CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-745

MEDICAL REVIEW

Clinical Review
NDA Resubmission

Division of Anesthesia, Analgesia, and Rheumatology Products
Center for Drug Evaluation and Research • Food and Drug Administration
Silver Spring • Maryland

NDA	21-745 N-000-AZ
DRUG NAME	Ryzolt (Tramadol OAD)
PROPOSED INDICATION	Moderate to moderately severe pain
APPLICANT	Labopharm
SUBMISSION TYPE	Complete Response to Action Letter
SUBMISSION DATE	December 18, 2006
REVIEW COMPLETE	May 15, 2007
PROJECT MANAGER	Paul Balcer

REVIEWER Jin Chen, *MD, PhD, MPH*

BACKGROUND

The original NDA for Ryzolt (tramadol HCl extended-release (ER) tablets, 100 mg, 200 mg and 300 mg) was submitted on November 25, 2005. The proposed indication was "management of moderate to moderately severe chronic pain." The division took an "approvable" action on September 28, 2006 due to the following major deficiencies:

1. You have not provided substantial evidence that Ryzolt is effective for your proposed indication of the management of moderate to moderately severe pain. Your conclusion that efficacy has been demonstrated in studies MDT3-003 and MDT3-005 depends on the use of a last observation carried forward (LOCF) imputation methodology for patients who dropped out of the studies. We consider this method of imputing missing data inappropriate, and efficacy was not confirmed when other methods, such as baseline observation carried forward (BOCF) or continuous responder analysis (of the patient's status at the end of the study) were employed. Provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial. Ryzolt produced at your commercial manufacturing site should be used in future clinical trials.

2. The pharmacokinetic profile of Ryzolt demonstrated low plasma levels of tramadol, compared to Ultram, for a significant portion of time during the proposed 24-hour dosing interval. This finding may be, at best, partially responsible for your inability to demonstrate efficacy in the clinical trials. Provide a discussion, and data as appropriate, to address this concern.

There are no ideal methods to handle missing data due to early dropouts in analgesic trials. The LOCF (last observation carried forward) method has commonly been used, however, LOCF method tends to impute/carry forward favorable scores for subjects who dropout due to "bad" outcome (such as intolerable adverse events). Thus, imputation with LOCF can inflate the treatment effect. When LOCF imputation is used for the primary efficacy analysis, the division requires that additional analyses are performed to assess the sensitivity of the study results are to the procedure for handling missing data. The applicant was advised of this during the clinical development of Ryzolt. The sensitivity analyses of the two pivotal trials (MDT3-003 and MDT3-005) that submitted in the original NDA submission failed to support the positive result found with LOCF imputation.

In this NDA resubmission, the applicant performed several new sensitivity analyses of LOCF imputation for dropouts in Study MDT3-005 to address the deficiencies indicated in the approvable action letter.

REGULATORY HISTORY:

1. November 28, 2005: The original NDA submission was received.
2. September 28, 2006: Approvable (AE) action letter was issued.
3. October 20, 2006: A teleconference was held to discuss the issues in the approvable action.
4. November 27, 2006: An End of Review (EOR) conference was held to discuss alternative approaches to handling dropouts in Study MDT3-005.

5. December 18, 2006: A Complete Response to the approval action letter was submitted (the current submission).
6. February 8, 2007: The applicant submitted a response to a statistical request..
7. March 14, 2007: The applicant's requests for formal dispute resolution on Class 2 designation of Complete Response submission and approvable issues were denied on April 13, 2007 (signed off by Dr. John Jenkins on the Class 2 designation and by CDER director, Dr. Steven Galson, on the AE issues).

The applicant's post-action meetings with the division focused primarily on the deficiencies related to Study MDT3-005, but not Study MDT3-003. Thus, the resubmission included only reanalyses of the primary efficacy data from Study MDT3-005.

REVIEW

Reanalysis of primary endpoint for Study MDT3-005

Background: Study MDT3-005 was a 12-week, multinational (US, Canada and Europe), randomized, double-blind, placebo-controlled trials in patients with osteoarthritis of the knee. The primary objective was to show superior analgesic efficacy of Ryzolt against placebo. The study enriched for patients who were able to tolerate 4 weeks of open-label treatment with Ryzolt (2-week titration, 1-week tapering, and 1-week washout). Only patients (55% from US, 8% from Canada and 37% from other countries) who tolerated to Ryzolt treatment and experienced analgesic effect were randomized in 2:1 ratio to Ryzolt (n=431) or placebo (n=214). Patients in the Ryzolt arm were titrated to 200 mg or 300 mg, followed by 12-week fixed-dose treatment. The overall dropout rate was 24% during the 12-week double-blind phase (25% in the combined Ryzolt group and 23% in the placebo group).

There were four visits during the 12-week double-blind treatment period (weeks 3, 6, 9 and 12); the baseline data were defined at the end of 1-week washout period during the open-labeling phase). The primary efficacy endpoint was the mean pain intensity (as measured on an 11-point numerical rating scale (NRS)) at the end of the 12-week fixed dose treatment period.

In the original NDA submission, the primary efficacy analysis used the LOCF method to impute missing data due to dropouts, with BOCF as one of the sensitivity analyses. Analysis with LOCF, but not BOCF, showed that Ryzolt treatment was statistically superior to placebo. The continuous responder analysis conducted by the Division's statistical team also showed no statistical superiority of Ryzolt over placebo.

Resubmission: The applicant employed the following four new sensitivity analysis methods to assess the treatment effect of Ryzolt observed using the LOCF method:

1) Placebo Mean or Median Trajectory Carried Forward:
   - The mean or median of trajectories was first calculated at each visit for the placebo group (Table 1) using the following three approaches:
     - Observed data at each visit for patients in placebo group

- LOCF to impute missing observations at each visit for patients in placebo group
- Maximum PI-NRS score (=10) to impute missing observations at each visit for patients in the placebo group

- The change in mean or median pain scores (placebo trajectories) between visits was then calculated (Table 2), which was defined as the decline in mean (or median) pain intensity score at each visit from previous visit. A negative change reflects an improvement in the pain intensity score.
- To impute missing data due to dropouts in the Ryzolt group, the change in placebo trajectories (shown in Table 2) was subtracted from the last observed pain score. The imputation therefore projects a pain value that potentially would have been observed by the end of treatment.

Table 1. **Applicant's Trajectory Estimates of Placebo PI-NRS Mean and Median**
(From the applicant's Table 1 in the Feb-8-07 submission)

Visit	Subject	Observed Value		LOCF		Maximum Score	
		Mean	Median	Mean	Median	Mean	Median
4	214	7.16	7	7.16	7	7.16	7
5	196	5.25	5	5.37	5	5.65	5
6	183	5.02	5	5.29	5	5.74	5
7	172	4.49	4	4.93	5	5.57	5
8	167	4.35	4	4.87	5	5.59	6
9	167	4.28	4	4.81	5	5.53	5

Observed Values: only those placebo patients contributing data at each study visit;
Maximum Score and LOCF: the 214 patients randomized to placebo, and for missing observations impute either the maximum score on the PI-NRS (10), or the last value recorded for that subject.

Table 2. **Applicant's Changes in Placebo Trajectories at Each Visit from Previous Visit**
(From the applicant's Table 2 in the Feb-8-07 submission)

Visit	Subject	Observed Value		LOCF		Maximum Score	
		Δ Mean	Δ Median	Δ Mean	Δ Median	Δ Mean	Δ Median
4	214	NA	NA	NA	NA	NA	NA
5	196	-1.91	-2	-1.79	-2	-1.51	-2
6	183	-0.23	0	-0.08	0	0.09	0
7	172	-0.53	-1	-0.36	0	-0.17	0
8	167	-0.14	0	-0.06	0	0.02	1
9	167	-0.07	0	-0.06	0	-0.06	-1

The change was defined as the decline in mean (or median) PI-NRS score at each visit from the previous visit; NA: not applicable

2) Last On-Study Observation Carried Forward (LOnSCF): This method imputed the pain intensity score at the last planned visit as the final visit (visit 9) value, instead of the pain score recorded at the discontinuation visit. This imputation strategy is similar to LOCF.

3) Time Weighed Average (TWA) analysis: TWA analysis with LOCF imputation was one of the secondary efficacy analyses in the original NDA submission. In this resubmission, the applicant performed two other TWA analyses in the Full Analysis population: LOCF and BOCF imputation methods for dropouts. The Full Analysis population was defined as all randomized patients who received at least one dose of study medication and at least one post baseline pain assessment.

4) Completer analysis: The analysis of primary efficacy data was based on the subjects who completed the 12-week treatment period.

Results from Applicant's Analysis

Placebo trajectory imputation for the drop-outs in the Ryzolt group: The difference in the change in mean pain score from baseline to the end of treatment between the Ryzolt and placebo group ranged from -0.471 to -0.49, depending on the imputation strategy (Table 3). The differences between Ryzolt and placebo were statistically significant ($P<0.05$).

Completer analysis: The effect size (Ryzolt-placebo) in the mean PI-NRS change from baseline to the end of treatment was -0.453 (Table 3) when analysis was based on the population who completed the 12-week treatment ($n=495$). The difference was not statistically significant ($p=0.053$).

Previous LOCF and BOCF imputation analyses: For comparison, the results from LOCF and BOCF analyses submitted in the original NDA were included in the Table 3. The effect size was -0.513 with LOCF ($P<0.05$) and -0.278 with BOCF ($P>0.1$).

Table 3. **Applicant's analysis: Primary endpoint (PI-NRS at the end of treatment) analysis using different imputation methods for drop-outs**
(Adapted from the applicant's Table 3 in the Feb-8-07 submission and Table 6 in the Dec-18-06 submission)

Imputation Method	LOCF	Full Analysis Population (N=495)*	
		95% CI	p-value
Initial NDA Submission (old)			
LOCF (Last Observation Carried Forward)	-0.513	(-0.93, -0.10)	0.015
BOCF (Baseline Observation Carried Forward)	**-0.278**	(-0.69, 0.14)	**0.19**
NDA Resubmission (new)			
Placebo Trajectory†			
Placebo Mean (Observed)	-0.490	(-0.88, -0.10)	0.013
Placebo Median (Observed)	-0.485	(-0.87, -0.10)	0.014
Placebo Mean (LOCF)	-0.480	(-0.87, -0.09)	0.015
Placebo Median (LOCF)	-0.471	(-0.86, -0.08)	0.018
Placebo Mean (Maximum)	-0.469	(-0.86, -0.08)	0.019
Placebo Median (Maximum)	-0.478	(-0.87, -0.09)	0.016
LOnSCF (Last On-Study Observation Carried Forward)	-0.460	(-0.87, -0.05)	0.027
Completers (n=495)‡	-0.453	(-0.91, 0.01)	**0.053**

* Full Analysis Population: randomized subjects who had at least one post-baseline observation; or "Naïve" subjects as described in the applicant's Table 3.

† Placebo mean or median trajectory was estimated as follows:
- Using observed data at each visit in placebo group, "Observed"
- Using LOCF to impute missing observations at each visit in placebo group, "LOCF"
- Using maximum PI-NRS score (=10) to impute missing observations at each visit in placebo group, "Maximum".

‡ The completers analysis is based on the patient population who were randomized and completed the study with complete data (n=495).

Time Weighed Average (TWA) analysis: The effect size (Ryzolt-placebo) based on TWA analysis of the pain intensity scores at each visit was -0.6 (using LOCF imputation) or -0.5 (using BOCF imputation). Both analyses showed that the difference between Ryzolt and placebo was statistically significant (Table 4).

The change in pain intensity from baseline to each time-point (visit), and the differences in the mean pain intensity scores between the Ryzolt and placebo groups are shown in Table 5. The greatest between-group difference was observed at 2 weeks post dosing. At

6 weeks, patients in placebo group had better improvement in pain than those in the Ryzolt group as compared to their pervious visit.

Table 4. **Applicant's Time Weighed Average (TWA) Analysis for PI-NRS (at End of Study)**
(from the applicant's Table 7 in Dec-18-06 submission)

Treatment	Mean±SD (95%CI)	
	LOCF	BOCF
Placebo (n=214)	5.2±1.9	5.3±2.0
	(4.9, 5.4)	(5.0, 5.5)
Ryzolt (n=431)	4.6±2.0	4.8±2.1
	(4.4, 4.8)	(4.6, 5.0)
Difference (Ryzolt-Placebo)	-0.6	-0.5
p-value (1)	0.0003	0.0082
p-value (2)	<0.0001	0.0015
p-value (3)	<0.0001	0.0024

(1) Van der Waerden one-way analysis
(2) ANCOVA with baseline as covariate
(3) ANCOVA based on ranks with baseline as covariate

Table 5. **Applicant's Analysis: Mean change in PI-NRS between visits**
(From the applicant's Table 1 in the Nov-6-06 submission)

Visit	Placebo (P)	Ryzolt (R)	Difference (R-P)
4 (Baseline)			
5 (week 2)	-1.9	-2.8	***-0.9***
6 (week 3)	-0.1	-0.2	-0.1
7 (week 6)	-0.5	-0.2	0.3
8 (week 9)	-0.1	-0.1	0
9 (week 12)	-0.1	-0.1	0

A negative value means that the pain intensity decreased from the previous visit (*) or favors to Ryzolt (#).

Results from Division's Reanalysis – Study MDT3-005

The statistical reviewer confirmed the applicant's analyses of primary efficacy outcome using the Placebo Mean Trajectory (with LOCF imputation for dropout in the placebo group) and the Placebo Median Trajectory (with maximum score imputation for dropouts in the placebo group) imputation methods. The applicant's completer analysis and TWA analyses were also verified.

The statistical reviewer conducted the following additional analyses of the primary efficacy data from study MDT3-005, including other imputation strategies. The results are summarized in Table 6.

1) Mean of placebo group (MPG)/LOCF imputation: The MPG was calculated after using LOCF imputation for dropouts in the placebo group. The MPG value was then used to impute scores for dropouts due to adverse events (AEs) in the Ryzolt group. The scores for non AE-related dropouts in the Ryzolt group were imputed with LOCF. The difference in mean pain intensity between Ryzolt and placebo was 0.38 (p=0.049).

   Although the difference between treatment groups was statistically significant, the division does not consider the MPG imputation to be an adequate imputation strategy. The MPG assigns a population average. This can alter the distribution of pain scores for the active group, with an underestimation of the variance (spread) and a shift of the mean pain value for the active group. If the shift of the mean is in a favorable direction, a positive treatment effect may be inferred.

2) LOCF/BOCF imputation: The scores for AE- or LOE (lack of efficacy)-related dropouts were imputed using BOCF, and LOCF was used for the other dropouts. Ryzolt was not statistically superior to placebo with respect to the change in mean pain intensity from baseline to endpoint (difference in mean pain score = 0.272, p=0.177).

   This mixed imputation strategy is acceptable to the Division because it does not attribute favorable scores to patients who discontinue treatment because of a negative outcomes (e.g. an adverse event).

3) Continuous responder reanalysis: Unlike the continuous responder analysis conducted in the previous statistical review in which all dropouts were counted as non-responders, only AE- or LOE-related dropouts were defined as non-responders in the reanalysis. The separation of the cumulated responder curves between Ryzolt and placebo was not statistically significant (p=0.342); this finding was similar to that of the previous analysis (p=0.347) (Figure 1).

Table 6. **Statistical reviewer's additional analyses of primary endpoint (PI-NRS) in Study MDT3-005**
(From the statistical review Table 10)

Analysis	LS Mean Difference† (Ryzolt-Placebo)	p-value
LOCF/BOCF Imputation *	-0.272	0.177
MPG/LOCF Imputation #	-0.377	0.049
Continuous Responder Analysis‡	(Figure 1)	0.342

† LS Mean: least square mean
* LOCF/BOCF combination: BOCF imputation for the dropouts due to AEs or lack of efficacy (LOE) and LOCF imputation for dropouts due to other reasons.
# MPG/LOCF: Mean of Placebo Group (MPG) imputation for dropouts due to AEs in the Ryzolt group and LOCF imputation for dropouts due to all reasons in the placebo group for MPG calculation and all non-AE-related reasons in the Ryzolt group.
‡ Continuous Responder Analysis: Only AE- or LOE-related dropouts were defined as non-responders.

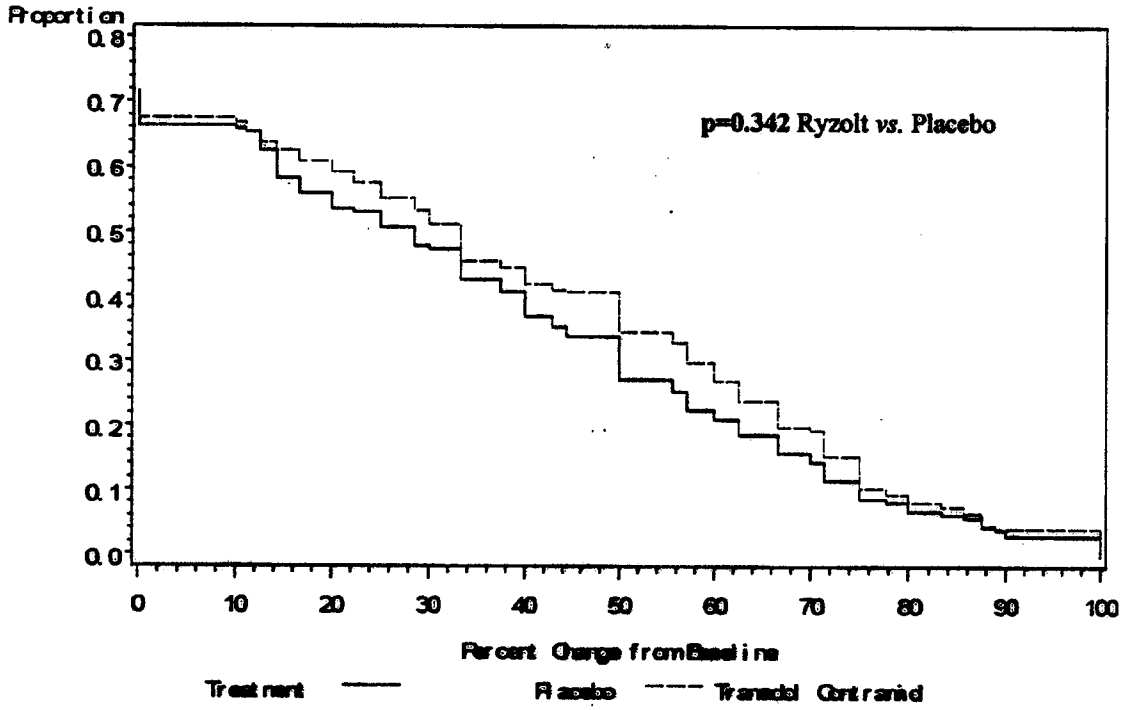

Figure 1. **Statistical reviewer's continuous responder re-analysis on the primary endpoint (pain intensity on 11-point NRS at week 12) of the study MDT3-005 (adapted from Figure 2 of the statistical review). The dropouts due to AEs or lack of efficacy were defined as non-responders, which is different from the analysis conducted in the first review cycle (all dropouts were counted as non-responders). The separation of the responder curves between Ryzolt and placebo was not statistically significant, with p=0.342 (with Van der Waerden non-parametric test), which is similar to the previous analysis (p=0.347).**

Results from Division's Reanalysis – Study MDT3-003

Study MDT3-003 was a 12-week, randomized, placebo-controlled, fixed-dose trial in OA patients in the US. The study did not incorporate an initial period of open-label treatment to enrich for patients who could tolerate Ryzolt. The primary efficacy endpoint was the change in mean WOMAC pain score from baseline to week 12. Dropout rates were 46% in the Ryzolt groups (100 mg, 200 mg and 300 mg) and 41% in the placebo group. The initial NDA review found that only the Ryzolt 300 mg was marginally superior to placebo with respect to the improvement in pain, using LOCF imputation (p=0.0165; <0.05/3=0.0167 after multiplicity adjustment, Table 7). Efficacy was not shown for any of the three Ryzolt doses based on analysis using BOCF imputation and a continuous responder analysis.

Table 7. **Statistical reviewer's analysis of change in WOMAC Pain score from baseline to Week 12 with LOCF imputation for dropouts in Study MDT3-003**

Analysis	Ryzolt 100 mg (n=103)	Ryzolt 200 mg (n=107)	Ryzolt 300 mg (n=105)	Placebo (n=224)
LS Mean Percent Change (SE)	42% (5%)	43% (5%)	46% (5%)	32% (3%)
Difference from placebo (95% CI)	10% (-2%, 21%)	11% (-0%, 22%)	14% (3%, 24%)	
p-value vs. placebo*	0.0933	0.0504	**0.0165**	
Holm's adjusted level	0.05	0.025 (=0.05/2)	0.0167 (=0.05/3)	

LS Means and p-values calculated from ANCOVA model: Y = treatment + baseline.

* p-values are compared with adjusted significance levels for multiplicity based on Holm's sequentially rejective method. The sequential testing procedure stops prior to calculating p-values in the parenthesis.

In the resubmission, the applicant did not address the efficacy deficiencies in study MDT3-003. The division conducted a "completer analysis" to determine whether efficacy could be shown for patients who did not drop out but remained on treatment over the entire 12 weeks. The analysis showed that among study completers, all three Ryzolt doses were not statistically superior to placebo with respect to the change in mean WOMAC Pain score from baseline to the end of treatment (Table 8).

Table 8. **Statistical reviewer's completer analysis of change in WOMAC Pain score from baseline to Week 12 in Study MDT3-003 (only patients who completed 12-week treatment)**

Analysis	Ryzolt 100 mg (N=72)	Ryzolt 200 mg (N=67)	Ryzolt 300 mg (N=72)	Placebo (N=73)
LS Mean % Change (SE)	57% (5%)	51% (5%)	61% (6%)	47% (4%)
Difference from Placebo (95% CI)	10% (-3%, 23%)	5% (-8%, 17%)	13% (-0%, 27%)	
p-value vs. placebo*	(0.1184)	(0.4718)	0.0535	
Holm's adjusted level	0.025 (=0.05/2)	0.05	0.0167 (=0.05/3)	

LS Means (least square mean) and p-values calculated from ANCOVA model: Y = treatment + baseline.

* p-values are compared with adjusted significance levels for multiplicity based on Holm's sequentially rejective method. The sequential testing procedure stops prior to calculating p-values in the parenthesis.

Pharmacokinetic reanalysis (to address deficiency #2):

In the first review cycle of the NDA submission, no major deficiencies in the clinical pharmacology studies were identified. However, the PK profile of Ryzolt showed a 9-hour window over the 24-hour dosing period during which the plasma level of Ryzolt was lower than the trough level of immediate-release tramadol (Ultram). This may be due to the formulation of the Ryzolt tablet. The PK profile may be responsible for the inability to show efficacy of Ryzolt in the clinical trials. The PK profile also suggests that the current Ryzolt formulation may not be suitable for once-a-day dosing.

To address this concern, the applicant re-summarized its own data regarding the PK profile of Ryzolt compared to Ultram, as well as the literature comparing the PK profiles of Ultram and Ultram ER. These data had been submitted in the original NDA:

- When compared to 50 mg Ultram administered every 6 hours for 5 days, Ryzolt 200 mg maintained a plasma level above the lowest mean plasma tramadol concentration from Ultram (i.e. 190 ng/ml) for 83% of the dosing interval.
- Ultram ER 200 mg maintained a tramadol concentration greater than the lowest mean plasma concentration of tramadol (220 ng/ml) from Ultram (50 mg administered every 6 hours for 10 days) for 70% of the dosing interval.
- Based on the literature, the threshold value for analgesic efficacy for tramadol is 100 ng/ml.

