7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety assessment of Tramadol OAD was based on the applicant's six Phase 3 trials in patients with pain due to OA of the knee (Table 7a), and 11 Phase 1 trials (PK studies in healthy subjects with single dose exposure). The safety data of the Phase 3 trials were used primary for assessment of total patient exposure and effects of high dose treatment. The safety analysis population composed all patients who took at least one dose of study medication.

The applicant did not submit an integrated safety dataset. The integrated safety review was summarized from individual study reports and datasets.

Table 7a. **Phase 3 Trials Included in The Safety Evaluation of Tramadol OAD**

Study No.	Study Type	Treatment	Duration	Study Location
MDT3-001-E1	Randomized double-blind 2-arm study (active control, non-inferiority) in OA patients	Tramadol Contramid OAD or Tramadol BID (Topalgic LP) 100, 200, 300 or 400 mg	12-week maintenance	Non-US
MDT3-001-E1-A1	Open-label safety follow-up in OA patients	Tramadol Contramid OAD 200, 300 or 400 mg	9-month extension from MDT3-001-E1	Non-US
MDT3-002	Randomized double-blind 4-arm study in OA patients	Tramadol Contramid OAD 100, 200, 300 mg or placebo	12-week maintenance	US
MDT3-003	Randomized double-blind 4-arm study in OA patients	Tramadol Contramid OAD 100, 200, 300 mg or placebo	12-week maintenance	US
MDT3-004	Open-label long-term safety study	Tramadol Contramid OAD 300 mg	6 & 12 months	Non-US
MDT3-005	Randomized double-blind 2-arm study in OA patients	Tramadol Contramid OAD (200 or 300 mg) or placebo	4-week open-label; 14-week double-blind phase (2-week titration and 12-week maintenance)	Both US and non-US

7.1.1 Deaths

A total of three deaths were reported during the clinical trials (all from Phase 3 trials): two were in patients treated with Tramadol OAD (one each from placebo-controlled trial MDT3-002 and active-controlled trial MDT3-001-E1) and one occurred in a patient from placebo group (MDT3-003) (Table 7b).

Death #1 (Patient 39-474, reported from Tramadol OAD in Study MDT3-002): This was a 67-year-old Caucasian female enrolled in the 100 mg tramadol OAD group who died from acute

myocardial infarction before the last visit (visit 5). The patient took Tramadol OAD 100 mg Tablets for approximately 2 month with good compliance (initial date was March 17, 2003).

The patient had a history of hypertension with total cholesterol of 215 mg/l (normal < 200) and K+ of 3.3 mmol/l (normal 3.5-5.2 mmol/l) at baseline screening.

The patient had heel surgery (subtalar procedure) on ——————and was transferred to an extended care facility. The patient became "agitated" and was transported to ER four days after the surgery. The ER evaluation was normal. She was then transferred and admitted to other medical center with a diagnosis of Bipolar Disorder. The patient collapsed and died 6 days after admission. The death cause was "acute myocardial infarction with atherosclerotic heart disease". It was unknown if the patient stopped taking the study medication during or after surgery of the heel. b(6)

Reviewer's comments: The investigator concluded the death cause was acute MI which was not related to the study medication. However, the investigator/applicant did not provide information on confirmatory diagnosis (cardiac tests prior to the event and autopsy after death) of acute MI and rationale about no relation to the study medication. The initial clinical symptom was "agitated" which is part of triad of serotonin syndrome. Thus a potential drug-drug or drug-disease interactions cannot be ruled out.

Death #2 (Patient 23-260, reported from Tramadol OAD in Study MDT3-001-E1): a 67-year-old Caucasian female experienced a fatal ischemic stroke after treatment with Tramadol OAD 400 mg for 36 days. The patient had a significant medical history, including cardiovascular disease and hyperlipidemia, and was on multiple medications. The stroke was *less likely related to* the study medication.

Death #3 (Patient 61-801, reported from Placebo in Study MDT3-003): a 72-year-old black male experienced myocardial infarction after received placebo doses for 6.5 weeks and died 10 days later. The patient had hypertension, hypercholesterolemia and coronary artery bypass about 5-6 years ago prior to entering the study.

7.1.2 Other Serious Adverse Events

Based on data from the individual trials and datasets, this reviewer counted a total of 47 serious adverse events (SAEs) in 43 patients during the Phase 3 trials, including 41 SAEs experienced by 37 patients who were treated with Tramadol OAD (in placebo-controlled and open-label trials). The incidence of SAEs associated with Tramadol OAD treatment was approximately 2.1 % of patients (37 of 1725) across trials. However, the applicant's summary lists 39 SAEs in 35 patients treated with Tramadol OAD without presenting SAEs from placebo group.

The SAEs occurred sporadically across different system organ class with relatively higher incidence in cardiovascular (such as MI, angina, stroke, venous thrombosis, hypertension), gastrointestinal (such as faecal impaction, gastritis, abdominal pain) and nervous systems (such as convulsion, syncope, bipolar disorder) (Tables 7b and 7c). Mostly, a single case of an SAE

was reported across study groups, making it difficult to estimate the trend of relationship to Tramadol OAD treatment.

In placebo-controlled trials: A total of 19 patients reported 21 SAEs in the Tramadol OAD group 6 patients in placebo group from MDT3-002, -003 and -005 trials. As shown in Table 7b, the overall incidence of SAE reports was slightly higher in the Tramadol OAD treatment group (1.7% patients) than in placebo group (0.9% patients); the incidence tends to increase with dose of Tramadol OAD.

The total SAEs in Table 7b included five SAEs reported during the Open-label phase (up to 3-week Tramadol OAD treatment) of Study MDT3-005 by five patients who were not randomized into the double-blind phase.

In non-placebo-controlled trials: a total of 18 patients reported 20 SAEs from MDT3-001 (12-week active-control followed by 9-month open-label extension) and MDT3-004 (12-month open-label) (Table 7c).

Causality of SAEs: SAEs had a temporal relationship to the study medication, and almost all patients who experienced SAEs had existing medical conditions under multi-medications. The causality of SAEs related to the study medication is difficulty to be established.

The following 6 SAEs reported by 5 patients were considered by the applicant *"possibly related to study medication"*. These occurred in patients in the Tramadol Contramid OAD 300 mg dose group (five in 12-week studies, and one in the long-term study).

1) Faecal Impaction (Patient 46-146, Study MDT3-002)
2) Gastritis (Patient 13-328, Study MDT3-003)
3) Constipation (Patient 33-18, Study MDT3-004)
4) Syncope with renal impairment (Patient 29-512, Study MDT3-005)
5) Hepatitis (Patient 86-899, Study MDT3-005)
6) Renal Impairment (Patient 86-899, Study MDT3-005)

The causality of these SAEs was estimated mostly based on a clearly temporal relationship, expectation (from the current tramadol product), and lack of explanation for the events. The laboratory abnormalities of liver and renal function are listed in the labeling of currently marketed tramadol product.

SAE Outcome: the following 17 patients (including two patients who died) discontinued from the study due to SAEs. The rest of the patients was recovered.

- two patients in the 100 mg dose group: both in the Placebo-controlled studies
- two patients in the 200 mg dose group: one on a Placebo-controlled study and one on the long-term safety follow-up study (MDT3-001-EI-A1)
- twelve patients in the 300 mg dose group: five in the Placebo-controlled studies, seven on the long-term fixed-dose safety study (MDT3-004) and one in the 400 mg dose group from Placebo-controlled study

Table 7b. **Serious AEs Experienced by Patients during Three Placebo-Controlled Trials**
(Extracted from the individual datasets of each trial)

SOC and PT	Tramadol OAD, n=1095			Placebo n=668	Study ID
	100 mg n=216	200 mg n=311	300 mg n=531		
Cardiac Disorders, n=3					
Angina Unstable			1		MDT3-005
Acute Myocardial Infarction	1†				MDT3-002
Myocardial Infarction				1‡	MDT3-003
Gastrointestinal Disorders, n=7					
Diverticulitis NOS			1		MDT3-005
Faecal Impaction			1		MDT3-002
Pancreatitis Aggravated			1		MDT3-002
Rectal Prolapse				1	MDT3-002
Gastritis NOS			1		MDT3-003
Abdominal Pain Lower				1	MDT3-003
Small Intestinal Obstruction NOS	1				MDT3-003
General Disorders and Administration Site Conditions, n=1					
Chest Pain			1		MDT3-005
Infections And Infestations, n=2					
Hepatitis NOS		1			MDT3-005*
Gastroenteritis Viral NOS				1	MDT3-002
Musculoskeletal And Connective Tissue Disorders, n=1					
Popliteal Bursitis			1		MDT3-005*
Neoplasms Benign, Malignant and Unspecified, n=4					
Prostate Cancer NOS			1		MDT3-005*
Breast Cancer NOS			1		MDT3-005
Breast Cancer Invasive NOS		1			MDT3-002
Thyroid Neoplasm NOS			1		MDT3-002
Nervous System Disorders, n=4					
Grand Mal Convulsion			1		MDT3-005*
Syncope			1#		MDT3-005
Ischaemic Stroke NOS				1	MDT3-005
Bipolar Disorder	1†				MDT3-002
Renal And Urinary Disorders, n=1					
Renal Impairment NOS		1	1#		MDT3-005*
Vascular Disorders, n=3					
Venous Thrombosis Limb NOS				1	MDT3-002
Deep Venous Thrombosis NOS	1				MDT3-002
Aortic Aneurysm			1		MDT3-002
Total (27 SAEs in 25 patients)	4 (1.9%)	3 (1.0%)	14 (2.4%)	6 (0.9%)	
	21 SAEs in 19 patients (1.7%)				
Total *(excluding SAEs prior to DB)** **(22 SAEs in 20 patients)**	4 (1.9%)	1 (0.3%)	11 (1.9%)	6 (0.9%)	
	15 SAEs in 14 patients				

† and # from the same patients, respectively.
‡ The fatal MI
* SAEs experienced by patients who received the open-label treatment but were not randomized to the double-blind (DB) phase in Study MDT3-005.

Table 7c. **Serious AEs Experienced by Patients during Two Open-label Long-Term Trials**
(Extracted from the individual datasets of each trial)

SOC and PT	Tramadol OAD, n=630	
	Study MDT3-001 (200-400 mg) N=238	Study MDT3-004 (300 mg) N=392
Cardiac Disorders, n=3		
Acute Pulmonary Oedema		1†
Coronary Artery Insufficiency	1*	
Atrial Fibrillation	1	
Gastrointestinal Disorders, n=2		
Constipation		1
Pancreatitis Chronic		1
Hepatobiliary Disorders, n=1		
Cholecystitis NOS		1
Injury, Poisoning And Procedural Complications, n=1		
Femoral Neck Fracture		1‡
Metabolism and Nutrition Disorders, n=1		
Diabetes Mellitus NOS		1†
Musculoskeletal And Connective Tissue Disorders, n=2		
Osteoarthritis Aggravated		1
Back Pain		1
Neoplasms Benign, Malignant And Unspecified, n=1		
Bladder Neoplasm NOS	1	
Carcinoid Tumour NOS	1	
Nervous System Disorders, n=3		
Paresis (sciatic)		1‡
Ischaemic Stroke NOS	1 (fatal)	
Cerebrovascular Disorder NOS	1	
Surgical And Medical Procedures, n=1		
Cholecystectomy		1
Vascular Disorders, n=3		
Cerebrovascular Accident		1
Essential Hypertension	3*	
Total	9 (3.8%)	11 (2.8%)
	20 SAEs in 18 patients (2.9%)	

† and ‡ the SAEs experienced by the same patient, respectively.
* From the 12-week trial (one of essential hypertensions).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The overall dropout rates were 37.8% for patients receiving Tramadol OAD and 33.7% for patients receiving placebo in the placebo-controlled trials, and 24.8% in the open-label safety trials (Table 7d). The dropout rates increased with increasing dose of Tramadol OAD, particularly AE-related dropouts. In the placebo-controlled trials, AEs were the most common reasons for dropout among Tramadol-treated patients, and placebo patients mainly dropped out due to lack of efficacy.

There were significant differences in the dropout rates across the four randomized controlled trials. The dropout rates were 21% in MDT3-001-E1 and 25% in MDT3-005, which were about half of those in MDT3-002 (47%) and MDT3-003 (45%). This was probably due to difference in study design:

1) In MDT3-001-E1 and MDT3-005, patients were titrated to the optimum fixed dose level by self-selection, not pre-assignment. In contrast, patients in MDT3-002 and MDT3-003 were pre-assigned to the fixed dose level that they had to be titrated to.

2) The patients in MDT3-005 received 4-week open-label treatment of Tramadol prior to randomization and only patients who responded to the Tramadol OAD treatment (flaring and tolerable) entered the double-blind phase. Therefore, more patients were likely to complete 12-week maintenance treatment in MDT3-005 and MDT3-001-E1 than in MDT3-002 and -003.

3) Enrollment of the study population from different countries (thus different culture background and others) may also have contributed to the different dropout rates across trials, particularly those different dropout rates in placebo treatment. All of the patients in studies MDT3-002 and -003 were enrolled from US, but 40% of patients in study MDT3-005 and 100% of patients in study MDT3-001-E1 and MDT3-004 were from outside the US.

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

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

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

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

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

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

7.1.3.2 Adverse events associated with dropouts

Randomized Controlled Trials: in the three placebo-control and one active-controlled 12-week efficacy trials, a total of 425 patients on any dose of Tramadol OAD (100 to 400 mg) discontinued from the study due to AEs. Approximately 78% (331 of 425) dropouts were due to the most common non-serious AEs (Table 7e) and 4% were due to SAEs (17 of 425) (see Section 7.1.2 above, *Other Serious Adverse Events* for details).

During the titration period (from 100, 200 to 300 mg Tramadol OAD for up to 2 weeks), the profile of the most common AEs leading to dropout was similar to that of the 12-week maintenance period (Table 7f).

Open-label long-term safety trials: AE-related dropouts were 3% in Study MDT3-001-E1-A1 (9-month open-label extension following 3-month efficacy trial) and 26% in Study MDT3-004 (12-month open-label trial).

The most common AEs associated with dropouts in Study MDT3-004, by SOC and preferred term, were: gastrointestinal disorders (nausea: 13%; vomiting 7% and constipation: 6%) and nervous system disorders (dizziness: 9%; somnolence: 4%; headache: 4%).

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

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

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

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

[3] During Open-label phase.

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

Table 7f. **Most common AEs during the titration period of randomized controlled efficacy trials**
(Applicant's Table 2.7.4.2.1.4-2)

	Tramadol Contramid® OAD			
	12-Week Placebo-Controlled Studies[1]			12-Week Active-Controlled Study[2]
Preferred term	MDT3-002 N=338	MDT3-003 N=325	MDT3-005[3] N=1023	MDT3-001/E1 N=215
Any TEAE	139 (41.1%)	137 (42.2%)	312 (30.5%)	139 (64.7%)
Constipation/Agravated	27 (8.0%)	21 (6.5%)	80 (7.8%)	40 (18.6%)
Dizziness / vertigo	48 (14.2%)	33 (10.2%)	99 (9.7%)	46 (21.4%)
Nausea	55 (16.3%)	41 (12.6%)	148 (14.5%)	46 (21.4%)
Somnolence	10 (3.0%)	28 (8.6%)	65 (6.4%)	58 (27.0%)
Vomiting	17 (5.0%)	18 (5.5%)	63 (6.2%)	7 (3.3%)
Headache	15 (4.4%)	13 (4.0%)	41 (4.0%)	15 (7.0%)

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

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

[3] During Open-label phase.

Source: Statistical Tables 5.2.1.1, 5.2.1.3, 5.2.2.1, 5.2.2.3, 5.2.3.1, 5.2.3.3, 5.2.4.1, 5.2.4.3 (01JUN2006).

7.1.4 Other Search Strategies

The following particular safety concerns were searched for throughout the NDA submission:

- ***Seizure and serotonin syndrome:*** these are two major serious adverse drug reactions associated with drug interaction of tramadol with SSRIs, SSNIs or MAOIs. They are included as warnings in the labeling of all current marketed Tramadol products.

- ***Dumping effect:*** Tramadol was formulated with both ER ——— and IP ——— forms in the product and a potential dose-dumping effect (a conversion of ER pharmacokinetic profile to the profile for an IR formulation) may occur through drug-food and/or drug-drug interactions or crushing tablets.

b(4)

- ***Overdose:*** like other opioids, acute overdose with tramadol can cause respiratory depression, coma and death.

One seizure case was reported in Study MDT3-005, which was a 73-year-old Caucasian male experienced one episode of Grand Mal Seizure 17 days after last dose of the open-label treatment (at final dose of 300 mg Tramadol OAD). The patient did not enter the double-blind phase due to a family reason. After hospitalization and anti-seizure therapy, the patient recovered and had no more seizure occurred at 2-week follow-up (after the initial seizure). The patient had no history of seizure but cerebral vascular accident and cardiovascular conditions. The seizure was unlikely related to the Tramadol OAD treatment because of timing and patient's medical history.

In the entire NDA submission, there were no reports of overdose, dose-dumping or typical serotonin syndrome reported by patients treated with Tramadol Contramid OAD. However, all potential drug-drug interaction risk factors were excluded from the subject selection and the study subjects were clearly instructed on the appropriate oral administration of Tramadol OAD during enrollment and subsequent visits. There was also no pharmacogenomic test (CYP2D6 polymorphism, a primary metabolic enzyme/clearance on Tramadol) on the study population was planned or required. Therefore, there was no adequate information in this NDA to assess the risk of seizure and serotonin syndrome associated with this product.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

A total of 11 Phase 1 (pharmacokinetic) studies were conducted in 301 healthy subjects treated with a single dose of Tramadol OAD. The study population (97% Caucasian) consisted of 253 males and 49 females with a mean age of 27 years. Adverse events reported during the study were typical of other tramadol products and occurred with mild intensity in the majority of subjects.

For the six Phase 3 trials, AE data were collected at all site visits (Table 7g) and included any unfavorable and unintended signs, symptoms or disease temporally associated with the study

medication (whether or not it is considered related to that products) and any abnormalities found on physical exam and clinical laboratory tests.

SAEs that occurred during the studies and within 30 days after the last dose of study medication were recorded.

Reports of AEs were elicited using a verbal probe and were recorded in the source documentation and on the CRF. The investigator or delegate was always to ask the same open-ended questions (as a verbal probe) "*Have you experienced any difficulties or problems since I saw you last?*", which was followed by additional questions for evaluation of severity, frequency, duration and causality.

Table 7g. Timing for collection of Safety data across all 6 Phase 3 trials
(Applicant's Table 2.7.4.1.1-1)

Study	Baseline	Titration/ Run-in	M0	M21	M42	M59	M84	M126	M182	M279	M364	Discontinuation	Post-Treatment Follow-up
MDT3-001/E1	X	X	X	X	X		X					X	
MDT3-001-E1-A1 (open-label safety follow-up of MDT3-001/E1)									X		X	X	X
MDT3-002	X	X	X	X	X		X					X	
MDT3-003	X	X	X	X	X		X					X	X
MDT3-004	X	X	TC	TC[1]		TC	X	TC	X	TC	X	X	
MDT3-005[2]	X	X, TC	X	X	X	X[3]	X					X	

M - Maintenance day; the number next to the "M" refers to the day of the maintenance period on which the visit or activity occurred (this does not include days on titration).

X - Study visit

TC - Telephone contact

[1] Telephone contacts actually occurred on day M29 rather than M21.

[2] This study started with a 4-week Open-label Phase.

[3] Visit actually occurred on day M63 rather than M59.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs were coded with MedDRA coding system and categorized by SOC followed by preferred terms. AEs were stratified by age ≤ 65 years and > 65 years and gender at difference dose levels of Tramadol OAD. AE categorization appears appropriate.

7.1.5.3 Incidence of common adverse events

Placebo-control trials: there were three 12-week placebo-controlled trials (MDT3-002, MDT3-003 and MDT3-005). The safety population consisted of 1095 patients on Tramadol OAD and 668 on placebo.

Overall incidence of patients experiencing all AEs (Table 7h):

- In Tramadol OAD treatment, 63% patients (690 of 1095) had "*at least one AE*", 1.3% patients (14 of 1095) experienced "*at least one SAE*" and 47% patients (509 of 1095) reported "*at least one possibly related AE*".
- In the Placebo group, 51% patients (338 of 668) had "*at least one AE*", 0.9% patients (6 of 668) experienced "*at least one SAE*" and 24% patients (161 of 668) had "*at least one possibly related AE*".

Table 7h. **Over summary of AEs reported during randomized controlled trials**
(Applicant's Table 2.7.4.2.1-1)

		Tramadol Contramid® OAD					
		12-Week Placebo-Controlled Studies[1]				12-Week Active-Controlled Study[2]	All studies / All active doses[3]
	Placebo	100 mg	200 mg	300 mg	Overall Active		
	N=660	N=216	N=313	N=530	N=1059	N=215	N=1310
Patients with at least one TEAE	338 (50.6%)	125 (57.9%)	184 (59.2%)	302 (57.0%)	690 (63.0%)	175 (81.4%)	865 (66.0%)
Patients with at least one severe TEAE	37 (5.5%)	18 (8.3%)	22 (7.1%)	36 (6.8%)	87 (7.9%)	30 (14.0%)	117 (8.9%)
Patients with at least one serious TEAE	6 (0.9%)	3 (1.4%)	1 (0.3%)	10 (1.9%)	14 (1.3%)	3 (1.4%)	17 (1.3%)
Patients with at least one related or possibly related TEAE	161 (24.1%)	78 (36.1%)	132 (42.4%)	214 (40.4%)	509 (46.5%)	164 (76.3%)	673 (51.4%)
Patients who discontinued prematurely due to TEAE	47 (7.0%)	37 (17.1%)	44 (14.1%)	93 (17.5%)	196 (17.9%)	19 (8.8%)	215 (16.4%)
Patients who died	1 (0.1%)	1 (0.5%)	-	-	1 (0.1%)	1 (0.5%)	2 (0.2%)

[1] Total of Tramadol Contramid® OAD treatment groups (100 mg, 200 mg and 300 mg) from MDT3-002, MDT3-003 and MDT3-005 (Dose-specific data from MDT3-005 include Maintenance Period only while Overall Active includes the entire Double-Blind Phase).
[2] Total of Tramadol Contramid® OAD treatment groups (100 mg, 200 mg, 300 mg and 400 mg) from MDT3-001/E1 (Tramadol BID group excluded).
[3] Total of Tramadol Contramid® OAD treatment groups from MDT3-002, MDT3-003, MDT3-005 and MDT3-001/E1 (Tramadol BID group and placebo not included).
Source: Clinical Study Reports MDT3-002, MDT3-003 and MDT3-001/E1, Statistical Table 5.3.1.1. MDT3-005, Statistical Tables 5.3.1.1, 5.3.1.4, 5.3.1.5.

