CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	200-533
Drug Name:	NUCYNTA ER
Indication(s):	Management of moderate to severe chronic pain
Applicant:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Date(s):	Letter date: Nov. 30, 2009
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Keywords:	NDA review, Clinical Studies, Missing data imputation

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant seeks approval to market NUCYNTA (tapentadol) extended-release (ER) tablets for the proposed 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 conducted four controlled clinical studies to assess the efficacy of NUCYNTA for the proposed indication. One study was conducted in subjects with chronic low back pain (LBP) while another study was conducted in subjects with diabetic peripheral neuropathy (DPN). Two studies included subjects with chronic pain due to osteoarthritis (OA) of the knee. In each study, the applicant evaluated the change in pain from baseline to the last week of the maintenance period. The applicant concluded that three studies demonstrated the superiority of NUCYNTA over placebo and that one OA study failed to demonstrate the efficacy of NUCYNTA. For the second OA study, my conclusions varied from those of the applicant. By using conservative missing data imputation methods, I found that the second OA study also failed to demonstrate the efficacy of NUCYNTA.

Based on my review, I concluded that the LBP study and DPN study successfully demonstrated the superiority of NUCYNTA over placebo. Thus, there is sufficient evidence to support the efficacy of NUCYNTA for the treatment of moderate to severe chronic pain.

1.2 Brief Overview of Clinical Studies

Tapentadol, the active ingredient in NUCYNTA, is an analgesic being developed by the applicant in an extended-release tablet formulation. A tapentadol immediate-release (IR) tablet formulation has been approved in the United States for the relief of moderate to severe acute pain in patients 18 years of age or older. The development program for the extended-release formulation was discussed between the applicant and the agency at several meetings. Key discussions focused on the study designs, primary endpoint, and statistical strategies for handling missing data.

The applicant conducted four Phase 2, four Phase 3 efficacy and safety studies, one long-term safety study and one study evaluating direct dose conversion between the tapentadol IR and ER formulations in adults suffering from three representative chronic pain conditions (chronic LBP, painful DPN and painful OA). The Phase 2 studies had different designs and were of shorter duration than the Phase 3 studies. The Phase 3 studies comprised the majority of subjects exposed and were the foundation for the overall efficacy of NUCYNTA.

Studies PAI-3011/KF23, PAI-3008/KF11 and PAI-3009/KF12 were similar in design, doses, treatment titration, maintenance period duration, efficacy endpoint and planned analyses. The studies varied with respect to the enrollment countries and pain conditions. Study PAI-3011/KF23 was conducted in subjects with chronic LBP in North America and Australia. Study

PAI-3008/KF11 was conducted in subjects with chronic painful OA in North America and Australia, while PAI-3009/KF12 was conducted in subjects with chronic painful OA in Europe.

After a 2-week screening period, patients started a washout period by discontinuing all analgesic medication they had previously been taking. Eligible subjects who completed the washout period had their baseline pain intensities measured and then were randomized in a 1:1:1 ratio to one of three treatments: NUCYNTA, oxycodone controlled release (CR) or placebo. Following a 3-week flexible titration period to achieve an optimal therapeutic dose, subjects entered into a 12-week maintenance period with controlled dose adjustment. The applicant's primary efficacy endpoint was the change in average pain intensity from baseline to the last week of the maintenance period at Week 12. Daily pain intensity was measured on an 11-point numerical rating scale (NRS). The primary analysis was an analysis of covariance (ANCOVA) with baseline average pain intensity score as a covariate. The primary imputation method was last observation carried forward (LOCF).

PAI-3015/KF36 was a randomized, multi-center, double-blind, placebo-controlled withdrawl design study in subjects with painful DPN. After washout and a pain evaluation period, subjects received open-label NUCYNTA titrated to an optimal dose over 3 weeks. Subjects who had at least 1-point improvement in pain intensity on the NRS at the end of the open-label titration period were then randomized to continue on their optimal dose or placebo. The applicant's primary efficacy endpoint was the change from baseline at randomization in average pain intensity over the last week of the double-blind maintenance period at Week 12. Daily pain intensity was measured on an 11-point NRS. The primary analysis was an ANCOVA with baseline average pain intensity score at randomization as a covariate. The primary imputation method was LOCF.

1.3 Statistical Issues and Findings

In chronic pain studies, the LOCF method is not appropriate since patients who drop out for adverse events may have good pain scores carried forward even though they are not successfully treated. Although the Division stated concerns with the use of a LOCF imputation strategy during the development process, the applicant used LOCF as the primary method of handling missing data. They also conducted sensitivity analyses which included baseline observation carried forward (BOCF), worst observation carried forward (WOCF), placebo mean imputation (PMI), and modified BOCF.

The BOCF and WOCF strategies have previously been used to address the Division's concerns regarding missing data. However, the PMI and modified BOCF methods are more novel and require additional evaluation. In the PMI method, the mean outcome of completers in the placebo group was imputed for dropouts in both treatment groups. This methodology resulted in the estimated treatment effect being the product of the treatment effect among completers and the proportion of completers in the active arm. The mathematical formulation follows:

- Let p_a and p_c be the proportions of completers in the active and placebo groups.
- Let Y_a and Y_c be the mean outcomes for completers.

- Then, the estimated treatment effect is the $[p_a Y_a + (1 - p_a)Y_c] - [p_c Y_c + (1 - p_c)Y_c]$, which is equal to $[p_a(Y_a - Y_c)]$.

Since the estimated treatment effect is only influenced by the data from patients completing the study, the PMI method is similar to an analysis of completers. Analyzing completers is problematic since the outcome of patients completing the study may not represent the outcome of patients not completing the study. In the placebo group, patients completing the study are likely to be the less severely afflicted patients; while in the NUCYNTA group, patients completing the study are likely to be the more severely afflicted patients. As a result, the PMI method assigned good scores from the placebo completers to patients dropping out due to adverse events in the treatment group. Based on these reasons, I conclude that the PMI method is not appropriate.

The applicant also proposed the modified BOCF imputation method as a sensitivity analysis. This method combined BOCF and LOCF based on the patient global impression of change (PGIC). If a subject rated their status as "much improved" or "very much improved" on the PGIC at their last post-baseline assessment, then LOCF was used, otherwise BOCF was applied to impute the missing pain intensity. This imputation method is not appropriate since it may assign treatment benefit to a patient that subsequently discontinued due to an adverse event.

In the BOCF imputation method, baseline observations were carried forward to impute missing pain assessments after treatment discontinuation up to the end of the double-blind treatment period. In Study PAI-3015/KF36 which utilized a randomized withdrawl design, the applicant's baseline was defined as the randomization baseline. However, imputing randomization baseline would assign efficacy benefit to study drug since subjects entering the randomization were those with at least 1-point improvement in pain intensity on the NRS at the end of the open-label titration period. In my analyses, I imputed the screening baseline.

In Study PAI-3015/KF36, subjects with at least 1-point improvement in pain intensity on the NRS at the end of the open-label titration period were to be randomized. However, there were 21 subjects who didn't meet this criterion but were randomized. During the review, the agency requested the applicant clarify the discrepancies. The applicant responded that investigators were instructed to randomize only patients with a change in pain intensity of at least one, and this was detailed in the statistical analysis plan (SAP). Despite the investigator instructions, these directions were not followed. The applicant didn't provide any further details regarding why investigators didn't follow the directions. I conducted additional analyses excluding these 21 subjects.

After performing analyses that addressed the statistical concerns, I concluded that NUCYNTA reduced the pain intensity in patients with moderate to severe chronic pain when compared to placebo in the LBP and DPN populations.

2. INTRODUCTION

2.1 Overview

NUCYNTA developed by Johnson & Johnson Inc. is an extended-release tablet formulation of Tapentadol proposed for the management of moderate to severe chronic pain in patients 18 years of age or older. The development program was discussed between the applicant and the division at several meetings.

