patients had hallucinations than oxycodone CR-treated patients (0.5% vs. 0.2%). Given the post-marketing cases, the biologic plausibility, association of other opioid products with hallucinations, and the imbalance of hallucinations in the tapentadol ER group compared to the control groups, hallucination should be included in the Adverse Reactions sections of the tapentadol ER label.

Table 7.8: Hallucination SAEs, DAEs, and AEs in the 3 induction trials and the 1-year safety study

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Tapentadol ER (n=980)	Oxycodone CR (n=1001)	Placebo (n=993)	Tapentadol ER (n=894)	Oxycodone CR (n=223)
SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DAEs	2 (0.2%)	2 (0.2%)	0 (0%)	1 (0.1%)	0 (0%)
AEs	5 (0.5%)	2 (0.2%)	0 (0%)	1 (0.1%)	0 (0%)

Reference: ISS, Appendix 4.1.4.2, Pages 14936-14989, Appendix 4.3.3.2, Page 18009-18018; ISS, Appendix 4.4.5.1, Pages 20387-20394; CSR of Study 7, Attachment 3.5.3, Pages 1721-1726; Attachment 3.1.2, Pages 933-952

Serotonin Syndrome: In the tapentadol ER database, there were no cases of serotonin syndrome. J & J did an exploratory analysis to identify symptoms and signs of serotonin syndrome in the tapentadol ER database using the following preferred terms: sinus tachycardia, tachycardia, mydriasis, diarrhea, hyperthermia, pyrexia, body temperature increased, ataxia, coordination abnormal, dyskinesia, muscle contractions involuntary, myoclonus, psychomotor hyperactivity, tremor, agitation, confusional state, hyperhidrosis, hypertension, and hypertensive crisis. Table 7.9 displays the incidence of patients having ≥ 1, ≥ 2, or ≥ 3 AEs seen in serotonin syndrome in the Phase 2 and 3 studies of tapentadol ER in chronic pain. Tapentadol ER had a similar incidence of these AEs compared to oxycodone CR. Therefore, in the clinical tapentadol ER, there was no clear evidence of serotonin syndrome.

Since most of the clinical studies excluded patients at greater risk for serotonin syndrome (e.g., patients taking concomitant SSRIs, SNRIs, tricyclic antidepressants, MAO inhibitors), the premarketing data may not be sufficient to rule out a serotonin syndrome signal. Since there have been 18 post-marketing cases of tapentadol IR associated with serotonin syndrome, the Warnings and Precautions section of the tapentadol ER label should state that post-marketing cases of serotonin syndrome associated with the use of tapentadol IR have been reported.

Table 7.9: Incidence of possible serotonin syndrome related AEs in the Phase 2 and Phase 3 studies

	Placebo (n=1498)	Tapentadol ER (n=3613)	Oxycodone CR (n=1472)	Tramadol PR (N=249)
≥ 1 AE	135 (9%)	484 (13%)	202 (14%)	45 (18%)
≥ 2 AEs	18 (1%)	80 (2%)	33 (2%)	10 (4%)
≥ 3 AEs	1 (<1%)	10 (<1%)	4 (<1%)	3 (1%)

Reference: ISS, Table 31, Page 188

Seizure: In the tapentadol ER database (4407 subjects/patients exposed to tapentadol ER), there was 1 case of seizure in a 47 year old male in Study HP10 (thorough QT study) with a history of a seizure disorder uncontrolled on valproic acid (the history of seizure was unknown to the investigator at the time of randomization). He received 2.5 days of 172 mg of tapentadol ER BID (5 doses) and had a tonic clonic seizure which required hospitalization. His work-up for causes of the seizure showed possible hypoplasia of the temporal lobe on MRI of the brain (his other studies were negative including chemistries, EEG, and CT brain). Since the clinical studies excluded patients at greater risk for seizure disorder (i.e., patients with a history of seizures; recent history of traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm; or metabolic disturbances), the premarketing data may not be sufficient to rule out a seizure signal.

Given the biologic plausibility [convulsions seen in animals at approximate human exposures and seizures seen in a related product in humans (tramadol)] and the 15 post-marketing cases of seizures seen in tapentadol IR-treated patients, seizure should be included in the Warnings and Precautions of the tapentadol ER label.

Suicidal Ideation: There was one suicidal attempt that lead to death in an ongoing OL, uncontrolled study of tapentadol ER in patients with chronic, non-malignant pain (Study 10). See Table 7.3 in Section 7.3.1 (Deaths) for the narrative of this case. Table 7.10 presents suicidal ideation SAEs, DAEs, and AEs in the 4 important safety studies. The tapentadol ER group, compared to the control groups, had a similar or lower proportion of patients with suicidal ideation SAEs, DAEs, or AEs.

Although, SNRIs have been associated with suicidal ideation in adolescents and young adults, the premarketing and post-marketing data does not clearly demonstrate a possible causal relationship between tapentadol ER use and suicide. The successful suicidal attempt that occurred in an uncontrolled, OL, ongoing study had confounding factors (prior history of depression and an acute stressor). The premarketing database did not demonstrate an imbalance in suicidal ideation in the tapentadol ER and control groups. Finally, there was few post-marketing reports of suicidal ideation (7) associated with tapentadol IR. At this time, no causal relationship between suicidal ideation and tapentadol ER use can be established.

Table 7.10: Suicidal ideation SAEs, DAEs, and AEs in the 4 important safety studies

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Tapentadol ER (n=980)	Oxycodone CR (n=1001)	Placebo (n=993)	Tapentadol ER (n=894)	Oxycodone CR (n=223)
Suicidal Ideation					
SAEs	0 (0%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0%)
DAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AEs	0 (0%)	2 (0.2%)	1 (0.1%)	0 (0%)	0 (0%)

Reference: ISS, Appendix 4.1.4.2, Pages 14936-14989, Appendix 4.3.3.2, Page 18009-18018; ISS, Appendix 4.4.5.1, Pages 20387-20394; CSR of Study 7, Attachment 3.5.3, Pages 1721-1726; Attachment 3.1.2, Pages 933-952

Atrial Fibrillation, Syncope, and Intestinal Obstruction: Since more tapentadol ER-treated patients than control-treated patients had SAEs of atrial fibrillation, syncope, and intestinal obstruction, these events are evaluated further in this section.

Atrial Fibrillation: Table 7.11 displays the number and rate (events per 100 patient-years) of atrial fibrillation (AF) SAEs, DAEs, and AEs in the 4 important safety studies. A similar rate of patients treated with tapentadol ER and placebo in the controlled induction trials had AF SAEs and AEs. The tapentadol ER and oxycodone CR groups had a similar rate of AF AEs in the 1-year safety study (Study 7); however, a slightly greater rate of tapentadol-ER treated patients had AF SAEs than oxycodone CR treated patients.

Table 7.12 presents the 3 narratives of AF SAEs in the tapentadol ER group in the OL Study 7. All of the cases were confounded. In 2 of the 3 cases, the patients had baseline AF and in the remaining case there was not a temporal association of the AF and tapentadol ER use (AF occurred about 3 days after discontinuation of tapentadol ER). Given the background frequency of AF in the population, lack of

biologic plausibility, and confounding nature of the AF cases, a relationship between AF and tapentadol ER use cannot be established.

Table 7.11: Number and rate of atrial fibrillation (AF) SAEs, DAEs, and AEs in the 4 important safety studies[1]

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Tapentadol ER (n=980)	Oxycodone CR (n=1001)	Placebo (n=993)	Tapentadol ER (n=894)	Oxycodone CR (n=223)
Patient-years	197	150	205	517	99
SAEs	1 (0.5)	0 (0)	1 (0.5)	3 (0.6)	0 (0)
DAEs	2 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
AEs	3 (1.5)	1 (0.7)	3 (1.5)	6 (1.2)	1 (1.0)

1 Number is based on the number of patients experiencing one AE; not the number of events; rate is the number of events per 100 person-years of exposure
Reference: August 5, 2010 response to information request, Amendment #16, Table 1, Page 5; Table 2, Page 6, Table 7, Page 7

Table 7.12: Narratives of AF SAEs in the OL safety study (Study 7)

Patient	Narratives
Tapentadol ER	
701129	72 year old male with history of AF, CAD (s/p CABG, s/p defibillator, MI), PVD, CHF, HTN, ventricular tachycardia, GERD, LBP, hyperlipidemia taking diltiazem, enoxaparin, pantoprazole, warfarin, aspirin, esomeprazole. On Day 219 had uncontrolled AF and syncope and hospitalized. On Day 222 his defibrillator shocked him and subsequently he was found to be in normal sinus rhythm. He was discharged on Day 223. On Day 239 had recurrence of AF which resolved later that day. On Day 319 he was hospitalized again for recurrent AF and his sotalol medication was increased. He was discharged on Day 322 in normal sinus rhythm.
703082	70 year old female with a history of COPD, MI, DM type 2, OA, restless leg syndrome treated with acyclovir, levofloxacin, and prednisone. On Day 317, patient had an asthma exacerbation and worse back pain, later that day her tapentadol ER was discontinued due to lack of therapeutic effect. On Day 320 (3 days after discontinuation of tapentadol ER), hospitalized for COPD exacerbation and bronchitis and found to have AF. On Day 327, she was discharged.
701474	68 year old male with a history of AF, COPD, HTN, OA, and right lung resection treated with warfarin, digoxin, diltiazem, bisacodyl, prednisone, ciprofloxacin, , aspirin, and enoxaparin. On Day 41, hospitalized for CP and found to be in AF. Treated with cardizem IV, cardioversion, and anticoagulation. These events resolved on Day 44. Study treatment was stopped on Day 117.

Reference: CSR Study 7, Attachment 3.5.6

Syncope: Table 7.13 presents the number of patients and rate (events per 100 patient-years) of syncope SAEs, DAEs, and AEs in the 4 important safety studies of tapentadol ER. The tapentadol ER group had a greater rate of patients with syncope SAEs, DAEs, and AEs compared to the control groups in the controlled induction trials and the 1-year OL study.

Table 7.14 displays the syncope narratives of SAEs and/or DAEs in the 4 important safety studies. Some of the cases present a temporal relationship between tapentadol ER use and syncope. Opioid products have been associated with syncope and several products are labeled for syncope (e.g., oxycodone CR and fentanyl patch). The tapentadol ER label should include syncope in the Adverse Reactions section.

Table 7.13: Number and rate of syncope SAEs, DAEs, and AEs in the 4 important safety studies[1]

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Tapentadol ER (n=980)	Oxycodone CR (n=1001)	Placebo (n=993)	Tapentadol ER (n=894)	Oxycodone CR (n=223)
Patient-years	197	150	205	517	99
SAEs	1 (0.5)	0 (0)	0 (0)	2 (0.4)	0 (0)
DAEs	1 (0.5)	0 (0)	0 (0)	3 (0.6)	0 (0)
AEs	4 (2.0)	1 (0.7)	0 (0)	7 (1.4)	0 (0)

1 Number is based on the number of patients experiencing one AE; not the number of events; rate is the number of events per 100 person-years of exposure
Reference: August 5, 2010 response to information request, Amendment #16, Table 1, Page 5; Table 2, Page 6, Table 7, Page 7

Table 7.14: Narratives of syncope SAEs and DAEs in the 4 important safety studies

Patient	Study		Narrative
Tapentadol ER			
701834	Study 7	SAE	78 year old female with history of hip pain and OA. On Day 124 had a syncopal event and hospitalized (study medication was discontinued on Day 124). The syncope work-up was negative and she was discharged on Day 138 (15 days later).
701129	Study 7	SAE	See the narrative in Table 7.12 above
701885	Study 7	DAE	66 year old women with AF, obesity, HTN, DM, OA, osteoporosis, s/p MVR, GERD, IBS, anxiety. On Day 58 she had a syncopal event and hyperglycemia. Study medication was discontinued on Day 60.
704068	Study 7	DAE	44 year old female with LBP, fibromyalgia, migraines, depression. On Day 2 had syncope and study medication was discontinued on Day 2.
900135	Study 9	SAE	62 year old female with history of cardiomyopathy, ventricular tachycardia, asthma, bradycardia, atrial bigeminy, MVP, gastritis, taking formoterol and nebivolol. On Day 4 she reported that she had dizziness, nausea, and had episodes of syncope. These events resolved while taking tapentadol ER. On Day 17 had recurrent syncope and was hospitalized. Testing (echo, Holter, carotid ultrasound) was negative. Discharged on Day 21, but rehospitalized on Day 31. Had a tilt table test (negative). On Day 38 had diarrhea which resolved in 3 days. On Day 50 tapentadol ER discontinued due to vomiting.
113687	Study 11	DAE	65 year old female with DM type 2, HTN, OA, osteoporosis, treated with alendronate, atorvastatin, felodipine, quinapril, hydrochlorothiazide, levothyroxine, and aspirin. On Day 2 had syncope with resolved on Day 4. Study medication was discontinued on Day 2.

Intestinal Obstruction: Table 7.15 displays the number of patients and rate of intestinal obstruction SAEs, DAEs, and AEs in the 4 important safety studies. There were 2 intestinal obstruction SAEs in tapentadol ER-treated patients in the 1-year long-term safety study (see the narratives in Table 7.16). These cases of ileus (non-mechanical disruption of GI motor activity) are known toxicities of opioid products. Tapentadol ER should containing Warnings and Precautions about the risk of paralytic ileus.

Table 7.15: Number and rate of intestinal obstruction SAEs, DAEs, and AEs in the 4 important safety studies

	Pooled DB 15-Week Trials[2]			1-Year OL Safety Study[3]	
	Tapentadol ER (n=980)	Oxycodone CR (n=1001)	Placebo (n=993)	Tapentadol ER (n=894)	Oxycodone CR (n=223)
Patient-years	197	150	205	517	99
SAEs	0 (0)	0 (0)	0 (0)	2 (0.4)	0 (0)
DAEs	0 (0)	0 (0)	0 (0)	2 (0.4)	0 (0)
AEs	0 (0)	0 (0)	0 (0)	2 (0.4)	0 (0)

1 Number is based on the number of patients experiencing one AE; not the number of events; rate is the number of events per 100 person-years of exposure

Reference: August 5, 2010 response to information request, Amendment #16, Table 1, Page 5; Table 2, Page 6, Table 7, Page 7

Table 7.16: Narratives of intestinal obstruction SAEs in the 4 important safety studies

Patient	Study	Narrative
Tapentadol ER		
701023	Study 7	**59 year old female with HTN, GERD, LBP, DDD, OA, treated with promethazine. On Day 7 had constipation. On Day 29 started to have abdominal pain worse with food intake and had anorexia, constipation, weight loss, nausea, and vomiting. Three days later discontinued tapentadol ER. Six days later (Day 35) diagnosed with intestinal obstruction treated with magnesium hydroxide and magnesium citrate.**
702177	Study 7	**54 year old male with HTN, DDD, GERD, and depression. On Day 14 discontinued tapentadol ER. On Day 15 hospitalized for abdominal pain and nausea and diagnosed with partial bowel obstruction and treated medically. The condition resolved on Day 18.**

Reference: CSR Study 7, Attachment 3.5.6

7.4 Supportive Safety Results

7.4.1 Laboratory Findings

Assessment of Hepatotoxicity and Liver Enzyme Elevations: In the controlled and uncontrolled portions of the tapentadol ER studies, there were no cases of acute liver failure or cases of Hy's Law. As shown in Table 7.17, there was no difference in the proportion of tapentadol ER-treated patients and control-treated patients who had liver test elevations in patients with normal and abnormal baseline liver test values. Therefore, there appeared to be no evidence of tapentadol ER-associated hepatotoxicity in the tapentadol ER clinical database.

Table 7.17: Incidence of liver test elevations at any time during Treatment Period in Phase 2 and 3 studies[1]

Normal liver enzyme tests at baseline				
	Placebo (n=955)	**Tapentadol ER (n=2254)**	**Oxycodone CR (n=736)**	**Tramadol (n=194)**
Any liver test > ULN	**79 (8%)**	**204 (9%)**	**71 (10%)**	**20 (10%)**
Any liver test > 2x ULN	**4 (<1%)**	**7 (<1%)**	**2 (<1%)**	**0 (0%)**
Any liver test > 5x ULN	**1 (<1%)**	**1 (<1%)**	**1 (<1%)**	**0 (0%)**
Liver enzyme tests abnormal at baseline				
	Placebo (n=173)	**Tapentadol ER (n=410)**	**Oxycodone CR (n=144)**	**Tramadol (n=17)**
Any liver test > ULN	**124 (72%)**	**283 (69%)**	**87 (60%)**	**9 (53%)**
Any liver test > 2x ULN	**10 (6%)**	**26 (6%)**	**7 (5%)**	**0 (0%)**
Any liver test > 5x ULN	**0 (0%)**	**1 (<1%)**	**0 (0%)**	**0 (0%)**

1 Liver tests included ALT, AST, alkaline phosphatase, and total bilirubin. The denominator is based on the number of patients who had post-baseline lab tests.
Reference: ISS, Appendix 7.2.3, Pages 41928-41930.

Table 7.18 presents the proportion of patients with normal baseline lab values in the pooled Phase 2 and 3 tapentadol ER studies with "potentially clinically important" laboratory abnormalities any time during the Treatment Period. See Table 7.19 for J & J's pre-specified definitions of "potentially clinically important" (PCI) laboratory abnormalities. Although J & J's definitions of PCI lab abnormalities are not conservative, their definitions are reasonable to use as a screening test for lab abnormalities because opioids not associated with lab test abnormalities. Tapentadol ER-treated patients and control-treated patients had similar proportions PCI lab abnormalities during the pooled Phase 2 and 3 studies.

