CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-692

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-692 (resubmission)
Drug Name:	Tramadol Extended Release Tablets
Indication(s):	The Management of Moderate to Moderately Severe Pain in Adults
Applicant:	Biovail Laboratories, Inc.
Date(s):	PDUFA: September 8, 2005
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-715)
Statistical Reviewer:	Yongman Kim, Ph.D.
Concurring Reviewers:	Thomas Permutt, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical Team:	Lourdes Villalba, M.D.
Project Manager:	Nancy Clark

Keywords: responder analysis

Background: Dr. Sharon Hertz asked me to do responder analyses on data from two studies 023 and 015 in the process of label negotiation with the sponsor. In a responder analysis, all the dropouts are treated as non-responders, therefore there are no imputation for missing data. By varying the response criterion from 0 to 100 percent improvement and comparing curves so obtained, the power for the comparison is shown comparable to analysis with raw continuous scale data. The following figures were created to look at the response profiles for the studies.

Figure 1. Study 023 Responder Analysis based on Change from Baseline to Week 12 WOMAC Pain Scores

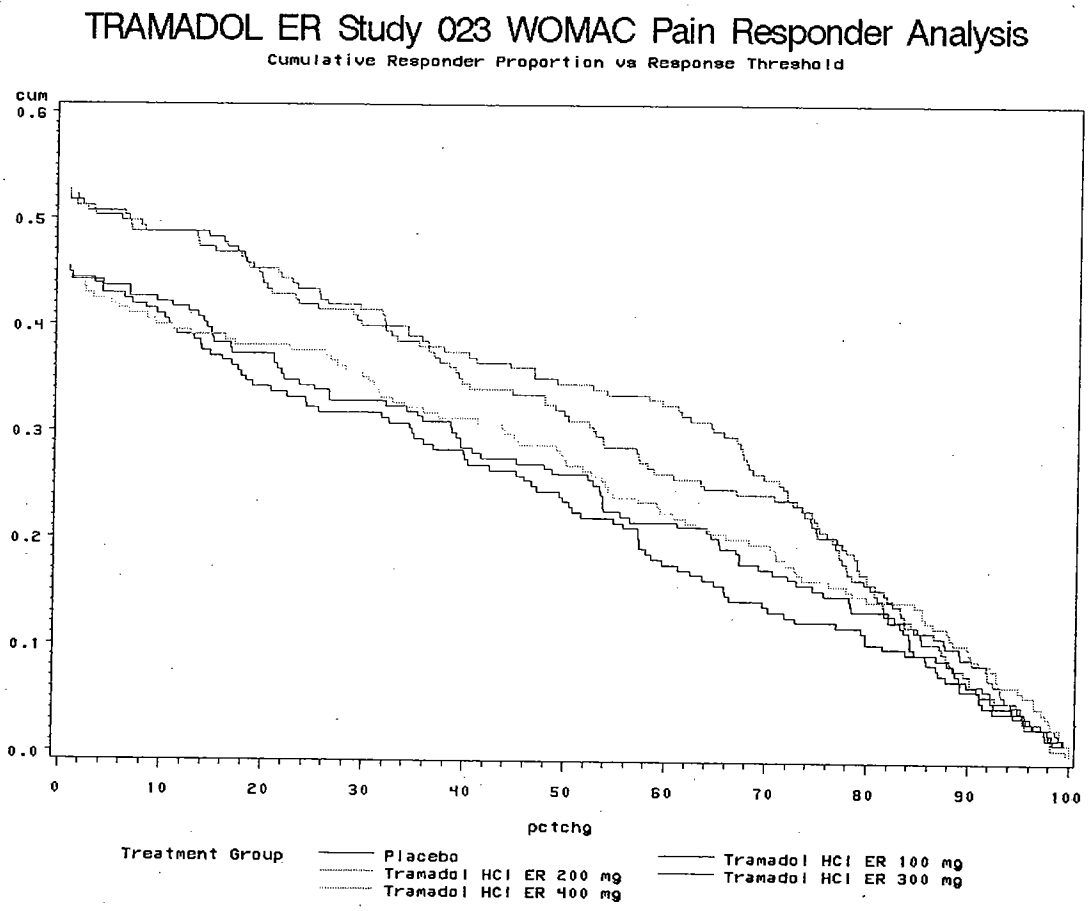
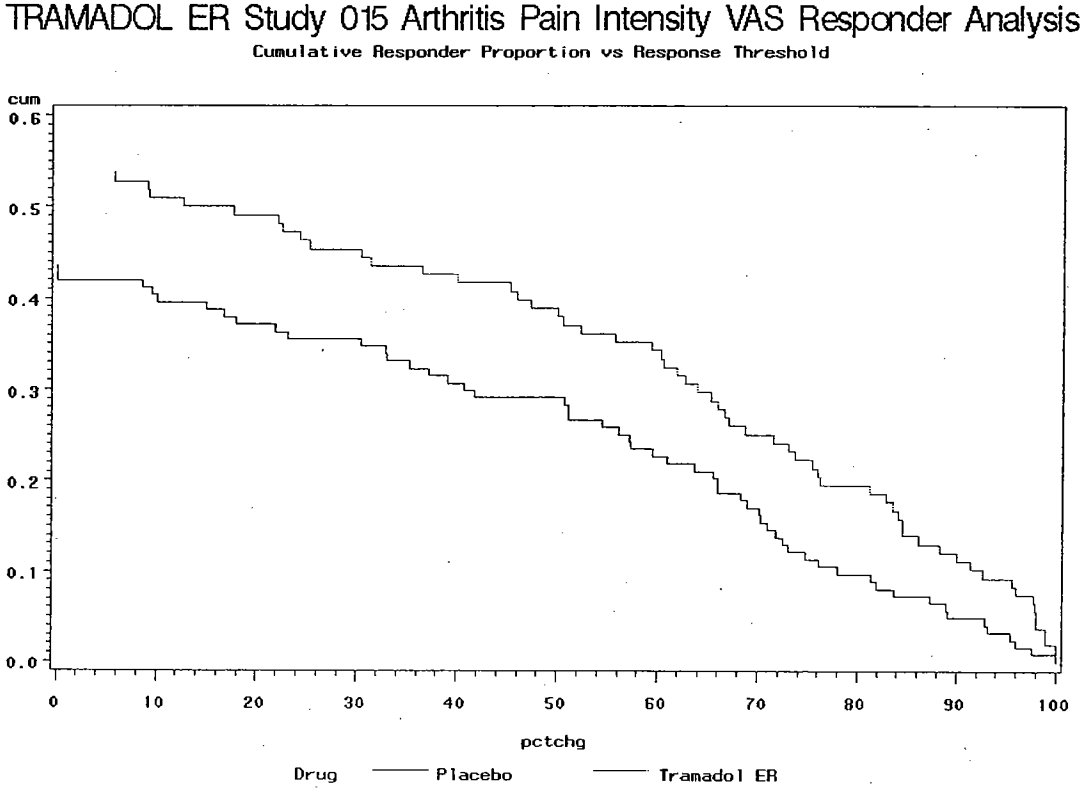


Figure 2. Study 015 Responder Analysis based on Change from Baseline to Week 12 Arthritis Pain Intensity Scores



SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Yongman Kim, Ph.D.
Mathematical Statistician

Date: September 8, 2005

Concurring Reviewer: Thomas Permutt, Ph.D.
Statistical Team Leader

cc:

DAARP/Nancy Clark
DAARP/Parinda Jani
DAARP/Lourdes Villalba, M.D.
DAARP/Sharon Hertz, M.D.

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/s/

Yongman Kim
9/8/2005 02:33:49 PM
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Thomas Permutt
9/8/2005 02:40:59 PM
BIOMETRICS
concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-692
Drug Name:	RALIVIA ER™ (Tramadol hydrochloride) Extended Release Tablets
Indication(s):	The Management of Moderate to Moderately Severe Pain in Adults
Applicant:	Biovail Laboratories, Inc.
Date(s):	Submitted: December 31, 2003
	Received: December 31, 2003
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Yongman Kim, Ph.D.
Concurring Reviewers:	Stan Lin, Ph.D.
Medical Division:	Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
Clinical Team:	Lourdes Villalba, M.D.
Project Manager:	Nancy Clark

Keywords: ANCOVA, missing data, sequential teasing procedure

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two studies B02.CT3.021.TRA P03 and B02.CT3.023.TRA P03 with OA patients of knee or hip failed to show an efficacy for the OA indication at daily doses of 100 mg, 200 mg, 300 mg, or 400 mg of tramadol HCl ER. In these studies, one or more of co-primary endpoints - pain, physical function, and patient global assessment - failed at each dose level. Between the two studies, only B02.CT3.023.TRA P03 showed efficacy for pain at daily doses of 100 mg, 200 mg, 300mg, and 400 mg of tramadol HCl ER based on LOCF analysis. However, the efficacy was not robust against other imputation methods for missing data (See Tables 5.2.1 and 5.2.2. in the Appendix). Study B00.CT3.015.TRA P03 with knee OA patients succeeded in showing an efficacy for pain at flexible daily doses ranging from 100 mg to 400 mg of tramadol HCl ER. But the data did not support an inference on efficacious daily dose(s) due to study design with non-randomized, flexible dosing. The other study, B00.CT3.014.TRA P03 with chronic low back pain patients comparing 200 mg and 300 mg of tramadol HCl ER with placebo showed efficacy for pain at daily dose of 300 mg of tramadol HCl ER. However, this study, with an open-label treatment run in period preceding the randomization, was inadequate for assessment of efficacy due to possible bias from selecting only patients tolerable to the drug.
Overall, the submitted data failed to provide statistically and clinically robust results supporting in either OA indication or pain indication of tramadol HCl ER.