At the End-of-Phase 2 meeting on August 24, 2006 (IND 61,345), the agency agreed to the use of a controlled dose adjustment design but specified the need for a fixed-dose pivotal study with a 12-week maintenance phase. The agency also accepted a titration-to-optimal dose design with a statistical comparison of all subjects treated with the study drug as one active group against the placebo group. At the meeting, it was stated that LOCF was not considered appropriate as the primary method of handling missing data, BOCF was instead recommended as the primary imputation method. A continuous responder analysis treating all discontinuations as non-responders was also recommended. In addition, the agency recommended that the primary endpoint in the pivotal Phase 3 studies be defined as the change from baseline of the average daily pain intensity on an 11-point NRS over the last week of the maintenance period at Week 12. The following is quoted from the meeting minutes.

Question 5
Does the Division concur with the proposed methods of imputation for statistical analyses?

Agency Response:

- **<u>For the OA and CLBP studies</u>, last observation carried forward (LOCF) is not considered appropriate as the primary method of handling missing data. Patients who drop out for adverse events may have good pain scores carried forward even though they were not successfully treated. Instead, we recommend that the alternate imputation method you proposed (baseline carried forward analysis) be applied as the primary method of handling missing data.**

In the pre-NDA meeting on January 23, 2009, the agency requested submission of narratives and case report forms for tapentadol-treated subjects who discontinued treatment from the Phase 2 or Phase 3 clinical studies for reasons coded as "lost to follow-up", "lack of efficacy", "violation of inclusion/exclusion criteria", "study medication non-compliant", "subject choice (subject withdrew consent)" or "other".

The development program included a total of four Phase 2 and four Phase 3 efficacy studies from three chronic pain conditions (chronic LBP, painful DPN and painful OA). My review evaluates Phase 3 studies PAI-3011/KF23, PAI-3008/KF11 and PAI-3015/KF36. Study PAI-3009/KF12 is not of focus in my review since the applicant concluded that the study failed on the primary efficacy analyses.

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. All necessary documentations, formats, and links were provided as well. The data and final study report for the electronic submission were archived under the network path location \\Cdsesub1\EVSPROD\NDA200533\0000\m5.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study PAI-3011/KF23

Study Design and Endpoints

PAI-3011/KF23 was a Phase 3, randomized, multi-center, double-blind, placebo- and active-controlled, parallel-group study conducted in North America and Australia. The primary objective was to evaluate the efficacy and safety of NUCYNTA in subjects with moderate to severe chronic LBP.

After a 2-week screening period, patients started a washout period by discontinuing all analgesic medication they had previously been taking. Eligible subjects who completed the washout period had their baseline pain intensities measured and then were randomized in a 1:1:1 ratio to one of three treatments: NUCYNTA, oxycodone CR or placebo. Patients randomized to NUCYNTA initiated therapy with a dose of 50 mg b.i.d. for three days. Subsequent titration was allowed over a 3-week titration period to a dose of 100 mg to 250 mg b.i.d. to achieve an optimal therapeutic dose. A titration scheme and dosing regimen was used for the active-control and placebo perspectively. During the titration period, acetaminophen was allowed as a rescue medication, limited to a total of 1000 mg daily. Before entering into the maintenance period, subjects had to maintain a stable optimal dose for the last 3 days of the titration period. During the maintenance period, subjects were to continue their study drug intake for 12 weeks with controlled dose adjustment.

Subjects were enrolled from 85 sites in the United States, 15 sites in Canada and 3 sites in Australia. Nine hundred and eighty-one subjects were randomized to three treatment groups.

The primary efficacy endpoint was the change from baseline to the end of the maintenance period in the average overall pain. Pain was measured on an 11-point NRS scale (0 – 10) which assessed the patient's overall pain during the past 12 hours. It was recorded twice daily (AM/PM) in the study diary. The baseline score was defined as the average of available pain intensity scores during the last 72 hours prior to randomization.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics are provided in the appendix. Most subjects were white (73%), and approximately 58% of all subjects were female. The mean age was 50 years.

Table 1 shows the patient disposition by treatment group. The reasons for discontinuation are shown for the overall double-blind period as well as by phase. Many dropouts occurred in the titration period and the most common reasons for study discontinuation in the active-treatment groups were adverse events followed by subject choice, while the most common reason for study discontinuation in the placebo group was lack of efficacy.

Table 1: Subjects' Disposition of PAI-3011/KF23

Disposition Status/Discontinuation Reason	**Placebo** (N=319) n (%)	**NUCYNTA** (N=318) n (%)	**Oxycodone CR** (N=328) n (%)
Complete Double-Blind Treatment Period	161 (51)	172 (54)	142 (43)
Discontinued During Double-blind Treatment Period	159 (50)	146 (46)	186 (57)
Patient Choice	30 (10)	32 (10)	36 (11)
Lost to Follow-up	12 (4)	11 (4)	6 (2)
Adverse Event	15 (5)	53 (17)	106 (32)
Lack of Efficacy	66 (21)	18 (6)	9 (3)
Study Medication Non-compliant	20 (6)	21 (7)	14 (4)
Other	15 (5)	11 (4)	15 (5)
Discontinued During Titration Period	108 (34)	83 (26)	129 (39)
Patient Choice	18 (6)	19 (6)	19 (6)
Lost to Follow-up	8 (3)	4 (1)	2 (1)
Adverse Event	8 (3)	34 (11)	87 (27)
Lack of Efficacy	51 (16)	13 (4)	7 (2)
Study Medication Non-compliant	12 (4)	9 (3)	9 (3)
Other	11 (3)	4 (1)	5 (2)
Discontinued During Maintenance Period	50 (16)	63 (20)	57 (17)
Patient Choice	12 (4)	13 (4)	17 (5)
Lost to Follow-up	4 (1)	7 (2)	4 (1)
Adverse Event	7 (2)	19 (6)	19 (6)
Lack of Efficacy	15 (5)	5 (2)	2 (1)
Study Medication Non-compliant	8 (3)	12 (4)	5 (2)
Other	4 (1)	7 (2)	10 (3)

Source: Reviewer's Analysis

Statistical Methodologies

For the primary efficacy variable, change from baseline to the last week of the maintenance period in the average pain intensity, the treatment groups were compared using an ANCOVA model with factors treatment, pooled center and baseline pain intensity as a covariate. The primary analysis population was the intention-to-treat (ITT) population which included all randomized subjects who took at least one dose of study drug following randomization.

The applicant used LOCF as the primary method of handling missing data and their sensitivity analyses included BOCF, WOCF including baseline, modified BOCF and PMI. The LOCF method was not appropriate since patients who dropped out for adverse events may have good pain scores carried forward even though they were not successfully treated. The BOCF and WOCF strategies have previously been used to address the Division's concerns regarding missing data. However, the PMI and modified BOCF methods are more novel and require additional evaluation. In the PMI method, the mean outcome of completers in the placebo group was imputed for dropouts in both treatment groups. This methodology resulted in the estimated treatment effect being the product of the treatment effect among completers and the proportion of completers in the active arm. The mathematical formulation follows:

- Let p_a and p_c be the proportions of completers in the active and placebo groups.
- Let Y_a and Y_c be the mean outcomes for completers.
- Then, the estimated treatment effect is the $[p_aY_a + (1 - p_a)Y_c] - [p_cY_c + (1 - p_c)Y_c]$, which is equal to $[p_a(Y_a - Y_c)]$.