Table 7.18: Proportion of patients with "potentially clinically important" lab results in the pooled Phase 2 and 3 studies of tapentadol ER[1]

	Placebo (N=1498)			All Tap ER (N=3613)			All Oxy CR (N=1472)		
Lab Type	Total	Abnormality, n (%)		Total	Abnormality, n (%)		Total	Abnormality, n (%)	
Parameter	n (%)	Low	High	n (%)	Low	High	n (%)	Low	High
Chemistry	1127 (75)	12 (1)	20 (2)	2662 (74)	19 (1)	40 (2)	880 (60)	10 (1)	24 (3)
Albumin (g/L)	645 (43)	0	0	1605 (44)	0	0	663 (45)	0	0
Alkaline phosphatase (U/L)	1056 (70)	0	1 (<1)	2512 (70)	0	3 (<1)	826 (56)	0	3 (<1)
ALT (SGPT) (U/L)	1012 (68)	0	1 (<1)	2415 (67)	0	4 (<1)	789 (54)	0	2 (<1)
AST (SGOT) (U/L)	1053 (70)	0	2 (<1)	2509 (69)	0	4 (<1)	826 (56)	0	3 (<1)
Bilirubin (umol/l)	1032 (69)	0	1 (<1)	2470 (68)	0	1 (<1)	787 (53)	0	2 (<1)
Calcium (mmol/L)	1036 (69)	1 (<1)	0	2468 (68)	0	0	814 (55)	0	0
Chloride (mmol/L)	1108 (74)	1 (<1)	0	2604 (72)	1 (<1)	0	869 (59)	3 (<1)	0
Cholesterol (mmol/L)	518 (35)	0	0	1128 (31)	0	0	522 (35)	0	0
Creatine kinase (U/L)	964 (64)	0	3 (<1)	2276 (63)	0	12 (1)	742 (50)	0	4 (1)
Creatinine (umol/l)	1062 (71)	0	3 (<1)	2507 (69)	0	2 (<1)	831 (56)	0	2 (<1)
GGT (U/L)	968 (65)	0	0	2238 (62)	0	2 (<1)	743 (50)	0	6 (1)
Glucose (mmol/L)	920 (61)	10 (1)	0	2089 (58)	18 (1)	1 (<1)	711 (48)	7 (1)	0
LDH (U/L)	1009 (67)	0	2 (<1)	2418 (67)	0	2 (<1)	809 (55)	0	1 (<1)
Lipase (U/L)	659 (44)	0	1 (<1)	1610 (45)	0	3 (<1)	675 (46)	0	2 (<1)
Phosphorus (mmol/L)	1069 (71)	0	1 (<1)	1747 (48)	0	2 (<1)	660 (45)	0	0
Potassium (mmol/L)	1072 (72)	0	3 (<1)	2564 (71)	0	6 (<1)	853 (58)	1 (<1)	2 (<1)
Protein (g/L)	1097 (73)	0	0	2593 (72)	0	0	859 (58)	0	0
Sodium (mmol/L)	1084 (72)	0	1 (<1)	2574 (71)	0	0	854 (58)	0	0
Triglycerides (mmol/L)	554 (37)	0	3 (1)	1339 (37)	0	4 (<1)	538 (37)	0	1 (<1)
Urea nitrogen (mmol/L)	887 (59)	0	0	2004 (55)	0	0	766 (52)	0	0
Uric acid (umol/l)	1001 (67)	0	0	2337 (65)	0	0	789 (54)	0	1 (<1)
Hematology	1088 (73)	2 (<1)	1 (<1)	2623 (73)	0	0	856 (58)	0	1 (<1)
Hemoglobin (g/L)	1005 (67)	0	1 (<1)	2429 (67)	0	0	807 (55)	0	1 (<1)
Platelets (giga/l)	1041 (69)	2 (<1)	0	2491 (69)	0	0	801 (54)	0	0
RBC (tera/l)	1004 (67)	1 (<1)	0	2390 (66)	0	0	775 (53)	0	0
WBC (giga/l)	1026 (68)	1 (<1)	0	2464 (68)	0	0	800 (54)	0	0

1 Lab values are included in this table if 1 or more patients had a potentially clinically important (PCI) change.
Reference: ISS, Table 33, Page 197

Table 7.19: Definitions of J & J's potentially clinically important (PCI) laboratory changes

Laboratory Parameter	Low	High
Albumin (g/L)	<20	> 2 x ULN
Alkaline phosphatase (U/L)	N/A	> 1.5 x ULN
Alanine transaminase (SGPT) (U/L)	N/A	> 3 x ULN
Aspartate transaminase (SGOT) (U/L)	N/A	> 3 x ULN
Bicarbonate (mmol/L)	N/A	N/A
Blood urea nitrogen (mmol/L)	N/A	> 3 x ULN
Calcium (mmol/L)	<1.75	>3
Chloride (mmol/L)	<90	>120
Cholesterol (mmol/L)	N/A	> 2 x ULN
Creatine phosphokinase (U/L)	N/A	> 3 x ULN
Creatinine (umol/L)	N/A	> 1.5 x ULN
Gamma glutamyl transferase (U/L)	N/A	> 3 x ULN
Glucose (mmol/L)	<3.33	> 3 x ULN
Phosphorus (mmol/L)	<0.484	> 1.5 x ULN
Potassium (mmol/L)	<2.80	>5.80
Sodium (mmol/L)	<125	>155
Total bilirubin (umol/L)	N/A	> 1.5 x ULN
Total protein (g/L)	N/A	> 2 x ULN
Triglycerides (mmol/L)	N/A	> 2 x ULN
Uric acid (umol/L)	N/A	> 1.5 x ULN
Hematocrit (%)	N/A	N/A
Hemoglobin (g/L)	<75	> 1.1 x ULN
Platelet count (giga/L)	<100.0	> 3 x ULN
Red blood cell count (tera/L)	<3	> 2 x ULN
White blood cell count (giga/L)	<2.50	> 2.5 x ULN
Lipase (U/L)	N/A	> 3 x ULN
LDH (U/L)	N/A	> 1.5 x ULN

Reference: Protocol for Study 8, Table 8, Page 53.

7.4.2 Vital Signs

Table 7.20 shows the incidence of potentially clinically important vital sign abnormalities in patients without clinically important abnormalities at baseline in the pooled Phase 2 and 3 studies. The tapentadol ER group had a similar or lower proportion of tachycardia, hypotension, hypertension, bradypnea, and tachypnea compared to the PC and active control groups.

The tapentadol ER group had a slightly greater proportion of bradycardia compared to the placebo and active control groups. Many of the tapentadol ER-treated patients with bradycardia (heart rate ≤ 45 beats per minute) had baseline bradycardia (heart rate 45 to 60 beats per minute). Opioids have been associated with bradycardia, especially opioid overdoses. Therefore, there is a possible causal relationship between bradycardia and tapentadol ER and the tapentadol ER label should include bradycardia.

Table 7.20: Incidence of potentially clinically important vital sign abnormalities in the Phase 2 and 3 studies[1]

		Placebo (n=1498)	Tapentadol ER (n=3613)	Oxycodone CR (N=1472)	Tramadol PR (n=249)
Heart Rate (beats per minute)					
Bradycardia	**Value ≤ 45 with baseline > 45**	**2 (0.1%)**	**10 (0.3%)**	**1 (0.1%)**	**0 (0%)**
Tachycardia	**Value ≥ 115 with baseline < 115**	**6 (0.4%)**	**21 (0.6%)**	**8 (0.7%)**	**3 (1.3%)**
Systolic Blood Pressure (mmHg)					
Hypotension	**Value ≤ 90 with baseline > 90**	**17 (1.2%)**	**57 (1.7%)**	**21 (1.7%)**	**2 (0.9%)**
Hypertension	**Value ≥ 180 with baseline < 180**	**12 (0.8%)**	**39 (1.2%)**	**10 (0.8%)**	**5 (2.2%)**
Respiratory Rate (respirations per minute)					
Bradypnea	**Value < 7 with baseline ≥ 7**	**2 (0.1%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Tachypnea	**Value > 25 with baseline ≤ 25**	**17 (1.2%)**	**24 (0.7%)**	**9 (0.7%)**	**2 (0.9%)**

1 In patients with no clinically important abnormal vital sign values at baseline. These values are based on the number of patients who had these vital sign measurements.
Reference: ISS, Table 34, Page 204.

7.4.3 Assessment of Pro-arrhythmic Effects and Electrocardiograms

Assessment of AEs for Potential Pro-arrhythmic Effects: It is important to assess for the presence of AEs that could indicate a pro-arrhythmic effect of small molecules. In the tapentadol ER clinical program, there were no cases of torsade de pointes and there was 1 case of ventricular fibrillation in a tapentadol ER-treated patient:

> Patient # 701313 in Study 7: A 64 year old male with a history of coronary artery disease, s/p cardiac bypass surgery, hypertension, diabetes type 2, hypercholesterolemia, sleep apnea, esophagitis, chronic low back pain, osteoarthritis, and depression was treated with OL tapentadol ER and dextromethorphan, cefdinir, and diphenhydramine. After 12 days of chest pain, he underwent a cardiac catheterization which was complicated by a severe episode of ventricular fibrillation on Day 50. Tapentadol ER was permanently discontinued on Day 56.

The ventricular fibrillation was likely due to the transient ischemia during the cardiac catheterization and not likely due to tapentadol ER.

Through QT Studies of Tapentadol: J & J sponsored 2 thorough QT studies of tapentadol:

- A thorough QT study of tapentadol IR (Study HP5503/25), submitted in the tapentadol IR NDA, was reviewed by Dr. Ellen Fields, the primary reviewer for tapentadol IR, and the through QT team (i.e., Interdisciplinary Review Team for QT Studies).
- A thorough QT study of tapentadol ER study submitted in this NDA (i.e., Study HP10).

Thorough QT Study of Tapentadol IR: Dr. Fields and the QT team found that the QT study of tapentadol IR was negative – there was no significant QT prolongation of the two tapentadol IR doses (100 mg every 6 hours and 150 mg every 6 hours). The largest upper bounds of the 2-sided 90% confidence interval for the mean difference between tapentadol IR groups (100 mg and 150 mg every 6 hours) and placebo were

below 10 ms. The upper bounds of the 2-sided 90% CI for the mean difference between moxifloxacin group (positive control) and placebo was greater than 10 ms. This QT study did not assess the QT interval at higher than anticipated exposures because of dose-limited toxicities of higher doses (e.g., dizziness, vomiting, nausea). For more details on the tapentadol IR thorough QT study see Dr. Fields review and the QT team's review.

Thorough QT Study of Tapentadol ER: Study HP10 was a randomized, crossover, DB, PC, moxifloxacin-controlled study of two doses of tapentadol ER. Patients were randomized 1:1:1:1 to receive tapentadol ER 86 mg BID (n=35), tapentadol ER 172 mg BID (n=36), or placebo (n=37) for 2.5 days or a single 800 mg dose of moxifloxacin (n=34). The largest upper bounds of the 2-sided 90% confidence interval for the mean difference between tapentadol ER groups (72 and 86 mg BID) and placebo were below 10 ms. The upper bounds of the 2-sided 90% CI for the mean difference between moxifloxacin group (positive control and placebo was greater than 10 ms. Although this thorough QT study was negative (tapentadol ER did not significantly prolong the QT interval) this study did not assess tapentadol exposures greater than anticipated exposures. However, a thorough QT study of tapentadol ER was not needed to assess tapentadol's effects on the QT interval because the thorough QT study of tapentadol IR was sufficient.

Assessment of Intervals in Phase 2 and 3 Studies: There was no difference in the proportion of patients (with normal baseline values) in the tapentadol ER, placebo control, and active control groups (i.e., oxycodone CR and tramadol PR) in the Phase 2 and 3 studies who had PR, QRS, and QT prolongation.

7.4.4 Special Safety Studies

See Section 7.4.3 (Assessment of Pro-arrhythmic Effects and Electrocardiograms) for an evaluation of the 2 thorough QT studies of tapentadol.

(b) (4)

[redacted]

7.4.5 Immunogenicity

Tapentadol ER is a small molecule and immunogenicity assessments are not required.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Table 7.21 displays AEs by dose category (high and low) for patients within the same dose category for ≥ 8, ≥ 10, or ≥12 weeks in the 12-week Maintenance Period in the pooled induction trials (Studies 8, 9, and 11). The proportion of patients with AEs was similar in the high and low dose tapentadol ER groups; whereas, patients in the high-dose oxycodone CR group had a greater incidence of AEs than patients in the low dose group. There was no clear evidence of a greater incidence of AEs by tapentadol ER dose within the proposed 100 to 250 mg BID dose range.

Table 7.21: AEs by dose in the pooled induction trials for patients within the same dose range in the 12-week Maintenance Periods[1]

	Oxycodone CR		Tapentadol ER	
	High Dose	**Low-Dose**	**High Dose**	**Low-Dose**
For patients within the same dose range for ≥ 8 weeks	**72% (n=116)**	**59% (n=243)**	**56% (n=182)**	**55% (n=295)**
For patients within the same dose range for ≥ 10 weeks	**73% (n=99)**	**58% (n=215)**	**55% (n=167)**	**53% (n=264)**
For patients within the same dose range for ≥ 12 weeks	**72% (n=60)**	**57% (n=162)**	**52% (n=113)**	**53% (n=174)**

1 Pooled Studies 8, 9, and 11.
Low Dose was defined as < 200 mg BID for tapentadol ER and < 40 mg BID for oxycodone CR.
High Dose was defined as ≥ 200 mg BID for tapentadol ER and ≥ 40 mg BID for oxycodone CR.
Reference: Appendix 4.1.6.6, Page 16517; Appendix 4.1.6.7, Page 16529; Appendix 4.1.6.8, Page 16540

7.5.2 Time Dependency for Adverse Events

Table 7.22 displays AEs within the gastrointestinal and nervous system SOCs by duration of treatment in the 3 pooled induction trials (Studies 8, 9, and 11) and the 1-year OL study. AEs were defined as any AE that occurred on or after the first intake of study medication (or that started before the first intake of study drug and worsened in intensity during the period) until 3 days of last treatment. In the first 12 weeks of the induction trials, the greatest incidence of AEs occurred within the first 4 weeks in all 3 treatment groups. Similarly, in the first 48 weeks of the 1-year open label safety study, the greatest incidence of AEs occurred within the first 4 weeks in all 3 treatment groups. This disparity in incidence of AEs was likely due to the design of these trials — forced titration occurred within the first 3 weeks of all 4 trials.

In the 3 induction trials, patients in all three groups had greater incidences of AEs after Week 12 and in the 1-year safety study patients in both groups had greater incidences of AEs after Week 48. A large portion of these AEs were withdrawal AEs — they occurred after stopping study medication up until 3 days after dosing. See Table 7.29 in Section 7.6.4 (Overdose, Drug Abuse Potential, Withdrawal and Rebound) for an analysis of withdrawal AEs.

There was no clear evidence of an increased incidence of AEs with increased duration in tapentadol ER-treated patients.

Table 7.22: GI and Nervous System AEs by duration in the 3 pooled DB induction trials and the 1-year open label study[1]

	Pooled DB 15-Week Trials[2]			1-Year OL Safety Study[3]	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
Gastrointestinal AEs (SOC)[2]	**657 (66%)**	**420 (43%)**	**264 (27%)**	**143 (64%)**	**467 (52%)**
≤ 4 weeks	32%	11%	6%	28%	10%
> 4 weeks and ≤ 8 weeks	7%	5%	2%	5%	5%
> 8 weeks and ≤ 12 weeks	3%	2%	1%	3%	3%
> 12 weeks and ≤ 24 weeks[3]	24%	25%	17%	4%	4%
> 12 weeks and ≤ 48 weeks	0%	0%	0%	3%	5%
> 48 weeks and ≤ 56 weeks	0%	0%	0%	23%	25%
Nervous System AEs (SOC)[2]	**463 (46%)**	**394 (40%)**	**223 (23%)**	**89 (40%)**	**405 (45%)**
≤ 4 weeks	23%	11%	4%	18%	10%
> 4 weeks and ≤ 8 weeks	4%	5%	2%	2%	6%
> 8 weeks and ≤ 12 weeks	2%	1%	1%	1%	2%
> 12 weeks and ≤ 24 weeks[3]	17%	23%	16%	2%	4%
> 12 weeks and ≤ 48 weeks	0%	0%	0%	2%	4%
> 48 weeks and ≤ 56 weeks	0%	0%	0%	14%	21%

1 AEs were defined as any AE that occurred on or after the first intake of study medication (or that started before the first intake of study drug and worsened in intensity during the period) until 3 days of last treatment.

2 GI AEs were AEs in the gastrointestinal disorders SOC and nervous system AEs were in the nervous system SOC. The most common GI AEs were nausea, constipation, and vomiting and the most common nervous system AEs were headache, dizziness, and somnolence.

3 In the pooled DB, patients received treatment for up to 15 weeks

Reference: ISS, Appendix 4.1.4.5, Pages 15046-15065.

7.5.3 Drug-Demographic Interactions

Table 7.23 displays AEs by baseline demographics in the pooled Phase 2 and 3 studies of tapentadol ER. There were no significant differences in the incidence of AEs in tapentadol ER-treated patients by age, gender, race, or weight. A greater proportion of patients in the tapentadol ER and placebo groups had AEs in North America compared to Europe.

Table 7.23: AEs by demographics in the pooled Phase 2 and 3 studies[1]

		Placebo	Tapentadol ER	Oxycodone CR	Tramadol
Entire Population		**817/1498 (55%)**	**2589/3613 (72%)**	**1271/1472 (86%)**	**163/249 (66%)**
Age	< 65	592/1102 (54%)	1835/2590 (71%)	917/1075 (85%)	128/193 (66%)
	≥ 65	225/396 (57%)	754/1023 (74%)	354/397 (89%)	35/56 (63%)
Gender	Male	120/277 (51%)	514/1015 (69%)	350/496 (86%)	59/99 (60%)
	Female	250/540 (57%)	950/1574 (74%)	602/775 (87%)	104/150 (69%)
Race[2]	White	703/1297 (54%)	2187/3069 (71%)	809/1068 (87%)	160/245 (65%)
	Black	72/120 (60%)	224/308 (73%)	125/141 (89%)	1/2 (50%)
	Hispanic	22/53 (42%)	72/126 (76%)	48/65 (74%)	–
Region[2]	North America	508/877 (58%)	1868/2468 (76%)	924/1070 (86%)	–
	Europe	288/598 (48%)	701/1125 (62%)	330/384 (86%)	163/249 (66%)
Weight (BMI)[2]	Normal	98/202 (49%)	353/525 (67%)	154/183 (84%)	48/75 (64%)
	Overweight	244/479 (51%)	769/1121 (69%)	358/409 (88%)	65/97 (67%)
	Obese	464/801 (58%)	1448/1942 (75%)	746/864 (86%)	50/77 (65%)

1 See Tables 5.1 and 5.2 for a list of the 10 Phase 2 and 3 studies.
2 Patients in the Other race category were not included in this table. There were too few patients in the underweight BMI category and they were not included in this table. There were too few patients in the "rest of the world" region category and they were not included in this table.
Reference: ISS, Appendix 11.1.3, Pages 15418-15420; Appendix 11.2.1, Pages 24204-24206; Appendix 11.3.3, Pages 16286-16290; Appendix 11.4.1, Pages 16787-16791; Appendix 11.8.1, Pages 19896-19900.

7.5.4 Drug-Disease Interactions

Table 7.24 displays AEs by prior opioid use and concomitant medication in the pooled Phase 2 and 3 studies. The proportion of tapentadol ER-treated patients with AEs was similar irrespective of prior opioid use. A greater proportion of tapentadol-ER treated patients who received concomitant opioids had AEs compared to tapentadol-ER treated patients who did not receive concomitant opioids. It is known that the concomitant use of opioids increases the risk of opioid-related toxicities and tapentadol ER label will contain this statement. Patients in the tapentadol ER and placebo groups who received concomitant non-opioids analgesics had a greater incidence of AEs compared to patients who did not receive concomitant non-opioid analgesics.

Table 7.24: AEs by prior opioid use and concomitant medication in the pooled Phase 2 and 3 studies[1]

		Placebo	Tapentadol ER	Oxycodone CR	Tramadol
Entire Population		**817/1498 (55%)**	**2589/3613 (72%)**	**1271/1472 (86%)**	**163/249 (66%)**
Prior Opioid Use	Yes	265/453 (59%)	937/1272 (74%)	430/491 (88%)	36/59 (61%)
	No	551/1044 (53%)	1642/2329 (71%)	840/980 (86%)	126/189 (67%)
Concomitant Opioid Use	Yes	82/124 (66%)	272/351 (78%)	91/99 (92%)	18/26 (69%)
	No	735/1374 (54%)	2317/3262 (71%)	1180/1373 (86%)	145/223 (65%)
Concomitant Non-Opioid Analgesic Use	Yes	315/476 (66%)	1041/1326 (79%)	405/456 (80%)	40/57 (70%)
	No	502/1022 (49%)	1548/2287 (68%)	866/1016 (85%)	123/192 (64%)

Reference: ISS, Appendix 11.6.1, Pages 17949-17951; Appendix 11.7.1, Pages 18308-18312

7.5.5 Drug-Drug Interactions

Five randomized, OL, crossover, drug-drug interaction (DDI) studies of tapentadol IR co-administered with metoclopramide, omeprazole, probenecid, naproxen and aspirin, or acetaminophen in healthy subjects were submitted to the tapentadol IR NDA. In all of these studies there were no significant changes in the PK of tapentadol. For additional information, see Dr. David Lee's review (clinical pharmacology) and Dr. Ellen Field's review (primary clinical reviewer) of the tapentadol IR NDA.

