***Table 2.* Patient Disposition and Dropouts**
(Extracted from the applicant's Figure 10.1-1 and Figure 10.1-2)

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	121.2%)		121.2%)
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

The disposition of patients who attained an optimum dose after titration is shown in Table 2:

- A majority of patients in both Tramadol and placebo groups chose 300 mg as an optimum dose level, with a higher percentage of patients in the placebo group.
- Of patients who titrated to 200 mg or 300 mg, 69-79% completed 12-week treatment at that final dose level in both Tramadol OAD and placebo groups.
- In the Tramadol OAD group, 73 patients on 200 mg and 255 patients on 300 mg at the end of study (week 12).
- Higher percentage of males chose 300 mg dose level (e.g., 84% male vs. 70% female on Tramadol OAD 300 mg); similar percentages among age and ethics.

[The final dose levels at 200 mg or 300 mg were "self-selected" by patients but not randomized or pre-assigned to. Therefore, the subgroups are not comparable (200 mg vs. 300 mg vs. placebo).]

Table 3. **Disposition of Patients at Final Dose Levels in the Double-blind Phase**
(Extracted from the applicant's Figure 10.1-3)

Treatment Group and Period	Final Dose Level	
	200 mg	300 mg
Entry to Titration (n=644)†		
Placebo (n=213)	24 (11%)	189 (89%)
Tramadol OAD (n=431)	106 (25%)	325 (75%)
End of Titration (n=591)‡		
Placebo (n=196)	19 (79%)	177 (94%)
Tramadol OAD (n=395)	87 (82%)	308 (95%)
End of Maintenance (n=495)‡		
Placebo (n=167)	17 (71%)	150 (79%)
Tramadol OAD (n=328)	73 (69%)	255 (78%)

† Final dose was not available for one patient in placebo group and one patient did not take any dose; percentage was based on the number of patients who entered the titration.
‡ Percentage was based on the number of patients in each Final Dose Level (e.g., n=24 for Placebo at 200 mg dose level)

Protocol Deviation:

There were few deviations (< 5%) related to eligibility criteria in the safety population (Table 4). About 12% (n=76 of 646) of the randomized patients had protocol deviation and were excluded from per-protocol population; 10% (n=22 of 214) in the placebo group and 13% (n=54 of 432) in the Tramadol OAD group; mainly due to "date of last dose not within 2 days before M84 PI score assessment" (7%) and concomitant mediations (4%).

Table 4. **Violations of Inclusion and Exclusion Criteria in Safety Population**
(Extracted from the applicant's Table 10.2-1)

Violation	Not randomized N=377	Randomized (to double-blind phase)		Overall N=1023
		Placebo N=214	Tramadol OAD N=432	
Inclusion criteria at enrollment	14 (4%)	2 (0.9%)	12 (3%)	28 (3%)
Exclusion criteria at enrollment	17 (5%)	3 (1%)	7 (2%)	27 (3%)
Inclusion criteria into Double-blind	41 (11%)			41 (4%)

Baseline Characteristics

Demographics:

In the Full Analysis (FA) population, there were no remarkable differences between the placebo and Tramadol OAD groups with respect to the gender (62% female), age (mean=62 years), BMI (mean=31) and ethnic origin (72% Caucasian) (Table 5).

Baseline Efficacy Parameters:

- The mean PI-NRS and WOMAC Pain Subscale scores in the FA population were almost identical between placebo and Tramadol OAD groups at baseline (i.e., at the end of Washout during the Open-label phase) (Table 6)
- The Physical Activity levels of patients were comparable in the FA population between placebo and Tramadol OAD group at baseline.

Past and Concurrent Medical History

- All enrolled patients had at least one past or concurrent medical conduction.
- The most common medical history was musculoskeletal and connective tissue disorders with the same proportion (97%) between the placebo and Tramadol OAD groups.
- Approximately, half of the patients in the placebo and Tramadol OAD groups had a previous surgical or medical procedure (55% vs. 57%) and vascular disorders (46% vs. 52%).
- GI disorders: 30% in the placebo vs. 32% in the Tramadol OAD
- Nervous system disorders: 18% in the placebo and 19% in the Tramadol OAD.

Prior Medication

- All enrolled patient had any prior medication
- The most common medications were NSAIDs (propionic acid derivatives and coxibs), 52% in the placebo and 56% in the Tramadol OAD, followed by cardiovascular medicine.
- The incidence of prior medication use was similar between the placebo and Tramadol OAD, and between randomized and non-randomized patients.

Table 5. **Demographics of Full analysis Population**
(Adapted from the applicant's Table 11.2.1-1)

	Treatment during Double-Blind Phase		
Variable	Placebo N=214	Tramadol Contramid® OAD N=431	Overall N=645
Gender			
Female n (%)	133 (62%)	274 (64%)	407 (63%)
Male n (%)	81 (38%)	157 (36%)	238 (37%)
Age (years)			
Mean ± SD	62 ± 9	62 ± 9	62 ± 9
Median	63	63	63
Min, Max	41, 79	41, 80	41, 80
Male (n)			
Mean ± SD	63 ± 9	62 ± 9	62 ± 9
Median	65	63	64
Min, Max	41, 79	41, 80	41, 80
Female (n)			
Mean ± SD	62 ± 9	62 ± 9	62 ± 9
Median	62	62	62
Min, Max	41, 79	41, 80	41, 80
Age group			
< 65 years n (%)	116 (54%)	252 (58%)	368 (57%)
≥ 65 years n (%)	98 (46%)	179 (42%)	277 (43%)
≥ 75 years n (%)	17 (7.9%)	30 (7.0%)	47 (7.3%)
Ethnic origin n (%)			
Asian	1 (0.5%)	1 (0.2%)	2 (0.3%)
Black	12 (6%)	21 (5%)	33 (5%)
Caucasian	185 (86%)	379 (88%)	564 (87%)
Hispanic	15 (7%)	28 (6%)	43 (7%)
Other	1 (0.5%)	2 (0.5%)	3 (0.5%)
BMI (kg/m^2)			
Mean ± SD	29.5 ± 4.3	29.7 ± 4.0	29.6 ± 4.1
Median	30.1	29.9	30.0
Min, Max	19.5, 37.4	19.5, 37.6	19.5, 37.6
Male (n)			
Mean ± SD	29.5 ± 3.9	30.0 ± 3.8	29.8 ± 3.8
Median	30.0	30.1	30.1
Min, Max	19.6, 36.1	21.0, 37.6	19.6, 37.6
Female (n)			
Mean ± SD	29.5 ± 4.5	29.5 ± 4.1	29.5 ± 4.2
Median	30.1	29.5	29.7
Min, Max	19.5, 37.4	19.5, 37.0	19.5, 37.4

Source: Statistical table 3.1.2
Note: Percentages are based on the total number of patients randomized given in the column headings
Note: Percentages ≥1% were rounded off to the nearest percentage point before the decimal point, so totals may not add up to 100%
Note: Age values were rounded off to the nearest whole figure
Note: BMI values were rounded off to the nearest decimal point

Table 6. **Baseline Efficacy Parameters in the Full Analysis (FA) Population**
(Adapted from the applicant's Table 11.2.1-2)

	Treatment during Double-Blind Phase	
Efficacy parameters	Placebo N=214	Tramadol Contramid® OAD N=431
Pain Intensity Score (PI-NRS)		
N	214	431
Mean ± SD	7.2 ± 1.6	7.2 ± 1.6
Median	7.0	7.0
Min, Max	4, 10	3, 10
WOMAC Pain Subscale Score		
N	214	431
Mean ± SD	11.1 ± 3.2	11.2 ± 3.5
Median	11.0	11.0
Min, Max	3, 20	2, 20

Source: Statistical tables 4.1.1.1, 4.2.1.1, 4.3.1.1
Baseline = Visit 4.
Note: The Pain Intensity Score ranges from 0 = no pain to 10 = worst possible pain.
Note: The WOMAC Pain Score ranges from 0 = no pain to 4= extreme pain for each item, for a maximum total score of 20 (5 items).

Baseline Physical Examination

- No notable differences in the baseline PE findings between the placebo and Tramadol OAD groups
- Slightly more cardiac abnormalities in patients who were not randomized (14% vs. 7% in the randomized patients).

Treatment Compliance

- The patients' compliance (%) was evaluated by tablet counting, "Number of Tablet Taken/Number of Table Planned", based on patients who entered the appropriate period.
- Run-in period of the Open-label phase: 99.2±90% (0-150%)
- Titration period of the Double-blind phase: 99.4±47% on placebo vs. 99.2±64% on Tramadol OAD
- Maintenance period of the Double-blind phase: 100.5±127% on placebo vs. 98.7±50% on Tramadol OAD

Efficacy Evaluation

Efficacy analyses were performed on both "Full Analysis (FA)" and "Per Protocol (PP)" populations (Figure 2). The primary analysis was based on the FA population, which was presented in the report, as summarized below. The results from the PP population analyses were presented in the appendix 16.5.3 of the applicant's submission.

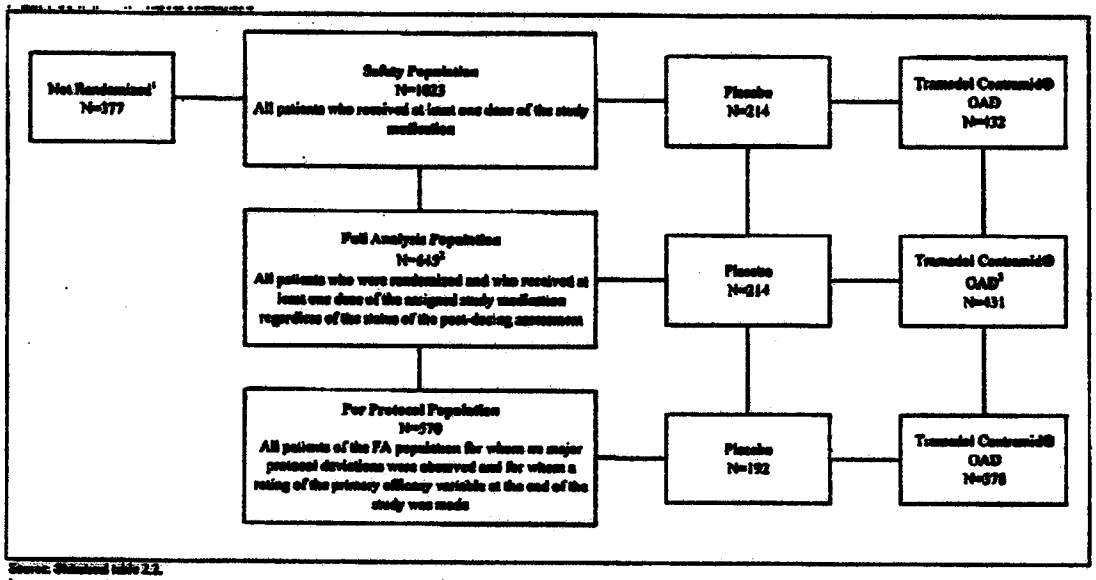

Figure 2. **Analysis Populations**

Primary Endpoint: Change in mean Pain Intensity Numerical Rating Score (PI-NRS) from baseline to end of treatment (week 12)

The PI-NRS data were analyzed with two pre-specified methods (LOCF imputation and time-weighted average) and three post-hoc analyses (responder analysis, repeated measures, sum of PI differences, and BOCF imputation method).

The applicant's primary analysis on the PI-NRS data was based on the LOCF imputation for missing data (Table 7a) with the following findings:

- At the end of the double-blind treatment (12 weeks), the mean change in pain intensity (PI-NRS) and % pain improvement from baseline (Visit 4, end of washout during the Open-label phase) were:
  - Tramadol OAD (n=428): 2.9±2.5 (95% CI: 2.9-3.1), or 40.3% from baseline
  - Placebo (n=211): 2.4±2.4 (95% CI: 2.1-2.7), or 33.3% from baseline
  - Difference (mean): *-0.48* (95% CI: -0.87 to -0.090), p = 0.0157 (ANCOVA)

    Or *7% difference between Tramadol OAD (40.3%) and placebo (33.3%)*

- At the end of Titration during the Double-blind phase, the mean pain intensity (PI-NRS) improvement from baseline (Visit 4, end of washout during the Open-label phase):
  - Tramadol OAD (n=395): 2.8±2.3 (95% CI: 2.6-3.0)
  - Placebo (n=196): 1.9±2.1 (95% CI: 1.6-2.2)
- At all other visits during the Double-blind phase, the mean differences in pain improvement ranged from 0.4 to 0.9 in favor of Tramadol OAD treatment, but with high variations (SD) at shown in Figure 3.
- Differences in pain improvement among gender, age and race at Week 12: no statistically significance between Tramadol OAD and placebo in patients aged < 65 years, males, and non-Caucasian.

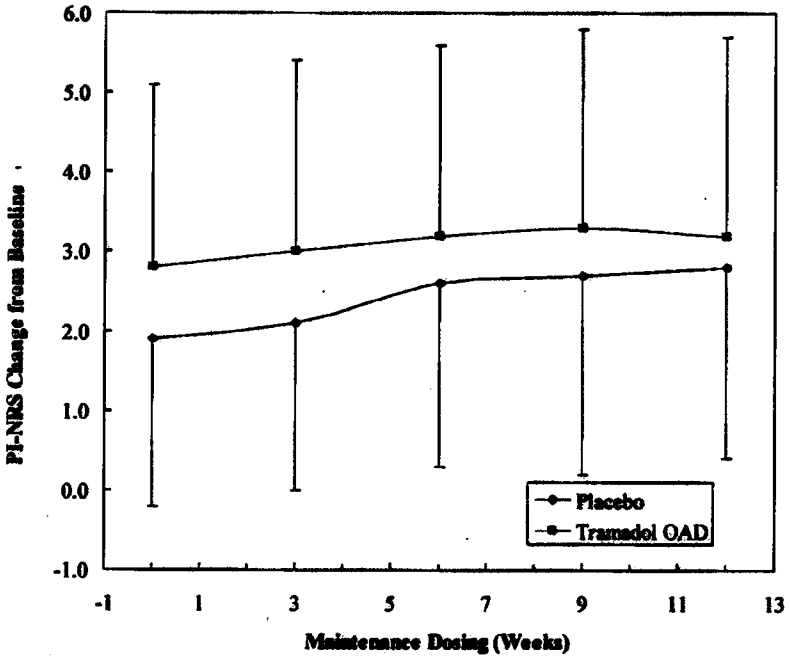

Figure 3. **Time-response of Pain Intensity NRS**
Data are mean ± SD, extracted from the applicant's Table 11.4.1.1.1-2
(LOCF imputation for missing data)

Time-weighted Average (Post-hoc): The PI-NRS data were analyzed using the Time-weighted Average (TWA) method in patients who had at least two post-baseline PI-NRS assessments (Table 7b).

- The pain improvement at the last individual visit:
  - Tramadol OAD (n=393): 3.03±2.12 (95% CI: 2.82-3.24)
  - Placebo (n=196): 2.29±1.97 (95% CI: 2.02-2.57)
  - Difference (mean): -0.70 (95% CI: -1.02 - -0.38), p<0.001 (ANCOVA)
- The pain improvement at the end of titration:
  - Tramadol OAD (n=428): 2.7±2.3 (95% CI: 2.5-2.9)
  - Placebo (n=211): 1.8±2.1 (95% CI: 1.5-2.1)

- The pain improvement across all visits during the Maintenance period: 0.5-0.9 in favor of the Tramadol OAD treatment.
- The statistically significant pain improvement showed in the age (< or ≥ 65 yo), gender and race (Caucasia and non-Caucasian) subgroups.

Table 7a. **Pain Intensity NRS Analysis with LOCF Imputation at Week 12**
(Adapted from the applicant's Table 11.4.1.1.1-1)

Pain Intensity Score	Placebo N=214	Tramadol Contramid® OAD N=431
Baseline (Visit 4)		
N	214	431
Mean ± SD	7.2 ± 1.6	7.2 ± 1.6
Median	7.0	7.0
Min, Max	4, 10	3, 10
Week 12 (Visit 9)		
N	167	328
Mean ± SD	4.3 ± 2.2	4.0 ± 2.4
Median	4.0	3.5
Min, Max	0, 9	0, 9
Last Individual Visit (LOCF)		
N	211	428
Mean ± SD	4.8 ± 2.4	4.3 ± 2.5
Median	5.0	4.0
Min, Max	0, 10	0, 10
Absolute Improvement (LOCF) (Baseline – Last Individual Visit)		
N	211	428
Mean ± SD	2.4 ± 2.4	2.9 ± 2.5
95% CI	[2.1; 2.7]	[2.7; 3.1]
Median	2.0	3.0
Min, Max (neg value=deterioration)	-3, 9	-4, 9
Difference in Absolute Improvement Between Tramadol Contramid® OAD and Placebo		
Estimate (mean)	-0.48	
95% CI	[-0.87; -0.09]	
p-value[1]	0.0157	

Source: Statistical tables 4.1.1.1, 4.1.2.1
The Pain Intensity Score ranges from 0 = no pain to 10 = worst possible pain.
Last individual visit = Visit 9 or time of discontinuation.
LOCF: Last Observation Carried Forward.
LOCF was calculated only for patients with at least one post-baseline assessment.
If the upper bound of the 95% CI is <0, superiority of Tramadol Contramid® OAD versus Placebo with regard to PI-NRS can be concluded.
[1]p-value based on an ANCOVA.