Since the estimated treatment effect is only influenced by the data from patients completing the study, the PMI method is similar to an analysis of completers. Analyzing completers is problematic since the outcome of patients completing the study may not represent the outcome of patients not completing the study. In the placebo group, patients completing the study are likely to be the less severely afflicted patients; while in the NUCYNTA group, patients completing the study are likely to be the more severely afflicted patients. As a result, the PMI method assigned good scores from the placebo completers to patients dropping out due to adverse events in the treatment group. Based on these reasons, I concluded that the PMI method was not appropriate.
The applicant also proposed the modified BOCF imputation method as a sensitivity analysis. This method combined BOCF and LOCF based on the patient global impression of change (PGIC). If a subject rated their status as "much improved" or "very much improved" on the PGIC at their last post-baseline assessment, then LOCF was used, otherwise BOCF was applied to impute the missing pain intensity. This imputation method is not appropriate since it may assign treatment benefit to a patient that subsequently discontinued due to an adverse event. I considered the PMI and modified BOCF strategies to be inappropriate, and consequently, I used the BOCF and WOCF including baseline strategies to impute missing values in the primary analyses.

For the primary endpoint, the continuous responder curves were also generated by treatment groups. In this analysis, all non-completers are classified as non-responders, and the curves are cumulative, such that every patient who achieves a 50% reduction in pain from baseline is also included in every level of improvement below 50%.

Results and Conclusions

Table 2 shows the results of both applicant's and my primary efficacy analyses. With the BOCF and WOCF imputation methods, my results indicate that NUCYNTA is statistically significantly different from and superior to placebo.

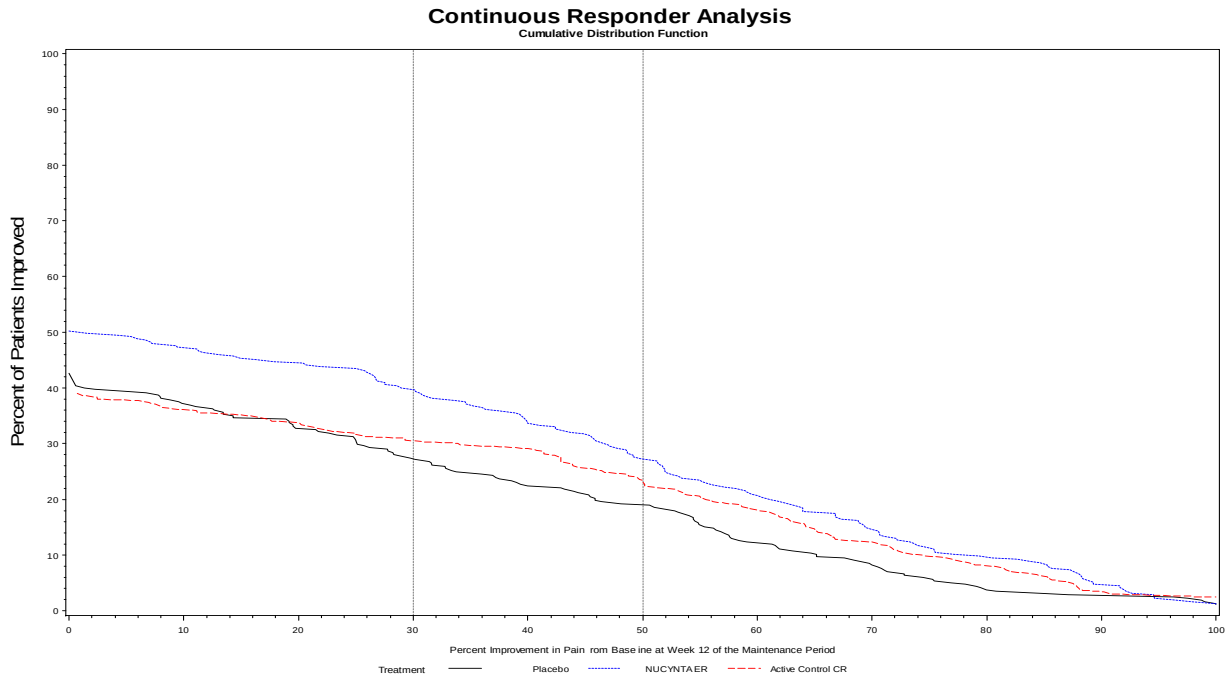
For the continuous responder analysis, my results confirmed the applicant results. As shown in Figure 1, the lines for the placebo and NUCYNTA show notable separation which indicates NUCYNTA is different from placebo.

Table 2: Primary Efficacy Results (Study PAI 3011/KF23)

Endpoint	Imputation	NUCYNTA (n=312)	Oxycodone CR (n=323)	Placebo (n=316)
Change in Average Pain from Baseline to Last Week of Maintenance				
Applicant's results				
LS means	LOCF	-2.9	-2.9	-2.1
p-value vs. placebo		<0.001	<0.001	
Reviewer's 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	

Source: Clinical Study Report Table 26 and Reviewer's Analyses

Figure 1: Percent Improvement in Pain from Baseline at Week 12 of the Maintenance Period (Study PAI-3011/KF23)



3.1.2 Study PAI-3008/KF11

Study Design and Endpoints

PAI-3008/KF11 was a Phase 3, randomized, multi-center, double-blind, placebo- and active-controlled, parallel group study conducted in North America, Australia and New Zealand. The primary objective was to evaluate the efficacy and safety of NUCYNTA in subjects with moderate to severe chronic pain from OA of the knee. The study design and endpoint were the same as Study PAI-3011/KF23.

Subjects were enrolled from 87 sites in the United States, 15 sites in Canada, 4 sites in Australia and 6 sites in New Zealand. One thousand and thirty subjects were randomized to three treatment groups.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics are provided in the appendix. Most subjects were white (76%), and approximately 60% of all subjects were female. The mean age was 58 years.

Table 3 shows the patient disposition by treatment group. The reasons for discontinuation are shown for the overall double-blind period as well as by phase. As in Study PAI-3011/KF23, many drop-outs occurred in the titration period and the most common reasons for study discontinuation in the active-treatment groups were adverse events followed by subject choice. The most common reason for study discontinuation in the placebo group was lack of efficacy.

Results and Conclusions

The statistical methodology was the same as in Study PAI-3011/KF23. Table 4 shows the results of the applicant's and my analysis. With the BOCF and WOCF imputation methods, none of the analyses provided sufficient evidence of a difference between NUCYNTA and placebo.

I generated the continuous responder curves by treatment group, using the same approach as in Study PAI-3011/KF23. As shown in Figure 2, the lines for the placebo and NUCYNTA show little separation along the whole range of percent improvement from baseline. In addition, statistical tests of the curves did not yield significant results. This provides additional evidence that NUCYNTA is not different from placebo.

Table 3: Subjects' Disposition of PAI-3008/KF11

Disposition Status/Discontinuation Reason	Placebo (N=337) n (%)	NUCYNTA (N=344) n (%)	Oxycodone CR (N=342) n (%)
Complete Double-Blind Treatment Period	207 (61)	197 (57)	121 (35)
Discontinued During Double-blind Treatment Period	130 (39)	147 (43)	221 (65)
Patient Choice	28 (8)	38 (11)	35 (10)
Lost to Follow-up	1 (0)	2 (1)	0 (0)
Adverse Event	22 (7)	66 (19)	147 (43)
Death	0 (0)	0(0)	1 (0)
Lack of Efficacy	56 (17)	22 (7)	13 (4)
Study Medication Non-compliant	8 (2)	6 (2)	12 (4)
Other	15 (5)	13 (4)	13 (4)
Discontinued During Titration Period	83 (25)	80 (23)	169 (49)
Patient Choice	17 (5)	17 (5)	24 (7)
Lost to Follow-up	1 (0)	1 (0)	0 (0)
Adverse Event	13 (4)	37 (11)	124 (36)
Lack of Efficacy	41 (12)	17 (5)	8 (2)
Study Medication Non-compliant	4 (1)	1 (0)	8 (2)
Other	7 (2)	7 (2)	5 (2)
Discontinued During Maintenance Period	47 (14)	67 (20)	52 (15)
Patient Choice	11 (3)	21 (6)	11 (3)
Lost to Follow-up	0 (0)	1 (0)	0 (0)
Adverse Event	9 (3)	29 (8)	23 (7)
Death	0 (0)	0 (0)	1 (0)
Lack of Efficacy	15 (5)	5 (2)	5 (2)
Study Medication Non-compliant	4 (1)	5 (2)	4 (1)
Other	8 (2)	6 (2)	8 (2)