No additional DDI studies were performed with tapentadol ER.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The use of opioid drug products has not been associated with an increased risk of malignancy. To assess for a possible malignancy signal, all malignancies except for non-melanoma skin cancer (NMSC) were evaluated in the pooled 15-week DB induction trials and the 1-year safety study of tapentadol ER in the chronic treatment of pain. As shown in Table 7.25, the tapentadol ER group had a lower proportion of malignancies except NMSC compared to the oxycodone CR and placebo groups in the pooled 15-week induction trials and the tapentadol ER group had a similar proportion of malignancies except NMSC as the oxycodone CR group in the 1-year safety study. Although these studies were relatively short in duration to assess malignancies, there was no evidence of an increased malignancy signal in the tapentadol ER studies in patients with chronic pain.

Table 7.25: All malignancies except NMSC in the 3 pooled, DB Phase 3 trials and 1 OL Phase 3 study of tapentadol ER in chronic pain[1]

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
Total	**3 (0.3%)**	**0 (0%)**	**1 (0.1%)**	**1 (0.4%)**	**4 (0.4%)**
Thyroid neoplasm	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	2 (0.2%)
Breast cancer	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Lung neoplasm	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Bladder cancer recurrent	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lung cancer metastatic	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rectal cancer	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myeloid leukemia	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)

1 Preferred terms in the Neoplasms benign, malignant, and unspecified SOC that were malignant except NMSC.
Reference: ISS, Appendix 4.1.4.2, Pages 14986-14987.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant women were excluded from all tapentadol studies and women of child-bearing potential were required to practice an effective method of birth control. There were a total of 12 reports of pregnant women who received any formulation of tapentadol in J & J sponsored studies including the complete tapentadol IR program (see Table 7.26). Of the 12 reports, 6 reports occurred in women who received

tapentadol ER and 6 reported occurred in women who received other formulations (4 reports with tapentadol IR, 1 report with intravenous tapentadol, and 1 report with tapentadol oral solution). Note, the reports with tapentadol IR and intravenous tapentadol were previously documented in Dr. Ellen Field's primary clinical review of the tapentadol IR NDA. For the sake of completeness, these reports are included in Table 7.26 below.

Of the 12 pregnancy reports with tapentadol use, there were 4 normal healthy children delivered, 4 reports had no additional information on the outcome, 2 had elective terminations, and 2 experienced miscarriages. It is difficult to determine the relationship between tapentadol use and miscarriages.

However, this reviewer agrees with J & J's proposal to include a statement in Section 8.1 (Pregnancy) of the tapentadol ER label that states that there "are no adequate and well controlled studies of tapentadol ER in pregnant women. Tapentadol ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." This statement is also in the approved tapentadol IR label.

Table 7.26: Pregnancies in tapentadol-treated subjects in any J & J sponsored study of all tapentadol formulations[1]

Subject	Study	Event	Outcome
Tapentadol ER			
112169	11	Female patient had about 15 days of exposure to tapentadol during her pregnancy.	Normal healthy child.
103408	34	Female patient received 1 dose of tapentadol ER during pregnancy.	No additional information
104630	46	Female patient received 1 dose of tapentadol ER during her pregnancy.	Elective termination of pregnancy.
105701	10	28 year-old female with history of schizophrenia, seizures, marijuana use, smoking, anxiety, and previous spontaneous abortion. Had 3 months of tapentadol ER exposure in Study 10 (after additional tapentadol ER exposure in a prior study).	Hospitalized for psychotic disorder associated with hyperemesis gravidarum (complicated intrauterine pregnancy) for 12 days then re-hospitalized 1.5 months later for the same conditions and had a miscarriage.
105576	10	29 year-old obese female gravida 4 para 3, became pregnant approximately 156 days after receiving the first dose of tapentadol ER and refused to stop tapentadol ER.	Hospitalized 2 months later for first trimester miscarriage.
105301	10	28 year old woman became pregnant about 367 days after receiving the first dose of tapentadol ER.	No additional information
Tapentadol IR			
101101	PAI-1011	Single dose of tapentadol IR	Elective termination of pregnancy.
301010	PAI-3003	Multiple doses of tapentadol IR	Normal healthy child.
302165	PAI-3003	Multiple doses of tapentadol IR	No additional information
7279/574	KF04	Multiple doses of tapentadol IR	Normal healthy child.
Tapentadol Oral Solution			
103313	33	Single dose of tapentadol oral solution	No additional information
Intravenous tapentadol			
0026	HP02	4 single doses of IV tapentadol	Normal healthy child.

1 As of September 30, 2009 (the cut-off for the 4-month Safety Update).

7.6.3 Pediatrics and Assessment of Effects on Growth

In this NDA, J & J did not submit any studies of tapentadol ER in pediatric patients and J & J has not initiated any pediatric studies of tapentadol ER. See Section 1.4 for a discussion of J & J's proposals for addressing PREA requirements.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose: In the Phase 2 and 3 tapentadol studies, 108 (3%) of tapentadol ER-treated patients and 50 (3%) of oxycodone CR-treated patients received doses greater than the maximum proposed tapentadol ER daily dose (> 500 mg) or exceeded the maximum allowed oxycodone daily dose (> 100 mg) at least once during the studies. Note these numbers include patients in Study 15 (the randomized withdrawal trial) who may have received up to 550 mg of tapentadol ER according to the protocol ─ up to 500 mg/day plus up to 50 mg for rescue analgesia. Tapentadol ER-treated patients who received doses greater than the maximum proposed daily dose (> 500 mg) had a similar proportion of AEs compared to all the tapentadol-ER-treated patients in the Phase 2 and 3 studies (69% vs. 72%). Similarly, oxycodone CR-treated patients who received daily doses > 100 mg had a similar proportion of AEs compared to all the oxycodone CR-treated patients in the Phase 2 and 3 studies (82% vs. 86%).

There was one tapentadol-ER-treated patient who overdosed. Patient 702277 (Study 7), a 48 year old woman with substance abuse, depression LBP, insomnia, attention deficit syndrome. On Day 39, she was diagnosed with severe visual disturbance and euphoria due to overdose that resolved 15 days later (Day 53). She took 57 tablets of tapentadol ER within ten days (instead of 20 tablets over the ten day period) ─ almost 3 times the maximum recommended daily dose.

The tapentadol ER label will contain the standard overdosage language for opioid agonists.

Drug Abuse: Table 7.27 shows the incidence of "possible abuse-related AEs" (about 130 MedDRA lowest level terms selected by the Agency's Control Substance Staff that could indicate drug abuse) in the 3 induction trials and the one-year safety study. The opioid groups had a greater incidence of one or more of these abuse-related AEs than the placebo group. Tapentadol ER had a slightly lower incidence of one or more of these abuse-related AEs than the oxycodone CR group.

In a drug accountability analysis, a similar proportion of dispensed pills were missing in the tapentadol ER, oxycodone CR, and placebo groups (1%). Table 7.28 presents the narratives of patients in the induction trials with reports of study medication loss. Patients in the tapentadol ER group [1/980 (0.1%)] had a similar or lower proportion of patients who reported study medication loss compared to the placebo group [1/993 (0.1%)] and the oxycodone CR group [4/1001 (0.4%)].

The tapentadol ER label will contain the standard labeling for opioid abuse.

Table 7.27: Possible abuse-related AEs (incidence ≥ 0.5% in any treatment group) in the 3 pooled induction trials and the 1 OL safety study[1]

	Pooled DB 15-Week Trials[2]			1-Year OL Safety Study[3]	
	Oxycodone CR (n=1001)	Tapentadol ER (n=980)	Placebo (n=993)	Oxycodone CR (n=223)	Tapentadol ER (n=894)
Total n (%)with selected AEs	**361 (36%)**	**265 (27%)**	**99 (10%)**	**69 (31%)**	**279 (31%)**
Dizziness	165 (17%)	132 (14%)	49 (5%)	33 (15%)	75 (8%)
Drowsiness	82 (8%)	56 (6%)	19 (2%)	10 (5%)	60 (7%)
Sleepiness	47 (5%)	28 (3%)	4 (<1%)	5 (2%)	27 (3%)
Somnolence	33 (3%)	25 (3%)	8 (1%)	8 (4%)	34 (4%)
Light-headed	16 (2%)	9 (1%)	10 (1%)	3 (1%)	24 (3%)
Concentration impaired	10 (1%)	5 (1%)	3 (<1%)	3 (1%)	12 (1%)
Disorientation	5 (1%)	1 (<1%)	1 (<1%)	2 (1%)	6 (1%)
Lightheadedness	4 (<1%)	4 (<1%)	3 (<1%)	0 (0%)	4 (<1%)
Irritability	4 (<1%)	4 (<1%)	4 (<1%)	2 (1%)	3 (<1%)
Sleepy	3 (<1%)	3 (<1%)	3 (<1%)	2 (1%)	9 (1%)

1 AEs were according to the lowest level term. Studies include the DB PC and oxycodone CR-controlled Studies 8, 9, and 11 and the OL, oxycodone CR controlled study (Study 7).). AEs are listed if they occurred in ≥ 0.5% in any treatment group (i.e., placebo, all tapentadol ER, or all oxycodone CR).
Reference: Adapted from Amendment #5, Attachment 1.3, Pages 11-15.

Table 7.28: Cases of study medication loss in Studies 8, 9, and 11

Patient #	Study	Discontinuation Characterization	Additional Information
Tapentadol ER			
112116	11	Study medication non-compliant	Study medication was stolen from patient's car. Investigator and sponsor decided to drop the patient from the trial.
Oxycodone CR			
806248	8	Study medication non-compliant	54 year old male with history of left knee OA stated that the study medication was stolen from his car. The PI discontinued the patient
113424	11	Study medication non-compliant	Patient lost study drug on the way to his clinic visit.
115160	11	Study medication non-compliant	Study drug was stolen.
116046	11	Study medication non-compliant	Study medication was eaten by dog and also stolen.
Placebo			
113545	11	Lost to follow-up	Car was broken into and study medication was stolen.

Reference: Subject Discontinuation Listing, Pages 222-453

Withdrawal: Table 7.29 displays the incidence of AEs that occurred after study medication discontinuation until 5 days after study medication discontinuation in the 3 induction trials and the one-year OL study. In these 4 studies, study medication was not tapered upon discontinuation. A slightly greater proportion of patients in the opioid groups compared to the placebo group experienced AEs within 5 days of study medication discontinuation. This imbalance was due to several AEs associated with opioid withdrawal (e.g., diarrhea, nausea, anxiety, hyperhidrosis, insomnia, irritability). This demonstrates evidence of withdrawal symptoms following discontinuation of tapentadol ER and is

consistent with other opioids. The tapentadol ER label should contain the standard withdrawal language for opioids.

Table 7.29: Incidence of AEs (incidence ≥ 0.5% in any treatment group) starting within 5 days from the last dose of study drug in the 3 induction trials and the 1-year safety study[1]

	Pooled DB 15-Week Trials			1-Year OL Safety Study	
	Oxycodone CR (n=799)	Tapentadol ER (n=679)	Placebo (n=690)	Oxycodone CR (n=178)	Tapentadol ER (n=645)
Total n (%) of patients with AEs	141 (18%)	93 (14%)	56 (8%)	15 (8%)	93 (14%)
Diarrhea	3%	2%	< 1%	2%	2%
Nausea	3%	2%	1%	1%	2%
Vomiting	2%	1%	1%	1%	1%
Anxiety	2%	1%	< 1%	1%	1%
Hyperhidrosis	1%	1%	< 1%	1%	1%
Headache	1%	1%	1%	0%	0%
Abdominal pain	1%	< 1%	< 1%	0%	1%
Arthralgia	1%	1%	< 1%	0%	1%
Insomnia	1%	1%	< 1%	0%	1%
Constipation	1%	1%	< 1%	1%	1%
Withdrawal syndrome	1%	< 1%	< 1%	1%	1%
Somnolence	1%	< 1%	0%	0%	< 1%
Chills	1%	1%	0%	0%	1%
Irritability	1%	< 1%	< 1%	0%	1%
Urinary tract infection	1%	< 1%	1%	0%	< 1%
Fatigue	< 1%	< 1%	< 1%	0%	1%

1 Using MedDRA preferred terms, incidence ≥ 0.5% in any one combined treatment group (i.e., all tapentadol ER, all oxycodone CR, placebo).
Reference: Adapted from Amendment #5, Attachment 2.1, Pages 16-25.

7.7 Additional Submissions

Table 7.30 displays additional clinical submissions to this NDA. All of the safety and efficacy information in these submissions have been incorporated into this review. Submissions related to CMC and proprietary name review are not included in this table.

Table 7.30: Additional clinical submissions in NDA 200533

#[1]	Type of Submission	Date of J & J Submission	Date of DAAP IR	Comments
0	Original NDA submission	11/30/09	N/A	The safety cut-off date for the original submission was 6/30/09
2	4-month Safety Update	3/30/10	N/A	Safety data from the period 7/1/09 through 9/30/09.[2]
4	Investigation of a Clinical Site	3/12/10	N/A	J & J described their teleconference with DSI on March 10, 2010 regarding potential misconduct at Dr. Allan Soo's clinical site. See Section 3.2 "Compliance with Good Clinical Practices"
5	Response to IR regarding possible abuse-related terms	3/25/10	3/9/10	J & J submitted the following analyses: 1. Possible drug-abuse related low level terms 2. AEs that occurred within 5 days of study drug

#[1]	Type of Submission	Date of J & J Submission	Date of DAAP IR	Comments
				discontinuation (evaluation of withdrawal AEs)
6	**Investigation of a Clinical Site**	**4/2/10**	**N/A**	**J & J described another teleconference with DSI on March 30, 2010 regarding potential misconduct at Dr. Allan Soo's clinical site. See Section 3.2 "Compliance with Good Clinical Practices"**
7	**Investigation of a Clinical Site**	**4/21/10**	**N/A**	**J & J described their teleconference with DSI on April 1, 2010 regarding potential misconduct of (b) (4) with another investigational J & J drug. However, J & J found no evidence of misconduct at (b) (4) clinical sites involving tapentadol ER including Study 7 (1-year long-term safety study) and Study 19 (Phase 2 crossover trial to determine the equianalgesic doses of tapentadol IR and ER).**
8	**Response to DSI IR**	**4/26/10**	**4/13/10**	**J & J responded to DSI's information requests regarding the location of source data, data generated by electronic diaries, site specific patient-level data (e.g., disposition, AEs, protocol violations, pain intensity datapoints, rescue medications, and SOWS and COWS assessments.**
9	**Investigation of a Clinical Site**	**4/26/10**	**N/A**	**J & J described their teleconference with DSI on April 1, 2010 regarding potential misconduct of (b) (4) in Studies 8 and 11 (e.g., improper delegation of authority, incomplete source documentation). J & J will conduct an on-site audit and will follow-up with DSI.**
12	**Response to a Statistical IR**	**5/21/10**	**5/3/10 and 5/19/10**	**J & J stated that 21 patients were included in the ITT statistical population although they did not have a change from baseline in pain intensity greater than 1. These patients were excluded in the per protocol population. The results of the primary endpoint using the ITT and PP populations were similar.**
14	**Response to REMS notification letter.**	**6/21/10**	**4/22/10**	**J & J's proposed REMS amendment in response to FDA's REMS April 2010 notification letter. J & J agreed with the FDA's request to add an elements to assure safe use (ETASU) as a REMS component for tapentadol ER.**
16	**Response to a Clinical IR**	**8/5/10**	**7/23/10**	**J & J responded to information requests regarding exposure adjusted rates of SAEs, DAEs, and AEs of atrial fibrillation, syncope, intestinal obstruction, COPD, depression, and hallucinations in pooled Studies 7, 8, 9, and 11. J & J also responded to information requests regarding the baseline disease characteristics of the patients in the ongoing cancer studies of tapentadol ER.**

IR is information request
1. # is sequence # in the NDA
2. The Safety Update provided complete study reports for 2 recently completed single-dose crossover, bioequivalence Phase 1 studies of tapentadol ER (Studies 49 and 51). It also included reports of deaths, SAEs, and pregnancies in the following 6 ongoing studies: 5 ongoing Phase 3 studies (Studies 10, 13, 14, KF42, and 20) and 1 ongoing Phase 2 study (Study C01). Studies 20 and 14 were recently completed (databases were recently locked) and final study reports have not yet been submitted to the FDA.

8 Post-marketing Experience

Tapentadol ER is not approved in the United States or any other country. See Section 2.3 (Availability of Tapentadol in the United States) for discussion of the post-marketing experience of tapentadol IR.

9 Appendices

9.1 Literature Review/References

Dworkin, Robert et al. "Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations." *The Journal of Pain 2008;9(2):*105-121.

Labeling and primary medical officer reviews for the following approved long-acting opioids in the treatment of chronic pain: oxycodone CR (OXYCONTIN), morphine sulfate and naltrexone (EMBEDA), tramadol (ULTRAM ER, RYZOLT), and hydromorphone (EXALGO).

Labeling and primary reviews for tapentadol IR (NUCYNTA).

Meldrum, Marcia. "A Capsule of Pain Management." *JAMA* 2003;290(18);1270-1275.

Rosenquist, Richard et al. "Practice Guidelines for Chronic Pain Management. An Updated Report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine." *Anesthesiology* 2010;112:810-833.

9.2 Labeling Recommendations

Below are the major changes recommended for J & J's proposed labeling for tapentadol ER. These recommendations may change after internal labeling discussions and after labeling discussions with J & J.

(b) (4)

(b) (4)

[redacted]

9.3 Advisory Committee Meeting

No advisory committee meeting was requested by the FDA for the tapentadol ER NDA for chronic pain because:

- Tapentadol ER would be the 8th long-acting opioid moiety (13th long-acting opioid product) approved for the chronic treatment of pain in the United States (long-acting forms of oxycodone, morphine, tramadol, oxymorphone, methadone, fentanyl, and hydromorphone are approved for chronic pain).
- The safety profile of long-acting opioids is well-established and tapentadol ER did not have a worse overall safety profile than oxycodone CR in the submitted studies.

(b) (4)

9.4 Individual Study Reports

9.4.1 Study 8 [abbreviation for Study R331333-PAI-3008 (KF5503/11)]

The following description of the protocol for Study 8 is based on amendment 1 of the protocol (dated January 9, 2008) and the original SAP (dated July 31, 2008). See Table 9.1 for the dates of all amendments to the protocol and SAP for Study 8. In Study 8, the study was initiated on February 7, 2007 and the study ended (the day of the last investigation on the last patient) on July 15, 2008.

Table 9.1: Amendments to the Study 8 protocol and SAP

	Amendment	Date
Protocol	Original Protocol	November 29, 2006
	Amendment 1	January 9, 2008
SAP	Original SAP	July 31, 2008

In amendment 1 of the protocol, there were no significant changes to the study design of Study 8 compared to the original protocol, except the definition of the primary statistical population for the efficacy analyses was changed to satisfy the FDA's recommendations (see Table 9.2). This change was acceptable.

Table 9.2: Changes to the original protocol of Study 8

Definition of the primary statistical population for the efficacy analyses	
Original Protocol (November 29, 2006)	All randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline pain assessment
Amendment 1 (January 9, 2008)	All randomized patients who received at least 1 dose of study medication.

The SAP had no changes from the statistical methods as described in the protocol except that the Cochran-Mantel-Haenszel (CMH) test was not adjusted for study center (due to sparse data) for the following endpoints: sleep questionnaire, response rates for achieving 30% and 50% improvement in pain intensity, and the patient global impression of change. This change was acceptable.

Title: Throughout this review, Study 8 will be the abbreviation for Study R331333-PAI-3008 (J & J's trial designation) and Study KF5503/11 (Grünenthal's trial designation). J & J and Grünenthal used different protocol numbers for the same study. Study 8 is entitled, "A Randomized Double-Blind, Placebo- and Active-Control, Parallel-arm, Phase III Trial with Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of CG5503 Extended-Release (ER) in Subjects with Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee."

Objectives of Study 8: The primary objective of Study 8 was to evaluate the efficacy and safety of orally administered tapentadol ER at doses of 100-250 mg twice daily in patients with moderate to severe chronic pain from knee OA. Secondary objectives included the collection of PK information for dose verification and population PK analyses.