Common AEs (≥ 10%) by SOC: Tramadol OAD *vs.* Placebo:

- gastrointestinal system: 35.5% vs. 16.3%
- nervous system: 23.4% vs. 14.4%
- skin and subcutaneous disorders: 12.2% vs. 3.7%
- Infections and Infestations: 9.4% vs. 13.2%

Overall incidence of common AEs in patients treated with Tramadol OAD at dose of 100-300 mg regardless causality (% of patients):

- ≥ 10%: Nausea, constipation, dizziness, somnolence.
- 5% to <10%: Headache, vomiting, pruritus.
- 1% to <5%: Dry mouth, sweating increased, anorexia, fatigue, weakness, vertigo, insomnia, upper abdominal pain, diarrhea, nasopharyngitis, decreased weight, abdominal pain, arthralgia, pain exacerbated, dyspepsia, upper respiratory tract infection, hot flushes, anxiety, tremor, and urinary tract infection

Intensity of AEs: Approximately 41% of AEs reported from the placebo-controlled trials were mild and 47% were moderate. The profile of AE intensity was similar across the doses in the placebo-controlled trials.

Active-control trial (MDT3-001-E1): in this 12-week non-inferiority trial, Tramadol OAD treatment (n=215) was compared with Tramadol BID (n=216) in OA patients.

Overall, 81 % of patients treated with Tramadol OAD and 79% of patients on Tramadol BID had at least one AE (Table 7h). The incidence of severe AEs was < 3% of patients.

The most common AEs by SOC and preferred term (as follows) were comparable in type and frequency between Tramadol OAD and BID: nausea (33%), constipation (32%), dizziness/vertigo (31%), somnolence (26%), weakness (13%) and vomiting (11%). The incidence of these AEs was also comparable in patients treated with Tramadol OAD between age < 65 or ≥ 65 years.

However, the incidence of common AEs for both the Tramadol OAD and BID treatment groups in this trial was higher than in other 5 trials (Table 7h, Table 7j-1 and Table 7l). The applicant did not provide an explanation in the submission. Likely, this was because the study population enrolled from the countries outside US may have different background in medical management and/or health care system.

Open-label long-term trial: There were two open-label safety trials, MDT3-004 (12 months) and MDT3-001-E1-A1 (an open-label extension of active-controlled trial MDT3-001-E1 for 9 additional months). The safety population was 340 patients for ≥ 6 month at 300 mg Tramadol OAD and 192 patients for 12 months at 300 mg Tramadol OAD. The overall frequency of AEs reported by patients during the trials is shown in Table 7i.

- ≥ 6-month exposure: 65% patients had *"at least one AE"* and 52% patients had *"at least one possibly related AE"*.
- 12-month exposure: 71% patients *"at least one AE"* and 56% patients had *"at least one possibly related AE"*.

Table 7i. **Overall Summary of AEs in Open-label Long-Term Safety Trials**
(Applicant's Table 2.7.4.2.1-2)

	Tramadol Contramid® OAD	
	6-month Population	12-month Population
Number (%) patients	N=340	N=192
Patients with at least one TEAE	220 (64.7%)	136 (70.8%)
Patients with at least one severe TEAE	33 (9.7%)	15 (7.8%)
Patients with at least one serious TEAE	2 (0.6%)	-
Patients with at least one related or possibly related TEAE	178 (52.3%)	108 (56.3%)
Patients who died	-	-

6-month: Patients who have taken 300 mg daily of Tramadol Contramid® OAD for at least 175 days.
12-month: Patients who have taken 300 mg daily of Tramadol Contramid® OAD for at least 350 days.
Source: Clinical Study Report MDT3-004, Statistical Tables 5.1.1.2 and 5.1.1.6
Clinical Study Report MDT3-001-E1-A1, Statistical Tables 5.1.2.1.1 and 5.1.4.1.1

In these open-label trials, the common AEs (with incidence of ≥ 10% patients) by SOC were (6-month *vs.* 12-month):

- gastrointestinal system: 45% vs. 48%
- nervous system: 26% vs. 33%
- Infections and Infestations: 15% vs. 17%
- Investigation: 6% vs. 16%

The overall incidence of AEs (% of patients) reported during the long-term safety trial are listed below. The common AEs (≥ 5% patients) were comparable to those identified from the placebo-controlled trials in terms of incidence and intensity. Some AEs experienced by < 5% of patients were not reported or less reported in the placebo-controlled trials; the incidence of those AEs seemed not to show a trend of relationship to the Tramadol OAD treatment.

- ≥ 10%: Constipation, nausea, headache, dizziness.
- 5% to < 10%: Somnolence, vomiting, nasopharyngitis, decreased weight, urinary tract infection, hypertension, anorexia.
- 1% to < 5%: Vertigo, abdominal pain, diarrhea, influenza, dry mouth, upper respiratory tract , infection, arthralgia, upper abdominal pain, paraesthesia, hypertension aggravated, blood LDH increased, RBC sedimentation rate increased, pharyngitis, fatigue, toothache, blood uric acid increased, laryngitis, acute bronchitis, weakness, decreased appetite, pain in limb, night sweats, dyspepsia, insomnia, sweating increased, osteopenia, blood glucose increased, blood pressure increased, hypercholesterolaemia, rhinitis.

7.1.5.4 Common adverse event tables

The commons AEs (regardless of causality) experienced by ≥ 1% patients are summarized in Table 7j for the 12-week placebo- and active-controlled trials, and in Table 7k for the two open-label trials.

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

		Tramadol Contramid OAD					
		12-Week Placebo-Controlled Studies				12-Week Active-Controlled Study[2]	All studies / All active doses[3]
Preferred Term	Placebo N=668	100 mg N=216	200 mg N=311	300 mg N=530	Overall Active[1] N=1058	N=215	N=1310
NAUSEA	39(5.8%)	29 (13.4%)	50(16.1%)	88(16.6%)	202(18.4%)	70 (32.6%)	272 (20.8%)
CONSTIPATION	27(4.0%)	21 (9.7%)	38(12.2%)	53(10.0%)	143(13.1%)	73 (34.0%)	216 (16.5%)
DIZZINESS	21(3.1%)	18 (8.3%)	31(10.0%)	59(11.1%)	119(10.9%)	51 (23.7%)	170 (13.0%)
SOMNOLENCE	13(1.9%)	12 (5.6%)	23(7.4%)	26(4.9%)	82(7.5%)	65 (30.2%)	147 (11.2%)
HEADACHE NOS	43(6.4%)	13 (6.0%)	18(5.8%)	26(4.9%)	64(5.8%)	27 (12.6%)	91 (6.9%)
VOMITING NOS	6(0.9%)	8 (3.7%)	19(6.1%)	34(6.8%)	71(6.5%)	18 (8.4%)	89 (6.8%)
PRURITUS NOS	7(1.0%)	11 (5.1%)	16(5.1%)	23(4.3%)	60(5.5%)	7 (3.3%)	67 (5.1%)
DRY MOUTH	8(1.2%)	7 (3.2%)	17(5.5%)	7(1.3%)	38(3.5%)	20 (9.3%)	58 (4.4%)
SWEATING INCREASED	6(0.9%)	1 (0.5%)	10(3.2%)	16(3.0%)	38(3.5%)	16 (7.4%)	54 (4.1%)
ANOREXIA	2(0.3%)	5 (2.3%)	4(1.3%)	11(2.1%)	27(2.5%)	16 (7.4%)	43 (3.3%)
FATIGUE	6(0.9%)	6 (2.8%)	10(3.2%)	9(1.7%)	29(2.6%)	9 (4.2%)	38 (2.9%)
WEAKNESS	1(0.1%)	3 (1.4%)	5(1.6%)	4(0.8%)	12(1.1%)	24 (11.2%)	36 (2.7%)
VERTIGO	3(0.4%)	3 (1.4%)	3(1.0%)	8(1.5%)	27(2.5%)	5 (2.3%)	32 (2.4%)
INSOMNIA	8(1.2%)	3 (1.4%)	9(2.9%)	11(2.1%)	25(2.3%)	6 (2.8%)	31 (2.4%)
ABDOMINAL PAIN UPPER	4(0.6%)	3 (1.4%)	4(1.3%)	9(1.7%)	18(1.6%)	9 (4.2%)	27 (2.1%)
DIARRHOEA NOS	20(3.0%)	6 (2.8%)	1(0.3%)	10(1.9%)	21(1.9%)	5 (2.3%)	26 (2.0%)
NASOPHARYNGITIS	18(2.7%)	4 (1.9%)	7(2.3%)	7(1.3%)	20(1.8%)	2 (0.9%)	22 (1.7%)
WEIGHT DECREASED	1(0.1%)	1 (0.5%)	5(1.6%)	11(2.1%)	20(1.8%)	2 (0.9%)	22 (1.7%)
ABDOMINAL PAIN NOS	7(1.0%)	2 (0.9%)	5(1.6%)	8(1.5%)	17(1.6%)	3 (1.4%)	20 (1.5%)
ARTHRALGIA	14(2.1%)	2 (0.9%)	3(1.0%)	8(1.5%)	15(1.4%)	3 (1.4%)	18 (1.4%)
PAIN EXACERBATED	16(2.4%)	6 (2.8%)	3(1.0%)	6(1.1%)	18(1.6%)	-	18 (1.4%)
DYSPEPSIA	7(1.0%)	3 (1.4%)	6(1.9%)	4(0.8%)	13(1.2%)	3 (1.4%)	16 (1.2%)
UPPER RESPIRATORY TRACT INFECTION NOS	17(2.5%)	3 (1.4%)	5(1.6%)	6(1.1%)	16(1.5%)	-	16 (1.2%)
HOT FLUSHES NOS	1(0.1%)	1 (0.5%)	3(1.0%)	7(1.3%)	12(1.1%)	2 (0.9%)	14 (1.1%)
ANXIETY NEC	1(0.1%)	1 (0.5%)	6(1.9%)	4(0.8%)	11(1.0%)	2 (0.9%)	13 (1.0%)
TREMOR	1(0.1%)	1 (0.5%)	3(1.0%)	6(1.1%)	11(1.0%)	2 (0.9%)	13 (1.0%)
HYPERTENSION NOS	4(0.6%)	1 (0.5%)	1(0.3%)	4(0.8%)	7(0.6%)	5 (2.3%)	12 (0.9%)
URINARY TRACT INFECTION NOS	10(1.5%)	2 (0.9%)	3(1.0%)	6(1.1%)	12(1.1%)	-	12 (0.9%)

[1] Total of Tramadol Contramid OAD treatment groups (100 mg, 200 mg and 300 mg) from MDT3-002, MDT3-003 and MDT3-05 (placebo not included).
[2] Total of Tramadol Contramid OAD treatment groups (100 mg, 200 mg, 300 mg and 400 mg) from MDT3-001/E1 (Tramadol BID group excluded).
[3] Total of Tramadol Contramid OAD treatment groups from MDT3-002, MDT3-003, MDT3-005 and MDT3-001/E1 (Tramadol BID group and placebo not included).
Source: Statistical Tables:
MDT3-001/E1: Table 5.2.2.1, pages 382 - 398
MDT3-002: Table 5.2.2.1, pages 574 - 589
MDT3-003: Table 5.2.2.1, pages 564 - 398
MDT3-005: Table 5.1.2.1 (1264AT2006).

Table 7k. **Incidence of Common AEs (Experienced by ≥ 1% of Patients) from Two Open-Label Long-Term Safety Trials**
(Applicant's Table 2.7.4.7.1-23)

Preferred Term	6 Months			12 Months		
	< 65 yrs N=211	≥65 yrs N=129	Overall N=340	< 65 yrs N=119	≥65 yrs N=73	Overall N=192
ANY TEAE	135 (64.0%)	85 (65.9%)	220 (64.7%)	82 (68.9%)	54 (74.0%)	136 (70.8%)
CONSTIPATION	51 (24.2%)	36 (27.9%)	87 (25.6%)	25 (21.0%)	16 (21.9%)	49 (25.5%)
NAUSEA	40 (19.0%)	28 (21.7%)	68 (20.0%)	30 (25.2%)	24 (32.9%)	46 (24.0%)
HEADACHE NOS	20 (9.5%)	11 (8.5%)	31 (9.1%)	21 (17.6%)	12 (16.4%)	33 (17.2%)
DIZZINESS	23 (10.9%)	9 (7.0%)	32 (9.4%)	16 (13.4%)	6 (8.2%)	22 (11.5%)
SOMNOLENCE	18 (8.5%)	14 (10.9%)	32 (9.4%)	9 (7.6%)	6 (8.2%)	15 (7.8%)
VOMITING NOS	16 (7.6%)	3 (2.3%)	19 (5.6%)	12 (10.1%)	3 (4.1%)	15 (7.8%)
NASOPHARYNGITIS	7 (3.3%)	9 (7.0%)	16 (4.7%)	5 (4.2%)	8 (11.0%)	13 (6.8%)
WEIGHT DECREASED	13 (6.2%)	4 (3.1%)	17 (5.0%)	6 (5.0%)	5 (6.8%)	11 (5.7%)
URINARY TRACT INFECTION NOS	4 (1.9%)	4 (3.1%)	8 (2.4%)	3 (2.5%)	7 (9.6%)	10 (5.2%)
HYPERTENSION NOS	4 (1.9%)	3 (2.3%)	7 (2.1%)	6 (5.0%)	4 (5.5%)	10 (5.2%)
ANOREXIA	12 (5.7%)	6 (4.7%)	18 (5.3%)	7 (5.9%)	3 (4.1%)	10 (5.2%)
VERTIGO	4 (1.9%)	4 (3.1%)	8 (2.4%)	4 (3.4%)	4 (5.5%)	8 (4.2%)
ABDOMINAL PAIN NOS	1 (0.5%)	1 (0.8%)	2 (0.6%)	3 (2.5%)	5 (6.8%)	8 (4.2%)
DIARRHOEA NOS	2 (0.9%)	3 (2.3%)	5 (1.5%)	3 (2.5%)	4 (5.5%)	7 (3.6%)
INFLUENZA	14 (6.6%)	5 (3.9%)	19 (5.6%)	4 (3.4%)	3 (4.1%)	7 (3.6%)
DRY MOUTH	7 (3.3%)	5 (3.9%)	12 (3.5%)	3 (2.5%)	2 (2.7%)	7 (3.6%)
UPPER RESPIRATORY TRACT INFECTION NOS	-	-	-	4 (3.4%)	3 (4.1%)	7 (3.6%)
ARTHRALGIA	7 (3.3%)	2 (1.6%)	9 (2.6%)	4 (3.4%)	1 (1.4%)	5 (2.6%)
ABDOMINAL PAIN UPPER	6 (2.8%)	2 (1.6%)	8 (2.4%)	4 (3.4%)	1 (1.4%)	5 (2.6%)
PARAESTHESIA	2 (0.9%)	1 (0.8%)	3 (0.9%)	3 (2.5%)	2 (2.7%)	5 (2.6%)
HYPERTENSION AGGRAVATED	3 (1.4%)	-	3 (0.9%)	4 (3.4%)	1 (1.4%)	5 (2.6%)
BLOOD LACTATE DEHYDROGENASE INCREASED	-	-	-	5 (4.2%)	-	5 (2.6%)
RED BLOOD CELL SEDIMENTATION RATE INCREASED	-	-	-	2 (1.7%)	3 (4.1%)	5 (2.6%)
PHARYNGITIS NOS	3 (1.4%)	1 (0.8%)	4 (1.2%)	2 (1.7%)	2 (2.7%)	4 (2.1%)
FATIGUE	10 (4.7%)	5 (3.9%)	15 (4.4%)	1 (0.8%)	3 (4.1%)	4 (2.1%)
TOOTHACHE	6 (2.8%)	1 (0.8%)	7 (2.1%)	3 (2.5%)	-	3 (1.6%)
BLOOD URIC ACID INCREASED	-	-	-	3 (2.5%)	-	3 (1.6%)
LARYNGITIS NOS	2 (0.9%)	1 (0.8%)	3 (0.9%)	-	2 (2.7%)	2 (1.0%)
BRONCHITIS ACUTE NOS	2 (0.9%)	-	2 (0.6%)	2 (1.7%)	-	2 (1.0%)

Source Data: MDT3-004 (Tables 5.2.1.1.2, pg 370; 5.2.1.1.6, pg 393 12JUL04)
MDT3-001E1A1 (Tables 5.2.1.4.1.1, pg 102; 5.2.1.4.1.2, pg 109; 5.2.1.4.1.3, 114 16NOV04)

[Reviewer's comments: headache was reported in > 5% of patients in Tramadol OAD and placebo groups from placebo- and active-controlled trials as well as from open-label trials. However, the applicant b(4) *See labeling review for detail.]*

7.1.5.5 Identifying common and drug-related adverse events

The five most common AEs (*nausea, constipation, dizziness, somnolence, and vomiting*) were considered related to the treatment of Tramadol OAD based on the following reasons:

1) In the placebo-controlled trials, the incidences of those AEs in Tramadol OAD groups tend to be higher than those in placebo (91% patients *vs.* 58% patients).
2) The onset of those AEs was earlier in patients treated with Tramadol OAD than those in placebo group.
3) The incidences of those AEs in Tramadol OAD tended to be dose-dependent in both placebo-controlled and open-label trials.

4) Almost all patients experiencing at least one of the common AEs during the open-label trials (96% at 6 months and 95% at 12 months).
5) The AEs are expected based on the safety profile of approved tramadol products

7.1.5.6 Additional analyses and explorations

Age comparison: The incidences of AEs were stratified by age < 65 years and ≥ 65 years in both randomized controlled (placebo- and active-controlled) and open-label trials (Table 7l). Patients with age ≥ 65 years composed 40% of the placebo-controlled trials, 44% of the active-controlled trials and 38% in the open-label trials.

The overall AE experience was comparable between patients aged < 65 years and ≥ 65 years, except in the placebo-controlled trials, in which more patients aged ≥ 65 years experienced constipation with Tramadol OAD treatment (18% vs. 9%). In the open-label trials, the frequency of constipation was similar for both age groups.

Table 7l. **Age comparison of Most Common AEs Experienced by % Patients Across All Trials**
(Extracted from the Applicant's Tables 2.7.4.7.1-17, -18, -19 and -20)

Adverse Event	Placebo-controlled Trial				Active-controlled Trial		Open-label Long-term Trial (300 mg Tramadol OAD, qd)			
	Placebo		Tramadol OAD				6 Months		12 Months	
	< 65 yr n=391	≥ 65 yr n=277	< 65 yr n=655	≥65 yr n=440	< 65 yr n=121	≥ 65 yr n=94	< 65 yr n=211	≥ 65 yr n=129	< 65 yr n=119	≥ 65 yr n=73
Any AEs	50	52	62	65	82	81	64	66	69	74
Nausea	5.4	6.5	18.6	18.2	30.6	35.1	19.0	21.7	25.2	32.9
Constipation	3.3	5.1	*9.5*	*18.4*	31.4	37.2	24.2	29.7	21.0	21.9
Dizziness	3.1	3.2	10.4	11.6	24.0	23.4	10.9	7.0	13.4	8.2
Somnolence	0.5	4.0	7.8	7.0	35.5	23.4	8.5	10.9	7.6	8.2
Headache	7.2	5.4	7.2	3.9	14.0	10.6	9.5	8.5	17.6	16.4
Vomiting	0.8	1.1	5.8	9.6	7.4	9.6	7.6	2.3	10.1	4.1
Pruritus	0.5	1.8	5.8	5.0	5.0	1.1	1.4	0.8	0	1.4

Dose-response: The incidence of common AEs in the Tramadol OAD treatment groups tended to increase with increasing dose (100, 200, 300 to 400 mg).

Time to onset most common AEs:

- The median time to onset of the most common AEs was within the first 2 weeks following initiation of treatment (placebo-controlled trials MDT3-002, MDT3-003, and open-label period of MDT3-005).

- Overall, patients in Tramadol OAD group experienced the most common AEs earlier than those in placebo group (1-6 days earlier). However, in study MDT3-005, the onset of most common AEs was later in both Tramadol OAD (8-36 days) and Placebo (2-40 days) during double-blind period. This was likely due to patient enrichment with 4-week open-label

treatment with Tramadol OAD prior to randomization. Thus more patients could tolerate Tramadol OAD treatment.

- The onset of the most common AEs in the open-label long-term trials and active-controlled trials was slightly later than in placebo-controlled trials (about 2-10 days later).

Duration of most common AEs:

- Across placebo- and active-controlled trials, the median duration of the most common AEs was less than 1 month:
  - Vomiting :1-4 days
  - Nausea and dizziness/vertigo: 2-7 days
  - Somnolence: 6-26 days
  - Constipation: 8-28 days.

- Across open-label long-term trials, the median duration of most common AEs was slightly longer than placebo-and active-controlled trials.
  - Vomiting: 3-4 days
  - Nausea, dizziness/vertigo and somnolence: 2-23 days
  - Constipation: 7-62 days

Gender comparison: The incidences of AEs were comparable between male and female patients.

7.1.6 Less Common Adverse Events

There were no noteworthy "uncommon" events reported in all trials as compared to the AE profiles of approved tramadol products. The incidence of less common AEs was sporadic and varied across trials.

The less common AEs experienced by 0.5% to < 1% of patients treated with Tramadol OAD across all trials are listed in Table 7m.