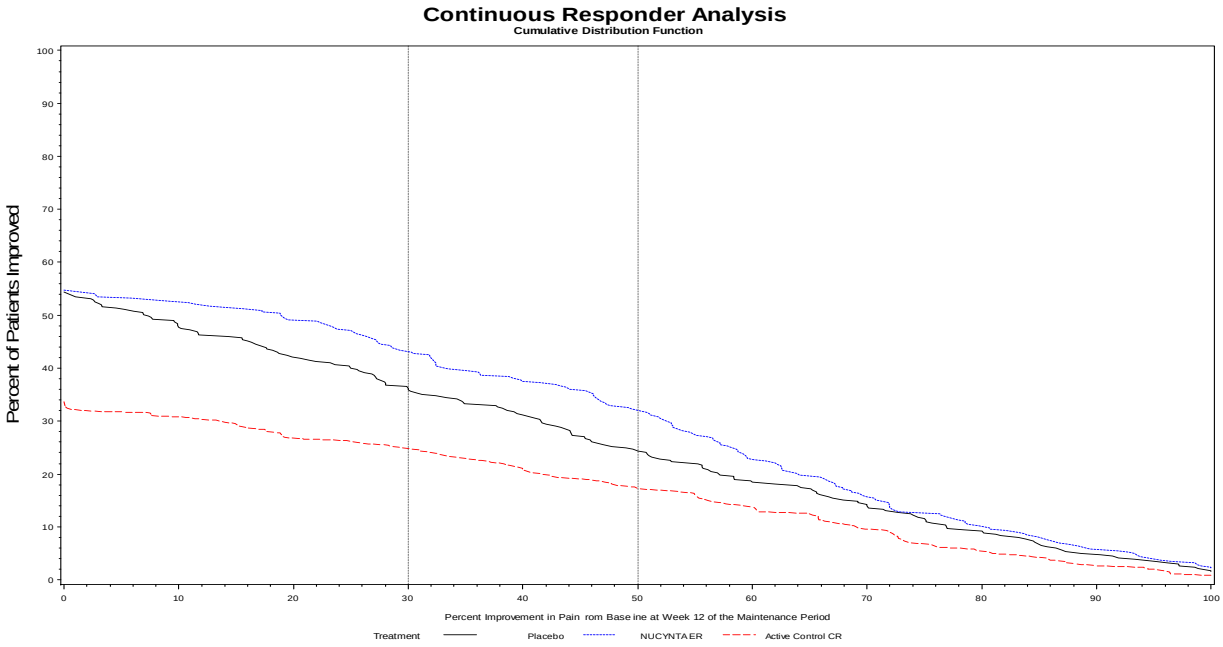
Source: Reviewer's Analysis

Table 4: Primary Efficacy Results (Study PAI 3008/KF11)

Endpoint	Imputation	NUCYNTA (n=344)	Oxycodone CR (n=342)	Placebo (n=336)
Change in Average Pain from Baseline to Last Week of Maintenance				
Applicant's results				
LS means	LOCF	-2.9	-2.6	-2.3
p-value vs. placebo		<0.001	0.069	
Reviewer's 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	

Source: Clinical Study Report Table 26 and Reviewer's Analyses

Figure 2: Percent Improvement in Pain from Baseline at Week 12 of the Maintenance Period (Study PAI-3008/KF11)



3.1.3 Study PAI-3015/KF36

Study Design and Endpoints

PAI-3015/KF36 was a Phase 3, multi-center, double-blind, placebo-controlled, randomized withdrawl study conducted in North America. The primary objective was to evaluate the efficacy and safety of NUCYNTA in subjects with moderate to severe chronic pain due to DPN.

After washout and a pain evaluation period, subjects received open-label NUCYNTA titrated to an optimal dose over 3 weeks. Subjects who had at least 1-point improvement in pain intensity on the NRS at the end of the open-label titration period were then randomized to receive their individually determined optimal open-label NUCYNTA dose or placebo for 12 weeks. Randomization was stratified by country, subject's NUCYNTA dose category at the end of open-label titration period, as well as subject's prior opioid use status. For subjects randomized to placebo, the dose of NUCYNTA was reduced to 100 mg b.i.d. for the first 3 days of the double-blind maintenance period and from Day 4 onwards, they received placebo b.i.d. During the first 4 days of the double-blind maintenance period, all randomized subjects were allowed 2 doses of NUCYNTA 25 mg at least 6 hours apart per day as supplemental analgesia. From Day 5 through the end of the double-blind maintenance period, subjects were allowed a single dose of NUCYNTA 25 mg per day as supplemental analgesia.

Subjects were enrolled from 87 sites in the United States and 6 sites in Canada. Five hundred and ninety-one subjects were enrolled in the open-label titration period, and three hundred and ninety-two subjects were randomized to continue on their optimal dose or placebo.

The primary efficacy endpoint was the change from baseline at randomization to the end of the maintenance period in the average pain intensity. Pain was measured on an 11-point NRS scale which assessed the patient's overall pain during the past 12 hours. It was recorded twice daily (AM/PM) in the study diary. The baseline score was defined as the average of available pain intensity scores during the last 3 days in the open-label titration phase.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics are provided in the appendix. Most subjects were white (70%), and approximately 60% of all subjects were male. The mean age was 60 years.

Table 5 shows the patient disposition by treatment group. The reasons for discontinuation are shown by phase. There were 34% of subjects who discontinued in the titration period. In the double-blind maintenance period, the most common reasons for study discontinuation in NUCYNTA group were adverse events followed by subject choice, while the most common reason for study discontinuation in the placebo group was lack of efficacy.

Table 5: Subjects' Disposition of PAI-3015/KF36

Open-Label Treatment Period	**Open-Label NUCYNTA (N=588) n (%)**
Complete Open-Label Titration Period	390 (66)
Discontinued During Open-Label Titration Period	198 (34)
Patient Choice	21 (4)
Lost to Follow-up	4 (1)
Adverse Event	102 (17)
Lack of Efficacy	19 (3)
Study Medication Non-compliant	15 (3)
Other	11 (2)
Subject not fulfill the criterion for randomization	26 (4)

Entire 12-week Double Blind Randomized Withdrawl Period

	NUCYNTA (n=196) n (%)	**Placebo (n=193) n (%)**
Complete DB Randomized Withdrawl Period	137 (70)	134 (69)
Discontinued During DB Treatment Period	59 (30)	60 (31)
Patient Choice	13 (7)	7 (4)
Lost to Follow-up	1 (1)	3 (2)
Adverse Event	29 (15)	15 (8)
Lack of Efficacy	8 (4)	27 (14)
Study Medication Non-compliant	4 (2)	2 (1)
Other	4 (2)	6 (3)

Source: Reviewer's Analysis

Statistical Methodologies

For the primary efficacy variable, change from baseline at randomization to the last week of the maintenance period in the average pain intensity, the treatment groups were compared using an

ANCOVA model with factors for treatment, country, dose category after open-label titration, prior opioid use and baseline pain intensity as a covariate.