The applicant's information regarding the PK profile of Ryzolt compared to Ultram and Ultram ER do not fully argue against the division's finding of a lack of clinical efficacy. Based on my review of the applicant's data, it appears that Ultram ER would have maintained a plasma concentration of tramadol that was greater than 190 ng/ml over the same proportion of the dosing interval as Ryzolt. Thus, Ryzolt may not have greater

plasma exposure and consequently, from a PK perspective, greater presumed efficacy. Furthermore, a pharmacokinetic/pharmacodynamic relationship (i.e. an exposure-response relationship) supporting a minimum therapeutic level for tramadol has not been established, and the 100 ng/mL value that is cited in the literature as being the "efficacious" tramadol concentration has not been validated.

Safety update since the original NDA submission:

There were no major safety issues raised during the first review cycle. The review found that the safety profile of Ryzolt was similar to that of approved tramadol products (Ultram and Ultra ER).

In the resubmission, the applicant integrated the safety data of five phase 3 trials into one dataset. The applicant did not provide an updated Integrated Safety Summary (ISS), but instead submitted three separate Periodic Safety Update Reports (PSURs).

1) New studies: No new studies have been conducted by the applicant since the "approvable action" on September 28, 2006.

2) Periodic safety update report (PSUR): In the resubmission, the applicant provided summaries of the following three PSURs:
   - 1st PSUR (February 2-August 2, 2005): The data from this reporting period were included in the initial NDA submission; so the PSUR is excluded from this review.
   - 2nd PSUR (August 3, 2005 to February 2, 2006): The data from this reporting period were also included in the initial NDA submission, so the PSUR is excluded from this review.
   - 3rd PSUR (February 2-August 3, 2006): The reporting period was partially covered by the 120-day safety updates submitted in the initial NDA. The data are summarized below.
     - The safety data from two PK studies (MDT1-016 and MDT1-014) and one phase III study (MDT3-005) were included in the updated safety database submitted during the first review cycle, and are therefore excluded from this review.
     - AEs from post-marketing reporting on this products currently marketed in 18 countries outside US:
       - February 05 to August, 06: the products was approved in 18 countries (mostly in Europe); it was first authorized in France (Feb 2, 2005), then under MR procedure (September 05). The product was first launched in Germany on Nov 16, 2005 (on market).
       - A total patient-year since the product was the first launch was 9,165 person-years; no SAEs and no new safety signals were reported.
     - Safety information from the literature: the applicant submitted several literature reprints related to the safety of tramadol. No new safety signals except one article which reported 6 cases of angioedema associated with tramadol (*Eur J Clin Pharmacol* 60: 901-903, 2005). Angioedema is not listed under Adverse Reactions of labeling of all approved tramadol products.

Further evaluation of the likelihood of an association between tramadol treatment and angioedema may be warranted.

Labeling

The applicant submitted updated labeling on February 28, 2007. The major difference between the updated label and the initial NDA version is that the trade-name, Ryzolt, has been inserted.

The common and less common adverse event information is unchanged, presenting only data regarding adverse events with a possible causal relationship to study drug. As was commented upon in the first review cycle, this presentation of adverse event information is unacceptable. Upon approval of this NDA, all adverse event data should be presented in the label, regardless of presumed causality.

DISCUSSION AND CONCLUSION

In this NDA resubmission, the applicant has provided the results of several reanalyses of primary efficacy data from Study MDT3-005 that were intended to address the efficacy deficiencies described in the "approvable" action letter. Although the applicant's results were confirmed, the resubmission does not provide substantial efficacy evidence of Ryzolt from the study MDT3-005 to support the proposed indication:

- The applicant's new imputation methods (placebo mean/median trajectory imputations) are inappropriate to handle missing data due to dropouts because the methods tend to assign favorable pain score to patients who discontinue due to adverse events or lack of efficacy. The imputation methods give benefit particularly to early dropouts. Ultimately, analysis using these methods leads to a favorable outcome for Ryzolt, but one that is driven by attribution of efficacy in patients who are unable to tolerate treatment or discontinue because of a lack of effect.
- The analysis of the primary efficacy endpoint within a completer population failed to demonstrate statistical superiority of Ryzolt to placebo. In general, subjects who stay in a study till the end tend to experience more benefit (efficacy) and/or to be higher tolerable (less AEs) to an active treatment than those dropouts. Thus a relatively larger treatment effects are expected from an analysis of a completer population than from other analyses using imputed data for dropouts. However, the effect size of Ryzolt from the completer analysis did not reach a statistically significant level ($p \leq 0.05$). The favorable outcome for Ryzolt may therefore have resulted from the applicant's imputation methods which overestimated the true effect by imputing favorable estimates of non-observed data.
- The time-weighed average (TWA) analyses averaged results across the duration of the treatment, which did not provide adequate evidence to support the proposed chronic pain indication because the TWA results were highly driven by the relatively large effect at week 2; the difference in treatment effect was not sustained after week 2 through week 12 post-dosing. Thus averaging of the efficacy over the treatment

period masks the lack of sustained efficacy of Ryzolt, and suggests that this treatment would not be efficacious for in chronic pain.

- Continuous responder reanalysis (by the Division) by defining AE- or LOE-related dropouts as non-responders showed that Ryzolt was not statistically superior to placebo, which is consistent with the result from the first review cycle.

The applicant did not reanalyze the data of Study MDT3-003, even though it evidenced the same problem regarding inadequate imputation methods for missing data due to dropouts. This study was characterized by a more significant proportion of dropouts and therefore the efficacy results may have been more vulnerable to the methods used for imputation. Therefore the division conducted a completer analysis of the primary endpoint (change in mean WOMAC pain score from baseline to the end of treatment) to evaluated effects of treatment in patients who did not discontinue the study. The division found that all 3 tested doses (100, 200 and 300 mg) of Ryzolt were not statistically superior to placebo. Thus, efficacy of Ryzolt was not demonstrated in patients able to remain on drug for the duration of the trial.

In Study MDT3.003, with LOCF imputation for missing data due to dropouts, the change in mean WOMAC pain score from baseline to the end of treatment showed statistical superiority of Ryzolt 300 mg to placebo in MDT3-003. This result was not observed for Study MDT3-005. Since Study MDT3-003 had smaller sample size and much higher dropout rate than study MDT3-005, the inability to show efficacy of Ryzolt 300 mg in MDT3-005 suggests that the analysis with LOCF imputation overestimated the effect size of Ryzolt treatment.

Therefore, regardless of the method used for imputation for missing data, and on the population analyzed (ITT or completers), both pivotal trials fail to support efficacy of Ryzolt as treatment for moderate-moderately severe chronic pain.

RECOMMENDATION

I recommend that an ***Approvable*** action be taken for this NDA. The applicant's two pivotal trials (MDT3-003 and MDT3-005) fail to demonstrate substantial evidence of efficacy after reanalyses of the primary efficacy data.

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/s/

Jin Chen
5/16/2007 03:07:58 PM
MEDICAL OFFICER

Mwango Kashoki
5/16/2007 03:18:28 PM
MEDICAL OFFICER
I concur with this review.

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, 10903 New Hampshire Ave., Silver Spring MD 20993

MEMORANDUM

DATE: September 23, 2006

TO: File, NDA 21-745

FROM: Mwango A. Kashoki, M.D., M.P.H
Medical Team Leader

RE: Supervisory Review of NDA 21-745
Tramadol Contramid® OAD (once-a-day)
Labopharm

Indication: "Management of moderate to moderately severe pain"

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1. BACKGROUND

The NDA for Tramadol Contramid® OAD was submitted by Labopharm on 11/28/05. Tramadol Contramid® OAD (to be referred to as "Tramadol OAD" in this memo) is a tablet reformulation of tramadol, comprising a dual-matrix delivery system with an outer layer containing tramadol [redacted] and [redacted], and an inner ore containing tramadol and Contramid®. Contramid is a modified starch (hydroxypropyl distarch phosphate) and is the applicant's proprietary product specifically developed for the delivery system. The outer coat layer of the tablet is designed to release tramadol in a controlled manner, but at a faster rate than the core layer – therefore the core provides the controlled-release characteristics of the drug. The desired indication for Tramadol OAD is the "treatment of moderate to moderately severe pain." b(4)

Tramadol is a centrally acting analgesic that, together with its M1 metabolite, acts as an agonist at the mu opioid receptor. Tramadol has also been shown to weakly inhibit reuptake of neuronal serotonin and norepinephrine. There are five other formulations of tramadol (either alone or in combination with acetaminophen) that have been approved for marketing in the United States:

- Ultram – immediate release tramadol, 50 mg tablet (NDA 20-281). Approved 03/03/1995 for moderate to moderately severe pain in adults.
- Ultracet –Immediate release tramadol (37.5 mg) and acetaminophen (325 mg) combination tablet (NDA 21-123). Approved 08/15/2001 for short term (≤ 5 days) management of acute pain
- Ultram ODT – immediate release, orally disintegrating tramadol, 50 mg tablet (NDA 21-693). Approved 05/05/2005 for moderate to moderately severe pain in adults.
- Ultram ER – extended release tramadol; 100, 200, and 300 mg tablets (NDA 21-692). Approved 09/08/2005 for management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

Notable aspects of the administrative history of this NDA are the change in treatment indication and subsequent modifications in the design of the clinical efficacy trials. Initially, the regulatory responsibility for tramadol lay with the Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products (DAAODP). DAAODP advised Labopharm that, for an evaluation of efficacy in an [redacted] population (the selected pain population), three co-primary endpoints would be required: change in WOMAC Pain and Function, and patient global assessment of pain relief at study end. The associated indication would be [redacted] b(4)
DAAODP also recommended use of fixed-dose Phase 3 trials, with patients randomized to a specific tramadol dose that was to be maintained over the double-blind period. However, as the Agency's experience with trials of opioid analgesics has increased, it has become evident that fixed-dose trials are not always suitable for reformulated opioids.

In general clinical practice, patients are started on a low dose of opioid which is progressively adjusted based on effect and tolerability. Efficacy trials should therefore reflect how opioids will be used in the clinical setting. Also, for reformulated opioids, the regulatory question is not whether the active moiety is efficacious or which specific doses are efficacious. Instead the regulatory question is whether the reformulation is efficacious within the proposed dose range, and poses no additional risks besides those identified for the active moiety/initial formulation.

The fixed-dose trial design does not reflect clinical practice, nor is it the only approach to address the regulatory concern in the setting of trials of reformulated opioids. The fixed-dose design also leads to considerable patient dropout because some patients are randomized to a dose that is excessive for their pain and is intolerable. Patients also dropout for the opposite reason: randomization to an inefficacious dose. High dropout was observed in the applicant's initial two efficacy trials and was theorized to be one reason for the applicant's inability to consistently show efficacy of Tramadol OAD. DAAODP therefore agreed with the applicant's proposal to conduct another efficacy study using an enriched population that had previously been titrated to a tolerable dose of tramadol. The protocol was initially submitted under Special Protocol Assessment; however DAAODP did not reach agreement with the applicant under a SPA. Nevertheless, with subsequent modifications to the design and statistical analysis plan, DAAODP considered the protocol to be acceptable (see Section 2.3). DAAODP also agreed to the applicant's proposal to change the treatment indication from [redacted] to "management of pain" (as based on studies of effect in a chronic pain condition such as OA). b(4)

A major issue for all trials of treatments for pain is how to statistically handle missing data due to patient dropout. Use of the Last Observation Carried Forward (LOCF) method is often favored by applicants. However, the Division discourages use of this method because it assigns "good" scores to patients who experience a decrease of their pain but discontinue due to intolerable side effects. For a drug to be considered an effective analgesic, it must decrease pain at a dose that is tolerable. The Division therefore favors imputation methods that are more conservative than LOCF and will not assign good scores to patients with "bad" outcomes, such as Baseline Observation Carried Forward (BOCF). The Division also recommends use of responder analyses in which dropouts are considered to be non-responders and data imputation becomes less of a concern. The applicant was encouraged to utilize alternative imputation methods to evaluate the primary efficacy endpoint, as well as to conduct responder analyses, based on a clinically meaningful definition of treatment response.

The studies in the application for Tramadol OAD include eleven Phase 1 trials, six Phase 3 trials, and one non-clinical toxicity study of the Contramid excipient. The clinical studies of efficacy and safety were reviewed by Dr. Jin Chen. The application has also been reviewed by Dr. Yongman Kim (biostatistics), Dr. Lei Zhang (clinical pharmacology and biopharmaceutics), Dr. Sue-Cheng Lin (chemistry), and Dr. Asoke Mukherjee (pharmacology/toxicology).

In this memo, I will briefly discuss regulatory issues related to trials of reformulated opioids, and will review the efficacy and safety data summarized in the primary clinical review, as well as any relevant information found in the primary reviews by the other disciplines. I will also make recommendations for action on the NDA.

2. EFFICACY

2.1. OVERVIEW

Two trials were submitted in support of efficacy of Tramadol OAD (MDT3-003, and MDT3-005). Based on the Division's preferred imputation methods and analyses, neither of these trials showed efficacy of the drug.

MDT3-002 was a third Phase 3 efficacy trial that had the same design as MDT3-003. Because the applicant found this study inefficacious, data from this study were used primarily to evaluate the relative safety of Tramadol OAD.

A non-inferiority trial comparing Tramadol OAD to Topologic (a sustained-release formulation of tramadol administered twice daily and not marketed in the US) was also conducted (study MDT3-001-E1). The Division did not consider this study when evaluating the efficacy of Tramadol OAD. This is because non-inferiority trials lack assay sensitivity. Because pain is a subjective outcome and can vary over time and across populations, trials must be able to detect that (a) patients have pain at the time of treatment and (b) treatment is having a measurable effect on pain that can be definitively attributed to drug. The Division requires that analgesic trials have a superiority design in order to show greater efficacy of the test product against a comparator and that the trials incorporate assay sensitivity. Because study MDT3-001-E1 was not considered sufficient to support efficacy, it will not be discussed further in this memo. For details regarding the trial, refer to Dr. Chen's review.

Table 2.1 (following pages) briefly summarizes the features and results of the clinical efficacy studies.

Table 2.1: Summary of the Phase 3 Efficacy Trials

PROTOCOL NUMBER/TITLE	DESIGN/RESULTS
MDT3-002 Four-arm study comparing the analgesic safety and efficacy of Tramadol Once-a-Day 100, 200, 300 mg versus placebo for the treatment of pain due to osteoarthritis of the knee	Randomized, double-blind, placebo-controlled, 4-arm, fixed-dose, parallel group study 75 US centers N = 565 randomized adults with osteoarthritis (OA) of the knee Dose = 0 mg (placebo), 100 mg, 200 mg, 300 mg Tramadol OAD Treatment duration = 12 weeks (fixed/stable dose) Primary efficacy endpoint: % change WOMAC Pain Score from baseline to end of study **Results (Applicant's analysis): None of the Tramadol doses showed superiority to placebo**
MDT3-003 Four-arm study comparing the analgesic safety and efficacy of Tramadol Once-a-Day 100, 200, 300 mg versus placebo for the treatment of pain due to osteoarthritis of the knee	Randomized, double-blind, placebo-controlled, 4-arm, fixed-dose, parallel group study 74 US centers N = 522 randomized adults with osteoarthritis (OA) of the knee Dose = 0 mg (placebo), 100 mg, 200 mg, 300 mg Tramadol OAD Treatment duration = 12 weeks (fixed/stable dose) Primary efficacy endpoint: % change WOMAC Pain Score from baseline to end of study **Results (Division's analysis):** • **BOCF imputation: None of the Tramadol OAD doses was superior to placebo** • **Cumulative responder analysis: None of the Tramadol OAD doses showed superiority to placebo** **Results (Applicant's analysis):** • LOCF imputation: Tramadol OAD 300 mg was superior to placebo • **BOCF imputation: None of the Tramadol OAD doses was superior to placebo**

Table 2.1: Summary of the Phase 3 Efficacy Trials (continued)

PROTOCOL NUMBER/TITLE	DESIGN/RESULTS
MDT3-005 **A two-arm study comparing the analgesic efficacy and safety of Tramadol Contramid OAD versus placebo for the treatment of pain due to osteoarthritis**	**Randomized, double-blind, placebo-controlled, 2-arm, parallel-group study** **Multinational study (68 US sites, 18 French sites, 14 Canadian sites, 9 Romanian sites)** **N = 1027 randomized adult patients with osteoarthritis of the knee** **Dose: Placebo or Tramadol OAD (100 to 300 mg) QD** **Primary efficacy endpoint: Group mean pain intensity (PI-NRS score) at study end** **Treatment duration:** - 4-wks open-label treatment to tolerable & efficacious (optimized) dose - 12-wks stable (unchanged) treatment at optimized dose **Results (Division's analysis):** • **Cumulative responder analysis: Tramadol OAD was not superior to placebo** **Results (Applicant's analysis)** • **BOCF imputation: Tramadol OAD was not superior to placebo** • LOCF imputation: Tramadol OAD was superior to placebo • "Responder" analysis: Tramadol OAD was superior to placebo
MDT3-001-E1 **A comparison of the analgesic efficacy and safety of once daily tramadol HCL/Contramid tablets to twice daily tramadol HCL (SR) for the treatment of osteoarthritis of the knee**	**Randomized, double-blind, active-controlled, parallel-group, non-inferiority study** **Foreign study (3 French sites, 8 Hungarian sites, 8 Russian sites, and 2 British sites)** **N = 408 adults with osteoarthritis of the knee** **Dose: Tramadol OAD (100 to 400 mg QD) or Topologic (tramadol 100 mg BID)** **Primary efficacy endpoint: % change in WOMAC Pain Score from baseline to endpoint (inferiority margin ≥ 15%** **Treatment duration:** - 4-12 day titration to optimized dose - 12 wks stable (unchanged) treatment at optimized dose **Results (Applicant's analysis): Tramadol OAD was non-inferior to tramadol BID**

2.2. POPULATION

The efficacy studies had similar inclusion and exclusion criteria. Eligible subjects were adults with symptomatic osteoarthritis of the knee (confirmed by either radiology or arthroscopy performed in the previous 5 years), had a minimal pain intensity score at baseline[1], had less than 30 minutes of morning stiffness, and had a BMI < 38. Subjects were excluded if they had rheumatic disease, secondary arthritis, were on current therapy with other pain medications, had corticosteroid injections in the target knee within the previous 3 months, or viscous injections in the target knee within the previous 6 months. The target knee could not have had bursitis, a meniscal tear, cartilage reconstruction, or a therapeutic arthroscopic procedure within the previous 12 months.

In addition to the aforementioned musculoskeletal-related exclusions, subjects were ineligible if they had a history of seizures or had had treatment with a drug that reduces the seizure threshold within 3 weeks of randomization. Also, subjects with significant liver disease (LFTS > 3x ULN), significant renal disease (creatinine clearance < 30 mL/min), current/previous substance abuse or dependence, and who were pregnant were not permitted to participate in the trials.

2.3. DESIGN AND ENDPOINTS

MDT3-002 and MDT3-003

Two of the three efficacy trials (MDT3-002 and MDT3-003) were conducted concurrently and the designs were basically identical. Following screening, eligible subjects were randomized to one of four treatment arms (Tramadol OAD 100mg, 200mg, 300 mg, or placebo). The dose of study drug was increased to the target dose over six days, and then patients were maintained at the target dose for 12 weeks. Use of analgesics for 'rescue' was not permitted, and patients with intolerable pain were withdrawn as treatment failures. During the maintenance phase, patients were assessed every 3 weeks for the first 3 weeks, and then after 6 weeks. At each visit, patients rated their pain using the WOMAC Pain Subscale (a 100-mm visual analog scale (VAS)), and the 24-hour Pain Questionnaire (also a VAS). Patients also rated their function and stiffness using the WOMAC Physical Function and Stiffness VAS subscales, as well as their overall pain relief.

Initially the protocols for studies MDT3-002 and MDT3-003 specified three co-primary efficacy endpoints, as required for an indication of "signs and symptoms of osteoarthritis." However, only a single pain-related endpoint was required for the "management of moderate-severe pain" endpoint, and the applicant selected the percent change in WOMAC pain score from baseline to the end of the study (week 12) as the primary efficacy outcome. Secondary endpoints included the percent change in WOMAC physical function score at endpoint, the average Patient Global Rating of Pain

[1] Studies MDT3-002 and -003: Total WOMAC Pain Subscale score > 150 mm at baseline; Study MDT3-005: Pain intensity ≥ 4 on an 11-point Pain Intensity-Numerical Rating Scale (PI-NRS)

over the maintenance phase, and the 24-hour Pain Score at endpoint. (Refer to the review by Dr. Jin Chen for details regarding other secondary endpoints.)

Study MDT3-005

Study MDT3-005 was submitted under a request for Special Protocol Assessment (SPA) (June 8, 2004) and as an effort to improve participant retention in and efficacy results for Tramadol OAD. Using an initial open-label phase during which patients were titrated to a tolerable and efficacious dose of Tramadol OAD (100 – 400 mg) over 2 weeks, the study enriched for a sample of patients that could tolerate the drug. Those patients who were able to achieve an optimal dose were tapered over a week, and then underwent drug washout over an additional week. Patients were then randomized to Tramadol OAD or placebo if they had a pain intensity score of at least 4 (on an 11-point numerical scale) at the end of the washout, and had not taken any prohibited analgesics during the open-label phase. The double-blind, placebo-controlled phase of the study comprised a 2-week titration phase followed by 12 weeks of maintenance at the patients' optimal dose. No chronic medication was allowed during the maintenance phase. However, patients were permitted to treat acute pain using short-acting analgesics such as acetaminophen for no more than 3 consecutive days. Patients were required to discontinue the short-term analgesic at least 3 days before a study visit.

Patients in Study MDT3-005 participated in 4 site visits and 2 telephone calls during the maintenance phase. The telephone calls were placed weekly during the 2-week titration, and patients were seen on-site every 3 weeks. They recorded their pain and function at the Week 2 titration visit, and at each site visit using the PI-NRS and WOMAC function subscale, respectively. Patients also provided a global rating of change.

The primary efficacy endpoint for this trial was the mean pain intensity score at the end of the study (week 12). Secondary endpoints included the mean WOMAC Pain and Physical Function scores at study end, and the Patient Global Impression of Change at study end. (Refer to the review by Dr. Jin Chen for details regarding other secondary endpoints.)

Following review of the initial SPA protocol, DAAODP found that the general study design was acceptable. DAAODP required that the applicant provide details on the statistical analysis plan, including the method for handling missing data. DAAODP recommended use of multiple approaches for a sensitivity analysis of the endpoint (for which the applicant proposed the LOCF method of imputation). DAAODP stated that the lack of information regarding the statistical analysis precluded final agreement and commitment under the SPA. Subsequent information describing the statistical analysis plan was considered to be acceptable, but because it was not submitted under a SPA there was no ultimately formal or binding agreement on the protocol between DAAODP and the applicant.

2.4. Outcome Measures and Analytic Approaches

The selected primary analgesia measures, namely the WOMAC Pain subscale and the PI-NRS are validated pain measures. The applicant's endpoints, the percent change in WOMAC Pain score and mean pain intensity score at endpoint, are acceptable; however it is important to note that their clinical relevance is dependent on the clinical context of the conducted trials.

The "group mean pain score" outcome is also of limited utility because it does not allow for prediction of an individual patient's response to treatment. Also, it is not easy to interpret since the mean score could be driven by a few patients having extreme pain values at endpoint (either high or low), or a lot of patients having pain scores that are only moderately different from baseline.