Table 7b. **Patients Intensity NRS Analysis with Time-weighted Average**
(Adapted from the applicant's Table 11.4.1.1.2-1)

Pain Intensity Score	Placebo N=214	Tramadol Contramid® OAD N=431
Baseline (Visit 4)		
N	214	431
Mean ± SD	7.2 ± 1.6	7.2 ± 1.6
Median	7.0	7.0
Min, Max	4, 10	3, 10
Week 12 (Visit 9)		
N	211	427[2]
Mean ± SD	4.8 ± 2.4	4.3 ± 2.5
Median	5.0	4.0
Min, Max	0, 10	0, 10
Last Individual Visit (Time Weighted Average (TWA))		
N	196	393
Mean ± SD	4.87 ± 1.94	4.20 ± 1.99
Median	5.00	4.00
Min, Max	0.8, 10.0	0.0, 9.4
Absolute Improvement (Baseline – Last Individual Visit)		
N	196	393
Mean ± SD	2.29 ± 1.97	3.03 ± 2.12
95% CI	[2.02; 2.57]	[2.82; 3.24]
Median	2.10	3.00
Min, Max (neg. value=deterioration)	-4.0, 8.0	-3.9, 9.0
Difference in Absolute Improvement Between Tramadol Contramid® OAD and Placebo		
Estimate (mean)	-0.70	
95% CI	[-1.02; -0.38]	
p-value[1]	<0.0001	

Source: Statistical tables 4.1.1.1, 4.1.2.1.
The Pain Intensity Score ranges from 0 = no pain to 10 = worst possible pain
Last individual visit = Visit 9 or time of discontinuation.
If the upper bound of the 95% CI is <0, superiority of Tramadol Contramid® OAD versus Placebo with regard to PI-NRS can be concluded on a descriptive level.
[1]p-value based on an ANCOVA.
[2]One patient who did not discontinue had a missing PI-NRS at Visit 9 (12 weeks), explaining the discrepancy with n=428 according to LOCF.

$$TWA = \frac{AUC}{t_1 + t_2 + \ldots t_i} = \sum d_i \times w_i \; ; \quad w_i = \frac{t_i + t_{i+1}}{2t}$$

TWA was calculated only if there were at least 2 post-baseline assessments available.

Responder Analysis (Post-hoc): The applicant performed a multiple-responder analysis. The pain improvement (response) from baseline to end of treatment (dropouts were imputed with LOCF or defined as non-responders) was categorized to 1 to 5 points and the cumulative curves were plotted against % responders in Tramadol OAD and placebo groups.

- The cumulative responder curves consistently separated between placebo and tramadol OAD for pain improvement points 1-5 when dropouts were imputed with LOCF or defined as non-responders (Figure 4a).

- The differences between Tramadol OAD and placebo were statistically significant at all five levels of pain improvement (for data with LOCF, Table 8c) and ≥ 3-5 points (for dropouts as non-responder, Table 7d).

- The differences in the pain improvement from 1-5 points between Tramadol OAD and Tramadol when the dropouts were defined non-responders were 5-14% (Table 7d). For the pain improvement ≥ 2 points, as a pre-specified response definition (concurred by the Division), Tramadol OAD treatment was only 5% superior to placebo with no statistically significance (p=0.099).

- The Tramadol OAD 300 mg treatment showed better response than 200 mg ($p < 0.05$ at all 5 levels) (Table 7d) with LOCF imputation [however, *subgroup comparison with non-LOCF imputation was not reported*].

- The median time to response was significantly shorter or earlier in the Tramadol OAD group than in the placebo; about 39 days on placebo vs. 16-20 days on Tramadol OAD with pain improvement of ≥ 3 points. The median onset time was similar between Tramadol OAD 200 mg and 300 mg.

- There were no notable difference between placebo and Tramadol OAD among gender, age and race for data with LOCF.

However, the continuous responder analysis performed by the statistics reviewer found differences in terms of number of responder at different levels of response (PI-NR change from baseline). When the dropouts were defined as non-responders, the continuous responder curves did not statistically separate (Figure 4b) between Tramadol OAD and placebo, and the difference between Tramadol OAD and placebo was much smaller than that from the applicant's analysis.

Table 7c. **Responder Analysis of PI-NRS with LOCF Imputation for Missing Data**
(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		Chi-square test p-value
	Evaluable Subject†	Responder n (%)	Evaluable Subject†	Responder n (%)	
≥ 1	211	187 (88.6%)	428	400 (93.5%)	0.036
≥ 2	211	170 (80.6%)	428	372 (86.9%)	0.035
≥ 3	211	134 (63.5%)	428	322 (75.2%)	0.002
≥ 4	211	99 (46.9%)	427	251 (58.8%)	0.005
≥ 5	203	61 (30.0%)	406	183 (45.1%)	0.000

* Pain intensity-numerical Rating Score (PI-NRS) change from baseline to Week 12 with LOCF imputation for early dropouts.

† 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)

Table 7d. **Responder Analysis of PI-NRS with 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)

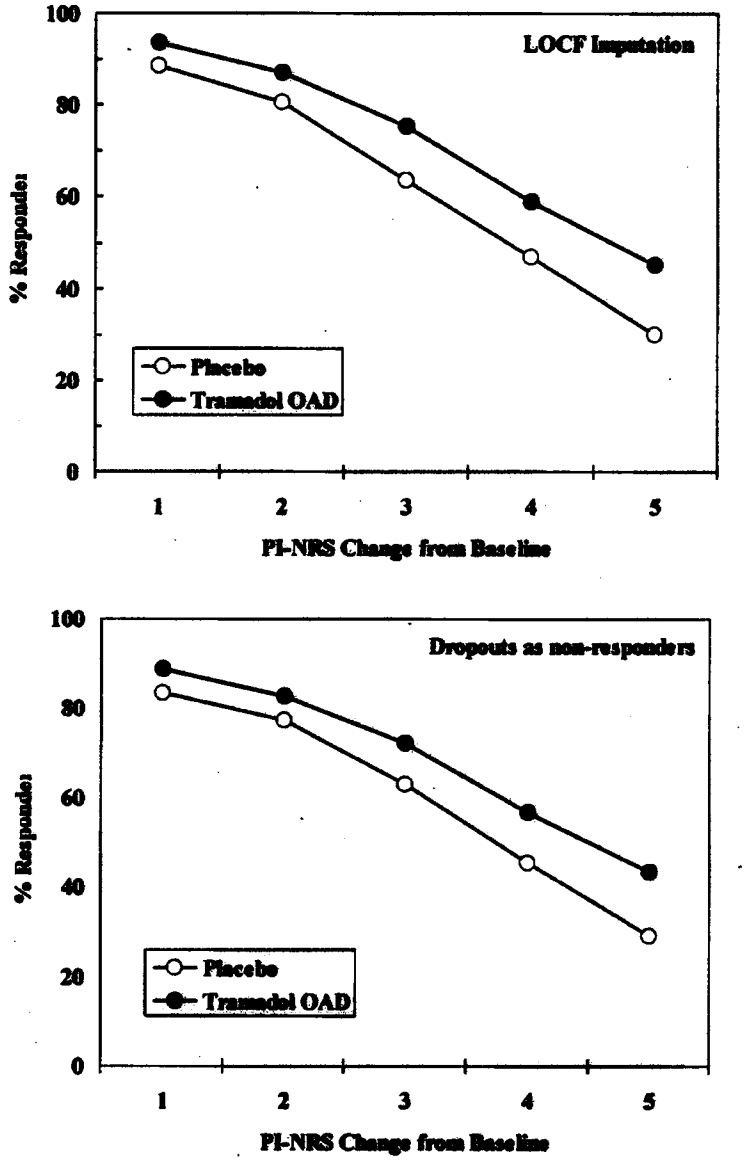

Figure 4a. **Applicant's Responder Analysis.** Percentage of patients who had the pain improvement (change on PI-NRS) by at least 1-5 points from baseline to Week 12 (end of Maintenance treatment). The missing data were imputed with LOCK (*upper panel*, $p<0.05$ with Chi-square for all points) or the dropouts were defined as non-responder (*lower panel*, $p<0.05$ with Chi-square for points 3-5). See Tables 8c & 8d for detail.

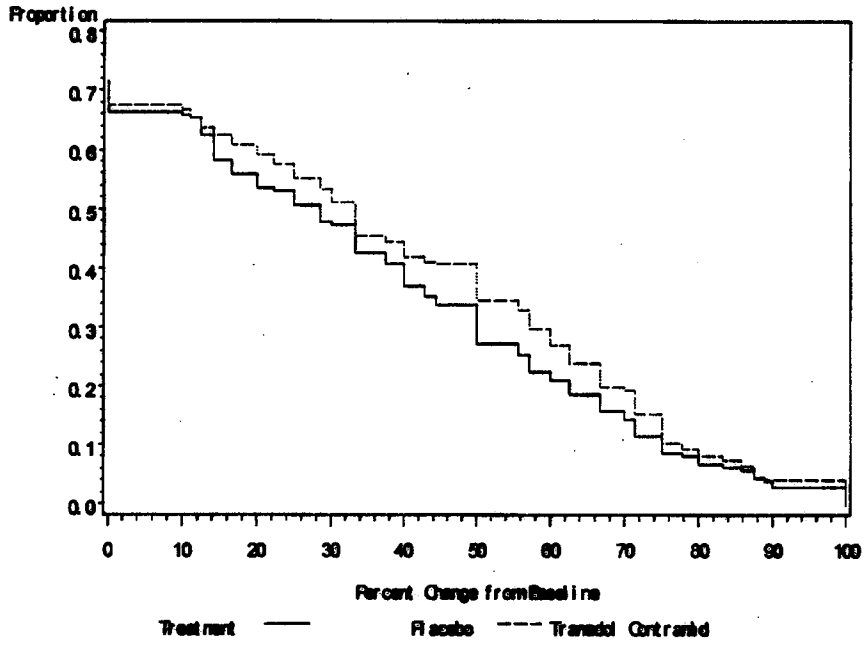

Figure 4b. **The FDA's Cumulative Continuous Responder Analysis on PI-NRS.** The statistical reviewer performed a reanalysis on the responder data based on the dataset submitted electronically by the applicant. The dropouts were defined as non-responders. The *solid* represents Placebo and the *dashed* represents Tramadol OAD (200 and 300 mg).

Table 7e. **Responder Analysis on PI-NRS with LOCF Imputation**
(Adapted from the applicant's Table 11.4.1.1.3.1-2)

	Treatment			
Response	Placebo N=214	Tramadol Contramid® OAD (all doses) N=431	Tramadol Contramid® OAD 200 mg N=106	Tramadol Contramid® OAD 300 mg N=325
Improvement of 1 point				
Responder n (%)	187 (88.6%)	400 (93.5%)	95 (92.2%)	305 (93.8%)
Responder (p-value)[1,2]	-	0.036	0.331	0.031
Time to response				
Median for number of days to response	14 [-;-]	14 [-;-]	14 [-;-]	14 [-;-]
3rd Quartile for number of days to response	21 [15.0;36.0]	15 [-;-]	15 [15.0;16.0]	15 [-;-]
Time to response (p-value)[1,3]	-	0.002	0.016	0.004
Improvement of 2 points				
Responder n (%)	170 (80.6%)	372 (86.5%)	86 (83.5%)	286 (88.6%)
Responder (p-value)[1,2]	-	0.035	0.530	0.018
Time to response				
Median for number of days to response	15 [14.0;16.0]	14 [14.0;15.0]	14 [14.0;15.0]	14 [14.0;15.0]
3rd Quartile for number of days to response	56 [35.0;57.0]	35 [35.0;36.0]	25 [15.0;61.0]	35 [35.0;57.0]
Time to response (p-value)[1,3]	-	0.017	0.077	0.024
Improvement of 3 points				
Responder n (%)	134 (63.5%)	322 (75.2%)	73 (70.9%)	249 (76.6%)
Responder (p-value)[1,2]	-	0.002	0.196	0.001
Time to response				
Median for number of days to response	29 [15.0;56.0]	16 [15.0;35.0]	16 [15.0;28.0]	28 [15.0;35.0]
3rd Quartile for number of days to response	101 [100;101]	59 [56.0;98.0]	77 [36.0;-]	57 [56.0;98.0]
Time to response (p-value)[1,3]	-	0.000	0.006	0.000
Improvement of 4 points				
Responder n (%)	99 (46.9%)	251 (58.8%)	54 (52.9%)	197 (60.6%)
Responder (p-value)[1,2]	-	0.000	0.318	0.002
Time to response				
1st Quartile for number of days to response	35 [35.0;56.0]	15 [14.0;15.0]	15 [14.0;33.0]	14 [14.0;15.0]
Median for number of days to response	98 [63.0;-]	56 [36.0;57.0]	57 [35.0;99.0]	56 [36.0;57.0]
Time to response (p-value)[1,3]	-	0.000	0.021	0.000
Improvement of 5 points				
Responder n (%)	61 (28.6%)	183 (45.1%)	37 (36.1%)	146 (47.2%)
Responder (p-value)[1,2]	-	0.000	0.162	0.000
Time to response				
1st Quartile for number of days to response	77 [56.0;99.0]	35 [15.0;35.0]	35 [15.0;57.0]	35 [15.0;35.0]
Median for number of days to response	- [101;-]	99 [77.0;-]	- [77.0;-]	99 [77.0;-]
Time to response (p-value)[1,3]	-	0.000	0.018	0.000

Source: Statistical tables 6.1.1.2, 6.1.2.2, 6.1.9.2, 6.1.4.2, 6.1.5.2, 6.2.1.2, 6.2.2.2, 6.2.3.2, 6.2.4.2, 6.2.5.2, 6.3.1.2, 6.3.2.2, 6.3.3.2, 6.3.4.2, 6.3.5.2
(Post-hoc analyses after unblinding, 28APR2006)

[1]Versus Placebo.
[2]Obtained with a chi-square test
[3]Obtained with a log rank test.
Median, 1st quartile and 3rd quartile of time to response (days) is given as estimate and 95% CI derived from unstratified life table analysis (Kaplan-Meier)

Repeated Measures Analysis (Post-hoc): the analysis, assessing analgesic effect throughout the study, showed that patients in Tramadol OAD group had higher pain improvement from baseline to end of study than those in placebo, with estimated difference of -0.39 (95% CI: -0.78, 0.00) but p=0.051 (Table 7f).

Table 7f. **Repeated Measures Analysis on PI-NRS**
(Adapted from the applicant's Table 11.4.1.1.3.2-1)

Model	Comparison with respect to % change from baseline to week 12	Estimate of the difference between treatment	95% Confidence interval[1] Lower	Upper	p-value
Treatment + baseline	All doses vs Placebo	-0.39	-0.78	0.00	0.0511
	200 mg vs Placebo	-0.57	-1.14	0.00	0.0491
	300 mg vs Placebo	-0.33	-0.74	0.07	0.1094

Source: Statistical table: 2.1 (Post-hoc analyses after unblinding, 29MAR2006)
[1]Repeated Measures ANCOVA: if the upper bound of the 95% CI is <0 superiority of Tramadol OAD versus Placebo can be concluded on a descriptive level
Estimated difference between Tramadol Contramid® OAD and Placebo derived from repeated measurement ANCOVA model including Pain Intensity Score at Baseline, Visit and Treatment*Visit
Analysis Based on Measured Values Without any Replacement of Missings

Sum of PI Differences Analysis (Post-hoc): The SPID was defined as the weighted sum of all differences from Baseline to each consecutive Visit by measuring AUC. There was statistically significant difference in the PI score between Tramadol OAD and Placebo (Table 7g).

Table 8g. **Sum of Pain Intensity Differences (SPID) Analysis**
(Adapted from the applicant's Table 11.4.1.1.3.3-1)

	Treatment	
	Placebo N=214	Tramadol Contramid® OAD N=431
N	211	428
Mean ± SD	2.2 ± 2.0	2.9 ± 2.2
Median	2.0	2.9
Min, Max	-4, 8	-4, 9
Estimate (mean)	0.67	
95% CI	0.35; 0.99	
p-value[1]	0.001	

Source: Statistical tables 3.1.1, 3.2.1 (Post-hoc analyses after unblinding, 29MAR2006)
SPID is defined as the weighted sum of all differences from Baseline to each consecutive Visit (Baseline minus Visit).
[1]p-value is based on an ANCOVA. (ANOVA with effect for treatment and baseline pain as a covariate).
If the lower bound of the 95% CI is >0, superiority of Tramadol Contramid® OAD versus Placebo with regard to PI-NRS can be concluded on a descriptive level.

BOCF analysis (Post-hoc): when the missing data were imputed with BOCF, the mean pain improvement for Tramadol OAD treatment was not statistically significant as compared to placebo at Week 12 (Table 7h).