The primary analysis population was the intention-to-treat (ITT) population which included all randomized subjects who took at least one dose of study medication during the double-blind maintenance period. Subjects with at least 1-point improvement in pain intensity on the NRS at the end of the open-label titration period were to be randomized. However, there were 21 subjects who didn't meet this criterion but were randomized. In my review, these 21 subjects were excluded from the primary efficacy analysis.

The applicant used LOCF as the primary method of handling missing data and their sensitivity analyses included BOCF, WOCF including baseline, modified BOCF and PMI. The applicant's baseline was defined as the randomization baseline. As discussed in Section 3.1.1, LOCF, PMI and modified BOCF were not appropriate. In my analyses, I used BOCF and WOCF including baseline to impute missing values, where baseline was defined as the screening baseline to avoid assigning efficacy benefit to dropouts.

Results and Conclusions

Table 6 shows the results of both applicant's and my primary efficacy analyses. My results indicate that NUCYNTA is statistically significantly different from and superior to placebo.

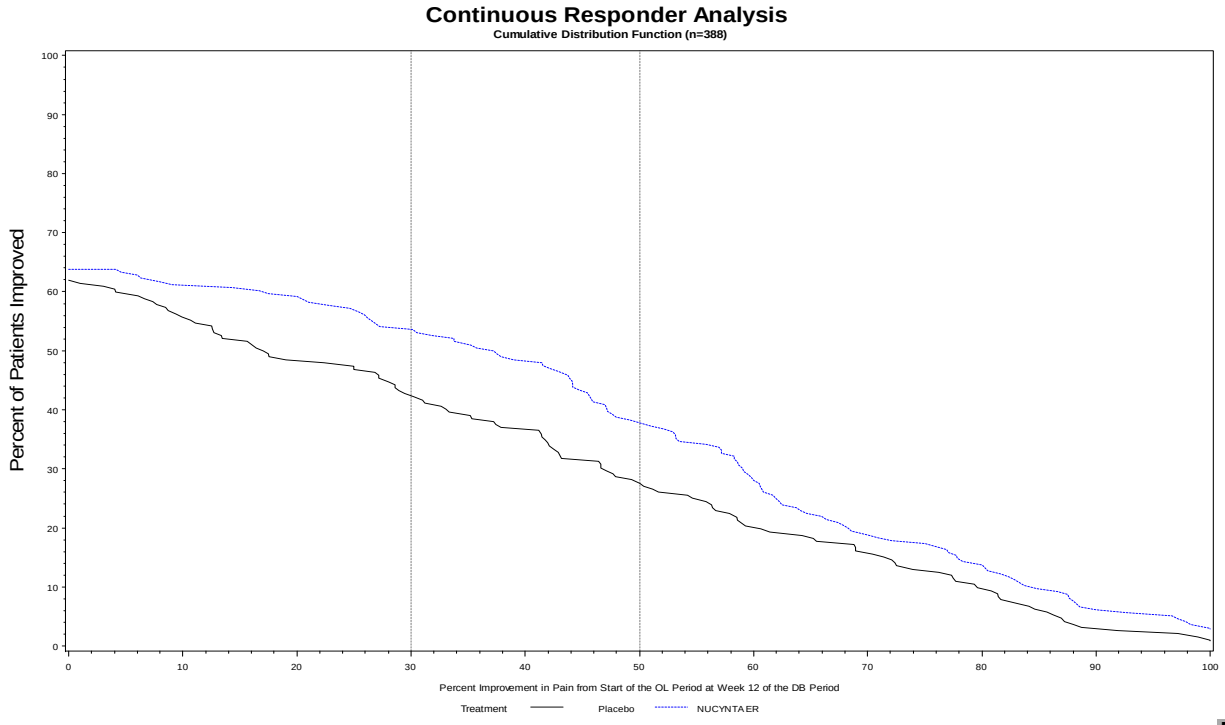
For the primary endpoint, I also generated the continuous responder curves by treatment groups including and excluding the 21 subjects who didn't meet the randomization criterion. In this analysis, all non-completers were classified as non-responders. My results confirmed the applicant's results. As shown in Figure 3, the lines for the placebo and NUCYNTA show notable separation which indicates NUCYNTA is different from placebo. Among 21 subjects (14 subjects in NUCYNTA group and 7 subjects in placebo group) who didn't meet the randomization criterion, most subjects dropped out during the double-blind maintenance period. Therefore, the responder analysis excluding these 21 subjects (as shown in figure 4) was similar to the responder analysis including them (as shown in figure 3).

Table 6: Primary Efficacy Results (Study PAI 3015/KF36)

Endpoint	Imputation	NUCYNTA	Placebo
Change in Average Pain from Baseline to Last Week of Maintenance			
Applicant's results		n=196	n=192
LS means	LOCF	0.0	1.4
p-value vs. placebo		<0.001	
Reviewer's results		n=179	n=188
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	

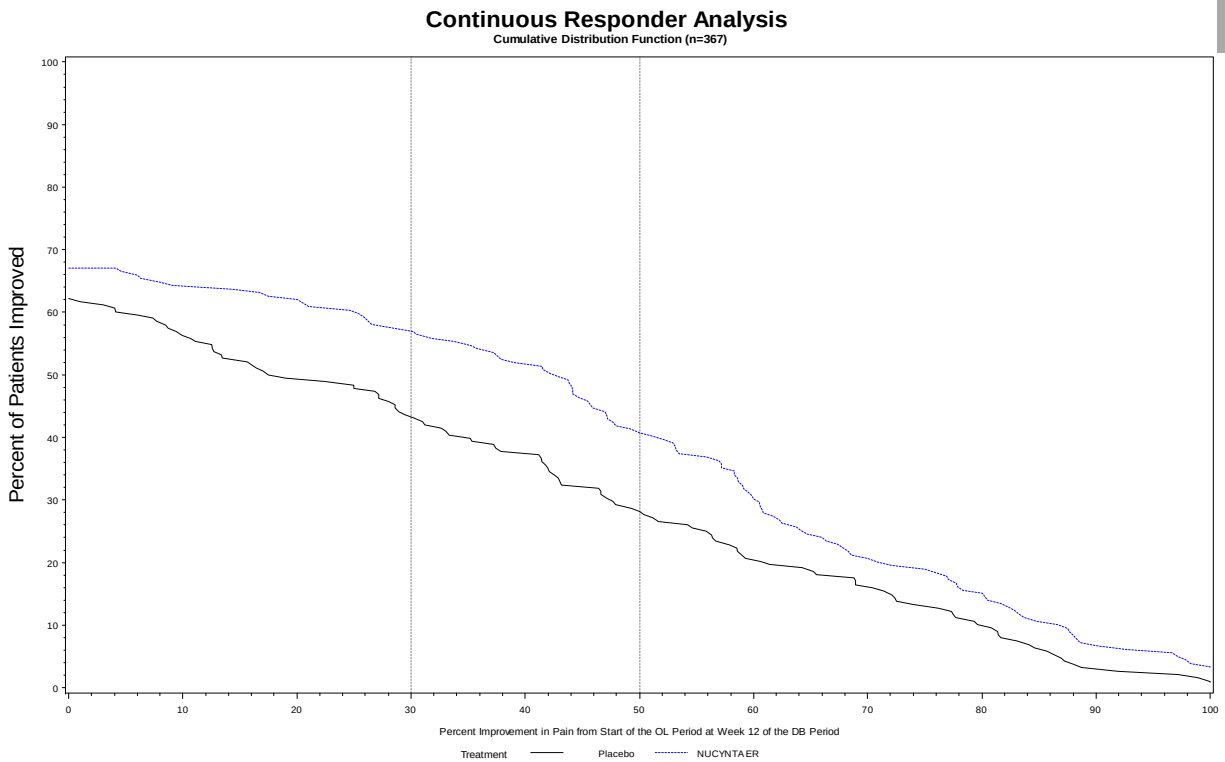
Source: Clinical Study Report Table 18 and Reviewer's Analyses

Figure 3: Percent Improvement in Pain from Baseline at Week 12 of the Maintenance Period (Study PAI-3015/KF36) including 21 subjects who didn't meet the randomization criterion



Best Available Copy

Figure 4: Percent Improvement in Pain from Baseline at Week 12 of the Maintenance Period (Study PAI-3015/KF36) excluding 21 subjects who didn't meet the randomization criterion



3.2 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Eric Brodsky. The reader is referred to Dr. Brodsky's review for information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant did subgroup analyses for Study PAI-3011/KF23, Study PAI-3008/KF11 and Study PAI-3015/KF36 by gender, age, race, country, prior opioid use and baseline pain category by using their primary imputation method LOCF. Since Study PAI-3008/KF11 failed to demonstrate the superiority of NUCYNTA over placebo, I only did subgroup analyses for studies PAI-3011/KF23 and PAI-3015/KF36 by using BOCF imputation method.