Table 7m. **Incidence of AEs Experienced by < 1% - ≥ 0.5% of Patients across All Phase 3 trials**
(Adapted from the applicant's Table 2.7.4.7.1-19)

		Tramadol Contramid OAD					
		12-Week Placebo-Controlled Studies				12-Week Active-Controlled Study[2]	All studies / All active dose[3]
Preferred Term	Placebo N=668	100 mg N=216	200 mg N=311	300 mg N=539	Overall Active[1] N=1066	N=215	N=1310
BACK PAIN	11(1.6%)	4 (1.9%)	3(1.0%)	2(0.4%)	10(0.9%)	1 (0.5%)	11 (0.8%)
INFLUENZA	3(0.4%)	2 (0.9%)	1(0.3%)	8(1.5%)	11(1.0%)	-	11 (0.8%)
PAIN IN LIMB	7(1.0%)	3 (1.4%)	4(1.3%)	3(0.6%)	10(0.9%)	1 (0.5%)	11 (0.8%)
COUGH	7(1.0%)	2 (0.9%)	3(1.0%)	5(0.9%)	10(0.9%)	-	10 (0.8%)
DYSGEUSIA	2(0.3%)	1 (0.5%)	-	-	2(0.2%)	8 (3.7%)	10 (0.8%)
RASH NOS	3(0.4%)	-	4(1.3%)	5(0.9%)	9(0.8%)	1 (0.5%)	10 (0.8%)
SINUSITIS NOS	9(1.3%)	2 (0.9%)	1(0.3%)	5(0.9%)	10(0.9%)	-	10 (0.8%)
APPETITE DECREASED NOS	2(0.3%)	1 (0.5%)	2(0.6%)	3(0.6%)	8(0.7%)	-	8 (0.6%)
BACK INJURY NOS	-	3 (1.4%)	4(1.3%)	1(0.2%)	8(0.7%)	-	8 (0.6%)
MUSCLE CRAMPS	7(1.0%)	2 (0.9%)	1(0.3%)	4(0.8%)	7(0.6%)	1 (0.5%)	8 (0.6%)
NERVOUSNESS	3(0.4%)	-	1(0.3%)	3(0.6%)	6(0.5%)	2 (0.9%)	8 (0.6%)
PHARYNGOLARYNGEAL PAIN	8(1.2%)	4 (1.9%)	2(0.6%)	-	7(0.6%)	1 (0.5%)	8 (0.6%)
CONTUSION	2(0.3%)	-	2(0.6%)	4(0.8%)	7(0.6%)	-	7 (0.5%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	4(0.6%)	-	1(0.3%)	4(0.8%)	6(0.5%)	1 (0.5%)	7 (0.5%)
MIGRAINE NOS	5(0.7%)	1 (0.5%)	-	5(0.9%)	7(0.6%)	-	7 (0.5%)
NASAL CONGESTION	1(0.1%)	3 (1.4%)	1(0.3%)	1(0.2%)	7(0.6%)	-	7 (0.5%)
NECK PAIN	4(0.6%)	1 (0.5%)	-	2(0.4%)	6(0.5%)	1 (0.5%)	7 (0.5%)
OEDEMA PERIPHERAL	8(1.2%)	1 (0.5%)	4(1.3%)	1(0.2%)	6(0.5%)	1 (0.5%)	7 (0.5%)
DIFFICULTY IN MICTURITION	-	-	2(0.6%)	1(0.2%)	5(0.5%)	1 (0.5%)	6 (0.5%)
FALL	2(0.3%)	-	1(0.3%)	3(0.6%)	6(0.5%)	-	6 (0.5%)
GASTRO-OESOPHAGEAL REFLUX DISEASE	2(0.3%)	-	2(0.6%)	4(0.8%)	6(0.5%)	-	6 (0.5%)
HYPERCHOLESTEROLAEMIA	3(0.4%)	1 (0.5%)	1(0.3%)	3(0.6%)	5(0.5%)	1 (0.5%)	6 (0.5%)
JOINT SWELLING	4(0.6%)	2 (0.9%)	3(1.0%)	1(0.2%)	6(0.5%)	-	6 (0.5%)
LETHARGY	-	1 (0.5%)	1(0.3%)	3(0.6%)	5(0.5%)	1 (0.5%)	6 (0.5%)
LIMB INJURY NOS	1(0.1%)	3 (1.4%)	-	3(0.6%)	6(0.5%)	-	6 (0.5%)
MUSCLE SPASMS	1(0.1%)	-	2(0.6%)	1(0.2%)	4(0.4%)	2 (0.9%)	6 (0.5%)
TOOTHACHE	3(0.4%)	1 (0.5%)	2(0.6%)	1(0.2%)	4(0.4%)	2 (0.9%)	6 (0.5%)
ABDOMINAL DISTENSION	1(0.1%)	1 (0.5%)	2(0.6%)	1(0.2%)	5(0.5%)	-	5 (0.4%)

7.1.7 Laboratory Findings

- Routine clinical laboratory tests, including hematology, blood chemistry and urinalysis, were conducted in all patients across the six Phase 3 trials, mostly at baseline and the end of the study.

- A total of 106 laboratory abnormalities occurred in 68 patients in all Phase 3 trails (Table 7n).

  - The RBC sedimentation rate increased in 16 patients, which was expected in the study population – patient with OA of the knee. This change is associated an inflammatory response.

  - The other abnormalities in laboratory tests were also very likely related to characteristics of the study population (aged, multiple concurrent medical conditions), including blood glucose increase (n=13), GGT (gamma glutamyltransferase) increase (n=10), blood cholesterol increase (n=5), blood uric acid increase (n=5) and blood LDH increase (n=5).

- The applicant did not stratify the abnormal laboratory data into placebo and Tramadol OAD treatment groups or by age. Because an integrated safety dataset was not provided, this reviewer has to rely on the applicant's summary table regarding laboratory-related AEs.

Table 7n. **Abnormal laboratory values experienced by patients across six Phase 3 trials**
(Applicant's Table 2.7.4.3-1)

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

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

7.1.8 Vital Signs

Vital signs, including temperature, blood pressure, heart rate and respiration were monitored at each visit during all six Phase 3 trials.

No remarkable changes in blood pressure, heart rate, respiratory rate, or body temperature were observed in patients treated with Tramadol OAD or placebo.

Physical examination, including special examination regarding OA of the knee, was conducted at baseline and the end of each study. There were no remarkable changes.

7.1.9 Electrocardiograms (ECGs)

ECG screening or monitoring was not performed in any of six Phase 3 trials.

7.1.10 Immunogenicity

Immunogenicity of Tramadol Contramid OAD was not evaluated in any of clinical trials. There were also no immunogenic concerns regarding the active ingredient, Tramadol, or the inactive ingredient, Contramid.

7.1.11 Human Carcinogenicity

There was no carcinogenic signal observed across all clinical trials on this product during the clinical development.

7.1.12 Special Safety Studies

No special safety studies were conducted or required by the Division.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The active ingredient in this product, Tramadol, is an opioid, which does have the potential to be abused, although Tramadol products (in any dose form) have not been scheduled by DEA.

Tramadol Contramid OAD, as an 505(b)(2) NDA, was not required to conduct a particular abuse trial since a great amount of information regarding abuse potential on Tramadol is available from approved Tramadol products and literature.

To collect information on dependence- and withdrawal-related symptoms in the placebo-controlled trials, MDT3-003, the applicant conducted a phone follow-up at 4 and 7 days after the last dose. The following symptoms were experienced by patients taking Tramadol OAD (100, 200, or 300 mg) vs. placebo: sleep disturbance (9-23% vs. 2%), diarrhea (5-11% vs. 1%), emotional disturbance (2010% vs. 0.4%), nausea (4-9% vs. 1.3%), sweating increase (3-6% vs. 0.4%), abdominal pain (1-7% vs. 0%) and tremor/rigors (4-5% vs. 0%). The data suggest that after sudden stopping of treatment, patients previously on Tramadol OAD treatment experienced

more withdrawal symptoms as compared to placebo. However, because this study was not specifically designed for assessment of withdrawal and dependence, a definitive conclusion can not be made.

7.1.14 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected during any clinical trials of Tramadol OAD.

Pregnant patients were excluded from all clinical trials. Female subjects of child-bearing potential had to have a confirmed negative pregnancy test and were advised to use contraception during the study. There were no pregnancy reports during the trials.

7.1.15 Assessment of Effect on Growth

Study population consisted of adults aged $\geq$ 18 years. Therefore, the effect of Tramadol OAD on growth in this study population was not a concern and was not assessed.

7.1.16 Overdose Experience

No cases of overdose were reported in any of the Phase 3 trials. The recommended maximum daily dose in the proposed labeling is 300 mg/day. The highest tested dose was 400 mg/day with n=48 healthy subjects during the Phase 1 trials (a single dose), n=21 during the 12-week active-controlled trial (MDT3-001-E1) and n=24 in the open-label extension of this trial (MDT3-001-E1-A2).

No remarkable AEs were reported in the healthy subjects who were treated 400 mg/day during the Phase 1 trials. Of patients who took 400 mg/day Tramadol OAD in Study MDT3-001, there were two SAEs reported: one fatal stroke (Patient 23-260) during the 12-week double-blind period (MDT3-01-E1) and one essential hypertension (Patient 005-097, received Topalgic 300 mg qd x12 weeks followed by Tramadol OAD 400 mg qd x3 month) during the open-label extension period (MDT3-001-E1-A1). Both SAEs appear unlikely related to study medication. The overall profile and frequency of AEs in the patients treated with 400 mg/day Tramadol OAD was similar to those treated with 100-300 mg/day but with slightly higher severity. However, the sample size was too small to make definitive comparative statement about the relative safety of Tramadol OAD 400 mg qd in this NDA.

7.1.17 Postmarketing Experience

Tramadol Contramid OAD was approved in France by the Regulatory Authorities (AFSSAPS) in February 2, 2005, in 22 additional countries in the European Union through the Mutual Recognition Procedure in September 2, 2005, and in Mexico in October 6, 2005. Tramadol OAD is currently marketed in Germany under the brand name Tramadolor, which was launched on November 16, 2005.

A post-marketing surveillance on this product was conducted by Office of Drug Safety (ODS) through an intra-center consult request. The results were pending at the time of this review.

Based on the 120-day safety update submitted by the applicant on March 20, 2006, a total of [redacted] Tramadolor (100, 200 and 300 mg) tablets were supplied to patients in Germany between November 16 and February 2, 2005. Of these, [redacted] were 100 mg tablets, [redacted] were 200 mg tablets, and [redacted] were 300 mg tablets. b(4)

As of March 13, 2006, no serious adverse events had yet been reported through the pharmacovigilance program for Tramadol OAD in Europe.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary clinical data sources for safety evaluation of this product were from six Phase 3 trials as listed in the above Table 7a (Section 7.1): four randomized controlled trials (three placebo-controlled and one active-controlled) and two open-label long-term safety trials (one 12-month trial and one 9-month open-label extension from the active-controlled trial). The six trials were conducted in the patients with pain associated with a confirmed diagnosis of OA.

7.2.1.2 Demographics and Baseline Characteristics

Demographics of the study population are listed in Table 7p (the four randomized controlled trials) and Table 7q (the two open-label safety trials).

- In the placebo-controlled controlled trials, the baseline characteristics were comparable between Tramadol OAD and Placebo across three trials and across the different dose of Tramadol OAD.
    - Gender: 62% of females in Tramadol OAD and Placebo groups
    - Age (mean): 61 years in both Tramadol OAD and Placebo groups
    - Ethnic: 80% Caucasian in Tramadol OAD and 78% in Placebo group
    - BMI (kg/m2): 30-31 (mean) in Tramadol OAD group and Placebo group
- In the active-controlled trial (MDT3-001-E1, conducted in Europe), the baseline characteristics of the study population were slightly different from the placebo-controlled trials (conducted primarily in US): 84% females with 100% Caucasian; the mean BMI was comparable to that of the placebo-controlled trials.

- In the two long-term trials (conducted in Europe), the baseline characteristics of the study population were similar to the active-controlled trial: 84-87% females, mean age 59 and 61 years (across doses), and 100% Caucasian; BMI was comparable to other trials.

Past and concurrent medical conditions across six trials: 98-100% of patients had ongoing concurrent medical conditions. The most commonly reported concomitant disorders by SOC were musculoskeletal and connective tissue, cardiovascular, surgical/medical procedures and GI disorders, as listed in Table 7o. The percent of patients who had concurrent medical disorders was comparable across dose levels, and between Tramadol OAD and placebo groups for each trial.

Table 7o. **Past and Concurrent Medical History of Study Population**
(% of patients)

System Organ Class	Placebo-Controlled Trial			Open-Label Trial	
	MDT3-003	MDT3-002	MDT3-005	MDT3-004	MDT3-001
Musculoskeletal and connective tissue disorders	85-88%	90-94%	97%	95%	96%
Surgical and medical procedure	46-55%	49-58%	55-57%	19%	20%
Vascular disorders	48-51%	45-53%	46-52%	48%	71%
Metabolism and nutrition disorders	31-43%	37-48%	34-36%	19%	17%
Gastrointestinal disorders	35-40%	37-46%	32-30%	18%	31%
Nervous system disorder	18-26%	26-37%	18-19%	4%	11%
Immune system disorder	17-25%	23-27%	16-27%	0.7%	ND
Infections and infestations	20-27%	21-28%	15-16%	12%	24%
Cardiac disorder	11-16%	11-16%	15-17%	29%	28%

ND: no data reported.

Prior medications: The majority (90-97%) of patients in the randomized controlled trials, and 46-69% of patients in the open-label trials took medications for a concurrent medical disorder prior to entering the randomized controlled trials. The most commonly used medications were for cardiovascular or GI disorders and analgesics opioids and non-opioids, such as:

- propionic acid (or acetic) derivatives and coxibs
- HMG-CoA reductase inhibitors, ACE inhibitors, platelet aggregation inhibitors (excluding heparin), calcium channel blockers and selective beta blockers
- proton pump inhibitors
- multivitamins
- other opioids

Concurrent medications: Approximately 68% of patients in placebo-controlled trials, 81% of patients in the active-controlled trial, and 76-79% of patients in the open-label trials took concomitant medications at any time during the studies, mostly for cardiovascular disorders or constipation.

Analgesics for chronic pain were not allowed during three pivotal trials. Acetaminophen was allowed in Study MDT3-005 for acute pain but was limited to short-acting acetaminophen product (dosage was not specified); dosing was allowed for up to three consecutive days with closely monitoring by investigator. In studies MDT3-002 and MDT3-003, no any pain medication was permitted; patients with intolerable pain could be withdrawn.

During the open-label long-term safety trials, patients whose pain was not well controlled to 300 or 400 mg Tramadol OAD could take acetaminophen (dose and duration were not specified) in Study MDT3-001-E1-A1, and pain medication (not specified) for medical conditions other than OA could be allowed after consulting with the investigator.

Table 7p. **Baseline characteristics of study population enrolled in randomized controlled trials**
(Adapted from the applicant's Table 2.7.4.1.3-1)

		Tramadol Contramid® OAD					
		12-Week Placebo-Controlled Studies[1]				12-Week Active-Controlled Study[2]	All studies / All active doses[3]
	Placebo	100 mg	200 mg	300 mg	Overall Active		
	N=668	N=216	N=311	N=538	N=1094	N=215	N=1309
Gender n (%)							
Male	255 (38.2%)	86 (39.8%)	110 (35.4%)	203 (38.3%)	415 (37.9%)	34 (15.8%)	449 (34.3%)
Female	413 (61.8%)	130 (60.2%)	201 (64.6%)	327 (61.7%)	679 (62.1%)	181 (84.2%)	860 (65.7%)
Ethnic Origin n (%)							
Caucasian	522 (78.1%)	157 (72.7%)	252 (81.0%)	439 (82.8%)	877 (80.2%)	215 (100%)	1092 (83.4%)
Hispanic	66 (9.9%)	29 (13.4%)	35 (11.3%)	43 (8.1%)	114 (10.4%)	-	114 (8.7%)
Black	69 (10.3%)	23 (10.6%)	20 (6.4%)	39 (7.4%)	83 (7.6%)	-	83 (6.3%)
Asian	4 (0.6%)	5 (2.3%)	2 (0.6%)	5 (0.9%)	12 (1.1%)	-	12 (0.9%)
Other	7 (1.0%)	2 (0.9%)	2 (0.6%)	4 (0.8%)	8 (0.7%)	-	8 (0.6%)
Age (years)							
Mean ± SD	61 ± 10	61 ± 9	61 ± 9	61 ± 9	61 ± 9	62 ± 9	61 ± 9
Range	40, 82	40, 76	39, 88	39, 88	39, 80	40, 75	39, 88

N=total number of patients in group; n=number of patients in subgroup with non-missing data.

[1] Total of Tramadol Contramid® OAD treatment groups (100 mg, 200 mg and 300 mg) from MDT3-002, MDT3-003 and MDT3-005 (Dose-specific data from MDT3-005 include Maintenance Period only while Overall Active includes the entire Double-Blind Phase).

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

[3] Total of Tramadol Contramid® OAD treatment groups from MDT3-002, MDT3-003, MDT3-005 and MDT3-001/E1 (Tramadol BID group and placebo not included).

Source: Clinical Study Reports MDT3-002, MDT3-003, MDT3-005 and MDT3-001/E1, Statistical Table 3.1.1

Table 7q. **Baseline characteristics of study population enrolled in open-label trials**
(Adapted from the applicant's Table 2.7.4.1.3-2)

	Tramadol Contramid® OAD[1]		
	200 mg N=141	300 mg N=462	400 mg N=25
Gender n (%)			
Male	18 (12.8%)	71 (15.4%)	4 (16.0%)
Female	123 (87.2%)	391 (84.6%)	21 (84.0%)
Ethnic Origin n (%)			
Caucasian	141 (100%)	462 (100%)	25 (100%)
Age (years)			
Mean (±SD)	60 ± 9	61 ± 9	59 ± 11
Range	42, 74	40, 75	40, 75

N=total number of patients in group; n=number of patients in subgroup with non-missing data

[1] Two patients on Study MDT3-001-E1-A1 who received Tramadol Contramid® OAD 100 mg in violation of the protocol are not included.

Source: Clinical Study Reports MDT3-004 and MDT3-001-E1-A1, Statistical Table 2.1.1

7.2.1.3 Extent of exposure (dose/duration)

A total of 3269 subjects were enrolled in all clinical studies, including 2145 OA patients from three pivotal trials, 431 OA patients from one active-controlled trial (238 of them had 9-month open-label extension treatment), 630 patients from the open-label long-term (up to 12 month) trials, and 301 healthy subjects (treated with a single dose of Tramadol OAD) from the 12 Phase 1 trials (Table 7r-1 and Table 7r-2).

Overall patient exposure to Tramadol OAD (i.e., at least one dose of 100 to 400 mg) during the Phase 3 trials was 1939 patients (Table 7r-1), including 1095 from the three placebo-controlled trials (548 were treated with Tramadol OAD 300 mg), 215 from the active-controlled trial (53 on Tramadol OAD 300 mg and 21 on Tramadol OAD 400 mg), and 630 from the open-label trials.

A total of 663 patients treated with Tramadol OAD were 65 years and older, including 534 during the 12-week studies and 129 in the open-label studies (≥ 6 months). The patient age was further stratified to ≥ 75 years in study MDT3-005 (but not in studies MDT3-001, 002, -003 and -004), in which 38 patients received the open-label Tramadol OAD treatment without previously entering the double-blind phase, and 30 patients were treated with Tramadol OAD during the 12-week maintenance period of the double-blind phase (n=17 on placebo).

After excluding dropouts, the number of patients who completed 12 weeks of treatment with Tramadol OAD 100-400 mg was 844 patients (400 patients on 300 mg); and 493 patients completed at least 6-month treatment with 300 mg (243 of them continued to 12 months) (Table 7r-2).

***Table 7r-1.* Overall patient exposure (the Safety Population) during Phase 1 and Phase 3 trials**
(Extracted from individual trial reviews in appendix)

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

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

***Table 7r-2.* Patient actual exposure (completed treatment) during Phase 3 trials**

Randomized trials

Study Type	Randomized Patient (PC) or Entered Patient (for OL)*				Completed Patients				
	100 mg	200 mg	300 mg	Placebo	100 mg	200 mg	300 mg	400 mg	Placebo
Placebo-controlled 12-week treatment									
MDT3-002	110	113	115	227	64	60	54		144
MDT3-003	106	111	108	227	62	65	50		134
MDT3-005		107	325	214		73	255		165
Active-controlled									
MDT3-001-E1	431				25	82	41	13	
Total					**151**	**280**	**400**	**13**	**443**

Open-label long-term safety Trials

Study	Entered Patients	Completed Patients			
		200 mg	300 mg	400 mg	Total
≥ 6 Months		**129**	**340**	**24**	**493**
MDT3-001-E1-A1	238	129	65	24	218
MDT3-004	392		275		275
12 Months		**43**	**192**	**8**	**243**
MDT3-001-E1-A1		43	24	8	75
MDT3-004			168		168

Placebo-controlled trials: During the three placebo-controlled trials, 1095 patients were treated with at least one dose of Tramadol OAD from dose 100 to 300 mg for up to 12 weeks (plus Titration for 1-2 weeks). Approximately 50% (n=548) of them were exposed to 300 mg Tramadol OAD. A total of 668 patients were treated with placebo.

Active-controlled trial: During the one active-controlled trial, 215 patients took Tramadol OAD 100-400 mg for up to 12 weeks (plus up to 2-week Titration); approximately 44% on 200 mg, 25% on 300 mg and 10% on 400 mg for up to 12 weeks.

Open-label trials: During the two open-label long-term safety trials, a total of 493 patients were exposed to Tramadol OAD 200-400 mg for up to 12 months; of which 340 patients were on 300 mg Tramadol for 6 months and 192 of them continued on the same dose for 12 months.

However, the 12-month data from the 9-month open-label extension, MDT3-001-E1-A1, may not reflect a true 12-month Tramadol OAD exposure because patients from Tramadol BID group who entered the 9-month trial should have had only 9 months on Tramadol OAD. The applicant did not address this in the submission's data analysis.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Information on adverse reactions presented in the labeling of Ultram ER (NDA 21-692) and Ultram (NDA 20-281) was used as a secondary clinical data source for comparison with Tramadol OAD (see the Appendix Section 10.3 for details).

The overall safety profile established from placebo-controlled trials and open-label long-term trials on Tramadol OAD in this NDA was comparable to Ultram and Ultram ER.

7.2.2.2 Postmarketing experience

There was about 1-year postmarketing experience with this product outside US (Europe and Mexico). The postmarketing surveillance on this product and other tramadol products was conducted by the Office of Drug Safety, CDER and results are pending at the time of this review.

7.2.2.3 Literature

Literature search and review were conducted to assess serotonin syndrome associated with Tramadol products, this included search ARES database.

Clearly, Tramadol increases the serotonin syndrome (SS) risk when used with SSRI, SSNRI or MAOI products, overdosed (including dose-dumping of tramadol ER form), or taken by patients who were CYP2D6 polymorphic (major metabolism enzyme for Tramadol). There were no typical SS case reports in this NDA, most likely due to exclusion of all potential drug-drug interaction factors during patient enrollment.

7.2.3 Adequacy of Overall Clinical Experience

- ***Number of subjects:*** a total of 2240 human subjects were exposed to Tramadol OAD during the clinical development:

    - 301 health subjects were from 11 Phase 1 PK trials, with single dose exposure
    - 1939 patients with OA of the knee from six Phase 3 trials

- ***Dose and duration:*** Tramadol OAD at dose of 100-400 mg was tested during the clinical development, mostly with 200 mg and 300 mg. The proposed labeling dose regimen is up to 300 mg Tramadol OAD once a day.

    - A total of 601 patients (548 from the placebo-controlled trial and 53 from active-controlled trial) were exposed to 300 mg Tramadol OAD for up to 12 weeks.
    - A total of 340 patients took 300 mg Tramadol for 6 months and 192 of them continued for 12 months.

- ***Elderly:*** Approximately 40% (n=663) of study population was patients aged ≥ 65 years during the Phase 3 trials.