- PI-NRS change from baseline to end of the Maintenance period (12 weeks):
  - Placebo (n=211): 2.2±2.4 (95% CI: 1.9-2.5)
  - Tramadol OAD (n=427): 2.5±2.6 (95% CI: 2.2-2.7)
  - Difference (mean): -0.25 (95% CI: -0.66, 0.15), p = 0.2134

- PI-NRS change from baseline to end of the Titration period (2 weeks):
  - Placebo (n=211): 1.8±2.1 (95% CI: 1.5-2.1)
  - Tramadol OAD (n=427): 2.7±2.3 (95% CI: 2.5-2.9)

Table 7h. **Pain Intensity-NRS Analysis with BOCF Imputation for Missing Data**
(Adapted from the applicant's Table 11.4.1.1.3.4-1)

		Titration Period	Maintenance Period				
Pain Intensity Score	Visit 4 (Baseline)	Visit 5 End of Titration	Visit 6 Week 3	Visit 7 Week 6	Visit 8 Week 9	Visit 9 Week 12	Difference[2]
Placebo							
Reported Values (BOCF):							
N	214	211	210	211	211	211	-
Mean ± SD	7.2 ± 1.6	5.4 ± 2.0	5.3 ± 2.1	5.0 ± 2.4	5.0 ± 2.6	5.0 ± 2.5	-
Median	7.0	5.0	5.0	5.0	5.0	5.0	-
Min, Max	4, 10	0, 10	0, 10	0, 10	0, 10	0, 10	-
Absolute Improvement from Baseline (BOCF)[1]:							
N	-	211	210	211	211	211	-
Mean ± SD	-	1.8 ± 2.1	1.9 ± 2.1	2.2 ± 2.3	2.1 ± 2.5	2.2 ± 2.4	-
95% CI	-	(1.5; 2.1)	(1.6; 2.2)	(1.9; 2.5)	(1.8; 2.5)	(1.9; 2.5)	-
Median	-	2.0	2.0	2.0	2.0	2.0	-
Min, Max (neg. value=deterioration)	-	-4, 9	-4, 8	-5, 9	-5, 10	-2, 9	-
Tramadol Contramid® OAD							
Reported Values (BOCF):							
N	431	428	428	427[3]	428	427[3]	-
Mean ± SD	7.2 ± 1.6	4.6 ± 2.3	4.5 ± 2.5	4.6 ± 2.5	4.6 ± 2.6	4.5 ± 2.6	-
Median	7.0	4.0	4.0	4.0	4.0	5.0	-
Min, Max	3, 10	0, 10	0, 10	0, 10	0, 10	0, 10	-
Absolute Improvement from Baseline (BOCF)[1]:							
N	-	428	428	427[3]	428	427[3]	
Mean ± SD	-	2.7 ± 2.3	2.7 ± 2.5	2.6 ± 2.5	2.6 ± 2.6	2.5 ± 2.6	Estimate (mean): -0.25
95% CI	-	(2.5; 2.9)	(2.5; 3.0)	(2.4; 2.8)	(2.4; 2.9)	(2.2; 2.7)	95% CI: (-0.66 ; 0.15)
Median	-	3.0	3.0	2.0	3.0	2.0	p-value: 0.2134
Min, Max (neg. value=deterioration)	-	-5, 9	-5, 9	-4, 10	-7, 9	-4, 9	

Source: Statistical table 1.1.1, 1.2.1 (Post-hoc analysis after unblinding, 28MAR2008)
[1]Baseline values versus values at each visit
[2]Between Tramadol Contramid® OAD and Placebo with regard to absolute improvement. The p-value is based on an ANCOVA.
[3]One patient who did not discontinue had a missing PI-NRS at Visit 7 and Visit 9 (12 weeks), explaining the discrepancy with n=428 according to LOCF.
The Pain Intensity Score ranges from 0 = no pain to 10 = worst possible pain.
BOCF: Baseline Observation Carried Forward.
BOCF was calculated only for patients with at least one post-baseline assessment.
If the upper bound of the 95% CI is <0, superiority of Tramadol Contramid® OAD versus Placebo with regard to PI-NRS can be concluded on a descriptive level.

Secondary endpoint

Time-response of PI-NRS: The difference between Tramadol OAD and placebo in the mean change in pain score from baseline was constant, but became smaller across visits (or time-points) during the 12-week Maintenance dosing period. There was high variation at each time-point (Figure 5). Missing data were imputed with LOCF.

At the middle (week 6) of Maintenance period, the mean changes in pain intensity from baseline (visit 4, end of washout) were:

- Placebo (n=172): 2.6±2.3 (95% CI: 2.3-2.9)
- Tramadol OAD (n=341): 3.2±2.4 (95 CI: 2.9-3.4)
- Difference (mean): -0.51 (95% CI: -0.91 - -0.12), p=0.011 (ANCOVA)

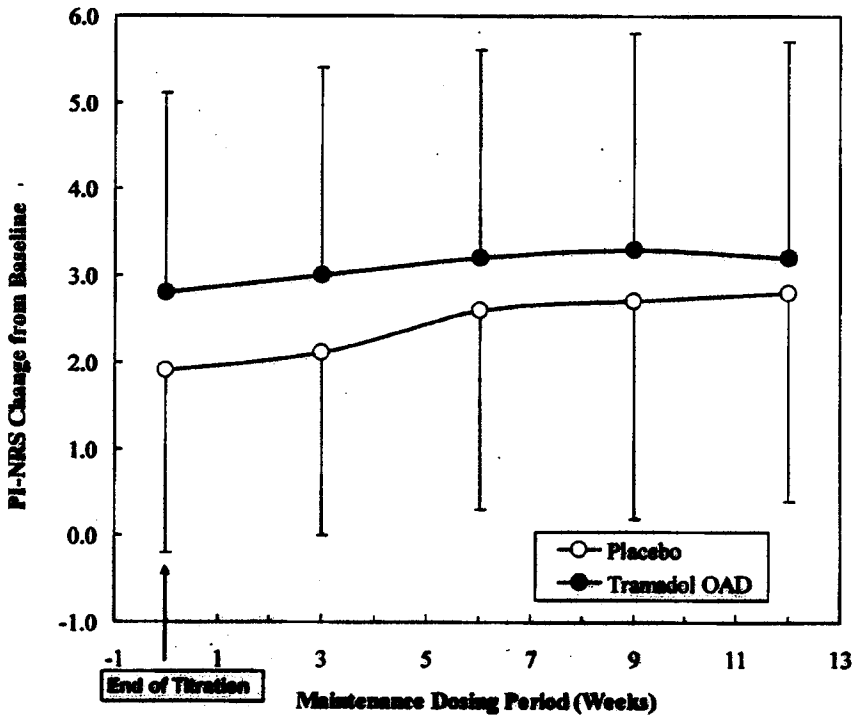

Figure 5. **Time-Course of PI-NRS and Differences between Tramadol OAD and Placebo during the Double-blind phase (2-week Titration period and 12-week Maintenance period). Data are Mean±SD, extracted from the applicant's Table 11.4.1.1.1-2. The missing data were imputed with LOCF.**

PI-NRS at end of treatment stratified by dose: The PI-NRS change from baseline to Week 12 (dropouts imputed by LOCF) for two dose cohorts of Tramadol OAD:

- Placebo (n=211): 2.4±2.4 (95% CI: 2.1-2.7)
- Tramadol OAD both doses (n=428): 2.9±2.5 (95% CI: 2.7-3.1), p=0.016 (vs. placebo)
- Tramadol OAD 200 mg (n=103): 2.9±2.7 (95% CI: 2.4-3.4), p=0.033 (vs. placebo)
- Tramadol OAD 300 mg (n=325): 2.9±2.5 (95% CI: 2.6-3.2), p=0.035 (vs. placebo)

[Reviewer's comment: the study was not designed for subgroup analysis by dose. Patients were not randomly assigned into the two Tramadol OAD dose groups. Also, multiplicity adjustment should be applied here.]

Patient and Physician Global Impression of Change: the global impression of change in overall conditions ("very much improved" and "much improved") at last visit:

- Patient Global:
  - Placebo (n=214): 46.2% (86/214)
  - Tramadol OAD (n=431): 54.2% (234/431)
  - Difference: 8.0%
- Physician Global:
  - Placebo (n=214): 44.8% (96/214)
  - Tramadol OAD (n=431): 53.3% (230/431)
  - Difference: 8.5%

WOMAC Pain Score: the pain score was measured by Likert scale (1-4) and missing data were imputed with LOCF without alternative imputation methods (Table 8). Responder analysis was not performed on the WOMAC Pain score.

- The baseline pain score (Visit 4, end of the washout from the Open-label treatment)
  - Placebo (n=214): 11.1±3.2
  - Tramadol OAD (n=431); 11.2±3.5
- The absolute pain score change from baseline to end of Titration (2 weeks)
  - Placebo (n=196): 2.8±3.4 (95% CI: 2.3-3.2)
  - Tramadol OAD (n=395): 4.0±3.9 (95% CI: 3.6-4.4)
- The absolute pain score change from baseline to end of Maintenance (12 weeks):
  - Placebo (n=211): 3.6±4.2 (95% CI: 3.1-4.2)
  - Tramadol OAD (n=430): 4.3±4.2 (95% CI: 3.9-4.7)
  - Difference between Tramadol OAD and Placebo in % change in Pain Intensity: ***6.1% (95% CI: -0.2, 12.4), p=0.058***

Table 8. **WOMAC Pain Subscale Score**
(Applicant's Table 11.4.1.2.4-2)

WOMAC Pain Subscale Score	Placebo N=214	Tramadol Contramid® OAD N=431
Baseline (Visit 4)		
N	214	431
Mean ± SD	11.1 ± 3.2	11.2 ± 3.5
Median	11.0	11.0
Min, Max	3, 20	2, 20
Week 12 (Visit 9)		
N	167	328
Mean ± SD	6.8 ± 3.9	6.1 ± 3.6
Median	7.0	6.0
Min, Max	0, 17	0, 16
Last Individual Visit		
N	211	430
Mean ± SD	7.5 ± 4.1	6.9 ± 4.0
Median	8.0	7.0
Min, Max	0, 18	0, 18
Absolute Improvement (Baseline – Last Individual Visit)		
N	211	430
Mean ± SD	3.6 ± 4.2	4.3 ± 4.2
95% CI	[3.1; 4.2]	[3.9; 4.7]
Median	3.0	4.0
Min, Max (neg. value=deterioration)	-8, 15	-10, 18
Percentage Improvement from Baseline $\frac{(\text{Baseline} - \text{Last Individual Visit}) \times 100}{\text{Baseline}}$		
N	211	430
Mean ± SD	30.8 ± 40.0	37.0 ± 37.7
95% CI	[25.4; 36.3]	[33.4; 40.6]
Median	33.3	38.0
Min, Max (neg. value=deterioration)	-200, 100	-200, 100
Difference in Percent Improvement Between Tramadol Contramid® OAD and Placebo		
Estimate (mean)	6.08	
95% CI	[-0.22; 12.37]	
p-value[1]	0.0584	

Source: Statistical tables 4.2.1.1, 4.2.2.1.
Each of the 5 underlying WOMAC scales ranged from 0 = no pain to 4 = extreme pain for a maximum total score of 20
If the lower value of the 95% CI is >0, superiority of Tramadol versus Placebo with regard to WOMAC Pain Score can be concluded on a descriptive level
[1]p-value based on an ANCOVA

Time-response of WOMAC Pain Score: Across all visits in the double-blind phase, absolute WOMAC Pain Score and the percent change from baseline showed a constant but slight difference between Tramadol OAD and Placebo (Figure 6). The results were consistent with the time-course observed with the PI-NRS (Figure 5).

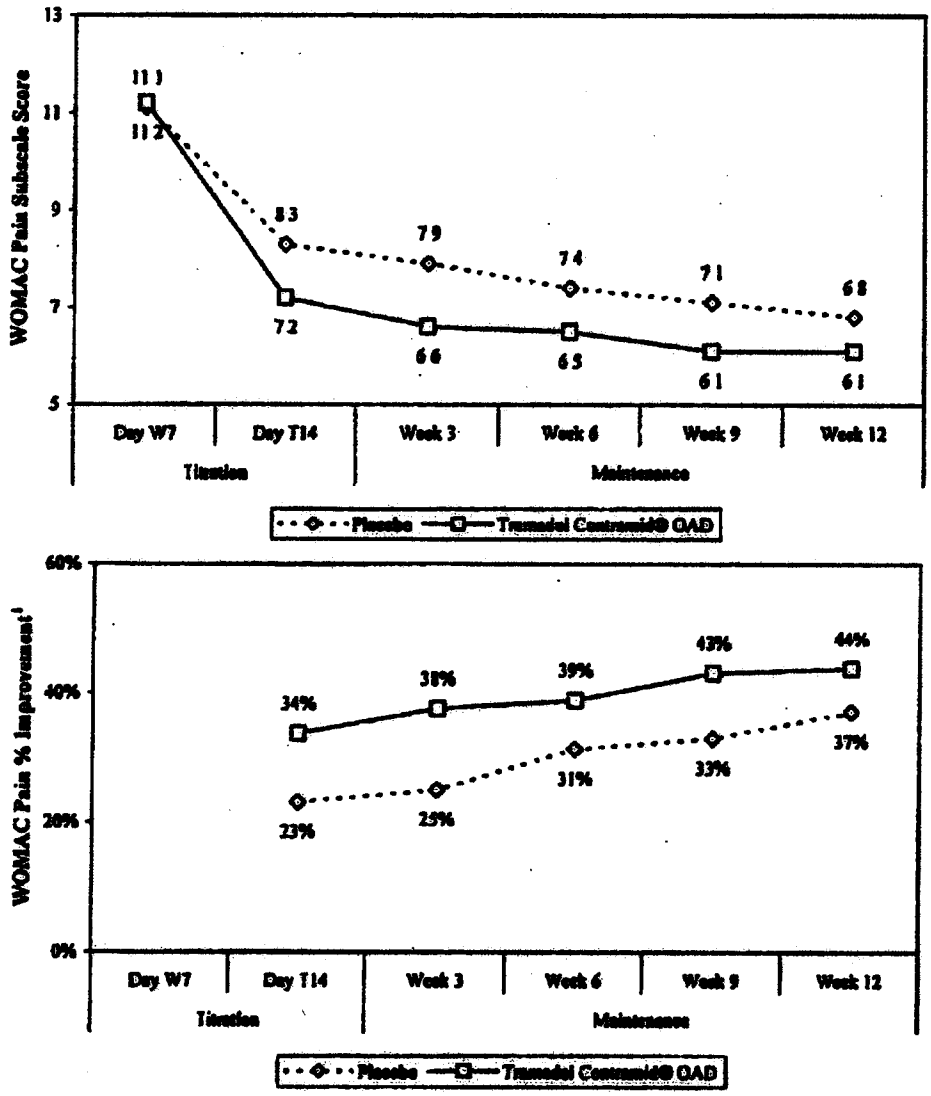

Figure 6. **Time-Course of WOMAC Pain Score and Differences between placebo and Tramadol OAD during the Double-blind Phase. The missing data were imputed with LOCF (the figures were adapted from the applicant's Figures 11.4.1.2.4-1 and 11.4.1.2.4-2; also see the applicant's Table 11.4.1.2.4-1 for detail)**

WOMAC Physical Function Subscale: the percentage improvement in function score from baseline to week 12 (by LOCF):

- Placebo (n=211): 29.3 ±33.6 (95% CI: 24.7-33.9)
- Tramadol OAD (n=424): 34.8 ±35.6 (95% CI: 31.4-38.2)
- Difference (mean): 5.52 (95% CI: -0.23; 11.27), p=0.06 (ANCOVA)

Dropouts due to lack of efficacy:

- Placebo (n=214): 10.3% (22/214)
- Tramadol OAD (n=431): 7.9% (34/431), p=0.31 (vs. placebo, Chi-square test)

[Reviewer's comment: the number of dropouts was inconsistent between the applicant's Table 11.4.1.2.6-1 and the applicant's Figure 10.1-1]

Safety Evaluation

Extent of exposure

A total of 1023 patients took at least one dose of Tramadol OAD (the Safety Population) during the Open-label Phase with the following demographics:

- Mean age: 63±9 years (63 for males and 62 got females)
- Age ≥ 65 years: 45% (456 of 1027)
- Gender: 63% females
- Ethnic: 85% Caucasian
- BMI: 29.7±4.1

During the Double-blind Phase, 432 patients (42% of 1027) were treated with Tramadol OAD and 214 patients with placebo. The following baseline characteristics were comparable between 2 groups:

- Mean age: 62±9 years
- Age ≥ 65 years: 58%
- Ethnicity: 88% Caucasian
- BMI: 29.7±4.0

Dose and Duration of study medication were as follows: Tramadol OAD 100-300 mg for 21 days during the Open-label Phase; Tramadol OAD 200 or 300 mg for 75±23 days; and placebo for 84±29 days (Table 9).