4.1 Gender, Race and Age

PAI-3011/KF23

Table 7 presents exploratory analyses for the primary endpoint by age, gender, and race. I utilized the same ANCOVA model as in the primary analysis with additional terms for each demographic variable and its interaction with treatment. There was no statistically significant interaction between treatment and any of age, gender and race.

Table 7: Primary Efficacy Results by Subgroup (Study PAI-3011/KF23)

	NUCYNTA		Placebo		Oxycodone CR	
Endpoint	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Change from Baseline in Average Pain Intensity Scores at Week 12						
Gender						
Female	194	-2.0 (2.6)	185	-1.4 (2.1)	180	-1.5 (2.3)
Male	124	-1.5 (2.0)	135	-1.1 (2.0)	147	-1.5 (2.3)
Age (years)						
< 65	279	-1.9 (2.4)	265	-1.3 (2.1)	272	-1.6 (2.4)
>= 65	39	-1.2 (1.8)	55	-1.2 (2.0)	55	-0.9 (1.7)
Race						
Black	62	-2.1 (2.5)	49	-1.3 (2.1)	55	-1.3 (2.2)
Hispanic	18	-1.9 (2.7)	22	-1.5 (2.0)	21	-1.6 (2.9)
White	229	-1.7 (2.3)	238	-1.2 (2.1)	241	-1.6 (2.3)
Other	9	-1.5 (3.0)	11	-1.2 (1.4)	10	-0.5 (1.0)

Source: Reviewer's Analysis

PAI-3015/KF36

Table 8 presents exploratory analyses for the primary endpoint by age, gender, and race. I utilized the same ANCOVA model with additional terms for each demographic variable and its interaction with treatment. There was no statistically significant interaction between treatment and any of age, gender and race.

Table 8: Primary Efficacy Results by Subgroup (Study PAI-3015/KF36)

Endpoint	NUCYNTA n	NUCYNTA Mean (SD)	Placebo n	Placebo Mean (SD)
Change from Baseline in Average Pain Intensity Scores at Week 12				
Gender				
Female	77	1.2 (2.5)	77	2.2 (2.5)
Male	119	1.5 (2.4)	115	1.9 (2.4)
Age (years)				
< 65	136	1.3 (2.5)	119	1.8 (2.6)
>= 65	60	1.6 (2.3)	73	2.3 (2.0)
Race				
Black	26	1.5 (2.8)	19	1.1 (2.7)
Hispanic	28	1.3 (1.6)	34	1.9 (2.7)
White	137	1.3 (2.4)	134	1.3 (2.2)
Other	5	0.0 (4.3)	5	2.2 (2.3)

Source: Reviewer's Analysis

4.2 Other Special/Subgroup Populations

PAI-3011/KF23

The majority of the subjects were enrolled in the United States. The summary statistics of the primary efficacy endpoint by country are shown in Table 9. By excluding subjects in Australia since there were only 3 subjects in each treatment group, I utilized the same ANCOVA model with additional terms for country and its interaction with treatment. The interaction between country and treatment was borderline significant (p-value=0.06). Furthermore, ANCOVA models conducted in each country indicated that the results in the United States were in favor of NUCYNTA while results in Canada failed to demonstrate the efficacy of NUCYNTA compared to placebo.

Table 9: Efficacy Results by Country (Study PAI-3011/KF23)

Endpoint	NUCYNTA n	NUCYNTA Mean (SD)	Placebo n	Placebo Mean (SD)	Oxycodone CR n	Oxycodone CR Mean (SD)
Change from Baseline in Average Pain Intensity Scores at Week 12						
Country						
United States of America	259	-2.0 (2.4)	269	-1.3 (2.1)	271	-1.5 (2.3)
Canada	53	-1.0 (1.8)	48	-1.3 (2.1)	51	-1.4 (2.4)
Australia	3	-2.0 (3.5)	3	-1.1 (1.9)	3	-1.5 (2.6)

Source: Reviewer's Analysis

Table 10 presents exploratory analyses for the primary endpoint by prior opioid use and baseline pain intensity. There were no significant differences in the treatment effect across any of these subgroups.

Table 10: Efficacy Results by prior opioid use and baseline pain intensity (Study PAI-3011/KF23)

Endpoint	NUCYNTA n	NUCYNTA Mean (SD)	Placebo n	Placebo Mean (SD)	Oxycodone CR n	Oxycodone CR Mean (SD)
Change from Baseline in Average Pain Intensity Scores at Week 12						
Prior Opioid Use						
Yes	176	-1.6 (2.3)	172	-1.2 (2.0)	162	-1.5 (2.2)
No	136	-2.1 (2.5)	144	-1.4 (2.2)	161	-1.4 (2.4)
Baseline Pain Category						
severe	277	-1.9 (2.5)	276	-1.4 (2.1)	290	-1.5 (2.3)
moderate	35	-1.5 (1.8)	40	-0.7 (1.6)	33	-0.9 (1.4)

Source: Reviewer's Analysis

PAI-3015/KF36

Table 11 presents exploratory analyses for the primary endpoint by country, prior opioid use and baseline pain intensity. There was no statistically significant interaction between treatment and any of these factors.

Table 11: Efficacy Results by country, prior opioid use and baseline pain intensity (Study PAI-3015/KF36)

Endpoint	NUCYNTA n	NUCYNTA Mean (SD)	Placebo n	Placebo Mean (SD)
Change from Baseline in Average Pain Intensity Scores at Week 12				
Country				
United States of America	174	1.3 (2.4)	184	2.0 (2.4)
Canada	5	4.3 (2.0)	4	2.3 (2.6)
Prior Opioid Use				
Yes	68	1.7 (2.6)	66	2.3 (2.8)
No	128	1.2 (2.3)	127	1.8 (2.2)
Baseline Pain Category				
moderate or severe	87	0.7 (2.2)	74	0.9 (2.0)
mild	103	1.8 (2.5)	113	2.6 (2.4)

Source: Reviewer's Analysis

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

The main statistical issue is the direct impact of dropouts on the efficacy results. In all three studies, the applicant applied the LOCF imputation method where the last observation was carried forward to the end of the maintenance period. Since many subjects dropped out due to adverse events, the LOCF method which possibly assigned some treatment benefit to dropouts was not appropriate.

The applicant also conducted sensitivity analyses using BOCF, WOCF, PMI, and modified BOCF imputation strategies. The BOCF and WOCF strategies have previously been used to address the Division's concerns regarding missing data. However, the PMI and modified BOCF methods are more novel and require additional evaluation. I evaluated the PMI method and thought that it was analogous to an analysis of completers in that the analysis results were primarily influenced by the data from patients completing the study. The PMI method was hence not appropriate because of the following reasons: (1) the outcome of patients completing the study may not represent the outcome of patients not completing the study; (2) the PMI method implemented in the studies assigned some treatment benefit to dropouts due to adverse events. In addition, the applicant's proposed modified BOCF imputation method was also not appropriate since it assigned some treatment benefit to dropouts due to adverse events.