An analysis of treatment responders addresses these uncertainties. Treatment response is defined *a priori*. Then, the proportion of responders in the test group is compared to that in the comparator group. The applicant conducted responder analyses for studies MDT3-003 and -005, as additional evaluations of drug effect. In study MDT3-003, three levels of response were defined: 10%, 30%, and 50% improvement in WOMAC pain score from baseline. In study MDT3-005, 5 levels of response were identified: $\geq$ 1, 2, 3, 4, or 5 point change in PI-NRS score from baseline. Analyses of response were performed by using LOCF to impute missing data due to dropouts, and by defining dropouts as non-responders.

The Division recommends calculation of response rates in analgesia trials. A comparison of response across multiple levels of response (i.e. a cumulative (continuous) responder analysis) is encouraged, with definition of patients who dropout as non-responders. The Division therefore recalculated response rates in trials MDT3-003 and -005 using its preferred methods.

Another concern regarding the applicant's efficacy evaluation was the method used to handle data missing data. In analgesia trials, data are missing data either due to skipped pain records, or due to patient discontinuation from the trial. Patients may discontinue due to intolerable side effects, even though there has been an improvement in their pain. In such cases, the Division does not consider the medication to have been efficacious. This is because, for a subjective outcome such as pain, a good analgesic is one that reduces pain at a dose that is tolerable to the patient. Therefore, the Division is strongly in favor of conservative imputation methods that impute "bad" scores to patients who have poor outcomes. Baseline Observation Carried Forward (BOCF) is one such method. Last Observation Carried Forward (LOCF) is not recommended, because it can assign "good" scores to patients who drop out even though they may have discontinued due to a negative effect of drug.

Consequently, the Division recommended that the applicant conduct analyses of the primary efficacy outcome using more conservative imputation strategies than the protocol-specified LOCF method.

2.5. RESULTS

The results of the three efficacy trials, as documented in the reviews by Dr. Chen and Dr. Kim, are briefly summarized below. Only key efficacy outcomes are presented. See the primary reviews for details regarding other efficacy analyses

2.5.1. STUDY MDT3-005

"A two-arm study comparing the analgesic efficacy and safety of Tramadol Contramid OAD versus placebo for the treatment of pain due to osteoarthritis."

This was a randomized, double-blind, placebo-controlled, parallel group, multinational study. The trial comprised an initial open-label phase which enriched for patients who experienced both an efficacious and tolerable (i.e. optimal) tramadol dose. Patients underwent drug washout followed by randomization to Tramadol OAD or placebo. In the double-blind phase, patients were titrated to their optimal dose over two weeks, and then maintained on that dose for 12 weeks.

Demographics and Disposition

Altogether, 1028 patients entered the open-label phase. There was no remarkable difference in demographics between the Tramadol OAD and placebo groups. Patients were aged 63 years, on average, were predominantly female (63%) and Caucasian (87%). The mean pain intensity score (measured on the PI-NRS) was 7.2.

Patient disposition is illustrated in the table below (taken from Dr. Chen's review). The table shows that 35% of the 1028 eligible patients dropped out during the open-label phase of the trial, mostly due to adverse events/intolerability. There were 646 patients who entered the double-blind phase, and these subjects demonstrated a somewhat lower dropout rate (25%), presumably because most patients were those who could tolerate tramadol treatment. Nevertheless, dropout due to adverse events (AEs) was still higher for the Tramadol OAD group (42%) than the placebo group (22%)

During the double-blind phase, over 25% of the reasons for patient discontinuation are "patient request" or "investigator initiated." Dr. Chen reviewed the CRFs for a sample of patients who discontinued for these reasons and found that the documented reason for discontinuation was consistent with that listed in the discontinuation dataset.

Reviewer's Table 2: Patient Disposition – MDT3-005

Disposition status	Tramadol OAD	Placebo	Total
Open-label Phase			
Enrolled to OL	1028	0	1028
Dropout, n(%)	360 (35%)	0	360 (35%)
Reasons for dropout			
AE	225 (22%)		225 (22%)
Lack of efficacy	28 (2.7%)		28 (2.7%)
Patient request	48 (4.7%)		48 (4.7%)
Protocol Deviation	47 (4.6%)		47 (4.6%)
Lost to F/U	12 (1.2%		12 (1.2%)
Double-blind Phase			
Randomized†	432	214	646
Overall dropout, n(%)	106 (25%)	49 (23%)	155 (24%)
Titration dropout, n(%)	37 (8.6%)	18 (8.4%)	55 (8.5%)
Maintenance dropout, n (%)‡	69 (17%)	31 (16%)	100 (24%)
Reason for dropout			
Adverse event	44 (41.5%)	11 (22.4%)	55 (35.5%)
Lack of efficacy	36 (34.0%)	24 (49.0%)	60 (38.7%)
Patient request	23 (21.7%)	6 (12.2%)	29 (18.7%)
Investigator initiated	4 (3.8%)	7 (14.3%)	11 (7.1&)
Administrative	1 (0.9%)	3 (6.1%)	4 (2.6%)

† A total of 646 patients who completed the Open-label treatment phase entered to the Double-blind phase by randomization at ratio of 2:1 to Tramadol OAD and Placebo groups.
‡ % of patients who completed the Titration period of the Double-blind phase

Efficacy results

(a) Primary efficacy outcome

The primary efficacy outcome was the change in group mean pain intensity score from baseline to week 12. Baseline was defined as the end of the washout period of the open-label phase.

Using LOCF for data imputation, the applicant found that the absolute change in mean pain intensity score for the Tramadol OAD group (2.9) was statistically greater than that for placebo (2.4) (absolute difference of 0.48, p = 0.0157).

However, upon reanalysis using BOCF imputation for missing data, there was no statistically significant difference between the groups with respect to the absolute mean change in pain intensity from baseline

Endpoint	Tramadol OAD	Placebo	Difference	p-value
LOCF imputation				
Absolute change in mean pain intensity from baseline to wk 12	2.4 ± 2.4	2.9 ± 2.5	- 0.48	0.0157
Percent change in mean pain intensity from baseline to wk 12	-40.3%	-33.3	7.3%	
BOCF imputation				
Absolute change in mean pain intensity from baseline to wk 12	4.8 ± 2.6	25.0 ± 2.5	- 0.25	0.2135

Dr. Chen also calculated the percent change from baseline in pain intensity. This was 40.3% for the Tramadol OAD group and 33.3% for the placebo group. The difference in percent improvement in pain intensity was numerically small (7.3%) and of unclear clinical relevance.

(b) Secondary efficacy outcomes

Responder analysis

The applicant conducted a responder analysis using 5 definitions of treatment response: ≥ 1, 2, 3, 4, or 5 point change in pain intensity (as measured on the PI-NRS) from baseline to study end. Results of the analysis in which dropouts were defined as non-responders are shown below, and are taken from Dr. Chen's review:

Reviewer's Table 7d. Responder Analysis, Defining Dropouts as Non-responders
(Data were extracted from the applicant's Table 11.4.1.1.3.1-1 and Table 14.2-10)

PI-NRS Change (Point)*	Placebo, n=214		Tramadol OAD, n=431		Difference (Tramadol – Placebo)	Chi-Sq p-value
	Evaluable Subject†	Responder N (%)	Evaluable Subject†	Responder N (%)		
≥ 1	211	176 (83.4%)	428	380 (88.8%)	5.4%	0.057
≥ 2	211	163 (77.3%)	428	354 (82.7%)	5.4%	0.099
≥ 3	211	133 (63.0%)	428	309 (72.2%)	9.2%	0.018
≥ 4	211	96 (45.5%)	427	242 (56.7%)	11.2%	0.008
≥ 5	203	59 (29.1%)	406	176 (43.3%)	14.2%	0.001

* Pain intensity-numerical Rating Score (PI-NRS) change from baseline to Week 12; the dropouts were defined as "non-responder".

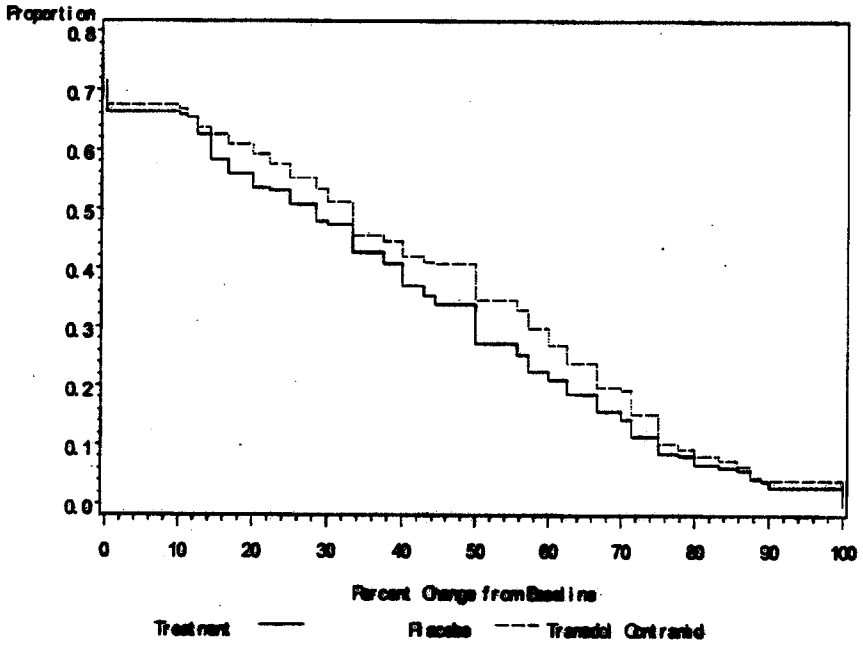
† Only patients who had at least one post-baseline value and whose baseline PI-NRS was not less than the response criterion (The applicant's Amendment 13 dated June 23, 2006 in response to the Division's request)

The table shows that, using a definition of treatment response, "≥ 2 point change from baseline," the Tramadol OAD group had numerically more treatment responders than the placebo group (83% vs. 77%). However, the difference in response rates between the groups was both numerically small and statistically non-significant (p = 0.099).

At higher cut-offs for treatment response (i.e. ≥ 3, 4, and 5), the applicant found that Tramadol OAD had statistically significantly more treatment responders than the placebo group. However, these results should be interpreted with caution for several reasons. First, the numerical differences are not considerably large. Second, the statistical analysis plan called for LOCF imputation for any missing data (from treatment responders). Finally, the applicant stated because there was no adjust for multiplicity that all other tests were to be interpreted on a descriptive level.

Dr. Yongman Kim, the statistics reviewer, performed a continuous responder analysis of the pain intensity data, defining "response" as a percent change from baseline, and using multiple definitions of response. Dropouts were considered non-responders. Dr Kim found that although the responder curves for the Tramadol OAD group separated from placebo, the separation was not statistically significant (p = 0.3466)

Reviewer's Figure 3: Continuous Responder Analysis: Study MDT3-005



Percent change in WOMAC Physical Function score

The applicant calculated (using LOCF imputation) that the percentage of improvement in WOMAC function score was greater for the Tramadol OAD group than the placebo group (35% vs. 29% improvement from baseline). This difference did not reach statistical significance.

Patient Global Impression of Change
At the end of the study, slightly more Tramadol OAD patients (54%) rated themselves as "much improved" or "very much improved" than did placebo patients (46%).

Efficacy conclusions – Study MDT3-005
Based on the Division's preferred analyses, the study does not provide evidence of efficacy of Tramadol OAD (100-400 mg) as treatment of pain due to osteoarthritis.

2.5.2. STUDY MDT3-003

"A four-arm study comparing the analgesic efficacy of Tramadol OAD 100, 200, 300 mg versus placebo for the treatment of pain due to osteoarthritis of the knee."

This was a randomized, double-blind, placebo-controlled, parallel-group trial in which 552 patients were randomized to one of three doses of Tramadol OAD, or to placebo. Dosing began with a 6-day titration to the target dose, followed by 12 weeks of unchanged treatment at that dose.

Demographics and disposition
Apart from age, there were no remarkable differences among the four groups with respect to gender (62% female), ethnicity (72% Caucasian), and mean body mass index (BMI) (31). The 300-mg Tramadol OAD arm had slightly fewer patients aged ≥ 65 years (33%) compared to the other Tramadol groups (46% each) and the placebo group (40%). The mean WOMAC pain score at baseline was also similar across groups (300 – 310).

Patient disposition is shown in the table below, taken from Dr. Chen's review.

Reviewer's Table 2. Patient Disposition

Disposition status	Tramadol OAD Dose Group				Placebo	Overall
	100 mg	200 mg	300 mg	All Doses		
Enrolled & Randomized	106	111	108	325	227	552
Dropout, n (%)	44 (42%)	46 (41%)	58 (54%)	148 (46%)	93 (41%)	241 (44%)
Adverse event	13 (12%)	20 (18%)	35 (32%)	68 (21%)	18 (8%)	86 (16%)
Lack of efficacy	21 (20%)	11 (10%)	11 (10%)	43 (13%)	47 (21%)	90 (16%)
Lost to follow-up	0	2 (2%)	3 (3%)	5 (2%)	10 (4%)	15 (3%)
Other*	10 (9%)	13 (12%)	9 (8%)	32 (10%)	18 (8%)	50 (9%)

* Other includes dropouts due to "patient request" and "investigator's initiation".

The overall dropout rate was comparable across the placebo, 100-mg, and 200-mg treatment arms (~41%) but was higher in the 300-mg Tramadol OAD arm (54%). There was a dose-related increase in discontinuations due to adverse events. Persons in the

placebo and 100-mg groups were more likely to discontinue the trial due to lack of efficacy.

About 10% of patients were coded as discontinuing treatment due to "patient request" or "investigator initiation."

Efficacy results

a) Primary efficacy outcome

The primary efficacy outcome was the percent change in WOMAC pain score from baseline to endpoint.

The applicant found that, using LOCF for imputation of missing data, only the 300-mg Tramadol OAD group had a statistically greater mean percent improvement in pain intensity compared to placebo (42% vs. 32%, p = 0.02). However, upon imputation using BOCF, none of the Tramadol OAD groups showed a difference from placebo with respect to mean percent pain improvement from baseline.

Dr. Kim's analysis using BOCF imputation also found that none of the Tramadol OAD groups showed a statistically significantly greater percentage improvement in WOMAC pain score compared to placebo (see table below).

Endpoint	Tramadol OAD			PBO
	100mg	200mg	300mg	
LOCF imputation				
Absolute change in mean pain intensity from baseline to wk 12	122.3	123.4	143.3	99.5
% change in mean pain intensity from baseline to wk 12	41.6%	42.8%	46.0%	32.3%
Difference in % change (Tramadol OAD vs. PBO); p-value	9.5 0.0933	10.8 0.0504	13.4 0.0162	-
BOCF imputation - Applicant				
Difference in % change (Tramadol OAD vs. PBO); p-value	6.44% 0.1910	2.35% 0.6292	0.00% 0.9997	-
BOCF imputation - FDA				
% change in mean pain intensity from baseline to wk 12	36%	32%	31%	29%
Difference in % change (Tramadol OAD vs. PBO); p-value*	7% 0.1682	3% 0.4843	2% 0.7064	-

* P-value adjusted for multiplicity

b) Secondary efficacy outcomes

Responder analysis
The applicant defined treatment response as 10%, 30%, or 50% improvement in pain intensity (as measured using the WOMAC pain subscale), and compared the frequency of responders across the treatment arms.

Per Dr. Chen's review:

> For the response definition of 30% improvement in pain, the 200 mg or 300 mg Tramadol OAD groups had a higher response rate (65% each) compared to placebo (50%); the differences (p=0.0095 and 0.0104, respectively) were statistically significant after adjustment for multiplicity ($p < 0.0167$).
>
> Using a response definition of 50% pain improvement, only the 300 mg Tramadol OAD group had a statistically significantly higher response rate than placebo (54% vs. 40%); the difference was statistically significant before (p= 0.0225) but not after multiplicity adjustment.
>
> The 100 mg Tramadol OAD group showed no difference from placebo at each of the levels of treatment response.

Reviewer's Table 10a. Applicant's Responder Analysis on WOMAC Pain Score
(Adapted from the applicant's Table 11.4.1.1.3-1)

Response	Comparison of the % of responders				P-value[1]
10% Improvement	100 mg:	70%	vs.	Placebo: 65%	0.3708
	200 mg:	80%	vs.	Placebo: 65%	0.0035
	300 mg:	74%	vs.	Placebo: 65%	0.0891
30% Improvement	100 mg:	58%	vs.	Placebo: 50%	0.2236
	200 mg:	65%	vs.	Placebo: 50%	0.0095
	300 mg:	65%	vs.	Placebo: 50%	0.0104
50% Improvement	100 mg:	50%	vs.	Placebo: 40%	0.1273
	200 mg:	51%	vs.	Placebo: 40%	0.0835
	300 mg:	54%	vs.	Placebo: 40%	0.0225

Source: Statistical tables: 5.1 (Post-hoc analyses after unblinding, June 14, 2005).
[1]Kruskal-Wallis test between respective treatment and Placebo.

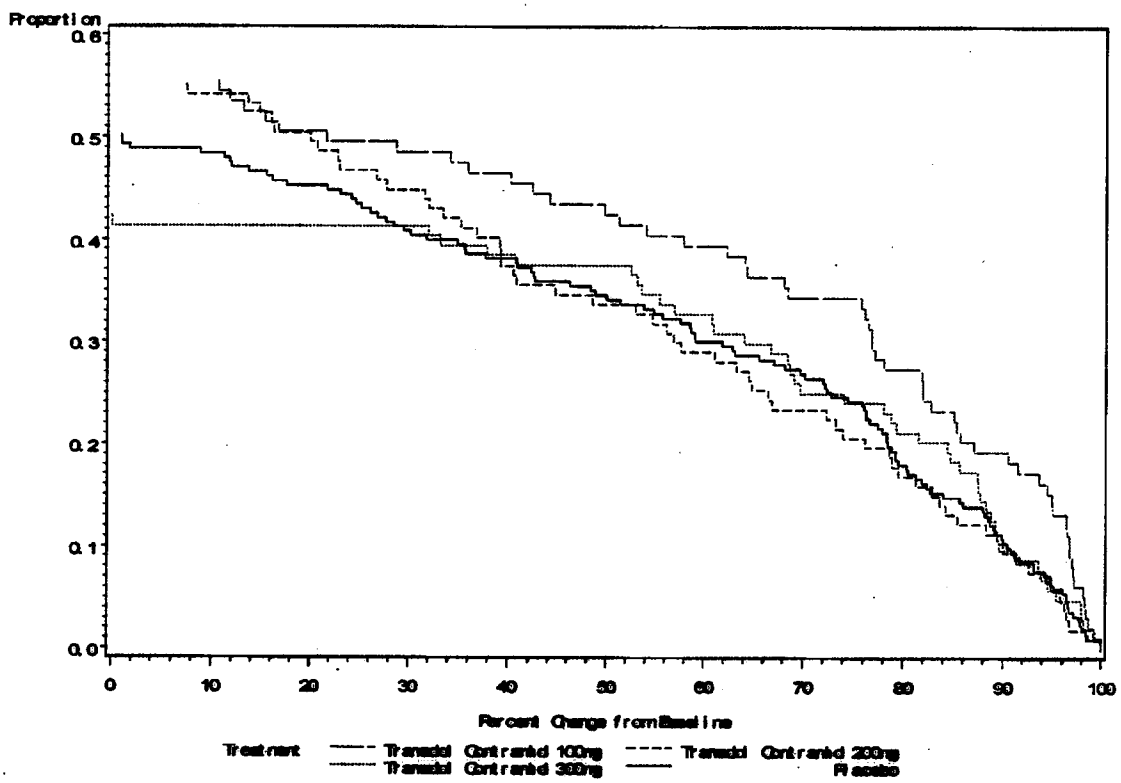
However, the applicant utilized LOCF imputation for its responder analysis which the Division does not consider appropriate.

Dr. Kim reanalyzed the data using a continuous responder analysis in which dropouts were defined as non-responders (see the figure below). This analysis showed no separation of the Tramadol OAD 200-mg and 300-mg curves from the placebo curve.

The curve for the 100-mg group did separate from placebo, but this separation was not statistically significant.

Although, similar to the applicant, Dr. Kim uses a "percent change in WOMAC Pain score" analysis, Dr. Kim's evaluation is of greater utility because it demonstrates the effect of treatment over a wide range of treatment responses, and compares entire curves, not just values at selected points along the curve (as done by the applicant).

Reviewer's Figure 2: Continuous Responder Analysis: Study MDT3-003



Percent change in WOMAC Physical function score
Based on an LOCF imputation for missing data, the percent improvement in WOMAC Physical Function, from baseline to week 12, was 31% for placebo-treated patients, 42% for both the Tramadol OAD 100 mg and 200 mg patients, and 39% for the Tramadol OAD 300 mg group. The values for all the Tramadol OAD groups were statistically significantly different from placebo.

Patient global rating of pain relief
Using the LOCF imputation method, the applicant found that, at the end of the study, the frequency of patients rating overall pain relief as "effective" or "very effective" was statistically significantly higher in the Tramadol OAD 200 mg (71%) and 300 mg (78%) groups compared to placebo (60%) ($p=0.002$ and <0.001, respectively). There was no statistically significant difference between the Tramadol OAD 100 mg group (68%) and placebo.

However, re-analysis of the data by Dr. Chen using BOCF imputation for missing data showed no statistically significant differences in the overall pain relief between any of the Tramadol OAD groups and placebo.

Efficacy conclusions – Study MDT3-003
Based on the reviewers' analyses, none of the doses of Tramadol OAD tested (100, 200, and 300 mg) was shown to be superior to placebo in the treatment of pain due to osteoarthritis.

2.5.3. STUDY MDT3-002

"A four-arm study comparing the analgesic efficacy of Tramadol OAD 100, 200, 300 mg versus placebo for the treatment of pain due to osteoarthritis of the knee."

This study was a duplicate of the previously discussed trial, MDT3-003.

Since this trial was considered a failed study by the applicant, I will discuss the results only briefly.

Disposition and Demographics
A total of 565 patients were randomized to study treatment with Tramadol OAD and placebo. There were no remarkable differences in demographic characteristics. The mean WOMAC pain score at baseline was also similar across groups (300 – 310).

Overall, the dropout rate was 43%, and showed an association with increasing dose. More patients in the Tramadol OAD group discontinued due to adverse events. Lack of efficacy was the predominant reason for dropout in the placebo group. Subject disposition is tabulated below (table taken from Dr. Chen's review):

Reviewer's Table 1. Patient Disposition

Disposition status	Tramadol OAD Dose Group				Placebo	Total
	100 mg	200 mg	300 mg	All Doses		
Enrolled & Randomized	110	113	115	338	227	565
Dropout, n (%)	46 (42%)	53 (47%)	61 (53%)	160 (47%)	83 (37%)	243 (43%)
Adverse event	22 (20%)	19 (17%)	41 (36%)	82 (24%)	10 (4%)	92 (16%)
Lack of efficacy	17 (15%)	15 (13%)	13 (11%)	45 (13%)	52 (23%)	97 (17%)
Other*	7 (6%)	19 (17%)	7 (6%)	33 (10%)	20 (9%)	53 (9%)

* Other includes dropouts due to "patient request" and "investigator's initiation".

Efficacy results

(a) Primary efficacy outcome

The primary efficacy outcome was the percent change in WOMAC pain score from baseline to the end of the trial. After imputing missing data using LOCF, the applicant found that there was no statistically significant difference in the mean percent change in pain intensity between any of the Tramadol OAD groups and placebo.