Table 9. **Extent of Exposure in Safety Population**
(Adapted from the applicant's Table 12.1.1-1)

	Treatment during Double-Blind Phase	
	Placebo N=214	Tramadol Contramid® OAD[1] N=432
Number of days on Double-Blind treatment		
Mean ± SD (days)	84.1 ± 29.0	82.4 ± 30.9
Median (days)	98.0	98.0
Min, Max (days)	8, 108	0, 119
Number of days in Maintenance Period		
Mean ± SD (days)	76.4 ± 20.4	75.2 ± 22.6
Median (days)	84.0	84.0
Min, Max (days)	3, 94	4, 105

Source: Statistical table 5.1.
Note: Percentages ≥1% were rounded to one decimal point
[1]One patient did not take any dose of randomized study medication

Adverse Events (AEs)

The profile of the treatment emergent adverse events (TEAEs) was similar to that seen in previous efficacy and safety trials (MDT3-002, MDT3-003 and MDT3-004), as well as the approved tramadol product Ultram and Ultram ER. The following is a brief summary of the TEAEs in this trial, and more details regarding AEs are presented in the ISS of this review.

Deaths: no deaths were reported during the study.

Serious AEs: A total of 11 serious AEs were reported from 10 patients during the study (up to 30 days after the last dose) (Table 10); nine patients from Tramadol OAD group and one patient from placebo.

Table 10. **Serious TEAEs reported in the Safety Population**
(Adapted from the applicant's Table 12.3.1.2-1)

Center	Patient Number	Patient Initials	Sex	Age	Date of first dose (Open-Label)	Preferred term	Study Phase	Date of onset	Date of resolution	Intensity	Relationship	Withdrawn due to SAE	Outcome
Patients not randomized													
59	25	[redacted]	M	73	26OCT2004	Grand mal convulsion[1]	Open-Label	03DEC2004	03DEC2004	Moderate	Not related	No	Recovered
56	113		M	78	09NOV2004	Prostate cancer	Open-Label	30NOV2004	08MAR2005	Moderate	Not related	Yes	Recovered
86	899		M	66	24AUG2005	Hepatitis[2]	Open-Label	05SEP2005	05SEP2005	Moderate	Possibly related	No	Recovered
86	899		M	66	24AUG2005	Renal impairment[3]	Open-Label	05SEP2005	05SEP2005	Moderate	Possibly related	No	Recovered
206	927	[redacted]	F	52	26AUG2005	Papillary bronchitis	Open-Label	21SEP2005	29SEP2005	Mild	Not related	Yes	Recovered
Treatment during Double-Blind Phase: Placebo													
209	699	[redacted]	F	69	16AUG2005	Ischaemic stroke	Double-Blind	03NOV2005	11NOV2005	Severe	Not related	Yes	Recovered with sequelae
Treatment during Double-Blind Phase: Tramadol Contramid® OAD													
2	103	[redacted]	M	64	09NOV2004	Diverticulitis	Double-Blind	12MAR2005	22MAR2005	Severe	Not related	No	Recovered
22	153		F	77	16NOV2004	Angina unstable	Double-Blind	26MAR2005	27MAR2005	Moderate	Not related	No	Recovered
29	513		M	66	10MAY2005	Syncope	Double-Blind	23AUG2005	27AUG2005	Severe	Possibly related	No[4]	Recovered
69	536		M	56	20MAY2005	Chest pain	Double-Blind	08JUL2005	11JUL2005	Severe	Not related	No[4]	Recovered
75	433	[redacted]	F	63	22MAR2005	Breast cancer	Double-Blind	02JUN2005	20JUN2005	Mild	Not related	No	Recovered

Source: Listing 14.2.7.4 (18APR2005) and Listing 4 of List of Individual Data (09MAY2005).
[1]Severe adverse event resulted in interruption of the study medication but not discontinuation.
[2]The SAE 'Elevation of liver enzymes leading to inflammation of liver' was coded as hepatitis as the most conservative approach.
[3]SAE occurred after the last dose of study medication and within 30 days of last dose.

b(6)

Frequency of Occurrence of TEAEs:

- During the Open-label Phase:
  - At least one TEAE: 66% (670 of 1023 patients)
  - TEAE-related withdrawals: 22% (228 of 1023 patients)
  - The most common TEAEs by SOC: GI (46%), NS (31%) and skin disorder (12%)
  - The most common TEAEs by PT: nausea (27%), constipation (20%), dizziness/vertigo (18%) and somnolence (15%).
  - Slight more patients in age ≥ 65 years experienced TEAEs
  - Similar in TEAE-related dropout between age < 65 and ≥ 65 years.

- During the Double-blind Phase
  - At least one TEAE (overall 56%): 59% on Tramadol OAD and 51% on Placebo
  - At least one SAE (overall 6%): 7% on Tramadol OAD and 4% on Placebo
  - TEAE-related withdrawals (overall 9%): 10% on Tramadol OAD and 6% on placebo
  - The most common TEAEs by SOC:
    - GI Disorders: 33% on Tramadol vs. 14% on placebo
    - Nervous System Disorders: 18% on Tramadol vs. 15% on Placebo
    - Infections and Infestations: 13% on Tramadol vs. 16% on Placebo
    - Skin and Subcutaneous Disorders: 12% on Tramadol vs. 3% on Placebo
  - The most common TEAEs by PT: nausea (15%), constipation (14%), dizziness/vertigo (10%) and somnolence (7%); occurred more commonly in the Tramadol OAD group (Table 11).

Table 11. The most common TEAEs during the Double-blind Phase
(Adapted from the applicant's Table 12.2.2.1-13)

	Treatment during Double-Blind Phase		
Preferred term	Placebo N=214	Tramadol Contramid® OAD N=432	p-value[1]
Nausea / nausea aggravated	12 (5.6%)	66 (15.3%)	0.000 (chisq)
Constipation / Constipation aggravated	9 (4.2%)	61 (14.1%)	0.000 (chisq)
Dizziness / Dizziness aggravated / Vertigo	8 (3.7%)	42 (9.7%)	0.007 (chisq)
Somnolence	8 (3.7%)	29 (6.7%)	0.126 (chisq)
Headache / Headache aggravated / Sinus headache	11 (5.1%)	19 (4.4%)	0.673 (chisq)
Vomiting	3 (1.4%)	19 (4.4%)	0.048 (chisq)

Source: Statistical table 5.3.2.2.1.
Note: Percentages are of total number of patients in the safety population.
Note: Multiple occurrences of the same adverse event in the same patient were counted only once
[1]t-test derived from one-way ANOVA.
Note: AEs with onset date during any period of the Double-Blind Phase, regardless of resolution date are presented here.

The remaining safety data are integrated with other trials (see Section 7 for detail)

SUMMARY AND CONCLUSION

Refer to Sections 6 (Efficacy) and 7 (Safety)

10.1.4 Study MDT3-001-E1

TITLE: 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

Study Period: March 7 – October 28, 2002
CRO: [redacted] b(4)

OBJECTIVES

Primary: To compare the efficacy (non-inferiority) of Tramadol Contramid OAD (tramadol ER) tablets and Tramadol BID (tramadol SR) tablets in patients with pain due to osteoarthritis (OA) for 3 months

Secondary: To compare the safety and benefit of Tramadol OAD and Tramadol BID in the treatment of pain due to osteoarthritis (OA) of the knee.

STUDY LOCATION

Outside USA: 21 sites (3 in France, 8 in Hungary, 8 in Russia and 2 in UK)

STUDY DESIGN AND PROCEDURE

The study was designed as a multicenter, randomized, double-blind, double dummy, active-controlled, and parallel group Phase 3 trial.

A total of 408 patients with symptomatic OA of the knee were originally planned for enrollment. The study subjects were to be randomized to once-daily tramadol (Tramadol OAD) or twice-daily tramadol (Tramadol SR).

The trial was to comprise three phases: Baseline, Run-in (titration), and Maintenance. Total study participation would be up to 14 weeks: Run-in phase for 4-12 days and Maintenance dosing phase for 12 weeks.

After screening and randomization (Visit 1) and appropriate washout of any prohibited analgesics, eligible subjects were to be given drug during the Run-in titration (4-12 days) followed by Maintenance treatment (12 weeks) at their optimized dose. During the titration phase, tramadol was to be increased every 2^{nd}-3^{rd} day by 100 mg as follows:

- Tramadol OAD group: from 100, 200, 300 to 400 mg daily (before breakfast)
- Tramadol BID group: from 200 (100 mg BID), 300 mg (150 mg BID) to 400 mg (200 mg BID) daily (before breakfast and 12 hour later)

Each patient's optimum dose from the titration would then be fixed and was to be taken throughout the Maintenance Phase. If a patient had to reduce the dose during the maintenance phase, he or she was to be withdrawn from the study.

Patients were to attend four site visits during the 12-week Maintenance phase: on the first day of the Maintenance dose (visit 2), and then at 3 weeks (visit 3), 6 weeks (visit 4) and 12 weeks (visit 5) after starting Maintenance dose.

Inclusion criteria

1) Males or females, 40 - 75 years of age
2) Moderate to severe OA of the knee according to the American College of Rheumatology (ACR) criteria:
   - Current knee pain.
   - < 30 minutes of morning stiffness with or without crepitus on active motion
   - Confirmation (confirmation of what?) by either arthroscopy or radiology report (X-rays showing osteophytes, joint space narrowing or subchondral sclerosis) within 5 years prior to the study
   - CPR< 8 ug/ml (if available) or ESR < 40 mm/hour and effusion < 15 ml (to rule out acute inflammation)
   - WOMAC Pain Subscale Total Score ≥ 150 mm at baseline (moderate to severe OA)
3) BMI < 35 kg/m2

Key Exclusion criteria

1) Known rheumatoid arthritis or any other rheumatoid disease.
2) Secondary arthritis (any of the following): septic arthritis, inflammatory joint disease, gout, pseudogout, Paget's disease, joint fracture, acromegaly, fibromyalgia, Wilson's disease, Ochronosis, Haemochromatosis, Osteoondromatosis, heritable arthritic disorders, or collagen gene mutations.
3) Treatment within the previous 3 weeks with any of the following medications: MAOIs, TCAs and other tricyclic compounds (e.g. cyclobenzaprine, promethiazine), neuroleptics, SSRIs, or other drugs which reduce seizure threshold
4) A history of seizure disorder other than infantile febrile seizures.
5) Previous failure or discontinuation (due to AEs) of tramadol HCl therapy.
6) Previous or current opioid dependence; or current substance abuse or dependence, other than nicotine
7) Significant liver disease (defined as active hepatitis or liver enzymes > 3x ULN) or significant renal disease (defined as creatinine clearance < 30 mL/min)

Table 1. **Treatment Schema and Blister Package Description**

Figure 3 Blister package description

	Active Treatment:			
	Tramadol OAD (TOD)		Tramadol BID (TB)	
Dose Level	TOD Active	TB Placebo	TB Active	TOD Placebo
I* (100 mg) Green	One 100 mg active tablet OAD	None	None	One '100 mg' placebo tablet OAD
II (200 mg) Blue	One 200 mg active tablet OAD	One '100 mg' placebo tablet BID	One 100 mg active tablet BID	One '200 mg' placebo tablet OAD
III (300 mg) Yellow	One 100 mg active tablet + One 200 mg active tablet OAD	One '150 mg' placebo tablet BID	One 150 mg active tablet BID	One '100 mg' placebo tablet + One '200' mg tablet OAD
IV (400 mg) White	Two 200 mg active tablets OAD	One '200 mg' placebo tablet BID	One 200 mg active tablet BID	Two '200 mg' placebo tablets OAD

* Dose Level 1: Patients randomized to the Tramadol BID group took their first dose of active medication at 100 mg BID (200 mg daily) as per the manufacturer's usual dosing recommendations. Placebo was used at the 100 mg dose level to maintain the study blind (50 mg BID tablets not being available).

Rescue medication

No rescue medication for pain due to OA was to be permitted during the study. Patients with intolerable pain could be withdrawn; the reason for withdrawal would be recorded as "treatment failure."

Efficacy Measures

- WOMAC Index: Comprises 3 subscales -- pain, stiffness and physical function which are measured using a 100-mm visual analog scale (VAS) at each visit (baseline and 4 visits during the maintenance phase)
- Walking Test: How many seconds it takes a patient to walk a distance of 15 m (50 ft) at each visit
- Patient's Global Assessment of Pain (VAS): Pain intensity on VAS during the 24 hours prior to the visit "best", "worst" and "average"
- Patient and Physician Overall Ratings of Efficacy: Overall assessment of the study medication during the Maintenance Phase (4 visits) using 4-point Likert scale: "very effective", "effective", "somewhat effective" and "ineffective".
- Patient Diary: Patients were asked to answer the following questions (Table 2) at each morning immediately prior to dosing:

Table 2. **Patient Diary**

Question	Rating
Arthritis pain in my worst knee	None, barely noticeable, mild, moderate, severe
Stiffness in my worst knee?	None, barely noticeable, mid, moderate, severe
Ability to get things done?	No problem, a bit slower than usual, a lot slower than usual, a few things didn't get done, a lot of things didn't get done
Difficulty in walking?	No problems, barely noticeable difficulty, mild problems, moderate difficulty, severe difficulty
Difficulty with stairs?	No problems, barely noticeable difficulty, mild problems, moderate difficulty, severe difficulty

Primary efficacy endpoint & analysis

The primary endpoint was the percentage change in WOMAC Pain Score from baseline to end of treatment (week 12)

A 1-sided non-inferiority test of Tramadol OAD over Tramadol BID was to be performed; a minimum 15% difference (δ) in mean percentage change between the 2 treatment groups defined the limit of non-inferiority. To conclude that Tramadol OAD is not inferior to Tramadol BID with a 2.5% type I error, the lower bound of the 97.5% CI (1-sided test) of δ was to be greater than 15%.

The applicant used both PP population and ITT population for efficacy analyses, but the PP population was used for the primary efficacy analysis. When efficacy data were analyzed with the ITT population (all randomized patients who received study medication and had at least one post-baseline assessment of any functional scale), the missing data due to early dropouts were imputed with LOCF (last observation carried forward).

Secondary efficacy endpoints:

- % change in WOMAC Stiffness and Physical Function Scores from baseline
- A 24-hour VAS pain ratings
- Patient and physician global ratings of efficacy
- patient diary (pain and knee function)

Safety Measures and Analysis

- Physical examination
  - Vital sign at (at all visits)
  - Body system examination including knee (baseline, weeks 6 and 12)
  - Body weight (baseline, study end)
- Laboratory tests: Hematology, biochemistry and urinalysis (baseline, weeks 6 and 12)
- Adverse events

- Patient overall rating of safety: Patients were to rate, on a 4-point Likert scale, the interference of "side effects" related to the study medication with their day to day activities, and to compare these effects with any past experience with tramadol.
- Safety data analysis: Descriptive statistics were to be used to summarize the safety data. All patients who received at lease one dose of study medication were included in the safety analysis.

Protocol amendments
All patients who completed the first 6-week study were offered to participate the 6-week extension trial (total of 12 weeks) to meet the recommendation fro Guidance on the OA trial (12 weeks). The amended protocol was not submitted to the Agency for review.

RESULTS

Subject Disposition (Table 4)

A total of 431 patients were enrolled from 21 study sites; 215 subjects were randomized to the Tramadol OAD group and 216 to the Tramadol SR (BID) group.

Total number of subjects who received at least 1 dose of study drug was 430 (ITT population) (1 patient did not take the study medication in the Tramadol BID group). The per-protocol population was 314 patients (161 on OAD and 153 on BID).

Of each of treatment groups, 171 patients completed the 12-week treatment. Overall dropout rate was approximately 21% from each group by the end of study (week 12). Of the dropouts, 43% on OAD and 49% on BID were AE-related, and 34% on OAD and 27% on BID were due to treatment failure (including pain score missing).

Table 4. **Analysis Populations**
(Extracted from the applicant's Tables 5)

Analysis Population	Treatment Group		Overall
	Tramadol OAD	Tramadol BID	
Randomized Population	215	216	431
ITT Population	215 (100%)	215 (99.5%)	430 (99.8%)
PP Population*	161 (74.9%)	153 (70.8%)	314 (72.9%)
Completed 12 weeks	171 (79.5%)	171 (79.5%)	342 (79.3%)

* Per-protocol population was used for primary efficacy analysis by the applicant

Table 5. **Patient Dropout Rates**
(Extracted from the applicant's Fig 4 and text at pages 60, 102 and 109)

Reason for Dropout	Treatment Group		Overall N=431
	Tramadol OAD N=215	Tramadol BID N=216	
Any reason	44 (20.5%)	45 (20.8%)	89 (20.6%)
Treatment failure	2	2	4
WOMAC Pain Score missing at week 12	13	10	23
Patient request	6	7	13
Protocol violation	3	4	7
Adverse events	19 (8.8%)	22 (10.2%)	41 (9.5%)
Death	1	0	1

Baseline Characteristics

Demographics:

In the ITT population, 83% of patients were females, the mean age was 61 years and the baseline WOMAC Pain score was 289 mm on VAS. There were no remarkable differences in the demographics between the two treatment groups, except that there were slightly more patients aged < 65 years in the Tramadol BID group than in the Tramadol OAD group (64% vs. 56%). The demographic profile was similar for the PP population

Efficacy Analysis

Optimum Tramadol dose
The optimum doses after titration varied from 100 to 400 mg/day and were not different in distribution between the Tramadol OAD and Tramadol BID groups. The median optimum dose taken by about 50% patients in both groups was 200 mg/day (both the PP and ITT populations) (Table 6).