1.2 Brief Overview of Clinical Study

The sponsor submitted the results of studies that document the efficacy and safety of tramadol HCl ER (extended release) in patients with OA (osteoarthritis) at hip or knee (Studies B02.CT3.021.TRA P03 and B02.CT3.023.TRA P03), with OA at knee only (Study B00.CT3.015.TRA P03), and with chronic low back pain (Study B00.CT3.014.TRA P03). These were a **12-Week**, double-blind, active- or placebo-controlled, multi-center studies to investigate the safety and analgesic effect of **tramadol HCl ER** in patients with OA at hip or knee, with OA at knee only, and with chronic low back pain.

In Study B02.CT3.021.TRA P03, 1011 patients were randomized to tramadol HCl ER 100 mg arm (n = 202), tramadol HCl ER 200 mg arm (n = 203), tramadol HCl ER 300 mg arm (n = 201), celecoxib 200 mg arm (n = 203), and placebo arm (n = 202) in 1:1:1:1:1 ratio. The primary objective of the study was to document an efficacy for therapy with tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, or tramadol HCl ER 300 mg when compared to placebo.

The primary efficacy endpoints were WOMAC (Western Ontario and McMaster Universities) OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity over 6 visits on Week 1, Week 2, Week 3, Week 6, Week 9 and Week 12.

In Study B02.CT3.023.TRA P03, 1020 patients were randomized to tramadol HCl ER 100 mg arm (n = 203), tramadol HCl ER 200 mg arm (n = 203), tramadol HCl ER 300 mg arm (n = 204), tramadol HCl ER 400 mg arm (n = 205), and placebo arm (n = 205) in 1:1:1:1:1 ratio. The primary objective of the study was to document an efficacy for therapy with tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, tramadol HCl ER 300 mg, or tramadol HCl ER 400 mg when compared to placebo.
The primary efficacy endpoints were WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity over 6 visits on Week 1, Week 2, Week 3, Week 6, Week 9 and Week 12.

In Study B00.CT3.015.TRA P03, 246 patients were randomized to tramadol HCl ER arm (n = 124) and placebo arm (n = 122) in 1:1 ratio. The primary objective of the study was to document an efficacy for therapy with tramadol HCl ER when compared to placebo. The primary efficacy endpoints was arthritis pain intensity VAS (visual analogue scale) score averaged over 5 visits on Week 1, Week 2, Week 4, Week 8 and Week 12.

In Study B00.CT3.014.TRA P03, 386 patients were randomized to tramadol HCl ER 200 mg arm (n = 129), tramadol HCl ER 300 mg arm (n = 128), and placebo arm (n = 129) in 1:1:1 ratio. The primary objective of the study was to document an efficacy for therapy with tramadol HCl ER 200 mg or tramadol HCl ER 300 mg when compared to placebo. The primary efficacy endpoints was arthritis pain intensity VAS score averaged over 5 visits on Week 1, Week 2, Week 4, Week 8 and Week 12.

1.3 Statistical Issues and Findings

For the efficacy analysis, the sponsor based its inferences on ITT (intent-to-treat) data from Studies B02.CT3.021.TRA P03, B02.CT3.023.TRA P03, B00.CT3.015.TRA P03, and B00.CT3.014.TRA P03 with LOCF (last observation carried forward) for missing data for the statistical significance of reduction in WOMAC OA index pain subscale, WOMAC OA index physical function subscale, patient global assessment of disease activity (Studies B02.CT3.021.TRA P03 and B02.CT3.023.TRA P03), arthritis pain intensity VAS score (Studies B00.CT3.015.TRA P03 and B00.CT3.014.TRA P03), Roland disability index, and patient global assessment of medication (Study B00.CT3.014.TRA P03) comparing tramadol HCl ER with placebo.

The sponsor did not provide sensitivity analyses assessing its conclusion especially with respect to imputation methods for missing data other than LOCF. Reviewer conducted some sensitivity analyses to assess study conclusion with respect to imputation methods. Reviewer employed BOCF (baseline observation carried forward) method for all missing

data, and also employed mixture of BOCF and LOCF – BOCF for dropouts due to adverse events and LOCF for remaining dropouts.

Study B00.CT3.015.TRA P03 with tramadol HCl ER flexible dose ranged from 100 to 400 mg daily did not allow an adequate assessment of dose-response in terms of efficacy of the drug. Primary endpoints of arthritis pain intensity VAS score was not the endpoint recommended for evaluation of OA.

Study B00.CT3.014.TRA P03 had a 3-week, open-label run in period preceding the randomization and is therefore inadequate for assessment of efficacy since it selects patients who tolerated the drug.

Sponsor's ITT population was defined as all randomized patients who received at least one dose of study medication. Therefore, number of patients in ITT population could be smaller than that of all randomized patients.

Based on our review of the data up to 12 weeks, we attained the following findings.

Data from Study B02.CT3.021.TRA P03 failed to show the superiority of tramadol HCl ER 300 mg, tramadol HCl ER 200 mg, or tramadol HCl ER 100 mg to placebo in terms of all three co-primary endpoints at 12-week landmark - WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity in patients with OA at knee or hip. The data only showed the superiority of tramadol HCl ER 300 mg in reduction of patient global assessment of disease activity.

Data from Study B02.CT3.023.TRA P03 failed to show the superiority of tramadol HCl ER 400 mg, tramadol HCl ER 300 mg, tramadol HCl ER 200 mg, or tramadol HCl ER 100 mg to placebo in all three co-primary endpoints at 12-week landmark analysis in patients with OA at knee or hip. The data showed the superiority of tramadol HCl ER at each dose level in reduction of WOMAC OA index pain subscale and WOMAC OA index physical function subscale, but not in reduction of patient global assessment of disease activity. The statistical significance for WOMAC OA index pain subscale was not supported by sensitivity analyses with respect to imputation methods, implying that the significance with LOCF was not robust considering high dropout rates.

Data from Study B00.CT3.015.TRA P03 showed the superiority of tramadol HCl ER to placebo in reduction of arthritis pain intensity VAS score averaged over 12 weeks in patients with OA at knee. The data also showed the superiority of tramadol HCl ER in reduction of WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity. Sensitivity analyses on arthritis pain intensity score with respect to imputation methods led to the same conclusions. But, the study with tramadol HCl ER flexible doses ranging from 100 to 400 mg daily did not allow an adequate assessment of dose-response in terms of efficacy of

the drug. Primary endpoints of arthritis pain intensity VAS score was not the endpoint recommended for evaluation of OA.

Data from Study B00.CT3.014.TRA P03 showed the superiority of tramadol HCl ER 300 mg to placebo in reduction of arthritis pain intensity VAS score averaged over 12 weeks in patients with chronic low back pain. The data also showed the superiority of tramadol HCl ER 300 mg to placebo in reduction of Roland disability index and patient global assessment of mediation. The data only showed the superiority of tramadol HCl ER 200 mg in reduction of patient global assessment of mediation, but not in reduction of either arthritis pain intensity VAS score or Roland disability index. The statistical significance for arthritis pain intensity VAS score disappeared when sensitivity analyses with respect to imputation methods were done, implying that the result with LOCF was not robust considering high dropout rates. The study had a 3-week, open-label run in period preceding the randomization and was therefore inadequate for assessment of efficacy since it selected patients who tolerated the drug.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug class and regulatory history

Tramadol is a widely available synthetic, centrally acting aminocyclohexanol analgesic. Tramadol exerts its analgesic effects by inhibiting the reuptake of norepinephrine and serotonin and by activation of mu-opioid receptors. Tramadol has very low affinity for opioidreceptors, although its principal active (M1) metabolite, mono-O-demethyl-tramadol is up to six times more potent than the parent drug in producing analgesia and 200 times more potent in mu-opioid receptor binding in animal models. The contribution of O-demethyl-tramadol to the antinociceptive effects of tramadol in humans is unknown. Inhibition of O-demethyl-tramadol production from the parent drug has no apparent effect on the analgesic properties of tramadol following experimentally induced pain. Administration of naloxone, a mu-opioid receptor antagonist, only partially inhibits the analgesic effects of tramadol in normal and arthritic rats, and following experimentally induced pain in man.

The binding of tramadol to opioid receptors contributes to the analgesic effect of the drug. Previous work has demonstrated a synergistic interaction between alpha-2-receptor agonists and opioids. In an experimental pain model, administration of the opioid receptor antagonist naloxone resulted in a 31% maximal inhibition of the antinociceptive effects by opioidergic mechanisms. However, tramadol is classified for regulatory purposes as an unscheduled analgesic.

The sponsor first discussed the possibility of submitting a 505(b)(2) application for the extended release formulation of tramadol HCl with FDA at the pre-IND meeting held on August 10, 1999. At that time, and during ensuing discussions, the sponsor intended to pursue new medications in [redacted] chronic pain. These indications differed from the approved indication for Ultram® (moderate to moderately severe pain in adults). At this pre-IND meeting, the Division advised that a bridging toxicology study would be needed to support the extended-release formulation. At the March 21, 2000 End-of-Phase II meeting, FDA stated that a 505(b)(2) was acceptable if the sponsor could meet the requirements of a 505(b)(2).]

[redacted] The Division noted that the sponsor could not make specific claims for particular pain indications that had not been studied.

[redacted] At the meeting with the Division on February 12, 2002, FDA indicated that a 505(b)(2) application for acute or chronic pain would not be appropriate because the Ultram® NDA did not contain any pivotal clinical studies for these indications. In addition, the Division stated that management of moderate to moderately severe pain in adults was no longer an indication.

2.1.2 Proposed Indication for RALIVIA ER

RALIVIA ER is indicated for the management of moderate to moderately severe pain in adults.