Endpoint	Tramadol OAD			PBO
	100mg	200mg	300mg	
LOCF imputation				
Absolute change in mean WOMAC pain from baseline to wk 12	107.6	117.4	129.3	112.3
% change in mean WOMAC pain from baseline to wk 12	36%	37%	41%	38%
Difference in % change (Tramadol OAD vs. PBO); p-value	-2% 0.72	-1.5% 0.77	2.9 0.56	-

(b) Secondary efficacy outcome

Percent improvement in WOMAC Physical Function Score:

The percent improvement in WOMAC Physical Function from baseline to week 12 was 34% in the placebo group, and ranged from 32-37% in the Tramadol OAD groups (100, 200 and 300 mg). There were no statistically significant differences among the groups.

24-hour VAS Pain Questionnaire:

There was no statistically significant difference in pain ratings between any of the Tramadol OAD and placebo groups.

Patient Global Rating of Pain Relief
The Tramadol OAD 300 mg groups (but not the 100 mg or 200 mg groups) showed a statistically significant difference in the overall rating of pain relief ("very effective" or "effective") compared to placebo.

Efficacy conclusions – Study MDT3-002
This trial failed to show that Tramadol OAD (100, 200, or 300 mg) was superior to placebo in treating pain due to osteoarthritis of the knee.

3. SAFETY

3.1. DATA SOURCES

The primary sources of safety data came from the applicant's six Phase 3 trials: 4 efficacy trials and 2 open-label studies. The efficacy trials have already been described above. The open-label safety studies are summarized below:

Study No.	Study Type	Treatment	Duration	Study Location
MDT3-001-E1-A1	Open-label safety follow-up in OA patients	Tramadol Contramid OAD 200, 300 or 400 mg	9-month extension of Study MDT3-001-E1	Non-US
MDT3-004	Open-label long-term safety study	Tramadol Contramid OAD 300 mg	6 & 12 months *	Non-US

* Patients who tolerated the first 6 months of treatment were permitted to continue on study drug for another 6 months.

Data from the Phase 1 trials were used primarily to assess total exposure, and effects of doses larger than those recommended in the proposed product label.

3.2. DATA REVIEW ISSUES

Although the applicant submitted an integrated summary of safety (ISS), a dataset for the ISS was not provided. Because variables for similar datasets (e.g. adverse events) were inconsistent across individual trials, the primary reviewer was unable to integrate the data, or to perform manipulations of the safety data to verify the accuracy of the applicant's ISS tables. Instead, the reviewer used summaries of individual trials as well as datasets for individual trials to attempt reconcile any major differences between the ISS and the individual summary reports.

The evaluation of safety was performed based on study type, specifically short-term controlled trials versus long term open-label trials.

3.3. EXPOSURE

Altogether, 3269 subjects were enrolled in the Phase 1 and Phase 3 clinical trials. There were 301 healthy subjects treated with Tramadol OAD in Phase 1 studies, and 1939 patients with osteoarthritis treated in the Phase 3 trials. A total of 844 osteoarthritis patients completed 12 weeks of Tramadol OAD treatment, 493 patients completed at least 6 months' of Tramadol OAD treatment, and 243 completed at least 12 months.

Total subject exposure is shown below (tables taken from Dr. Chen's review):

Reviewer's Table 7r-1. Overall patient exposure - Phase 1 and Phase 3 trials
(Extracted from individual trial reviews in appendix)

Study Type	Total enrollee	Placebo	Tramadol OAD				
			100 mg	200 mg	300 mg	400 mg	Total
Phase I (PK) Trials (single dose)	301		50	262	86	48	301*
Placebo-controlled Trial	**2145**	**668**	**216**	**330**	**548**		**1095**
MDT3-002	565	227	110	113	115		338
MDT3-003	552	227	106	111	108		325
MDT3-005	1028	214		106	325		432†
Active-controlled Trial							
MDT3-001-E1	431	(216)‡	33	95	53	21	215

* All healthy subjects; some subjects were treated with more than one dose levels (cross-over design).
† Including patients whose optimum dose was not available after Titration (dropouts). In Study MDT3-005, a total of 1028 patients were enrolled and entered the open-label treatment phase; 646 patients were then randomized to placebo (n=214) and Tramadol OAD (n=432) groups; and 382 patients who received Tramadol OAD treatment during the open-label phase but were not randomized to the double-blind phase.
‡ The patients in the active-controlled trial were treated with active comparator Tramadol BID (Topologic LP).

Study/ Total duration	# Patients				
	100 mg	200 mg	300 mg	400 mg	Total
12 weeks					
MDT3-002	64	60	54	-	144
MDT3-003	62	65	50	-	134
MDT3-005	-	73	255	-	165
MDT3-001-E1	25	82	41	13	161
≥ 6 Months		129	340	24	493
MDT3-001-E1-A1	238	129	65	24	218
MDT3-004	392		275		275
12 Months		43	192	8	243
MDT3-001-E1-A1		43	24	8	75
MDT3-004			168		168

The total number exposed, as well as the number of exposures at the highest to-be-marketed dose (300 mg) met ICH requirements and were adequate to characterize the safety profile of Tramadol OAD.

3.4. DEATHS

Three deaths were reported during the development program, all of which occurred in the Phase 3 trials. Two deaths were in patients treated with Tramadol OAD (MDT3-002 and MDT3-001-E1), and one was in a placebo-treated patient (MDT3-003). The causes of death were acute MI (n = 2; Tramadol OAD 100 mg and placebo, MDT3-002), ischemic stroke (Tramadol OAD 400 mg, MDT3-001-E1).

The applicant did not consider any of the deaths to be related to treatment with Tramadol OAD. Both of the cases of myocardial infarction occurred in patients with risk factors for cardiac disease. However, because the death in the patient treated with Tramadol OAD was preceded by agitation, and due to the lack of data regarding confirmatory tests for infarction, Dr. Chen theorized that the patient's agitation could have been due to serotonin syndrome and could have led to the infarction.

3.5. DISCONTINUATIONS

Overall, in the placebo controlled trials, the incidence of patient dropout was slightly greater for patients treated with Tramadol OAD (38%) than for placebo-treated patients (34%). Among Tramadol OAD patients, dropout was most frequent in the trials in which patients were randomized to a specific tramadol dose (trials MDT3-002 and 003. Dropout rate was ~ 46%) compared to the trial which enriched for patients who could tolerate tramadol and in which patients self-titrated to an efficacious dose (study MDT3-005; dropout rate was ~ 23%). The frequency of discontinuations increased with increasing Tramadol OAD dose.

In the open-label studies, the drop-out rates were 11% for the extension study of the active-controlled trial (study MDT3-001-E1-A1) and 33% in the long-term study evaluating the safety of 300 mg Tramadol OAD (study MDT3-004).

Across all trials, the reasons for patient discontinuation varied by their treatment assignment. Placebo-treated patients were more likely to discontinue due to 'treatment failure' (i.e. lack of efficacy), whereas the majority Tramadol OAD patients discontinued due to an adverse event.

The frequency of dropouts (by study type and treatment assignment) is shown in the table below.

Primary Reviewer's Table 7d. Overall dropout rates (%) during the Phase 3 trials
(Summarized from individual trial reviews included in the Appendix)

Placebo-controlled and Active-controlled Trials
(Dropout rate, % of enrollee)

Study	Randomized Patients		Total Dropouts		Adverse Event		Treatment Failure		Other*	
	Tramadol OAD (N)	Placebo (N)	Tramadol OAD (%)	Placebo (%)	Tramadol OAD (%)	Placebo (%)	Tramadol OAD (%)	Placebo (%)	Tramadol OAD (N)	Placebo (%)
MDT3-005	432	214	24.5	22.9	10.2	5.1	8.3	11.2	6.5	7.5
MDT3-003†	325	227	45.5	41.0	20.9	7.9	13.2	20.7	11.4	12.3
MDT3-002†	338	227	47.3	36.6	24.3	4.4	13.3	22.9	9.8	9.3
Total	1095	668	37.8	33.7	17.7	5.8	11.3	18.4	8.9	9.7
MDT3-001-E1‡	215	(216)	20.5	(20.8)	9.3	(10.2)	0.9	(0.9)	10.2	(9.7)

* Others include patient request, investigators' initiation and administrative reason
† Data in the Tramadol OAD group were pooled from 3 dose groups (100, 200 and 300 mg)
‡ The active-controlled trial, the data in parenthesis under Placebo are from Tramadol BID (twice a day) not placebo.

Open-label Long-term Trials
(Dropout rate, % of enrollee)

Study	Total Enrollee	Total Dropout	AE-Dropout	Efficacy-Dropout	Other* Dropout
MDT3-001-E1-A1	238	11.3	2.9	0.4	7.9
MDT3-004	392	32.9	24.7	1.3	6.9
Total	630	24.8	16.5	0.9	7.3

3.5.1. Discontinuations due to Adverse Events

Across the placebo-controlled controlled trials, the incidence of discontinuation due to an AE was variable. In studies MDT3-003 and 002, 21% and 24% of patients (respectively) stopped Tramadol treatment because of an AE, compared to 4% and 8% (respectively) of placebo patients. However, in MDT3-005, the discontinuation rate was 10% for the Tramadol OAD group and 5% for the placebo group. The lower dropout rate in this

study is likely due to the fact that the study enriched for patients who were initially able to achieve a tolerable dose of Tramadol OAD.

The types of AEs leading to discontinuation from Tramadol OAD treatment were typical of tramadol and of opioids in general: nausea, vomiting, constipation, dizziness/vertigo and headache. Adverse events leading to dropout were similar in both the titration and stable-dose phases of the controlled trials.

Table 7e. **Dropouts due to most common AEs during the randomized controlled trials**
(Applicant's Table 2.7.4.2.1.4-1; dropouts from Placebo were not presented)

	Tramadol Contramid® OAD			
	12-Week Placebo-Controlled Studies[1]			12-Week Active-Controlled Study[2]
Preferred term	MDT3-002 N=338	MDT3-003 N=325	MDT3-005[3] N=1023	MDT3-001/E1 N=215
Any TEAE	48 (14.2%)	44 (13.5%)	228 (22.3%)	11 (5.1%)
Constipation	2 (0.6%)	7 (2.2%)	27 (2.6%)	2 (0.9%)
Dizziness / vertigo	21 (6.2%)	15 (4.6%)	61 (6.0%)	1 (0.5%)
Nausea	24 (7.1%)	17 (5.2%)	101 (9.9%)	5 (2.3%)
Somnolence	5 (1.5%)	8 (2.5%)	33 (3.2%)	3 (1.4%)
Vomiting	12 (3.6%)	13 (4.0%)	49 (4.8%)	1 (0.5%)
Headache	6 (1.8%)	3 (0.9%)	24 (2.3%)	1 (0.5%)

[1] Total of Tramadol Contramid® OAD treatment groups (100 mg, 200 mg and 300 mg) from MDT3-002 MDT3-003 and MDT3-005 (placebo not included).

[2] Total of Tramadol Contramid® OAD treatment groups (100 mg, 200 mg, 300 mg and 400 mg) from MDT3-001/E1 (Tramadol BID group excluded)

[3] During Open-label phase.

Source: Statistical Tables 5.1.1, 5.2.1, 5.3.1, 5.4.1 (30MAY2006).

3.6. Serious Adverse Events (SAEs)

Dr. Chen counted a total of 47 SAEs that occurred in 43 patients participating in the Phase 3 trials. The frequency of SAEs in the placebo-controlled trials[2] was 1.7% for the Tramadol OAD patients and 0.9% for the placebo group. The frequency of SAEs did not show a clear dose-response relationship, with 1.9% of the 100-mg group, 1% of the 200-mg group, and 2.4% of the 300-mg group reporting an SAE.

SAEs occurred sporadically by System Organ Class (SOC), with a slightly higher incidence in the gastrointestinal, nervous, and cardiovascular systems. SAEs by preferred term included gastritis, diverticulitis, fecal impaction, angina, chest pain, hepatitis, renal impairment, convulsion, and syncope. In most cases, there was only a single occurrence of each type of SAE, making it difficult to evaluate for trends in serious adverse effects.

The sole convulsion event is described below:

[2] Studies MDT3-002, -003, and -005.

Patient 55-025/Study MDT3-005
This was a 73 yo male patient with a history of hypertension and evidence of "chronic ischemic changes of the brain." Concomitant medications were aspirin, clopidogrel (Plavix), celecoxib (Celebrex), fexofenadine (Allegra), and galantamine (Reminyl). The patient's final Tramadol OAD dose during the open-label run-in period was 300 mg/d. The patient completed the washout out period but discontinued due to family circumstances. Seventeen days after the last dose of study drug, the patient experienced a grand mal seizure lasting 2 minutes. Upon admission to the ER, the patient complained of chest pain. Hospital evaluation was significant for elevated blood pressure, CK, CK-MB, and myoglobin levels, with normal electrolytes, troponin, and ECG. CT imaging of the brain showed small densities that were of "questionable" significance. An MRI showed that the changes were not due to bleeding. The patient had had no further seizures at last follow-up.

The close temporal relationship of the event to study treatment suggests that the seizure was due to Tramadol OAD. However the patient had potential risk factors for seizure including hypertension with ischemic changes, and use of a drug that has been associated with seizures (galantamine). In addition, based on the half-life of Tramadol OAD, the drug had probably washed out within a week after the last dose. Nevertheless, the possibility of a relationship to study drug still remains.

With respect to the other serious adverse events, the majority of patients who had an SAE had risk-factors for the events, and potential causality of study drug was based solely on the temporal relationship of the SAE with use of study medication.

None of the reported SAEs was inconsistent with the adverse event profile described in the product label for Ultram ER.

3.7. Other Significant Adverse Events

Tramadol is an opioid analgesic therefore, similar to other opioids, overdose with tramadol can cause respiratory depression, coma, and death. As a weak inhibitor of noreipnephrine and serotonin reuptake, tramadol may interact with SSRIs, SSNIs or MOAIs to cause seizure and serotonin syndrome. Finally, as an modified-release formulation, there is the potential that Tramadol OAD, in the presence of alcohol or other solution, may undergo compromise of its modified-release mechanism, leading to immediate availability of the total tramadol dose (i.e. dose dumping).

In the NDA, there were no reports of acute overdose, dose-dumping or typical serotonin syndrome. The report of seizure is described in the section above.

3.8. Common Adverse Events

In the placebo-controlled trials, 63% of Tramadol OAD patients had at least one adverse event, compared to 51% of placebo patients. The most common AEs (> 5% of patients), reported more frequently in the Tramadol OAD group than the placebo group, were nausea (17% vs. 6%), constipation (13% vs. 4%), dizziness (11% vs. 3%), somnolence (6% vs. 2%), vomiting (7% vs. 1%), and pruritus (6% vs. 1%) (see table below). These AEs are similar to those reported for Ultram ER.

Reviewer's Table 7j. Incidence of Common AEs (Experienced by ≥ 1% of Patients) from Three Placebo-Controlled Trials and One Active-Controlled Trial
(Applicant's Table 2.7.4.7.1-19)

		Tramadol Contramid® OAD					
		12-Week Placebo-Controlled Studies				12-Week Active-Controlled Study[2]	All studies / All active doses[3]
Preferred Term	Placebo N=668	100 mg N=216	200 mg N=311	300 mg N=539	Overall Active[1] N=1095	N=215	N=1310
NAUSEA	39(5.8%)	29 (13.4%)	50(16.1%)	88(16.6%)	202(18.4%)	70 (32.6%)	272 (20.8%)
CONSTIPATION	27(4.0%)	21 (9.7%)	38(12.2%)	53(10.0%)	143(13.1%)	73 (34.0%)	216 (16.5%)
DIZZINESS	21(3.1%)	18 (8.3%)	31(10.0%)	59(11.1%)	119(10.9%)	51 (23.7%)	170 (13.0%)
SOMNOLENCE	13(1.9%)	12 (5.6%)	23(7.4%)	26(4.9%)	82(7.5%)	65 (30.2%)	147 (11.2%)
HEADACHE NOS	43(6.4%)	13 (6.0%)	18(5.8%)	26(4.9%)	64(5.8%)	27 (12.6%)	91 (6.9%)
VOMITING NOS	6(0.9%)	8 (3.7%)	19(6.1%)	36(6.8%)	71(6.5%)	18 (8.4%)	89 (6.8%)
PRURITUS NOS	7(1.0%)	11 (5.1%)	16(5.1%)	23(4.3%)	60(5.5%)	7 (3.3%)	67 (5.1%)
DRY MOUTH	8(1.2%)	7 (3.2%)	17(5.5%)	7(1.3%)	38(3.5%)	20 (9.3%)	58 (4.4%)
SWEATING INCREASED	6(0.9%)	1 (0.5%)	10(3.2%)	16(3.0%)	38(3.5%)	16 (7.4%)	54 (4.1%)
ANOREXIA	2(0.3%)	5 (2.3%)	4(1.3%)	11(2.1%)	27(2.5%)	16 (7.4%)	43 (3.3%)
FATIGUE	6(0.9%)	6 (2.8%)	10(3.2%)	9(1.7%)	29(2.6%)	9 (4.2%)	38 (2.9%)
WEAKNESS	1(0.1%)	3 (1.4%)	5(1.6%)	4(0.8%)	12(1.1%)	24 (11.2%)	36 (2.7%)
VERTIGO	3(0.4%)	3 (1.4%)	3(1.0%)	8(1.5%)	27(2.5%)	5 (2.3%)	32 (2.4%)
INSOMNIA	8(1.2%)	3 (1.4%)	9(2.9%)	11(2.1%)	25(2.3%)	6 (2.8%)	31 (2.4%)
ABDOMINAL PAIN UPPER	4(0.6%)	3 (1.4%)	4(1.3%)	9(1.7%)	18(1.6%)	9 (4.2%)	27 (2.1%)
DIARRHOEA NOS	20(3.0%)	6 (2.8%)	1(0.3%)	10(1.9%)	21(1.9%)	5 (2.3%)	26 (2.0%)
NASOPHARYNGITIS	18(2.7%)	4 (1.9%)	7(2.3%)	7(1.3%)	20(1.8%)	2 (0.9%)	22 (1.7%)
WEIGHT DECREASED	1(0.1%)	1 (0.5%)	5(1.6%)	11(2.1%)	20(1.8%)	2 (0.9%)	22 (1.7%)
ABDOMINAL PAIN NOS	7(1.0%)	2 (0.9%)	5(1.6%)	8(1.5%)	17(1.6%)	3 (1.4%)	20 (1.5%)
ARTHRALGIA	14(2.1%)	2 (0.9%)	3(1.0%)	8(1.5%)	15(1.4%)	3 (1.4%)	18 (1.4%)
PAIN EXACERBATED	16(2.4%)	6 (2.8%)	3(1.0%)	6(1.1%)	18(1.6%)	-	18 (1.4%)
DYSPEPSIA	7(1.0%)	3 (1.4%)	6(1.9%)	4(0.8%)	13(1.2%)	3 (1.4%)	16 (1.2%)
UPPER RESPIRATORY TRACT INFECTION NOS	17(2.5%)	3 (1.4%)	5(1.6%)	6(1.1%)	16(1.5%)	-	16 (1.2%)
HOT FLUSHES NOS	1(0.1%)	1 (0.5%)	3(1.0%)	7(1.3%)	12(1.1%)	2 (0.9%)	14 (1.1%)
ANXIETY NEC	1(0.1%)	1 (0.5%)	6(1.9%)	4(0.8%)	11(1.0%)	2 (0.9%)	13 (1.0%)
TREMOR	1(0.1%)	1 (0.5%)	3(1.0%)	6(1.1%)	11(1.0%)	2 (0.9%)	13 (1.0%)
HYPERTENSION NOS	4(0.6%)	1 (0.5%)	1(0.3%)	4(0.8%)	7(0.6%)	5 (2.3%)	12 (0.9%)
URINARY TRACT INFECTION NOS	10(1.5%)	2 (0.9%)	3(1.0%)	6(1.1%)	12(1.1%)	-	12 (0.9%)

3.9. LABORATORY DATA

Clinical laboratory tests (hematology, chemistry, and urinalysis) were generally performed at baseline and study end. A total of 106 laboratory abnormalities were reported by 68 patients in the six Phase 3 trials and are listed in the table that follows. The most common laboratory abnormalities were elevated sedimentation rate, abnormal blood glucose, increased GGT, increased blood cholesterol, and increased LDH.

Since the applicant did not stratify laboratory results by study type (controlled vs. open-label), a comparison of rates by treatment assignment (Tramadol OAD vs. placebo) was not possible.

Of the laboratory changes, elevated sedimentation rate is not unexpected in osteoarthritis and is associated with an inflammatory response. The other abnormalities are consistent with those observed in the target patient population (older patients with multiple medical conditions and on multiple medications).

3.10. VITAL SIGNS

Vital signs were monitored at each site visit. No remarkable changes in blood pressure, heart rate, respiratory rate, or body temperature were observed in patients treated with Tramadol OAD compared to placebo.

3.11. ECGs

ECG screening was not performed in any of the Phase 3 trials.

3.12. SAFETY UPDATE

Data from the 120-day Safety Update were included in the analysis of safety.

Reviewer's Table 7n. Laboratory abnormalities in reported across the Phase 3 trials
(Applicant's Table 2.7.4.3-1)

Abnormal Laboratory Values	Number of patients with Abnormal Lab Value
Sedimentation rate increased	16
Blood glucose increased / abnormal	13
GGT increased	10
Blood cholesterol increased / abnormal	5
Blood LDH increased	5
Blood uric acid increased	5
Haemoglobin decreased	4
RBC count decreased	4
Haematocrit decreased	3
Alanine aminotransferase increased	2
Aspartate aminotransferase increased	2
Blood urea increased	2
Liver function tests abnormal	2
Alanine aminotransferase decreased	1
Aspartate aminotransferase decreased	1
Blood amylase increased	1
Blood bilirubin increased	1
Blood calcium increased	1
Blood creatinine increased	1
Blood in stool	1
Blood potassium abnormal NOS	1
Blood urine present	1
CRP increased	1
Haematocrit increased	1
Haemoglobin increased	1
Hyperuricaemia	1
Leukocyturia and bacteriuria	1
Low density lipoprotein increased	1
Lymphocyte count decreased	1
Mean platelet volume decreased	1
Neutrophil count decreased	1
Platelet count decreased	1
Protein total decreased	1
RBC count increased	1
Red cell distribution width increased	1
White blood cell count increased	1

Source: Clinical Study Reports MDT3-002, MDT3-003, MDT3-001/E1, MDT3-004 and MDT3-001-E1-A1, Statistical Table 5.2.2.1. MDT3-005, Statistical Table 5.3.2.1.1.

3.13. DRUG ABUSE, WITHDRAWAL, AND OVERDOSE EXPERIENCE

No cases of Tramadol OAD overdose were reported in any of the Phase 3 trials. The highest tested dose in the Phase 1 and 3 clinical trials was 400 mg/day, and no remarkable AEs were noted that were considered related to study drug.

Tramadol OAD is marketed in Europe and in Mexico. As of March 13, 2006, no SAEs had been reported through the European pharmacovigilance program for Tramadol OAD.

The Office of Surveillance and Epidemiology (OSE, formerly Office of Drug Safety) has noted that tramadol has been marketed for approximately 11 years and has not, to date, required risk management tools beyond standard product labeling and post-marketing safety surveillance. Tramadol is not currently regulated as a controlled substance in the United States.

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4. CHEMISTRY, MANUFACTURING, AND CONTROL (CMC) ISSUES

The chemistry review team found the CMC portion of the application to be acceptable. Adequate CMC information for synthesis, purification, and controls of the drug substance and drug product were submitted. b(4) the chemistry review team considered the stability data to support an expiry of only 24 months.