Therefore, the size of the safety database for Tramadol OAD submitted in this NDA appears adequate according to ICH criteria.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There were no special pharmacology/toxicology studies submitted in this NDA.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of the study population in this NDA, including monitoring of vital signs, physical examination, clinical laboratory testing, and eliciting AE data appear adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Comparative PK studies (using Ultram as a reference) and drug-food interaction studies (including in vitro dose-dumping test with alcohol) were conducted during the Phase 1 trials. See Section 5 of this review and the Biopharm review for details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The serious risks of tramadol-associated opioid and non-opioid effects are well known, including respiratory depression, interaction with CBS depressants, withdrawal symptoms/physical dependence, seizure and serotonin syndrome. However, Tramadol OAD is a novel formulation with Contramid (a controlled release formation) and additional risks may occur. The applicant

made appropriate efforts, as based on the study design and conduct, to avoid or detect expected adverse events associated with tramadol. For example, studies excluded all potential drug-drug interaction that may potentially induce seizure and serotonin syndrome. No new safety signals or AEs with higher severity were observed during the clinical development of Tramadol OAD as compared to the approved tramadol products.

7.2.8 Assessment of Quality and Completeness of Data

As a 505(b)(2) application, the safety data provided in each of six Phase 3 trials were generally acceptable in quality to conduct the safety review. However, the following issues in the submission impacted analyses of the safety data:

- An integrated safety dataset for all clinical trials were not submitted.
- Variables for similar datasets (e.g., adverse events) were inconsistent across individual clinical trials, thereby making integration of these datasets difficult.
- Study medication and dose information were not clearly coded or presented in the AE datasets, particularly for studies MDT3-005, MDT3-004 and MDT3-001.
- CRFs for dropouts due to reasons other than AEs and treatment failure, such as dropouts due to "patient request", "investigator's initiation" and "administrative" were not provided in the original NDA submission.
- In the updated Summary of Clinical Safety, data from placebo groups were missing in several summary tables, for example, Table 2.7.4.7.1-28 and many others.
- SAEs across all trials were not appropriately summarized and analyzed in the updated Summary of Clinical Safety. Instead, a brief description was provided. SAEs from the placebo treatment groups were not presented in the SAE list table.
- There were no comparisons of the safety profile made between Tramadol OAD and approved tramadol products, such as Ultram and Ultram ER.
- Headache was experienced by > 5% of patient treated with Tramadol OAD across all trials, but it was not included in the list of common AEs.
- The applicant did not discuss in the submission why the incidence of common AEs was much higher in the studies conducted in Europe (studies MDT3-001 and MDT3-004) than in the placebo-controlled trials primarily conducted in US.

7.2.9 Additional Submissions, Including Safety Update

The following additional submissions were received during the review process and have been incorporated into the safety evaluation of this NDA:

- The 120-day safety update was submitted on March 28, 2006.
- The third pivotal trial, MDT3-005, was submitted on May 30, 2006 (6 months after the initial NDA submission).
- The updated Summary of Clinical Safety, which included data from study MDT3-005, was submitted on June 12, 2006.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The majority of common AEs experienced by ≥5% of patients were related to Tramadol OAD treatment, which mainly determined by temporal relationship with the treatment, pharmacological rationale and expectation from safety profile of approved tramadol products.

There were no new safety signals associated with Tramadol OAD identified during the clinical development.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The data presented in Sections 7.1-7.3 were based on the individual trial reviews, together with the applicant's updated Summary of Clinical Safety. The applicant did not submit an integrated safety dataset with the Summary of Clinical Safety. Where there was inconsistency between the Summary and individual trial reports, the datasets from the individual trials were analyzed using the JMP program for verification. The results from the JMP analyses were used for conclusions in this review. For example, the SAE data in the applicant's Summary were different from the individual reports. The final data resulted from reanalysis of datasets of individual trials.

The safety data were processed and analyzed using a similar approach as the applicant presented in the Updated Summary of Clinical Safety. The pooled safety data were stratified based on study design: placebo-controlled trials, active-controlled trials and open-label long-term trials. Patients who experienced AEs were combined from each type of trials and used as the numerator. The incidences were calculated using the pooled patients who received at least one dose during the trial as the denominator.

7.4.1.2 Combining data

See Section 7.4.11

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The common AEs in the trials tested with different dose levels of Tramadol OAD showed dose-dependent increase in incidence of patients from 100 mg to 400 mg Tramadol OAD. This was consistent with findings from the approved Tramadol products.

7.4.2.2 Explorations for time dependency for adverse findings

The common AEs occurred mostly within one week after dosing and last less than one month.

7.4.2.3 Explorations for drug-demographic interactions

There were no remarkable drug-demographic interactions, including gender, age (< 65 years and ≥ 65 years), BMI and ethnics. The incidence of some common AEs tended to be higher in elderly (age ≥ 65 years), for example, constipation, which were showed in both Tramadol OA and placebo groups.

7.4.2.4 Explorations for drug-disease interactions

There were no remarkable drug-disease interactions associated with the common AEs observed during the 12-week randomized controlled trials and 12-month open-label trials. However, any diseases that may potentially interact with Tramadol OAD were excluded during subject selection.

7.4.2.5 Explorations for drug-drug interactions

There were no remarkable drug-drug interactions associated with the common AEs observed during the 12-week randomized controlled trials and 12-month open-label trials. However, any therapeutic agents that may potentially interact with Tramadol OAD were excluded during subject selection.

7.4.3 Causality Determination

The causality of any AEs associated with the study medication was determined by temporal relationship, underlying medical conditions and medications, and previous experience with approved tramadol products. The guideline that the applicant used to assess the causality is listed in the following table 7w, which is generally acceptable for products filed under 505(b)(2) regulation.

Table 7w. **Guideline for assessment of causal relationship between an AE and the study medication**
(Applicant's Table 9.5.1.3.38.8-1 of Study MDT3-005 report)

Rating of relationship	Temporal Relationship		Underlying causality		Previous occurrence
Not related	Onset of event and consumption of the study medication had no relationship in time.	A N D	The event could clearly be linked to another underlying cause.	A N D	The event was not listed in the investigator's brochure.
Possibly related	A temporal relationship existed between onset of event and consumption of the study medication.	A N D	The event could not clearly be linked to another underlying cause.	A N D	The event was not listed in the investigator's brochure.
Probably related	A temporal relationship existed between onset of event and consumption of the study medication	A N D	The event could not clearly be linked to another underlying cause or to the study medication.	A N D	The event was listed in the investigator's brochure.
Definitely	The event was clearly temporally related to taking the study medication.	A N D	The underlying cause clearly the study was medication.	O R	The event was listed in the investigator's brochure.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Tramadol OAD was studied in three Phase 3 efficacy trials at doses of 100, 200 and 300 mg (MDA3-002 and MDT3-003), and doses of 200 mg and 300 mg (MDT3-005). A dose titration was used in all Phase 3 trials with the following titration regimen: 100 mg qd x2 day and 200 mg qd x3 days then 300 mg qd in studies MDT3-002 and -003, and 100 mg qd x3 days and 200 mg qd x5 days then 300 mg qd x6 days in study MDT3-005. The dosing regimen tested in the pivotal trials is consistent with the dosing instruction in the proposed labeling.

8.2 Drug-Drug Interactions

Drug interactions with Tramadol OAD were not studied in this NDA. However, it is well known that tramadol interacts with many other drugs (through CYP2D6 and CYP3A4 metabolism pathways) or via pharmacodynamic effects (through serotonergic activity, with resultant seizure and serotonin syndrome). Using the 505(b)(2) mechanism, [redacted] b(4)

8.3 Special Populations

Tramadol Contramid OAD was not specifically studied in special populations (geriatric, pediatric, renal or hepatic impaired patients). However, in the six Phase 3 trials, approximately

40% of patients were aged ≥ 65 years, and no remarkable differences in clinical outcomes (efficacy and safety) between patients aged ≥ 65 year and < 65 years were noted. The applicant adapted the language from the labeling of Ultram to describe effects and dosing of Tramadol OAD in special population.

8.4 Pediatrics

Tramadol Contramid OAD was not studied in pediatric patients.

The applicant has requested a pediatric deferral based on Section 505B(a)(3)(A)(i) of the Pediatric Research Equity Act (PREA). The basis for the deferral is that the product is ready for approval for use in adults, and pediatric studies have not yet been completed. At the pre-NDA meeting of February 25, 2004, the Division agreed to a deferral of pediatric studies for Tramadol OAD until after approval of this NDA.

The applicant has also requested a partial waiver for pediatric studies in infants ——— based on Section 505B(a)(4)(B)(iii) of PREA. The basis for this request is that the drug product does not represent a meaningful therapeutic benefit for pediatric patients ——— and it is unlikely to be used by a substantial number of patients in this age group. b(4)

8.5 Advisory Committee Meeting

An advisory committee meeting regarding this NDA was not indicated.

8.6 Literature Review

No separate literature review was performed in the clinical review of this NDA.

8.7 Postmarketing Risk Management Plan

The applicant did not submit a postmarketing risk management plan, but has conveyed potential risks of treatment in the proposed labeling.

There were no new safety signals identified during the clinical development on Tramadol Contramid OAD as compared to the approved tramadol products. The office of Drug Safety (ODS) was consulted and concluded that there are no unique safety issues with this product for which a Risk Minimization Action Plan (RiskMAP) to minimize risk normally would be associated.

ODS also noted that tramadol products, marketed for approximately 11 years, to date have not required risk management tools beyond standard product labeling and routine post-marketing safety surveillance.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy: The applicant concluded that two of three pivotal trials (MDT3-003 and MDT3-005) on Tramadol OAD were statistically successful in demonstrating the analgesic effectiveness of Tramadol OAD 300 mg or 200 mg in patients with moderate to severe pain due to the knee osteoarthritis. This conclusion was made from the primary efficacy analyses of the full analysis population (patients receiving $\geq$ 1 dose with $\geq$ 1 post-baseline assessment), with LOCF imputation for missing data due to early dropouts.The primary efficacy endpoints were percent change from baseline to the end of treatment in WOMAC Pain Score and Patient Global Rating of Pain Relief (MDT3-003) and Pain intensity on 11-point NRS (MDT3-005).

However, BOCF imputation for missing data due to dropouts and a continuous responder analysis (defining dropouts as non-responders) show no statistically analgesic superiority of Tramadol OAD to placebo for both studies MDT3-003 and MDT3-005. BOCF is generally conservative alternative analysis method to test the impact of dropouts on analgesic outcome for pain trials, and is the most commonly used for sensitivity analysis on handling missing data. The continuous responder analysis describes the response profile of an analgesic. Both analyses are required by the Division as alternatives for primary efficacy analyses compare group mean outcomes or that incorporate a less conservative data imputation method such as LOCF.

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

Safety: No new safety signals associated with Tramadol Contramid OAD were identified during the clinical development program and the same safety profile as compared to the approved tramadol products. The safety assessment was based on evaluation of the safety database established from the six Phase 3 trials, which included a total of 1939 patients treated with at least one dose of Tramadol OAD 100 to 400 mg; the actual exposure was 1337 patients, including 844 patients who completed 12-week treatment (400 patients on 300 mg), and 493 patients who completed at least 6-month treatment with 300 mg (243 of them continued to 12 months).

9.2 Recommendation on Regulatory Action

The applicant did not provide sufficient evidence of efficacy in this NDA to support Tramadol OAD for the proposed indication. The NDA should not be approved at this review cycle because of the following deficiencies:

The analgesic effects of Tramadol OAD demonstrated in two of three pivotal trials, as the applicant claimed, were based on the LOCF imputation method to handle the missing data due to dropouts. However, the analgesic superiority of Tramadol OAD over placebo is not statistically supported by sensitivity tests using conservative BOCF imputation method for dropouts and the continuous responder analyses (defining dropouts as non-responder). In addition, the LOCF-based superiority of Tramadol OAD to placebo in pain improvement was marginal and may not be clinically meaningful in context of risk/benefit ratio.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Referred to Section 8.9

9.3.2 Required Phase 4 Commitments

No phase 4 commitments are required at this review cycle.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests at this review cycle.

9.4 Labeling Review

The applicant proposed two trade names which were rejected by DMETS. The new trade name is under proposal.

The major changes that the applicant should make in the next review cycle are with respect to the efficacy data in the Clinical Studies section. In next review cycle, the applicant should be advised that results from placebo treatment should be presented with the Tramadol OAD treatment. Results that show no statistically significant differences between Tramadol OAD and placebo should be clearly indicated "not statistically significant" or should not be presented.

The information presented under Adverse Reactions section is inconsistent with the reviewer's analysis on the extent of exposure. The common and less common AEs that the applicant presented are only those with presumed causal relationship to the treatment, which is inappropriate. The AEs regardless of causality should be presented in the common AE table, and listed under less common AEs.

9.5 Comments to Applicant

1. Results from the LOCF-based efficacy analysis are not statistically supported by BOCF imputation methods and continuous responder analysis for both studies MDT3-003 and MDT3-005.

2. Further efficacy study is recommended with the following considerations for the study design:
    a. Different pain populations
    b. Flexible dose to minimize dropouts due to AEs and/or lack of efficacy
    c. Alternative dosing regimen to compensate the low plasma level of tramadol of 9-hour window (as compared to Ultram) and [redacted] ER form of tramadol in the final tablets
    d. Using Tramadol OAD 300 mg tablets produced from the new manufacture sites
    e. Patients should be instructed to take around breakfast time (because of the food interaction).

b(4)

3. Other issues/comments:
    a. Integrated safety dataset from all phase 3 clinical trials should be submitted.
    b. Variables among datasets should be consistent across trials.
    c. Across county comparison of major efficacy endpoints in Study MDT3-005 should be performed.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study MDT3-002

TITLE: A four-arm study comparing the analgesic efficacy and safety of Tramadol Once a Day 100, 200, 300 mg versus placebo for the treatment of pain due to Osteoarthritis of the knee

Study Period: January 24 to August 15, 2003
CRO: [redacted] b(4)

OBJECTIVES

Primary:
To compare the efficacy of Tramadol OAD 100, 200 and 300 mg vs. placebo in the treatment of pain due to the knee OA for up to 14 weeks

Secondary:
To compare the safety and benefit of Tramadol OAD 100, 200 and 300 mg vs. placebo in the treatment of pain due to the knee OA

STUDY LOCATION
USA, a total of 75 study sites

STUDY DESIGN AND PROCEDURE

This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, and parallel group trial. The study population was adult patients with confirmed, symptomatic OA of the knee. A total of 520 patients were to be enrolled and randomized to four groups at ratio of 1:1:1:2 (100 patients each of three dose groups of Tramadol OAD and 220 patients in the placebo).

The trial consisted of three phases: Baseline, Run-in and Maintenance. After baseline screening and randomization, the subjects received the run-in (titration) treatment for up to 5 days followed by Maintenance dosing (12 weeks) with Tramadol OAD or placebo as follows:

- 100-mg group: 100 mg of Tramadol OAD for both Run-in period (0-day Run-in) and the Maintenance period
- 200-mg group: 100 mg of Tramadol OAD for 2 days (2-day Run-in) and then 200 mg for Maintenance
- 300-mg group: 100 mg of Tramadol OAD for 2 days followed by 200 mg for 3 days (5-day Run-in) and then 300 mg for Maintenance (one 100 mg tablet and one 200 mg tablet)

- Placebo group: placebo tablets for the entire Run-in and Maintenance.

There were 4 visits to a study site during 12-week Maintenance treatment: week 0 (visit 2, the first day of Maintenance dose, week 3 (visit 3), week 6 (visit 4) and week 12 (visit 5) post. [*The visit 1 was the baseline screening*].

The primary efficacy analysis was based on the three co-primary endpoints, percent change from baseline to end of treatment (with LOCF) in *WOMAC Pain score, WOMAC function score and Average of Patient Global Ratings of Pain Relief.* Safety assessment included physical examination, clinical laboratory testing, vital signs, adverse event (AE) monitoring and concomitant medication.

Subject Selection

Inclusion criteria

1) Males or females, 40 - 75 years of age
2) Moderate to severe OA of the knee according to the ACR criteria:
   - Current knee pain.
   - < 30 minutes of morning stiffness with or without crepitus on active motion
   - Confirmation 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 or ESR < 40 mm/hour
   - WOMAC Pain Subscale Total Score > 150 mm at baseline
3) BMI < 38

Exclusion criteria

1) Known rheumatoid arthritis or any other rheumatoid disease.
2) Secondary arthritis i.e. 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) Evidence of effusion greater than 15 ml upon physical examination at baseline
4) Major illness requiring hospitalization during the 3 months before commencement of the screening period.
5) Unwillingness to cease taking analgesics for OA pain or any other concomitant pain or OA medications
6) Previous failure or discontinuation (due to AEs) of tramadol HCl therapy.
7) Treatment within the last 3 weeks with any of the following medications: monoamine oxidase inhibitors, tricyclic antidepressants and other tricyclic compounds (e.g. cyclobenzaprine, promethiazine), neuroleptics, selective serotonin reuptake inhibitors, or other drugs which reduce seizure threshold.
8) Treatment with another investigational agent within the last 30 days.
9) A history of seizure disorder other than infantile febrile seizures.
10) Previous or current opioid dependence; or current substance abuse or dependence, other than nicotine
11) Bowel disease causing malabsorption.

12) Significant Liver Disease (defined as active hepatitis or liver enzymes > 3x ULN)
13) Significant renal disease (defined as creatinine clearance < 30 mL/min as estimated by the method of Levey et al., 1999)
14) Allergy or an adverse reaction to Tramadol or any structurally similar drugs (e.g. opiates)

Rescue medication

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

Concomitant Medication

- Patient could take Nytol (Valerian) for sleep disturbances.
- Patients could not take sedative hypnotics, topical preparations/medications and anesthetics and/or muscle relaxants; or these had to be stopped for ≥ 5x half-life before Visit 1 (R1).
- Herbal remedies, such as glucosamine sulphate and chondroitin sulphate, were to be washed out (*period was not specified*) and not taken during the trial.
- Patients with previous intra-articular corticosteroid injection were to wait for at least 2 month prior to entering the study; additional waiting month for viscous injections.
- Patients under low-dose ASA for cardioprotection with stable dose >3 months were to continue at the same dose.
- Patients under physical therapy had to be on a stable regimen for ≥ 3 months.
- Medication for tramadol-associated AEs: dimenhydrinate/Dramamine for nausea and psyllium hydrophilic mucilloids, docusate sodium, sennosides for constipation, or other medications for AEs were collected in CRFs.

Efficacy Measures

- ***WOMAC Index:*** 3 subscales -- Pain, Stiffness and Physical function on 100-mm VAS
- ***24-Hour Pain Rating Questionnaire***: A self-administrated questionnaire on VAS rating of the knee pain of 24 hours prior to the study visit: lunchtime, bedtime and right before the morning dose on the visit day
- ***Physician and Patients Global Ratings:*** Rating of overall OA pain relief using the Likert-scale: "very effective", "effective" or ineffective" during the Maintenance Phase (4 visits).

Safety Measures

- ***Physical examination:*** Vital sign at all visits; body system examination including inspection of the knee (palpation and mobilization) at baseline and the end of study
- ***Clinical laboratory testing***: hematology, biochemistry and urinalysis at baseline and end of study
- ***AE Monitoring:*** throughout the duration of the study with MedDRA coding.

Statistical Analysis

Analysis populations:

- Safety Population: all randomized patients who received at least one dose of the study medication
- Full analysis population: all randomized patients who received at least one dose of the study medication and had at least one post-baseline assessment of any functional scale. This was used for primary efficacy analysis.
- Per protocol population: all patients of the full analysis population without no major protocol deviations and with a rating of the primary efficacy variables at the end of the study

Primary efficacy analysis: Three co-primary endpoints

- % change in WOMAC pain score from baseline to the end of treatment (week 12)
- % change in Physical Function Score from baseline to the end of treatment (week 12)
- Average of Patient Global Rating of Pain at visits 2-5 (12-week maintenance period)

LOCF (last observation carried forward) was used for imputation of missing data due to early dropouts.

Secondary efficacy analysis:

- % difference in pain between baseline and each visit
- % difference in physical function subscale score between baseline and each visit
- multiple-dose effect evaluation by 24-hour pain questionnaire
- Average of the Physician Global Ratings of Pain Relief during Maintenance phase

Sample size: A total of 520 patients was planned for enrollment and randomized to three tramadol OAD dose groups and placebo at ratio of 1:1:1:2, with the following assumptions:

- Minimal change in primary efficacy variables from baseline considered clinically significant: 15%
- SD = 25%
- Power = 90%
- Expected dropout rate: 30% in tramadol groups and 65-70% in placebo

Others

- Superiority analysis of each primary efficacy endpoint between tramadol OAD 100, 200 and 300 mg vs. placebo, tested by 2-way ANCOVA.
- Multiplicity (type I error) due to multiple comparison of treatments (tramadol OAD 100, 200, 300 mg vs. placebo) was adjusted by the Holm-Bonferroni method. There was no multiplicity adjustment on the multiple primary variables (co-primary endpoints).
- No inter-/intra-center analyses were performed due to the higher number of centers (75 sites) and the small number of patients per center (1/3 centers enrolled < 5 patients). Three "pseudo-centers" were created by grouping centers according to geographical regions (western, central and eastern) and results were presented in appendix of the report.

Protocol Amendment

- The protocol was amended on Jan 14, 2003: arthroscopy or radiology performed within 5 years of the assessment visit were accepted rather than within 1 year as originally designed (*the applicant did not mention if there was an agreement from the Division*).
- No adjustment on center effects due to >1/3 of centers had enrolled < 5 patients, as per Feb 2004 meeting (*with the Division?*).

RESULTS

Subject Disposition

A total of 565 patients were enrolled and randomized to the following four groups: Tramadol OAD 100 mg, 200 mg, 300 mg and Placebo (Table 1)

The overall dropout was 47% in the Tramadol OAD groups (n=160) and 37% in the placebo group. Approximately third of dropouts occurred during the Run-in/titration Phase.

The main reasons for discontinuation from the trial were adverse events (24% of patients on Tramadol OAD vs. 4% on Placebo) and lack of efficacy (13% of patients on Tramadol OAD vs. 23% on Placebo) (Table 1).

Table 1. **Patient Disposition**

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

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

Baseline Characteristics

Demographics:

Overall, there were no remarkable differences among the four groups with respect to gender (60% females), age (mean=60 years), BMI (mean=31) and ethnic origin (78% Caucasian) for the Full Analysis population (Table 2).