2.2 Data Sources

The original electronic submission on December 31, 2003 can be found on the FDA, CDER electronic document room (EDR).

Final Report:
\\Cdsesub1\n21692\N_000\2003-12-31\clinstat

Data set:
\\Cdsesub1\n21692\N_000\2004-08-06\Efficacy

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study B02.CT3.021.TRA P03 was a 12-week, multi-center, double-blind study of the safety and efficacy of tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, tramadol HCl ER 300 mg, celecoxib 200 mg compared with placebo in patients with OA at hip or knee. Celecoxib 200 mg was the active treatment control. Patients were randomized to tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, tramadol HCl ER 300 mg, celecoxib 200 mg, or placebo in 1:1:1:1:1 ratio.

Study B02.CT3.023.TRA P03 was a 12-week, multi-center, double-blind study of the safety and efficacy of tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, tramadol HCl ER 300 mg, or tramadol HCl ER 400 mg compared with placebo in patients with OA at hip or knee. Patients were randomized to tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, tramadol HCl ER 300 mg, tramadol HCl ER 400 mg, or placebo in 1:1:1:1:1 ratio.

Study B00.CT3.015.TRA P03 was a 12-week, multi-center, double-blind study of the safety and efficacy of tramadol HCl ER compared with placebo in patients with OA at knee. Patients were randomized to tramadol HCl ER or placebo in 1:1 ratio.

Study B00.CT3.014.TRA P03 was a 12-week, multi-center, double-blind study of the safety and efficacy of tramadol HCl ER 200 mg or tramadol HCl ER 300 mg compared with placebo in patients with chronic low back pain. Patients were randomized to tramadol HCl ER 200 mg, tramadol HCl ER 300 mg or placebo in 1:1:1 ratio.

Figure 1 in Appendix show schematic of study design for Studies B02.CT3.021.TRA P03, B02.CT3.023.TRA P03, B00.CT3.015.TRA P03, and B00.CT3.014.TRA P03.

70 investigators enrolled subjects from US sites and participated in the clinical trial Study B02.CT3.021.TRA P03.

66 investigators enrolled subjects from US sites and participated in the clinical trial Study B02.CT3.023.TRA P03.

16 investigators enrolled subjects from US sites and participated in the clinical trial Study B00.CT3.015.TRA P03.

30 investigators enrolled subjects from US sites and participated in the clinical trial Study B00.CT3.014.TRA P03.

The primary efficacy endpoints for Studies B02.CT3.021.TRA P03 and B02.CT3.023.TRA P03 were WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity over 6 visits on Week 1, Week 2, Week 3, Week 6, Week 9 and Week 12.

The primary efficacy endpoints for Studies B00.CT3.015.TRA P03 and B00.CT3.014.TRA P03 were arthritis pain intensity score over 5 visits on Week 1, Week 2, Week 4, Week 8 and Week 12.

In Studies B02.CT3.021.TRA P03 and B02.CT3.021.TRA P03, the change from baseline in WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity were compared at Week 12 between tramadol HCl ER and placebo using ANCOVA model with terms for treatment, site, stratum for hip/knee, and baseline value as covariate. The sequential testing procedure was employed to adjust for the multiple comparisons.

In Study B00.CT3.015.TRA P03, the average change from baseline over 12 weeks in arthritis pain intensity VAS score values were compared between tramadol HCl ER and placebo using ANCOVA model with terms for treatment, site, and baseline value as covariate.

In Study B00.CT3.014.TRA P03, the average change from baseline over 12 weeks in arthritis pain intensity VAS score values were compared between tramadol HCl ER 200 mg or tramadol HCl ER 300 mg and placebo using ANCOVA model with terms for treatment, site, and baseline value as covariate. The sequential testing procedure was employed to adjust for the multiple comparisons.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

As shown in Tables 1 and 2 and Figure 2 in Appendix, about 45%, 45%, 50% and 38% of the patients discontinued from Studies B02.CT3.021.TRA P03, B02.CT3.023.TRA P03, B00.CT3.015.TRA P03, and B00.CT3.014.TRA P03, respectively.

For the missing data due to discontinuation, LOCF was used in the efficacy analysis on ITT data from four studies.

Table 3 in Appendix shows patient demographics by treatment groups for Studies B02.CT3.021.TRA P03, B02.CT3.023.TRA P03, B00.CT3.015.TRA P03, and B00.CT3.014.TRA P03, respectively. There were no statistically significant imbalances among treatment groups with respect to demographic variables except for age group and race variables for the study B02.CT3.023.TRA P03 and weight variable for the study B00.CT3.014.TRA P03.

The table also shows baseline values for the primary efficacy variables by treatment groups for Studies B02.CT3.021.TRA P03 and B02.CT3.023.TRA P03, respectively. Mean baseline values for the primary efficacy variables were comparable among treatment groups.

3.1.3 Statistical Methodologies

In Studies B02.CT3.021.TRA P03 and B02.CT3.021.TRA P03, the change from baseline in WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity were compared at Week 12 between tramadol HCl ER and placebo using ANCOVA model with terms for treatment, site, stratum for hip/knee, and baseline value as covariate. The sequential testing procedure was employed to adjust for the multiple comparisons.

In Study B00.CT3.015.TRA P03, the average change from baseline over 12 weeks in arthritis pain intensity VAS score values were compared between tramadol HCl ER and placebo using ANCOVA model with terms for treatment, site, and baseline value as covariate.

In Study B00.CT3.014.TRA P03, the average change from baseline over 12 weeks in arthritis pain intensity VAS score values were compared between tramadol HCl ER 200 mg or tramadol HCl ER 300 mg and placebo using ANCOVA model with terms for treatment, site, and baseline value as covariate. The sequential testing procedure was employed to adjust for the multiple comparisons.

3.1.4 Results and Conclusions

Tables 4.1.1 – 5.4.2 in Appendix present the statistical analyses done by sponsor and reviewer. Following are review results of the analyses.

Study B02.CT3.021.TRA P03

Data from the study failed to show the superiority of tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, or tramadol HCl ER 300 mg to placebo in reduction of all three co-primary endpoints - WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity in patients with OA at knee or hip. The data only showed the superiority of tramadol HCl ER 300 mg in reduction of patient global assessment of disease activity.

The statistically significant difference in patient global assessment of disease activity was shown when comparing tramadol HCl ER 300 mg with placebo in ITT LOCF analysis (p=.023). The statistically marginally significant difference in WOMAC OA index pain subscale was shown when comparing tramadol HCl ER 300 mg with placebo in ITT LOCF analysis (p=.058). (See Tables 4.1.1 – 4.1.3 in Appendix.)
The marginal statistical significance disappeared when analyses with ITT BOCF (p=.895) or ITT BOCF for AE dropouts and LOCF for other dropouts (p=.874) were done. (See Tables 5.1.1 – 5.1.2 in Appendix.)

Study B02.CT3.023.TRA P03

Data from the study failed to show the superiority of tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, tramadol HCl ER 300 mg, or tramadol HCl ER 400 mg to placebo in reduction of all three co-primary endpoints - WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity in patients with OA at knee or hip. The data showed the superiority of tramadol HCl ER at each dose level in reduction of WOMAC OA index pain subscale and WOMAC OA index physical function, but not in reduction of patient global assessment of disease activity.

The statistically significant difference in WOMAC OA index pain subscale was shown when comparing tramadol HCl ER 100 mg with placebo (p=.005), tramadol HCl ER 200 mg with placebo (p=.002), tramadol HCl ER 300 mg with placebo (p=.012), tramadol HCl ER 400 mg with placebo (p=.004), in ITT LOCF analysis.
The statistically significant difference in WOMAC OA index physical function was shown when comparing tramadol HCl ER 100 mg with placebo (p=.012), when comparing tramadol HCl ER 200 mg with placebo (p=.003), when comparing tramadol HCl ER 300 mg with placebo (p=.009), when comparing tramadol HCl ER 400 mg with placebo (p=.014) in ITT LOCF analysis.
The statistically marginally significant difference in patient global assessment of disease activity was shown when comparing tramadol HCl ER 400 mg with placebo in ITT LOCF analysis (p=.084). Because the sequential procedure was employed for multiple comparisons and the p-value for comparing tramadol HCl ER 400 mg with placebo was greater than .05, the procedure stopped after the first step. If the Bonferroni adjustment was employed, then the statistically significant difference in patient global assessment of disease activity was shown when comparing tramadol HCl ER 300 mg with placebo (p=.024). (See Tables 4.2.1 – 4.1.3 in Appendix.)
The statistical significance for WOMAC OA index pain subscale disappeared when sensitivity analyses with respect to imputation methods were done, giving p=.212 for ITT BOCF and p=.567 for ITT BOCF for AE dropouts and LOCF for other dropouts. (See Tables 5.2.1 – 5.2.2 in Appendix.)

Study B00.CT3.015.TRA P03

Data from the study showed the superiority of tramadol HCl ER to placebo in reduction of arthritis pain intensity VAS score in patients with OA at knee. The data also showed the superiority of tramadol HCl ER in reduction of WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity.

The statistically significant difference in arthritis pain intensity VAS score averaged over 12 weeks was shown when comparing tramadol HCl ER with placebo in ITT LOCF analysis (p< .001).

The statistically significant difference in WOMAC OA index pain subscale was shown when comparing tramadol HCl ER with placebo in ITT LOCF analysis ($p < .001$).
The statistically significant difference in WOMAC OA index physical function subscale was shown when comparing tramadol HCl ER with placebo in ITT LOCF analysis ($p < .001$).
The statistically significant difference in patient global assessment of disease activity was shown when comparing tramadol HCl ER with placebo in ITT LOCF analysis ($p < .001$). (See Tables 4.3.1. – 4.3.4 in Appendix.)