One concern raised during the CMC review was the integrity of the tablet core layer during handling and compressio The applicant provided satisfactory information demonstrating thr b(4)

5. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICAL ISSUES

The clinical pharmacology review team found that the application adequately characterized the pharmacokinetic profile of Tramadol OAD.

Tramadol OAD has a median Tmax of 4 hours. The mean terminal half-life is between 6.5 and 7.5 hours. The AUC and Cmax of the tramadol increase proportionally with dose. Low concentrations were observed in the absorption phase (0-3 hours post-dose) and at the terminal phase (18-24 hours post-dose) when compared to dosing of Ultram

(immediate-release tramadol) every 6 hours. This translates into, for once-daily administered Tramadol OAD, a relative lack of 'coverage' over a 9-hour window extending from the late evening to the early morning. Food increases the Cmax by 67%, but does not alter the Tmax or the AUC considerably.

An *in vitro* evaluation showed that there is no potential for dose-dumping of Tramadol OAD in the presence of alcohol. In fact, the rate of tramadol release decreased in proportion to the alcohol concentration. The clinical pharmacology reviewer theorized that the decrease may be due to the insoluble component of the formulation in the presence of alcohol. Based on these data, an *in vivo* assessment of the effects of alcohol was not required.

The sponsor changed manufacturing sites during drug development, and all of the pivotal pharmacokinetic and clinical trials used tablets manufactured at the initial site. The sponsor conducted a bioequivalence study comparing tablets manufactured at both sites and found that the tablets differed with respect to Cmax (13% higher at the new site compared to the old), but not AUC (total exposure). The clinical pharmacology team recommends that any future clinical studies conducted to support the efficacy of Tramadol OAD use tablets manufactured at the new site.

> COMMENT: although the Cmax of the tablets manufactured at the new site is higher, the Cmax of the "old" tablets was approximately 20% lower than that of a corresponding total daily dose of Ultram (immediate release). Therefore, the Cmax for the new Tramadol OAD tablets may not necessarily be considerably greater than that of the reference drug.

6. NON-CLINICAL PHARMACOLOGY/TOXICOLOGY ISSUES

Except for the excipient Contramid, all of the inactive ingredients in Tramadol OAD are found in previously approved drug products at comparable exposure levels. The applicant conducted a single-dose toxicity study of Contramid in rats. No significant adverse effects were observed.

No other non-clinical studies were indicated for this product.

There were no pharmacology/toxicology issues and, from this perspective, the application can be approved.

7. DATA INTEGRITY

The Division selected two sites from Study MDT3-005 for inspection by the Division of Scientific Investigations (DSI). Inspection found two minor protocol violations at one site (enrollment of a patient who had therapeutic arthroscopy of the target knee less than

1 year prior to enrollment; administration of study drug before complete washout of prohibited analgesics). However, these violations were infrequent and not significant enough to have impacted the efficacy results. DSI concluded that, with the exception of these two violations, the data generated from the studies was acceptable and could be used to support an approval decision for the NDA.

8. PROPRIETARY NAME

The applicant proposed the proprietary names ——— and Ryzolt. The Division of Drug Marketing, Advertising, and Communications (DDMAC) initially rejected both names. However, upon clarification by the company that the latter name (Ryzolt) was to be pronounced as "rye-zahlt" and not "rhee-zhalt," DDMAC withdrew its objection that the name overstates the effectiveness of Tramadol OAD.

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Because DDMAC at first found the proposed names unacceptable, the Division of Medication Errors and Technical Support (DMETS) did not review the names. However, a request for name review was re-submitted when DDMAC withdrew its objection to Ryzolt. The DMETS consult was pending at the time this memo was written. However, a proprietary name is not required for NDA action therefore a decision can still be made regarding whether or not the application can be approved.

9. CONCLUSIONS AND RECOMMENDATIONS

The clinical and statistical review teams have found that this application lacks substantial evidence that Tramadol OAD (100 – 400 mg) is efficacious in reducing pain in adult patients with osteoarthritis of the knee. Because trials of other tramadol formulations have been successful, it is likely that the studies of Tramadol OAD failed because of the study design (trials randomized patients to a pre-specified dose), because of the study population (only patients with osteoarthritis), because of the pharmacokinetics of the formulation, or because of a combination of all of these reasons.

As discussed in the Background section, the Division has found that fixed-dose opioid trials often lead to significant patient dropout due to intolerability. When conservative imputation methods are used to handle data missing due to premature terminations, these studies are rarely successful.

The Division recommends evaluating efficacy in chronic pain populations other than osteoarthritis. This is because the pain of osteoarthritis waxes and wanes considerably over time, and may make it difficult to distinguish drug effect from placebo.

Finally, the clinical pharmacology review showed that there is a 9-hour window (extending from the late evening to the early morning) in which the concentration profile of Tramadol OAD falls below that obtained with dosing of immediate-release tramadol every 6 hours. In osteoarthritis, pain is often greatest in the evening through the morning.

The low concentration of Tramadol OAD during this time may have contributed to the lack of efficacy observed in the clinical trials.

The safety data show that use of Tramadol OAD is associated with adverse events that have been reported with other tramadol products. The most common events are nausea, constipation, dizziness, somnolence, vomiting, and pruritus. SAEs varied considerably, with no clear demonstration of a relationship to the dose of Tramadol OAD. The sole event of a convulsion was possibly related to treatment with Tramadol OAD; seizure has previously been associated with the use of tramadol. Of the three reported deaths, only one was remotely possibly related to Tramadol OAD (myocardial infarction preceded by agitation). There is no evidence of increased risk of overdose or withdrawal with Tramadol OAD compared to what has been observed with other tramadol products.

Despite the comparability of the safety profile of Tramadol OAD to that of the approved extended release tramadol product (Ultram ER), I recommend against approval of this application for the desired indication, "treatment of moderate to moderately severe pain," due to the absence of evidence of efficacy.

The applicant should conduct another efficacy trial to show efficacy of Tramadol OAD. The trial should utilize a different patient population that has less variability in pain over time (e.g. patients with low-back pain), and should incorporate an enrichment scheme to reduce patient dropout due to drug intolerance. The primary efficacy measure should assess pain intensity, and the efficacy outcome should evaluate effect at study end (to evaluate durability of effect). A cumulative (continuous) responder analysis is recommended.

The action letter should detail approaches to resubmission of the safety data to facilitate more definitive review. The resubmitted safety data should integrate the experience from all Phase 2 and 3 trials of Tramadol OAD, and should describe all post-marketing experience with tramadol.

Should the applicant conduct another efficacy trial, consideration will have to be given regarding the indication that the data would support. Because of the patient population studied, and the nature of the study design, a more appropriate indication would probably be "treatment of moderate to moderately severe chronic pain in adults."

Finally, because of the findings of increased drug release upon bisection of the tablets, the applicant should be advised to study the effects of other types of physical manipulation, such as crushing, on the pharmacokinetics of Tramadol OAD.

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/s/

Mwango Kashoki
9/23/2006 01:52:14 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	21-745
Submission Number	N-000
Submission Code	
Letter Date	November 25, 2005
Stamp Date	November 28, 2005
PDUFA Goal Date	September 28, 2006
Reviewer Name	Jin Chen, MD, PhD, MPH
Review Completion Date	September 11, 2006
Established Name	Tramadol Contramid OAD tablets
Proposed Trade Name	——— or Ryzolt
Therapeutic Class	Opioid Analgesics
Applicant	Labopharm Inc.
Priority Designation	Standard
Formulation	IR/ER, Oral tablets
Dosing Regimen	Once a day
Indication	Moderate to Moderately Severe Pain
Intended Population	Adult

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Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Tramadol Contramid OAD, submitted as 505(b)(2) NDA, is ***approvable*** based on the following evidence:

Of the three pivotal efficacy trials conducted in patients with moderate to severe pain due to osteoarthritis of the knee, the applicant found that two trials showed that Tramadol OAD was statistically superior to placebo with respect to pain improvement, as based on the primary efficacy endpoint WOMAC Pain Score and Patient Global Rating of Pain Relief (in one trial) and Pain Intensity on 11-point NRS (in another trial). In the applicant's analyses, missing data due to early dropouts were imputed with LOCF (last observation carried forward). However, the LOCF-based superiority of Tramadol OAD was not supported by the Division's sensitivity analyses of the primary endpoints using BOCF imputation for missing data or upon continuous responder analysis (defining dropouts as non-responders). In addition, the superiority of Tramadol OAD in pain improvement based on LOCF analysis was marginal, 13% with WOMAC Pain score and 7% with the pain intensity-NRS, which is less likely clinically meaningful in context of risk/benefit ratio.

The safety data six Phase 3 trials in this NDA, together with safety information from approved tramadol products showed that Tramadol Contramid OAD is safe as per its recommended use in the proposed labeling.

Therefore, another clinical efficacy study is recommended and it should be conducted in different pain population (other than osteoarthritis patients) and using a flexible-dose design (to minimize dropout rate and potentially increase superiority margin). An alternative doing regimen should also be considered in the new trial because the formulation of the Tramadol OAD tablets (comprising ——of the drug in extended release (ER) form) with a once-a-day dosing interval may have led to a 9-hour under-exposure of tramadol (by plasma levels). b(4)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

A risk management plan is not indicated for Tramadol Contramid OAD. No new safety signal was identified during the NDA review as compared to approved tramadol products. The Office of Drug Safety (ODS) concluded that there are no unique safety issues with this product for which a Risk Minimization Action Plan (RiskMAP) to minimize risk normally would be associated. Tramadol products, marketed for approximately 11 years to date, have not required risk management tools beyond standard product labeling and routine post-marketing safety surveillance.

1.2.2 Required Phase 4 Commitments

Not applicable for this review cycle.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The proposed trade name of this product was ——— Ryzolt, both of which were rejected by DMETS in the Office of Drug Safety. Since this product has been identified as Tramadol Contramid OAD in the applicant's clinical development program, ***Tramadol OAD*** will be used in this review. b(4)

Tramadol OAD is a tablet formulation of tramadol HCl (active ingredient) with a cross-linked ——— starch excipient (Contramid) for oral administration. Tramadol is an opioid analgesic. The tablets comprise ——— immediate-release (IR) tramadol (outer coat) and ——— extended-release (ER) tramadol (core of tablets). Therefore, Tramadol OAD is a partial tramadol ER formulation tablet. b(4)

The applicant's proposed indication of Tramadol Contramid OAD was "for the management of moderate to moderately severe pain". However, it is unclear if this indicated for both chronic and acute pain. The Phase 3 trials submitted to support this indication were designed to assess the chronic pain (patients with moderate to severe pain due to osteoarthritis of the knee). There were no trials conducted with Tramadol OAD to support acute pain indication or claim. The study population in all trials was adult patients (age ≥ 18 years). Therefore, the proposed indication should be "*for management of moderate to moderately severe chronic pain in adults*".

The applicant submitted six Phase 3 trials, including three pivotal efficacy (placebo-controlled) trials, one supportive efficacy (active-controlled) trial, one 12-month open-label safety trial and one 9-month open-label extension safety trial (extended from the active-controlled trial).

A total of 3269 subjects were enrolled in the clinical studies, including 2968 OA patients in the six Phase 3 trials, and 301 healthy subjects in the 11 Phase 1 trials (PK studies with a single dose of Tramadol OAD). Of the 2968 patients in the Phase 3 trials, 1095 in the three placebo-controlled trials, 215 in the active-controlled trial and 630 in the open-label long-term trials were treated with Tramadol OAD (at least one dose of 100 to 400 mg).

1.3.2 Efficacy

The applicant relied upon three placebo-controlled trials as a basis for efficacy assessment of Tramadol OAD. The trials were conducted in patients with moderate to severe pain due to OA of the knee. Two trials (MDT3-002 and MDT3-003) utilized a fixed-dose design, with patients randomized and titrated to a fixed *pre-assigned* dose of Tramadol OAD (100, 200 or 300 mg). The third trial (MDT3-005) utilized an optimum fixed-dose design, in which patients received open-label Tramadol OAD treatment and then were randomized and titrated to optimum dose

(not pre-assigned) of 200 mg or 300 mg that was fixed (stable) during the double-blind phase. In all three trials, the patients were treated with the titrated fixed dose (Tramadol OAD or placebo) for 12 weeks.

Three co-primary efficacy endpoints, namely, WOMAC Pain Subscale, WOMAC Physical Function Subscale and Patient Global Rating of Pain Relief, were used in MDT3-002 and MDT3-003. Pain intensity on 11-point Numerical Rating Scale (NRS) at end of treatment (week 12) was a primary endpoint for MDT3-005 (WOMAC Pain Subscale was one of secondary endpoints in this trial). The main secondary efficacy endpoints were patient and physician global impression, 24-hour pain questionnaire, and time-course of pain improvement. These efficacy endpoints were considered acceptable by the Division for assessment of analgesic efficacy of this product in the OA population.

The applicant's primary efficacy analysis was based on the full analysis population (patients who received at least one dose and had at least one post-baseline efficacy assessment), with LOCF (last observation carried forward) imputation for missing data due to early dropouts. In Study MDT3-003, the mean percentage change in WOMAC Pain score from baseline to end of treatment showed statistically significant superiority of Tramadol OAD 300 mg (but not 100 and 200 mg) to placebo (difference of 13.4%, p=0.0162) after multiplicity adjustment for type I error (α =0.0167). However, an alternative imputation method, BOCF (baseline carried forward), and the continuous responder analysis (defining dropouts as non-responders) did not show that Tramadol Contramid OAD was statistically superior to placebo with respect to percent pain improvement in WOMAC Pain. Similarly, using LOCF imputation method, there was no statistically significant difference in the WOMAC Pain score between Tramadol OAD and placebo in the Study MDT3-002, nor in MDT3-005 in which WOMAC Pain Score was as a secondary endpoint.

As for the pain intensity on 11-point NRS, the primary efficacy measure for Study MDT3-005, the applicant found the statistically significant superiority of Tramadol OAD (200 and 300 mg) to placebo in the mean change of pain intensity from baseline to end of treatment by 0.48 point (2.9 ±2.5 vs. 2.4±2.4, p=0.016) or 7% differences (40.3% *vs.*33.3%) with LOCF imputation for missing data. However, BOCF imputation method and continuous responder analysis did not statically support the LOCF-based superiority of Tramadol OAD to placebo.

Regardless, the differences in pain improvement between Tramadol OAD and placebo, 13% in Study MDAT3-003 (WOMAC Pain) and 7% in Study MDT3-005 (PI-NRS), are too small to be clinically meaningful in context of benefit/risk ratio.

Results from analyses on the Patient Global Ratings of Pain Relief (studies MDT3-002 and MDT3-003) showed that, with LOCF imputation method, 11%-18% more patients on Tramadol OAD 200 mg or 300 mg rated the study medication "very effective" or "effective" as compared to placebo (the differences were statistically significant). However, reanalysis of the data with BOCF imputation method showed no statistically significant differences between Tramadol OAD and placebo. The Patient Global Impression on Change was one of secondary endpoints in Study MDT3-005 had approximately 11% more patients in Tramadol OAD treatment reporting overall improvement as compared to placebo-treated patients (LOCF analysis).

1.3.3 Safety

The safety of Tramadol OAD was evaluated in 11 Phase 1 trials (single-dose treatment) in healthy subjects and six Phase 3 trials (multiple-dose treatment for 3-12 months) in patients with osteoarthritis of the knee. Overall the safety profile of Tramadol OAD was similar to that of approved tramadol products, Ultram and Ultram ER, and there were no new safety signals identified with Tramadol OAD treatment.

In the six Phase 3 trials, 1939 patients with osteoarthritis were treated with at least one dose of Tramadol OAD (100 to 400 mg). There were 1095 patients in the three placebo-controlled trials (548 were treated with Tramadol OAD 300 mg), 215 in the active-controlled trial (53 on Tramadol OAD 300 mg and 21 on Tramadol OAD 400 mg), and 630 in the open-label studies (majority were on Tramadol OAD 300 mg). The mean age of the study population was 62 years with approximately 40% of patients at age $\geq$ 65 years; 62-87% of patients were females and 80-100% were Caucasian. The actual patient exposure (by excluding dropouts) to Tramadol OAD 100-400 mg was 1337 patients, including 844 patients who completed 12-week treatment (400 patients on 300 mg), and 493 patients who completed at least 6-month treatment with 300 mg (243 of them continued to 12 months).

There were three deaths reported during the clinical studies, two on Tramadol OAD treatment (one each from placebo-controlled and active-controlled trials) and one on placebo treatment. The causes of death were fatal MI (n=2) and ischemic stroke (n=1), and were considered unrelated to study medication.

A total of 44 other serious adverse events (SAEs) were reported from 40 patients treated with Tramadol OAD or placebo during the six Phase 3 trials; 17 of these patients withdraw from the studies. Overall, the incidence of patients with SAEs (including deaths) was 2.1 % in patients treated with Tramadol OAD. In the three placebo-controlled trials, 25 patients reported 27 SAEs, including 19 (1.3%) patients treated with Tramadol OAD and 6 (0.9%) patients on placebo. The overall incidence of SAEs tended to increase with increasing dose of Tramadol OAD. There were 20 SAEs reported by 18 patients during the open-label studies.

The SAEs occurred sporadically across different system organ class categories, with relatively higher incidence in cardiovascular (such as MI, angina, stroke, venous thrombosis, hypertension), gastrointestinal (such as faecal impaction, gastritis, abdominal pain) and nervous systems (such as convulsion, syncope, bipolar disorder). Mostly, a single case of SAEs was reported across study groups, which made it difficult to estimate the trend of an association with Tramadol OAD treatment.

Although there was a temporal relationship between the SAEs (including the deaths) and study medication, occurrences of the events were confounded by patients' complicated existing medical conditions. Therefore, a causal relationship can not completely be established. The following six SAEs were considered by the applicant "possibly related to study medication" and occurred in patients treated with Tramadol OAD 300 mg: fecal impaction, gastritis, constipation, syncope, hepatitis (abnormal liver and renal lab tests), and renal impairment. The causality of these SAEs was estimated mostly based on a clearly temporal relationship, expectation (experience with the approved tramadol products) or unknown explanation on the events.

In addition, grand mal convulsion and some serious cardiovascular events (such as angina unstable, MI, and cerebrovascular event) were reported from patients treated with Tramadol OAD during the studies. Although the causal association with Tramadol OAD can not be determined, this reviewer recognizes that the reactions may be related to serotonergic activity of tramadol, which may exacerbate the existing nervous and cardiovascular disorders. This is supported by a finding in the previous safety review of Ultram ER (NDA ———, in which there was a trend in increasing the cardiovascular events associated with tramadol ER treatment. b(4)

The most common adverse events reported in the placebo-controlled trials were nausea, constipation, dizziness, somnolence, headache, vomiting, pruritus, dry mouth, and sweating increased. Patients on Tramadol OAD were much more likely than on placebo to experience those adverse events, except for headache. A similar profile of adverse events was reported in the open-label trials.

Overall, the safety profile of Tramadol OAD was comparable to that of previous approved tramadol products when compared to the AE summary in the Ultram ER NDA review and its labeling.

1.3.4 Dosing Regimen and Administration

The applicant proposed that Tramadol OAD should be taken once a day with the following titration regimen: initiate at dose of 100 mg/day, followed by 100 mg/day increments every 2 days to achieve a balance between adequate pain control and tolerability for the individual patients. For patients requiring 300 mg/day, titration should take at least 4 days (i.e. 300 mg/day on day 5). Tramadol OAD should not be administrated at a dose exceeding 300 mg/day.

The proposed titration dosing regimen was tested in the three pivotal trials and other Phase 3 trials. In addition, the safety and efficacy of Tramadol OAD at three dose levels 100, 200 and 300 mg, were assessed in the two pivotal trials (MDT3-002 and MDT3-003). Therefore, the dosing regimen in the proposed labeling is acceptable.

1.3.5 Drug-Drug Interactions

Drug-drug interactions of Tramadol OAD were not specifically studied for this NDA. However, information on drug interactions with tramadol is available from the approved tramadol products and literature, including pharmacokinetic interactions (such as CYP2D6 and CYP3A4) and pharmacodynamic interactions (such as serotonergic activity).

1.3.6 Special Populations

Tramadol OAD was not studied in any special population. However, the Phase 3 trials included males and females age 40-80 years.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Tramadol Contramid OAD tablets are a re-formulation of tramadol HCl with a cross-linked high-amylose starch excipient (Contramid), comprised of ——— immediate-release (IR) tramadol (outer coat of tablets) and ——— extended-release (ER) tramadol (core of tablets) for oral administration. The active ingredient, tramadol HCl, is classified as a centrally acting synthetic opioid analgesic. The product is filed under 505(b)(2) NDA by referring to the prior approval of Ultram (tramadol IR tablets). b(4)

The established name is Tramadol Contramid OAD and the proposed trade names were ——— and Ryzolt. Both trade names were reviewed and rejected by DMETS in the Office of Drug Safety. b(4)

The applicant has proposed three dose strengths of Tramadol OAD tablets, 100 mg, 200 mg and 300 mg, based on the amount of tramadol HCl per tablet.

The proposed indication is *"for management of moderate to moderately severe pain"*. However, the population studied in this NDA was the adult patients with moderate to severe chronic pain due to osteoarthritis, which does not specifically support the applicant's indication. A more appropriate indication is therefore *"for management of moderate to moderately severe chronic pain in adults"*.

Tramadol OAD tablets are intended for oral once a day administration, with titration from 100 mg up to 300 mg a day. The drug is to be titrated in 100 mg/day increments every 2 days to achieve a balance between adequate pain control and tolerability for the individual patients. For patients requiring 300 mg/day, titration should take at least 4 days (i.e. 300 mg/day on day 5). Tramadol OAD is not to be administrated at a dose exceeding 300 mg/day.

2.2 Currently Available Treatment for Indications

There are various treatments available in US for management of moderate to severe pain, including pharmacotherapy (such as NSAIDs, opioids) and non-pharmacotherapy (such as interventional procedure, acupuncture).

2.3 Availability of Proposed Active Ingredient in the United States

The following five Tramadol products have been approved for marketing in US in last 10 years:

1) Ultram (tramadol IR tablets 50 mg) approved on March 3, 1995 under NDA 20-281 is indicated for *"the management of moderate to moderately severe pain in adults"*.

2) Ultracet (37.5 mg tramadol and 325 mg acetaminophen combination tablets) approved on August 15, 2001 under NDA 21-123 is indicated *"the short-term (five days or less) management of acute pain"*.

3) Ultram ODT (tramadol orally disintegrating tablets 50 mg) approved May 5, 2005 under NDA 21-693 is indicated *"for management of moderate to moderately sever pain in adults"*.

4) Ultram ER (tramadol ER tablets 100 mg, 200 mg and 300 mg) approved on September 8, 2005 under NDA 21-692 is indicated *"for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time"*.

2.4 Important Issues with Pharmacologically Related Products

In addition to its selective u-opioid receptor agonistic effects, tramadol has been shown to inhibit reuptake of neuronal serotonin and norepinephrine. Post-marketing surveillance and literature reports on the approved tramadol product have suggested that therapeutic dose or concomitant use of tramadol with SSRI, SNRI, and MAO inhibitor may increase the risk of seizure and serotonin syndrome. The appropriate warnings on these risks have been updated in all tramadol products.

In this NDA submission, the applicant did not specifically assess these risks associated with Tramadol OAD and all potential risk factors were excluded from subject selection during the clinical studies. The same warning information has been adapted in the proposed labeling of Tramadol OAD.