Table 6. **Applicant's Analysis: Optimum Dose (ITT and PP Populations)**
(Extracted from the applicant's Tables 28 and 30)

Optimum Tramadol Dose (mg/day)	ITT Population		PP Population	
	Tramadol OAD N=215	Tramadol BID N=215	Tramadol OAD N=161	Tramadol BID N=153
100	33 (15.3%)	31 (14.9%)	25 (15.5%)	21 (13.7%)
200	***95 (44.2%)***	***93 (43.3%)***	***82 (50.9%)***	***75 (49.0%)***
300	53 (24.7%)	55 (25.6%)	41 (25.5%)	40 (26.1%)
400	21 (9.8%)	21 (9.8%)	13 (8.1%)	17 (11.1%)

Primary Efficacy Endpoint

The Applicant found that, using ITT population with LOCF imputation for missing data, the mean percentage change in WOMAC Pain Score from baseline to the last visit was approximately 53% in both the Tramadol OAD and Tramadol BID groups (Table 7).

A similar WOMAC pain improvement (58%) in patients treated with Tramadol OAD and Tramadol BID was found when the analysis was done using the per-protocol population (Table 7).

Table 7. **Applicant's Analysis: Mean Change in WOMAC Pain Score (ITT and PP Populations)**
(Extracted from the applicant's Tables 11-14)

WOMAC Pain Improvement from Baseline	Statistics	ITT Population		PP Population	
		OAD	BID	OAD	BID
End of Titration % (Baseline-visit 2)	N Patient	199	196	161	153
	Mean ± SD	41.6 ±30.1	41.9 ±31.0	42.6 ±30.3	39.6 ±29.5
	95% CI	37.4-45.8	37.6-46.3	37.9-47.2	34.9-44.3
End of Maintenance % (Baseline-week 12 with LOCF)	N Patient	212	215	161	153
	Mean ± SD	53.3 ±32.3	53.2 ±34.4	58.3 ±29.9	58.7 ±27.0
	95% CI	49.0-57.7	48.6-57.8	53.7-62.9	54.4-63.0
ANCOVA Test (2-side) on difference between OAD and BID)	p-value	0.9309		0.5093	
	Difference 95% CI	-5.75, 6.28 (estimate: 0.27)		-7.67, 3.82 (estimate: -1.93)	

Secondary Efficacy Endpoints

24-hour pain assessment from patient diary: The Applicant found that for the PP population, the median weekly pain score in the worst knee showed continuous improvement during the

maintenance dosing. There was no significant difference in median pain scores between the Tramadol OAD and Tramadol BID groups.

WOMAC Stiffness Score: Similarly, per the Applicant's analysis, in both the PP and ITT populations, the improvement in WOMAC Stiffness Score from baseline to the end of treatment was similar between Tramadol OAD and BID treatments (LOCF imputation) (Table 8).

Table 8. **Applicant's Analysis: Improvement (%) in the WOMAC Stiffness Score**
(Extracted from the applicant's Tables 16-18)

Analysis Population	Statistics	Tramadol OAD	Tramadol BID
PP Population	Patient N	161	153
	Mean ± SD	49.1 ±60.8	49.5 ±37.9
	95% CI	40-59	44-56
ITT Population	Patient N	213	215
	Mean ± SD	43.2 ±57.7	44.4 ±43.2
	95% CI	36-51	39-50
ANCOVA test (2-side) on the difference between OAD and BID: no significant with either population			

WOMAC Physical Function Score: The applicant found that with either the PP population or ITT population, the improvement in WOMAC Physical Function Score from baseline to the end of treatment was similar between the Tramadol OAD and BID groups (LOCF imputation) (Table 9).

Table 9. **Applicant's Analysis: Improvement (%) in the WOMAC Stiffness Score**
(Extracted from the applicant's Tables 19-21)

Analysis Population	Statistics	Tramadol OAD	Tramadol BID
PP Population	Patient N	161	153
	Mean ± SD	40.5 ±32.5	49.8 ±29.7
	95% CI	46-56	45-55
ITT Population	Patient N	213	214
	Mean ± SD	45.2 ±34.4	46.6 ±32.0
	95% CI	41-50	42-51
ANCOVA test (2-side) on the difference between OAD and BID: no significant with either population			

A 24-hour pain VAS: The Applicant showed no difference between the Tramadol OAD and BID for "current pain" "worst pain" and "least pain" within the last 24 hours.

Walking time for 15 meters: The applicant found that the mean time for walking 15 meters decreased to 18.9 seconds for patients treated with Tramadol OAD and to 19.1 seconds for the Tramadol BID patients from a Baseline time of 24 seconds.

Patient and investigator global assessment: In both PP and ITT populations, 98-99% of patients or physician considered the study medications effective and there were no differences between 2 treatments.

Safety Analysis

Extent of Exposure

A total of 215 patients in each of the two treatment groups were exposed to the study medication for 3-121 days (the Safety Population); the mean duration of treatment was 82 days. About 79% of patients in both groups took the study medication for ≥ 84 days (Table 10)

In both treatment groups, approximately 50% of patients took 200 mg/day (median optimum dose), 25% of patients took 300 mg/day, and 10% of patients took 400 mg/day during the 12-week maintenance period (Table 6). Among subjects who completed 12-week treatment, 81 patients (41 in the Tramadol OAD group and 40 in the Tramadol SR BID group) were treated with 300 mg/day, and 30 patients (13 in the Tramadol OAD group and 17 in the Tramadol SR BID group) took 400 mg/day.

Table 10. **Applicant's Analysis: Duration of Treatment in the Safety Population**
(Adapted from the applicant's Table 29)

Table 29 Safety Population: Extent of exposure

	Treatment			
	Tramadol OAD		Tramadol BID	
Duration of treatment between Visit 1 and last dose				
Number of patients	215		215	
Mean ± SD (days)	81.7	±28.2	82.5	±29.3
Median (days)	93.0		94.0	
Min – Max (days)	3,	121	3,	117
Treatment duration < 84 days N (%)	45	(20.9%)	45	(20.9%)
Treatment duration ≥ 84 days N (%)	170	(79.1%)	170	(79.1%)

Source: Statistical Table 4.1.2.3

Adverse Events (AEs)

Approximately 80% of patients in each treatment group experienced at least one TEAEs; 12% of them prematurely discontinued from the study due to TEAEs (Table 11). Overall, the occurrence of TEAEs was comparable between Tramadol OAD and Tramadol BID in the patients < 65 or ≥ 65 years old.

***Table 11.* Summary of Patients with TEAEs in the Safety Population**
(Adapted from the applicant's Table 31)

Table 31 Safety Population: Summary of treatment-emergent adverse events

Number of Patients (%)	Treatment						p*
	Tramadol OAD N = 215		Tramadol BID N = 215		Overall N = 430		
– With at least one TEAE	175	(81.4%)	170	(79.1%)	345	(80.2%)	0.6283
– With at least one severe TEAE	30	(14.0%)	32	(14.9%)	62	(14.4%)	0.8909
– With at least one serious TEAE	3	(1.4%)	8	(3.7%)	11	(2.6%)	0.2285
– With at least one possibly drug related TEAE	164	(76.3%)	161	(74.9%)	325	(75.6%)	0.8224
– Who terminated the study prematurely due to TEAE	19	(8.8%)	22	(10.2%)	41	(9.5%)	0.7430
– Who died	1	(0.5%)	–		1	(0.2%)	

* p-value: two-sided Fisher's Exact test.

Source: Statistical Table 5.2.1.1

Serious AEs: 11 SAEs from 11 patients (3 on OAD and 8 on BID) (Table 12):

- One death in the Tramadol OAD group: a 67-year-old Caucasian female experienced a fatal ischemic stroke 36 days after starting Tramadol OAD. The patients had multiple medical history and medications, including cardiovascular disease and hyperlipidemia. The stroke was less likely related to the study medication.
- Ten other SAEs in 10 patients:
  - 2 on Tramadol OAD and 8 on Tramadol BID.
  - 3 SAEs (cerebrovascular disorder, chest pain and bladder neoplasm) from the Tramadol BID group were considered by investigator "possibly drug related".
  - All 10 SAEs were resolved

The Most Frequent TEAEs: by system organ class

- 61% in gastrointestinal disorders
- 54% in nervous system disorders
- Comparable between OAD and BID
- Comparable between age < 65 and ≥ 65 years old

Table 12. SAEs

Table 44 Safety population: Listing of treatment-emergent serious adverse events

Pat.	Date of first medication	Preferred term	Start date	Stop date	Intensity	Relationship	Withdrawn due to AE	Outcome
Tramadol OAD								
201	06 Apr 2002	Coronary artery insufficiency	14 Jun 2002	21 Jun 2002	Moderate	Not Related	No	Resolved
280	15 May 2002	Ischaemic stroke NOS	29 Jun 2002	17 Jul 2002	Severe	Not Related	Yes	Death
364	22 Jun 2002	Essential hypertension	12 Aug 2002	17 Sep 2002	Mild	Not Related	No	Resolved
Tramadol BID								
46	19 Apr 2002	Peritoneal adhesions	05 Jul 2002	11 Jul 2002	Moderate	Not Related	Yes	Resolved
124	29 Apr 2002	Tibia fracture	27 Apr 2002	24 Sep 2002	Severe	Not Related	Yes	Resolved
191	30 Apr 2002	Cerebrovascular disorder	07 May 2002	26 Jun 2002	Severe	Possibly Related	Yes	Resolved
172	07 Apr 2002	Chest pain	26 Jun 2002	30 Jun 2002	Moderate	Possibly Related	No	Resolved
181	30 Apr 2002	Cholelithiasis	25 Jun 2002	10 Jul 2002	Moderate	Not Related	No	Resolved
246	23 Apr 2002	Bladder neoplasm	08 Jun 2002	10 Jun 2002	Moderate	Possibly Related	Yes	Resolved with sequelae
373	18 Jun 2002	Unstable Angina	04 Jul 2002	29 Jul 2002	Moderate	Not Related	No	Resolved
483	08 Jun 2002	Renal colic	05 Aug 2002	05 Aug 2002	Moderate	Not Related	No	Resolved

Source: Statistical Table 5.2.12

The Most Common TEAE (Table 13)

- Nausea (33%), constipation (32%), dizziness/vertigo (31%), somnolence (26%), weakness (13%) and vomiting (11%)
- Comparable between OAD and BID in patients <65 or ≥ 65 years old
- Overall, slight more patients experienced nausea and constipation at age ≥ 65 years and dizziness/vertigo and headache at age < 65 years.

Drug-related TEAEs:

- Overall TEAEs reported by 75% of patients in each group were at least possibly drug-related.
- Comparable between 2 groups

Intensity of TEAEs:

- Most AEs were mild to moderate
- Comparable between OAD and BID groups

Table 13. **The most common TEAEs**

Table 35 Safety Population: Summary of most common** adverse events

Adverse Event N(%)	Treatment: Tramadol QAD <65 years N=121	Tramadol QAD ≥65 years N=94	Tramadol QAD Overall N=215	Tramadol BID <65 years N=137	Tramadol BID ≥65 years N=78	Tramadol BID Overall N=215	p-value*
Dizziness or vertigo	32 (26.4%)	23 (24.5%)	55 (25.6%)	54 (39.4%)	25 (32.1%)	79 (36.7%)	0.0165
Nausea	37 (30.6%)	33 (35.1%)	70 (32.6%)	44 (32.1%)	29 (37.2%)	73 (34.0%)	0.3378
Constipation	38 (31.4%)	35 (37.2%)	73 (34.0%)	36 (26.3%)	29 (37.2%)	65 (30.2%)	0.4697
Somnolence	43 (35.5%)	22 (23.4%)	65 (30.2%)	25 (18.2%)	21 (26.9%)	46 (21.4%)	0.0470
Headache	17 (14.0%)	10 (10.6%)	27 (12.6%)	26 (19.0%)	12 (15.4%)	38 (17.7%)	0.1779
Vomiting	9 (7.4%)	9 (9.6%)	18 (8.4%)	18 (13.1%)	13 (16.7%)	31 (14.4%)	0.8877
Weakness	12 (9.9%)	12 (12.8%)	24 (11.2%)	20 (14.6%)	11 (14.1%)	31 (14.4%)	0.3865

Note: Percentages are of total number of patients in the respective (sub-) group. Multiple occurrences of the same AE in the same patient were counted only once.

* p-value: two-sided Fisher's Exact test for comparison of treatment groups.

** TEAEs experienced by at least 10% of patients in at least one of the treatment groups.

Source: Statistical Table 5.2.2.4

Time to Onset and Duration of TEAEs:

- The median onset of the most common TEAEs was 3-13 days, with a slightly early onset of constipation and later onset of vomiting on Tramadol OAD.
- The median duration of TEAEs by system organ class was 2-18 days and comparable between OAD and BID groups.

AE-related Dropouts: About 21% (41 of 431) of patients in both tramadol groups terminated the study early due to AE; most of them were drug-related and mild-moderated in the intensity. Majority of the AEs were under list of the common AEs. The drop-out rates were comparable between 2 groups.

Concomitant medication: Only concomitant medications to treat the most common TEAEs were presented in the report. The percentage of patients who received the medications was comparable between Tramadol OAD and BID groups.

Clinical Laboratory Evaluation

A total of 9 patients with abnormal laboratory values were reported as TEAEs: 6 in Tramadol OAD and 3 in Tramadol BID. One patient with increased ALT and GGT was considered by the investigator "possibly drug related" and all others were "not related".

Vital Signs and Physical Examination

- There were no remarkable changes in vital signs (Respiratory rate, blood pressure, temperature, heart rate) for all patients, and comparable between 2 treatment groups.

- PE: New neurological abnormalities were diagnosed in both treatment groups:
    - Tramadol OAD: 1 case: tremor (escalation of tremor in Romberg's pose)
    - Tramadol BID: 7 cases: lumbalgia, tender upon paravertebral palpation, dizziness/weakness, headache/dizziness, dizziness, Rocking in Romberg's position, insomnia. 6 of them (except tender) were at the discontinuation from the study.

Patient global assessment of safety

The patient ratings of the interference of TEAEs with day-to-day activities were similar between 2 groups.

SUMMARY AND CONCLUSION

As 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 played very limited supportive rule in efficacy evaluation of Tramadol OAD for the following reasons:

1. Adequacy of the 15% of non-inferiority margin is unknown. The applicant did not provide a rationale in the study design and the discussion of the results for the pre-specified non-inferiority margin.

2. In general, the intrinsic variability of pain trials is too high for estimation of 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).

3. A placebo-controlled arm should have been included in the trial to validate the efficacy of active comparator (ie, for assay sensitivity).

4. The active comparator used in this trial was Topalgesic (Tramadol SR) for BID regimen, which is not a tramadol product marketed in US.

Clarification: In the narrative of SAEs, 5 patients in the Tramadol BID group received "100 mg daily" Tramadol BID, which was conflict with the study design, starting 100 mg bid (= 200 mg/day).

10.1.5 Study MDT3-004

TITLE: An open label long-term safety study of tramadol OAD (once a day) 300 mg in the treatment of pain due to osteoarthritis of the knee

Study Period: April 17, 2003 – Dec 31, 2004
CRO: [redacted] b(4)

OBJECTIVES

To collect information regarding the long-term safety (6 and 12 months) of Tramadol OAD 300 mg tablets in patients treated for pain due to OA of the knee

STUDY LOCATION

Outside USA: 22 sites in Romania (19 of them recruited patients)

STUDY DESIGN AND PROCEDURE

This was open-label, multi-center, fixed dose (300 mg Tramadol OAD), single arm trial in 380 patients with confirmed, symptomatic OA of the knee. The patient selection criteria were similar to studies MDT3-002 and MDT3-003.

The trial consisted of the following three phases:

1) Run-in (6 days): 100 mg qd x2 days and 200 mg qd x3 days; 300 mg qd on 6th day
2) Maintenance Phase I: 300 mg qd for 6 months
3) Maintenance Phase II: 300 mg qd for additional 6 months (total of 12 months)
   [*Two dose strength tablets of Tramadol OAD were used. For dose level of 300 mg, patients took one 100 mg tablet and one 200 mg tablet.]*

The patients had four visits to the study sites (baseline, months 3, 6 and 12) and five telephone contacts (at Maintenance days 0, 29, 59, 155 and 279).

Baseline screening included analgesic washout, eligibility assessment, medical history, physical exam (vital signs and clinical lab test).

Safety monitoring

- Physical examination (including the knees) and clinical laboratory (hematology, biochemistry and urinalysis) at visits of baseline, months 6 and 12.
- Vital signs at 4 visits.
- AEs from the time of first dose to the end of the study (final visit), coded with MedDRA

Concomitant medications: recorded at run-in phase, 3 visits during maintenance and all 5 phone contacts:

- Rescue medication of pain due to OA was not allowed during the study. Patients with intolerable pain could be withdrawn and considered a treatment failure.
- Pain medication for medical conditions other than OA was to be avoided, but could be allowed after consulting with the investigator.
- Medications for tramadol-associated AEs were allowed.
- ASA for cardioprotection was permitted if patients were on a stable dose for ≥ 3 months prior to entry the trial.