The statistically significant difference in arthritis pain intensity VAS score remained after sensitivity analyses with ITT BOCF ($p=.021$) or ITT BOCF for AE dropouts and LOCF for other dropouts ($p < .001$). (See Tables 5.3.1 – 5.3.2 in Appendix.)

Study B00.CT3.014.TRA P03

Data from Study B00.CT3.014.TRA P03 showed the superiority of tramadol HCl ER 300 mg to placebo in reduction of arthritis pain intensity VAS score averaged over 12 weeks in patients with chronic low back pain. The data also showed the superiority of tramadol HCl ER 300 mg to placebo in reduction of Roland disability index and patient global assessment of mediation. The data only showed the superiority of tramadol HCl ER 200 mg in reduction of patient global assessment of mediation, but not in reduction of either arthritis pain intensity VAS score or Roland disability index.

The statistically significant difference in arthritis pain intensity VAS score was shown when comparing tramadol HCl ER 300 mg with placebo in ITT LOCF analysis ($p=.009$).
The statistically significant difference in Roland disability index was shown when comparing tramadol HCl ER 300 mg with placebo in ITT LOCF analysis ($p < .001$).
The statistically significant difference in patient global assessment of medication was shown when comparing tramadol HCl ER 200 mg with placebo ($p=.017$) and when comparing tramadol HCl ER 300 mg with placebo ($p < .001$) in ITT LOCF analysis. (See Tables 4.4.1 – 4.4.3 in Appendix.)

The statistically significant difference in arthritis pain intensity VAS score between tramadol HCl ER 300 mg and placebo disappeared after sensitivity analyses with ITT BOCF ($p=.176$), but remained after sensitivity analysis with ITT BOCF for AE dropouts and LOCF for other dropouts ($p=.010$). (See Tables 5.4.1 – 5.4.2 in Appendix.)

3.2 Evaluation of Safety

Safety analyses were done by Clinical reviewer, Lourdes Villalba, M.D.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In a subgroup analysis for Study B02.CT3.021.TRA P03, there were no significant interactions between treatment and index joint (hip or knee), age (<65 years, ≥65 years), gender (male, female), OA duration (<5 years, ≥5 years), functional class (I, II, or III), co-presence of symptomatic knee/hip OA (yes, no).

In subgroup analyses for Studies B02.CT3.023.TRA P03, B00.CT3.015.TRA P03, and B00.CT3.014.TRA P03, there were no significant interactions between treatment and age, gender, OA duration, functional class, co-presence of symptomatic knee/hip OA.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

For the efficacy analysis, the sponsor based its inferences on ITT data from Studies B02.CT3.021.TRA P03, B02.CT3.023.TRA P03, B00.CT3.015.TRA P03, and B00.CT3.014.TRA P03 with LOCF for missing data for the statistical significance of reduction in WOMAC OA index pain subscale, WOMAC OA index physical function subscale, patient global assessment of disease activity (Studies B02.CT3.021.TRA P03 and B02.CT3.023.TRA P03), arthritis pain intensity VAS score (Studies B00.CT3.015.TRA P03 and B00.CT3.014.TRA P03), Roland disability index, and patient global assessment of medication (Study B00.CT3.014.TRA P03) comparing tramadol HCl ER with placebo.

The sponsor did not provide sensitivity analyses assessing its conclusion especially with respect to imputation methods for missing data other than LOCF. Reviewer conducted some sensitivity analyses to assess study conclusion with respect to imputation methods. Reviewer employed BOCF method for all missing data, and also employed mixture of BOCF and LOCF – BOCF for dropouts due to adverse events and LOCF for remaining dropouts.

Study B00.CT3.015.TRA P03 with tramadol HCl ER flexible dose ranged from 100 to 400 mg daily did not allow an adequate assessment of dose-response in terms of efficacy of the drug. Primary endpoints of arthritis pain intensity VAS score was not the endpoint recommended for evaluation of OA.

Study B00.CT3.014.TRA P03 had a 3-week, open-label run in period preceding the randomization and is therefore inadequate for assessment of efficacy since it selects patients who tolerated the drug.

5.1.2 Collective Evidence

Based on our review of the data up to 12 weeks we conclude the following.

Study B02.CT3.021.TRA P03

Data from the study failed to show the superiority of tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, or tramadol HCl ER 300 mg to placebo in reduction of all three co-primary endpoints - WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity in patients with OA at knee or hip. The data only showed the superiority of tramadol HCl ER 300 mg in reduction of patient global assessment of disease activity.

The statistically significant difference in patient global assessment of disease activity was shown when comparing tramadol HCl ER 300 mg with placebo in ITT LOCF analysis (p=.023). The statistically marginally significant difference in WOMAC OA index pain subscale was shown when comparing tramadol HCl ER 300 mg with placebo in ITT LOCF analysis (p=.058). The marginal statistical significance disappeared when analyses with ITT BOCF (p=.895) or ITT BOCF for AE dropouts and LOCF for other dropouts (p=.874) were done.

Study B02.CT3.023.TRA P03

Data from the study failed to show the superiority of tramadol HCl ER 100 mg, tramadol HCl ER 200 mg, tramadol HCl ER 300 mg, or tramadol HCl ER 400 mg to placebo in reduction of all three co-primary endpoints - WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity in patients with OA at knee or hip. The data showed the superiority of tramadol HCl ER at each dose level in reduction of WOMAC OA index pain subscale and WOMAC OA index physical function, but not in reduction of patient global assessment of disease activity.

The statistically significant difference in WOMAC OA index pain subscale was shown when comparing tramadol HCl ER 100 mg with placebo (p=.005), tramadol HCl ER 200 mg with placebo (p=.002), tramadol HCl ER 300 mg with placebo (p=.012), tramadol HCl ER 400 mg with placebo (p=.004), in ITT LOCF analysis.
The statistically significant difference in WOMAC OA index physical function was shown when comparing tramadol HCl ER 100 mg with placebo (p=.012), when comparing tramadol HCl ER 200 mg with placebo (p=.003), when comparing tramadol HCl ER 300 mg with placebo (p=.009), when comparing tramadol HCl ER 400 mg with placebo (p=.014) in ITT LOCF analysis.
The statistically marginally significant difference in patient global assessment of disease activity was shown when comparing tramadol HCl ER 400 mg with placebo in ITT

LOCF analysis (p=.084). Because the sequential procedure was employed for multiple comparisons and the p-value for comparing tramadol HCl ER 400 mg with placebo was greater than .05, the procedure stopped after the first step. If the Bonferroni adjustment was employed, then the statistically significant difference in patient global assessment of disease activity was shown when comparing tramadol HCl ER 300 mg with placebo (p=.024).
The statistical significance for WOMAC OA index pain subscale disappeared when sensitivity analyses with respect to imputation methods were done, giving p=.212 for ITT BOCF and p=.567 for ITT BOCF for AE dropouts and LOCF for other dropouts.

Study B00.CT3.015.TRA P03

Data from the study showed the superiority of tramadol HCl ER to placebo in reduction of arthritis pain intensity VAS score in patients with OA at knee. The data also showed the superiority of tramadol HCl ER in reduction of WOMAC OA index pain subscale, WOMAC OA index physical function subscale, and patient global assessment of disease activity.

The statistically significant difference in arthritis pain intensity VAS score averaged over 12 weeks was shown when comparing tramadol HCl ER with placebo in ITT LOCF analysis (p< .001).
The statistically significant difference in WOMAC OA index pain subscale was shown when comparing tramadol HCl ER with placebo in ITT LOCF analysis (p< .001).
The statistically significant difference in WOMAC OA index physical function subscale was shown when comparing tramadol HCl ER with placebo in ITT LOCF analysis (p< .001).
The statistically significant difference in patient global assessment of disease activity was shown when comparing tramadol HCl ER with placebo in ITT LOCF analysis (p< .001).

The statistically significant difference in arthritis pain intensity VAS score remained after sensitivity analyses with ITT BOCF (p=.021) or ITT BOCF for AE dropouts and LOCF for other dropouts (p< .001).

Study B00.CT3.014.TRA P03

Data from Study B00.CT3.014.TRA P03 showed the superiority of tramadol HCl ER 300 mg to placebo in reduction of arthritis pain intensity VAS score averaged over 12 weeks in patients with chronic low back pain. The data also showed the superiority of tramadol HCl ER 300 mg to placebo in reduction of Roland disability index and patient global assessment of mediation. The data only showed the superiority of tramadol HCl ER 200 mg in reduction of patient global assessment of mediation, but not in reduction of either arthritis pain intensity VAS score or Roland disability index.

The statistically significant difference in arthritis pain intensity VAS score was shown when comparing tramadol HCl ER 300 mg with placebo in ITT LOCF analysis (p=.009). The statistically significant difference in Roland disability index was shown when comparing tramadol HCl ER 300 mg with placebo in ITT LOCF analysis (p< .001). The statistically significant difference in patient global assessment of medication was shown when comparing tramadol HCl ER 200 mg with placebo (p=.017) and when comparing tramadol HCl ER 300 mg with placebo (p< .001) in ITT LOCF analysis.

The statistically significant difference in arthritis pain intensity VAS score between tramadol HCl ER 300 mg and placebo disappeared after sensitivity analyses with ITT BOCF (p=.176), but remained after sensitivity analysis with ITT BOCF for AE dropouts and LOCF for other dropouts (p=.010).