In the randomized withdrawl study PAI-3015/KF36, baseline was defined as the randomization baseline. The applicant used a BOCF methodology carrying forward the randomization baseline to dropouts. To avoid assigning benefit to dropouts, I imputed the screening baseline to the missing pain intensity score. Additionally, there were 21 subjects who didn't meet the randomization criterion but were randomized. I analyzed the data excluding these 21 patients, but the overall conclusions remained the same.

5.1.2 Collective Evidence

By using LOCF as the primary imputation method, the applicant concluded that studies PAI-3011/KF23, PAI-3008/KF11, and PAI-3015/KF36 successfully demonstrated the efficacy of NUCYNTA. However, by using more conservative imputation methods, only the data in studies PAI-3011/KF23 and PAI-3015/KF36 provided statistically significant evidence of efficacy of NUCYNTA as a treatment of moderate to severe chronic pain.

5.2 Conclusions and Recommendations

Based on my review, I conclude that patients receiving NUCYNTA for moderate to severe chronic pain experienced a greater reduction in pain intensity compared to patients receiving placebo. The studies in patients with LBP and DPN provide evidence of the analgesic effect of NUCYNTA.

5.2.1 Labeling

The applicant submitted the following wording for the draft label:

(b) (4)

6 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDICES

Summary of Demographics and Baseline Characteristics

Study PAI 3011/KF23 (Source: Clinical Study Report Table 10)

	Placebo (N=319)	Tapentadol ER (N=318)	Oxycodone CR (N=328)	Total (N=965)
Age (Years)				
N	319	318	328	965
Mean (SD)	50.4 (14.05)	49.4 (13.21)	50.0 (14.21)	49.9 (13.83)
Median	50.0	50.0	49.0	50.0
Range	(19;86)	(18;83)	(21;89)	(18;89)
Age Groups, n (%)				
N	319	318	328	965
<65 Years	264 (82.8)	279 (87.7)	273 (83.2)	816 (84.6)
≥65 Years	55 (17.2)	39 (12.3)	55 (16.8)	149 (15.4)
Racial/ethnic Group[a], n (%)				
N	319	318	328	965
White	237 (74.3)	229 (72.0)	241 (73.5)	707 (73.3)
Black	50 (15.7)	62 (19.5)	55 (16.8)	167 (17.3)
Hispanic	21 (6.6)	18 (5.7)	21 (6.4)	60 (6.2)
Other	11 (3.4)	9 (2.8)	11 (3.4)	31 (3.2)
Country, n (%)				
N	319	318	328	965
Australia	3 (0.9)	3 (0.9)	3 (0.9)	9 (0.9)
Canada	48 (15.0)	53 (16.7)	52 (15.9)	153 (15.9)
United States of America	268 (84.0)	262 (82.4)	273 (83.2)	803 (83.2)
Sex, n (%)				
N	319	318	328	965
Male	135 (42.3)	124 (39.0)	147 (44.8)	406 (42.1)
Female	184 (57.7)	194 (61.0)	181 (55.2)	559 (57.9)
Weight (kg)				
N	319	318	328	965
Mean (SD)	88.41 (23.184)	91.69 (25.621)	88.88 (21.560)	89.65 (23.514)
Median	85.30	87.90	85.85	86.30
Range	(46.6;205.9)	(49.9;204.3)	(41.3;163.3)	(41.3;205.9)
Baseline Body Mass Index (kg/m²)				
N	316	317	328	961
Mean (SD)	31.33 (8.143)	32.09 (9.121)	31.36 (7.449)	31.59 (8.256)
Median	29.78	30.00	29.98	29.97
Range	(17.8;75.5)	(18.9;107.6)	(15.2;61.1)	(15.2;107.6)
Baseline Pain Intensity Score[b]				
N	318	315	325	958
Mean (SD)	7.6 (1.33)	7.5 (1.33)	7.5 (1.21)	7.5 (1.29)
Median	7.5	7.4	7.5	7.5
Range	(5;10)	(4;10)	(5;10)	(4;10)
Baseline Pain Intensity Category, n (%)				
N	318	315	325	959
Moderate	42 (13.2)	35 (11.1)	33 (10.2)	110 (11.5)
Severe[c]	276 (86.8)	280 (88.9)	292 (89.8)	848 (88.5)
Prior Opioid Use[d], n (%)				
N	319	318	328	965
No	147 (46.1)	140 (44.0)	163 (49.7)	450 (46.6)
Yes	172 (53.9)	178 (56.0)	165 (50.3)	515 (53.4)

Study PAI-3-11/KF11 (Source: Clinical Study Report Table 10)

	Placebo (N=337)	Tapentadol ER (N=344)	Oxycodone CR (N=342)	Total (N=1023)
Age (Years)				
N	337	344	342	1023
Mean (SD)	58.2 (9.15)	58.4 (10.09)	58.2 (10.29)	58.3 (9.85)
Median	58.0	57.0	56.0	58.0
Range	(40;89)	(40;91)	(40;86)	(40;91)
Age Groups, n (%)				
N	337	344	342	1023
<65 Years	260 (77.2)	249 (72.4)	249 (72.8)	758 (74.1)
≥65 Years	77 (22.8)	95 (27.6)	93 (27.2)	265 (25.9)
Racial/ethnic Group[a], n (%)				
N	337	344	342	1023
White	267 (79.2)	260 (75.6)	245 (71.6)	772 (75.5)
Black	38 (11.3)	49 (14.2)	45 (13.2)	132 (12.9)
Hispanic	20 (5.9)	21 (6.1)	37 (10.8)	78 (7.6)
Other	12 (3.6)	14 (4.1)	15 (4.4)	41 (4.0)
Country, n (%)				
N	337	344	342	1023
Australia	9 (2.7)	8 (2.3)	7 (2.0)	24 (2.3)
Canada	58 (17.2)	62 (18.0)	56 (16.4)	176 (17.2)
New Zealand	11 (3.3)	9 (2.6)	8 (2.3)	28 (2.7)
United States of America	259 (76.9)	265 (77.0)	271 (79.2)	795 (77.7)
Sex, n (%)				
N	337	344	342	1023
Male	137 (40.7)	128 (37.2)	140 (40.9)	405 (39.6)
Female	200 (59.3)	216 (62.8)	202 (59.1)	618 (60.4)
Weight (kg)				
N	337	344	342	1023
Mean (SD)	100.28 (26.720)	94.80 (23.664)	97.43 (24.445)	97.48 (25.041)
Median	96.60	90.70	94.55	93.80
Range	(42.2;182.3)	(44.9;179.6)	(46.7;174.1)	(42.2;182.3)
Baseline Body Mass Index (kg/m²)				
N	336	344	341	1021
Mean (SD)	35.08 (9.329)	33.61 (7.967)	34.16 (8.185)	34.28 (8.522)
Median	32.58	31.76	33.41	32.54
Range	(17.6;67.8)	(18.9;62.6)	(16.6;65.8)	(16.6;67.8)
Baseline Pain Intensity Score[b]				
N	336	344	342	1022
Mean (SD)	7.2 (1.29)	7.4 (1.35)	7.2 (1.29)	7.3 (1.31)
Median	7.2	7.3	7.2	7.2
Range	(4;10)	(3;10)	(4;10)	(3;10)
Baseline Pain Intensity Category[c], n (%)				
N	336	344	342	1022
Mild	0	2 (0.6)	0	2 (0.2)
Moderate	61 (18.2)	49 (14.2)	58 (17.0)	168 (16.4)
Severe	275 (81.8)	293 (85.2)	284 (83.0)	852 (83.4)
Prior Opioid Use[d], n (%)				
N	337	344	342	1023
No	223 (66.2)	235 (68.3)	234 (68.4)	692 (67.6)
Yes	114 (33.8)	109 (31.7)	108 (31.6)	331 (32.4)