***Table 2.* Demographics of Full Analysis Population**
(Adapted from the applicant's Table 11.2.1.1-1)

Demographics	Tramadol OAD			Placebo	Overall
	100mg	200 mg	300 mg		
	(n=109)	(n=110)	(n=113)	(n=226)	(n=558)
Gender n(%)					
Male	45(41%)	47 (43%)	43 (38%)	87 (38%)	222 (40%)
Female	64 (59%)	63 (57%)	70 (62%)	139 (62%)	336 (60%)
Age (year)					
Mean ± SD	60±9	60±8	61±10	61±10	60±9
Median	61	59	62	62	62
Range	40-75	40-74	40-76	41-80	40-80
Age group n(%)					
< 65 years	69 (63%)	75 (68%)	64 (57%)	138 (61%)	346 (62%)
≥ 65years	40 (37%)	35 (32%)	49 (43%)	88 (39%)	212 (38%)
Ethnic n(%)					
Asian	3 (3%)	1 (0.9%)	2 (2%)	3 (1%)	9 (2%)
Black	11 (10%)	9 (8%)	11 (10%)	31 (14%)	62 (11%)
Caucasian	83 (76%)	87 (79%)	92 (81%)	176 (78%)	438 (78%)
Hispanic	11 (10%)	13 (12%)	8 (7%)	15 (7%)	47 (8%)
Other	1 (0.9%)	-	-	1 (0.4%)	2 (0.4%)
BMI (kg/m2)					
Mean ± SD	30.5 ± 4.8	30.6 ± 4.3	30.4 ± 4.5	31.2 ± 4.7	30.8 ± 4.6
Median	31.2	30.2	30.9	32,0	31.2
Range	20.1 - 39.8	18.4 - 38.7	19.8 - 41.8	19.6 - 44.4	18.4 - 44.4

***Baseline Efficacy Parameters*:**

There were slightly higher WOMAC subscale scores (pain, physical function and stiffness) in the 200-mg and 300-mg tramadol groups than in 100 mg tramadol and placebo groups in the full analysis population (Table 3).

Past and Concurrent Medical History

The most common medical history was musculoskeletal and connective tissue disorders (90-94%) followed by surgical and medical procedure (49-58%), vascular disorders (45-53%), metabolism and nutrition disorders (37-48%), GI disorders (37-46%), immune system disorders (26-37%) and infections and infestations (21-28%). Patients in 100 mg tramadol and placebo groups tended to have less past and concurrent disorders.

***Table 3.* Baseline Efficacy Parameters in the Full Analysis (FA) Population**
(Adapted from the applicant's Table 11.2.1.1-2)

Efficacy Parameters	Tramadol OAD Treatment			Placebo
	100 mg	200 mg	300 mg	
WOMAC Pain Score				
FA Population	109	110	113	226
Mean ± SD	299.6 ± 81.4	310.5 ± 96.5	308.7 ± 89.2	302.4 ±85.9
Median	294.0	316.5	311.0	304.5
Range	162 - 485	114 - 495	145 - 495	145 - 494
WOMAC Physical Function Score				
FA Population	108	107	112	223
Mean ± SD	1014.8 ± 326.5	1089.3 ± 327.7	1062.3 ± 333.3	1055.7 ± 325.5
Median	1008.0	1166.0	1056.0	1101.0
Range	144 - 1650	136 - 1674	215 - 1683	268 - 1677
WOMAC Stiffness Score				
FA Population	109	110	113	225
Mean ± SD	128.1 ± 43.1	135.9 ± 39.3	137.0 ± 43.0	136.6 ± 41.6
Median	132.0	140.5	146.0	140.0
Range	4 - 198	18 - 199	26 - 198	15 - 200
WOMAC Total Score				
FA Population	108	107	112	222
Mean ± SD	1442.1 ± 422.8	15.35.1 ± 439.6	1509.5 ± 441.1	1496.4 ± 430.1
Median	1429.0	16i5.0	1473.5	1540.0
Range	514 - 2312	414 - 2330	386 - 2373	478 - 2351
24-Hour Pain Rating Questionnaire				
At lunch time				
FA Population	104	101	102	208
Mean ± SD	56.5 ± 23.5	58.8 ± 25.4	54.5 ± 28.5	57.8 ± 23.7
Median	59.5	61.0	54.5	60.5
Range	2 - 98	3 - 100	0 - 98	2 - 100
At bedtime				
FA Population	106	104	108	218
Mean ± SD	57.1 ± 122.6	61. 7 ± 25.1	55.8 ± 26.3	60.3 ± 25:7
Median	59.5	66.0	58.5	66.0
Range	6 - 97	1 - 100	2 - 99	4 - 100
Before next. AM dose				
FA Population	106	104	107	217
Mean ± SD	57.7 ± 25.2	59.3 ± 24.1	55.6 ± 26.7	58.5 ± 25.4
Median	61.0	62.0	58.0	62.0
Range	2 - 99	3 - 98	2 - 98	4 -100

Prior Medication

Prior to study entry, the most common medications were NSAIDs (propionic acid derivatives and coxibs), cardiovascular medicine, and anilides.

The distribution of those medications was slightly different among groups; there were more patients with coxib (25%) and less patients with anilides (13%) in the 300 mg tramadol group used coxibs than other tramadol and placebo groups (18% and 22-23%, respectively). However, there was less imbalance of concomitant medication among the groups (see Concomitant Medication below).

Baseline Physical Examination

There were no notable differences in overall physical exam (PE) findings at Baseline among groups, but the musculoskeletal abnormality was slightly higher in placebo group (81%) than tramadol groups (74-76%).

Applicant's Efficacy Evaluation

Primary endpoints

The percent changes in the three co-primary endpoints from baseline to end of treatment (week 12) were analyzed for the Full Analysis population using LOCF imputation for missing data due to early dropouts, as pre-specified in the applicant's study design. However, because the proposed indication was for management of chronic pain, the WOMAC Pain score would be the preferred sole primary efficacy endpoint for the study.

WOMAC Pain Score (Table 4): The % change in WOMAC pain score from baseline to the week 12 was 38% in placebo group and 36-41% in tramadol OAD groups (100, 200 and 300 mg). The difference among groups was not statistically significant.

Patient Global Rating of Pain Relief: (Tables 5a-c): Tramadol OAD 300 mg (but not 100 mg or 200 mg) showed a statistically significant difference in the overall pain relief (very effective + effective) based on *median rating* (of 4 visits) as compared to placebo (73% vs. 59%, p = 0.0008) after multiplicity adjustment of type I error ($\alpha/3$). The pain relief tended to be dose-dependent from 100 to 300 mg and time-dependent in the Tramadol OAD 300 mg group.

However, with BOCF (baseline observation carried forward) imputation. There was no statistically significant difference in the pain relief at any dose groups of Tramadol OAD as compared to placebo (Table 4b).

Table 4. **WOMAC Pain Subscale Score**
(Adapted from the applicant's Table 11.4.1.1.2-1)

	Treatment			
	Tramadol OAD 100 mg [n=109]	Tramadol OAD 200 mg [n=110]	Tramadol OAD 300 mg [n=113]	Placebo [n=226]
WOMAC Pain Subscale Baseline Score				
N	109	110	113	226
Mean ± SD	299.6 ± 81.4	310.5 ± 96.5	308.7 ± 89.2	302.4 ± 85.9
Median	294.0	316.5	311.0	304.5
Min, Max	162, 485	114, 495	145, 495	145, 494
WOMAC Pain Subscale Week 12 Score				
N	64	60	55	146
Mean ± SD	169.2 ± 129.0	176.6 ± 122.0	140.1 ± 136.7	157.1 ± 131.2
Median	140.5	172.0	96.0	126.5
Min, Max	0, 493	0, 455	5, 471	0, 463
WOMAC Pain Subscale Last Individual Visit Score				
N	107	106	112	223
Mean ± SD	191.5 ± 142.0	194.2 ± 134.6	179.1 ± 137.5	188.9 ± 139.6
Median	168.0	173.0	147.5	160.0
Min, Max	0, 493	0, 490	5, 471	0, 497
Total Absolute Improvement[1] (Baseline – Last Individual Visit)				
N	107	106	112	223
Mean ± SD	107.6 ± 138.3	117.4 ± 133.0	129.3 ± 135.5	112.3 ± 125.9
Median	121	98.5	117	108
Min, Max	-183, 466	-174, 455	-256, 438	-137, 419
Percentage Improvement from Baseline[1] (Baseline – Last Individual Visit) x 100 / Baseline				
N	107	106	112	223
Mean ± SD	36.3 ± 45.3	36.6 ± 40.9	41.0 ± 44.5	38.0 ± 41.7
95% CI	[27.6;44.9]	[28.7;44.5]	[32.6;49.3]	[32.5;43.6]
Median	42.0	37.0	43.0	41.0
Min, Max	-80, 100	-75, 100	-143, 99	-63, 100
Absolute Difference in Percent Improvement Between Active and Placebo				
Estimate (mean)	-1.81	-1.49	2.91	-
95% CI	[-11.74; 8.11]	[-11.46; 8.47]	[-6.87; 12.69]	-
P-Value[2]	0.7197	0.7688	0.5591	-

Table 5a. Patient Global Rating of Pain Relief in Full Analysis Population
(Applicant's Table 11.4.1.1.1-1)

Table 11.4.1.1.1-1 Full Analysis Population: Patient Global Rating of Overall Pain Relief

	Day M0 (V2)	Day M21 (V3)	Day M42 (V4)	Day M84 (V5)	Individual last visit	Median rating[1]	p-Value[2]	p-Value[3]
Tramadol OAD 100 mg [n=109]								
Very effective	15 (15.2%)	19 (23.2%)	17 (23.3%)	19 (29.2%)	26 (24.1%)	19 (17.6%)		
Effective	53 (53.5%)	45 (54.9%)	39 (53.4%)	31 (47.7%)	44 (40.7%)	50 (46.3%)		
Ineffective	31 (31.3%)	18 (22.0%)	17 (23.3%)	15 (23.1%)	38 (35.2%)	39 (36.1%)	0.1174	0.1032
Tramadol OAD 200 mg [n=110]								
Very effective	10 (10.6%)	14 (18.9%)	13 (23.8%)	12 (19.7%)	20 (18.3%)	16 (14.7%)		
Effective	65 (69.1%)	43 (58.1%)	30 (47.6%)	36 (59.0%)	52 (47.7%)	56 (51.4%)		
Ineffective	19 (20.2%)	17 (23.0%)	18 (28.6%)	13 (21.3%)	37 (33.9%)	37 (33.9%)	0.0866	0.0920
Tramadol OAD 300 mg [n=113]								
Very effective	23 (25.6%)	22 (34.4%)	28 (50.0%)	25 (45.5%)	36 (31.9%)	26 (23.0%)		
Effective	49 (54.4%)	33 (51.6%)	21 (37.5%)	23 (41.8%)	46 (40.7%)	56 (49.6%)		
Ineffective	18 (20.0%)	9 (14.1%)	7 (12.5%)	7 (12.7%)	31 (27.4%)	31 (27.4%)	0.0008	0.0008
Placebo [n=226]								
Very effective	19 (9.2%)	41 (23.7%)	44 (26.3%)	48 (32.7%)	53 (23.8%)	29 (13.0%)		
Effective	103 (50.0%)	86 (49.7%)	79 (50.6%)	63 (42.9%)	78 (35.0%)	94 (42.2%)		
Ineffective	84 (40.8%)	46 (26.6%)	36 (23.1%)	36 (24.5%)	92 (41.3%)	100 (44.8%)		

Source: Statistical table: 4.2.5.1

Note: Percentages are based on the total number of patients with data available at the respective visit.

[1]Median of ratings at Visit 2, Visit 3, Visit 4, and Visit 5 or discontinuation.

[2]Cochran-Mantel-Haenszel test (allowing stratification adjustment for centres) between respective treatment and placebo (Centres were pooled by region) Test is based on median rating.

[3]Kruskal-Wallis test between respective treatment and placebo. Test is based on median rating.

Table 5b. Patient Global Rating of Overall Pain Relief (% of patients) at Week 12 with LOCF and BOCF Imputation for Missing Data
(Data extracted from the applicant's Table 11.4.1.1.1-1)

Treatment	FA Population	No Imputation			BOCF Imputation*		LOCF Imputation	
		Total FA Subject	Overall Effective	Ineffective	Overall Effective	Ineffective	Overall Effective	Ineffective
Placebo	226	147	75.6	24.5	49.1	50.9	58.8	41.3
100 mg Tramadol	109	65	76.9	23.1	45.9	54.1	64.8	35.2
200 mg Tramadol	110	61	78.7	21.3	43.6	56.4	66.0	33.9
300 mg Tramadol	113	55	87.3	12.7	42.5	57.5	72.6	27.4

* The baseline information for early termination subjects are considered "non-response" or "ineffective".

Table 5c. **Time-course of overall pain relief among treatment groups based on evaluable patients**
(% of patients with overall pain relief)

Treatment	Days during Maintenance Dosing			
	0	21	42	84
Placebo	59.2	73.4	76.9	75.6
100 mg Tramadol OAD	68.7	78.1	76.7	76.9
200 mg Tramadol OAD	79.7	77.0	71.4	78.7
300 mg Tramadol OAD	80.0	86.0	87.5	87.3

Data are extracted from the applicant's Table 11.4.1.1.1-1

WOMAC Physical Function Score: Improvement in WOMAC Physical Function from Baseline to week 12 was 34% in placebo and 32-37% in tramadol OAD groups (100, 200 and 300 mg). There were no statistically significant differences among the groups.

Secondary Efficacy Parameters

24-hour VAS Pain Questionnaire: There was no statistically significant difference in pain ratings between Tramadol OAD and placebo groups and among different time-points (immediately after dose (morning), at lunch time, and immediately before the next dose).

Investigator Global Rating of Pain Relief: A similar profile to the Patient Global Rating of Pain Relief was observed. The overall pain relief at week 12, based on LOCF imputation for missing data, was 71% of patients in tramadol OAD 300 mg and 59% of patients in placebo group (p=0.0083). There appeared to be a dose response relationship (100 mg: 64%; 200 mg: 66%, 300mg: 71%).

WOMAC Pain and function Scores (Intervening Visits): At Visits 2 (day 0), 3 (day 21) and 4 (day 42) during Maintenance dosing, patients in the Tramadol OAD 300 mg group appeared to have a slightly higher percentage of improvement in WOMAC Pain and physical function Scores than placebo group.

Applicant's Safety Evaluation

Extent of exposure

A total of 565 patients entered the study received at least one dose of the study medication (338 on tramadol OAD and 227 on placebo). These patients were defined as the Safety Population.

Of 338 patients randomized to Tramadol OAD groups, 179 (53%) completed the 12-week treatment. The % patients who completed the 12-week treatment decreased with increasing dose of Tramadol OAD (58% on 100 mg, 53% on 200 mg and 48% on 300 mg) with 64% on placebo.

Adverse Events (AEs)

Overall, 65% patients experienced at least one treatment emergent adverse event (TEAE) in the Tramadol OAD groups which increased with dose (Table 6):

- 57% of patients on Tramadol OAD 100 mg
- 66% of patients on Tramadol OAD 200 mg
- 71% of patients on Tramadol OAD 300 mg
- 50% of patients on placebo

***Table 6.* Summary of Patients with TEAEs in the Safety Population**
(Adapted from the applicant's Table 12.2.2.1-1)

Patients with TEAE	Tramadol OAD			Placebo (n=227)	p-value*
	100 mg (n=110)	200 mg (n=113)	300 mg (n=115)		
at least one TEAE	63 (57.3%)	75 (66.4%)	82 (71.3%)	114 (50.2%)	0.0007
at least one severe TEAE	9 (8.2%)	6 (5.3%)	13 (11. %)	11 (4.8%)	0.1278
at least one serious TEAE	2 (1.8%)	1 (0.9%)	4 (3.5%)	3 (1.3%)	0.5390 #
at least one possibly drug related TEAE	40 (36.4%)	53 (46.9%)	63 (54.8%)	55 (24.2%)	<0.0001
Dropout due to TEAE	24 (21.8%)	21 (18.6%)	40 (34.8%)	14(6.2%)	<0.0001
died	1 (0.9%)				0.1947 #

* p-value from Chi-square and Fisher's exact test (#) (2-sided) respectively

Death: one death due to MI in the 100 mg tramadol group

This was a 67-year-old Caucasian female enrolled in the 100 mg tramadol OAD group and died from acute myocardial infarction before the last visit (visit 5). The patient had a good compliance to the first 4 visits and well responded to 100 mg tramadol treatment.

During the baseline screening, the patient had unremarkable physical examination and medical history with normal lab values except total cholesterol of 215 mg/l (normal < 200), Ca2+ of 10.5 mg/dl (normal 8.4-10.4) and K+ of 3.3 mmol/l (normal 3.5-5.2 mmol/l). During the study, the patient responded well to the study drug and normal affect and behavior.

The patient had the heel surgery (subtalar procedure) at near end of study and was transferred to an extended care facility. The patient became "agitated" and was transported to ER 4 days after

the surgery. The ER evaluation was normal vital sign, normal ECG-Lead II, normal Hb/Hct and electrolytes.

The patient was then transferred and admitted to other medical center with a diagnosis of Bipolar Disorder. Upon admission, her PE and lab were unremarkable. The patient collapsed and died 6 days after admission. The death cause was "acute myocardial infarction with arteriosclerotic heart disease". The patient had unremarkable finding as per internal medicine consultant and psychiatric staff at early of the death day.

Patient's medical history: bipolar disorder diagnosed 17 years ago and recovered from Lithium therapy, alcohol abuse 26 years ago and a 23-year history of sobriety, hypertension started from 1990.

Patient's medications history

- Lotrisone cream, Pepcid, metoprolol, Lozol *prior to and during the study*
- Framim (dalteparin), Vioxx and Percocet (acetaminophen/oxycodone) *started with the heel surgery*
- Prevacid (replace Pepcid), metoprolol (increased dose), lithium, risperdal (risperidone), and catapres (clonidine) patch *during psychiatric hospitalization*

[Comments: the investigator concluded the death cause was acute MI which was not related to the study medication. However, the investigator/applicant did not provide information about confirmatory diagnosis (cardiac tests prior to the event and autopsy after death) of acute MI and rationale about no relation to the study medication. The initial clinical symptom was "agitated" which is part of triad of serotonin syndrome. A potential drug-drug interaction and/or drug-disease interaction can not be ruled out.]

Serious AEs: a total of 9 patients reported 11 SAEs; 1 patient each on 100 mg and 200 mg, 4 patient on 300 mg, and 3 patients on placebo; 6 of them were withdrawn from the study. All patients with SAEs recovered.

- 2 SAE in the 100 mg group
  - 1 severe DVT
  - 1 moderate bipolar disorder (in the same death case)
- 1 SAE in the 200 mg group
  - 1 mild invasive breast cancer
- 4 SAEs in the 300 mg groups:
  - 1 moderate fecal impaction: probably related to drug
  - 1 severe aortic aneurysm
  - 1 severe aggravated pancreatitis
  - 1 moderate thyroid neoplasm
- 3 SAEs in the placebo group
  - 1 moderate gastroenteritis
  - 1 severe rectal prolapse
  - 1 moderate limb venous thrombosis

The applicant considered only 1 SAE (fecal impaction, from 300 mg group) as probably related to the study medication. Based on the narratives of the SAEs, all had a temporal relationship with the study medication but were confounded by concurrent medical conditions and/or multiple medications. The causal relationship of the SAEs therefore can not be definitively established.

Withdrawal due to AEs: The frequency of AE-related withdrawal was 18% (99 of 565 patients), with dose-dependent increase from 100 mg to 300 mg tramadol OAD.

- 22% in the 100 mg group
- 19% in the 200 mg group
- 35% in the 300 mg group
- 6% in the Placebo group

The Most Common TEAEs: The TEAEs experienced by ≥10% patients are shown in Table 7 by system organ class(SOC) and Table 8 by preferred term(PT).

Table 7. **Common TEAEs by System Organ Class (% Patient)**

System Organ Class (SOC)	Tramadol OAD Dose			Placebo
	100 mg	200 mg	300 mg	
Gastrointestinal disorders	30.9	38.1	44.3	18.5
Nervous system disorders	16.4	22.1	34.8	12.8

Table 8. **The Most Common TEAEs in the Safety Population**
(Adapted from the applicant's Table 12.2.2.1-3)

Preferred Term (PT)	Tramadol OAD			Placebo (n=227)
	100 mg (n=110)	200 mg (n=113)	300 mg (n=115)	
Constipation	10 (9.1%)	17(15.0%)	18 (15.7%)	17 (7.5%)
Dizziness/Vertigo	9 (8.2%)	21 (18.6%)	28 (24.3%)	5 (2.2%)
Nausea	17 (15.5%)	25 (22.1%)	32 (27.8%)	14 (6.2%)
Somnolence	3 (2.7%)	2 (1.8%)	9 (7.8%)	3 (1.3%)
Vomiting NOS	4 (3.6%)	8 (7.1%)	14 (12.2%)	2 (0.9%)

- There were no remarkable differences in TEAEs by age, gender or race, except that more frequent constipation was noted in patients with age ≥ 65 years from all tramadol groups.
- TEAEs by SOC or PT in Tramadol OAD groups were higher than in placebo and increased with dose of Tramadol OAD.

- The applicant concluded that majority of the most common TEAEs were "possibly related" to the study medication in all dose groups because they were expected based on the previous experience with tramadol products.

Intensity of TEAEs:

- The intensity of TEAEs that most patients experienced in all treatment groups was rated as "mild" to "moderate":
  - 86% of patients on 100 mg tramadol OAD
  - 92% of patients on 200 mg tramadol OAD
  - 84% of patients on 300 mg tramadol OAD
  - 89% of patients on placebo

- The proportions of patients with severe TEAEs were 8% on 100 mg, 5% on 200 mg, 11% on 300 mg and 5% on placebo. The severity of all TEAEs appeared to be dose-dependent.
- Patients reported "severe" AE intensity for the most common TEAEs (constipation, dizziness/vertigo, nausea, somnolence and vomiting) were <1% on 100 mg, 200 mg and placebo groups and 2-4% on 300 mg group.
- The severity of TEAEs showed no remarkable differences among age groups.

Time to Onset and Duration of TEAEs:

- The median onset of the most common TEAEs was within the first week of treatment:
  - 1-2 days for onset of nausea, vomiting and dizziness/vertigo occurred earliest
  - 1-8 days for onset of somnolence
  - 2-6 days for onset of constipation in tramadol groups and 7 days in placebo group
- The median duration of the most common TEAEs was < 3 weeks in all treatment groups:
  - 1-4 days for vomiting
  - 2-7 days for dizziness/vertigo
  - 4-7 days for nausea
  - 5-18 days for somnolence (14 days for placebo)
  - 8-18 days for constipation

Concomitant medication:

The percentage of patients who took concomitant medications during the study was similar in all treatment groups and comparable between tramadol and placebo groups.