5.2 Conclusions and Recommendations

Two studies B02.CT3.021.TRA P03 and B02.CT3.023.TRA P03 with OA patients of knee or hip failed to show an efficacy for the OA indication at daily doses of 100 mg, 200 mg, 300 mg, or 400 mg of tramadol HCl ER. In these studies, one or more of co-primary endpoints - pain, physical function, and patient global assessment - failed at each dose level. Between the two studies, only B02.CT3.023.TRA P03 showed efficacy for pain at daily doses of 100 mg, 200 mg, 300mg, and 400 mg of tramadol HCl ER based on LOCF analysis. However, the efficacy was not robust against other imputation methods for missing data (See Tables 5.2.1 and 5.2.2. in the Appendix). Study B00.CT3.015.TRA P03 with knee OA patients succeeded in showing an efficacy for pain at flexible daily doses ranging from 100 mg to 400 mg of tramadol HCl ER. But the data did not support an inference on efficacious daily dose(s) due to study design with non-randomized, flexible dosing. The other study, B00.CT3.014.TRA P03 with chronic low back pain patients comparing 200 mg and 300 mg of tramadol HCl ER with placebo showed efficacy for pain at daily dose of 300 mg of tramadol HCl ER. However, this study, with an open-label treatment run in period preceding the randomization, was inadequate for assessment of efficacy due to possible bias from selecting only patients tolerable to the drug.
Overall, the submitted data failed to provide statistically and clinically robust results supporting in either OA indication or pain indication of tramadol HCl ER.

APPENDIX

Table 1. Patient Disposition by Treatment Group

Study B02.CT3.021.TRA P03:

	TRAMADOL ER 300 MG	TRAMADOL ER 200 MG	TRAMADOL ER 100 MG	CELECOXIB 200 MG	PLACEBO
RANDOMIZED:	201	203	202	203	202
ITT:	199	199	201	202	200
COMPLETED, n (%):	101 (50.8)	109 (54.8)	107 (53.2)	135 (66.8)	103 (51.5)
DISCONTINUED, n (%):	98 (49.2)	90 (45.2)	94 (46.8)	67 (33.2)	97 (48.5)
Insufficient therapeutic effect	22	33	51	30	65
Adverse Event	61	46	25	20	15
Patient Decision	7	1	4	2	4
Lost to Follow-Up	3	2	6	2	3
Other	5	8	8	13	10

Study B02.CT3.023.TRA P03:

	TRAMADOL ER 400 MG	TRAMADOL ER 300 MG	TRAMADOL ER 200 MG	TRAMADOL ER 100 MG	PLACEBO
RANDOMIZED:	205	204	203	203	205
ITT:	202	201	201	202	205
COMPLETED, n (%):	103 (51.0)	104 (51.7)	116 (57.7)	120 (59.4)	115 (56.1)
DISCONTINUED, n (%):	99 (49.0)	97 (48.3)	85 (42.3)	82 (40.6)	90 (43.9)
Insufficient therapeutic effect	23	18	29	31	46
Adverse Event	60	54	40	29	21
Patient Decision	8	14	6	11	9
Lost to Follow-Up	1	5	2	3	3
Other	7	6	8	8	11

Study B00.CT3.015.TRA P03:

	TRAMADOLER	PLACEBO
RANDOMIZED:	124	122
ITT:	124	122
COMPLETED, n (%):	61 (49.2)	63 (51.6)
DISCONTINUED, n (%):	63 (50.8)	59 (48.4)
Insufficient therapeutic effect	19	45
Adverse Event	33	9
Patient Decision	5	4
Lost to Follow-Up	3	0
Other	3	1

Study B00.CT3.014.TRA P03:

	TRAMADOL ER 300 MG	TRAMADOL ER 200 MG	PLACEBO
RANDOMIZED:	128	129	129
ITT:	127	129	126
COMPLETED, n (%):	86 (67.2)	87 (67.4)	68 (52.7)
DISCONTINUED, n (%):	42 (32.8)	42 (32.6)	61 (47.3)
Insufficient therapeutic effect	13	11	21
Adverse Event	13	13	18
Patient Decision	5	9	3
Other	11	9	19

Table 2. Number of Patients Remaining at Each Time Point by Treatment Group (ITT Patients)

Study B02.CT3.021.TRA P03:

TIME POINT	TRAMADOL ER 300 MG	TRAMADOL ER 200 MG	TRAMADOL ER 100 MG	CELECOXIB 200 MG	PLACEBO
Baseline	201	199	199	202	200
Week 1	169	167	170	192	169
Week 2	149	146	151	178	149
Week 3	132	135	131	168	135
Week 6	117	115	109	149	120
Week 9	111	110	101	138	105
Week 12	107	109	101	135	103

Study B02.CT3.023.TRA P03:

TIME POINT	TRAMADOL ER 400 MG	TRAMADOL ER 300 MG	TRAMADOL ER 200 MG	TRAMADOL ER 100 MG	PLACEBO
Baseline	202	201	201	202	205
Week 1	179	174	173	117	184
Week 2	162	152	160	162	166
Week 3	140	137	147	147	150
Week 6	116	119	131	134	133
Week 9	105	108	120	126	122
Week 12	103	105	116	121	116

Study B00.CT3.015.TRA P03:

TIME POINT	TRAMADOL ER	PLACEBO
Baseline	124	122
Week 1	92	108
Week 2	85	92
Week 4	72	72
Week 8	64	65
Week 12	61	63

Study B00.CT3.014.TRA P03:

TIME POINT	TRAMADOL ER 300 MG	TRAMADOL ER 200 MG	PLACEBO
Baseline	128	129	127
Week 1	118	119	110
Week 2	111	108	92
Week 4	101	100	83
Week 8	95	89	75
Week 12	88	87	71

Table 3. Patient Demographics and Baseline Characteristics by Treatment Group (ITT Patients)

Study B02.CT3.021.TRA P03:

	TRAMADOL ER 300 MG (N =199)		TRAMADOL ER 200 MG (N = 199)		TRAMADOL ER 100 MG (N = 201)		CELECOXIB 100 MG (N = 202)		PLACEBO (N = 200)		
	n	%	n	%	n	%	n	%	n	%	p-value
Age (years)											
Mean ± SD	59.7 ± 11.4		62.0 ± 9.9		59.5 ± 10.2		60.0 ± 11.3		58.9 ± 11.6		.055
Range	21 - 79		36 - 80		31 - 79		20 - 80		20 - 80		
Age Group											
<65 years	127	63.8	116	58.3	131	65.2	129	63.9	127	63.5	.655
≥65 years	72	36.2	83	41.7	70	34.8	73	36.1	73	36.5	
Gender											
Male	76	38.2	75	37.7	84	41.8	71	35.1	63	31.5	.284
Female	123	61.8	124	62.3	117	58.2	131	64.9	137	68.5	
Race											
Asian	1	0.5	1	0.5	1	0.5	1	0.5	1	0.5	.871
Black	26	13.1	30	15.1	22	10.9	18	8.9	25	12.5	
Hispanic	11	5.5	12	6.0	14	7.0	8	4.0	8	4.0	
White	161	80.9	156	78.4	164	81.6	174	86.1	165	82.5	
Other	0	0.0	0	0.0	0	0.0	1	0.5	1	0.5	
Weight (kg)											
Mean ± SD	92.0 ± 20.7		92.2 ± 22.3		92.3 ± 21.4		92.3 ± 22.6		92.5 ± 22.4		1.000
Range	51.8 – 155.3		49.5 – 161.6		48.1 – 199.8		46.8 – 157.5		49.9 – 172.5		
Primary Efficacy											
WOMAC Pain	306.2 ± 107.3		302.9 ± 96.1		298.4 ± 101.3		286.9 ± 96.1		300.8 ± 103.5		.377
WOMAC Physical Function	1023.6 ± 364.7		1045.1 ± 319.9		1034.0 ± 341.6		991.1 ± 351.1		1019.0 ± 354.7		.604
Patient Global	66.2 ± 21.9		65.8 ± 21.6		66.3 ± 22.4		64.5 ± 21.3		67.2 ± 21.9		.801
Index Joint											
Knee	149	74.9	146	73.4	148	73.6	149	73.8	149	74.5	.997
Hip	50	25.1	53	26.6	53	26.4	53	26.2	51	25.5	
OA Duration											
<5 years	93	46.7	77	38.7	83	41.3	97	48.5	79	39.7	.183
≥5 years	106	53.3	122	61.3	118	58.7	103	51.5	120	60.3	

Study B02.CT3.023.TRA P03:

	TRAMADOL ER 400 MG (N =199)		TRAMADOL ER 300 MG (N = 199)		TRAMADOL ER 200 MG (N = 201)		TRAMADOL ER 100 MG (N = 202)		PLACEBO (N = 200)		
	n	%	n	%	n	%	n	%	n	%	p-value
Age (years)											
Mean ± SD	58.4 ± 9.7		58.5 ± 9.4		59.1 ± 9.9		58.4 ± 10.9		56.4 ± 9.8		.082
Range	27 - 74		28 - 74		33 - 74		22 - 74		25 - 73		
Age Group											
<65 years	143	70.8	135	67.2	132	65.7	127	62.9	157	76.6	.031
≥65 years	59	29.2	66	32.8	69	34.3	75	37.1	48	23.4	
Gender											
Male	85	42.1	82	40.8	73	36.3	76	37.6	64	31.2	.178
Female	117	57.9	119	59.2	128	63.7	126	62.4	141	68.8	
Race											
Asian	0	0.0	1	0.5	0	0.0	6	3.0	1	0.5	.015
Black	34	16.8	31	15.4	40	19.9	37	18.3	32	15.6	
Hispanic	7	3.5	5	2.5	7	3.5	9	4.5	4	2.0	
White	161	79.7	164	81.6	153	76.1	146	72.3	167	81.5	
Other	0	0.0	0	0.0	1	0.5	4	2.0	1	0.5	
Weight (kg)											
Mean ± SD	98.9 ± 10.0		95.1 ± 22.2		98.6 ± 24.5		94.1 ± 23.1		93.6 ± 23.6		.050
Range	52.2 – 166.2		47.7 – 172.5		51.8 – 204.3		47.7 – 190.7		45.4 – 186.1		
Primary Efficacy											
WOMAC Pain	298.0 ± 93.7		296.6 ± 96.3		315.2 ± 92.4		308.2 ± 99.3		305.9 ± 95.2		.271
WOMAC Physical Function	1010.9 ± 331.7		1026.6 ± 337.6		1096.2 ± 298.7		1071.6 ± 331.2		1058.7 ± 340.3		.067
Patient Global	61.4 ± 22.6		64.6 ± 20.7		67.4 ± 20.1		65.4 ± 22.3		66.6 ± 21.5		.054
OA Duration											
<5 years	75	37.1	87	43.3	78	38.8	80	39.8	89	43.6	.608
≥5 years	127	62.9	114	56.7	123	61.2	121	60.2	115	56.4	
Index Joint											
Knee	150	74.3	149	74.1	148	73.6	151	74.8	150	73.2	.997
Hip	52	25.7	52	25.9	53	26.4	51	25.2	55	26.8	