Overall Design of Study 8: Randomized, DB, PC and oxycodone CR-controlled, parallel group, MC (112 sites in the U.S., Canada, New Zealand, and Australia), Phase 3 trial of controlled adjustment of tapentadol ER in patients with moderate to severe chronic pain (≥ 3 months) due to knee OA. Patients must have been at least 40 years old, taking analgesic medications for their knee OA ≥ 3 months, and dissatisfied with their current analgesics due inadequate analgesia or intolerability. If patients were receiving opioids at the start of the trial, they must have been taking daily doses of opioids equivalent to ≤ 160 mg of oral morphine.

Prior to receiving study medication and prior to randomization, patients entered a 3- to 7-day Washout Period where all analgesics (including acetaminophen) were discontinued and new analgesics were not allowed. To be randomized and receive study medication, patients needed to have an average pain intensity score of ≥ 5 on an 11-point NRS during the last 3 days of the Washout Period. After completion of the Washout Period, patients entered the 3-week Titration Period and were randomized 1:1:1 to tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID and then after 3 days the dose was increased to tapentadol ER 100 mg BID, oxycodone CR 20 mg BID, and placebo BID, respectively. In the Titration Period, upward or downward titration was allowed in increments of tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID (at a minimum of 3-day intervals for upward titration) to optimize the patients' analgesic needs and tolerability. Following the Titration Period, patients entered the 12-week Maintenance Period where dose adjustment was discouraged; however, up or down titration was permitted if needed. The allowed dose ranges in the 15-week treatment period (Titration and Maintenance Periods) were tapentadol 100 to 250 mg BID, oxycodone CR 20 to 50 mg BID, and placebo BID. All analgesics were not allowed during the Titration and Maintenance Periods of Study 8 with the following exceptions:

- Study medication
- Daily aspirin doses ≤ 325 mg per day for cardiovascular prophylaxis
- Up to 1000 mg of daily acetaminophen for rescue analgesia during the Titration Period (except for the last 3 days) and up to 1000 mg of acetaminophen per day for ≤ 3 consecutive days for non-trial-relating pain (not pain from knee OA) during the Maintenance Period.

At the end of the Maintenance Period, patients stopped their study medication without a taper and may have been started on appropriate analgesic medication according to local practice standards.

Eligibility Criteria of Study 8 at the Screening Visit: Table 9.3 displays the eligibility criteria in Study 8 at the Screening Visit.

Table 9.3: Eligibility criteria in Study 8 at the Screening Visit[4]

Inclusion Criteria: To have been eligible to participate in the study, patients had to have met all of the following criteria:	**Exclusion Criteria: If patients had any of the following conditions, they were not eligible to participate in the study:**
1. ≥ 40 years old with knee OA based on ACR criteria[2] and functional capacity class of I-III[3] and pain at the reference joint ≥ 3 months. **2. Taking analgesic medications for knee OA ≥ 3 months prior to the Screening Visit and dissatisfied with current therapy (i.e., for patients taking opioids, dissatisfied with efficacy or tolerability; and for patients taking non-opioids dissatisfied with efficacy).[4]** **3. Patients requiring opioids must be taking daily doses of opioid-based analgesic equivalent to ≤ 160 mg of oral morphine.[4]** **4. Men and non-pregnant, non-lactating women. Sexually active women must be post menopausal, surgically sterile, or practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double barrier method, contraceptive patch, male partner sterilization) before entry and throughout the trial. Women must have a negative serum ß-hCG pregnancy test at screening.** **5. Patients must have signed an informed consent document indicating that they understand the purpose of and procedures required for the trial and are willing to participate in the trial.**	**1. Taking prohibited medications at the Screening Visit (antipsychotics, SNRIs, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, MAO inhibitors, corticosteroids (including oral, intramuscular, soft tissue, intra-articular, depot steroids), or hyaluronic acid.[4]** **2. Has a clinically significant disease that may affect efficacy or safety assessments, e.g., significant unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, psychiatric (resulting in disorientation, memory impairment or inability to report accurately) or metabolic disturbances.** **3. Presence of conditions other than OA of the reference joint that could confound the assessment or self-evaluation of pain, (e.g., anatomical deformities, significant skin conditions such as abscess, fibromyalgia).** **4. History and clinical signs at reference joint from crystal induced (e.g., gout, pseudogout), metabolic, infectious and autoimmune disease.** **5. Life-long history of seizure disorder or epilepsy. Any of the following within 1 year: mild/moderate traumatic brain injury, stroke, transient ischemic attack, and brain neoplasm. Severe traumatic brain injury within 15 years (consisting of ≥ 1 of the following: brain contusion, intracranial hematoma, either unconsciousness or post traumatic amnesia lasting for more than 24 hours) or residual sequelae suggesting transient changes in consciousness.** **6. History of significant liver insufficiency; chronic hepatitis B or C, or HIV, presence of active hepatitis B or C within the past 3 months.** **7. History of malignancy within past 2 years, with exception of basal cell carcinoma that has been successfully treated.** **8. Surgery of the reference joint within 3 months of screening or the patient is expected to require surgical intervention on reference joint during the trial.** **9. Uncontrolled hypertension (repeated systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg).** **10. Laboratory values above or below limits of normal that may affect the safety of the patient.** **11. Patients with severely impaired renal function.** **12. Patients with moderately or severely impaired hepatic function, or patients with laboratory values reflecting inadequate hepatic function (ALT, AST greater than threefold upper limit of normal).** **13. Clinically relevant history of hypersensitivity, allergy, or contraindication to oxycodone or acetaminophen (or ingredients).** **14. History of alcohol and/or drug abuse.** **15. Pending litigation due to chronic pain or disability.** **16. Any painful procedure during the trial (e.g., major surgery) that may affect the efficacy or safety assessments.** **17. Participation in another trial concurrently, or within 30 days of enrollment into this trial.** **18. Previous participation in this trial or other trials with tapentadol.** **19. Known to or suspected of not being able to comply with the protocol and the use of the investigational products.** **20. Employees of Investigator or trial site, with direct involvement in proposed trial or other studies under the direction of that Investigator or trial site, as well as family members of employees or the Investigator.**

1 The Screening Visit was 3 to 21 days prior to initial dosing.
2 ACR criteria for OA: Satisfy one of the following:

- At least 5 of the following 9 clinical or laboratory criteria: ≥ 50 years old, stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth, ESR < 40 mm/hour, rheumatoid factor < 1:40, and SF OA.
- At least 1 of the following clinical or Xray criteria: ≥ 50 years old, stiffness < 30 minutes, crepitus, osteophytes.

- At least 3 of the following 6 clinical criteria: 50 years old, stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth.

3 Functional class of OA:

- Class I: Complete functional capacity with ability to carry on all usual duties without handicaps.
- Class II: Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints.
- Class III: Functional capacity adequate to perform only a few or none of the duties of usual occupation or of self-care.
- Class IV: Largely or wholly incapacitated with subject bedridden or confined to a wheelchair, permitting little or no self-care.

4 Patients must have been taken analgesics (including NSAIDs such as COX-II inhibitors, or opioids) for knee OA ≥ 3 months at the Screening Visit (for at least 3 months); however, they must washout of their analgesics during the Washout Period, prior to randomization.

Reference: Adapted from Protocol 8 (amendment 1), Pages 3900-3903

Eligibility Criteria Prior to Randomization: Prior to randomization, patients needed to have a baseline pain intensity score of ≥ 5 on an 11-point NRS, calculated as the average pain intensity during the last 3 days prior to randomization (during the Washout Period). Patients needed to have a minimum of 5 out of 6 possible assessments (twice daily assessments for the last 3 days of the Washout Period).

Study Medication: At completion of the Washout Period, patients were randomized 1:1:1 to tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID (with or without food) and then entered the Titration Period. After 3 days of receiving the initial dose, the dose was increased to tapentadol ER 100 mg BID, oxycodone CR 20 mg BID, and placebo BID in the 3 groups, respectively. This was the minimum dose allowed for the remainder of the trial. Subsequently, upward titration may have occurred in increments of tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID at a minimum of 3-day intervals (6 consecutive doses) in this Titration Period. The maximum doses of treatment allowed was tapentadol ER 250 mg BID, oxycodone CR 50 mg BID, and placebo BID, respectively. Downward titration (not below the minimum dose) was also permitted using the same decrements without a time restriction during the Titration Period. During the 12-week Maintenance Period, patients were instructed to try to maintain a steady dose of study medication. However, patients may have received up or down titration of their dose based on their individual analgesia requirements and/or tolerability experience. After the completion of the 12-week Maintenance Period, study medication was stopped and patients may have been given analgesics according to local practice during the Follow-up Period.

Concomitant Medication in Study 8:

Analgesics: Analgesics (including NSAIDs, opioids other than the study medication) were prohibited during the trial with the following exceptions:

1. Aspirin at oral doses ≤ 325 mg per day may have been continued for cardiovascular prophylaxis.
2. Acetaminophen up to 1000 mg daily during the Titration Period was allowed as a rescue analgesic medication. However, patients could not have received acetaminophen during the last 3 days of the Titration Period. During the Maintenance Period acetaminophen was prohibited, with the only exception of up to 1000 mg daily for no more than 3 consecutive days for reasons other than the trial-related chronic pain, if absolutely necessary.

Antipsychotics, SNRIs, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs MAO inhibitors: Anti-psychotics, serotonin norepinephrine re-uptake inhibitors (SNRIs), tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, and monoamine oxidase (MAO) inhibitors were

prohibited within 14 days prior to the screening visit and during the trial. Patients with psychiatric or neurological disorders requiring treatment (e.g., major depressive disorder), may have participated in the trial, if they were treated with medications other than those listed above and were on controlled stable doses for at least 3 months prior to randomization.

Corticosteroids: Corticosteroids should not have been taken during the trial or within the following timelines prior to Screening: within 4 weeks (oral), within 8 weeks (intramuscular or soft tissue administration), within 3 months (intra-articular administration), or within 6 months (injection of depot steroids).

Hyaluronic acid: Intra-articular injections of hyaluronic acid in the reference joint were prohibited within 3 months prior to the Screening visit and during the trial.

Other Allowed Interventions in Study 8: Transcutaneous Electrical Nerve Stimulation, acupuncture, and other interventional adjunctive therapy were allowed during the trial, provided that the patients had been on that therapy for at least 14 days, and continued to undergo therapy for the duration of the trial at the same frequency and intensity as before. Physiotherapy, packs and massages (if started at least 14 days prior to the Screening visit) may have been utilized during the trial at the same frequency as before the trial.

Study Monitoring and Evaluation in Study 8: See Table 9.4 for the schedule of procedures and evaluations in Study 8. Study 8 consisted of 5 periods: Screening, Washout, Titration, Maintenance, and Follow-up Periods.

Period 1 (Screening): The Screening Visit was 0 to 14 days prior to the Washout Period.
Period 2 (Washout): The Washout Period lasted 3 to 7 days prior to study medication dosing (3 to 21 days prior to the initial study medication dosing). Patients started the Washout Period by discontinuing all analgesic medication. Washout was for 7 days; however, if patients could not continue washout any longer than 3 days because of their pain that required intervention, the Washout Period could have been shortened (it had to be at least 3 days). Baseline pain intensity was defined as an average of the pain intensity scores measured over the last 3 days of the Washout Period.
Period 3 (Titration): At completion of the Washout Period, patients were randomized 1:1:1 to tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID. Patients were titrated to the optimal individual dose of the study treatment (i.e., tapentadol ER, oxycodone CR, or placebo) over 3 weeks during the Titration Period. The optimal dose was defined as the dose providing a meaningful improvement of pain with acceptable side effects. Before entering into the Maintenance Period, patients had to demonstrate that they have been stabilized at the optimal dose for the last 3 days of the Titration Period.
Period 4 (Maintenance)**:** Patients continued their investigational drug for 12 weeks during the Maintenance Period. Medication may have been adjusted up or down with a minimum of 3 days between each incremental dose adjustment with the following increments: tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo BID. It may have been necessary to adjust the dose between visits.
Period 5 (Follow up)**:** The Follow-up Period of 2 weeks followed treatment discontinuation.

Table 9.4: Schedule of procedures and evaluations in Study 8

	Screening	Washout	Titration (3 weeks)			Maintenance (12 weeks)								Follow up (days)	
	0-14 days	3-7 days	Baseline/ 1st dose										End IMP	+4	+10-14
Visits	**V1**	**V2**	**T1**	**T2**	**T3**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**F1**	**F2**
Time (weeks)			**1**	**2**	**3**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13**		
Informed consent	X														
Distribute Subject's trial card	X														
Demography and medical history	X														
Inclusion/exclusion criteria	X	X	X												
Subject randomization			X												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant/additional analgesic medication intake	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WOMAC			X			X		X	X	X	X	X	X		
PAC-SYM			X										X		
Short Form-36 Health Survey			X			X			X		X		X		
EuroQol-5 Dimension function questionnaire			X			X			X		X		X		
Withdrawal Assessment (COWS & SOWS)														X	
Check for sleep questionnaire entries			X	X	X	X	X	X	X	X	X	X	X		
Review of 11-point NRS pain intensity and diary compliance	X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient's Global Impression of Change									X		X		X		
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination*			X										X		
12-lead ECG	X					X			X				X		
Urine drug screen	X														
Serum ß-hCG pregnancy screen**	X												X		
Clinical laboratory samples	X												X		
PK blood sample	X					X			X				X	X	
Pharmacogenomics blood sample	X														
Drug accountability (check and collect blisters)				X	X	X	X	X	X	X	X	X	X		
Dispense IMP			X	X	X	X	X	X	X	X	X	X			
Paracetamol/ acetaminophen dispensing			X	X	X										
Trial diary distribution/ training	X														

The pain intensity scores and the sleep items were recorded by patients in their diaries. The WOMAC, PAC-SYM, SF-36, EuroQol-5, and COWS were recorded at the visits. The SOWS was recorded by patients in their diaries and at visits.
* including body weight, and height at Visit T1
** monthly in countries where this is required
Screening Visit was within 0-14 days of the Washout Period. The Washout Period was within 3-7 days of the Titration Period. Visit #2 (the start of the Washout Period) may have been skipped if eligibility for the trial could have been determined at Visit #1 (Screening Visit) ─ patients may have started Washout during the Screening visit (V1). Visit 2 could also have been performed as a phone contact.
Reference: Protocol 8 (amendment 1) in CSR for 8, Table 16.1, Pages 3936-3937

Pain Assessment in Study 8: The 11-pont pain intensity NRS was recorded twice daily (in the morning and evening) during the Screening, Washout, Titration, and Maintenance Periods (starting on Visit V1 and ending on Visit M8) using a patient diary.

The following question was asked:

"What has your average pain level been for the past 12 hours? (circle one)"

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Efficacy Endpoints in Study 8:

Primary Efficacy Endpoint in Study 8: The primary efficacy endpoint was the change from baseline (average during the last 3 days prior to randomization) of the average pain intensity using an 11-point (0-10) numerical rating scale (NRS) over the last week of the Maintenance Period (Week 15).

Pre-Specified Exploratory Efficacy Endpoints in Study 8: There were approximately 166 additional pre-specified exploratory efficacy endpoints in Study 8 (several endpoints were assessed at different times). These endpoints were exploratory because there was no appropriate gate-keeping.

1. 1 endpoints: Distribution of Responders: Proportion of patients achieving at least an x% improvement ($0 \leq x \leq 100\%$ in 10% increments) in pain intensity from baseline at Week 15 (responder analysis).
2. 2 endpoints: The proportion of patients who achieved at least 30% and at least 50% improvement in the change from baseline in pain intensity at Week 15.
3. 1 endpoint: Change from baseline of the average pain intensity over the 12-week Maintenance Period (this was the primary endpoint for non-U.S. regulatory authorities).
4. 28 endpoints: Change from baseline (Visit T1) of the **Western Ontario MacMaster Questionnaire (WOMAC)** stiffness, pain, and physical function subscores and the WOMAC global score at Visits M1, M3, M4, M5, M6, M7, and M8. The stiffness, pain, and physical function patient-reported outcome (PRO) subscores have 2, 5, and 17 questions, respectively, and the responses contain 5-point (0 to 4) Likert scales. The subscore ranges are as follows: stiffness (0-8), pain (0-20), and stiffness (0-68). The global WOMAC score is calculated by summing the scores for the 3 subscales and using coefficients as follows: 0.42xpain subscale + 0.21 x stiffness subscale + 0.37 x physical function subscale. See the WOMAC instrument in Table 9.5.
5. 60 endpoints: Four items in the **Sleep Questionnaire** (i.e., latency, time slept, number of awakenings, and quality) were assessed by patients in their diaries once a week every week during the 15-week Treatment Period (see Table 9.6).
6. 3 endpoints: The **patient global impression of change (PGIC)** was assessed at Visits M4, M6, and M8. The PGIC question was "since I began trial treatment, my overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7)."
7. 1 endpoint: Time to treatment discontinuation due to lack of efficacy (the time in days from the initial dose of study medication to the time of treatment discontinuation due to lack of efficacy).
8. 40 endpoints: Changes from baseline of the 8 subscales and the 2 summary scores of the **Short Form 36 (SF-36) Health Survey** at Visits M1, M4, M6, and M8. The 8 subscale of the SF-36 range from 0 to 100 (0 being poor health and 100 being good health). The 8 subscales are Physical

Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. The 2 summary scores of the SF-36 are the Physical Component Summary (PCS) and the Mental Component Summary (MCS). See Table 9.7 for the questions in the SF-36.

9. 8 endpoints: Changes from baseline of the **EuroQol-5 Dimension (EQ-5D)** score at Visits M1, M4, M6, and M8. The EQ-5D is patient reported outcome measure with a single value (see Table 9.8 for the components of the EQ-5D). Also the change from baseline in a 0-100 point VAS (where 0 is the worst imaginable health state and 100 is the best imaginable health state) will be assessed at Visits MI, M4, M6, and M8 will be performed.
10. 12 endpoints: Changes from baseline of the **Patient's Assessment of Constipation Symptoms (PAC-SYM)** 3 subscales and overall score at Visit M8. These analyses were performed for 3 groups (the ITT population, ITT patients who reported a constipation AE, and ITT patients who did not report a constipation AE. The PAC-SYM is a patient-reported outcome measure containing 12 items that measure the severity of constipation-related symptoms over the past 2 weeks (see Table 9.9). The 3 subscales include abdominal symptoms (items 1-4), rectal symptoms (items 5-7), and stool symptoms (items 8-12).
11. 2 endpoints: The **Clinical Opiate Withdrawal Scale (COWS) score** at Visit F1 (4 days after the last dose) for two groups of patients (patients restarted on opioids after study medication discontinuation and patients not restarted on opioids after study medication discontinuation). Only patients who do not enter the OL extension study (Study 10) will be included in the COWS analyses. The COWS is an 11-item scale that evaluates the physical components of opioid withdrawal and is based on questions and clinical observations (see Table 9.10). Responses are rated on a Likert-type scale ranging from 0 to 4 or 5 depending on the item. Scores are rated by the sum of all 11 items as: < 5 = no withdrawal, 5-12 = mild withdrawal, 13-24 = moderate withdrawal, 25-36 = moderately severe withdrawal, and >36 = severe withdrawal.
12. 8 endpoints: The **Subject's Opiate Withdrawal Scale (SOWS)** score at 24, 48, and 72 hours after stopping study medication (recorded in patient diaries) and 4 days after stopping study medication (at Visit F1) for two groups of patients (patients who restarted opioids and patients who did not restart opioids). The SOWS will only be performed on English-speaking patients who do not enter the OL extension study (Study 10). The SOWS is a 15-item patient-reported outcome measure of the severity of opioid withdrawal symptoms (see Table 9.11). Each item is rated on a 5-point response scale ranging from 0 (not at all) to 4 (extremely). A total score was calculated by summing the scores of the first 15 items.