Statistical Methods

- Analysis population: all patients who entered the trial and received at least one dose of tramadol OAD:
  - 6-Month Safety Analysis: Patients who received Tramadol OAD ≥ 175 days
  - 9-Month Safety Analysis: Patients who received Tramadol OAD ≥ 265 days
  - 12-Month Safety Analysis: Patients who received Tramadol OAD ≥ 350 days
- Extent of exposure: duration of treatment was calculated as the difference: Last Stop Date – Start Date of First Dose + 1
- Data process: tabulation of AE data (number and % of patients) by age (< or ≥ 65 years), gender and BMI.

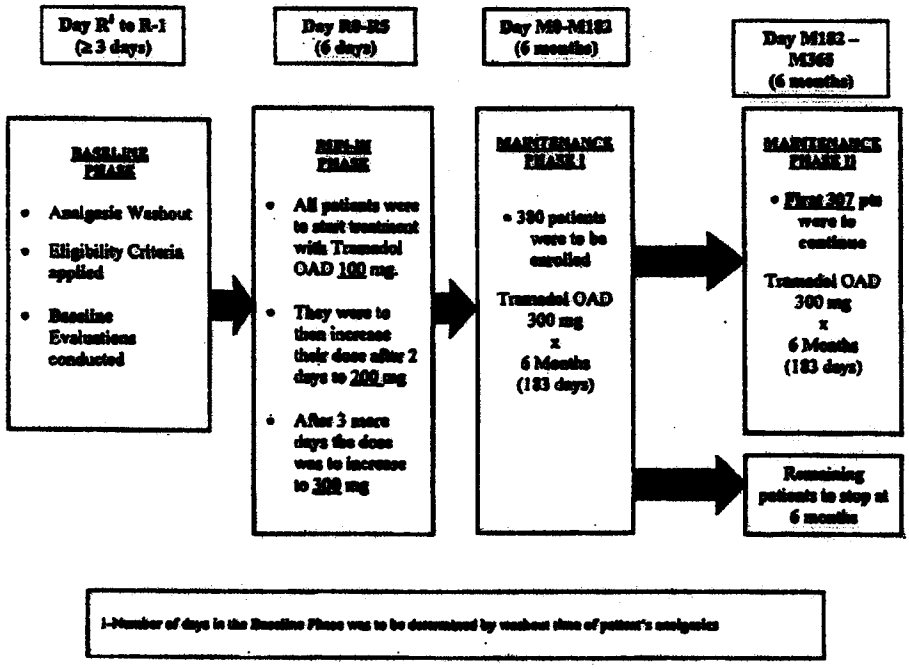

Figure 1. **Study Design Flowchart**
(Applicant's Figure 9.1-1)

RESULTS

Subject Disposition and Dropouts

- A total of 392 patients enrolled into the study:
  - N=371 (of 392) completed Run-In phase and entered the Maintenance Phase I
  - N=275 (of 371) completed Maintenance Phase I (6 months)
  - N=168 (of 176 from phase I) completed Maintenance Phase II (12-months)

- Total dropouts: overall 33% (Table 1)
  - At different phases during the trial:
    - Run-in phase: n=21 (from 392 entered patients, 5.4%)
    - Maintenance Phase I: n=98 (from 371 entered patients, 26.4%)
    - Maintenance Phase II: n=10 (from 176 entered patients, 5.7%)
  - Reasons (of 129 dropouts)
    - Adverse events: n=97 (75%)
    - Patient request: n=15 (12%)
    - Investigator initiated: n=12 (9%)
    - Lack of efficacy: n=5 (4%)

Table 1. **Patient dropouts**
(Extracted from the applicant's Figure 10.1-1)

Patients	Treatment phase of Tramadol OAD			Overall
	Run-In	6-Month	12-Month	
Entered into trial	392	371	176	
Dropouts	21	98	10	129
AE	18	73	6	97
Patient request	3	11	1	15
Investigator initiated	0	10	2	12
Lack of efficacy	0	4	1	5

Baseline Characteristics

Demographics:

Of 443 patients (275 for months and 168 for 12 months), 85-86% were females, mean age was 61 years (38-40% ≥ 65 years old) and mean BMI was 29 (±4).

Concurrent Medical History

- The most common medical history was musculoskeletal and cardiovascular diseases, followed by metabolism/nutrition and gastrointestinal disorders. The frequencies of past and concurrent medical conditions were comparable in patients between 6-month and 12-month treatments.

- The most frequent prior medications were acetylsalicylate derivatives and related substances, cardiovascular therapy (ACE inhibitors, organic nitrates, beta blockers, etc.), oxicams (analgesics) and sulfonamides. Prior medications were comparable in patients between 6-month and 12-month treatments.
- The most common abnormalities (>10% patients) from physical Examination were musculoskeletal, heart, eyes and hair/skin, and they were comparable in patients between 6-month and 12-month treatments.

Compliance

Per visit treatment compliance data were collected but no compliance rates were compiled and calculated because of the open-label nature of the study. [*Reviewer: treatment compliance should be valuable for assessment of exposure and thus safety for any study design*].

Efficacy evaluation

Efficacy assessment was not an objective for this study, but the applicant collected data regard to Patient's and Physician's Global Rating of Pain Relief [*Reviewer: which may indirectly reflex the compliance to treatment*].

- Patients rated the Tramadol OAD treatment as "very effective" and "effective" in 96% for 6-month treatment and 99% for the 12-month treatment.
- Physicians rated the Tramadol OAD treatment as "very effective" and "effective" in 90% of patients for 6-month treatment and 98% of patients for the 12-month treatment.

Safety Evaluation

Extent of exposure

- 371 patients (95% of 392 patients entered) completed titration of Tramadol OAD from 100 mg qd x2 days then 200 mg qd x 3 days.
- 275 patients (74% of 371 patients entered) received Tramadol OAD 300 mg qd for 6 months.
- 168 patients (95% of 176 patients entered) received Tramadol OAD 300 mg qd for 12 months.

Adverse Events (AEs)

Occurrence of TEAEs: overall, 88% of patients (n=346 of 392 enrolled patients) experienced at least one TEAE. The TEAEs reported by 92% (n=318) of these patients were "possibly drug related" (Table 2). Female patients reported more TEAEs (higher frequency and intensity) than male patients at both 6 and 12 months. No other remarkable differences in incidence of TEAEs were observed by comparisons of age, gender or BMI.

Table 2. **Overall Summery of Treatment Emergent Adverse Events (TEAEs)**
(Adapted from the applicant's Table 12.2.2.1-1)

	Tramadol OAD Entire Study[1] (n=392)
Patients n (%)	
with at least one TEAE	346 (88%)
with at least one severe TEAE	85 (22%)
with at least one serious TEAE	9 (2%)
with at least one possibly drug related TEAE	318 (81%)
who died	-
withdrawn	129 (33%)
withdrawn due to TEAE - not including increased pain	97 (25%)
withdrawn due to TEAE - increased pain only	3 (0.8%)

Source: Statistical table: 5.1.1.1
[1] End of Maintenance Phase II (Titration + 12 months)
Note: Percentages are of total number of patients in the long term safety population
Percentages ≥1% were rounded off to the nearest percentage point before the decimal point
n: Number of patients
Multiple occurrences of the same adverse event in the same patient were counted only once

Deaths: there were no deaths during the study.

Serious AEs: A total of 11 SAEs occurred in 9 patients; none of them were considered related to the study medication:

The most frequent TEAEs (≥ 10% of patients by system organ class): gastrointestinal disorders, nervous system, infections and infestations. These AEs showed similar frequency at 6 and 12 months, expect TEAEs related to Investigations increased from 6.5% to 18.5% between 6 and 12 months (Table 3).

The most common TEAEs by PT (≥ 10% of patients): constipation, nausea, dizziness/vertigo, somnolence, headache, and vomiting; the incidence seemed to be comparable between 6- and 12-months treatments (Table 4).

Table 3. **The most common TEASE by System Organ Class (≥ 10%) and Preferred term (> 1%)**
(Applicant's Table 12.2.2.1-3)

	Tramadol OAD 300 mg	
System organ class Preferred Term	6 Months (n=175)	12 Months (n=165)
Gastrointestinal disorders	132 (48.0%)	79 (47.0%)
Constipation	74 (26.9%)	40 (23.8%)
Nausea	62 (22.5%)	42 (25.0%)
Vomiting NOS	17 (6.2%)	13 (7.7%)
Dry mouth	10 (3.6%)	5 (3.0%)
Abdominal pain upper	6 (2.2%)	4 (2.4%)
Toothache	6 (2.2%)	3 (1.8%)
Diarrhea NOS	3 (1.1%)	6 (3.6%)
Abdominal pain NOS	2 (0.7%)	8 (4.8%)
Dyspepsia	2 (0.7%)	2 (1.2%)
Nervous system disorders	75 (27.3%)	56 (33.3%)
Dizziness	30 (10.9%)	22 (13.1%)
Somnolence	29 (10.5%)	13 (7.7%)
Headache NOS	25 (9.1%)	22 (13.1%)
Migraine NOS	4 (1.5%)	-
Paresthesia	3 (1.1%)	5 (3.0%)
Coordination abnormal NOS	-	-
Infections and infestations	43 (15.6%)	28 (16.7%)
Influenza	18 (6.5%)	7 (4.2%)
Nasopharyngitis	16 (5.8%)	13 (7.7%)
Urinary tract infection NOS	7 (2.5%)	10 (6.0%)
Laryngitis NOS	3 (1.1%)	2 (1.2%)
Pharyngitis NOS	3 (1.1%)	3 (1.8%)
Upper respiratory tract infection NOS	-	7 (4.2%)
Investigations	18 (6.5%)	31 (18.5%)
Weight decreased	16 (5.8%)	11 (6.5%)
Blood lactate dehydrogenase increased	-	5 (3.0%)
Red blood cell sedimentation rate increased	-	5 (3.0%)
Blood uric acid increased	-	3 (1.8%)
Blood glucose increased	-	2 (1.2%)
Blood pressure increased	-	2 (1.2%)
Blood cholesterol increased	-	1 (0.6%)
Blood alkaline phosphatase NOS increased	-	1 (0.6%)
Alanine aminotransferase increased	-	1 (0.6%)
Aspartate aminotransferase increased	-	1 (0.6%)
Blood amylase increased	-	-
Gamma-glutamyltransferase increased	-	1 (0.6%)

Source: Statistical tables 5.3.1.1.2, 5.3.1.1.6
Note: Percentages are of total number of patients in the respective (sub-) group
n: Number of patients
Multiple occurrences of the same adverse event in the same patient were counted only once

Table 4. **The most common TEAEs**
(Adapted from the applicant's Table 12.2.2.1-4)

Preferred term	Tramadol OAD 300 mg	
	6 Months (n=275)	12 Months (n=168)
Patients n (%)		
Constipation	74 (26 9%)	40 (23 8%)
Dizziness/Vertigo	37 (13 5%)	30 (17 9%)
Nausea	62 (22 5%)	42 (25 0%)
Somnolence	29 (10 5%)	13 (7 7%)
Vomiting NOS	17 (6 2%)	13 (7 7%)
Headache NOS	25 (9 1%)	28 (16 7%)

Source: Statistical tables 522121, 522141
[1]TEAEs that occured in at least 10% of the overall long-term safety population, regardless of relationship to study drug
Note: Percentages are of total number of patients in the respective (sub-) group
n: Number of patients
Multiple occurrences of the same adverse event in the same patient were counted only once

SUMMARY

See Section 7 (Integrated Review of Safety)

COMMENTS:

The TEAEs may not be comparable between 6- and 12-month treatment because a different population entered into the 2-period treatment; those patients well-tolerated to the 6-month Tramadol OAD treatment continued or willed to continue for the additional 6 months and thus had different experiences of TEAEs.

10.1.6 Study MDT3-001-E1-A1

TITLE: A comparison of the analgesic efficacy and safety of once daily tramadol OAD tablets to twice daily tramadol BID for the treatment of osteoarthritis of the knee (extension protocol) and open label safety follow-up

Study Period: March 7 – October 28, 2002
CRO: [redacted] b(4)

OBJECTIVES

To evaluate the long-term (up to 1 year) of Tramadol OAD at dose of 200-400 mg in patient with the knee OA pain (the open-label extension study of MDT3-001-E1)

The study MDT3-001-E1 was originally designed for 6-week efficacy (non-inferiority) and safety trial in OA patients. In order to comply with the EMEA Guidance for pain study released just prior to the start of this study, the duration of treatment was extended to 12 weeks and subsequently the study was amended with the additional ***9-month open-label*** *treatment (Tramadol OAD 200-400 mg;* ***focusing on 300 mg dose level****) for long-term safety follow-up in patients who completed the 12-week double-blind treatment.*

STUDY LOCATION

Outside USA: 21 sites (3 in France, 8 in Hungary, 8 in Russia and 2 in UK)

STUDY DESIGN

This was an open-label, single arm, flexible Tramadol OAD dose (200-400 mg qd), 9-month extension trial (following the 12-week double-blind non-inferiority trial MDT3-001-E1, for a total of treatment up to 12 months).

The study subjects were all patients who successfully completed the double-blind efficacy period were offered the opportunity to participate in the additional 9-month open-label treatment of Tramadol OAD. A total of 238 patients (from 346 anticipated patients) participated.

- Patients in the Tramadol BID group had to agree to switch to Tramadol OAD
- Patients previous dosed at 100 mg were willing to increase dose to 200-400 mg tramadol

The patients took Tramadol OAD 200, 300 or 400 mg tablets (before breakfast) once daily for 9 months; the dosage can be adjusted (200-400 mg Tramadol OAD) based on efficacy and AEs in consultation with investigator site during the open-label trial. Two dose strength tablets of Tramadol OAD were used, 100 mg and 200 mg tablets. Patients received one 100 mg table and 200 mg tablet for the dose level of 300 mg and two 200 mg tablets for the dose level of 400 mg.

Concomitant medications

- Acetaminophen was taken for patients whose pain was not well-controlled at 300 or 400 Tramadol OAD, but no other rescue medications were permitted.
- Medications for tramadol-associated AEs were allowed.
- ASA for cardioprotection was permitted if patients were on a stable dose for ≥ 3 months prior to entry the trial.

Safety assessment:

Two visits to the study sites during the 9-month open-label treatment for collection of safety data (Table 1)

- Physical examination: at entry to the open-label trial (week 12 of double-blind period) and at end of the open-label trial (week 52, or early termination)
- Vital sign: at weeks 26 and 52 (or early termination)
- Clinical laboratory: hematology, biochemistry and urinalysis at weeks 26 and 52 (or early termination)
- AEs: monitoring from the first dose to the end of study (or early termination) using MedDRA coding system
- For dose switch during the study, a TEAE was associated with a particular dose if the patient received the dose for 2 days prior to the onset of the TEAE.
- Concomitant medication
- Evaluation of withdrawal symptoms at 3 and 7 days after the last dose

Data analysis:

a. Analysis population was all patients who entered the open-label extension trial and received at least one dose of Tramadol OAD:
   - 6-month safety analysis: all patients who received Tramadol OAD ≥ 175 days.
   - 12-month safety analysis: all patients who received Tramadol OAD ≥ 350 days.
   - 9-month safety analysis (exploratory analysis): all patients who received Tramadol OAD ≥ 265 days
   - <6-month safety analysis: all patients who received Tramadol OAD < 175 days

b. AE Data were tabulated as number and % of patients for each analysis population by dose level (200, 300 and 400 mg Tramadol OAD), age (< or ≥ 65 years), gender and BMI

c. Incidence density (ID) of a given AE was also calculated as number of patients with AE/sum of patient time (in days). [*but no results were presented in the report*]

Table 1. **Schedule and assessment of open-label safety study**

SAFETY FOLLOW-UP PHASE	Follow-Up			Withdrawal
Day	M 84 (Entry into Safety Follow-up Phase)[1,2]	M 182	M 364	3 & 7 days after last dose.
Visit	Visit 5	Visit 6	Visit 7 or Disc.[4]	
Informed Consent	X			
Hematology		X	X	
ESR			X[6]	
Biochemistry		X	X	
Urinalysis[3]		X	X	
Physical Exam		X	X	
Vital Signs		X	X	
Adverse Events		X	X	X
Concomitant Meds.		X	X	
Dispense Medication	X	X		
Return Used and Unused Medication		X	X	
Telephone Contact to follow for Withdrawal or Dependence				X
Record of Death [5]			X	

[1] Patients should enter into 1 for Safety Follow-Up Phase on day M84 immediately after completing the Maintenance Phase Visit 5 evaluations.
[2] The data collected at Day T-1 (Visit 1) or Day 168 (Visit3) of the MRT3-001 protocol, as appropriate, will be considered to be the baseline values for the specific evaluations of the extension protocol MRT3-001-E1
[3] Sediment Microscopy is only to be done if indicated by dipstick urinalysis
[4] Discont: If the patient discontinues from the study between Day M182 and Day M364, the patient must be seen for a Safety Follow-Up Discontinuation Visit
[5] If the patient dies during the study, a Record of Death Form must be completed
[6] ESR to be done only at Visit 7 or discontinuation

RESULTS

Subject Disposition

A total of 238 patients (from 365 who completed 12-week double-blind period) continued the 9-month extension open-label treatment.