Study B00.CT3.015.TRA P03:

	TRAMADOL ER (N =124)		PLACEBO (N = 122)		
	n	%	n	%	p-value
Age (years)					
Mean ± SD	61.2 ± 10.0		61.5 ± 10.2		.832
Range	32 - 85		30 - 82		
Weight (kg)					
Mean ± SD	93.8 ± 21.9		97.3 ± 23.5		.229
Range	50 - 165		55 - 174		
Gender					
Male	42	33.9	53	43.4	.150
Female	82	66.1	69	56.6	
Race					
Black	18	14.5	12	9.8	.097
White	97	78.2	105	86.1	
Hispanic	7	5.6	1	0.8	
Other	2	1.6	4	3.3	
Duration of OA (years)					
Mean ± SD	13.5 ± 10.7		12.3 ± 10.3		.359
Range	0.4 – 47.0		0.3 – 5.0		

Study B00.CT3.014.TRA P03:

	TRAMADOL ER 300 MG (N =128)		TRAMADOL ER 200 MG (N =129)		PLACEBO (N =127)		P-VALUE
	n	%	n	%	n	%	
Age (years)							
Mean ± SD	48.5 ± 13.7		47.4 ± 13.8		47.6 ± 15.5		.806
Range	19 - 79		20 - 80		20 -79		
Weight (kg)							
Mean ± SD	91.8 ± 19.9		87.2 ± 21.0		85.6 ± 17.6		.031
Range	53.1 – 156.2		49.5 – 158.9		49.0 – 157.5		
Gender							
Male	68	53.1	60	46.5	64	50.4	.578
Female	60	46.9	69	53.5	63	49.6	
Race							
Asian	0	0.0	0	0.0	1	0.8	.057
Black	7	5.5	11	8.5	6	4.7	
White	106	82.8	108	83.7	110	86.6	
Hispanic	15	11.7	10	7.8	6	4.7	
Other	0	0.0	0	0.0	4	3.1	

Table 4.1.1. Analysis of Data from Study B02.CT3.021.TRA P03: WOMAC Pain (ITT with LOCF)

WOMAC OA Index **Pain** Subscale: Change from Baseline to Endpoint					
	TRA300mg (n=199)	**TRA200mg (n=199)**	**TRA100mg (n=201)**	**CELE200mg (n=202)**	**PBO (n=200)**
LSMean Change (SE)	117.8 (8.9)	90.4 (8.9)	82.5 (8.9)	130.0 (9.0)	94.9 (8.9)
Diff. from PBO (95% CI)	22.8 (-.8, 46.5)	-4.5 (-28.4, 19.3)	-12.4 (-36.2, 11.4)	35.1 (11.2, 58.9)	
p-value* (sequential)	.058	(.708)	(.308)	.004	
(bonferroni)	.174	1.000	.924		

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
*p-values by sequential testing procedure were provided by the Sponsor and the bonferroni p-values were added by the reviewer. The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 4.1.2. Analysis of Data from Study B02.CT3.021.TRA P03: WOMAC Physical Function (ITT with LOCF)

WOMAC OA Index Physical **Function** Subscale: Change from Baseline to Endpoint					
	TRA300mg (n=199)	**TRA200mg (n=199)**	**TRA100mg (n=201)**	**CELE200mg (n=202)**	**PBO (n=200)**
LSMean Change (SE)	357.2 (29.0)	271.0 (29.1)	272.3 (29.0)	429.2 (29.3)	290.1 (29.1)
Diff. from PBO (95% CI)	67.1 (-10.2, 144.4)	-19.1 (-97.0, 58.7)	-17.8 (-95.6, 60.0)	139.1 (61.2, 217.1)	
p-value* (sequential)	.089	(.630)	(.653)	<.001	
(bonferroni)	.269	1.000	1.000		

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
*p-values by sequential testing procedure were provided by the Sponsor and the bonferroni p-values were added by the reviewer. The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 4.1.3. Analysis of Data from Study B02.CT3.021.TRA P03: Patient Global Assessment of Disease Activity (ITT with LOCF)

Patient **Global** Assessment of Disease Activity: Change from Baseline to Endpoint					
	TRA300mg (n=199)	**TRA200mg (n=199)**	**TRA100mg (n=201)**	**CELE200mg (n=202)**	**PBO (n=200)**
LSMean Change (SE)	26.4 (2.0)	20.6 (2.0)	18.8 (2.0)	28.6 (2.0)	20.2 (2.0)
Diff. from PBO (95% CI)	6.1 (.8, 11.4)	0.3 (-5.0, 5.6)	-1.5 (-6.8, 3.8)	8.4 (3.0, 13.7)	
p-value* (sequential)	**.023**	.905	(.583)	.002	
(bonferroni)	.069	1.000	1.000		

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
*p-values by sequential testing procedure were provided by the Sponsor and the bonferroni p-values were added by the reviewer. The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 4.2.1. Analysis of Data from Study B02.CT3.023.TRA P03: WOMAC Pain (ITT with LOCF)

WOMAC OA Index **Pain** Subscale: Change from Baseline to Endpoint					
	TRA400mg (n=202)	**TRA300mg (n=201)**	**TRA200mg (n=201)**	**TRA100mg (n=202)**	**PBO (n=205)**
LSMean Change (SE)	107.8 (8.7)	103.9 (8.7)	111.5 (8.7)	107.2 (8.6)	74.2 (8.5)
Diff. from PBO (95% CI)	33.6 (10.5, 56.6)	29.7 (6.6, 52.7)	37.3 (14.2, 60.4)	32.9 (10.0, 55.9)	
p-value* (sequential)	**.004**	**.012**	**.002**	**.005**	
(bonferroni)	**.016**	**.048**	**.008**	**.020**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
*p-values by sequential testing procedure were provided by the Sponsor and the bonferroni p-values were added by the reviewer. The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 4.2.2. Analysis of Data from Study B02.CT3.023.TRA P03: WOMAC Physical Function (ITT with LOCF)

WOMAC OA Index Physical **Function** Subscale: Change from Baseline to Endpoint					
	TRA400mg (n=202)	**TRA300mg (n=201)**	**TRA200mg (n=201)**	**TRA100mg (n=202)**	**PBO n=205)**
LSMean Change (SE)	329.8 (28.8)	336.1 (28.8)	350.2 (29.0)	331.7 (28.5)	234.3 (28.1)
Diff. from PBO (95% CI)	95.5 (19.0, 171.9)	101.8 (25.5, 178.1)	115.9 (39.4, 192.4)	97.4 (21.3, 173.4)	
p-value* (sequential)	**.014**	**.009**	**.003**	**.012**	
(bonferroni)	.056	**.036**	**.012**	**.048**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
*p-values by sequential testing procedure were provided by the Sponsor and the bonferroni p-values were added by the reviewer. The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 4.2.3. Analysis of Data from Study B02.CT3.023.TRA P03: Patient Global Assessment of Disease Activity (ITT with LOCF)

Patient **Global** Assessment of Disease Activity: Change from Baseline to Endpoint					
	TRA400mg (n=202)	**TRA300mg (n=201)**	**TRA200mg (n=201)**	**TRA100mg (n=202)**	**PBO (n=205)**
LSMean Change (SE)	20.8 (2.0)	23.5 (2.0)	21.8 (2.0)	21.3 (1.9)	16.2 (1.9)
Diff. from PBO (95% CI)	4.6 (-.6, 9.8)	7.2 (2.0, 12.4)	5.5 (.3, 10.7)	5.1 (-.1, 10.2)	
p-value* (sequential)	.084	(.006)	(.037)	(.055)	
(bonferroni)	.336	**.024**	.148	.220	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
*p-values by sequential testing procedure were provided by the Sponsor and the bonferroni p-values were added by the reviewer. The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 4.3.1. Analysis of Data from Study B00.CT3.015.TRA P03: Arthritis Pain Intensity VAS Score (ITT with LOCF)

Pain Intensity VAS: *Average* Change from Baseline *over 12 weeks*		
	TRAMADOL HCl (n=124)	**PBO (n=122)**
LSMean Change (SE)	30.1 (2.2)	17.7 (2.1)
Diff. from PBO (95% CI)	12.4 (6.3, 18.3)	
p-value	**<.001**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 4.3.2. Analysis of Data from Study B00.CT3.015.TRA P03: WOMAC Pain (ITT with LOCF)