Table 9.5: Western Ontario MacMaster (WOMAC) questionnaire[1]

1 For every question in the WOMAC, patients rate their pain, stiffness, or function using five Likert responses: none (0), mild (1), moderate (2), severe (3), and extreme (4).
Reference: Adopted from Protocol for Study 8 (CSR for Study 8), Appendix 16.6, Pages 3964-3968

Table 9.6: Sleep Questionnaire

1. How long after bedtime/lights out did you fall asleep last night? ☐ hour(s) ☐ minutes

2. How many times did you wake up during the night? ☐ (number of times)

3. How long did you sleep last night? ☐ hour(s) ☐ minutes

4. Please rate the overall quality of your sleep last night
(*Mark an* [X] *in the box that best describes your answer*)

Excellent	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4

Reference: Protocol for Study 8 (CSR for Study 8), Appendix 16.4, Page 3962

Table 9.7: Short Form 36 (SF-36) Health Survey[1]

Reference: Adopted from Protocol for Study 8 (CSR for Study 8), Appendix 16.11, Pages 3974-3978

Table 9.8: EuroQol-5 Dimension (EQ-5D) Health Questionnaire

Reference: Adopted from Protocol for Study 8 (CSR for Study 8), Appendix 16.12, Pages 3979-3980

Table 9.9: Patient Assessment of Constipation Symptoms (PAC-SYM)[1]

How severe have each of these symptoms been in the **last two weeks?**	**Absent** 0	**Mild** 1	**Moderate** 2	**Severe** 3	**Very severe** 4
1. discomfort in your abdomen	☐	☐	☐	☐	☐
2. pain in your abdomen	☐	☐	☐	☐	☐
3. bloating in your abdomen	☐	☐	☐	☐	☐
4. stomach cramps	☐	☐	☐	☐	☐
5. painful bowel movements	☐	☐	☐	☐	☐
6. rectal burning during or after a bowel movement	☐	☐	☐	☐	☐
7. rectal bleeding or tearing during or after a bowel movement	☐	☐	☐	☐	☐
8. incomplete bowel movement, like you didn't "finish"	☐	☐	☐	☐	☐
9. bowel movements that were too hard	☐	☐	☐	☐	☐
10. bowel movements that were too small	☐	☐	☐	☐	☐
11. straining or squeezing to try to pass bowel movements	☐	☐	☐	☐	☐
12. feeling like you had to pass a bowel movement but you couldn't (false alarm)	☐	☐	☐	☐	☐

"This questionnaire asks you about your constipation symptoms in **past two weeks**."

Reference: Protocol for Study 8 (CSR for Study 8), Appendix 16.8, Page 3970

Table 9.10: Clinical Opioid Withdrawal Scale (COWS)

Reference: Protocol for Study 8 (CSR for Study 8), Appendix 16.9, Pages 3971-3972

Table 9.11: Subjective Opioid Withdrawal Scale (SOWS)[1]

1 Patients are asked to score each item on how they feel at the time they are completing the rating sheet.

Reference: Protocol for Study 8 (CSR for Study 8), Appendix 16.10, Page 3973

Statistics in Study 8:

Populations: The pre-specified populations were:

1. The intent-to-treat (ITT) population: The ITT population included all randomized patients who received at least one dose of study medication. The ITT population served as the primary statistical population for the efficacy and safety analyses.
2. The per-protocol (PP) population: The PP population was a subset of the ITT population. It included ITT patients who did not one or more major protocol violations that may have impacted efficacy, e.g., did not meet eligibility criteria that may have had impacted efficacy, took prohibited concomitant medication that may have impacted efficacy (e.g., other analgesics), did not receive a certain amount of study medication (e.g., received less than 80% of the number of doses of study medication, missed more than 6 consecutive doses), unblinding of patients, or patients at a site with major audit findings.

Statistics for the Primary Efficacy Endpoint:

Definitions for the Components of the Primary Endpoint:

- Baseline Pain Intensity Score: The baseline pain score was the average of the available pain intensity scores during the 72 hours prior to randomization. The baseline value was calculated by averaging the mean 24-hour period pain intensity scores, which were averages of two consecutive morning/evening or evening/morning scores. If a pain score was missing within a 24-hour period then the corresponding mean 24-hour period score was equal to the pain score available within this period. If both morning/evening pain scores within such a period were missing then the baseline value was calculated from all available scores during the 72 hour period. If there were more than 2 scores available in a 24-hour period all scores were included in the calculation (therefore the baseline value may have consisted of more than 6 pain scores).
- Average Pain Intensity Score Over the Last Week of the Maintenance Period: The sum included daily pain scores for the last seven 24-hour periods (Week 12 of the Maintenance Period) after all imputation methods have been carried out.

Methods: Comparison of the primary efficacy endpoint results between the tapentadol ER and placebo groups (the primary comparison) was performed using a 2-sided analysis of covariance (ANCOVA) test at the 5% significance level. The model included treatment and pooled analysis center as factors and baseline pain intensity score as a covariate. Treatment effect of tapentadol ER versus placebo was estimated based on least-square means of the difference (LSD). The p-value for the treatment difference along with the two-sided 95% confidence interval was presented. The primary efficacy analysis was performed using the ITT population and the LOCF imputation method for missing values.

Handling of Missing Data During the Treatment Period (After Baseline):

Last Score Missing: The last available post-baseline pain score was carried forward (LOCF) to impute the pain scores that were missing up to Day 105 of the DB Treatment Period. This applied to patients who did not have pain intensity scores up to Day 105, whether they completed, or

discontinued treatment. For patients without any post-baseline data, the baseline measurement was carried forward.

Intermittent Missing Values: If an intermittent post-baseline pain score is missing then it was interpolated using the previous available pain score and the next available pain score. By plotting the values on a graph where time was on the horizontal axis and the pain intensity score was on the vertical axis, the imputation calculated the slope between the two available pain scores in order to impute the missing value. For example, if there was a morning assessment missing (point A) but the scores are available for the previous evening (point X) and for the next evening (point Y) then the following formula was used to interpolate a value for point A (see Figure 9.12). If a patient's first post-baseline pain score was missing, baseline values were used for interpolation of post-baseline pain scores.

Figure 9.12: Linear imputation for missing data during the Treatment Period

$$\text{Value A} = ValueX + \left[\frac{(ValueY - ValueX) * (TimeA - TimeX)}{TimeY - TimeX} \right]$$

Handling of Additional Pain Scores: If there were more than 2 scores within a 24-hour period then all scores were used to calculate the daily pain intensity. In this case the denominator was replaced by the number of pain scores used in the calculation.

Exploratory Imputation Methods for the Primary Endpoint: In addition to the LOCF imputation method, the following exploratory imputation methods were used for missing data:

1. Baseline observation carried forward (BOCF): Baseline observation, using the derived baseline average pain intensity, was carried forward to impute the missing pain assessment after discontinuation of treatment or after the last pain score.
2. Worst observation carried forward (WOCF): The worst observation (including baseline average pain intensity) was carried forward to impute the missing pain assessment after discontinuation of treatment or after the last pain score.
3. Placebo mean imputation (PMI): The missing pain measurements for each day after discontinuation were replaced by the mean of all available pain intensity scores for all placebo-treated patients who completed treatment. Therefore if a patient discontinued treatment or recorded their last pain score at Week 8 of the Maintenance Period, the pain intensity score at Week 12 was imputed using the Week 12 mean pain intensity score for all placebo-treated patients who completed treatment. Also a placebo missing pain score at some time-point was imputed by the observed placebo group mean pain intensity at the same time-point.
4. Modified BOCF (Modified BOCF): This method was a combination of BOCF and LOCF and was based on the patient global impression of change (PGIC). If a patient was rated as 'much improved' or 'very much improved' on the PGIC at their last post-baseline assessment, then LOCF was used to carry forward the last available post baseline on-treatment pain intensity score. If the patient was rated as anything other than 'much improved' or 'very much improved' at the last post-baseline PGIC assessment, or if the patient had no PGIC assessment, then BOCF was applied to pain intensity.

5. No imputation - observed cases (OC): No imputations were performed to impute pain assessments after discontinuation of treatment, or to impute missing intermittent pain assessments.

Additional Comparisons for the Primary Endpoint: Comparisons of oxycodone CR and placebo were evaluated using the ANCOVA model using the ITT population and LOCF imputation method for missing values with the same factors and covariate as used for the primary comparison between tapentadol ER and placebo. According to the sponsor, this comparison was made to assess for assay sensitivity and the assay was considered sensitive if oxycodone CR separated significantly from placebo on the primary efficacy endpoint and the assay was considered insensitive if oxycodone CR did not differ significantly from placebo on the primary efficacy endpoint. Comparisons between tapentadol ER and oxycodone CR using the identical statistical methods were also performed as exploratory analyses.

Statistics for the Distribution of Responders: The proportion of patients achieving various levels of pain improvement based on the percent change from baseline at Week 15 was a pre-specified endpoint. Patients who worsened or prematurely discontinued from the Treatment Period prior to the end of the Week 15 were assigned a value of 0. Patients with no change were assigned a nominal value close to zero (0.00001). Responder rates for a given percent improvement value was defined as the proportion of patients equal to and above that threshold value, where threshold values were presented as 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%. The graphical representation of the distribution of responder rates was presented for each treatment group. The distribution of time to improvement was estimated by the Kaplan-Meier estimate and compared among the treatment groups using log-rank test.

The proportion of patients who achieved at least 30% and at least 50% improvement in the change from baseline in pain intensity at Week 15 was calculated using the Cochran-Mantel-Haenszel test. These analyses were performed using the ITT population, comparing tapentadol ER with placebo and comparing oxycodone CR versus placebo (for assay sensitivity).

Results for Study 8:

Protocol Deviations: Table 9.13 displays the major protocol deviations in Study 8. A lower proportion of tapentadol ER-treated patients had protocol deviations than control-treated patients.

Table 9.13: Major protocol deviations in Study 8[1]

	Placebo (n=337)	Tapentadol ER (n=346)	Oxycodone CR (n=345)
Total # of Patients with Deviations	**16%**	**13%**	**21%**
Excluded Concomitant Treatment	**8%**	**5%**	**5%**
Prohibited Medication	**8%**	**5%**	**5%**
Non-compliance	**4%**	**3%**	**11%**
Fewer Than 80% Doses Taken	**3%**	**2%**	**11%**
Selection Criteria Not Met	**3%**	**3%**	**4%**
Inclusion Criteria Not Met: Baseline NRS	**2%**	**2%**	**3%**
Treatment Deviation	**1%**	**2%**	**1%**
Medkit Number Inconsistent	**1%**	**2%**	**1%**

1 ITT population. Only protocol deviations that occurred in more than 2% in any treatment group are listed. Patients may appear in more than one category.
Reference: Adapted from CSR for Study 8, Attachment 1.5.1, Page 996.

Disposition: See Table 6.4 in Section 6.1.4 (Subject Disposition) for a display of the disposition in Study 8.

Demographics: As shown in Table 9.14, the baseline demographics were similar across the 3 treatment groups in Study 8.

Table 9.14: Baseline demographics at baseline in Study 8[1]

		Placebo (n=337)	Tapentadol ER (n=344)	Oxycodone CR (n=342)
Age	Mean (SD)	58 (9)	58 (10)	58 (10)
	< 65 years old	77%	72%	72%
	≥ 65 years old	23%	28%	27%
Sex	Male	41%	37%	41%
	Female	59%	63%	59%
Race	Caucasian	79%	76%	72%
	Black	11%	14%	13%
	Hispanic	6%	6%	11%
	Other	4%	4%	4%
Country	United States	77%	77%	79%
	Canada	17%	18%	16%
	New Zealand	3%	3%	2%
	Australia	3%	2%	2%
Weight	Median, kg	97	91	95
BMI	Median, kg/m^2	33	32	33

1 ITT population: all randomized patients who received at least 1 dose of study medication
Reference: Adapted from the CSR for Study 8, Table 10, Pages 97-98

Baseline Disease Characteristics: As shown in Table 9.1.5, the baseline pain intensity was similar in the three treatment groups in Study 8.

Table 9.15: Baseline pain intensity in Study 8[1]

		Placebo (n=337)	Tapentadol ER (n=344)	Oxycodone CR (n=342)
Baseline Pain Intensity Score[2]	Mean (SD)	7.2 (1.3)	7.4 (1.4)	7.2 (1.3)
Baseline Pain Intensity Category[3]	Mild	0%	1%	0%
	Moderate	18%	14%	17%
	Severe	82%	85%	83%

1 ITT population: all randomized patients who received at least 1 dose of study medication
2 Baseline pain intensity score is the average pain intensity score, using a 0-10, 11-point NRS, over 72 hours prior to randomization (after the Washout Period)
3 Baseline pain intensity category of mild, moderate, and severe were defined as 1 to < 4, ≥ 4 to < 6, and ≥6, respectively.
Reference: Adapted from the CSR for Study 8, Table 10, Pages 97-98.

Prior Medications: As shown in Table 9.16, the proportion of patients who received analgesic medication prior to the first dose of study medication was similar in the 3 treatment groups in Study 8.

Table 9.16: Prior use of analgesic medication in Study 8[1]

		Placebo (n=337)	Tapentadol ER (n=344)	Oxycodone CR (n=342)
Prior Use of Any Analgesic[2]		99%	99%	100%
Reason for Dissatisfaction With Analgesic	**Inadequate analgesia**	99%	99%	99%
	Poor tolerability	1%	1%	1%
Opioid Analgesics[3]		36%	34%	34%
Hydrocodone/acetaminophen		9%	7%	11%
Codeine/acetaminophen		5%	7%	4%
Propoxyphene/acetaminophen		3%	4%	3%
Tramadol		4%	4%	3%
Oxycodone/acetaminophen		3%	3%	2%
Tramadol HCl		2%	3%	2%
Hydrocodone		5%	2%	3%
oxycodone		2%	1%	1%
Non-Opioid Analgesics[3]		87%	86%	88%
Acetaminophen		30%	29%	29%
Ibuprofen		24%	27%	29%
Aspirin		18%	18%	17%
Celecoxib		11%	14%	10%
Naproxen		8%	8%	9%
Naproxen sodium		6%	6%	6%
Meloxicam		7%	5%	8%
Naproxen sodium & pseudoephedrine		8%	4%	5%
Diclofenac		5%	4%	3%
Diclofenac/misoprostol		2%	2%	3%
Etodolac		2%	3%	1%

1 Greater than 2% use in any treatment group. ITT population: all randomized patients who received at least 1 dose of study medication.
2 Prior use was defined as used during the 3 months prior to the Screening Visit
3 Prior use was defined as used prior to the first dose of study medication. Patients may have received more than one analgesic medication prior to the first dose of study medication.
Reference: Adapted from the CSR for Study 8, Attachment 1.4.2, Pages 927-928; Attachment 1.4.3, Pages 929-930; Attachment 1.4.1, Page 926

Efficacy Results: See Section 6.1.5 (Analysis of Primary Endpoint) and Section 6.1.6 (Analysis of Secondary Endpoints) for results of the important endpoints in Study 8.

Safety: See Sections 7.3, 7.4, 7.5, and 7.6 for a discussion of the pooled safety results of the 3 Phase 3 trials.

9.4.2 Study 9 [abbreviation for Study R331333-PAI-3009 (KF5503/12)]

The following description of the protocol for Study 9 is based on amendment 2 of the protocol (dated February 25, 2008) and the original SAP (dated September 9, 2008). See Table 9.17 for the dates of all amendments to the protocol and the SAP for Study 9. In Study 9, the study was initiated on June 4, 2007 and the study ended (the day of the last investigation on the last patient) on July 18, 2008.

Table 9.17: Amendments to the Study 9 protocol and SAP

	Amendment	Date
Protocol	Original Protocol	November 29, 2006
	Amendment 1	June 22, 2007
	Amendment 2	February 25, 2008
SAP	Original SAP	September 9, 2008

In amendment 2 of the protocol, there were no significant changes to the study design of Study 9 compared to amendment 1 of the protocol, except the definition of the primary statistical population for the efficacy analyses was changed to satisfy the FDA's recommendations. The change was identical to the significant change in Study 8 and was acceptable (see Table 9.2 for more details). In amendment 1 of the protocol, there were no significant changes to the study design of Study 9 compared to the original protocol.

The SAP had no changes from the statistics as described in the protocol except that the Cochran-Mantel-Haenszel (CMH) test was not adjusted for study center (due to sparse data) for the following endpoints: sleep questionnaire, response rates for achieving 30% and 50% improvement in pain intensity, and the patient global impression of change. This change was acceptable.

Title: Throughout this review, Study 9 will be the abbreviation for Study R331333-PAI-3009 (J & J's trial designation) and Study KF5503/12 (Grünenthal's trial designation). J & J and Grünenthal used different protocol numbers for the same study. Study 9 is entitled, "A Randomized Double-Blind, Placebo- and Active-Control, Parallel-arm, Phase III Trial with Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of CG5503 Prolonged-Release (PR) in Subjects with Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee."

Design of Study 9: The design of Study 9 was identical to the design of Study 8 (i.e., the objectives, overall design, eligibility criteria, study medication, allowed and prohibited concomitant medication, primary endpoints, exploratory endpoints, and statistical analysis plan) with exceptions outlined in Table 9.18. For more details on the design of Study 9, see the individual study report for Study 8 in Section 9.4.1.

Table 9.18: Differences in the design of Studies 9 and 8

	Study 9	Study 8
Location of sites	U.S., Canada, New Zealand, and Australia.	Sites in 12 European countries (Austria, Croatia, Germany, Hungary, Latvia, Poland, Portugal, Romania, Slovakia, Spain, the Netherlands, and the United Kingdom)
Exploratory Endpoints	No SOWS endpoints (SOWS not assessed)	8 SOWS exploratory endpoints
Number of Pre-Specified Exploratory Endpoints	158	166 (includes the 8 additional SOWS endpoints)
Visit 2 (the first visit during the Washout Period)	A telephone call may have been substituted for Visit 2.	Visit 2 may have been skipped.
OL extension study	Patients did not participate in the OL extension study	Allowed to enter an OL extension study after completion of Study 8.

Results for Study 9:

Protocol Deviations: Table 9.19 displays the major protocol deviations in Study 9. A lower proportion of tapentadol ER-treated patients had protocol deviations than control-treated patients.

Table 9.19: Major protocol deviations in Study 9[1]

	Placebo (n=337)	Tapentadol ER (n=319)	Oxycodone CR (n=331)
Total # of Patients with Deviations	**12%**	**8%**	**13%**
Excluded Concomitant Treatment	**6%**	**3%**	**3%**
Prohibited Medication	**6%**	**3%**	**3%**
Non-compliance	**2%**	**3%**	**9%**
Fewer Than 80% Doses Taken	**2%**	**2%**	**8%**
Treatment Deviation	**3%**	**3%**	**1%**
Medkit Number Inconsistent	**3%**	**3%**	**1%**

1 ITT population (all randomized patients who received at least 1 dose of study medication).
Only protocol deviations that occurred in more than 2% in any treatment group are listed.
Patients may appear in more than one category.
Reference: Adapted from CSR for Study 9, Attachment 1.5.2, Page 882.

Disposition: See Table 6.4 in Section 6.1.4 (Subject Disposition) for a display of the disposition in Study 9.

Demographics: As shown in Table 9.20, the baseline demographics were similar across the 3 treatment groups in Study 9.