- N=218 completed 6-month Tramadol OAD
- N=193 completed 9-months Tramadol OAD
- N=75 completed 12-month Tramadol OAD

The overall dropout rate was 11% (27 of 238); 75 patients completed the 12-month treatment (211 patients completed the Month 12 visit). The reasons for dropout were

- Treatment failure: 4% (n=1 on 200 mg)
- AE: 26% (n=7 on 100 and 200 mg)
- Patient request: 70% (n=19 on 200, 300 and 400 mg)

Baseline Characteristics

Demographics:
Of 238 patients who continued the open-label study, 85% (n=203) were females, the mean age was 60 years (38% of patients aged ≥ 65 years) and the mean BMI was 29. The baseline characteristics (age, BMI, ethnic origin) were comparable among difference dose levels.

Concurrent Medical History
The most common medical history was musculoskeletal and cardiovascular diseases. The frequencies of past and concurrent medical conditions were comparable among difference dose levels.

The most common prior medications were analgesics or cardiovascular therapy. They were comparable among different dose levels.

Compliance

Per visit treatment compliance data were collected but no compliance rates were compiled and calculated.

Safety Evaluation
(Integrated to other trials, see Section 7 for details)

Extent of exposure
During the 9-month follow-up period, dosage adjustments from 200 mg to 400 mg Tramadol OAD were allowed at any time. Of 238 patients who entered the open-label extension study, the majority of patients took 200 mg Tramadol OAD (Table 2):

- 59% (n=141) of patient on 200 mg for 287 ±72 days
- 29% (n=70) of patients on 300 mg for 294 ±68 days
- 11% (n=25) of patients on 400 mg for 292 ±64 days
- 0.8% (n=2) of patients on 100 mg (protocol deviation)

Table 2. **Disposition of patients at different dose levels**
(Adapted from the applicant's Table 12.1.1-1)

Table 12.1.1-1 Disposition of Patients

Patients:		Dose of Tramadol OAD at which the patient spent the longest time				
		100 mg (n=2)	200 mg (n=141)	300 mg (n=70)	400 mg (n=25)	Overall (n=238)
With assessments at (1):	Visit 6 (M182)	1 (50%)	130 (92%)	66 (94%)	24 (96%)	221 (93%)
	Visit 7 (M364)	1 (50%)	130 (92%)	66 (94%)	24 (96%)	221 (93%)
Who completed:	6 months at a specific dose	-	129 (91%)	65 (93%)	24 (96%)	218 (92%)
	9 Months at a specific dose	-	114 (81%)	57 (81%)	22 (88%)	193 (81%)
	12 Months at a specific dose	-	43 (30%)	24 (34%)	8 (32%)	75 (32%)

Source: Statistical table 1.1
(1): With assessment of vital signs or drug accountability at each visit
Note: 12 Patients discontinued after M182 and had assessments of vital signs at M364
Percentages ≥1% were rounded off to the nearest percentage point before the decimal point, so totals may not add up to 100%
Percentages are of total number of patients at the respective dose

Dose of Tramadol OAD at which the patient spent any time		Dose of Tramadol OAD at which the patient spent the longest time			
		100 mg (n=2)	200 mg (n=141)	300 mg (n=70)	400 mg (n=25)
100 mg	n (days)	2	79	36	9
	Mean ± SD (days)	74 ± 19	28 ± 40	3 ± 1	2 ± 1
	Median	74	3	2	2
	Range (Min, Max)	60, 87	2, 113	2, 7	2, 4
200 mg	n (days)	2	141	42	9
	Mean ± SD (days)	36 ± 2	287 ± 72	25 ± 43	4 ± 3
	Median	36	279	4	2
	Range (Min, Max)	34, 37	14, 381	2, 142	2, 10
300 mg	n (days)	1	23	70	10
	Mean ± SD (days)	-	32 ± 48	294 ± 68	7 ± 11
	Median	37	5	280	4
	Range (Min, Max)	-	1, 180	89, 373	2, 37
400 mg	n (days)	-	1	10	25
	Mean ± SD (days)	-	-	4 ± 4	292 ± 64
	Median	-	1	3	279
	Range (Min, Max)	-	-	1, 12	108, 370

Source: Statistical table 3.2.1
Note: Number of days were rounded off to the nearest whole figure

Adverse Events (AEs)

Occurrence of TEAEs: overall, 51% and 69% of patients who completed the treatment for 6 or 12 months experienced TEAEs.

Patients who received 400 mg Tramadol OAD tended to report less TEAEs than those on 200 mg or 300 mg in both 6-month and 12-month analysis populations. [*Perhaps was because fewer patients stayed at the 400 mg levels (thus small sample size)].*

There were no remarkable differences in TEAEs across age groups (< or ≥ 65 yo), gender or BMI.

Deaths: there were no deaths reported during the study.

Serious AEs: A total of 6 SAEs occurred in 6 patients; none of them were considered related to the study medication.

1) A 56-year-old Caucasian female suffered from mild pain over urinary bladder 6 weeks after Tramadol OAD treatment and urinary bladder tumor (transitional carcinoma) was diagnosed with cystoscopy at the same day. The investigator considered "possible related to the study medication" due to temporal relationship. The patient discontinued from the study.

2) A 67-year-old Caucasian male suffered from headache and dizziness about 6 months after Tramadol OAD treatment with BP 170/100 mmHg (usual 150/80 mmHg) and essential hypertension was diagnosed (a moderate AE). The patients was withdrawn from the study. After about 1-month anti-hypertension therapy, the patient's BP was 125/85 mmHg. The patient had no history of hypertension and related medical conditions. The investigator considered "not related to the study medication". [*Reviewer: the relationship to the study drug can not be ruled out due to negative medical history and temporal relationship.*]

3) A 74-year-old Caucasian female was hospitalized for diagnostic procedure and re-evaluation of therapy of essential hypertension 10 after Tramadol OAD treatment. The patient had essential hypertension history (a year ago) and medical condition was not worsened for hospitalization. The investigator considered "not related to the study medication".

4) A 74-year-old Caucasian female underwent gastroscopy due to epigastric pain about 4 month after Tramadol OAD treatment; carcinoid tumor (in the duodenal bulb) was diagnosed. The patient had a history of (and concomitant) multiple medical conditions and medications. The investigator considered "not related to the study medication".

5) A 68-year-old Caucasian female was hospitalized due to recurrence of paroxysmal atrial fibrillation about 4 month after Tramadol OAD treatment. The patient responded to the therapy and recovered 1 month later. She was not withdrawn from the study. The patient

had a history of MI, paroxysmal atrial fibrillation, hypertension and other medication conditions. The investigator considered "not relate to the study medication".

6) A 76-year-olf Caucasian was hospitalized for weakness and numb sensation in the left arm, which was diagnosed cerebral ischemia (right media cerebral artery) 9 months after Tramadol OAD treatment. The patient responded to the ischemic therapy and recovered. The patient had a history of cardiovascular disease and was under multiple medications. The investigator considered "not related to the study medication".

The most frequent TEAEs by SOC (≥ 10% of patients after combining all dose levels):

- Of 218 patients who received the study medication for ≥ 6 months:
  - Any TEAEs: 50.5%
  - Gastrointestinal disorders: 26.6%
  - Nervous system: 18.8%
  - Infections and infestations: 13.8%
  - Vascular disorders: 3.9%

- Of 75 patients who received the study medication for ≥ 12 months:
  - Any TEAEs: 69.3%
  - Gastrointestinal disorders: 50.7%
  - Nervous system: 36.0%
  - Infections and infestations: 17.3%
  - Vascular disorder: 13.3%

The most common TEAEs by PT (≥ 10% of patients):

- Of 218 patients who received the study medication for ≥ 6 months:
  - Constipation: 13.3%
  - Nausea: 11.0%
  - Dizziness/vertigo: 8.3%
  - Headache NOS: 8.3%
  - Somnolence: 6.9%

- Of 75 patients who received the study medication for ≥ 12 months:
  - Constipation: 32.0%
  - Nausea: 20.0%
  - Dizziness/vertigo: 13.3%
  - Headache NOS: 18.7%
  - Somnolence: 10.7%

Intensity of TEAEs:

TEAEs reported by majority of patients received 300 mg for 6 or 12 months were mild to moderate.

Drug-related TEAEs:

- Of patients received 300 mg for 6 Months, 29.2% reported a TEAE that the applicant considered to be "at least possibly related to the study drug".
  - Gastrointestinal system disorders: 15 of 20 (75%) cases
  - Nervous system disorders: 7 of 12 (58%) cases.

- Of patients received 300 mg for 12 Months, 45.8% reported a TEAE that was considered "at least possibly related to the study drug";
  - Gastrointestinal system disorders: 10 of 13 (77%) cases
  - Nervous system disorders: 4 of 7 (57%) cases

Time to Onset of TEAEs:

The median time to onset of the most common TEAEs (except headache) was within the first 2 weeks of treatment, which was consistent across different dose levels (200-400 mg), but slightly later in onset in patients taking 400 mg.

- Dizziness/vertigo 3 days
- Somnolence: 3 days
- Nausea: 8 days
- Constipation: 10 days
- Headache: 23 days.

Duration of TEAEs:

The median duration of the most common TEAEs (constipation, dizziness/vertigo, nausea, somnolence and headache) was 3-9 days across all dose levels (200-400 mg); the maximum duration was up to 1 year.

AE-related Dropouts:

Of 238 patients entered the open-label trail, 7 were discontinued due to TEAEs. The TEAEs leading to withdrawal from the study were upper abdominal pain, anorexia, constipation, fatigue, pruritus, somnolence, vomiting and weakness; one patient developed a carcinoid tumor.

Concomitant medication:

Of patients received 300 mg Tramadol OAD and experienced a common TEAE, 29% (in the 6-month) and 38% (in the 12-month) required concomitant treatment.

Post-treatment follow-up:

Patients were contacted by telephone 3 and 7 days after the last dose for assessment of AEs related to withdrawal or dependence. Four patients reported AEs, such as fatigue, insomnia, weakness, pruritus, fatigue, arthralgia, irritability, or restlessness. All adverse events were mild to moderate in intensity. [*Reviewer' comments: the number of patients who were followed up for the post-treatment AEs was not provided in the report and Appendix 16.2.7.1*]

The applicant admitted that the open method of questioning may not have been appropriate to identify all cases, and developed a site tool in subsequent pivotal trial MDT3-003.

Clinical Laboratory Evaluation

Clinically relevant abnormal laboratory values were included as part of TEAE summaries. No details were provided under this section of the report.

Vital Signs and Physical Examination

There were no remarkable changes in vital signs (Respiratory rate, blood pressure, temperature, heart rate) and PE during the 12-month study.

SUMMARY AND COMMENTS

This was an open-label, single arm, flexible Tramadol OAD dose (200-400 mg qd), 9-month extension trial (a total of 12 months by including 3-month double-blind period) in patients with pain due to the knee OA.

A total of 238 patients (from 365 patients who completed 12-week double-blind trial) participated the open-label treatment with Tramadol OAD 200-400 mg; mean age was 60 years old (38% of patients aged ≥ 65 years) and 85% of patients were females.

Of 238 patients, 218 completed the 6-month treatment and 75 patients completed 12-month treatment. The majority of patients took 200 mg Tramadol OAD (59% of patients), 29% on 300 mg and 11% on 400 mg for 9-10 months during the trial. The following is an overall summary of the safety results:

1. Overall AEs from this study appeared to be comparable in profile, intensity and frequency to the observation from double-blinding treatment period.
2. There were 6 serious AEs (no death) during the 9-month extension treatment with Tramadol OAD. None of them was considered related to the study medication.
3. The most common AEs were in gastrointestinal and nervous systems, including Nausea, dizziness/vertigo, constipation and vomiting with intensity from mild to moderate.
4. The patients who received 400 mg Tramadol OAD for 6 months (n=24) and for 12 months (n=8) seemed to experience fewer AEs than those on 200 and 300 mg dose levels. However, this was most likely contributed by too small sample size of the 400 mg subset.

10.2 Line-by-Line Labeling Review

The following review is based on the latest version of proposed package insert (annotated) was submitted on June 12, 2006 (Amendment #10).

Drug Name:

Line #1: drug name "TRAMADOL CONTRAMID® OAD TABLETS" is inappropriate. The applicant has proposed two trade names which were rejected by the Office of Drug Safety. The new trade name is pending from the applicant.

Description:

Line 10-11: [redacted] b(4)

[redacted] This statement should be deleted because it is not supported by PK data; there was a 9-hour window of low level of plasma tramadol at each dosing interval (24 hours) of Tramadol OAD. See Section 5.1 (Pharmacokinetics) for details.

Clinical Pharmacology:

The applicant adapted most of PK and PD information on tramadol HCl from the Ultram product label, including distribution/metabolism/elimination, DDIs and special population. New data supplied by the applicant are the PK profile of Tramadol OAD, and PK comparisons with Ultram. These data appear adequate. See the Clinical Pharmacology review by Dr. Lei Zhang for details.

Clinical Studies:

Upon resubmission of the NDA, this section should be replaced by data from a new efficacy trial because the applicant's efficacy results are not supported by the re-analyses performed by the statistical reviewer (Dr. Yongman Kim).

The applicant briefly describes the four Phase 3 trials: three pivotal trials (MDT3-002, -003 and -005) and one active-controlled trial (MDT3-001-E1) and presents the following three figures:

1) Multiple responder analysis of PI-NRS (Study MDT3-005): the % responders of 1-point to 5-point change from baseline to end of treatment (week 12, with LOCF)
2) Continuous responder analysis of WOMAC Pain score (Study MDT3-003): the % responders of 0-50% change from baseline to end of treatment (week 12, with LOCF)
3) Time-course of pain intensity (Study MDT3-003): WOMAC Pain Scores at each of 5 visits (0-12 weeks).

Lines #300-309: The applicant also presents the results from three pivotal trials of the *patient global rating of pain relief* for patients treated with Tramadol OAD but not for placebo-treated patients. The data from the active-controlled trial (MDT3-001-E1) should not be included in the product label, because they offer no supportive evidence of efficacy of Tramadol OAD.

Lines 311-316: the percentage of responders from placebo group should also be presented. If data from studies MDT3-002 and -003 are presented in the proposed label, data regarding a dose-response relationship () should be omitted or else noted as "not statistically significant).

Lines 321-328: the results from placebo group should be presented.
Lines 335-338 [redacted] b(4)
[redacted] Therefore the claim ' [redacted] (line 338) is inaccurate. This whole paragraph should be deleted.

Indications and Usage:

Lines 349-350: "TRAMADOL CONTRAMID® OAD is indicated for the management of moderate to moderately severe pain."

The proposed indication is unacceptable because the pivotal clinical trials were conducted in adult patients with chronic moderate to severe pain due to OA of the knee. If another efficacy trial is successful upon the next review cycle, the appropriate indication should be "TRAMADOL CONTRAMID® OAD is indicated for the management of moderate to moderately severe chronic pain in adults.",.

Contraindications:
The contraindication information from Ultram labeling is adapted; acceptable.

Warnings:
The warning information (including abuse) from Ultram labeling is adapted; acceptable.

Precautions:
The precaution information from Ultram labeling is adapted; acceptable.

Information for patients:
The information from Ultram labeling is adapted; acceptable.

Adverse reactions (line 711)
Lines 713-720: the extent of exposure is incorrect.

[redacted] b(4)

However, because an additional efficacy trial is recommended, the total number will have to be changed.

Lines 720-816: [redacted]

b(4)

Drug Abuse and Addiction (line 818)
The information from Ultram and Ultram ER labeling is adapted; acceptable.

Overdosage (line 856)
The information from Ultram labeling is adapted; acceptable.

Dosage and Administration (line 880)
The applicant proposed a titration dosing regimen, which needs to be supported by the recommended efficacy trial upon next review cycle.

[redacted]

b(4)

[redacted]

10.3 AEs in Labeling of Ultram ER and Ultram

10.3.1 Ultram ER (NDA 21-692)

The following adverse event data were extracted from the current labeling of Ultram ER (version of January 20, 2006).