WOMAC OA Index **Pain** Subscale: Change from Baseline to Endpoint		
	TRAMADOL HCl (n=124)	**PBO (n=122)**
LSMean Change (SE)	151.9 (12.0)	87.5 (11.5)
Diff. from PBO (95% CI)	64.4 (32.3, 96.6)	
p-value	**<.001**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 4.3.3. Analysis of Data from Study B00.CT3.015.TRA P03: WOMAC Physical Function (ITT with LOCF)

WOMAC OA Index Physical **Function** Subscale: Change from Baseline to Endpoint		
	TRAMADOL HCl (n=124)	**PBO (n=122)**
LSMean Change (SE)	498.7 (39.8)	272.4 (38.0)
Diff. from PBO (95% CI)	226.3 (119.6, 333.1)	
p-value	**<.001**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 4.3.4. Analysis of Data from Study B00.CT3.015.TRA P03: Patient Global Assessment of Disease Activity (ITT with LOCF)

Patient **Global** Assessment of Disease Activity: Change from Baseline to Endpoint		
	TRAMADOL HCl (n=124)	**PBO (n=122)**
LSMean Change (SE)	32.0 (2.7)	18.6 (2.6)
Diff. from PBO (95% CI)	13.4 (6.2, 20.5)	
p-value	**<.001**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 4.4.1. Analysis of Data from Study B00.CT3.014.TRA P03: Arthritis Pain Intensity VAS Score (ITT with LOCF)

Pain Intensity VAS (mm) Score Since the Previous Visit: ***Average*** Change from Baseline ***over 12 weeks***			
	TRA300mg (n=127)	**TRA200mg (n=129)**	**PBO (n=126)**
LSMean Change (SE)	-4.8 (2.0)	-6.8 (2.0)	-12.3 (2.1)
Diff. from PBO (95% CI)	7.5 (1.9, 13.1)	5.5 (-.0, 11.1)	
p-value	**.009**	.052	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 4.4.2. Analysis of Data from Study B00.CT3.014.TRA P03: Roland Disability Index (ITT with LOCF)

Roland Disability Index: ***Average*** Change from Baseline ***over 12 weeks***			
	TRA300mg (n=127)	**TRA200mg (n=129)**	**PBO (n=126)**
LSMean Change (SE)	.29 (.33)	-.42 (.33)	-1.33 (.34)
Diff. from PBO (95% CI)	1.62 (.69, 2.55)	.91 (-.01, 1.83)	
p-value	**<.001**	.052	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 4.4.3. Analysis of Data from Study B00.CT3.014.TRA P03: Patient Global Assessment of Medication (ITT with LOCF)

Patient **Global** Assessment of Medication: ***Average*** Change from Baseline ***over 12 weeks***			
	TRA300mg (n=127)	**TRA200mg (n=129)**	**PBO (n=126)**
LSMean Change (SE)	-.28 (.09)	-.41 (.09)	-.70 (.09)
Diff. from PBO (95% CI)	.42 (.17, .66)	.30 (.05, .54)	
p-value	**<.001**	**.017**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.

Table 5.1.1. Sensitivity Analysis of Data from Study B02.CT3.021.TRA P03: WOMAC Pain (ITT with BOCF)

WOMAC OA Index **Pain** Subscale: Change from Baseline to Endpoint					
	TRA300mg (n=199)	**TRA200mg (n=199)**	**TRA100mg (n=201)**	**CELE200mg (n=202)**	**PBO (n=200)**
LSMean Change (SE)	76.2 (8.4)	67.3 (8.4)	67.9 (8.4)	102.0 (8.5)	74.7 (8.5)
Diff. from PBO (95% CI)	1.5 (-21.0, 24.0)	-7.4 (-30.0, 15.2)	-6.8 (-29.4, 15.8)	27.3 (4.6, 50.0)	
p-value*	.895	(.521)	(.556)	.018	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
BOCF (Baseline Observation Carried Forward) was employed.
* The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 5.1.2. Sensitivity Analysis of Data from Study B02.CT3.021.TRA P03: WOMAC Pain (ITT with BOCF for AE Dropouts and LOCF for Other Dropouts)

WOMAC OA Index **Pain** Subscale: Change from Baseline to Endpoint					
	TRA300mg (n=199)	**TRA200mg (n=199)**	**TRA100mg (n=201)**	**CELE200mg (n=202)**	**PBO (n=200)**
LSMean Change (SE)	86.1 (8.9)	73.4 (8.9)	73.2 (8.9)	116.1 (9.0)	88.0 (8.9)
Diff. from PBO (95% CI)	-1.9 (-25.6, 21.8)	-14.6 (-38.5, 9.3)	-14.8 (-38.7, 9.1)	28.1 (4.2, 52.1)	
p-value*	.874	(.232)	(.225)	.007	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
BOCF for AE Dropouts and LOCF for Other Dropouts were employed.
* The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 5.2.1. Sensitivity Analysis of Data from Study B02.CT3.023.TRA P03: WOMAC Pain (ITT with BOCF)

WOMAC OA Index **Pain** Subscale: Change from Baseline to Endpoint					
	TRA400mg (n=202)	**TRA300mg (n=201)**	**TRA200mg (n=201)**	**TRA100mg (n=202)**	**PBO (n=205)**
LSMean Change (SE)	70.8 (8.4)	63.5 (8.4)	87.3 (8.5)	84.6 (8.3)	56.6 (8.2)
Diff. from PBO (95% CI)	14.2 (-8.1, 36.5)	6.9 (-15.4, 29.2)	30.7 (8.3, 53.1)	28.0 (5.8, 50.3)	
p-value*	.212	(.544)	(.007)	(.013)	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
BOCF (Baseline Observation Carried Forward) was employed.
* The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 5.2.2. Sensitivity Analysis of Data from Study B02.CT3.023.TRA P03: WOMAC Pain (ITT with BOCF for AE Dropouts and LOCF for Other Dropouts)

WOMAC OA Index **Pain** Subscale: Change from Baseline to Endpoint					
	TRA400mg (n=202)	**TRA300mg (n=201)**	**TRA200mg (n=201)**	**TRA100mg (n=202)**	**PBO (n=205)**
LSMean Change (SE)	78.1 (8.7)	75.9 (8.7)	98.8 (8.8)	98.4 (8.6)	71.4 (8.5)
Diff. from PBO (95% CI)	6.7 (-16.4, 29.8)	4.6 (-18.5, 27.7)	27.5 (4.3, 50.6)	27.0 (4.0, 50.0)	
p-value*	.567	(.698)	(.020)	(.021)	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+stratum(hip or knee)+baseline.
BOCF for AE Dropouts and LOCF for Other Dropouts were employed.
* The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Table 5.3.1. Sensitivity Analysis of Data from Study B00.CT3.015.TRA P03: Arthritis Pain Intensity VAS Score (ITT with BOCF)

Pain Intensity VAS: *Average* Change from Baseline *over 12 weeks*		
	TRAMADOL HCl (n=124)	**PBO (n=122)**
LSMean Change (SE)	22.3 (1.9)	16.1 (1.9)
Diff. from PBO (95% CI)	6.2 (1.0, 11.5)	
p-value	**.021**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.
BOCF (Baseline Observation Carried Forward) was employed.

Table 5.3.2. Sensitivity Analysis of Data from Study B00.CT3.015.TRA P03: Arthritis Pain Intensity VAS Score (ITT with BOCF for AE Dropouts and LOCF for Other Dropouts)

Pain Intensity VAS: *Average* Change from Baseline *over 12 weeks*		
	TRAMADOL HCl (n=124)	**PBO (n=122)**
LSMean Change (SE)	28.0 (2.1)	17.5 (2.1)
Diff. from PBO (95% CI)	10.5 (4.7, 16.3)	
p-value	**<.001**	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.
BOCF for AE Dropouts and LOCF for Other Dropouts were employed.

Table 5.4.1. Sensitivity Analysis of Data from Study B00.CT3.014.TRA P03: Arthritis Pain Intensity VAS Score (ITT with BOCF)

Pain Intensity VAS: *Average* Change from Baseline *over 12 Weeks*			
	TRA300mg (n=127)	**TRA200mg (n=129)**	**PBO (n=126)**
LSMean Change (SE)	-4.1 (1.6)	-3.5 (1.5)	-7.0 (1.6)
Diff. from PBO (95% CI)	3.0 (-1.3, 7.2)	3.5 (-.8, 7.8)	
p-value	.176	.106	

LSMeans and p-values calculated from ANCOVA model: Y = trt +site+baseline.
BOCF (Baseline Observation Carried Forward) was employed.