Table 9.20: Baseline demographics in Study 9

		Placebo (n=337)	Tapentadol ER (n=319)	Oxycodone CR (n=331)
Age	**Mean (SD)**	**62 (9)**	**62 (9)**	**62 (9)**
	< 65 years old	**58%**	**61%**	**64%**
	≥ 65 years old	**42%**	**39%**	**36%**
Sex	**Male**	**24%**	**28%**	**34%**
	Female	**76%**	**72%**	**66%**
Race	**Caucasian**	**99%**	**99%**	**99%**
	Other	**1%**	**1%**	**1%**
Country	**Romania**	**32%**	**32%**	**31%**
	Germany	**17%**	**19%**	**18%**
	Hungary	**11%**	**11%**	**10%**
	Spain	**9%**	**7%**	**8%**
	UK	**7%**	**8%**	**9%**
	Latvia	**7%**	**7%**	**7%**
	Austria	**4%**	**4%**	**5%**
	Croatia	**4%**	**3%**	**2%**
	Poland	**3%**	**3%**	**4%**
	Slovakia	**2%**	**3%**	**3%**
	The Netherlands	**2%**	**3%**	**3%**
	Portugal	**2%**	**1%**	**1%**
Weight	**Median, kg**	**81**	**82**	**84**
BMI	**Median, kg/m^2**	**30**	**31**	**31**

Reference: Adapted from the CSR for Study 9, Table 10, Pages 89-90.

Baseline Disease Characteristics: As shown in Table 9.21, the baseline pain intensity was similar in the three treatment groups in Study 9.

Table 9.21: Baseline pain intensity in Study 9[1]

		Placebo (n=337)	Tapentadol ER (n=319)	Oxycodone CR (n=331)
Baseline Pain Intensity Score[2]	**Mean (SD)**	**7.3 (1.1)**	**7.3 (1.1)**	**7.3 (1.1)**
Baseline Pain Intensity Category[3]	**Mild**	**0%**	**0%**	**0%**
	Moderate	**13%**	**11%**	**10%**
	Severe	**88%**	**89%**	**90%**

1 ITT population: all randomized patients who received at least 1 dose of study medication
2 Baseline pain intensity score is the average pain intensity score, using a 0-10, 11-point NRS, over 72 hours prior to randomization (after the Washout Period)
3 Baseline pain intensity category of mild, moderate, and severe were defined as 1 to < 4, ≥ 4 to < 6, and ≥6, respectively.
Reference: Adapted from the CSR for Study 9, Table 10, Pages 89-90.

Prior Medications: As shown in Table 9.22, the proportion of patients who received analgesic medication prior to the first dose of study medication was similar in the 3 treatment groups in Study 9.

Table 9.22: Prior use of analgesic medication in Study 9[1]

		Placebo (n=337)	Tapentadol ER (n=319)	Oxycodone CR (n=331)
Prior Use of Any Analgesic[2]		100%	100%	100%
Reason for Dissatisfaction With Analgesic	Inadequate analgesia	99%	99%	100%
	Poor tolerability	1%	1%	<1%
Opioid Analgesics[3]		18%	17%	16%
Tramadol		4%	7%	5%
Tramadol/acetaminophen		5%	3%	3%
Tramadol HCl		3%	4%	2%
Codeine/acetaminophen		3%	3%	2%
Non-Opioid Analgesics[3]		94%	94%	94%
Diclofenac		25%	26%	23%
Acetaminophen		20%	26%	23%
Nimesulide		16%	17%	14%
Ibuprofen		15%	15%	17%
Aspirin		13%	14%	15%
Piroxicam		11%	9%	6%
Diclofenac sodium		9%	6%	8%
Etoricoxib		9%	6%	8%
Meloxicam		8%	9%	10%
Ketoprofen		8%	8%	11%
Aceclofenac		5%	8%	8%
Celecoxib		5%	4%	4%
Metamizole		3%	3%	4%
Indomethacin		2%	3%	3%

1 Greater than 2% use in any treatment group for the opioid analgesics and greater than 3% use in any treatment group for the non-opioid analgesics. ITT population: all randomized patients who received at least 1 dose of study medication.
2 Prior use was defined as used during the 3 months prior to the Screening Visit
3 Prior use was defined as used prior to the first dose of study medication. Patients may have received more than one analgesic medication prior to the first dose of study medication.
Reference: Adapted from the CSR for Study 9, Attachment 1.4.1, Page 819 Attachment 1.4.2, Page 820; Attachment 1.4.3, Pages 821-823.

Efficacy Results: See Section 6.1.5 (Analysis of Primary Endpoint) and Section 6.1.6 (Analysis of Secondary Endpoints) for results of the important endpoints in Study 9.

Safety: See Sections 7.3, 7.4, 7.5, and 7.6 for a discussion of the pooled safety results of the 3 Phase 3 trials.

9.4.3 Study 11 [abbreviation for Study R331333-PAI-3011 (Study KF5503/23)]

The description of the protocol for Study 11 is based on amendment 1 of the protocol (dated January 9, 2008) and the original SAP (dated May 29, 2008). See Table 9.23 for the dates of all amendments to the protocol and SAP for Study 11. In Study 11, the study was initiated on February 21, 2007 and the study ended (the day of the last investigation on the last patient) on March 12, 2008.

Table 9.23: Amendments to the Study 11 protocol and SAP

	Amendment	Date
Protocol	Original Protocol	November 29, 2006
	Amendment 1	January 9, 2008
SAP	Original SAP	May 29, 2008

In amendment 1 of the protocol, there were no significant changes to the study design of Study 11 compared to the original protocol, except the definition of the primary statistical population for the efficacy analyses was changed to satisfy the FDA's recommendations. The change was identical to the significant change in Study 8 and was acceptable (see Table 9.2 for more details).

The SAP had no changes from the statistical methods section of the protocol except that the Cochran-Mantel-Haenszel (CMH) test was not adjusted for study center (due to sparse data) for the following endpoints: sleep questionnaire, response rates for achieving 30% and 50% improvement in pain intensity, and the patient global impression of change. This change was acceptable.

Title: Study 11 is the abbreviation for Study R331333-PAI-3011 (J & J's trial designation) and Study KF5503/23 (Grünenthal's trial designation). J & J and Grünenthal used different protocol numbers for the same study. Study 11 is entitled, "A Randomized Double-Blind, Placebo- and Active-Control, Parallel-arm, Phase III Trial with Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of CG5503 Extended-Release (ER) in Subjects with Moderate to Severe Chronic Low Back Pain."

Design of Study 11: Randomized, DB, PC and oxycodone CR-controlled, parallel group, MC (97 sites in the United States, Canada, and Australia), Phase 3 trial of controlled adjustment of tapentadol ER in 965 patients with moderate to severe chronic ($\geq$ 3 months) LBP. Patients must have been at least 18 years old, taking analgesic medications for their LBP $\geq$ 3 months, and dissatisfied with their current analgesics due inadequate analgesia or intolerability. If patients were receiving opioids at the start of the trial, they must have been taking daily doses of opioids equivalent to $\leq$ 160 mg of oral morphine.

The design of Study 11 was identical to the design of Study 8 (i.e., objectives, overall design, eligibility criteria, study medication, allowed and prohibited concomitant medication, primary endpoints, exploratory endpoints, and statistical analysis plan) with the exceptions displayed in Table 9.24. The main differences between the two trials was that Study 11 was in patients with chronic LBP at least 18 years old; whereas, Study 8 was in patients with chronic knee OA at least 40 years old. Furthermore, Study 11 included Brief Pain Inventory (BPI) pre-specified exploratory endpoints; whereas, Study 8 included WOMAC pre-specified exploratory endpoints (BPI is not specific to any pain location; whereas, WOMAC is specific to pain from OA). See the BPI instrument in Table 9.25.

Table 9.24: Differences in the designs of Studies 8 and 11

Study 11	Study 8
Eligibility Criteria	
Had to have a diagnosis of LBP of non-malignant origin present for at least 3 months	Had to have a diagnosis of knee OA for at least 3 months
Had to be ≥ 18 years old	Had to be ≥ 40 years old
Could not have had surgery in the low back area within 3 months of screening or could not have been expected to require surgical intervention in the low back area during the study.	Could not have had surgery of the reference knee joint within 3 months of screening or could not have been expected to require surgical intervention on the knee during the study
	Could not have had intra-articular injections of hyaluronic acid in the reference knee joint within 3 months before the screening visit and during the study. Could not have had signs and symptoms at the reference knee joint from non-OA disorders such as gout, pseudogout, metabolic, infectious or autoimmune disease.
Exploratory Endpoints	
Approximate # of exploratory endpoints was 159.	Approximate # of exploratory endpoints was 166.
Brief Pain Inventory (BPI) endpoints: Change from baseline of the total score, pain subscore, and the pain interference with function subscore at Visits M1, M3, M4, M5, M6, M7, and M8. The BPI is a patient-reported outcome measure. The pain subscore is the mean of items 3 to 6 (0-10 scale); the pain interference subscore is the mean of items 9A to 9F (0-10 scale); and the total score is the mean of the pain and interference subscores. There were 21 BPI endpoints.	WOMAC endpoints. Change from baseline (Visit T1) of the WOMAC stiffness, pain, and physical function subscores and the WOMAC global score at Visits M1, M3, M4, M5, M6, M7, and M8. There were 28 WOMAC endpoints.

Table 9.25: Brief Pain Inventory (BPI)[1]

1 Items 2 and 7 of the BPI were not collected in the database of Study 11 and are not presented in this table.
The pain subscore is the mean of scores from items 3 to 6. The interference subscore is the mean of the 7 items in Question 9.
The total BPI score is the mean of the interference and pain subscores.
Reference: Protocol for Study 11 in CSR for Study 11, Appendix 16.6, Pages 2685-2686

Results for Study 11:

Protocol Deviations: Table 9.26 displays the major protocol deviations in Study 11. A similar proportion of tapentadol ER-treated patients had protocol deviations as control-treated patients.

Table 9.26: Major protocol deviations in Study 11[1]

	Placebo (n=317)	Tapentadol ER (n=315)	Oxycodone CR (n=326)
Total # of Patients with Deviations	**24%**	**21%**	**22%**
Excluded Concomitant Treatment	**17%**	**14%**	**11%**
Prohibited Medication	**17%**	**14%**	**11%**
Non-compliance	**4%**	**4%**	**6%**
≥ 7 consecutive missed doses	**1%**	**2%**	**1%**
Fewer Than 80% Doses Taken	**3%**	**3%**	**6%**
Regulatory Requirement	**1%**	**0%**	**2%**
Randomization Code Broken	**1%**	**0%**	**2%**
Selection Criteria Not Met	**3%**	**4%**	**2%**
Inclusion Criteria Not Met: Baseline NRS	**2%**	**3%**	**2%**
Treatment Deviation	**<1%**	**<1%**	**2%**
Medkit Number Inconsistent	**<1%**	**<1%**	**2%**

1 ITT population (all randomized patients who received at least 1 dose of study medication).
Only protocol deviations that occurred in more than 2% in any treatment group are listed.
Patients may appear in more than one category.
Reference: Adapted from CSR for Study 11, Attachment 1.6.1, Page 328.

Disposition: See Table 6.4 in Section 6.1.4 (Subject Disposition) for a display of the disposition in Study 11.

Demographics: As shown in Table 9.27, the baseline demographics were similar across the 3 treatment groups in Study 11.

Table 9.27: Baseline demographics at baseline in Study 11[1]

		Placebo (n=319)	Tapentadol ER (n=318)	Oxycodone CR (n=328)
Age	**Mean (SD)**	**50 (14)**	**49 (13)**	**50 (14)**
	< 65 years old	**83%**	**88%**	**83%**
	≥ 65 years old	**17%**	**12%**	**17%**
Sex	**Male**	**42%**	**39%**	**45%**
	Female	**58%**	**61%**	**55%**
Race	**Caucasian**	**74%**	**72%**	**74%**
	Black	**16%**	**20%**	**17%**
	Hispanic	**7%**	**6%**	**6%**
	Other	**3%**	**3%**	**3%**
Country	**United States**	**84%**	**82%**	**83%**
	Canada	**15%**	**17%**	**16%**
	Australia	**1%**	**1%**	**1%**
Weight	**Median, kg**	**85**	**88**	**86**
BMI	**Median, kg/m^2**	**30**	**30**	**30**

1 ITT population: all randomized patients who received at least 1 dose of study medication
Reference: Adapted from the CSR for Study 11, Table 10, Pages 90-91

Baseline Disease Characteristics: As shown in Table 9.28, the baseline pain intensity was similar in the three treatment groups in Study 11.

Table 9.28: Baseline pain intensity in Study 11[1]

		Placebo (n=319)	Tapentadol ER (n=318)	Oxycodone CR (n=328)
Baseline Pain Intensity Score[2]	Mean (SD)	7.6 (1.3)	7.5 (1.3)	7.5 (1.2)
Baseline Pain Intensity Category[3]	Severe	87%	89%	90%
	Moderate	13%	11%	10%
	Mild	0%	0%	0%

1 ITT population: all randomized patients who received at least 1 dose of study medication
2 Baseline pain intensity score is the average pain intensity score, using a 0-10, 11-point NRS, over 72 hours prior to randomization (after the Washout Period)
3 Baseline pain intensity category of mild, moderate, and severe were defined as 1 to < 4, ≥ 4 to < 6, and ≥6, respectively.
Reference: Adapted from the CSR for Study 11, Table 10, Pages 90-91.

Prior Medications: As shown in Table 9.29, the proportion of patients who received analgesic medication prior to the first dose of study medication was similar in the 3 treatment groups in Study 11.

Table 9.29: Prior use of analgesic medication in Study 11[1]

		Placebo (n=319)	Tapentadol ER (n=318)	Oxycodone CR (n=328)
Prior Use of Any Analgesic[2]		100%	100%	100%
Reason for Dissatisfaction With Analgesic	Inadequate analgesia	98%	98%	99%
	Poor tolerability	2%	3%	1%
Opioid Analgesics[3]		**56%**	**56%**	**52%**
Hydrocodone/acetaminophen		21%	18%	20%
Codeine/acetaminophen		10%	9%	6%
Oxycodone/acetaminophen		6%	5%	5%
Hydrocodone		5%	6%	5%
Propoxyphene/aceptaminophen		5%	5%	3%
Tramadol		5%	4%	3%
Oxycodone HCl		2%	2%	2%
Non-Opioid Analgesics[3]		**82%**	**81%**	**83%**
Ibuprofen		35%	39%	36%
Acetaminophen		28%	26%	24%
Aspirin		14%	14%	14%
Naproxen sodium		7%	9%	13%
Naproxen		6%	5%	7%
Celecoxib		6%	4%	4%
Meloxicam		3%	4%	4%
Acetaminophen/diphenhydramine		3%	4%	2%
Diclofenac		2%	2%	1%
Acetaminophen/aspirin/caffeine		1%	3%	2%

1 Greater than 2% use in any treatment group. ITT population: all randomized patients who received at least 1 dose of study medication.
2 Prior use was defined as used during the 3 months prior to the Screening Visit
3 Prior use was defined as used prior to the first dose of study medication. Patients may have received more than one analgesic medication prior to the first dose of study medication.
Reference: Adapted from the CSR for Study 11, Attachment 1.5.1, Page 260; Attachment 1.5.2, Pages 261-262; Attachment 1.5.3, Pages 263-264

Efficacy Results: See Section 6.1.5 (Analysis of Primary Endpoint) and Section 6.1.6 (Analysis of Secondary Endpoints) for results of the important endpoints in Study 11.

Safety: See Sections 7.3, 7.4, 7.5, and 7.6 for a discussion of the pooled safety results of the 3 Phase 3 trials.

9.4.4 Study 15 [abbreviation for Study R331333-PAI-3015 (KF5503/36)]

The description of the protocol for Study 15 is based on amendment 1 of the protocol (dated May 31, 2007) and the original SAP (dated October 2, 2008). See Table 9.30 for the dates of all amendments to the protocol and SAP for Study 11. Study 15 was initiated on March 15, 2007 and the study ended (the day of the last investigation on the last patient) on August 20, 2008.

Table 9.30: Amendments to the Study 15 protocol and SAP

	Amendment	Date
Protocol	**Original Protocol**	**December 1, 2006**
	Amendment 1	**May 31, 2007**
SAP	**Original SAP**	**October 2, 2008**

In amendment 1 of the protocol, there were no significant changes to the study design of Study 15 compared to the original protocol. The following changes to the original protocol are acceptable: patients could have supplemental analgesia (tapentadol ER 25 mg) after randomization in the withdrawal period to maintain the blind and the length of the Washout Period could have exceeded 14 days if pre-screening analgesic medication had a long half-life.

The SAP had no changes from the statistical methods section of the protocol except for the following changes, which are acceptable:

1. The baseline pain score calculation was changed from the average of the pain scores over the last 3 days of the OL Titration Period to the average of the pain scores over the last 72 hours prior to randomization. Similarly, the Week 15 pain scores were based on the last 168 hours (7 x 24 hours) rather than the last 7 complete days.
2. The analysis of the number of awakenings in the Sleep Questionnaire was changed from an ANCOVA model to a Cochran-Mantel-Haenszel test with the following categories: 0, 1, 2, 3, 4, and ≥ 5 (because the data was skewed).
3. The ITT population was originally all randomized patients who received at least one dose of study medication during the DB Randomized-Withdrawal Period and have at least one pain assessment on the 11-point NRS during the DB period. After FDA input, the ITT population was changed to all randomized patients who received at least one dose of study medication during the DB Randomized-Withdrawal Period.

Title: Throughout this review, Study 15 is abbreviated for Study R331333-PAI-3015 (J & J's trial designation) and Study KF5503/36 (Grünenthal's trial designation). J & J and Grünenthal used different protocol numbers for the same study. Study 15 is entitled, "A Randomized-Withdrawal Phase III Study Evaluating the Safety and Efficacy of CG5503 Extended-Release (ER) in Subjects with Painful Diabetic Peripheral Neuropathy (DPN)."

Objectives of Study 15: The primary objective of Study 15 was to demonstrate the efficacy of tapentadol ER versus placebo and to assess safety and tolerability of tapentadol ER at doses 100 to 250 mg BID in patients with moderate to severe pain due to chronic DPN who demonstrated an initial treatment effect after a 3-week OL titration period. Secondary objectives included the collection of PK for the assessment of compliance and for population PK analyses, and the comparison of patient reported outcomes between the two treatment groups.

Overall Design of Study 15: DB, parallel-group, MC (88 sites in the United States and Canada), randomized-withdrawal Phase 3 trial of tapentadol ER in diabetic patients (type I or type II) with chronic pain (≥ 6 months) from diabetic peripheral neuropathy (DPN). Patients must have been taking analgesic medications for their pain due to DPN ≥ 3 months, and dissatisfied with their current analgesics due inadequate analgesia or intolerability. If patients were receiving opioids at the start of the trial, they must have been taking daily doses of opioids equivalent to ≤ 160 mg of oral morphine.

Prior to receiving study medication, patients entered a 3- to 14-day Washout Period where all analgesics were discontinued and new analgesics were not allowed (except for 2000 mg of acetaminophen per day). Acetaminophen was not allowed on the last day of the Washout Period. Patients who received methadone may have required a longer Washout Period.

Patients needed to have an average pain intensity score of ≥ 5 on an 11-point NRS during the 3 days of the Pain Intensity Evaluation Period (this period occurred right after the Washout Period ended and before the OL Titration Period) to enter the Titration Period. During the Titration Period, all patients received tapentadol ER 50 mg BID for the first 3 days then 100 mg BID for the next 3 days. In the Titration Period, upward or downward titration was allowed in increments of tapentadol ER 50 mg BID (at a minimum of 3-day intervals for upward titration) to optimize the patients' analgesic needs and tolerability. The allowed dose ranges in the Titration Period was tapentadol ER 100 to 250 mg BID.

If during the last three days of the Titration Period, if the change in the patient's average NRS pain score was ≥ 1 point reduction in the average NRS from the OL baseline, then patients entered the DB Randomized Withdrawal Period and were randomized 1:1 to continue treatment with tapentadol ER (at the dose used during the last 4 days of the Titration Period) or placebo. Patients who received placebo had their tapentadol ER tapered (100 mg BID for the first 3 days of the Randomized Withdrawal Period and then no tapentadol ER thereafter). During the first four days of this period, patients were allowed to receive 2 doses of 25 mg of tapentadol ER at least 6 hours apart for rescue analgesia, and from Day 5 through the end of the 12-week Randomized Withdrawal Period, patients were allowed to receive a single 25 mg tapentadol ER dose every day for rescue analgesia.