Adverse events with incidence ≥ 5% patients (Table 7s):

Table 7s. **Incidence (%) of patients with adverse event rates ≥ 5% from two 12-week placebo-controlled studies in patients with moderate to moderately severe chronic pain by dose**
(Adapted from the labeling of Ultram ER, version January 20, 2006)

MedDRA Preferred Term	ULTRAM ER				Placebo
	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	(N=406) n (%)
Dizziness (not vertigo)	64 (15.9)	81 (20.3)	90 (22.5)	57 (28.2)	28 (6.9)
Nausea	61 (15.1)	90 (22.5)	102 (25.5)	53 (26.2)	32 (7.9)
Constipation	49 (12.2)	68 (17.0)	85 (21.3)	60 (29.7)	17 (4.2)
Somnolence	33 (8.2)	45 (11.3)	29 (7.3)	41 (20.3)	7 (1.7)
Flushing	31 (7.7)	40 (10.0)	35 (8.8)	32 (15.8)	18 (4.4)
Pruritus	25 (6.2)	34 (8.5)	30 (7.5)	24 (11.9)	4 (1.0)
Vomiting	20 (5.0)	29 (7.3)	34 (8.5)	19 (9.4)	11 (2.7)
Insomnia	26 (6.5)	32 (8.0)	36 (9.0)	22 (10.9)	13 (3.2)
Asthenia	14 (3.5)	24 (6.0)	26 (6.5)	13 (6.4)	7 (1.7)
Postural hypotension	7 (1.7)	17 (4.3)	8 (2.0)	11 (5.4)	9 (2.2)
Sweating increased	6 (1.5)	8 (2.0)	15 (3.8)	13 (6.4)	1 (0.2)
Weakness	3 (0.7)	8 (2.0)	14 (3.5)	9 (4.5)	5 (1.2)
Rigors	3 (0.7)	2 (0.5)	9 (2.3)	7 (3.5)	1 (0.2)
Anorexia	3 (0.7)	7 (1.8)	21 (5.3)	12 (5.9)	1 (0.2)
Influenza like illness	1 (0.2)	6 (1.5)	7 (1.8)	4 (2.0)	2 (0.5)

Adverse events with incidence of 1.0% to <5.0% patients:

Eye disorders: vision blurred
Gastrointestinal disorders: abdominal pain upper, dyspepsia, abdominal pain, sore throat
General disorders: weakness, pain, feeling hot, influenza like illness, fall, rigors, lethargy, pyrexia, chest pain
Infections and infestations: nasopharyngitis, upper respiratory tract infection, sinusitis, influenza, gastroenteritis viral, urinary tract infection, bronchitis
Investigations: blood creatine phosphokinase increased
Metabolism and nutrition disorders: appetite decreased, weight decreased, anorexia
Musculoskeletal, connective tissue and bone disorders: arthralgia, back pain, pain in limb, neck pain

Nervous system disorders: tremor, paraesthesia, hypoaesthesia
Psychiatric disorders: nervousness, anxiety, depression, restlessness
Respiratory, thoracic and mediastinal disorders: rhinorrhoea, nasal congestion, dyspnoea, sinus congestion, cough, sneezing
Skin and subcutaneous tissue disorders: sweating increased, dermatitis
Vascular disorders: postural hypotension, hot flashes, vasodilatation

Adverse events with incidence <1.0% patients

Cardiac disorders: palpitations, myocardial infarction
Ear and labyrinth disorders: tinnitus
Gastrointestinal disorders: flatulence, constipation aggravated, toothache, pancreatitis
General disorders: feeling jittery, oedema lower limb, shivering, joint swelling, malaise, drug withdrawal syndrome, peripheral swelling
Hepato-biliary disorders: cholelithiasis, cholecystitis
Infections and infestations: appendicitis, cellulitis, ear infection, gastroenteritis, pneumonia, urinary tract infection, viral infection
Injury and poisoning: joint sprain, muscle injury
Investigations: heart rate increased, liver function tests abnormal, blood pressure increased, alanine aminotransferase, aspartate aminotransferase increased, blood glucose increased, weight decreased
Musculoskeletal, connective tissue and bone disorders: joint stiffness, myalgia, muscle cramps, muscle spasms, muscle twitching, osteoarthritis aggravated
Nervous system disorders: migraine, syncope, disturbance in attention, dizziness aggravated, vertigo, sedation
Psychiatric disorders: irritability, libido decreased, euphoric mood, sleep disorder , agitation, disorientation, abnormal dreams

10.3.2 Ultram (NDA 20-281)

The following adverse data were extracted from the current labeling of Ultram (version of April 14, 2004):

Adverse even with incidence ≥ 5% patients (Table 7v).

Table 7v. **Cumulative Incidence of Adverse Reactions for ULTRAM in Chronic Trials of Nonmalignant Pain (N=427)**
(Adapted from the Ultram labeling, Table 2)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation"*	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

* "CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional liability and hallucinations.

Adverse event with incidence of 1% to < 5% patients, possibly causally related:

Body as a Whole: Malaise.
Cardiovascular: Vasodilation.
Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.
Gastrointestinal: Abdominal pain, Anorexia, Flatulence.
Musculoskeletal: Hypertonia.
Skin: Rash.
Special Senses: Visual disturbance.
Urogenital: Menopausal symptoms, Urinary frequency, Urinary retention.

Adverse event with incidence of < 1%, possibly causally related:

Body as a Whole: Accidental injury, Allergic reaction, Anaphylaxis, Death, Suicidal tendency, Weight loss, Serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).
Cardiovascular: Orthostatic hypotension, Syncope, Tachycardia.
Central Nervous System: Abnormal gait, Amnesia, Cognitive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Seizure (see WARNINGS), Tremor.
Respiratory: Dyspnea.
Skin: Stevens-Johnson syndrome/Toxic epidermal necrolysis, Urticaria, Vesicles.
Special Senses: Dysgeusia.

Urogenital: Dysuria, Menstrual disorder.

Other adverse experiences, causal relationship unknown

Cardiovascular: Abnormal ECG, Hypertension, Hypotension, Myocardial ischemia, Palpitations, Pulmonary edema, Pulmonary embolism.
Central Nervous System: Migraine, Speech disorders.
Gastrointestinal: Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure.
Laboratory Abnormalities: Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria.
Sensory: Cataracts, Deafness, Tinnitus.

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/s/

Jin Chen
9/21/2006 01:08:09 PM
MEDICAL OFFICER

Mwango Kashoki
9/21/2006 05:17:23 PM
MEDICAL OFFICER

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: August 22, 2006

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products
(HFD-170)

Through: Deborah Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader
Controlled Substances Staff (HFD-009)

From: Patricia Beaston, M.D., Ph.D., Medical Officer

Subject: Consult to the DAARP on labeling for TRAMADOL CONTRAMID OAD (NDA 21-745).
Indication: Management of moderate to moderately severe pain.
Proposed Doses: 100 mg, 200 mg, and 300 mg once daily.

Company: Labopharm

Materials received: Link to the labeling for the NDA[1] and consult requesting CSS to 'review Labopharm's language on the abuse potential for this drug (drug liability program) and use with MAO inhibitors and SSRIs'.

Summary: This memorandum reviews the proposed labeling for TRAMADOL CONTRAMID OAD and provides comments to DAARP in preparation for the Division's labeling meeting with Labopharm. For the reader's convenience this document is organized as follows: I) a brief background describing the drug, its regulatory history and known pharmacology and pharmacokinetics are provided, II) sections taken from the proposed label for which CSS has made comments; and III) recommended comments to be relayed to Labopharm.

I. Background

Tramadol, the parent drug, primarily acts as a serotonin and norepinephrine re-uptake inhibition and is a centrally acting analgesic. Although tramadol has a weak affinity for

[1] Of note: NDA 21-745 is not an electronic submission and therefore the entire submission was not readily accessible to CSS reviewers. Portions of the submission were copied and forwarded by the primary reviewers.

the μ-opioid receptor, it has an active O-demethylated metabolite (M1)[2] which has a high affinity for the μ-opioid receptor. The M1 binding affinity is ten-fold less than morphine and 100-fold greater than codeine[3].

Tramadol use is associated with adverse events consistent with those in the opioid drug class. In addition to these adverse events tramadol has been associated with serotonin syndrome. Although the occurrence of serotonin syndrome does not appear to be a prominent dose related phenomenon[4], it is increased by the concomitant use of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs).

Regulatory History: Tramadol Contramid OAD is a new formulation (combination immediate release and extended release) of an approved product. Tramadol was first marketed in Germany in 1977, was approved in the United States in 1995, and is currently marketed in more than 70 countries under several formulations. Although the M1 active metabolite of tramadol works through the μ-opioid receptor, tramadol is not currently regulated as a controlled substance in the United States.

Tramadol is marketed in several forms (immediate release, orally disintegrating, and extended release) alone or in combination with another analgesic (acetaminophen). Comparisons of the proposed label to labels for other approved tramadol products were made for the purpose of this consult.

Drug Product: Tramadol Contramid OAD consists of an outer coat with an immediate-release matrix and a core of controlled-release matrix. Approximately 25% of the tramadol is released within 1.5 hours with the remainder being released through the 12 hour period. b(4)

The following table presents the PK parameters for Tramadol Contramid OAD and tramadol immediate release (as reported in the label):

Table 1. Mean (%CV) Steady-State Pharmacokinetic Parameter Values (n=26).

Pharmacokinetic Parameter	Tramadol		M1 Metabolite	
	Tramadol Contramid® OAD 200 mg Tablet Once-Daily	Immediate- release tramadol 50 mg Tablet Every 6 Hours	Tramadol Contramid® OAD 200 mg Tablet Once-Daily	Immediate- release tramadol 50 mg Tablet Every 6 Hours
AUC_{0-24} (ng·h/mL)	5991 (22)	6399 (28)	1361 (27)	1438 (23)
C_{max} (ng/mL)	345 (21)	423 (23)	71 (27)	79 (22)
C_{min} (ng/mL)	157 (31)	190 (34)	41 (30)	50 (29)
T_{max} (hr)*	4.0 (3.0 – 9.0)	1.0 (1.0 – 3.0)	5.0 (3.0 – 20.0)	1.5 (1.0 – 3.0)
Fluctuation (%)	77 (26)	91 (22)	53 (29)	49 (26)

*T_{max} is presented as Median (Range)

[2] Gillen, C., M. Haurand, D. J. Kobelt & S. Wendt, 2000. "Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor," *Naunyn-Schmiedeberg's Arch Pharmacol.* 362: 116-21.

[3] Frink, M.Ch., H.H. Hennies, W. Englberger, M. Haurand & B. Wilffert, 1996. "Influence of tramadol on neurotransmitter systems of the rat brain," *Arzneim. Forsch.*, 46: 1029-36.

[4] Based on the conclusion of the Office of Drug Safety Review for NDA 20-281 (Ultram) dated5/8/2006.

II. Selected Sections from the Proposed Label and CSS comments
This section provides selected text from the proposed label (italicized) and comments from CSS (bolded).

A. Factors Affecting Dissolution

1. Physical Manipulation

*TRAMADOL CONTRAMID® OAD extended-release tablets should be taken once a day. **The tablets should be swallowed whole with liquid and not split, chewed, dissolved or crushed.** TRAMADOL CONTRAMID® OAD tablets produce a continuous release of active ingredient over 24 hours: a repeat dosage within 24 hours is not recommended.*

2. Alcohol

An in vitro dissolution study conducted with various concentrations of ethanol demonstrated that there was no increase in the release rate of tramadol from the TRAMADOL CONTRAMID® OAD tablets in the presence of ethanol.

CSS comment: [redacted]

b(4)

[redacted]

The *in vitro* data for dissolution in the presence of 1 to 4 doses (equivalent of 'shots') of ethanol added to the dissolution material shows a decrease in dissolution with increased concentration of ethanol. (Labopharm's figure 21 is provided in the appendix.) This finding appears to be inconsistent with the label statement that *Tramadol hydrochloride is a white crystalline powder that is freely soluble in water and ethanol.* It is of concern that this *in vitro* data may be inconsistent with *in vitro* experience and although patients are cautioned not to take tramadol the proposed labeling may be falsely reassuring. Of note is that no other label contains language describing the effect of ethanol on tramadol pharmacokinetics.

b(4)

Recommendations: The effects of [redacted] **the in vivo exposure with ethanol and other solvents on the dissolution properties of the Tramadol Contramid OAD tablet should be better studied and described.**

b(4)

B. Contraindications

b(4)

CSS comment: Based on the findings of enhanced dissolution of tramadol by merely bisecting the tablet this product should be contraindicated in patients who are not able to swallow a tablet whole.

Recommendation: The label should include a contraindication for patients unable to swallow tablets whole.

C. Withdrawal

b(4)

CSS comment: This language in the 1st and 3rd paragraphs is consistent with other tramadol products. The second paragraph b(4)

Therefore this paragraph should be omitted or additional information provided to more clearly define adverse events associated with withdrawal from Tramadol Contramid OAD.

Recommendation: Future studies should make daily inquiries for the first week after discontinuation from Tramadol Contramid OAD to identify adverse events associated with withdrawal. Although it has been reported that the majority of symptoms were 'mild to moderate' the severe adverse events, even if infrequent,

should be documented. Adverse events during the withdrawal period should be presented and any dose relationship defined.

D. Misuse, Abuse and Diversion of Opioids

b(4)

CSS comment: This language is consistent with other tramadol products.

E. Risk of Overdosage

Serious potential consequences of overdosage with TRAMADOL CONTRAMID® OAD are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (See OVERDOSAGE). ——— b(4)

CSS comment: This language is consistent with other tramadol products.

F. Drug Abuse and Addiction

TRAMADOL CONTRAMID® OAD is a μ-agonist opioid. Tramadol, like other opioids used in analgesia, can be abused and is subject to criminal diversion.

b(4)

CSS comment: This language is consistent with other tramadol products.

G. _____

b(4)

b(4)

CSS comment: This language is consistent with other tramadol products.

H. Dosage and Administration

1. Initiation of treatment with tramadol:

b(4)

2.

b(4)

b(4)

I. **Serotonin Syndrome**

b(4)

CSS comment: Serotonin syndrome can be a serious and sometimes fatal adverse event. The proposed labeling does not adequately highlight the potential for tramadol to cause serotonin syndrome especially when combined with other drugs targeting serotonin receptors. The risk for seizure with concomitant use of tramadol and MAOIs or SSRIs is well outlined under Seizure Risk in the Warnings section. The risk for serotonin syndrome should be similarly highlighted.

Recommendation: The proposed labeling in the Warnings sections should better illuminate and discuss the risk for serotonin syndrome similar to that addressing the risk for seizure.

III. Recommended Comments to the Company:

1) The effects of _____ the in vivo exposure with ethanol and other solvents on the dissolution properties of the Tramadol Contramid OAD tablet should be better studied and described. b(4)

2) _____

3) Future studies should make daily inquiries for the first week after discontinuation from Tramadol Contramid OAD to identify adverse events associated with withdrawal. Although it has been reported that the majority of symptoms were 'mild to moderate'

the severe adverse events, even if infrequent, should be documented. Adverse events during the withdrawal period should be presented and any dose relationship defined.

4) [redacted] b(4)

5) The proposed labeling in the Warnings sections should better illuminate and discuss the risk for serotonin syndrome similar to that addressing the risk for seizure.

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Appendix:

Dissolution studies after physical manipulation:

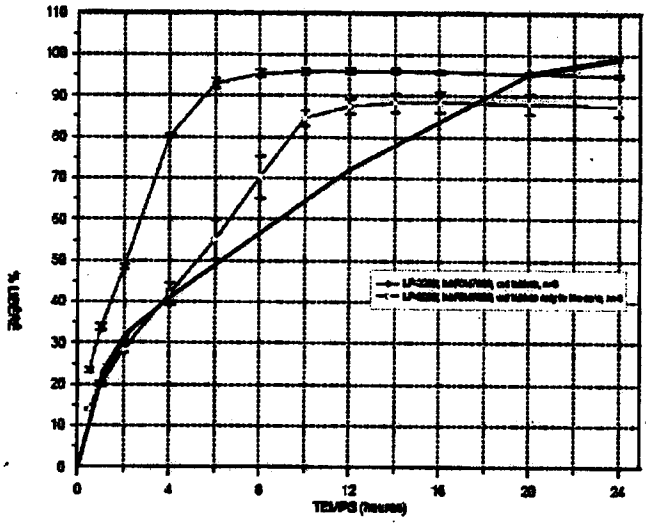

Figure 19 (a): Dissolution profiles of 6 tablets either bisected or shaved to remove coating and marginally expose the tablet core. Type III USP conditions were used[5].

OF NOTE: Not labeled on the table – the solid black line represents the dissolution of the intact Tramadol Contramid OAD tablet.

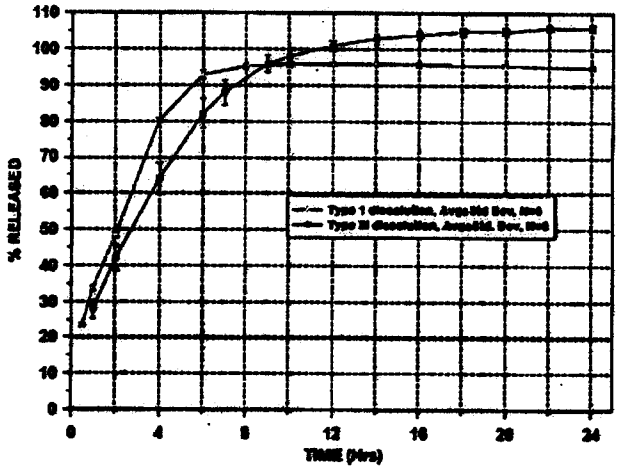

Figure 19 (b): Dissolution profiles of 6 bisected 200 mg strength tablets run under either Type I or Type III conditions.

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✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

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