The most common concomitant medications (received by ≥10% of patients in the Safety population): HMGCOA reductase inhibitors, platelet aggregation inhibitors (excluding heparin), multivitamins, calcium, other vitamin preparations, proton pump inhibitors, ace-inhibitors, anilides, selective beta blocking agents, thyroid hormones, natural and semi-synthetic estrogens and ascorbic acid.

The percentage of patients with other concomitant medications: 7-10% on propionic acid derivatives, 6-9% on coxibs and 5% on SSRIs in the 200 mg group and 3% on SSRIs in placebo.

Clinical Laboratory Evaluation

A total of 12 abnormal laboratory values were reported in 8 patients:

The increased uric acid, C-reactive protein and Gamma-glutamyltransferase were reported in three patients (2 on 200 mg tramadol and 1 on placebo). [*x UNL was not provided*].

Vital Signs and Physical Examination

There were no remarkable changes in vital signs (Respiratory rate, blood pressure, temperature, pulse) and PE findings for patients in all treatment groups.

SUMMARY AND CONCLUSION

This trial failed to demonstrate that Tramadol OAD (100, 200 or 300 mg) was superior to placebo in improving pain in the OA patients based on the primary efficacy endpoint, the percent change in WOMAC Pain Score at end of treatment (with LOCF imputation for missing data). The applicant also concluded that this was a failed efficacy trial and intended to utilize the trial for safety evaluation (see Section 7 for details).

10.1.2 Study MDT3-003

TITLE: A four-arm study comparing the analgesic efficacy and safety of Tramadol Once a Day (OAD) 100, 200, 300 mg versus placebo for the treatment of pain due to osteoarthritis of the knee

Study Period: January 24 to August 15, 2003
CRO: [redacted] b(4)

OBJECTIVES

Primary:
To compare the efficacy of Tramadol OAD 100, 200 and 300 mg vs. placebo in the treatment of pain due to the knee OA for up to 14 weeks

Secondary:
To compare the safety and benefit of Tramadol OAD 100, 200 and 300 mg vs. placebo in the treatment of pain due to the knee OA

STUDY LOCATION
USA, a total of 74 study sites

STUDY DESIGN AND PROCEDURE

The study was designed as a multicenter, randomized, double –blind, double dummy, placebo-controlled, and parallel group phase II trial. There study consisted of four phases: Baseline, Run-in (6 days), Maintenance (12 weeks), and post-treatment follow-up (1 week). Total study participation would be up to 14 weeks (Figure 1).

A total of 520 patients with confirmed, symptomatic OA of the knee were to be enrolled and randomized to 4 groups in ratio of 1:1:1:2 (100 patients in each of the three Tramadol OAD groups and 220 patients in the placebo group).

After baseline screening (including analgesic washout over a period of $\geq$ 5 half-lives) and randomization, the subjects were to undergo titration over a 0-5 day period (Run-in titration phase), followed by 12-week Maintenance treatment at the fixed dose. Titration of study drug would occur as follows:

- 100-mg group: 100 mg of Tramadol OAD for both Run-in period (0-day Run-in) and the Maintenance period.
- 200-mg group: 100 mg of Tramadol OAD for 2 days, (2-day Run-in) and then 200 mg for maintenance.
- 300-mg group: 100 mg of Tramadol OAD for 2 days, followed by 200 mg for 3 days (5-day Run-in) and then 300 mg (one 100 mg tablet and one 200 mg tablet) for maintenance.

- Placebo group: placebo tablets for the entire Run-in and Maintenance phases.

Four clinic visits occurred during the Maintenance phase: on the first day of maintenance dose (visit 2), and then at 3 weeks (visit 3), 6 weeks (visit 4), and 12 weeks (visit 5) after starting Maintenance dose (Table 1)

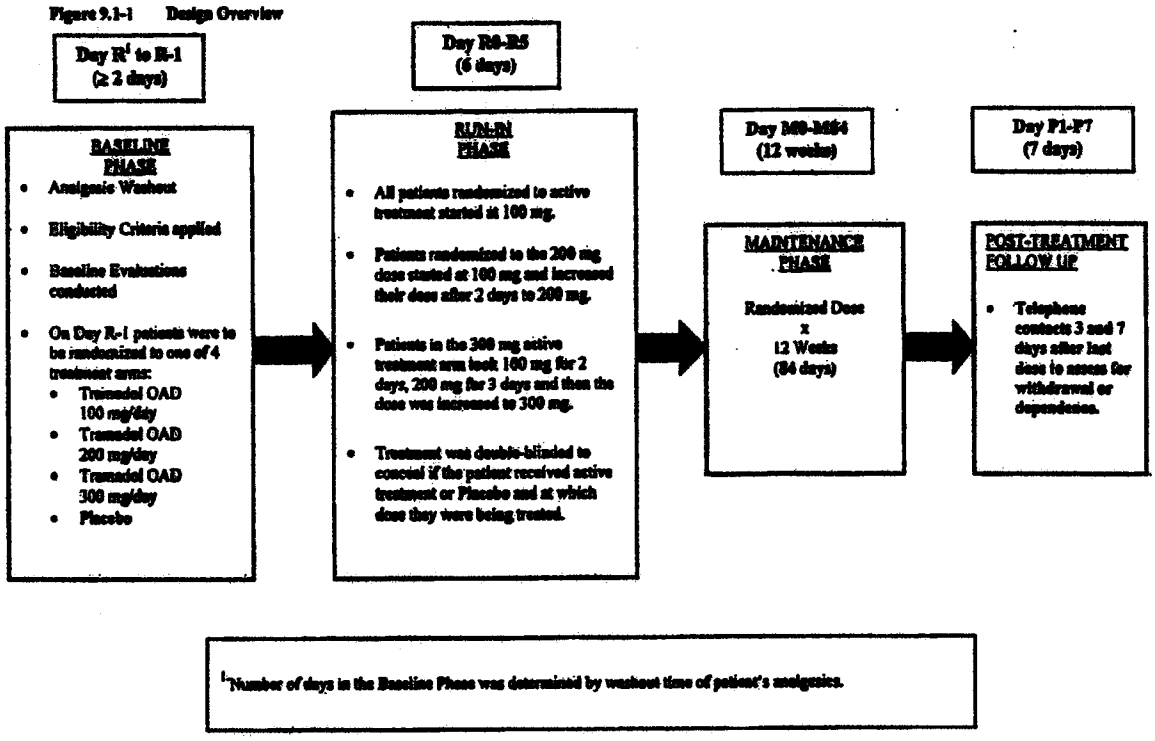


Figure 1. **Overview of the study design**
(From the applicant's Figure 9.1-1, vol 34, p34)

Appears This Way
On Original

Table 1: **Assessment Schedule – Study MDT-003**
(From the applicant's Table 9.5.1-1, vol 34, p45)

PHASE	Baseline		RUN IN	MAINTENANCE				Post-Treatment
Day	R[1] (Wash out)	R-1 (Assessment)	R 0 To R5	M0	M21	M42	M84	P3 & P7[6]
Visit		V1[1]		V2	V3	V4	V5/ Disc.[5]	
Informed Consent	X							
Discontinue Analgesic Medications	X							
Hematology: (RBC, Hgb, hematocrit Plt. WBC & Differential, ESR)		X[2]					X	
Biochemistry: (Protein, GGT, LDH, NA, K, Cl, Glucose, tBili, AST. ALT. triglycerol, Albumin, BUN, Ca, Creatinine, Uric Acid, Alk Phos., amylase)		X[2]					X	
Urine Pregnancy Test		X[2]						
Urinalysis[3] (pH, Spec Grav, Glucose, Protein, Ketones, blood, sediment)		X[2]					X	
Physical Exam		X					X	
Vital Signs (BP, Pulse, Respirations, Temperature, Weight (V1 and V4 or discontinuation only) and Height (Visit 1 only))		X		X	X	X	X	
Medical History & Concurrent Medications.		X						
Arthroscopy or Radiology (Within 5 years of Assessment Visit)		X						
Pain and Physical Function Scales[4] (24-hour Pain Questionnaire[8], WOMAC, Global Rating)		X[8]		X[7]	X[7]	X[7]	X[7]	
Randomization		X						
Dispense Medication		X		X	X	X		
Adverse Events			X	X	X	X	X	X
Concomitant Meds.			X	X	X	X	X	X
Return Used and Unused Medication				X	X	X	X	
Record of Death[6]							X	

[1] Days R-3 to R-1 encompassed the phase between signing of consent and enrollment in the study. It may have lasted longer than 3 days depending upon the required washout time and time to obtain eligibility information for an individual patient.
[2] These evaluations could be done within 14 days prior to the Assessment Visit (V1).
[3] Sediment Microscopy was only to be done if indicated by dipstick urinalysis.
[4] Patient and Investigator Global Rating were not to be done at Visit 1 (as the patient had not yet have taken medication).
[5] Discuss: If the patient discontinued from the study prior to Day M84, the patient was to be seen for a discontinuation Visit and have the Withdrawal assessments done 3 and 7 days after last dose.
[6] If the patient died during the study, a Record of Death Form was to be completed.
[7] Patients were to be contacted by telephone on the day before the Visit and reminded to complete their 24-hour Pain Questionnaire. If patients forgot or were not able to complete the questionnaire the day prior to discontinuing, it could be completed on the day of the Visit.
[8] Patients were to complete their 24-hour Pain Questionnaire for the Baseline Visit on the day of the Visit.

Subject Selection

Key inclusion criteria

1) Males or females, 40 - 75 years of age
2) Moderate to severe OA of the knee according to the ACR criteria:
   - Current knee pain.
   - < 30 minutes of morning stiffness with or without crepitus on active motion
   - Confirmation 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 < 38

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) Major illness requiring hospitalization during the 3 months before the screening period.
6) Unwillingness to cease taking analgesics for OA pain or any other concomitant pain or OA medications
7) Previous failure or discontinuation (due to AEs) of tramadol HCl therapy.
8) Treatment with another investigational agent within the last 30 days.
9) Previous or current opioid dependence; or current substance abuse or dependence, other than nicotine
10) Bowel disease causing malabsorption.
11) Pregnancy or lactating or childbearing potential and unwilling to utilize a medically approved method of contraception during participation in this clinical trial.
12) Significant liver disease (defined as active hepatitis or liver enzymes > 3x ULN)
13) Significant renal disease (defined as creatinine clearance < 30 mL/min)
14) Allergy or an adverse reaction to Tramadol or any structurally similar drugs (e.g. opiates)
15) Any other condition that, in the opinion of the Investigators, would have adversely affected the patient's ability to complete the study or its measures.

Rescue medication

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

Permitted concomitant therapies

- Nytol (Valerian) for sleep disturbances
- Low-dose ASA for cardioprotection, as long as patients had been on a stable dose >3 months
- Physical therapy, as long as patients had been stable regimen for ≥ 3 months
- Medication for tramadol-associated AEs including: dimenhydrinate/Dramamine for nausea and psyllium hydrophilic mucilloids, docusate sodium, including sennosides for constipation

Prohibited concomitant therapies

- Sedative hypnotics
- Topical preparations/medications (*the applicant did not specify in the report*)
- Anesthetics and/or muscle relaxants.
- Herbal remedies, such as glucosamine sulphate and chondroitin sulphate
- Previous intra-articular corticosteroid injection within 2 months prior to study entry.
- Previous intra-articular viscous injections within 3 months of study entry.

Efficacy Measures

- WOMAC Subscales: Pain, Physical Function and Stiffness on 100-mm VAS (at each visit)
- 24-hour Pain Questionnaire: Patient's VAS rating of knee pain over the previous 24 hours (at lunchtime, bedtime and right before the morning dose on the visit day)
- Physician and Patient Global Rating of Overall Pain Relief on "very effective", "effective" or ineffective" during the Maintenance Phase

Safety Measures

- Physical examination: vital signs, exam of the knee (inspection, palpation and mobilization at baseline and the end of study) and body weight
- Laboratory tests (Hematology, biochemistry and urinalysis)
- AEs including withdrawal and dependence

Statistical Analysis

Primary efficacy analysis

Percent changes in the following three endpoints from baseline to end of treatment (week12) were analyzed with LOCF (last observation carried forward) imputation for missing data due to dropouts. The Full Analysis population was defined as all randomized patients who received at least one dose of the study medication and who had at least one post-baseline efficacy assessment.

- % change in WOMAC pain score from baseline to the end of treatment (week 12)
- % change in WOMAC Physical Function Score from baseline to the end of treatment (week 12)
- Average of the Patient Global Rating of Pain at visits over the Maintenance period.

To support the proposed indication for management of chronic pain, the percent change in WOMAC Pain score would be the primary efficacy endpoint.

A superiority analysis was performed on the endpoint, for each Tramadol OAD dose (100, 200 or 300 mg) compared to placebo. Multiplicity adjustment was made for dose levels.

Secondary efficacy analyses

- *% change of the Physical Function score from baseline to each of clinic visits*
- % difference in WOMAC pain between baseline and each visit
- % difference in physical function subscale score between baseline and each visit
- multiple-dose effect evaluation by 24-hour pain questionnaire
- Average of the Physician Global Ratings of Pain Relief during Maintenance phase

Sample size

A total of 520 patients were planned for enrollment, n=100 each of 3 tramadol OAD dose groups and n=220 for placebo, based on the following assumptions:

- Minimal change in WOMAC pain or Function score from baseline to end of study = 15% (with Tramadol OAD treatment)
- SD = 25%
- Power = 90%
- Expected dropout rate: 30% in tramadol groups and 65-70% in placebo

The size of the placebo group was doubled in order to compensate for a potentially higher dropout rate in placebo group as compared to the tramadol group.

Safety Evaluation

The MedDRA (version 4.1 or later) dictionary was to be used to code adverse events, as well as patients' previous and concurrent medical history. AEs would be analyzed as both post-treatment AEs (PTAEs; events reported during the withdrawal assessment 3-7 days after last dose) and treatment-emergent AEs (TEAEs). PTAEs were to be scored by incorporating both severity and duration of AEs.

All patients who took at least one dose of study medication were to be included in the safety analysis. Data were presented using descriptive statistics.

Protocol Amendments

- Arthroscopy or radiology could have been performed within 5 years of the assessment visit, rather than within 1 year as per the original protocol on Jan 14, 2003.
- No adjustment would be made for center effects because more than 1/3 of the centers enrolled < 5 patients in February 2004.

RESULTS

Subject Disposition

A total of 522 patients were enrolled and randomized to four groups: Tramadol OAD 100 mg (n=106), 200 mg (n=111), 300 mg (n=108) and Placebo (n=227).

Almost half of the enrolled patients (44%, n= 241) discontinued from the trial, with more dropouts in the in the Tramadol OAD group (46%) than the placebo group (41%). The frequency of dropouts increased with increasing Tramadol OAD dose (see Table 2).

The main reasons for discontinuation from the trial were adverse events (21% on Tramadol OAD vs. 8% on Placebo) and lack of efficacy (13% on Tramadol OAD vs. 21% on Placebo) (Table 3).

Table 2. **Patient Disposition**

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

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

Table 3. **Patient Dropout Rates**
(Adapted from the applicant's table 10.1-2)

Reason for Dropout	Tramadol OAD Treatment			Placebo (n=227)	Overall (n=552)
	100 mg (n=106)	200 mg (n=111)	300 mg (n=108)		
Any reason	44 (42%)	46 (41%)	58 (54%)	93 (41%)	241 (44%)
Treatment failure	21 (20%)	11 (10%)	11 (10%)	47 (21%)	90 (16%)
Patient request	4 (4%)	8 (7%)	10 (9%)	9 (4%)	31 (6%)
Investigator initiated	6 (6%)	7 (6%)	2 (2%)	19 (8%)	34 (6%)
Adverse events	13 (12%)	20 (18%)	35 (32%)	17 (7%)	85 (15%)
Death				1 (0.4%)	1 (0.2%)

Baseline Characteristics

Demographics:
In general, there were no remarkable differences among the four groups with respect to gender (62% female), age (mean=61 years), BMI (mean=31) and ethnic origin (72% Caucasian) for the full analysis population (Table 4).

However, there were slightly more patients with < 65 years old in the Tramadol OAD 300 mg group (67%) compared to the other groups (54-60%).

Baseline Efficacy Parameters (Table 5):
Patients in the 300 mg group appeared to have slightly more severe pain than the other groups:

- The 300 mg group's mean WOMAC pain score was 10% higher than the 100 mg or 200 mg groups, and 5% higher than placebo.
- The mean WOMAC Physical Function Score for the 300 mg-treated patients was 9% higher than the 100 mg or 200 mg groups, and 4% higher than Placebo
- The 24-Hour Pain Questionnaire: 7-16% higher than other groups

Past and Concurrent Medical History
The most commonly occurring condition (per MedDRA coding) was musculoskeletal and connective tissue disorders (85-88%), followed by surgical and medical procedure (46-55%), vascular disorders (48-51%), metabolism and nutrition disorders (31-43%), GI disorders (35-40%), nervous system disorders (18-26%) and infections and infestations (20-27%). There were no remarkable differences among the groups.

The knee OA was included in the category "musculoskeletal disorder", as per the applicant and all study subjects were the OA patients. However, the applicant did not discuss why only 85-88% (but not 100%) of patients had musculoskeletal history and 80-82% (but not 100%) of patients had musculoskeletal abnormality in PE.

Prior Medication
Approximately 93-98% of patients used at least one prior medication. The most commonly used medications were NSAIDs (propionic acid derivatives and coxibs), cardiovascular medicine, and anilides. As compared to the other treatment arms, slightly more patients in the Tramadol OAD 300 mg group took nonselective NSAIDs (36% vs. 23-26%), and coxibs (27% vs. 21-23%), which was consistent with the find that this group has greater pain at baseline. There was no remarkable difference across groups with respect to use of other opioids.

Baseline Physical Examination
There were no notable differences among the groups in overall physical examination findings at baseline.

Concomitant medication:
The percentage of patients who took concomitant medications during the study was similar in all treatment groups and comparable between tramadol and placebo groups; however slightly more patients in the 300 mg tramadol group took coxibs (10% vs. 5-6% of the other groups). Also

more Tramadol-treated patients took propionic acid derivatives (6-12% vs. 9% of placebo patients).

The most common concomitant medications (taken by ≥10% of patients in the Safety population) were HMGCoA reductase inhibitors, platelet aggregation inhibitors (excluding heparin), multivitamins, calcium, other vitamin preparations, proton pump inhibitors, ace-inhibitors, anilides, selective beta blocking agents, thyroid hormones, natural and semi-synthetic estrogens and ascorbic acid. Laxatives were used by 2-6% of patients for treatment of constipation.

Table 4. **Demographics of Full analysis Population**
(Adapted from the applicant's Table 11.2.1.1-1)

	Treatment				
Variable	Tramadol OAD 100 mg (n=103)	Tramadol OAD 200 mg (n=107)	Tramadol OAD 300 mg (n=105)	Placebo (n=224)	Overall (n=539)
Gender					
Male n (%)	41 (40%)	43 (40%)	36 (34%)	86 (38%)	206 (38%)
Female n (%)	62 (60%)	64 (60%)	69 (66%)	138 (62%)	333 (62%)
Age (years)					
Mean±SD	63 ± 8	61 ± 9	60 ± 9	61 ± 10	61 ± 9
Median	63	62	61	62	62
Range (Min, Max)	40, 76	39, 75	39, 75	40, 82	39, 82
Male (n)	41	43	36	86	206
Mean±SD	65 ± 8	61 ± 11	58 ± 11	61 ± 9	61 ± 10
Median	65	64	57	61	61
Range (Min, Max)	48, 76	39, 75	39, 75	41, 75	39, 76
Female (n)	62	64	69	138	333
Mean±SD	62 ± 9	62 ± 8	62 ± 9	61 ± 10	61 ± 9
Median	61	62	62	62	62
Range (Min, Max)	40, 75	40, 74	41, 75	40, 82	40, 82
Age group					
< 65 years n (%)	56 (54%)	58 (54%)	70 (67%)	134 (60%)	318 (59%)
≥ 65 years n (%)	47 (46%)	49 (46%)	35 (33%)	90 (40%)	221 (41%)
Ethnic origin n (%)					
Asian	2 (2%)	1 (0.9%)	2 (2%)	-	5 (0.9%)
Black	10 (10%)	6 (6%)	12 (11%)	25 (11%)	53 (10%)
Caucasian	72 (70%)	83 (78%)	73 (70%)	159 (71%)	387 (72%)
Hispanic	18 (17%)	16 (15%)	17 (16%)	35 (16%)	86 (16%)
Other	1 (1%)	1 (0.9%)	1 (1%)	5 (2%)	8 (1%)
BMI (kg/m²)					
Mean±SD	30.7±4.5	30.2±4.6	31.0±4.0	30.7±4.6	30.6±4.4
Median	30.5	30.6	31.0	30.5	30.6
Range (Min, Max)	21.4, 39.9	19.5, 38.1	22.0, 43.2	19.1, 46.2	19.1, 46.2
Male (n)	41	43	36	86	206
Mean±SD	30.6±4.4	29.7±5.0	29.6±4.0	30.9±3.8	30.4±4.2
Median	30.4	28.6	29.6	30.9	30.3
Range (Min, Max)	21.4, 39.9	21.7, 38.0	22.0, 36.6	22.2, 39.2	21.4, 39.9
Female (n)	62	64	69	138	333
Mean±SD	30.7±4.5	30.6±4.3	31.7±3.8	30.5±5.0	30.8±4.6
Median	30.8	30.0	31.7	30.2	30.7
Range (Min, Max)	22.6, 39.9	19.5, 38.1	23.0, 43.2	19.1, 46.2	19.1, 46.2

Table 5. **Baseline Efficacy Parameters in the Full Analysis (FA) Population**
(Applicant's Table 11.2.1.1-2)

	Treatment			
Efficacy parameters	**Tramadol OAD 100 mg [n=103]**	**Tramadol OAD 200 mg [n=107]**	**Tramadol OAD 300 mg [n=105]**	**Placebo [n=224]**
WOMAC Pain Score				
N	103	107	105	224
Mean ± SD	287.8 ± 78.8	283.8 ± 81.7	314.4 ± 97.1	300.7 ± 88.8
Median	286.0	278.0	308.0	295.0
Min, Max	161, 480	149, 458	63, 497	94, 495
WOMAC Physical Function Score				
N	102	102	104	217
Mean ± SD	1018.4 ± 319.3	999.2 ± 323.0	1096.3 ± 349.4	1051.2 ± 325.4
Median	1046.0	1030.0	1100.5	1051.0
Min, Max	168, 1622	199, 1629	165, 1687	292, 1700
WOMAC Stiffness Score				
N	102	106	104	221
Mean ± SD	125.3 ± 40.9	129.9 ± 42.2	137.3 ± 44.1	132.5 ± 41.5
Median	127.0	129.5	142.5	135.0
Min, Max	23, 200	7, 199	25, 200	3, 200
WOMAC Total Score				
N	102	102	103	216
Mean ± SD	1431.3 ± 416.0	1408.5 ± 420.8	1543.6 ± 466.8	1483.0 ± 428.5
Median	1454.5	1426.5	1548.0	1456.5
Min, Max	371, 2285	483, 2282	439, 2384	556, 2395
24-Hour Pain Rating Questionnaire				
At lunch time				
N	96	99	96	206
Mean ± SD	54.1 ± 25.2	57.9 ± 22.9	63.0 ± 24.2	58.9 ± 24.7
Median	55.5	60.0	66.5	63.0
Min, Max	7, 99	4, 100	6, 100	0, 100
At bedtime				
N	99	102	102	214
Mean ± SD	57.1 ± 24.0	55.8 ± 24.5	63.1 ± 24.1	62.5 ± 25.3
Median	59.0	56.5	65.0	67.0
Min, Max	2, 98	2, 100	7, 100	1, 100
Before next morning dose				
N	99	102	101	213
Mean ± SD	56.1 ± 26.2	54.2 ± 25.2	57.3 ± 26.1	60.9 ± 25.8
Median	55.0	54.0	60.0	65.0
Min, Max	2, 99	3, 98	3, 100	1, 100

Source: Statistical tables: 3.8.1, 4.2.3.1, 4.3.1.1, 4.4.1.1, 4.6.1.1

Efficacy Evaluation

The applicant analyzed the efficacy data on both "Full Analysis (FA)" population and "Per Protocol (PP)" population. The following results are based on the FA population analysis.