2.5 Presubmission Regulatory Activity

Tramadol Contramid OAD was developed under IND 64,317 ——————— and key milestones in clinical development program are noted below:

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1. The first pre-IND meeting was held on November 1, 2001 and the following clinical guidance was provided to the applicant:

   - Number of efficacy study to support the proposed indication "for management of moderate to moderately severe pain" should be dependent on bioequivalence of Tramadol OAD to tramadol IR:

     - One efficacy study would be necessary if there was bioequivalence at Tmax, Cmax and AUC.
     - Two efficacy studies would be necessary if there was bioequivalence at Cmax and AUC.
     - Two efficacy studies in two pain models would be necessary if there was no bioequivalence at either single dose or steady state.

- A single well-controlled non-inferiority (vs. Ultram) multiple-center study in US would be acceptable to support the proposed indication if two 3-arm (placebo- and active-controlled trials) were conduced in chronic pain models. OA was considered acceptable as a chronic pain model.

- Comments on the draft Phase 3 protocol synopsis (MDT3-002):

  - Should be designed as a fixed dose
  - Use pain curve as a primary measure instead of WOMAC pain score.
  - If labeling mentioned ——— was studied, three WOMAC subscales should be used
  - For pain indication only, the study need not succeeding the three WOMAC subscales.
  - The agency had not enough experience with low back pain but advised this might be a separate indication
  - LOCF imputation method for dropouts would be acceptable but the dropouts should be summarized by patients, treatment and time.
  - Duration of study (treatment) should be 12 weeks and it would be possible to do one 12-week study and one 6-week study to support efficacy.

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2. [redacted]

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3. Two further pre-IND meetings were held on September 4, 2002 and November 12, 2002. The following clinical guidance was provided to the applicant, which reflected the recommendations of the Arthritis Advisory Committee meeting:

   - The applicant may submit 505(b)(1) application with elements of a 505(b)(2) application.
   - Two replicated placebo-controlled studies would be sufficient but the applicant was urged to test with active comparator.
   - ———————, the study population should be the patients with OA of the knee and the hip.
   - The applicant may pursue a ——————————— by means of three pain models, such as OA, low back pain and fibromyalgia.
   - Three co-primary endpoints, WOMAC Pain and Function Subscales and patient global rating, would be required for the efficacy evaluation ———
   - The use of rescue medication should not be a primary endpoint.
   - The maintenance treatment at fixed dose levels (e.g. 200 mg vs. 400 mg, or 200 mg vs. 300 mg) instead of dose range of 100 to 400 mg was recommended for the purpose of obtaining useful information on doe-response.
   - The long-term multiple dose effect might be measured by obtaining a weekly average of daily pain scores, such as daily average pain, instantaneous pain art s pre-specified time after drug intake, 24-hour total pain, worst or least pain in 24 hours.
   - A weekly average of daily pain may help describe and better demonstrate the treatment effects measured by cross sectional assessments at 3, 6 and 12 weeks.

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- Long-term safety studies on 300 patients for 6 month and 100 patients for 12 month would be minimum requirements, and the level of exposure should be the recommended maximum dose of the proposed labeling.
- Referring pharm/tox data to the approved Ultram would be acceptable and no further animal study may be needed.

4. ———— IND 64,317 and was received on December 2, 2002. The IND contained protocols for one PK study and two Phase 3 studies (MDT3-002 and MDT3-003). The following comments on the Phase 3 protocols were provided: b(4)

- The applicant's primary analysis should be based on full analysis population with LOCF imputation for missing data (regardless of reason for dropout).
- Intended superiority test procedure and multiplicity testing for comparisons between placebo and 100 mg, 200 mg and300 mg should be provided for review.
- Baseline pain intensity should be included as one of the covariates in the ANCOVA model.

5. Pre-NDA meeting dated on February 25, 2004 with the following clinical and regulatory guidance:

- The division agreed to file this product as a 505(b)(2) NDA with references to mainly pharm/tox data and additional clinical safety information.
- Two adequate well-controlled studies in OA patients would be suitable to support a chronic pain indication because the formulation changed from IR to ER.
- If Study MDT3-003 were successful, a second trial in OA or in another suitable patient population would be required. The results of Study MDT3-003 had to be replicated in a suitable patient population.
- The Division did not agree that LOCF should be only method of imputation for handling missing data. Sensitivity analyses using alternative imputation methods should be performed and more than one imputation method should be used.

6. Follow-up to the pre-NDA meeting held on April 28, 2004 and teleconference on May 27, 2004 to discuss the design of an additional Phase 3 trial (MDT3-005) as requested in the pre-NDA meeting and the division's comments on the SPA protocol of this trial:

- It was acceptable that the initial open-label phase of the trial, as an enrichment approach, included titration, taper and washout to avoid carry-over effects and withdrawal symptoms in patient who would be assigned to placebo group during the double-blind phase.
- The applicant was advised to explore whether patient were still blinded about their treatments at the completion of dose titration following randomization (the double-blind phase).
- Enrichment of baseline pain intensity as that measured at end of 7-day washout during the open-label phase was acceptable.

- Inclusion of patients experiencing pain on a regular basis (a history of positive therapeutic benefit with NSAIDs, COX-II inhibitors or tramadol) and exclusion of patients taking strong opioids was acceptable.
- The results from this enrichment deign trial may not determine the overall response from a general population.
- For ' indication, three co-primary endpoints (pain, function and patient global rating) were recommended.
- The time-weighted average was suggested as one of efficacy analyses.
- As designed, the study would not provide dose-response information.

b(4)

7. Study MDT3-005 protocol for Special Protocol Assessment (SPA) was received on June 8, 2004. The protocol incorporated the division's comments and recommendations from the previous meeting. After reviewing the protocol, the division sent the following comments to the applicant:

   - Regarding method of handling missing data in addition to LOCF, multiple approaches of imputation for sensitivity analysis were recommended.
   - The open-label phase (run-in, taper and washout) for patient enrichment was acceptable.
   - Subgroup analyses of "200 mg vs. placebo" and "300 mg vs. place" should be conducted as secondary efficacy analyses.
   - The results from Study MDT3-005 in conjunction with the findings of efficacy from Study MDT3-003 would fulfill the requirement for at least two adequate clinical trials to support efficacy.

8. Face-to-face meeting regarding the indication " for management of ——— chronic pain" on May 3, 2005

   - [redacted]

b(4)

   - [redacted]

   - The applicant decided to focus on the chronic pain indication for its NDA submission.
   - The division recommended that the applicant investigate alcohol interaction with Tramadol OAD for potential dose-dumping effect.

2.6 Other Relevant Background Information

Tramadol Contramid OAD has been approved for marketing in Europe and Mexico in 2005, as follows:

In Europe: Tramadol Contramid OAD was approved for marketing in France on February 2, 2005 and then approved through the Mutual Recognition Procedure (MCP) on September, 2005 for marketing in 21 other European countries. The final labeling (Summary of Product Characteristics, SmPC) approved through MCP was submitted with this NDA.

- Dose strength: 100 mg, 200 mg and 300 mg tablets.
- Indication: "*treatment of moderate to severe pain*" in adults and adolescent (12 years and over). There are no clinical efficacy data included in the labeling.
- Dosing regimen: initial dose of 100 mg/day titrated up to 400 mg once daily (the increment of dose/day is not specified).

In Mexico: Tramadol Contramid OAD was approved in Mexico on October 6, 2005 under trade name LABTRAM. The English-translated labeling (from the Spanish final labeling (Prescribing Information) approved by the Mexican Health Authorities was submitted with this NDA.

- Dose strengths: 100, 200, and 300 mg tablets.
- Indication: "*LABTRAM is indicated in conditions accompanied by moderate to severe pain, of acute or chronic origin (e.g. osteoarthritis, fracture, luxations, acute myocardial infarction, cancer, etc.); it can also be used as a pre-operative analgesics, as a complement to surgical anesthesia, in the postoperative period and in procedures of diagnostic investigation associated with pain*" in adults and adolescents over 12 years old. The brief efficacy information quoted in the labeling is from the active-controlled trial (comparable to tramadol twice a day).
- Dosing regimen: 100 mg/day titrated up to 400 mg/day in increment of 100 mg every 2 or 3 days.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There are no outstanding CMC issues identified from the CMC review team, and the recommendation on regulatory action is ***approval***. The significant issue is the ratio of ER/IR in Tramadol OAD tablets is approximately——which is different from the——ER" the applicant claimed during the clinical development. The following is a brief summary of the chemistry of Tramadol Contramid OAD. b(4)

Tramadol Contramid OAD comprises of a dual-matrix delivery system which controls the release of tramadol hydrochloride providing both immediate-release (outer coat) and extended-release (core) characteristics (Figure 3-1).

The applicant claimed in the submission that ——of tramadol was in IR form and ——in ER form in the Tramadol OAD tablets. However, the chemistry reviewer found that, based on the CMC data submitted in NDA, the proportion of IR and ER components in Tramadol OAD tablets of 100, 200 and 300 mg are similar.—— IR tramadol in 100 mg and 200 mg Tablets and —— IR tramadol in 300 mg Tablets (Table 3.1). b(4)

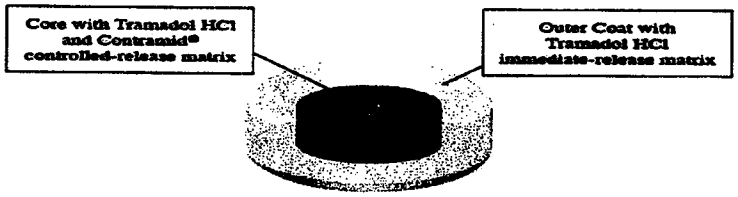
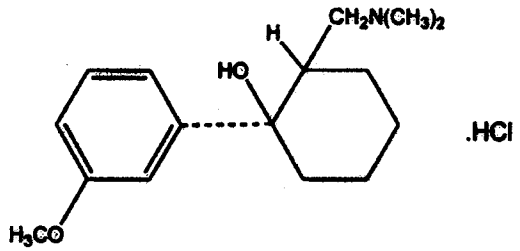


Figure 3-1. **Tablet Configuration of Tramadol Contramid OAD: the Immediate-Release Matrix (lighter outer part) and the Extended Release Matrix (dark inner part)**

Active ingredient: tramadol HCl, the active ingredient, is (±)*cis*-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride, and its structural formula shows in Figure 3-2.



$C_{16}H_{25}NO_2 \cdot HCl$, MW=299.8

Figure 3-2. **Chemical Structure of Tramadol HCl**

Inactive ingredients: Contramid®, a modified starch, in the table core functions as an *ER matrix*) and—— in the table outer coat acts as an *IR matrix*. ——

——As per the chemistry reviewer, the —— matrix provides a sustained release function and, thus, the IR form in Tramadol OAD tablets may function as "immediate but controlled" release. b(4)

The Ultram IR formulation of tramadol contained different inactive ingredients to that of Tramadol OAD. According to the labeling, Ultram tables contain corn starch, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and wax. The differences in the IR matrices between Tramadol OAD and Ultram may partly explain the different slopes of tramadol absorption in the comparative PK studies (See Section 5. "Clinical Pharmacology" for details).

***Table 3.1.* Composition of Tablet Core (ER) and Coat (IR)**
(From applicant's submission Section 2.3.P.2.1.2 Excipients, provided by a CMC reviewer)

Component	Reference to Quality Standard	Function	100 mg Tablet (mg)	200 mg Tablet (mg)	300 mg Tablet (mg)
[redacted]					
…ting Ink					
[redacted] Black Ink	In-house	[redacted]			

b(4)

3.2 Animal Pharmacology/Toxicology

There are no outstanding issues on this product from Pharm/Tox review team, and the recommendation on regulatory action is ***approval***.

The applicant did not conduct any pharm/tox studies on Tramadol Contramid OAD other than one 14-day toxicology study on Contramid (inactive ingredient) in rats. The applicant referred the pre-clinical safety information of tramadol HCl (active ingredient) contained in the approved tramadol product (Ultram) NDA. The following is brief summary extracted from the Pharm/Tox review (by Asoke Mukherjee, PhD):

The applicant developed a once a day oral dosage regimen for tramadol. Except for the excipient Contramid, the inactive ingredients used in the formulation can be found in other FDA approved drug products at comparable exposure levels. The applicant stated that Contramid is the proprietary product developed for the drug delivery system and it is a modified starch, i.e. hydroxypropyl distarch phosphate. A single dose toxicity study for Contramid was conducted in rats at doses up to 2000 mg/kg/oral. No treatment-related mortality was observed in rats. The applicant provided literature articles on the toxicity and reproductive effects of feeding several modified starches. In general, up to 30% of modified starch in the diet increased the weight of cecum and did not show any effect on the reproductive performance in a 3 generation study. A publication by Leegwater et al. suggested that the effect of the modified starch on cecum resulted from the physiological adaptation. Hydroxypropyl distarch phosphate is not mutagenic in the Ames assay.

The amount of Contramid in the formulation is about —— of the weight of the formulation and per day intake would be about ——— The modified starch is considered to be generally safe and used in the food industry. The acceptability of the use of modified starch in food is published in the 21 CFR 172.892. Based on the safety and regulatory status, hydroxypropyl distarch phosphate is considered a modified starch. In consultation with the chemistry review team, Contramid falls under the classification of a modified starch. As the Agency has previously determined that modified starches are acceptable as food products, the use of Contramid as an inactive ingredient for an oral drug product is acceptable without additional toxicity studies

b(4)

The applicant referenced previous correspondence with the Agency on November 2001. The Division agreed that the applicant may request to reference nonclinical data for Pharm/Tox information from Ultram NDA file in support of 505(b)(2) application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

- Eleven Phase 1 and six Phase 3 trials conducted and submitted by the applicant.
- Literature information regarding safety tramadol as a drug class.
- Safety data from approved Tramadol products, Ultram and Ultram ER, were used for comparison, including ISS from Ultram ER (NDA 21-692) and labeling of both products.

4.2 Tables of Clinical Studies

The applicants conducted and submitted in this NDA a total of 11 Phase 1 trials (Table 4.2a) and six Phase 3 trials (Table 4.2b).

Table 4.2a. **Phase 1 Trial Submitted in the NDA**

Study ID	Study Objective	Study Design	Subject & Age	Treatment Tramadol OAD vs. Reference	Study Location
MDT1-011	Dose linearity study (new 300 mg formulation)	Open-label, single dose, randomized, crossover in healthy subjects	N=27 28 yr (19-44)	Tramadol OAD 100 mg, 200 mg and 300 mg	France
MDT1-006	Effects of food on BA#		N=28 21 yr (18-28)	Tramadol OAD 200 mg; fasting & Fed	South Africa
MDT1-013	BE#: coated *vs* uncoated tablets		N=26 25 yr (19-51)	Tramadol OAD 200 mg (film-coated) and 200 mg (uncoated)	South Africa
MDT1-016	BE: new *vs.* old manufacturing sites; effects of food on BA		N=36 39 yr (19-55)	Tramadol OAD 300 mg, Confab (new site)* and Trillium (old site); fasting & Fed	Canada
MDT1-005	BE: OAD *vs.* BID (ref) †		N=24 27 yr (19-40)	Tramadol OAD 200 mg & 2x200 mg, Topalgic 100 mg & 200mg BID (ref)	France
MDT1-012	BE: OAD *vs.* Zytram (ref) ‡		N=26 26 yr (20-33)	Tramadol OAD 200 mg, Zytram 200 mg (ref)	Spain
MDT1-004	Dose linearity study		N=24 30 yr (19-43)	Tramadol OAD 100 mg, 200 mg, 300 mg* & 2x200 mg	France
MDT1-002	Pilot fed/fasting BE: OAD *vs.* BID (ref)		N=16 22 yr (18-30)	Tramadol OAD 200 mg, Topalgic 100 mg BID (ref); fasting & Fed	South Africa
MDT1-007	BE: OAD *vs.* QID (ref, at steady-state)	Open-label, multiple-dose, randomized, crossover in healthy subjects	N=30 22 yr (18-45)	Tramadol OAD 200 mg, Topalgic 50 mg QID (ref)	South Africa
MDT1-009	BE: OAD *vs.* QID (ref, at steady-state)		N=26 28 yr (19-55)	Tramadol OAD 200 mg. Ultram 50 mg QID (ref)	South Africa
MDT1-010	BE: ODA *vs.* BID (ref, at steady-state)		N=26 22 yr (18-45)	Tramadol OAD 200 mg, Topalgic 100 mg BID (ref)	South Africa

BA: Bioavailability and BE: Bioequivalence;.
‡ Zytram®: tramadol ER marketed in Spain
† Topalgic® LP: Tramadol SE (BID dosing regime) marketed in Europe
* The 300 mg tablets manufactured in the new site is the commercial version (to-be-marketed formulation); all others used in the PK studies were from old manufacturing sites.

As per the Clinical Pharmacology reviewer (Lei Zhang, PhD), the bolded four studies in Table 4.2a were considered pivotal for this NDA and were reviewed in detail.

***Table 4.2b.* Phase 3 Trials Submitted in this NDA**

Study No.	Study Type	Treatment	Duration	Study Location
MDT3-002 (pivotal)	Randomized, double-blind, placebo-controlled study in OA patients	Tramadol OAD 100, 200, 300 mg or placebo	12-week maintenance	US
MDT3-003 (pivotal)	Randomized, double-blind, placebo-controlled study in OA patients	Tramadol OAD 100, 200, 300 mg or placebo	12-week maintenance	US
MDT3-005 (pivotal)	Randomized, double-blind, placebo-controlled study in OA patients	Tramadol OAD (200 or 300 mg) or placebo	4-week open-label & 12-week maintenance	US and non-US
MDT3-001-E1	Randomized, double-blind, active control study in OA patients	Tramadol OAD & Tramadol BID 100, 200, 300 or 400 mg/day	12-week maintenance	Non-US
MDT3-001-E1-A1	Open-label extension safety study in OA patients	Tramadol OAD 200, 300 or 400 mg	9-month extension from MDT3-001-E1	Non-US
MDT3-004	Open-label long-term safety study	Tramadol OAD 300 mg	6 & 12 months	Non-US

4.3 Review Strategy

- Individual trial review, check the consistence between the summary tables included in the trial reports and the integrated summary tables and datasets.
- The efficacy and safety data from the individual reviews were then integrated to form ISE and ISS.
- The safety profile of Tramadol OAD was compared to those of approved tramadol products (the package inserts of Ultram and Ultram ER, and ISS of Ultram ER NDA review).

4.4 Data Quality and Integrity

Two study sites with relatively higher enrollment were selected from Study MDT3-005 (the latest pivotal trial submitted on May 30, 2006) for inspection by the Division of Scientific Investigation (DSI).

Site #29: **Vista Medical Research Inc., Mesa, AZ 85206; PI was Nicholas J. Messina III, MD; a total of 20 patients were enrolled from this site.**
Site #97: **Radiant Research San Antonio Northeast, San Antonio, TX 78217; PI: Francis X. Burch, M.D; a total of 45 patients were enrolled from this site.**

DSI concluded that except one subject from Site #29 violated the study protocol the remaining data generated from both study sites appear acceptable. The violated subject was Patient 023/067 who had therapeutic arthroscopy nine months prior to entering the study (should be ≥ 12 months) and took piroxicam for 2 months with 4-day washout (should be five half-lives or ≥11 days). The patient was randomized to the Tramadol OAD (300 mg) group during the double-blind phase but withdrawn after about 10-week dosing due to Patient Request.

4.5 Compliance with Good Clinical Practices

All clinical trials were complied with GCP.

4.6 Financial Disclosures

The applicant provided financial disclosure information for all investigators who participated in the six Phase 3 trials (MDT3-001-E1, MDT3-001-E1-A1, MDT3-002, MDT3-003, MDT3-004 and MDT3-005) and certified no any financial arrangement with the clinical investigators.

5 CLINICAL PHARMACOLOGY

The applicant conducted 11 pharmacokinetic (PK) studies, 10 of which were submitted in the original NDA and one was submitted about 3 months prior to PDUFA date. According to the Clinical Pharmacology reviewer (Dr. Lei Zhang), only four studies were mostly relevant to this NDA (considered pivotal PK studies): MDT1-011 (dose proportionality), MDT1-009 (relative bioavailability and bioequivalence to Ultram), MDT1-006 (food-drug interaction with 200 mg Tablets) and MDT1-016 (food-drug interaction with 300 mg tablets, and bioequivalence between new and old manufacturing sites). The rest of PK studies were for the applicant's registration of Tramadol OAD in Europe or were pilot studies.

Based on the detailed review of the four pivotal PK studies submitted in this NDA, the clinical pharmacology review team concluded that the application is ***acceptable*** from a clinical pharmacology perspective.

5.1 Pharmacokinetics

The pharmacokinetic (PK) profile of Tramadol OAD was adequately characterized in this NDA. The following brief summary is extracted from the clinical pharmacology review:

PK profile comparison with Ultram (tramadol IR): As compared to Ultram (tramadol IR, 50 mg q6h) (Table 5.1), Tramadol OAD 200 mg had lower C_{max} (15-20% lower than Ultram) and longer T_{max} (4 hours vs. 1 hour) at steady-state. There was 9-hour less exposure window per dosing interval (at the first 3 hours during absorption phase and the last 6 hours during elimination phase) (Figure 5.1). The lack of coverage for the 9 hour window (mostly at evening and night) may be related to the less efficacy of Tramadol OAD observed in the clinical trials.

The slower absorption rate of Tramadol OAD 200 mg (containing about 100 mg IR tramadol) than that of Ultram 50 mg (50 mg tramadol IR) was likely due to different controlled-release excipients. As per a CMC reviewer, the tablet coat layer (tramadol IR) of Tramadol OAD contains [redacted] while tramadol IR in Ultram is formulated with corn starch, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and wax. b(4)

PK profile comparison with Ultram ER (tramadol ER): Tramadol OAD was not concomitantly compared to Ultram ER (an approved tramadol ER tablet) in any PK studies submitted in this NDA. Based on cross-study comparison with Ultram ER as per the clinical pharmacology reviewer, Tramadol OAD had similar Cmax and AUC, but a shorter Tmax than Ultram ER (4 hours vs. 12 hours). This is because Tramadol OAD contains approximately —— IR and —— ER forms of tramadol (according to CMC data submitted in the NDA) but —— ramadol is ER form in the Ultram ER tablets. b(4)

Table 5.1. **Pharmacokinetic Comparison in Tramadol and Its Metabolite M1 Between Tramadol OAD 200 mg and Ultram 50 mg Q6h**
(Adapted from the Biopharm review)

PK Parameters	Tramadol Contramid OAD	Ultram (Tramadol IR)	Point Estimate (%)	90% CI (%)
Tramadol				
Cmax (ng/mL)	345 ± 73	423 ± 97	81.8	77.5 - 86.3
Cmin (ng/mL)	157 ± 48	190 ± 64	83.4	78.7 – 88.4
AUC (ng·h/mL)	5991 ± 1330	6399 ± 1766	94.7	91.1 – 98.5
Tmax* (hr)	4 (3-9)	1.03 (1-3)		
Active Metabolite (M1)				
Cmax (ng/mL)	71 ± 19	79 ± 17	88.5	84.1 – 93.2
Cmin (ng/mL)	41 ± 12	50 ± 15	80.7	75.9 – 85.8
AUC (ng·h/mL)	1361 ± 365	1438 ± 329	93.6	89.2 – 98.2
Tmax* (hr)	5 (3-20)	1.5 (1-3)		

* Medians (range)

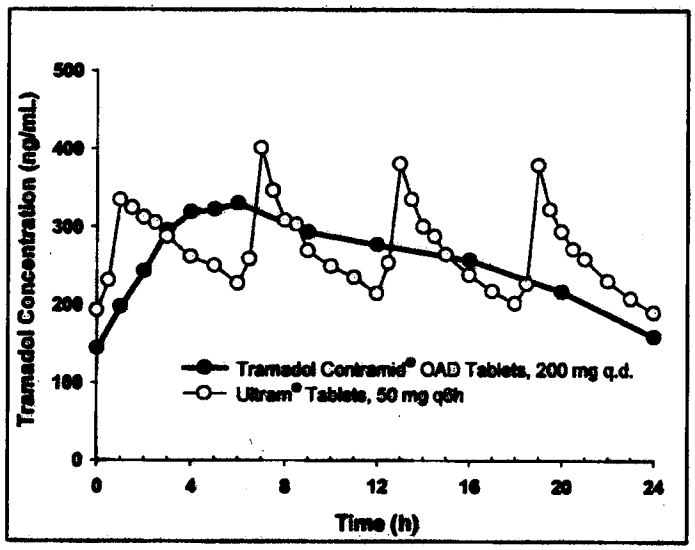
Food Interactions: Food increased Cmax of tramadol by 50-70% without significant change on AUC. During the Phase 3 trials, patients were instructed to take the study medication around breakfast and the safety profile should reflect the food interactions.

b(4)

PK Comparison between new and old manufacturing sites: The applicant changed the manufacturing sites for commercial version of Tramadol OAD tablets after having completed Phase 3 trials. As per the division's request, the applicant conducted a bioequivalence study to compare PK profile of Tramadol OAD tablets 300 mg manufactured from old sites to the one from the new sites. The tablets from the new sites had 10-15% higher Cmax and comparable AUC. However, variability of both Cmax and AUC was high and 90% confidence interval was across 100%. In addition, maximum recommended daily dose of tramadol IR (Ultram) is 400 mg. Therefore, the higher AUC from the new manufacture site may not significantly impact the safety profile of Tramadol Contramid OAD. The Tramadol Contramid OAD 300 mg tablets

manufactured from the new sites should be tested in the future clinical study together with clinical issues and submitted for further evaluation in the next review cycle.