Analysis Set: DB Safety

	Placebo (N=193)	All Tapentadol ER (N=196)	Total (N=389)
Sex, n (%)			
N	193	196	389
Male	116 (60.1)	119 (60.7)	235 (60.4)
Female	77 (39.9)	77 (39.3)	154 (39.6)
Race/ethnicity, n (%)			
N	193	196	389
White	135 (69.9)	137 (69.9)	272 (69.9)
American Indian or Alaska Native	1 (0.5)	2 (1.0)	3 (0.8)
Asian	1 (0.5)	1 (0.5)	2 (0.5)
Black or African Descent	19 (9.8)	26 (13.3)	45 (11.6)
Hispanic or Latino	34 (17.6)	28 (14.3)	62 (15.9)
Native Hawaiian / Other Pacific Islander	1 (0.5)	1 (0.5)	2 (0.5)
Other	2 (1.0)	1 (0.5)	3 (0.8)
Race Group (+), n (%)			
N	193	196	389
White	135 (69.9)	137 (69.9)	272 (69.9)
Black	19 (9.8)	26 (13.3)	45 (11.6)
Hispanic	34 (17.6)	28 (14.3)	62 (15.9)
Other	5 (2.6)	5 (2.6)	10 (2.6)
Age (Years)			
N	193	196	389
Category, n (%)			
<65	120 (62.2)	136 (69.4)	256 (65.8)
>=65	73 (37.8)	60 (30.6)	133 (34.2)
Mean (SD)	60.6 (10.56)	59.9 (10.68)	60.2 (10.62)
Median	60.0	59.0	60.0
Range	(29;87)	(37;86)	(29;87)
Weight (kg)			
N	193	196	389
Mean (SD)	101.62 (24.843)	102.43 (24.677)	102.03 (24.731)
Median	99.70	99.70	99.30
Range	(59.9;204.1)	(50.6;204.1)	(50.6;204.1)
Height (cm)			
N	193	196	389
Mean (SD)	170.28 (11.669)	171.12 (11.477)	170.71 (11.565)
Median	171.50	172.70	172.20
Range	(121.1;193.0)	(129.5;198.1)	(121.1;198.1)
Is the Subject Opioid Naive? (*)			
N	193	196	389
Category, n (%)			
Yes	127 (65.8)	128 (65.3)	255 (65.6)
No	66 (34.2)	68 (34.7)	134 (34.4)
Pre-treatment Body Mass Index (kg/m2)**			
N	193	196	389
Mean (SD)	35.27 (9.795)	35.06 (8.261)	35.17 (9.043)
Median	33.62	33.48	33.57
Range	(20.5;119.0)	(20.1;60.2)	(20.1;119.0)
Duration of DPN (Weeks)			
N	193	196	389
Mean (SD)	317.96 (261.614)	284.90 (258.852)	301.30 (260.417)
Median	262.00	213.50	233.00
Range	(30.0;1595.0)	(27.0;1939.0)	(27.0;1939.0)
Length of Treatment for DPN (Weeks)			
N	193	196	389
Mean (SD)	221.45 (215.336)	212.96 (206.314)	217.17 (210.609)
Median	167.00	148.00	161.00
Range	(12.0;1595.0)	(0.0;1309.0)	(0.0;1595.0)
Start OL Pain Intensity Category ($)			
N	192	194	386
Category, n (%)			
Mild	0	2 (1.0)	2 (0.5)
Moderate	30 (15.5)	44 (22.4)	74 (19.0)
Severe	162 (83.9)	148 (75.5)	310 (79.7)
Mean (SD)	7.3 (1.31)	7.2 (1.52)	7.3 (1.41)
Median	7.3	7.2	7.2
Range	(5;10)	(3;10)	(3;10)
Start DB Pain Intensity Category (#)			
N	192	193	385
Category, n (%)			
None	5 (2.6)	3 (1.5)	8 (2.1)
Mild	113 (58.5)	103 (52.6)	216 (55.5)
Moderate	50 (25.9)	65 (33.2)	115 (29.6)
Severe	24 (12.4)	22 (11.2)	46 (11.8)
Mean (SD)	3.4 (1.88)	3.6 (1.90)	3.5 (1.89)
Median	3.3	3.8	3.5

Signature/Distribution List

Primary Statistical Reviewer:	Yan Zhou, Ph.D. Mathematical Statistician
Date:	July 21, 2010
Concurring Reviewer:	Dionne Price, Ph.D. Team Leader
	Thomas Permutt, Ph.D. Division Director

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/

YAN ZHOU
08/27/2010

DIONNE L PRICE
08/27/2010
Concur.

THOMAS J PERMUTT
08/27/2010
concur

Statistics Filing Checklist of New NDA
Division of Biometrics II

Date: 01/29/10

NDA #: 200-533 Priority Classification: S

Trade Name: NUCYNTA^{TM} ER

Applicant: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Generic Name: Tapentadol extended-release tablets Date of Submission: 11/30/09

Indication: management of moderate to severe chronic pain.

No. of Controlled Studies: 3

User Fee Goal Date: 10/01/10

Date of 45-Day Meeting: 01/04/10

Medical Officer: Eric Brodsky (DAARP)

Project Manager: Dominic Chiapperino (DAARP)

Statistical Reviewer: Yan Zhou, Ph.D.

Statistical sections: Sections 2.5, 2.7, and 5.3.5

Anticipated Review Completion Date: 08/01/10

Comments:

1. It is fileable.

CHECKLIST

Item	**Check (NA if not applicable)**
Index sufficient to locate necessary reports, tables, etc.	**Yes**
Original protocols & subsequent amendments available in the NDA	**Yes**
Designs utilized appropriate for the indications requested	**Yes**
Endpoints and methods of analysis spelled out in the protocols	**Yes**
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	**NA**
Appropriate references included for novel statistical methodology (if present)	**NA**
Sufficient data listings and intermediate analysis tables to permit statistical review	**Yes**
Data from primary studies in electronic data room	**Yes**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**Yes**
Safety and efficacy for gender, racial, and geriatric subgroups investigated	**Yes**

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS

Study Number (Dates Conducted)	Number of Centers (Locations)	Sample Size	Type of Control	Design	Duration of Treatment
PAI-3011/KF23 (2/07 – 5/08)	103 sites Australia: 3 Canada: 15 US: 85	Titration: n = 981 Randomization: Tapentadol n=321 Oxycodone N=334 Placebo n=326	Oxycodone Placebo	randomized, double-blind, placebo- and active-controlled, multicenter with a flexible titration phase	Titration: 3 weeks Double-Blind Treatment: 12 weeks
PAI-3008/KF11 (2/07 – 7/08)	112 sites Australia: 4 Canada: 15 New Zealand: 6 US: 87	Titration: n = 1030 Randomization: Tapentadol n=346 Oxycodone N=345 Placebo n=339	Oxycodone Placebo	randomized, double-blind, placebo- and active-controlled, multicenter with a flexible titration phase	Titration: 3 weeks Double-Blind Treatment: 12 weeks
PAI-3015/KF36 (3/07 – 8/08)	93 sites Canada: 6 US: 87	Titration: n = 591 Randomization: Tapentadol n=199 Placebo n=196	placebo	double-blind, placebo-controlled, randomized withdraw, multicenter with an open-label titration phase	Titration: 3 weeks Double-Blind Treatment: 12 weeks

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Mathematical Statistician

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Team Leader

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/

YAN ZHOU
01/29/2010

DIONNE L PRICE
01/29/2010
Concur