Primary efficacy analysis

Percent change in WOMAC Pain Score: The % change in WOMAC Pain score from baseline to end of treatment (week 12, with LOCF imputation for early dropouts) was as follows: 32% for placebo, 42% for Tramadol OAD 100 mg, 43% for 200 mg and 46% for 300 mg (Table 6). Only the difference between Tramadol OAD 300 mg and placebo (13.4%) reached statistical significance ($p = 0.0162$) after adjustment for multiplicity for the 3-dose comparisons.

Table 6 also suggests that there was a slight dose-response in WOMAC pain improvement for the Tramadol OAD treatment, based on the percentage of pain improvement and absolute differences in % improvement between each dose and placebo.

The Applicant performed several sensitivity analyses of the primary endpoint using alternative methods to handle missing data due to dropouts (Table 7). The MOCF (Median Observation Carried Forward) method showed a statistical difference between placebo and Tramadol OAD 100 and 300 mg, but not Tramadol OAD 200 mg; BOCF showed no difference between placebo and any of the Tramadol OAD groups.

Table 6. **WOMAC Pain Subscale Score**
(Applicant's Table 11.4.1.1.2-1)

	Treatment			
	Tramadol OAD 100 mg [n=103]	Tramadol OAD 200 mg [n=107]	Tramadol OAD 300 mg [n=105]	Placebo [n=224]
WOMAC Pain Subscale Baseline Score				
N	103	107	105	224
Mean ± SD	287.8 ± 78.8	283.8 ± 81.7	314.4 ± 97.1	300.7 ± 88.8
Median	286.0	278.0	308.0	295.0
Min, Max	161, 490	149, 458	63, 497	94, 495
WOMAC Pain Subscale Week 12 Score				
N	63	66	51	137
Mean ± SD	112.3 ± 117.6	131.2 ± 104.0	108.8 ± 98.2	156.8 ± 137.0
Median	57.0	100.5	70.0	113.0
Min, Max	0, 457	0, 468	0, 383	0, 494
WOMAC Pain Subscale Last Individual Visit Score				
N	99	107	104	223
Mean ± SD	167.1 ± 145.3	160.4 ± 128.9	171.8 ± 138.1	201.8 ± 149.1
Median	138.0	132.0	138.5	179.0
Min, Max	0, 492	0, 500	0, 491	0, 496
Total Absolute Improvement[1] (Baseline – Last Individual Visit)				
N	99	107	104	223
Mean ± SD	122.3 ± 143.6	123.4 ± 128.7	143.3 ± 136.2	99.5 ± 145.6
95% CI	[93.7;150.9]	[98.8 ; 148.1]	[116.8 ; 169.8]	[80.3 ; 118.7]
Median	145.0	141.0	137.0	93.0
Min, Max	-229, 474	-320, 439	-117, 443	-223, 462
Percentage Improvement from Baseline[1] $\frac{\text{(Baseline – Last Individual Visit)}}{\text{Baseline}} \times 100$				
N	99	107	104	223
Mean ± SD	41.6 ± 50.2	42.8 ± 46.4	46.0 ± 39.9	32.3 ± 48.2
95% CI	[31.5;51.6]	[33.9;51.6]	[38.2;53.7]	[25.9;38.6]
Median	50.0	53.0	55.0	32.0
Min, Max	-132, 100	-178, 100	-44, 100	-100, 100
Absolute Difference in Percent Improvement Between Active and Placebo				
Estimate (mean)	9.50	10.81	13.41	-
95% CI	[-1.60; 20.60]	[-0.02; 21.64]	[2.49; 24.33]	-
P-Value[2]	0.0933	0.0504	0.0162	-

Source: Statistical tables: 4.2.1.1 (March 8, 2004)
1.1.2 (Post-hoc analyses after unblinding (A), June 14, 2005).

Each of the 5 underlying scales ranged from 0 mm = no pain to 100 mm = extreme pain for a maximum total score of 500 mm.

[1]A negative value represents a deterioration

[2]p-value based on an ANCOVA

Table 7. **Different Imputation Methods for Missing Data on WOMAC Pain Score**
(Applicant's Table 11.4.1.1.4.1-1)

Method	Comparison with respect to % change from baseline to week 12	Estimate of the difference between treatment[1]	Confidence interval[2]		P-value
LOCF	100 mg vs. Placebo	9.50	-1.60	20.60	0.0933
	200 mg vs. Placebo	10.81	-0.02	21.64	0.0504
	300 mg vs. Placebo	13.41	2.49	24.33	0.0162
BOCF	100 mg vs. Placebo	6.44	-3.22	16.09	0.1910
	200 mg vs. Placebo	2.35	-7.22	11.93	0.6292
	300 mg vs. Placebo	0.00	-9.64	9.64	0.9997
Group Median	100 mg vs. Placebo	15.60	7.87	23.33	0.0001
	200 mg vs. Placebo	5.45	-2.19	13.08	0.1618
	300 mg vs. Placebo	15.33	7.66	23.01	0.0001
Reason specific[3]	100 mg vs. Placebo	6.91	-3.71	17.53	0.2017
	200 mg vs. Placebo	8.88	-1.62	19.37	0.0972
	300 mg vs. Placebo	10.19	-0.36	20.74	0.0584

Source: Statistical tables: 1.1.2 (Post-hoc analyses after unblinding (A), June 14, 2005).
1.2.3 (Post-hoc analyses after unblinding, March 16, 2004).
1.2.2 (Post-hoc analyses after unblinding (A), June 14, 2005).
2.1.2 (Post-hoc analyses after unblinding, June 16, 2005).

[1]LOCF, BOCF, Reason specific = estimate of the mean; Group median = estimate of the median.

[2]If the lower bound of the 95% CI is >0, superiority of Tramadol OAD versus Placebo with regard to Pain concluded on a descritive level.

[3]Missing values at Visit 5 were imputed as follows:
Reason for discontinuation: AE or death - mean of last 2 measured values
Lack of efficacy - last measured value
All other reasons - within group median of completers.

Patient Global Rating of Pain Relief: Using the LOCF imputation method, the applicant found that, at the end of the study, the frequency of patients rating overall pain relief as "effective" or "very effective" was statistically significantly higher in the Tramadol OAD 200 mg (71%) and 300 mg (78%) groups compared to Placebo (60%) (p=0.002 and <0.001, respectively). There was no statistically significant difference between the Tramadol OAD 100 mg group (68%) vs. placebo (Tables 8).

However, re-analysis (by this reviewer) with BOCF imputation for the missing data showed no statistically significant differences in the overall pain relief between Tramadol OAD and Placebo (Table 8).

In addition, the LOCF-based results were inconsistent with or not supported by the results from the 24-Hour VAS Pain Questionnaire (see Secondary Endpoint Analyses).

Table 8. **Patient Global Rating of Overall Pain Relief (very effective + effective) At End of Treatment with LOCF or BOCF Imputation for Missing Data**

Treatment	BOCF Imputation		LOCF Imputation		
	Overall Effective (n)†	Overall Effective (%)	Overall Effective (n)‡	Overall Effective (%)	p-value*
Placebo n=224	109	48.7	135	60.3	
Tramadol OAD 100 mg, n=103	57	55.3	69	67.0	0.107
Tramadol OAD 200 mg, n=107	52	48.6	76	71.0	0.002
Tramadol OAD 300 mg, n=105	45	42.9	82	78.1	<0.0001

Data are extracted from the applicant's Table 11.4.1.1.1-1 and include the results from this reviewer's analysis with BOCF imputation.

† Number of patients who reported "very effective" and "effective" at the week 12 visit (excluding early dropouts).

‡ Number of patients who reported "very effective" and "effective" at "Individual Last Visit" (including early dropouts)

* Cochran-Mantel-Haenszel test

WOMAC Physical Function Score (Table 9): Based on an LOCF imputation for missing data, the percent improvement in WOMAC Physical Function from Baseline to end of the treatment (week 12) was 31% for placebo-treated patients, 42% for Tramadol OAD 100 mg and 200 mg patients, 42%, and 39% for the Tramadol OAD 300 mg group.

The Applicant compared the difference between the median percent improvement values, instead of mean, and found a statistically significant difference between each of the Tramadol OAD groups (45%, 46%, and 48%) as compared to placebo (27%). However, after multiplicity adjustment, the differences were not statistically significant. In addition, the statistical test on WOMAC Physical Function Score was not appropriate, parametric test on Mean ± SD, instead of non-parametric test on Median values, should be used to compare different treatment groups.

Table 9. **WOMAC Physical Function Score**
(Applicant's Table 11.4.1.1.5-1)

	Treatment			
	Tramadol OAD 100 mg [n=103]	Tramadol OAD 200 mg [n=107]	Tramadol OAD 300 mg [n=105]	Placebo [n=224]
WOMAC Physical Function Subscale Baseline Score				
N	102	102	104	217
Mean ± SD	1018.4 ± 319.3	999.2 ± 323.0	1096.3 ± 349.4	1051.2 ± 325.4
Median	1046.0	1030.0	1100.5	1051.0
Min, Max	168, 1622	199, 1629	165, 1687	292, 1700
WOMAC Physical Function Subscale Week 12 Score				
N	63	66	50	136
Mean ± SD	409.9 ± 414.4	498.2 ± 376.7	413.7 ± 326.2	578.8 ± 469.2
Median	264.0	435.0	351.5	446.0
Min, Max	6, 1596)	0, 1581)	0, 1260)	0, 1683)
WOMAC Physical Function Subscale Last Individual Visit Score				
N	99	107	105	223
Mean ± SD	595.5 ± 511.3	580.0 ± 436.6	620.0 ± 459.9	722.4 ± 493.0
Median	415.0	493.0	543.0	668.0
Min, Max	6, 1672	0, 1596	0, 1631	0, 1686
Total Absolute Improvement[1] (Baseline – Last Individual Visit)				
N	98	102	104	216
Mean ± SD	434.5 ± 513.3	416.7 ± 400.3	472.6 ± 472.5	330.7 ± 463.3
95% CI	[331.6; 537.5]	[338.1; 495.3]	[380.7; 564.5]	[268.6; 392.8]
Median	342.0	366.5	420.5	266.5
Min, Max	-521, 1598	-457, 1552	-914, 1518	-759, 1532
Percentage Improvement from Baseline[1] (Baseline – Last Individual Visit) x 100 / Baseline				
N	98	102	104	216
Mean ± SD	42.3 ± 46.1	42.0 ± 39.5	38.7 ± 70.0	30.9 ± 44.4
95% CI	[33.0;51.5]	[34.2;49.8]	[25.1;52.3]	[25.0;36.9]
Median	48.0	44.5	46.0	27.0
Min, Max	-65, 100	-109, 100	-554, 100	-97, 100
Absolute Difference in Percent Improvement Between Active and Placebo				
Estimate (median)	11.0	11.0	12.0	-
P-Value[2]	0.0268	0.0450	0.0211	-

Source: Statistical tables: 4.2.3.1, 4.2.4.3

Each of the 17 underlying scales ranged from 0 mm = no difficulty to 100 mm = extreme difficulty for a maximum total score of 1700 mm.

[1] A negative value represents a deterioration.

[2] p-value based on a non-parametric ANCOVA.

Post-hoc Analyses:

Responder analysis: The Applicant defined treatment response based on the percentage improvement in the WOMAC pain score from baseline to the end of treatment with LOCF imputation for dropouts. Three 'levels' of response were evaluated as follows:

- 10% improvement from Baseline
- 30% improvement from Baseline
- 50% improvement from Baseline

The frequency of responders by treatment group is shown in Table 10a. For the response definition of 30% improvement in pain, the 200 mg or 300 mg Tramadol OAD groups had a higher response rate (65% each) compared to placebo (50%); the differences (p=0.0095 and 0.0104, respectively) were statistically significant after adjustment for multiplicity ($p < 0.0167$).

Using a response definition of 50% pain improvement, only the 300 mg Tramadol OAD group had a statistically significantly higher response rate than placebo (54% vs. 40%); the difference was statistically significant before (p= 0.0225) but not after multiplicity adjustment.

The 100 mg Tramadol OAD group showed no difference from placebo at each of the levels of treatment response.

Table 10a. **Applicant's Responder Analysis on WOMAC Pain Score**
(Applicant's Table 11.4.1.1.3-1)

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

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

The Applicant also evaluated the time to treatment response (Table 10b). For patients with a 30% pain improvement, the median time to response for the placebo and Tramadol 100 mg was 29 days, compared to 11 and 20 days for the 200mg and 300 mg groups, respectively. Seventy-five percent of patients in the Tramadol OAD 300 mg group had a 30% pain improvement by 33 days, compared to 50 days for the 100 mg or 200 mg groups and 94 days for the placebo group.

Table 10b. **Time to Response Analysis on WOMAC Pain Score**
(Applicant's Table 11.4.1.13-2)

Response	Treatment group	Time to improvement: 50th percentile	Time to improvement: 75th percentile	% patients with no response by day 90[1]
10% Improvement	100 mg	9 days	29 days	8.40%
	200 mg	8 days	29 days	7.40%
	300 mg	9 days	29 days	4.50%
	Placebo	12 days	32 days	14.30%
		Log-rank p-value: 0.0262		
30% Improvement	100 mg	29 days	50 days	15.80%
	200 mg	11 days	50 days	17.20%
	300 mg	20 days	33 days	8.70%
	Placebo	29 days	94 days	30.30%
		Log-rank p-value: 0.0210		
50% Improvement	100 mg	29 days	92 days	23.20%
	200 mg	31 days	-	30.70%
	300 mg	30 days	77 days	16.50%
	Placebo	50 days	99 days	41.00%
		Log-rank p-value: 0.0067		

Source: Statistical tables: 3.1, 3.1.2, 3.2, 3.2.2, 3.3, 3.3.2 (Post-hoc analyses after unblinding, June 14, 2005).
[1]Six (6) days of Titration + 84 days of Maintenance.

Continuous Responder analysis: The applicant did not perform a continuous responder analysis. The continuous responder analysis on WOMAC Pain score shown in Figure 2 was conducted by the statistical reviewer, Dr. Yongman Kim, in which the dropouts were defined as non-responders. The continuous responder curves from patients treated with Tramadol OAD (all three dose group) were not statistically separated from placebo's curve and the responder curve from the Tramadol OAD 200 mg group was cross the placebo line. The result, together with that from BOCF analysis of mean % change on WOMAC pain score, suggests that the apparent pain improvement of Tramadol OAD treatment based on LOCF analysis may not reflect a true analgesic effect.

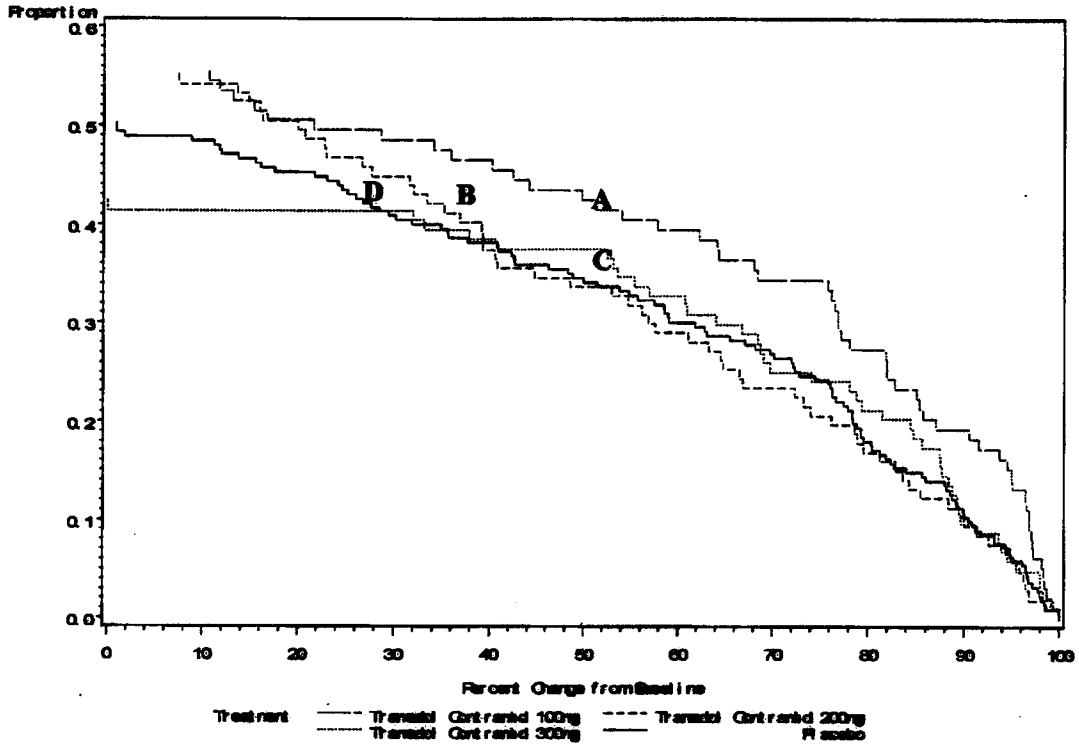


Figure 2. **Continuous Responder Analysis of WOMAC Pain score (Study MDT3-003).** The analysis was performed by a statistical reviewer based on the applicant's dataset. A= Tramadol OAD 100 mg, B=Tramadol OAD 200 mg, C=Tramadol OAD 300 mg and D=Placebo.

AUC analysis (Table 11): AUC analysis on WOMAC Pain Score was performed with and without imputation (LOCF) for missing data. The applicant reported that there was statistically significant difference only in the LOCF-imputed AUC between Tramadol OAD 300 mg and placebo. However, the detailed data processing for the AUC analysis (with and without LOCF imputation) on WOMAC Pain Score should be provided.

Repeated Measure Analysis (Table 12): The analysis was performed with 2 models: with and without baseline adjustment. The Tramadol OAD 300 mg group had statistically significantly higher percentage of pain improvement as compared to placebo (p=0.006).

Table 11. **AUC Analysis of WOMAC Pain Score**
(Adapted from the applicant's Table 11.4.1.1.4.2-1)

Method	Comparison of the AUC[1]	P-value
AUC on measured values + LOCF	100 mg vs Placebo	0.1793
	200 mg vs Placebo	0.1475
	300 mg vs Placebo	0.0089
AUC on measured values	100 mg vs Placebo	0.0780
	200 mg vs Placebo	0.3809
	300 mg vs Placebo	0.2497

Source: Statistical tables: 1.1, 1.2.1, 1.2.2 (Post-hoc analyses after unblinding, June 14, 2005).

[1]AUC calculated as 500 minus measured value adjusted for baseline, with and without replacing missing values by LOCF.

Table 12. **Repeated Measures Analysis on WOMAC Pain Score**
(Adapted from the applicant's Table 11.4.11.4.2-2)

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	100 mg vs. Placebo	6.86	-4.36	18.08	0.2308
	200 mg vs. Placebo	6.67	-4.29	17.63	0.2328
	300 mg vs. Placebo	16.30	4.69	27.91	0.0060

Source: Statistical table: 1 (Post-hoc analyses after unblinding, June 15, 2005)

[1]Repeated Measures ANOVA: if the lower bound of the 95% CI is >0 superiority of Tramadol OAD versus Placebo can be concluded on a descriptive level.

Secondary Efficacy Parameters

24-hour VAS Pain Questionnaire: Pain was rated at each visit after the last dose of tramadol or placebo: immediately after dose (morning), at lunch time, and immediately before the next dose (after 24 hours). The Applicant found no difference in pain ratings between any of the tramadol OAD groups and the placebo group, or across clinic visits.

Investigator Global Rating of Pain Relief: The percentage of patients with investigator ratings of "very effective" and "effective" pain relief at the end of treatment (LOCF imputation) was lowest for the placebo group and greatest for the Tramadol OAD 300 mg group, with slight dose-response (Table 13).

Table 13. **Investigator Global Rating of Pain Relief**

Treatment group	% patients "very effective" or "effective"	p-value*
Placebo	58%	-
Tramadol OAD 100 mg	66%	0.078
Tramadol OAD 200 mg	72%	0.0009
Tramadol OAD 300 mg	81%	<0.0001

* compared to placebo

Time-Course of WOMAC Pain and function Scores: At each of the 3 visits during the Maintenance phase (days 0, 21, and 42), patients in all 3 dose groups of Tramadol OAD had a higher percentage improvement in WOMAC Pain and physical function scores than those in the placebo group. The data analysis was based on all evaluable patients at each respective visit.

The time-response curves on WOAMC Pain score were parallel with each other among Tramadol OAD 100 mg and 300 mg and placebo, and Tramadol OAD 200 mg curve tended to cross the placebo's by the end of treatment (Figure 3), suggesting analgesic effects of Tramadol OAD tended to wear off with increasing duration of treatment.