Plasma Tramadol



Plasma Tramadol Metabolite M1

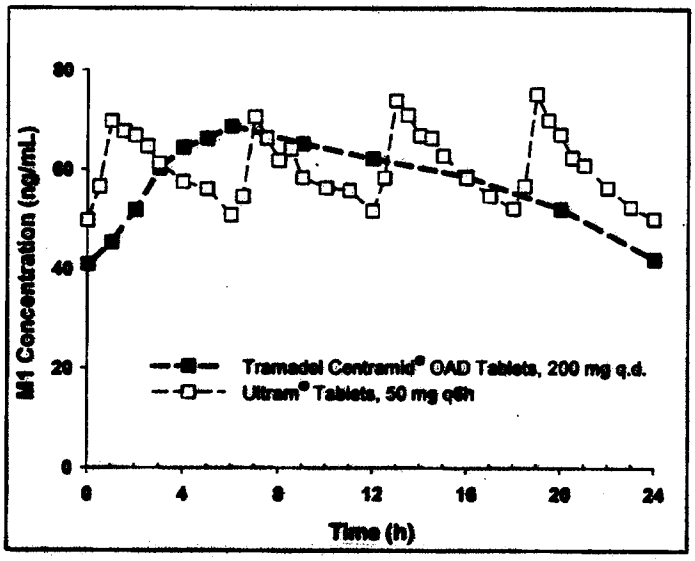


Figure 5.1. **Relative Bioavailability of Tramadol (*upper panel*) and Its Metabolite M1 (*lower panel*) after a single dose of Tramadol Contramid OAD 200 mg as compared with Ultram Tablets 50 mg q6-hr (200 mg/day). The lower Cmax, Cmin and lack of exposure of plasma tramadol and M1 for the 9-hour window after a single dose of Tramadol Contramid OAD (the first 3 hours and last 6 hours). The figures are adapted from the Clinical Pharmacology reviewer's wrap-up presentation.**

b(4)

Conclusion: Overall, the clinical pharmacology review team has no outstanding issues with this NDA, but has the following comments (extracted from the review):

1) Lack of exposure coverage for 9 hours every 24 hours on every proposed dosing interval of Tramadol Contramid OAD as compared to Ultram (tramadol IR).

2) Food significantly increased bioavailability (mainly Cmax) of Tramadol Contramid OAD by 50-75%.

3) Tramadol Contramid OAD 300mg Tablets manufacture from the new sites (commercial manufacturing) had higher bioavailability (mainly AUC) by 10-15% as compared with the tabulated manufactured in the old sites (used for all Phase 3 trials).

5.2 Pharmacodynamics

No pharmacodynamic studies of Tramadol OAD were submitted.

5.3 Exposure-Response Relationships

The applicant did not conduct dose-response studies of Tramadol OAD. With opioids, titration to an optimum dose (i.e., a dose that is both efficacious and tolerable) is needed for individual patients. Therefore, the applicant selected the dosing regimen of Tramadol OAD based on that of approved tramadol products, with a titration period incorporated into the Phase 3 trials.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant's proposed indication of Tramadol Contramid OAD was "for the management of moderate to moderately severe pain". However, it is unclear if this indicated for both chronic and acute pain. The Phase 3 trials submitted to support this indication were designed to assess the chronic pain (patients with moderate to severe pain due to osteoarthritis of the knee). There were no trials conducted with Tramadol OAD to support acute pain indication or claim. The study population in all trials was adult patients (age ≥ 18 years). Therefore, the proposed indication should be "*for management of moderate to moderately severe chronic pain in adults*".

6.1.1 Methods

The clinical data that the applicant used to support the proposed indication were from three placebo-controlled pivotal trials and one active-controlled supportive trial in patients with moderate to severe pain due to the knee osteoarthritis (OA) (Table 6a). See the individual trial reviews in the Appendix for details.

Table 6a. **Phase 3 Trials Included in the Efficacy Evaluation of Tramadol OAD**
(See individual trail review in the appendix for detail)

Study No. (location)	Study Type	Treatment	Duration	Primary endpoint
MDT3-005 (US and non-US)	Randomized, placebo-controlled, 2-arm, fixed-dose study in OA patients	Tramadol OAD (200 or 300 mg) or placebo	4-week open-label; 14-week double-blind (2-week titration and 12-week fixed pre-assigned dose)	Pain Intensity on 11-point NRS at week 12
MDT3-003 (US)	Randomized, placebo-controlled, 4-arm, fixed-dose study in OA patients	Tramadol OAD 100, 200, 300 mg or placebo	Titration for 1-2 weeks with Tramadol OAD or placebo after randomization and then 12-week fixed pre-assigned dose	Three co-primary: WOMAC Pain, WOMAC Function & Patient global rating of pain relief at week 12
MDT3-002 (US)	Randomized, placebo-controlled, 4-arm, fixed-dose study in OA patients	Tramadol OAD 100, 200, 300 mg or placebo		
MDT3-001-E1 (non-US)	Randomized active-controlled, 2-arm, fixed-dose study in OA patients	Tramadol OAD or Tramadol BID (Topalgic LP) 100, 200, 300 or 400 mg	Titration for 1-2 weeks, then 12-week fixed optimum dose.	WOMAC Pain at week 12

6.1.2 General Discussion of Endpoints

Overall, the primary and secondary efficacy endpoints tested in three pivotal placebo-controlled trials and one supportive active-controlled trial were acceptable instruments to assess analgesic effects in the study population (patients with osteoarthritis of the knee) and to support a chronic pain indication.

Primary endpoints: Different, but related, primary efficacy endpoints were used among four Phase 3 trials:

In trials MDT3-002 and Study MDT3-003, three co-primary endpoints were used, including changes from baseline to end of treatment in WOMAC Pain Subscale, WOMAC Physical Function Subscale and Patient Global Ratings of Pain Relief. These co-primary endpoints were normally required to develop a product for treatment of osteoarthritis. Although the study population in both trials was patients with osteoarthritis, the proposed indication of Tramadol OAD and the intent of the trials were management of moderate to severe pain rather than osteoarthritis. The pain improvement based on the WOMAC Pain Subscale is considered a major primary endpoint.

In trial MDT3-005, the primary endpoint was change in pain intensity, as measured on an 11-point NRS, from baseline to end of treatment (week 12). WOMAC Pain Subscale was one of several secondary endpoints in this trial.

In the supportive trial MDT3-001-E1, a non-inferiority trial that compared Tramadol OAD to Tramadol BID (Topalgic), the primary endpoint was the WOMAC Pain Subscale at end of treatment (week 12).

Secondary endpoints: WOMAC Physical Function and Stiffness subscales, time-course of pain intensity, Patient and Physician Global Ratings of Pain Relief (in all trials). These efficacy measures are acceptable to support the primary endpoints for efficacy assessment of chronic pain.

6.1.3 Study Design

The three placebo-controlled trials (MDT3-002, -003 and -005) and one supportive non-inferiority trial (MDT3-0010E1) were randomized, double-blind, fixed-dose studies in patients with moderate to severe pain due to the knee OA. Duration of the treatment was 12 weeks at the fixed maintenance dose (following a titration period of 1-2 weeks). There were some differences in study design across the four trials, as follows:

Study MDT3-002 and MDT3-003: These were duplicate trials. Both were designed as randomized, double-blind, double-dummy, placebo-controlled, fixed-dose (100, 200 and 300 mg Tramadol OAD) studies.

Study population: Patients with moderate to severe pain due to osteoarthritis of the knee were recruited from US; n=565 patients from 75 centers for MDT3-002 and n=552 patients from 74 centers for MDT3-003

Study conduction: The studies consisted of three phases: Baseline (analgesic washout and eligibility assessment), Run-In (titration to the pre-assigned dose: 100, 200 and 300 mg), and Maintenance (treatment at the fixed pre-assigned dose for 12 weeks). MDT3-003 included an additional phase, the post-treatment follow-up (7-day follow-up for withdrawal/dependence symptoms).

Randomization: Patients were randomly assigned to Tramadol OAD (100 mg, 200 mg or 300 mg) or to Placebo at ratio of 1:1:1:2.

Treatment: Patients were titrated with Tramadol OAD or placebo (double-dummy design) over a period of up to 6 days to reach the pre-assigned dose levels (100, 200 or 300 mg). The subjects were then treated with the fixed dose for 12 weeks (Maintenance dosing phase). [*Two dose strength tablets were used, 100 mg and 200 mg tablets, in both trials. Patients in the 300 mg group received one 100 mg tablet and one 200 mg tablets*].

Assessment visits: there were four visits during the 12-week maintenance treatment, for efficacy and safety assessments.

Primary efficacy analysis: The full analysis population (patients who received at least and one post-baseline assessment), with LOCF imputation for missing data due to dropouts, was used for the primary efficacy analyses on the three co-primary endpoints (WOMAC Pain and Function Subscale and Patient global rating of pain relief).

Study MDT3-005: The trial was designed as a randomized, double-blind, placebo-controlled, self-selected/optimum fixed-dose (200 mg or 300 mg Tramadol OAD) study.

Study Population: A total of 1028 patients with moderate to severe pain due to the knee OA were from 108 centers (67 in US, 18 in France, 14 in Canada and 9 in Romania).

Open-label phase: The trial included a 2-week run-In dose titration from 100 mg to 200 mg or 300 mg Tramadol OAD and then a 1-week tapering down from 300 mg or 200 mg to 100 mg Tramadol OAD, followed by a 1-week Wash-out.

Randomization: Patients with pain intensity ≥ 4 (on 11-point NRS) and total pain increase ≥ 2 (compared to the end of run-In) at end of wash-out of the open-label phase were randomized to the double-blind phase. A total of 646 patients (from 1028) met the eligibility criteria and were randomized at ratio of 2:1 into the Tramadol OAD (200 or 300 mg) and Placebo arms.

Double-blind phase: After randomization, the patients had a 2-week titration with Tramadol OAD or placebo to an optimum dose level (200 mg *or* 300 mg Tramadol OAD or Placebo), as based on efficacy and tolerability, followed by 12-week maintenance treatment at the optimum dose level. The dose was unchanged during the 12-week maintenance period.

Assessment visits: There were five visits (one during 2-week Titration and four during 12-week maintenance period) to collect efficacy and safety data during the double-blind phase.

Primary efficacy analysis: The full analysis (or ITT) population, with LOCF imputation for missing data, was used for the primary efficacy analyses on the primary endpoint "difference in mean pain intensity-NRS between Tramadol OAD and Placebo at end of treatment". The BOCF imputation method was an alternative for sensitivity testing. Post-hoc analyses (as per the

Division's request during SPA review stage) included continuous responder analysis, time-weighted analysis and repeated-measure analysis.

Reviewer's Comments: This trial was different from the other two pivotal trials in study design:

- *The study population was enriched by the 4-week open-label treatment; only patients who responded to the Tramadol OAD treatment (effective and tolerable) were randomized to the double-blind phase.*

- *Patients were titrated to their optimum dose during the double-blind phase, either 200 mg or 300 mg. The dose group was not pre-assigned instead the patients self-selected the dose based on their response and tolerability to Tramadol OAD. This design was similar to MDT3-0010E1, but significantly different from MDT3-002 and -003. Selection of only those able to tolerate and respond (analgesia) to Tramadol OAD resulted in a dropout rate of approximately 25%, which was about half of that observed in the "true" fixed-dose trials, MDT3-002 and -003 (dropout rates were 45-47%) (See Table 7d in Section 7.13.1).*

- *Short-acting acetaminophen were allowed for acute pain during the trial, although it was limited for up to three consecutive days and stopped at least three days before any study visit. In studies MDT3-002 and -003, no rescue medication for pain was permitted.*

- *Three dose strength tablets (100 mg, 200 mg and 300 mg) were used in this trial. This was different from other Phase 3 trials, in which only two dose strength tablets, 100 mg and 300 mg, were used. Patients took one 100 mg tablet and one 200 mg tablet for the dose level of 300 mg and two 200 mg tablets for the 400 mg dose level.*

Study MDT3-001-E1: a non-inferiority Phase 3 trial. This was a randomized, double-blind, active-controlled, fixed-dose trial to compare efficacy and safety between Tramadol OAD and Tramadol BID.

Study Population: A total of 431 patients with moderate to severe pain due to the knee OA were enrolled from 21 centers in Europe (3 in France, 8 in Hungary, 8 in Russia and 2 in UK).

Randomization: Patients were randomized at ratio of 1:1 to two treatment arms: Tramadol OAD (n=215) and Tramadol BID (n=216).

Treatment: Patients were titrated to their optimum dose, 100-400 mg/day on Tramadol OAD or 200-400 mg/day on Tramadol BID based on efficacy and tolerability, followed by a 12-week maintenance treatment on the fixed optimum dose level. At the end of the treatment, there were approximately 50% of patients on 200 mg/day (medium optimum dose), 25% on 300 mg/day and 10% on 400 mg/day in both treatment arms.

Reviewer Comments: Unlike Studies MDT3-002 and -003, patients in this trial were not randomized to a fixed pre-assigned dose. The dose selection was based on patients' tolerability and analgesic effects by the end of titration. Therefore, patient retention was much higher than that in MDT3-002 and -003 (in which patients were assigned to the particular dose group

whatever tolerability and response were); the dropout rate was approximately 21%, which was less than half of those from MDT3-002 and -003 (about 45-47%) (See Table 7d in Section 7.13.1 for details).

It was also possible that the different culture background of study populations across studies impacted the dropout rates since the dropout rates were different in placebo groups, 100% US patients in studies MDT3-002 and -003 (with higher dropouts) vs. 0% in study MDT3-001 and 60% in study MDT3-005 (with lower dropouts).

Assessment visit: there were four visits during the 12-week Maintenance treatment to collect efficacy and safety data.

Primary efficacy analysis: Per-protocol population was used for the primary efficacy analyses on the primary endpoint "percent change in WOMAC pain score from baseline to end of treatment". The Intent-to-treatment (ITT) population with LOCF imputation for missing data was used as an alternative analysis.

6.1.4 Efficacy Findings

Two of three pivotal trials showed that Tramadol OAD was superior to placebo in pain improvement when primary efficacy analysis was performed with LOCF imputation for missing data. However, BOCF imputation analysis and continuous responder analysis failed to support the superiority of Tramadol OAD to Placebo statistically.

Study MDT3-002: *"A four-arm study comparing the analgesic efficacy and safety of Tramadol Once a Day 100, 200, 300 mg versus placebo for the treatment of pain due to Osteoarthritis of the knee"* (See the detailed review in the Appendix)

Subject Disposition: A total of 565 patients with moderate to severe pain (PI-NRS $\geq$ 4) due to the knee OA were enrolled from 75 centers in USA and randomized to placebo group and three dose groups of Tramadol OAD (100, 200 and 300 mg) at ratio of 1:1:1:2 (n=227, 110, 113, and 115). After 1-week titration (13% dropout rate), the patients were treated with the randomized fixed dose for 12 weeks. The overall dropout rate was 43% (243 of 565): 42-53% in the Tramadol OAD groups (100, 200 to 300 mg) and 37% in placebo group. The major reasons for dropout were treatment failure (11-15% on Tramadol OAD vs. 23% on placebo) and adverse events (17-36% on Tramadol OAD vs. 4% on Placebo). The dropout rates in the Tramadol OAD groups dose-dependently increased with respect to the adverse events and decreased with respect to the treatment failure.

Primary Efficacy Analysis: The applicant used the full analysis population for the primary efficacy analysis with LOCF method for missing data and BOCF as an alternative imputation method.

WOMAC Pain Score: the primary efficacy endpoint was the mean percent change in WOMAC Pain score from baseline to end of treatment (week 12). The applicant's analysis showed that there was no statistically significant percent pain improvement in the WOMAC pain score at end

of treatment in patients treated with Tramadol OAD (36% on 100 mg or 200 mg, and 41% on 300 mg) as compared to placebo (38%, p=0.60.8). The applicant did not perform further analyses on the WOMAC Pain data.

A continuous responder analysis was conducted by the statistical reviewer, Dr. Yongman Kim. This analysis assesses the percentage of patients who had 0-100% pain improvement from baseline to end of treatment (week 12). Patient dropouts are defined as non-responders to test if the primary efficacy outcome (the mean % change in pain improvement) is statistically sensitive enough to higher conservative methods for handling dropouts. Other conservative strategies to address dropouts include BOCF imputation method.

In this trial, Tramadol OAD treatment was not superior to placebo in the mean % improvement on WOMAC Pain and no further sensitivity tests is needed. However, the continuous analysis was performed for cross-trial comparison purpose (to compare to studies MDT3-003 and MDT3-005). As expected, although the continuous response curves from the Tramadol OAD-treated patients (all three dose groups) are separated from placebo (Figure 1), there are no statistically significant differences between Tramadol OAD (all three dose groups) and placebo.

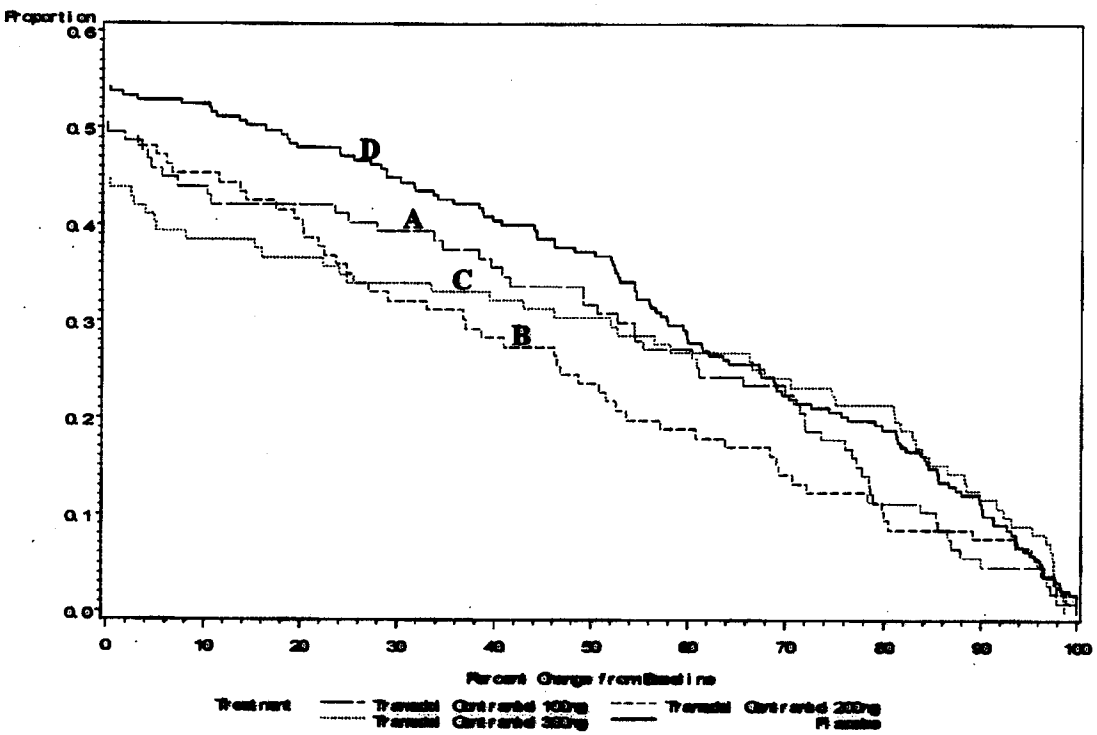


Figure 1. **Continuous Responder Analysis of WOMAC Pain score (Study MDT3-002).** The analysis was performed by the statistical reviewer based on the applicant's dataset. A= Tramadol OAD 100 mg, B=Tramadol OAD 200 mg, C=Tramadol OAD 300 mg and D=Placebo.

Secondary Efficacy Analyses: Patient Global Ratings of Pain Relief was one of co-primary endpoint in the study design, but was later considered a secondary endpoint to support the indication. Based on the applicant's analysis with LOCF imputation for missing data, more patients in the Tramadol OAD 300 mg, but not in the 100 or 200 mg, rated the pain relief "very effective" and "effective" at end of treatment (week 12), 73% of patients on Tramadol OAD 300 mg vs. 59% on placebo; the difference was statistical significant. However, analysis using BOCF as an alternative imputation method (performed by this reviewer) did not support the statistical significance.

The 24-hour VA Pain Questionnaire and WOMAC Function Subscale were other secondary efficacy endpoints; both did not show statistically significant differences between Tramadol Contramid OAD and placebo with LOCF imputation analysis.

Conclusion: This trial failed to demonstrate that Tramadol OAD (100, 200 or 300 mg) was superior to placebo in improving pain in the OA patients. The applicant also concluded that this was a failed efficacy trial.

Study MDT3-003: *"A four-arm study comparing the analgesic efficacy and safety of Tramadol Once a Day 100, 200, 300 mg versus placebo for the treatment of pain due to Osteoarthritis of the knee"* (This was a replicate trial of MDT3-002; see the detailed review in the Appendix)

Subject Disposition: A total of 550 patients with moderate to severe pain due to knee OA enrolled from 74 study centers in USA. The subjects were randomized to placebo and three dose groups of Tramadol OAD (100, 200 and 300 mg) at ratio of 1:1:1:2 (n=227, 106, 111 and 108, respectively). After 1-week titration (15% dropout rate), the patients were treated with the randomized fixed dose for 12 weeks. The overall dropout rate was 44% (241 of 552): 41-54% in the Tramadol OAD groups (100, 200 to 300 mg) and 41% in placebo group. The major reasons for dropout were treatment failure (10-20% on Tramadol OAD vs. 21% on placebo) and adverse events (12-32% on Tramadol OAD vs. 7% on Placebo). The dropout rates in the Tramadol OAD groups dose-dependently increased with respect to the adverse events and decreased with respect to the treatment failure.