At the end of the Randomized Withdrawal Period, patients stopped their study medication without a taper and may have been started on appropriate analgesic medication according to local practice standards.

Eligibility Criteria of Study 15 at the Screening Visit: The eligibility criteria in Study 15 was identical to that of Study 8 with exceptions displayed in Table 9.31 (for the eligibility criteria for Study 8 see Table 9.3 in Section 9.4.1). The main differences in the eligibility criteria in the two trials was that Study 15 selected diabetic patients with chronic painful DPN and at least 18 years old; whereas, Study 8 selected patients with chronic pain due to knee OA at least 40 years old. The differences in selection criteria were primarily due to the differences in the underlying patient populations.

Table 9.31: Differences in the eligibility criteria in Studies 15 and 8 at the Screening Visit[4]

Study 15	Study 8
Inclusion Criteria	
≥ 18 years old with type I or type II diabetes mellitus with documented clinical diagnosis of painful DPN with symptoms and signs for at least 6 months and with pain that was present at the time of screening.	**≥ 40 years old with knee OA based on ACR criteria and functional capacity class of I-III and pain at the reference knee joint ≥ 3 months**
Blood glucose was controlled by a diet, oral hypoglycemics, or insulin for at least 3 months prior to enrollment [documented by of glycated hemoglobin (HbA1c) no greater than 11% at screening].	
Exclusion Criteria	
Severe or extensive diabetic ulcers or amputation (more than 2 toes) of the limbs, or Charcot joints.	**History and clinical signs at reference joint from gout, pseudogout, metabolic, infectious, or autoimmune disease.**
Significant cardiac disease (e.g., unstable angina pectoris, angina pectoris Canadian Cardiovascular Society class III-IV, acute myocardial infarction within the last 3 months, cardiac insufficiency New York Heart Association class III-IV) or significant vascular disease (e.g., peripheral arterial occlusive disease Fontaine class IIb-IV).	**Has a clinically significant disease that may affect efficacy or safety assessments, e.g., significant unstable cardiac disturbances. Has uncontrolled hypertension (repeated systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg).**
Was unable to swallow oral study drug whole with the aid of water.	
	HIV
	Surgery of the reference joint within 3 months of screening or the patient was expected to require surgical intervention on reference joint during the trial.

Reference: Adapted from Protocol 8 (amendment 1), Pages 3900-3903, adapted from Protocol 15 (amendment 1), Pages 2645-2649

Eligibility Criteria Prior to Randomization: Patients must have had an average pain intensity score at the beginning of the OL phase of ≥ 5 on an 11-point NRS, calculated as the average pain intensity (twice daily measurements) during the 3 days after the Washout Period (before the OL Titration Period).

Study Medication: At completion of the Washout Period and after patients had an average baseline pain intensity score of ≥ 5 on an 11-point NRS, all patients received OL treatment with 50 mg of tapentadol ER BID (with or without food) for the first 3 days then 100 mg BID for the next 3 days. In the Titration Period, upward or downward titration was allowed in increments of 50 mg of tapentadol ER BID (at a minimum of 3-day intervals for upward titration) to optimize the patients' analgesic needs and tolerability. The allowed dose range in the Titration Period was 100 to 250 mg of tapentadol ER BID.

If during the last three days of the Titration Period, if the change in the patient's average NRS pain score was ≤ 1 from the average NRS during the baseline pain intensity score, then patients entered the DB Randomized Withdrawal Period and were randomized 1:1 to continue treatment with tapentadol ER (at the dose used during the last 4 days of the Titration Period) or placebo. Patients who received placebo had their tapentadol ER tapered (100 mg BID for the first 3 days of the Randomized Withdrawal Period and then no tapentadol ER thereafter).

Concomitant Medication in Study 15:

Analgesics: Analgesics (including NSAIDs, opioids other than the study medication, topical capsaicin, topical anesthetics) were prohibited during the trial except for:

1. Aspirin at oral doses ≤ 325 mg per day may have been continued for cardiovascular prophylaxis.
2. Acetaminophen up to 2000 mg/day during the Screening and Washout periods, except the last day of the Washout Period. Acetaminophen up to 2000 mg/day was also allowed during the OL Titration Period except the last 4 days of the Titration Period. Acetaminophen was prohibited during the DB Randomized Withdrawal Period.
3. Tapentadol ER 25 mg was allowed (a maximum of two doses at least 6 hours apart) as rescue analgesia during the first 4 days of the DB, randomized withdrawal period. From Day 5 through the end of the DB randomized withdrawal treatment period (up to Visit 12), patients were allowed a single dose of 25 mg of tapentadol ER every day for rescue.

Antipsychotics, SNRIs, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, MAO inhibitors, sedatives: Anti-psychotics, SNRIs, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, and MAO inhibitors were prohibited within 14 days prior to the screening visit and during the trial. Patients with psychiatric or neurological disorders requiring treatment (e.g., major depressive disorder), may have participated in the trial, if they were treated with medications other than those listed above and were on controlled stable doses for at least 3 months prior to randomization. SSRIs were allowed if dosing was stable for at least 30 days prior to Screening visit. Benzodiazepines and non-benzodiazepine hypnotics, if previously used as needed, were allowed for occasional use.

Anti-Hyperglycemic Medication: Throughout the course of the study, any changes can be made to the anti-hyperglycemic medication used to maintain glycemic control.

Corticosteroids: Corticosteroids should not have been taken during the trial or within the following timelines prior to Screening: within 4 weeks (oral), within 8 weeks (intramuscular or soft tissue administration), within 3 months (intra-articular administration), or within 6 months (injection of depot steroids).

Other Allowed Interventions in Study 15: Transcutaneous Electrical Nerve Stimulation, acupuncture, and other interventional adjunctive therapy were allowed during the trial, provided that the patients had been on that therapy for at least 14 days, and continued to undergo therapy for the duration of the trial at the same frequency and intensity as before. Physiotherapy, packs and massages (if started at least 14 days prior to the Screening visit) may have been utilized during the trial at the same frequency as before the trial.

Study Monitoring and Evaluation in Study 15: See Table 9.32 for the schedule of procedures and evaluations in Study 15. Study 15 consisted of the OL Phase (Screening, Washout, Pain Intensity Evaluation, and Titration Periods) and the DB Phase (Randomized Withdrawal and Follow-Up Periods).

Table 9.32: Schedule of procedures and evaluations in Study 15

	Open label phase					Double blind phase								
Period	**Screening**	**Start of Washout**	**Pain Intensity Evaluation**	**Titration**		**Maintenance**							**Follow up (days)**	
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 End of Treatment/Early discontinuation**	**13 Visit**	**14 Telephone call**
Week	**Days -14 to -3**	**Days -14 to -1[g]**	**0**	**1**	**2**	**0[a]**	**2[a]**	**4[a]**	**6[a]**	**8[a]**	**10[a]**	**12[a]**	**4[b]**	**10-14**
Informed consent	X													
Inclusion/Exclusion Criteria	X	X	X											
Randomization						X								
Medical history	X													
Physical exam (incl. weight and height[c])	X											X		
Vital signs[f]	X		X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X		X			X						X		
Clinical laboratory	X											X		
Serology (HBV, HCV)	X													
Pregnancy test[d]	X											X		
PK samples			X			X				X		X		
Pharmacogenomics sample			X											
Drugs of abuse (urine)	X													
Discontinue current analgesics	X													
NRS pain intensity review of diary compliance[e]		X	X	X	X	X	X	X	X	X	X	X	X	
Patient's global impression of change							X		X			X		
BPI			X			X	X	X	X	X	X	X	X	
EQ-5D			X			X			X			X		
SF-36			X			X			X			X		
COWS													X	
SOWS													X	
Sleep Questionnaires			X			X	X	X	X	X	X	X		
Collect/dispense Investigational drug			X	X	X	X	X	X	X	X	X	X		
Record use of CG5503 ER as supplemental analgesia							X	X	X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a One week from the first visit in the Maintenance Period (Randomized Withdrawal Period).
b Days from the last dose of randomized study medication in the Randomized Withdrawal Period.
c Height at screening only.
d Serum pregnancy test at Screening and at the Visit 12 or early discontinuation visit. Urine pregnancy tests could have been performed at any time during the trial.
e NRS pain intensity (11-point scale) was entered twice daily by patient.
f Body temperature was only recorded at Visits 1, 3, and 12.
g Length of washout period was dependent on the half life of the analgesic medication and may have exceed 14 days
Reference: Adopted from Protocol 15 (amendment 1), Pages 2716-2719

Pain Assessment in Study 15: The 11-pont pain intensity NRS was assessed twice daily (in the morning and evening) during the Pain Intensity Evaluation, Titration, Randomized Withdrawal Periods (ending on Visit 13) using a patient diary. The following question was asked:

"What is your pain level for the past 12 hours?"

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Efficacy Endpoints in Study 15:

Primary Efficacy Endpoint in Study 15: The primary efficacy endpoint was the change from the DB baseline in the average pain intensity using an 11-point (0-10) NRS over the last week of the Randomized Withdrawal Period (Week 15). The baseline average pain intensity was the average score during the last 3 days of the OL Titration Period.

Pre-Specified Exploratory Efficacy Endpoints in Study 15: There were approximately 80 additional pre-specified exploratory efficacy endpoints in Study 15 (several endpoints were assessed at different times). These endpoints were exploratory because there was no appropriate gate-keeping.

1. **1 endpoints:** Distribution of Responders: Proportion of patients achieving at least an x% improvement ($0 \leq x \leq 100\%$ in 10% increments) in the 11-point NRS from the OL baseline at Week 15. Baseline was the average pain intensity over 3 days before the start of the OL treatment with tapentadol ER in the Titration Period.
2. **2 endpoints:** The proportion of patients who achieved at least 30% and at least 50% improvement in the change from the OL baseline in pain intensity at Week 15.
3. **9 endpoints:** Brief Pain Inventory (BPI) endpoints: change from baseline (before the start of the DB Randomized Withdrawal Period) of the total score, pain subscore, and the pain interference subscore at Week 15. The change from the OL baseline (during the 3-day Pain Intensity Evaluation Period) in the total score, pain subscore, and the pain interference subscore at Week 15. Finally, the change from the OL baseline to the DB baseline in the total score, pain subscore, and the pain interference subscore at Week 15. See the individual study report for Study 11 in Section 9.4.3 for the BPI instrument.
4. **20 endpoints:** There are four items in the Sleep Questionnaire (i.e., latency, time slept, number of awakenings, and quality) assessed by patients in their diaries in the morning. The change from the DB baseline in latency and time slept at Week 15; the change from the OL baseline in latency and time slept to Week 15; and the change from OL baseline in latency and time slept to DB baseline. The number of awakenings and sleep quality at Week 15. The change from the DB baseline in sleep quality to Weeks 5, 7, 9, 11, 13, and 15. The change from the OL baseline in sleep quality to Weeks 5, 7, 9, 11, 13, and 15. See Table 9.6 in the individual study report for Study 8 in Section 9.4.1 for the Sleep Questionnaire instrument.
5. **3 endpoints:** The patient global impression of change (PGIC) scores at Weeks 5, 9, and 15. See the individual study report for Study 8 in Section 9.4.1 for the PGIC instrument.

6. **1 endpoint:** Time (in days) to treatment discontinuation due to lack of efficacy (the time from the start of the DB Randomized Withdrawal Period to the time of treatment discontinuation due to lack of efficacy). See the individual study report for Study 8 in Section 9.4.1 for the statistics analysis for this endpoint.
7. **20 endpoints:** Change from the DB baseline of the 8 subscales and the 2 summary scores (Physical Component and Mental Component) of the Short Form 36 (SF-36) Health Survey at Week 15**.** Change from the OL baseline of the 8 subscales and the 2 summary scores at Week 15. See the individual study report for Study 8 in Section 9.4.1 for the SF-36 instrument.
8. **14 endpoints:** Change from the DB baseline of the total EuroQol-5 Dimension (EQ-5D) score and the subscores at Week 15. The change from the OL baseline of the EQ-5D score and the subscores at Week 15. Also the change from DB baseline in a 0-100 point VAS (where 0 is the worst imaginable health state and 100 is the best imaginable health state) at Week 15 and the change from the OL baseline in the VAS at Week 15. See the individual study report for Study 8 in Section 9.4.1 for the EQ-5D instrument.
9. **2 endpoints:** The Clinical Opiate Withdrawal Scale (COWS) score at the Follow-Up Visit (Visit 13), 4 days after the last dose, for two groups of patients (patients restarted on opioids after study medication discontinuation and patients not restarted on opioids after study medication discontinuation). See the individual study report for Study 8 in Section 9.4.1 for the COWS instrument.
10. **8 endpoints:** The Subject's Opiate Withdrawal Scale (SOWS) score at 24, 48, and 72 hours after stopping study medication (recorded in patient diaries) and 4 days after stopping study medication (at the Follow-Up Visit) for two groups of patients (patients who restarted opioids and patients who did not restart opioids). See the individual study report for Study 8 in Section 9.4.1 for the SOWS instrument.

Statistical Analysis Plan

Populations: The pre-specified populations were:

1. The intent-to-treat (ITT) population: The ITT population included all randomized patients who received at least one dose of study medication during the DB randomized withdrawal period. The ITT population served as the primary statistical population for the efficacy and safety analyses.
2. The per-protocol (PP) population: The PP population was a subset of the ITT population. It included ITT patients who did not one or more major protocol violations that may have impacted efficacy.
3. The OL safety population: All patients who received at least one dose of study medication during the OL phase of the study.
4. The DB safety population: All patients who received at least one dose of study medication during the DB phase of the study.

Statistics for the Primary Efficacy Endpoint:

Definition for the DB Baseline Pain Intensity Score: The DB baseline pain score was defined as the average of the available pain intensity scores during the 72 hours prior to randomization (end of the OL Titration Period). The baseline value was calculated by averaging the mean 24-hour period pain intensity scores, which were averages of two consecutive morning/evening or evening/morning scores. If a pain score was missing within a 24-hour period then the corresponding mean 24-hour period score was equal

to the pain score available within this period. If there were more than 2 scores available in a 24-hour period all scores were included in the calculation (therefore the baseline value may have consisted of more than 6 pain scores).

Definition for the Week 15 Pain Intensity Score: The Week 15 pain intensity score was the average of seven 24-hourly averages during Week 15.

Methods: Comparison of the primary efficacy endpoint results between the tapentadol ER and placebo groups was performed using a 2-sided analysis of covariance (ANCOVA) test at the 5% significance level. The model included treatment, country, tapentadol ER dose at the DB baseline (100-150 mg BID vs. 200-250 mg BID), and prior opioid use status (opioid-naive vs. opioid-experienced) as factors and DB baseline average pain intensity score as a covariate. Treatment effect of tapentadol ER versus placebo was estimated based on least-square means of the difference (LSD). The p-value for the treatment difference along with the two-sided 95% confidence interval was presented. The primary efficacy analysis was performed using the ITT population and the LOCF imputation method for missing values.

Handling of Missing Data During the DB Treatment Period: The last available post DB baseline pain score was carried forward (LOCF) to impute the pain scores that were missing up to Day 84 in the DB Randomized Withdrawal Period. This applied to patients who did not have pain intensity scores up to Day 85, whether they completed, or discontinued treatment. For patients without any post DB baseline data, the DB baseline measurement was carried forward.

Handling of Additional Pain Scores: If there were more than 2 scores within a 24-hour period then all scores were used to calculate the daily pain intensity. In this case the denominator was replaced by the number of pain scores used in the calculation.

Exploratory Imputation Methods for the Primary Endpoint: In addition to the LOCF imputation method, the following exploratory imputation methods were used for missing data:

1. **Baseline (start of DB Period) observation carried forward (BOCF):** Baseline observation, using the derived baseline average pain intensity prior to the DB period, was carried forward to impute the missing pain assessment after discontinuation of treatment or after the last pain score. The score was carried forward until the end to the scheduled end of treatment, i.e., Day 84 of the DB Withdrawal Period.
2. **Worst observation carried forward (WOCF):** The worst observation (including baseline average pain intensity) was carried forward to impute the missing pain assessment after discontinuation of treatment or after the last pain score. The score was carried forward until the end to the scheduled end of treatment, i.e., Day 84 of the DB Withdrawal Period.
3. **Placebo mean imputation (PMI):** The missing pain measurements for each day after discontinuation were replaced by the mean of all available pain intensity scores for all placebo-treated patients who completed treatment. Therefore if a patient discontinued treatment or recorded their last pain score at Week 8 of the Withdrawal Period, the pain intensity score at Week 12 was imputed using the Week 12 mean pain intensity score for all placebo-treated patients who completed treatment. Also a placebo missing pain score at some time-point was imputed by the observed placebo group mean pain intensity at the same time-point.

4. **Modified BOCF:** This method is a combination of BOCF and LOCF and is based on the PGIC. If a patient was rated as 'much improved' or 'very much improved' on the PGIC at their last post-baseline assessment, then LOCF was used to carry forward the last available post baseline on-treatment pain intensity score. If the patient was rated as anything other than 'much improved' or 'very much improved' at the last post-baseline PGIC assessment, or if the patient had no PGIC assessment, then BOCF was applied to pain intensity.
5. **No imputation - observed cases (OC):** No imputations were performed to impute pain assessments after discontinuation of treatment, or to impute missing intermittent pain assessments.

Statistics for the Time to Treatment Discontinuation: The time to treatment discontinuation due to lack of efficacy was calculated in days as the duration from the DB baseline to treatment discontinuation. Patients who completed the DB treatment period of the study were censored at the last observation time point. Patients who discontinued from the DB Period for reason other than lack of efficacy were censored at the time of discontinuation. The distribution of the time to treatment discontinuation due to lack of efficacy was estimated by the Kaplan-Meier estimate and compared among the treatment groups using the log-rank test.

Results for Study 15:

Protocol Deviations: Table 9.33 displays the major protocol deviations in the Randomized Withdrawal Period of Study 15. A slightly greater proportion of tapentadol ER-treated patients had protocol deviations than control-treated patients.

Table 9.33: Major protocol deviations in the Randomized Withdrawal Period in Study 15[1]

	Placebo (n=195)	Tapentadol ER (n=197)
Total % of Patients with Deviations	**17%**	**23%**
Excluded Concomitant Treatment	**7%**	**8%**
Prohibited Medication	**7%**	**8%**
Non-compliance	**5%**	**10%**
Doses Missed During Baseline or Primary Endpoint Week	**3%**	**2%**
Improvement in Pain During OL Titration	**2%**	**6%**
Selection Criteria Not Met	**3%**	**7%**
Inclusion Criteria Not Met: Baseline NRS	**3%**	**6%**
Treatment Deviation	**3%**	**1%**
Medkit Number Inconsistent	**3%**	**1%**

1 All randomized patients in the Randomized Withdrawal Period (patients may or may not have received study medication). Only protocol deviations that occurred in more than 2% in any treatment group are listed. Patients may appear in more than one category.
Reference: Adapted from CSR for Study 15, Attachment 1.12.1, Page 265.

Disposition: See Table 6.6 in Section 6.1.4 (Subject Disposition) for a display of the disposition in Study 15.

Demographics: As shown in Table 9.34, the baseline demographics were similar across the 2 treatment groups in the Randomized Withdrawal Period in Study 15.