Table 5.4.2. Sensitivity Analysis of Data from Study B00.CT3.014.TRA P03: Arthritis Pain Intensity VAS Score - Average (ITT with BOCF for AE Dropouts and LOCF for Other Dropouts)

Pain Intensity VAS: *Average* Change from Baseline *over 12 weeks*			
	TRA300mg (n=127)	**TRA200mg (n=129)**	**PBO (n=126)**
LSMean Change (SE)	-4.4 (1.9)	-6.9 (1.9)	-11.5 (1.9)
Diff. from PBO (95% CI)	7.0 (1.7, 12.4)	4.5 (-.8, 9.8)	
p-value	**.010**	.093	

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Figure 1. Schematic of Study Design

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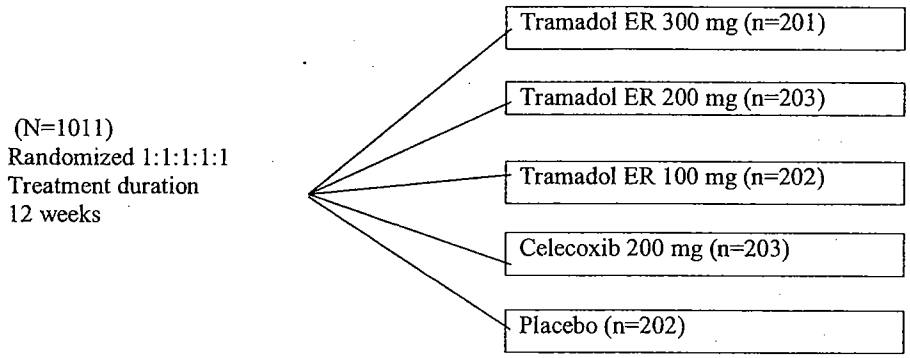

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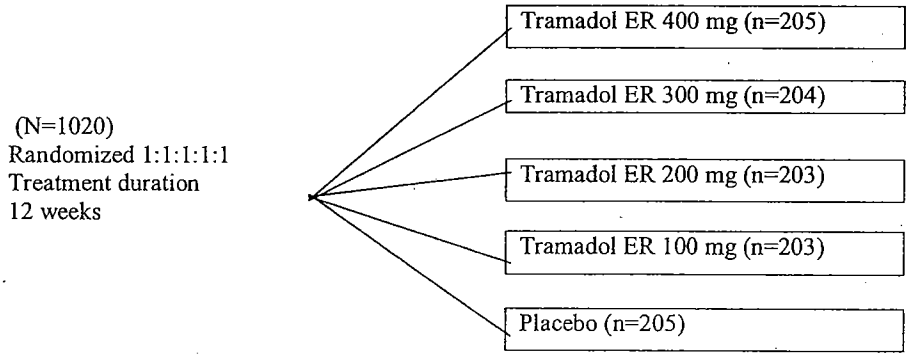

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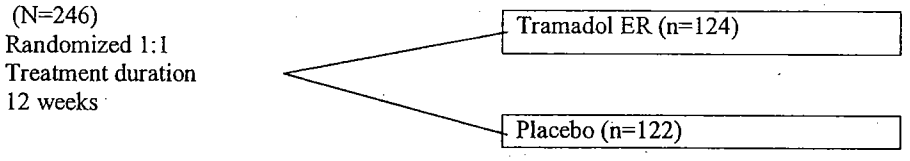

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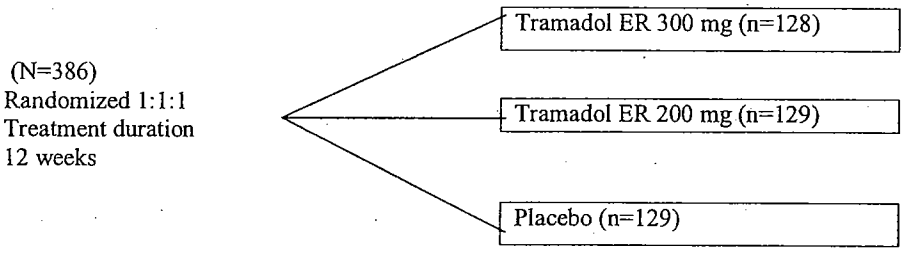
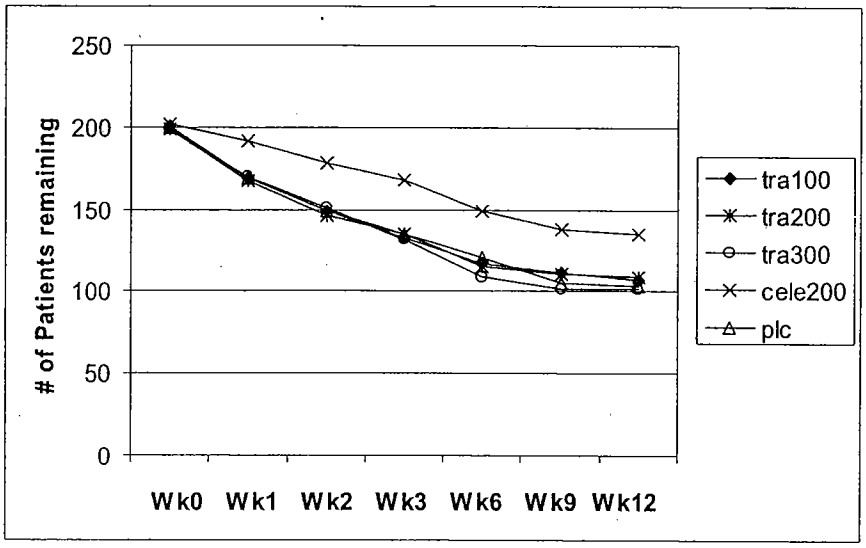


Figure 2. Number of Patients Remaining at Each Time Point by Treatment Group (ITT Patients)

Study B02.CT3.021.TRA P03:



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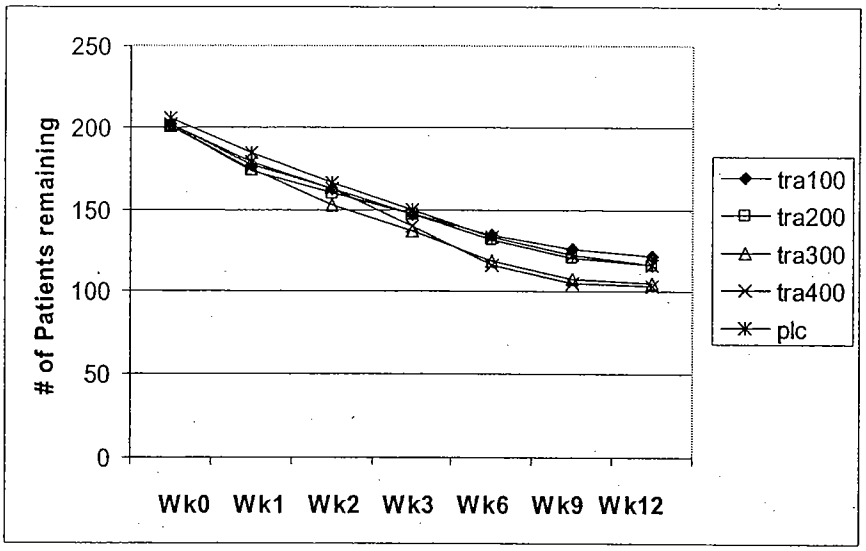

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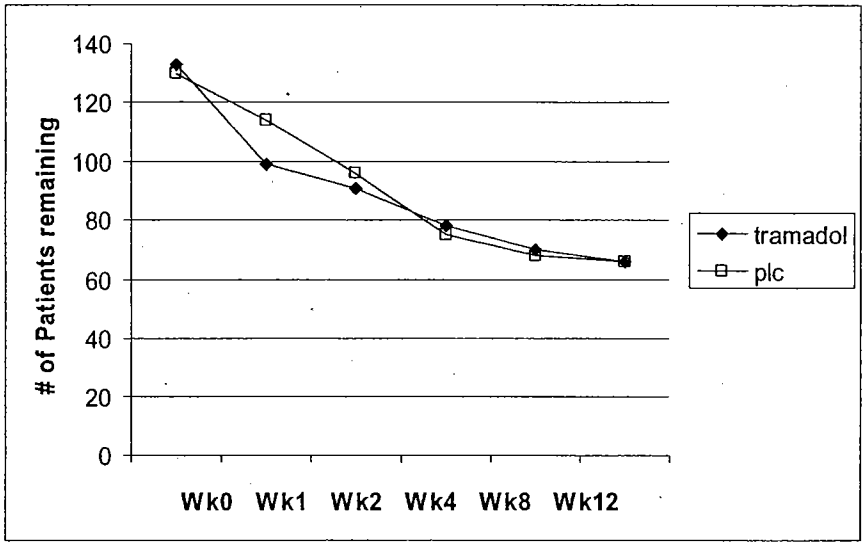

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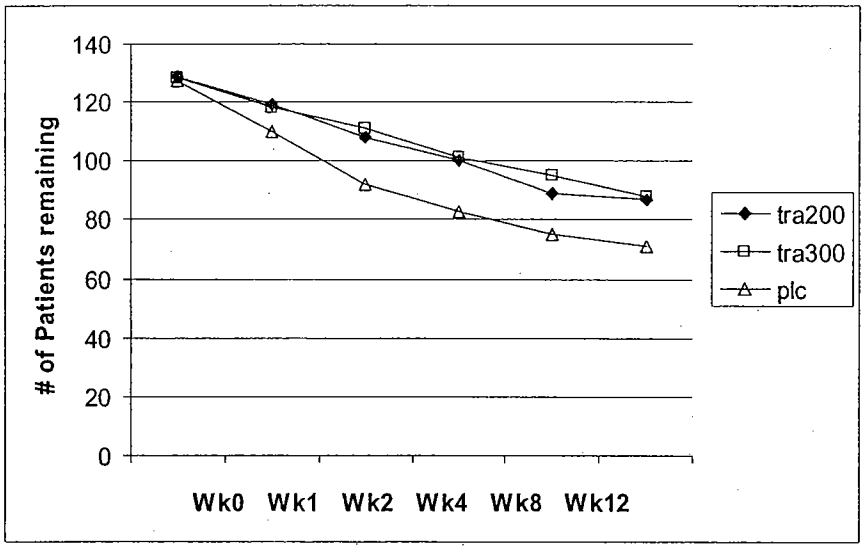

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Yongman Kim, Ph.D.
Mathematical Statistician

Date: September 30, 2004

Concurring Reviewer: Stan Lin, Ph.D.
Statistical Team Leader

cc:

HFD-550/Nancy Clark
HFD-550/Lourdes Villalba, M.D.
HFD-550/James Witter, M.D.
HFD-725/Yongman Kim, Ph.D.
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