Primary Efficacy Analysis: The applicant used the same analysis approach as in MDT3-002, the full analysis population with LOCF imputation.

WOMAC Pain Score: In the applicant's primary analysis, the mean percent change in WOMAC Pain score from baseline to end of treatment (week 12), with LOCF imputation for missing data, was 42% on Tramadol OAD 100 mg, 43% on 200 mg 46% on 300 mg and 32% on placebo. The difference in the percent pain improvement between Tramadol OAD 300 mg (but no 100 mg or 200 mg) and placebo was statistically significant, 13.4% (95% CI: 2.5-24.4, p=0.0162), even after multiplicity adjustment for type I error (α =0.0167). However, with alternative imputation methods, RSOCF (reason specific observation carried forward) and BOCF (baseline observation carried forward), the applicant could not reproduce the statistically significant differences between Tramadol OAD and placebo. Although MOCF (median observation carried forward) method showed statistical significance between Tramadol OAD 100 mg or 300 mg and placebo, the middle dose level, Tramadol OAD 200 mg, showed no significant difference from placebo.

The applicant also performed a multiple (but not continuous) responder analysis on WOAMC Pain score, with response (pain improvement from baseline) cut-offs of 10%, 30% and 50%. However, the dropouts were not defined as non-responders in this analysis. The proportion of patients with 30% pain improvement was 58% on Tramadol OAD 100 mg, 65% on 200 mg or 300 mg, and 50% on placebo. The differences between Tramadol OAD 200 mg or 300 mg and placebo were statistically significant after multiplicity adjustment. The responders in the Tramadol OAD groups also required shorter time to response than those in placebo (33 days on 300 mg, 50 days on 100 or 200 mg and 94 days on placebo in the 75% responders).

The statistical reviewer, Dr. Yongman Kim, performed a continuous responder analysis using the applicant's dataset of WOMAC Pain score (defining dropouts as non-responders). As shown in Figure 2, the continuous responder curves from patients treated with Tramadol OAD (all three dose groups) were not statistically separated from placebo, and the responder curve from the Tramadol OAD 200 mg group crossed the placebo line. The result, together with BOCF analysis on the mean % change in WOMAC Pain score, suggests that the pain improvement of Tramadol OAD treatment based on LOCF analysis may not reflex a true analgesic effect.

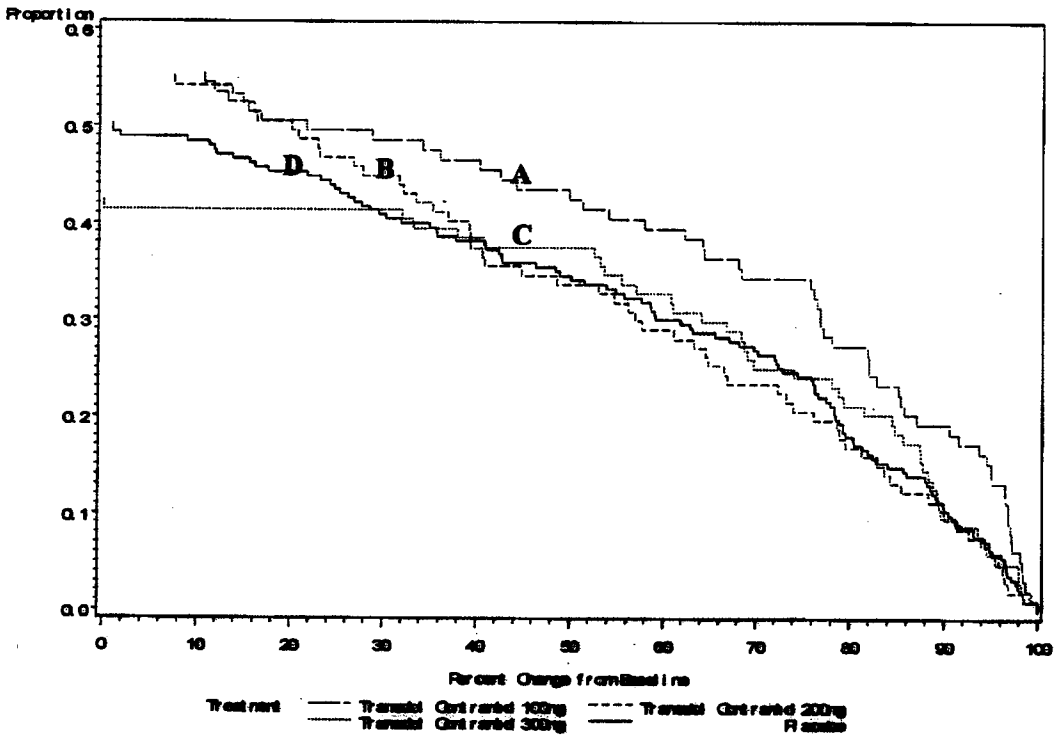


Figure 2. **Continuous Responder Analysis of WOMAC Pain score (Study MDT3-003).** The analysis was performed by the statistical reviewer. A= Tramadol OAD 100 mg, B=Tramadol OAD 200 mg, C=Tramadol OAD 300 mg and D=Placebo.

Secondary Efficacy Analysis: The applicant's time-course of change in WOMAC Pain Score (Figure 3) showed that starting from week 0 (end of Titration), the Tramadol OAD curves were parallel to the placebo curve during the 12-week maintenance treatment period. The curves did not separate with increasing duration of treatment, but tended to cross, particularly in Tramadol OAD 200 mg group, suggesting that there were no sustained analgesic effects.

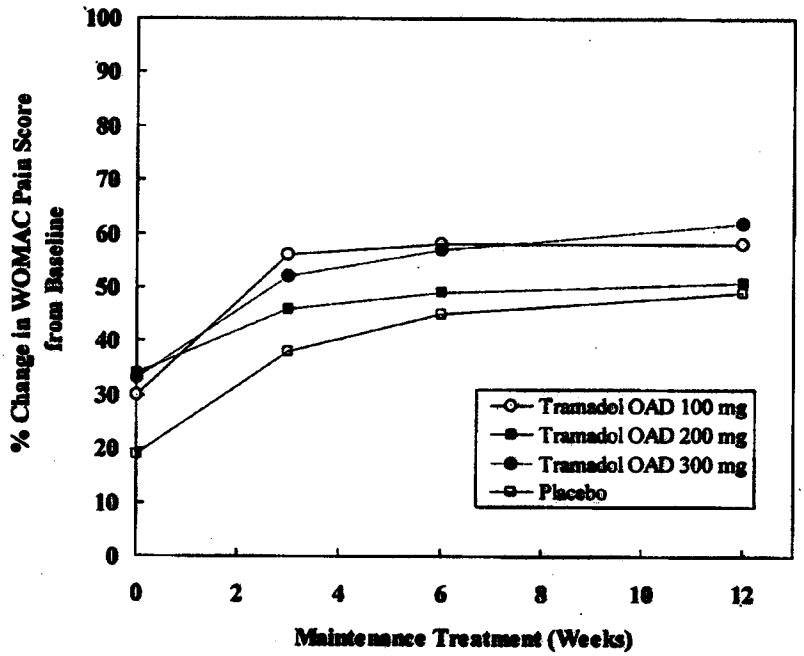


Figure 3. **Time-Course of Pain Improvement in WOMAC Pain Score (MDT3-003)** in patients treated with Tramadol OAD or placebo during the 12-week maintenance dosing period. The data were extracted from the applicant's Table 14.2-13, and the analysis was based on the evaluable patients at each respective visit (without imputation for missing data).

Patient Global Rating of Pain Relief The applicant found that the proportion of patients rating overall pain relief "very effective" and "effective" was 68% for Tramadol OAD 100 mg, 71% for 200 mg, 78% for 300 mg and 60% for placebo at end of treatment with LOCF imputation for dropouts. The differences between Tramadol OAD 200 mg or 300 mg and placebo were statistically significant after multiplicity adjustment for type I error. However, reanalysis of the data with BOCF imputation method (by this reviewer) showed no statistically significant differences between Tramadol OAD at all three dose levels and placebo.

The 24-hour VAS Pain Questionnaire: There were no statistically significant differences in pain ratings between Tramadol OAD and placebo at all visits during the 12-week maintenance treatment period with respect to 24-hour VAS pain ratings.

Conclusion: The applicant's analysis showed that with LOCF imputation for missing data there was a statistically significantly difference in the mean percent change in WOMAC pain score from baseline to end of treatment between Tramadol OAD 300 mg and placebo. However, the difference was not statistically supported by analyses with BOCF imputation for missing data, the continuous responder analysis, and the time-response relationship analysis. Therefore, treatment with Tramadol OAD 100, 200 or 300 mg for 12 weeks in patients with pain due to osteoarthritis did not result in statistically significant pain improvement in WOAMC Pain score.

MDT3-005: ***"A Two-arm Study Comparing the Analgesic Efficacy and Safety of Tramadol Contramid OAD versus Placebo for the Treatment of Pain due to Osteoarthritis"*** (See the detailed review in the Appendix)

Subject disposition: A total of 1028 patients with moderate to severe pain associated with the knee OA were enrolled into the open-label Tramadol OAD (100-300 mg) treatment phase (run-in titration, taper and washout). Approximately 37% of patients (381 of 1028) withdrew by the end of the open-label phase.

Of 1028 patients, 646 patients (63%) who experienced flaring pain by the end of washout and tolerated 200-300 mg Tramadol OAD well entered the double-blind phase. They were randomized to Tramadol OAD (n=432) and Placebo (n=214). After a 2-week titration to an optimum dose of Tramadol OAD 200 mg (n=103) or 300 mg (n=325), 91% of patient on Tramadol OAD (n=395) and 92% of patient on placebo (n=196) entered the 12-week Maintenance treatment (at a fixed dose).

Overall, 24% of patients (155 of 646) dropped out during the double-blind phase; 25% (106 of 432) on Tramadol OAD and 23% (49 of 214) on Placebo. The main reasons for dropouts were treatment failure (34% on Tramadol OAD and 49% on Placebo) and AEs (42% on Tramadol OAD and 22% on Placebo).

Efficacy analysis: The applicant' primary efficacy endpoint was the mean change in pain intensity as measured by an 11-point NSR (PI-NRS) from baseline to end of treatment (week 12, with LOCF imputation for missing data). Tramadol OAD (200 mg and 300 mg combined) treatment was statistically superior to placebo by a mean difference of 0.48 points (2.9 ±2.5 vs. 2.4±2.4, p=0.016), or 7% (40.3% vs. 33.3% change from baseline). However, further analyses did not support this marginal superiority:

1. BOCF imputation for missing data and the repeated measure analyses did not show statistical superiority of Tramadol OAD to placebo.

2. Continuous responder analysis based on the statistic reviewer's reanalysis showed that, overall, Tramadol OAD treatment was not superior to placebo (Figure 4).

3. Time-response relationship analysis of the percent change in pain intensity (PI-NRS) with LOCF imputation for missing data showed that with increasing duration of treatment the time curve of Tramadol OAD tended to cross with that of placebo (Figure 5).

4. The applicant's analysis of the mean change in WOMAC Pain score from baseline to end of treatment (a main secondary endpoint) did not show statistically significant superiority of Tramadol OAD to placebo (with difference of 6.1%, p=0.058) with LOCF imputation for missing data. There was the same trend in time-response as in the PI-NRS analysis (Figure 6).

5. There was also no significant superiority of the Tramadol OAD treatment to placebo on the Patient or Physician Global Impression of Change ("very much improved" and "much improved") with LOCF imputation for missing data.

Conclusion: With LOCF imputation analysis, Tramadol OAD (200 mg or 300 mg) treatment was marginally superior (7%) to placebo in pain improvement based on the primary endpoint, mean change in pain intensity on 11-point NRS. However, this marginal superiority was not sensitive to the more conservative BOCF imputation method for missing data due to dropouts, and was not seen in the continuous responder analysis. In addition, mean change in WOMAC Pain Score from baseline, a secondary endpoint in this trial, showed no statistically significant difference between Tramadol OAD and placebo. The results of the WOAMC Pain score did not support findings from Study MDT3-003, in which the mean change in WOMAC Pain Score was a primary endpoint and showed greater improvement for the Tramadol OAD group compared to placebo.

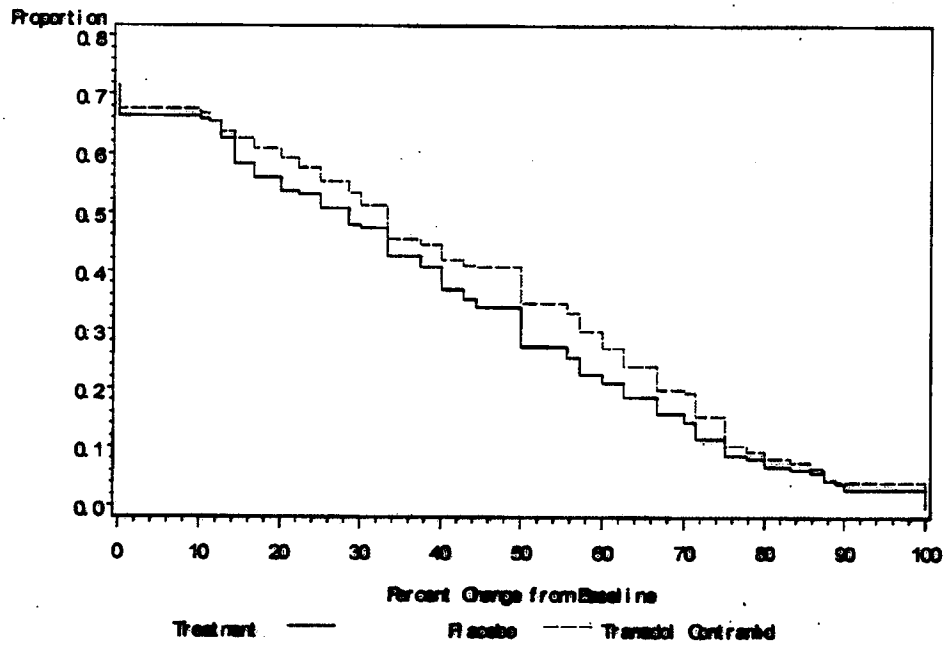


Figure 4. **Continuous Responder Analysis of Pain Intensity-NRS (MDT3-005) performed by the statistical reviewer. The dropouts were defined as non-responders. The percent responders are expressed as proportion (0-0.8, or 0-80%). The *black solid line* represents placebo and the *red broken line* represents Tramadol OAD (200 mg and 300 mg).**

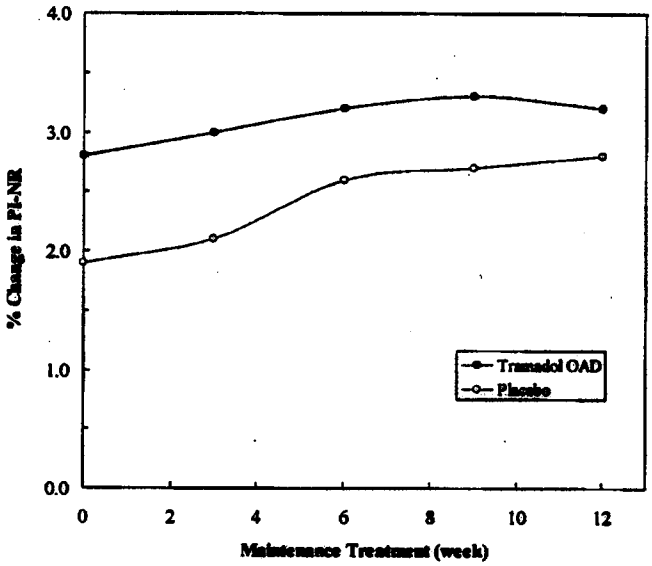


Figure 5. **Time-response Analysis of Pain Intensity NRS (MDT3-005)** in patients treated with Tramadol OAD (200 and 300 mg) or placebo with LOCF imputation for early dropouts. Data extracted from the applicant's Table 11.4.1.1.1-2 (MDT3-005 report).

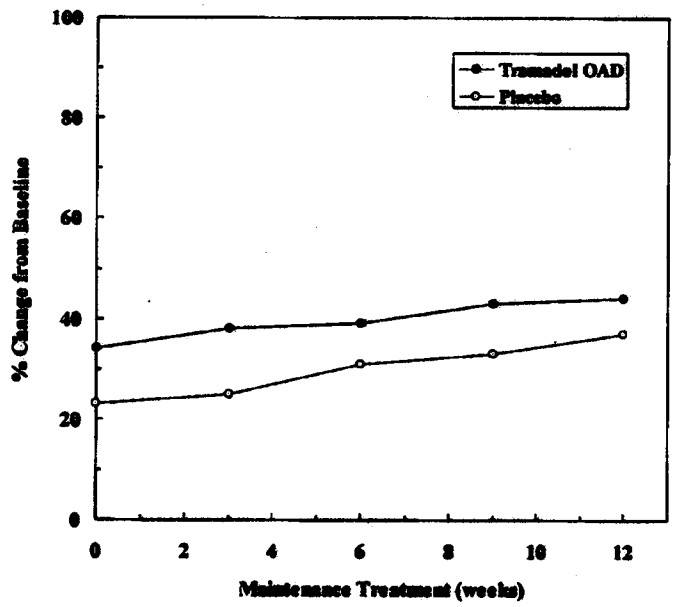


Figure 6. **Time-response Analysis of WOMAC Pain Score (MDT3-005)** in patients treated with Tramadol OAD (200 and 300 mg) or placebo with LOCF imputation for early dropouts. Data were extracted from the applicant's Table 11.4.1.2.4-2 (MDT3-005 report).

Study MDT3-001-E1: *"A comparison of the analgesic efficacy and safety of once daily tramadol HCl/Contramid Tablets to twice daily tramadol HCl (SR) for the treatment of osteoarthritis of the knee"* (See the detailed review in the Appendix)

Subject disposition: A total of 431 patients were enrolled from 21 study centers and randomized to 2 groups, Tramadol OAD (n=215) and Tramadol BID (n= 216). After up to 2 weeks of titration (from 100 to 400 mg/day), the patients were treated with the fixed optimum dose for 12 weeks (Maintenance treatment); the median optimum dose (taken by about 50% of patients) was 200 mg/day in both groups. Overall dropout rate was 21% in both group, or 79% of patients (171 each group) completed the 12-week maintenance treatment.

Of 89 dropouts, 43% in Tramadol OAD and 49% in Tramadol BID were due to AEs; 34% in Tramadol OAD and 27% in Tramadol BID were associated with treatment failure.

Efficacy analysis: The mean % change in WOAMC Pain scores (primary endpoint) from baseline was 53% (in ITT population with LOCF imputation for missing data) and 58% (in per-protocol population) for both Tramadol OAD and Tramadol BID groups. The difference in the percent pain improvement (95% CI) between Tramadol OAD and Tramadol BID was -5.75% to 6.28% (in ITT) or -7.67% to 3.82% (in PP), which were within 15% predefined non-inferiority margin.

The secondary endpoints (a 24-hour pain VAS ratings, WOMAC Stiffness and Physical Function Scores, and patient global assessment) were similar between Tramadol OAD and Tramadol BID treatments in either PP or ITT population. The applicant concluded the non-inferiority of Tramadol OAD to Tramadol BID.

Conclusion: Per the applicant's analyses using either PP or ITT population (with LOCF imputation) and pre-specified non-inferiority margin (15% difference), Tramadol OAD was non-inferior to Tramadol BID based on the primary efficacy endpoint, mean change in WOMAC pain score from baseline to the end of the study. This non-inferiority was supported by the secondary efficacy endpoints. The safety profiles were also comparable between Tramadol OAD and BID. However, the results from this trial play very limited supportive rule in the efficacy evaluation of Tramadol OAD for the following reasons:

- Adequacy of the 15% of non-inferiority margin was unknown. The applicant did not provide a rationale for the pre-specified non-inferiority margin in the study design or the discussion of the results.
- In general, the intrinsic variability of pain trials is too high for estimation of a non-inferiority margin. For example, in this NDA, the differences in WOMAC Pain score change from baseline to end of treatment (LOCF method) between Tramadol OAD and placebo were 10-13% in Study MDT3-003 and 6% in Study MDT3-005; both were less than 15% (the pre-specified non-inferiority margin).
- A placebo-controlled arm should be included in the trial to validate the efficacy of active comparator.
- The active comparator used in this trial was Topalgic (Tramadol SR) for BID regimen, which is not a tramadol product marketed in US.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Among the three pivotal trials, with LOCF imputation for missing data, one trial (MDT3-002) failed to show and two trials (MDT3-003 and MDT3-005) suggest that Tramadol OAD (at doses of 300 mg or 200 mg) was statistically superior to placebo in pain improvement in patients with moderate to sever pain sue to the knee OA (Table 6.1.6).

However, this superiority was not supported by further analyses. BOCF imputation and the continuous responder analysis (defining dropouts as non-responders) show no statistically analgesic superiority of Tramadol OAD to placebo. Both analyses are generally conservative with respect to handling of missing data due to dropouts.

The LOCF-based superiority of Tramadol OAD to placebo was too small to be clinically meaningful in context of benefit and risk ratio of tramadol. The difference in percent pain improvement between Tramadol OAD 300 mg and placebo was 13% based on WOAMC Pain score in Study MDT3-003 and 7% based on PI-NRS in Study MDT3-005.

Therefore, in order to gain both statistically and clinically meaningful superiority, it is recommended that the applicant conduct a further efficacy study in different pain populations (other than OA patients) with flexible-dose design to minimize dropout rate and to increase the difference in pain improvement between Tramadol OAD and placebo. An alternative doing regimen should also be considered in the new trial because a 9-hour under-exposure of tramadol (by plasma levels) with once-a-day dosing may have led to less efficacy.

Table 6.1.6. **Overall Summary of Efficacy Findings from Three Pivotal Trials**
(LOCF imputation for missing data due to early dropouts)*

Study	Primary Endpoint	Score at Baseline		Score at End of Treatment		Change from Baseline: Mean (%)		% Superior to placebo	P-value‡
		Tramadol	Placebo	Tramadol	Placebo	Tramadol	Placebo		
MDT3-002	WOMAC Pain†	309±89	302±86	179±136	189±140	129±136 (41%)	112±126 (38%)	2.9	0.56
MDT3-003	WOMAC Pain†	314±97	301±89	172±138	202±149	143±136 (46%)	100±146 (32%)	13.4	***0.016***
MDT3-005	PI-NRS#	7.2±1.6	7.2±1.6	4.3±2.5	4.8±2.4	2.9±2.5 (40%)	2.4±2.2 (33%)	7.0	***0.016***
	WOMAC Pain†	11.2±3.5	11.1±3.2	6.9±4.0	7.5±4.1	4.3±4.2 (37%)	3.6±4.2 (31%)	6.1	0.058

* Data are mean ± SD, based on the applicant's primary analysis in the Full Analysis population (at least one dose and one post-baseline assessment) with LOCF imputation for missing data due to dropouts, which is consistent with the Division's reanalysis (by statistical reviewer). "Tramadol" represents Tramadol OAD 300 mg for MDT3-002 and MDT3-003 and Tramadol OAD (200mg+300 mg) for MDT3-005.

† WOMAC Pain Score in studies MDT3-002 and -003 was based on VAS with a total of 500 points, but in study MDT3-005, as a secondary endpoint, based on Likert scale (0-4) with a total of 20 points.

PI-NRS: paint intensity on 11-point numerical scale (NRS)

‡ p-value for MDT3-003 and MDT3-002 but not MDT3-005 was adjusted by multiplicity to α=0.05/3=0.167.