Table 9.34: Baseline demographics at the DB baseline in Study 15[1]

		Placebo (n=193)	Tapentadol ER (n=196)
Age	Mean (SD)	61 (11)	60 (11)
	< 65 years old	62%	69%
	≥ 65 years old	38%	31%
Sex	Male	60%	61%
	Female	40%	39%
Race	Caucasian	70%	70%
	Black	10%	13%
	Hispanic	18%	14%
	Other	3%	3%
Country	United States	98%	97%
	Canada	2%	3%
Weight	Median, kg	99	100
BMI	Median, kg/m^2	34	33

1 ITT population: all randomized patients who received at least 1 dose of study medication in the Randomized Withdrawal Period

Reference: Adapted from the CSR for Study 15, Table 10, Pages 76-77; JMP KDEMOG datasets for Study 15.

Baseline Disease Characteristics: As shown in Table 9.35, the baseline disease characteristics were similar in the 2 treatment groups in the Randomized Withdrawal Period in Study 15.

Table 9.35: Baseline disease characteristics in Study 15[1]

		Placebo (n=193)	Tapentadol ER (n=196)
Diabetic Peripheral Neuropathy Characteristics			
Duration of DPN	Mean (SD), years	6.1 (5)	5.5 (5)
Duration of Treatment for DPN	Mean (SD), years	4.3 (4)	4.1 (4)
Opioid Experience			
Opioid-experienced[2]		34%	35%
OL Baseline Pain Intensity			
OL Baseline Pain Intensity Score[3]		7.3 (1.3)	7.2 (1.5)
OL Baseline Pain Intensity Category[3]	Mild	0%	1%
	Moderate	16%	22%
	Severe	84%	76%
DB Baseline Pain Intensity			
DB Baseline Pain Intensity Score[4]	Mean (SD)	3.4 (1.9)	3.6 (1.9)
DB Baseline Pain Intensity Category[4]	None	3%	2%
	Mild	59%	53%
	Moderate	26%	33%
	Severe	12%	11%

1 ITT population: all randomized patients who received at least 1 dose of study medication in the Randomized Withdrawal Period.
2 An opioid-experienced patient was defined as a patient who previously received an opioid analgesic for the treatment of painful DPN for at least intermittent treatment for 3 weeks, regardless of the response to the opioid analgesic.
3 OL baseline pain intensity category of mild, moderate, and severe were defined as none, mild, moderate, and severe were defined as 0, >0 to < 4, ≥ 4 to < 6, and ≥6, respectively. The OL baseline pain intensity was the average of the pain scores over 3 days prior to the start of the OL Titration Period.
4 DB baseline pain intensity score was the average pain intensity score over 72 hours prior to randomization (after the Washout Period) prior to the DB Period. DB baseline pain intensity category of none, mild, moderate, and severe were defined as 0, >0 to < 4, ≥ 4 to < 6, and ≥6, respectively.
Reference: Adapted from the CSR for Study 15, Table 10, Pages 76-77; Attachment 1.5.2, Pages 190-193

Prior Medications: See Table 6.3 in Section 6.1.3 (Disease Characteristics) for a list of the analgesics utilized prior to the OL baseline in Study 15.

Efficacy Results: See Section 6.1.5 (Analysis of Primary Endpoint) and Section 6.1.6 (Analysis of Secondary Endpoints) for results of the important endpoints in Study 15.

Safety: See Sections 7.3, 7.4, 7.5, and 7.6 for a discussion of the pooled safety results of the 3 Phase 3 trials.

9.4.5 Study 7 [abbreviation for Study R331333-PAI-3007 (KF5503/24)]

The following description of the protocol for Study 7 is based on amendment 1 of the protocol (dated December 20, 2006) and the SAP (dated September 17, 2008). See Table 9.36 for the dates of all amendments to the protocol and SAP for Study 7. Study 7 was initiated on November 14, 2006 and the study ended (the day of the last investigation on the last patient) on July 25, 2008. In amendment 1 of the protocol, there were no significant changes to the study design of Study 7 compared to the original protocol.

Table 9.36: Amendments to the Study 7 protocol and SAP

	Amendment	Date
Protocol	Original Protocol	September 14, 2006
	Amendment 1	December 20, 2006
SAP	SAP	September 17, 2008

Title: Throughout this review, Study 7 will be the abbreviation for Study R331333-PAI-3007 (J & J's trial designation) and Study KF5503/24 (Grünenthal's trial designation). J & J and Grünenthal used different protocol numbers for the same study. Study 7 is entitled, "A One-Year, Randomized, Open-Label, Parallel-Arm, Phase III Long-Term Safety Trial, with Controlled Adjustment of Dose, of Multiple Doses of CG5503 PR and Oxycodone CR in Subjects with Chronic Pain."

Objectives of Study 7: The primary objective of Study 7 was to evaluate the safety of orally administered tapentadol ER at doses of 100-250 mg twice daily over a long-term exposure of up to 1 year. Secondary objectives included the assessment of tapentadol ER and oxycodone CR dose requirements during long-term exposure; symptoms related to constipation using the Patient's Assessment of Constipation Symptom (PAC-SYM), sleep quality by using Sleep Questionnaire (SQ), symptoms of withdrawal following discontinuation of treatment using both the COWS and, in the US, the SOWS questionnaires; efficacy based on the subject's and Investigator's global assessment; pain intensity, using an 11-point NRS, over the one-year trial period; efficacy based on PGIC using a 7-point verbal rating scale; quality of life based on EuroQol-5 Dimension (EQ-5D); and quality of life based on SF-36.

Overall Design of Study 7: One-year OL, randomized, oxycodone CR-controlled, parallel group, MC (89 sites in the United States, Canada, and Europe), Phase 3 study of controlled adjustment of tapentadol ER in patients with chronic pain (≥ 3 months) from knee OA, hip OA, or non-malignant low back pain. Patients must have been at least 18 years old, taking analgesic medications, and dissatisfied with their current analgesics due inadequate analgesia or intolerability.

Prior to receiving study medication and prior to randomization, patients entered a 3- to 7-day Washout Period where all analgesics (including acetaminophen) were discontinued and new analgesics were not allowed. To be randomized and receive study medication, patients needed to have an average pain intensity score of ≥ 4 on an 11-point NRS during the 24 hours prior to the Titration Period (after washout). After completion of the Washout Period, patients entered the 1-week Titration Period and were randomized 4:1 to tapentadol ER 50 mg BID or oxycodone CR 10 mg BID and then after 3 days the dose was increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID, respectively. Patients remained on tapentadol ER 100 mg BID or oxycodone CR 20 mg BID for the last 4 days of the Titration

Period. In the 51-week Maintenance Period, upward or downward titration was allowed in increments of tapentadol ER 50 mg BID or oxycodone CR 10 mg BID (at a minimum of 3-day intervals for upward titration) to optimize the patients' analgesic needs and tolerability. The allowed dose range in the 51-week Maintenance Period was tapentadol ER 100 to 250 mg BID and oxycodone CR 20 to 50 mg BID. All analgesics or other interventions to treat pain were not allowed during the Titration and Maintenance Periods of Study 7 with the following exceptions:

- Study medication
- Short-term use of NSAIDs for pain or fever
- Daily aspirin doses < 325 mg per day for cardiovascular prophylaxis
- Up to 1000 mg of daily acetaminophen for rescue analgesia during the 1-week Titration Period and up to 1000 mg of acetaminophen per day for a maximum of 7 consecutive days and no more than 14 out of 30 days during the Maintenance Period.
- Stable doses of tricyclic antidepressants for pain (not for depression or other psychiatric disorders).
- Stable doses of selective SSRIs, SNRIs, benzodiazepines, mood stabilizers used as minor tranquilizers or hypnotics, anti-Parkinsonian drugs, and anticonvulsants.
- Stable intensity and frequency of Transcutaneous Electrical Nerve Stimulation, acupuncture, and other interventional adjunctive therapy.

At the end of the Maintenance Period, patients either entered an OL extension study (Study 10) or stopped their study medication without a taper and may have been started on appropriate analgesic medication according to local practice standards.

Eligibility Criteria of Study 7 at the Screening Visit: Table 9.37 displays the eligibility criteria in Study 7 at the Screening Visit.

Table 9.37: Eligibility criteria in Study 7 at the Screening Visit

Inclusion Criteria: To have been eligible to participate in the study, patients had to have met all of the following criteria:	**Exclusion Criteria: If patients had any of the following conditions, they were not eligible to participate in the study:**
1. ≥ 18 years old with knee OA, hip OA, or nonmalignant low back pain with pain at the reference joint or back ≥ 3 months. **2. Taking analgesic medication and dissatisfied with current therapy.** **3. Men and non-pregnant, non-lactating women. Sexually active women must be post menopausal, surgically sterile, or practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double barrier method, contraceptive patch, male partner sterilization) before entry and throughout the trial. Women must have a negative serum ß-hCG pregnancy test at screening.** **4. Patients must have signed an informed consent document indicating that they understand the purpose of and procedures required for the trial and are willing to participate in the trial.**	**1. Taking prohibited medications at the Screening Visit (antipsychotics, MAO inhibitors, corticosteroids (including oral, intramuscular, soft tissue, intra-articular, depot steroids).** **2. Has a clinically significant disease that may affect efficacy or safety assessments.** **3. Presence of conditions associated with conditions other than OA or low back pain that could confound the assessment or self-evaluation of pain.** **4. Life-long history of seizure disorder or epilepsy. Any of the following within 1 year: mild/moderate traumatic brain injury, stroke, transient ischemic attack, and brain neoplasm. Severe traumatic brain injury within 15 years (consisting of ≥ 1 of the following: brain contusion, intracranial hematoma, either unconsciousness or post traumatic amnesia lasting for more than 24 hours) or residual sequelae suggesting transient changes in consciousness.** **5. History of chronic hepatitis B or C, or HIV, presence of active hepatitis B or C within the past 3 months.** **6. History of malignancy within past 2 years, with exception of basal cell carcinoma that has been successfully treated.** **7. Patient is expected to require major surgical intervention during the trial or surgery of the back or reference joint within 3 months of screening.** **8. Uncontrolled hypertension (repeated systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg).** **9. Patients with severely impaired renal function.** **10. Patients with moderately or severely impaired hepatic function, or patients with laboratory values reflecting inadequate hepatic function (ALT, AST greater than threefold upper limit of normal).** **11. Clinically relevant history of hypersensitivity, allergy, or contraindication to oxycodone or acetaminophen.** **12. History of alcohol and/or drug abuse.** **13. Pending litigation due to chronic pain or disability.** **14. Participation in another trial concurrently, or within 30 days of enrollment into this trial.** **15. Previous participation in this trial or other trials with tapentadol.** **16. Known to or suspected of not being able to comply with the protocol and the use of the investigational products.** **17. Employees of Investigator or trial site, with direct involvement in proposed trial or other studies under the direction of that Investigator or trial site, as well as family members of employees or the Investigator.**

Reference: Protocol 7 from final study report for Study 7, Pages 9898-9990

Eligibility Criteria Prior to Randomization: After washout and prior to randomization, patients needed to have a baseline pain intensity score of ≥ 4 on an 11-point NRS.

Concomitant Medication in Study 7:

Analgesics: Analgesics [including NSAIDs such as COX-II inhibitors, opioids other than the study medication] were prohibited during the trial with the following exceptions:

1. Aspirin at oral doses ≤ 325 mg per day may have been continued for CV prophylaxis.

2. NSAIDs could have been used for reasons other than chronic pain such as short-term pain (e.g., toothache, headache) or fever.
3. Acetaminophen up to 1000 mg daily was allowed as a rescue analgesic medication during the 1-week Titration Period. During the 51-week Maintenance Period, acetaminophen was allowed for a maximum of 7 consecutive days and no more than 14 days out of 30 days.

Antipsychotics, MAO inhibitors, tricyclic antidepressants, SSRIs, SNRIs, benzodiazepines, hypnotics, anti-Parkinsonian drugs, and anticonvulsants: Anti-psychotics and MAO inhibitors were prohibited within 14 days prior to the screening visit and during the trial.

Tricyclic antidepressants were allowed if the patient was on a stable dose exclusively for pain (not for depression or other psychiatric disorders). SSRIs, SNRIs, benzodiazepines, mood stabilizers used as minor tranquilizers or hypnotics, anti-Parkinsonian drugs, and anticonvulsants were allowed if dosing was stable for at least 30 days prior to screening visit and was kept approximately stable during study.

Corticosteroids: Corticosteroids should not have been taken during the trial or within the following timelines prior to Screening: within 4 weeks (oral), within 8 weeks (intramuscular or soft tissue administration), within 3 months (intra-articular administration), or within 6 months (injection of depot steroids).

Other Allowed Interventions in Study 7: Transcutaneous Electrical Nerve Stimulation, acupuncture, and other interventional adjunctive therapy were allowed during the trial, provided that the patients had been on that therapy for at least 14 days, and continued to undergo therapy for the duration of the trial at the same frequency and intensity as before.

Study Monitoring and Evaluation in Study 7: See Table 9.38 for the schedule of procedures and evaluations in Study 7. Study 7 consisted of 5 periods: Screening, Washout, Titration, Maintenance, and Follow-up Periods.

Table 9.38: Schedule of procedures and evaluations in Study 7

	Screening	Wash Out	Baseline/ Titration	Maintenance (Visit 4 is the first week of the maintenance phase)[1]															Follow-Up (days)	
	0-14 days	3-7 days	First dose															End IMP	+4	+10-14
Visits[2]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	Phone
Time (Week)			W 1	W 2	W 3	W 4	W 5	W 9	W 13	W 17	W 21	W 25	W 29	W 33	W 37	W 41	W 45	W 49	W 53		
Informed consent	X																				
Assessment of pain (NRS)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
In- and exclusion criteria	X	X	X																		
Screening log and identification register	X																				
Subject's trial card	X																			X	
Demography	X																				
Previous medical history	X																				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/ additional analgesics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EQ-5D questionnaire			X				X	X	X	X			X			X			X		
SF-36 questionnaire			X				X	X	X	X			X			X			X		
Sleep questionnaire			X				X	X	X	X			X			X			X		
PAC-SYM questionnaire			X						X				X						X		
Investigator's global assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subject's global assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient's global impression of change				X								X							X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination/ body weight			X									X								X	
Height			X																		
ECG	X			X									X						X		
Urine drug test	X																				
Clinical laboratory (blood and urine samples)	X			X									X						X		
Pregnancy test[3]	X																		X		
Pharmacokinetic sample[4]	X			X		X				X			X						X	X	
Pharmacogenomic sample in consenting subjects	X																				
Subject randomization			X																		
Drug accountability (collect and check blisters)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense IMP			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dispense paracetamol/acetominophen			X	X			X	X	X	X	X	X	X	X	X	X	X	X			
Withdrawal assessments[5]																			X	X	

1 All visits in the Maintenance Period had to have been scheduled within 7 ± 1 days in Week 2 to Week 5 and within 1 month ± 3 days for the rest of the treatment duration, respectively.
2 Each visit took place at the beginning of the week indicated in the chart.
3 ß-hCG pregnancy screen was to be performed monthly in those countries requiring this.
4 Patients should have recorded dose and time of intake of study medication for each of the 2 days preceding the visit and for the intake of the study medication on the morning of the visit.
5 Withdrawal Assessment (should have been completed at 24, 48, and 72 hours after stopping the study medication; and should have completed SOWS and COWS at Visit 20). The SOWS questionnaire was only completed by U.S. patients.
Reference: Protocol 7 (amendment 1) in CSR for 7, Table 16.1, Pages 9973-9974

Pain Assessment in Study 7: The 11-point pain intensity NRS was assessed once daily at Screening and at Weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 52 (i.e., Visits 1 and Visits 3 to 19) at these visits**.** In contrast to Studies 8, 9, 11, and 15, in Study 7 electronic diaries were not used to capture pain intensity scores every morning and evening. Pain intensity scores were not done every day and were only done during the study visits in Study 7. Finally, pain intensity scores were based on the past 24 hours in Study 7; whereas, they were based on the last 12 hours in Studies 8, 9, 11, and 15.

The following question was asked:

"What has your average pain level been for the past 24 hours? (circle one)"

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Parameters in Study 7: The following safety parameters were collected in Study 7:

- Multiple analyses of adverse events
- Proportion of patients with each of the following events: nausea, vomiting, vomiting or nausea, constipation, all gastrointestinal events, dizziness, somnolence, pruritus.
- SOWS
- COWS
- Sleep Questionnaire
- Constipation Assessment (PAC-SYM)

The following efficacy parameters were collected in Study 7:

- Pain intensity scores
- Patient's global impression of change
- Patient and investigator global assessments
- SF-36
- EuroQoL-5 Dimension (EQ-5D) Questionnaire

Endpoints in Study 7: There were no primary or secondary endpoints because this study was a primary safety study.

Statistics in Study 7:

Populations: The pre-specified populations were:

1. The intent-to-treat (ITT) population: The ITT population included all randomized patients who received at least one dose of study medication. The ITT population served as the primary statistical population for the efficacy analyses.
2. The safety population: The safety population included all patients who received at least one dose of study medication. The safety population served as the primary statistical population for the safety analyses.

Statistical Methods: There was no formal hypothesis testing in Study 7 because it was a primary safety study. All confidence intervals (unless stated otherwise) were 2-sided at the 95% confidence level. All statistical tests were 2-sided at a significance level of 0.05 and were interpreted in an exploratory manner. Summaries of data at the endpoint included imputation by LOCF and other time points will include no

imputation (observed data only). Since pain intensity scores were not of primary interest in Study 7 (unlike for Studies 8, 9, 11, and 15), no other imputations or alternative sensitivity analysis for missing data was implemented.

Efficacy Results: Since this study was a primary safety study, efficacy results were exploratory and therefore not presented in this review.

Safety: See Sections 7.3, 7.4, 7.5, and 7.6 for a discussion of the pooled safety results of the induction trials (Studies 8, 9, and 11) and Study 7.

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/

ERIC R BRODSKY
08/19/2010

SARAH K OKADA
08/19/2010

Clinical Filing Checklist for Original NDA Submission for Tapentadol ER

NDA Number: 200533

Product Name: tapentadol ER (Nucynta ER)
Applicant: Johnson and Johnson
NDA Type: original submission
Received Date: December 1, 2009

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	Yes			eCTD
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	Yes			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	Yes			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	Yes			
5.	Are all documents submitted in English, or are English translations provided when necessary?	Yes			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	Yes			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	Yes			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	Yes			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	Yes			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	Yes			
11.	Has the applicant submitted a benefit-risk analysis for the product?	Yes			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1) application
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	Yes			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

Clinical Filing Checklist for Original NDA Submission for Tapentadol ER

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	Yes			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	Yes			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	Yes			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			N/A	Not needed. Applicant submitted 3 Phase 3 studies primarily based in the U.S.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	Yes			
19.	Has the applicant submitted adequate information to assess the arhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	Yes			Thorough QT study was submitted (i.e., Study HP10)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	Yes			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	Yes			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			N/A	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	Yes			
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	Yes			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	Yes			
OTHER STUDIES					

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Clinical Filing Checklist for Original NDA Submission for Tapentadol ER

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			N/A	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			N/A	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	Yes			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	Yes			Tapentadol ER contains tapentadol, a Schedule II controlled substance
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			N/A	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	Yes			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	Yes			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	Yes			
34.	Are all datasets to support the critical safety analyses available and complete?	Yes			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	Yes			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	Yes			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	Yes			As requested at the Pre-NDA meeting the sponsor provided CRFs for the following drop-outs: "protocol violation", "lack of efficacy", "lost to follow-up", "subject choice", "non-compliance to study medication or procedures", and for "other".
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	Yes			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	Yes			
CONCLUSION					

Clinical Filing Checklist for Original NDA Submission for Tapentadol ER

	Content Parameter	Yes	No	NA	Comment
40.	From a clinical perspective, is this application fileable? If not, please state why.	Yes			

Identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

I have no potential review issues or information requests regarding this NDA for tapentadol ER at this time.

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

/s/

ERIC R BRODSKY
01/21/2010
Clinical Filing Checklist for Tapentadol ER Original NDA Submission

SARAH K OKADA
01/22/2010
I concur.