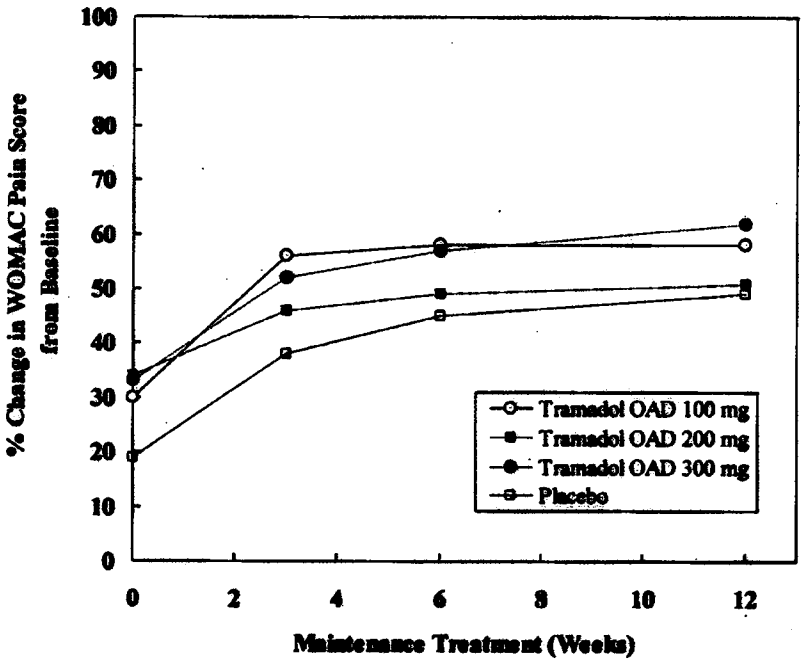


Figure 3. **Time-Course of Pain Improvement in WOMAC Pain Score in patients treated with Tramadol OAD or placebo during the 12-week maintenance dosing period. The data were extracted from the applicant's Table 14.2-13, and the analysis was based on the evaluable patients at each respective visit (without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

Safety Analysis

Extent of exposure

A total of 552 patients entered the study and received at least one dose of the study medication (325 on tramadol OAD and 227 on placebo). These patients were defined as the Safety Population.

The proportion of patients who completed the entire 12-week treatment was similar for the placebo and 100 mg and 200 mg Tramadol OAD groups (60%). The Tramadol 300 mg group had the lowest proportion of completers (47%) (Table 14):

Table 14. **Extent of Exposure: duration, dosage and number of patients**
(Applicant's Table 12.1.1-1: Disposition of Patients)

			Treatment				
			Tramadol OAD 100 mg	Tramadol OAD 200 mg	Tramadol OAD 300 mg	Placebo	Overall
Patients:			[n=196]	[n=111]	[n=108]	[n=227]	[n=552]
Who completed:	Visit 2 (Day 140)	n (%)	89 (84%)	98 (88%)	85 (79%)	199 (88%)	471 (85%)
	Visit 3 (Day 21)	n (%)	73 (69%)	80 (72%)	60 (56%)	165 (73%)	378 (68%)
	Visit 4 (Day 42)	n (%)	65 (61%)	73 (66%)	57 (53%)	143 (63%)	338 (61%)
	Visit 5 (Day 84)	n (%)	63 (59%)	66 (60%)	51 (47%)	137 (60%)	317 (57%)

Source: Statistical table: 1-1

Notes:

1. Patients were considered to have completed a visit if they had completed a WOMAC assessment and had drug accountability information for that visit.
2. The reason why 317 patients are considered to have completed instead of 311 (552 minus 241) is that 6 patients who discontinued prematurely did so close to the time that their Visit 5 was scheduled. Therefore, a WOMAC assessment and drug accountability were available for these patients.
3. Some of the patients who were discontinued due to "Patient Request" or "Investigator Initiated Discontinuation" were reclassified as "Treatment Failure" or "Adverse Events" if comments on the CRF supported this reclassification

Adverse Events (AEs)

The overall proportion of patients in the Safety Population who experienced treatment emergent adverse events (TEAEs) was

- 57% of patients on Tramadol OAD 100 mg
- 67% of patients on Tramadol OAD 200 mg
- 75% of patients on Tramadol OAD 300 mg
- 51% of patients on placebo

The incidence of TEAEs increased with dose of Tramadol OAD. There were no unexpected adverse reactions reported during the study.

Death: There was one death reported during the trial. The death occurred in a placebo-treated patient.

Serious AEs: A total of 3 serious AEs occurred during the study: 1 each in the Tramadol OAD 100 and 300-mg groups, and 1 in the placebo group. Only one of these SAES (gastritis in a patient treated with Tramadol OAD 300 mg (see below)) was likely to have been related to study drug.

1. Severe gastritis in the 300 mg group: a 70-year-old Caucasian female developed gastritis after the first dose (300 mg tramadol OAD + placebo) during titration. She was withdrawn from the study and recovered later.
2. Severe small intestinal obstruction in the 100 mg group: a 75-year-old Caucasian female developed partial small bowel obstruction 2.5 months after treatment with 100 mg Tramadol OAD. The patient had a previous history of multiple abdominal surgeries and adhesions. This AE therefore may not be related to treatment.
3. Severe lower abdominal pain in placebo group: a 73-year-old Caucasian male developed lower quadrant pain of unknown etiology 25 days after placebo treatment, withdrawn from the study and recovered on the same day. The patient had history of duodenal bleeding and colonic polyps.

The most common AEs by SOC: The most frequent categories of TEAEs occurring in ≥10% were gastrointestinal disorders (28% of patients) and nervous system disorders (24% of patients). The incidence of these AEs appeared dose related (Table 15). There were no remarkable differences in TEAEs among ages.

Table 15. **Common TEAEs by System Organ Class (% Patient)**

System Organ Class	Tramadol OAD Dose			Placebo
	100 mg	200 mg	300 mg	
Gastrointestinal disorders	26%	41%	43%	16%
Nervous system disorders	22%	30%	35%	16%

The most common AEs by PT: The TEAEs experienced by ≥ 10% patients, as shown in Table 16, were nausea, occurring in approximately 61% of all treated patients, dizziness/vertigo (47% of all patients), constipation (37% of all patients), somnolence (36%) and vomiting (24%). A dose-dependent increase in these AEs was observed. Most AEs were mild-moderate in severity.

Constipation appeared to be more frequent constipation in patients aged ≥ 65 years treated with tramadol; otherwise, there were no remarkable differences in AE frequency and type across age groups.

Time to Onset and Duration of TEAEs: The median time to onset for the most common TEAEs was within one week of treatment initiation:

- 1-7 days for onset of nausea, vomiting and dizziness/vertigo occurred earliest
- 1-3 days for onset of somnolence
- 4-7 days for onset of constipation

Table 16. **The Most Common TEAEs in the Safety Population**
(Applicant's Table 12.2.2.1-3)

	Treatment			
Preferred term	Tramadol OAD 100 mg (n=106)	Tramadol OAD 200 mg (n=111)	Tramadol OAD 300 mg (n=108)	Placebo (n=227)
Constipation	12 (11.3%)	16 (14.4%)	11 (10.2%)	3 (1.3%)
Dizziness / Vertigo	12 (11.3%)	11 (9.9%)	23 (21.3%)	11 (4.8%)
Nausea	12 (11.3%)	22 (19.8%)	28 (25.9%)	13 (5.7%)
Somnolence	9 (8.5%)	17 (15.3%)	13 (12.0%)	2 (0.9%)
Vomiting NOS	4 (3.8%)	6 (5.4%)	16 (14.8%)	1 (0.4%)

Source: Statistical table: 5.2.2.4
Notes: Percentages are of total number of patients in the respective (sub-) group.
Multiple occurrences of the same adverse event in the same patient were counted only once.

The median duration of the most common TEAEs was < 3 weeks in all treatment groups:

- 3-5 days for nausea and vomiting
- 3-7 days for dizziness/vertigo
- 12-26 days for somnolence (but 3 days on placebo)
- 12-16 days for constipation (but 51 days on placebo)

AE-related Dropouts: About 21% (67 of 325) of patients in the tramadol groups and 9% of placebo patients terminated the study early due to an AE. There was a dose-dependent increase in dropouts: 12% of the Tramadol OAD 100-mg patients, 16% of the 200-mg patients, and 33% of the 300 mg patients. Most of the AEs that led to discontinuation were mild to moderate in intensity (Table 17). The majority of the AEs that led to discontinuation were the commonly occurring AEs (nausea, constipation, etc.).

Table 17. **AE-related Dropouts**
(Data are extracted from the applicant's Tables 12.1.1-1)

Tramadol Treatment	AE-related Dropouts	AE Intensity		
		Mild	Moderate	Severe
100 mg n=106	13 (12.3%)	1	10	2
200 mg n=111	18 (16.2%)	2	12	4
300 mg n=108	36 (33.3%)	7	22	7
Placebo n=227	21 (9.3%)	4	8	9

Post-treatment AEs (PTAEs)

Patients were contacted by 2 telephone follow-up calls on days 4 and 7 after the last dose to assess specific symptoms associated with withdrawal and dependence as well as any AEs (Table 18). Of the 325 patients randomized to Tramadol OAD groups, 88 (27%) experienced at least 1 PTAE.

Most common PTAEs: sleep disturbance (23% at 200 mg group and 15% at 300 mg) followed by diarrhea, emotional disturbance, nausea, sweating increase, abdominal pain and tremor/rigors (5% in the 200 mg, 4% in the 300 mg and 0 in placebo)

Dose-relation: the symptoms decreased frequency from high dose to low dose: 200 mg > 300 mg > 100 mg > placebo.

Time to Onset: Most PTAEs occurred in the first 3 days after end of treatment, and were reported at the first phone follow-up. If the same patients were contacted at the 2nd follow-up, this would suggest that the withdrawal/dependence symptom appear to be reversible.

Intensity of PTAEs: the sleep disturbance and sweating increase were reported as severe in some patients. All others were mild-moderate.

- Severe sleep disturbance: 22% (2 of 9) in the 100mg, 23% (6 of 26) in the 200 mg, 19% (3 of 16) in the 300 mg and 0 in placebo.
- Severe "sweating increased" reported 1/3 in the 100 mg, 0/7 in the 200 mg, 1/5 in the 300 mg and 0 in placebo

Drug-relation: The majority of PTAEs were considered "related" or "possibly related" to treatment.

Table 18. **Post-treatment AEs and Withdrawal/Dependence Symptoms**
(Adapted from the applicant's Table 12.2.2.7-1)

	Treatment during double-blind phase			
Preferred term	Tramadol OAD 100 mg (n=186)	Tramadol OAD 200 mg (n=111)	Tramadol OAD 300 mg (n=108)	Placebo (n=227)
Emotional disturbance[1]	2 (1.9%)	11 (9.9%)	2 (1.9%)	1 (0.4%)
Sleep disturbances	9 (8.5%)	26 (23.4%)	16 (14.8%)	4 (1.8%)
Visual or auditory disturbances	-	3 (2.7%)	-	-
Tremor/Rigors	-	5 (4.5%)	4 (3.7%)	-
Dizziness	2 (1.9%)	6 (5.4%)	3 (2.8%)	2 (0.9%)
Nausea	4 (3.8%)	10 (9.0%)	7 (6.5%)	3 (1.3%)
Vomiting NOS	-	3 (2.7%)	2 (1.9%)	-
Diarrhea NOS	5 (4.7%)	12 (10.8%)	6 (5.6%)	2 (0.9%)
Abdominal pain NOS	1 (0.5%)	8 (7.2%)	3 (2.8%)	-
Sweating increased	3 (2.8%)	7 (6.3%)	5 (4.6%)	1 (0.4%)

Source: Statistical table: 5.2.19.1 (August 24, 2005; September 26, 2005).

[1]Agitation, Irritability, Other.

Notes: 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.

Clinical Laboratory Evaluation

A total of 21 abnormal laboratory values were reported in 12 patients:

Four patients (3 on placebo and 1 on 100 mg tramadol) experienced abnormal values which were considered possibly related to the study medication: increased blood amylase, blood alkaline phosphatase and increased Gamma-glutamyltransferase.
Reviewer comment: Information on the magnitude (xUNL) and resolution of these laboratory changes was not provided in the report.

Vital Signs and Physical Examination

There were no remarkable changes in vital signs (Respiratory rate, blood pressure, temperature, and pulse) body weight or post study physical examination for patients in all treatment groups

SUMMARY AND CONCLUSION

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

Safety: All 552 patients enrolled into the study received at least one dose of the study medication (325 on tramadol OAD and 227 on placebo); 180 (55% of 325 patients) completed the 12-week treatment of Tramadol OAD (62 on 100 mg, 66 on 200 mg and 51 on 300 mg) and 137 (60% of 227 patients) complete the study in placebo group.

Overall AEs from this study appeared to be comparable in profile, intensity and frequency to the approved tramadol products (Ultram IR and ER), and similar to those observed in study MDT3-002.

- ***SAEs:*** One fatal AE was reported during the study, which was a fatal MI in the placebo group and considered "not related to treatment". There were three other SAEs in 3 patients, including one severe gastritis in the 300 mg group, one severe lower abdominal pain in placebo and one severe small intestinal obstruction in the 100 mg. All the SAEs were recovered.

- ***The most common AEs*** were in gastrointestinal and nervous systems, including Nausea, dizziness/vertigo, constipation and vomiting with intensity from mild to moderate. All AEs showed dose-dependent increase from 0 (placebo), 100, 200 to 300 mg tramadol OAD.

- ***AE-related dropouts:*** About 21% (67 of 325) of patients in the tramadol OAD groups terminated the study early due to an AE, which was dose-dependent increased; most of these AEs were drug-related, mild-moderated in the intensity, and the expected common AEs.

- ***The concomitant medications*** were balanced among tramadol OAD and placebo groups. The potential drug-drug interaction agents, such as SSRIs, TCAs and MAOIs, were excluded during the subject selection. No seizure and other AEs related to the potential drug-drug interactions were reported.

- ***Overdose:*** There were no overdose cases reported; the study was designed as "fixed dose" during the 12-week Maintenance phase.

- ***Dependence and Withdrawal Symptom:*** Based on the phone follow-up at 4 and 7 days after the last dose, about 27% of patients in the tramadol OAD groups (n=325) experienced at least 1 post-treatment AEs; the majority of AEs were considered "related to treatment" with mild-moderate and onset in the first 3 days. The common AEs (from high to low frequency) were sleep disturbance, diarrhea, emotional disturbance, nausea, sweating increase, abdominal pain and tremor/rigors. The patients in the 200 mg group had the highest incidence of the AEs, followed by 300 mg, 100 mg and placebo. However, the compliance to the post-treatment follow-up was not reported.

10.1.3 Study MDT3-005

TITLE: A Two-arm Study Comparing the Analgesic Efficacy and Safety of Tramadol Contramid OAD versus Placebo for the Treatment of Pain due to Osteoarthritis

Study Period: October 18, 2004 to January 06, 2006
CRO: [redacted] b(4)

OBJECTIVES

Primary: To show superior analgesic efficacy of Tramadol Contramid OAD against placebo

Secondary: To compare the safety and benefit of Tramadol OAD vs. placebo

STUDY LOCATION
A total of 108 centers: 67 in USA, 18 in France, 14 in Canada and 9 in Romania

STUDY DESIGN AND PROCEDURE

The study was designed as a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group study.

The study population was patients aged 40-80 years old with confirmed, symptomatic OA of the knee who had regular (OA) pain medications (NSAIDs or tramadol) with analgesic response during the 30 days prior to enrollment. A total of 550 patients were planned for enrollment and 465 patients were expected to enter the randomized Double-blind phase at the randomization ratio of 2:1 (Tramadol OAD vs. Placebo).

The trial consisted of two phases: the open-label and the double-blind (Figure 1):

Open-label phase: 4 weeks (after 3-14 days of Screening for pre-study analgesic washout and eligibility assessment):

1) Run-in: dose escalation over 14 days: 100 mg x3 days, 200 mg x5 days and 300 mg x6 days to reach an Optimum dose 200 or 300 mg; patients who could not tolerate 200 mg exited the study. [*Tablets of three dose strengths were used*].
2) Taper: dose down-titration over 7 days: for Optimum Dose 300-mg: 200 mg x 4 days then 100 mg x3 days; for Optimum Dose 200-mg: 100 mg x 7 days
3) Wash-out: over 7 days; acetaminophen 500 mg tid for 5 days followed by 2 days without treatment; at the end of Washout (Visit 4, W7), patients were randomized by centralized allocation to Tramadol OAD or Placebo for the double-blind phase

Criteria for a patient to enter the Double-blind phase were:

- Pain intensity on NRS $\geq$ 4 at end of Wash-out, with a total increase of $\geq$ 2 as compared to the previous visit (end of run-in)
- Not taken any prohibited medication during the open-label period

Double-blind period: 14 weeks divided into 2 periods

Titration Period: 2 weeks, using the same dosing schedule as in Run-in period of Open-label phase; except with placebo treatment incorporated.

- Patients could decrease dose from 300 mg to 200 mg (Tramadol OAD or placebo) due to lack of tolerability, and stay at 200 mg for the remaining titration period
- Patient could not tolerate 100 mg or 200 mg (tramadol or placebo) exited the study.

Maintenance Period: Patients were treated for 12 weeks at their final optimum dose established from the Titration: 200 mg or 300 mg of Tramadol OAD or placebo.

The patients had nine visits and seven phone contacts during the study (Table 1):

Four visits and three phone contacts were during the Open-label phase:

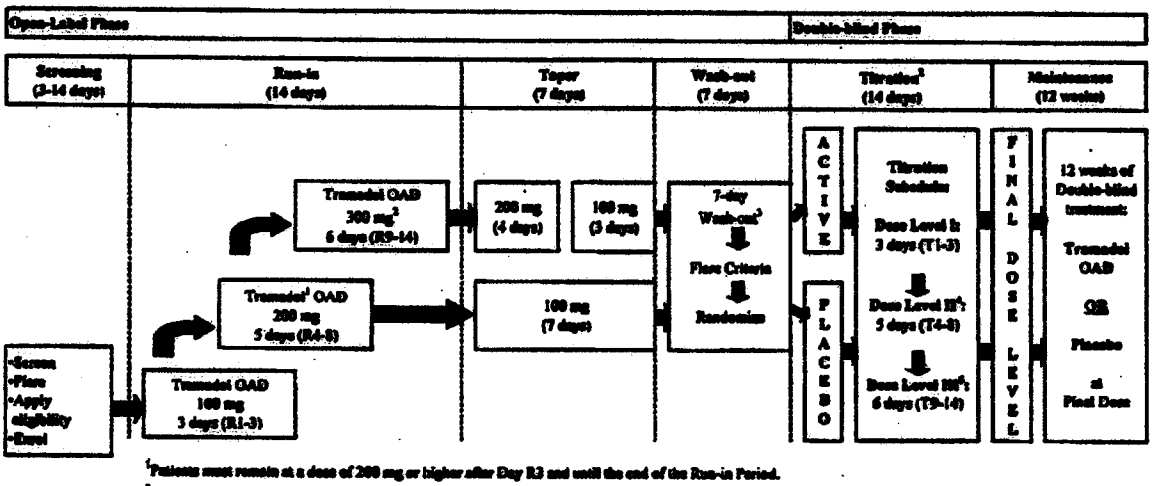
1) Screening: Visit 1 (SX, evaluation) and Visit 2 (S0, verify eligibility and washout)
2) Run-in: Visit 3 (at end of 14-day run-in); 3 telephone contacts during the 14-day
3) Washout: Visit 4 (at end of 7-day washout)
4) Taper: one phone contact at day 3 (middle of 7-day taper)

During the Double-blind phase: five visits and three phone contacts

1) Titration: Visit 5 (at end of 14-day titration) and 3 phone contacts during the 14-day titration period
2) Maintenance: Visit 6 (M21), Visit 7 (M42), Visit 8 (M63) and Visit 9 (M84, end of treatment); "M21" means day 21 after starting Double-blind phase.

The primary efficacy endpoint was the group mean pain intensity on 11-point numerical scale (PI-NRS) at end of treatment (week 12). The secondary endpoints included the PI-NRS at Week 6, PI-NRS stratified by dose at Week 12, WOMAC Pain and Physical Function subscales at Week 12, the Patient and Physician Global Impression of Change at Week 12, time to response and time to early discontinuation due to lack of efficacy.

Safety assessment included vital signs, physical examination, clinical laboratory and concomitant medications



[1] Patients must remain at a dose of 200 mg or higher after Day R3 and until the end of the Run-in Period.
[2] Patients who reach a dose of 300 mg may decrease their dose once to 200 mg until Day R11 of the Run-in Period.
[3] Patients may take acetaminophen 500 mg three-times daily for the first 5 days of the Wash-out Period (Days W1-5) but may not take any acetaminophen after Day W5.
[4] Patients must remain at Dose Level II or higher after day T3 and for the rest of the Study.
[5] Patients who reach Dose Level III may decrease once to Dose Level II up until Day T11 of the Titration Period.

Figure 1. **Overview of the study design**

Appears This Way
On Original

Table 1. **Schedule of Evaluation**
(Applicant's Table 9.5.1.1-1)

Phase	Open-Label						Double-Blind						
PERIOD	Screening		Run-in	Taper	Wash-out	Open-Label Early Term.	Titration	Maintenance					Discont. Visit[5]
Day	S X[1]	S 0	R 14	Tp 1-7	W 7		T 1-13	T 14	M 21	M 42	M 63	M 84	
Visit	1	2	3		4			5	6	7	8	9	
Informed Consent	X												
Discontinue Analgesic Medications	X	V		X									
Physical Activity Level Rating	X	X	X		X	X		X	X	X	X	X	X
Pain Criteria and Other Eligibility Criteria	X	X,V			X,V								
Hematology: (RBC, Hgb, hematocrit, Plt, WBC & Differential, ESR)	X[2]	V				X						X	X
Biochemistry: (Protein, GGT, LDH, NA, K, Cl, Glucose, BUN, AST, ALT, cholesterol, Albumin, BUN, Ca, Creatinine, Uric Acid, Alk Phos, amylase)	X[2]	V				X						X	X
Urine Pregnancy Test	X[2]	V				X				X		X	X
Urinalysis[3] (pH, Spec. Grav., Glucose, Protein, Ketones, blood, sediment)	X[2]	V				X						X	X
Physical Exam	X	V				X						X	X
Calculate BMI (Height and Weight)	X	V											
Vital Signs (BP, Pulse, Respirations, Temperature)	X	X	X		X	X		X	X	X	X	X	X
Medical History & Concurrent Medications	X	V											
Arthroscopy or Radiology Report (Within 5 years of Visit 1)	X	V											
Pain and Functional Scales[4] (NRS, WOMAC)	X	X,V	X		X,V	X		X	X	X	X	X	X
Global Ratings (Patient and Physician)									X	X	X	X	X
Patient indicates opinion regarding which treatment s/he received (Active or Placebo)												X	X
Telephone Contact (Day R4, R5 and R10; Tp3, Day T4, T8, T10)			X	X			X						
Wash-out: Open-label Study Med. (Days W1-7)					X								
Randomization (Day W7)					X								
Glucosamine Medication		X	X		X			X	X	X	X		
Adverse Events			X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds.			X	X	X	X	X	X	X	X	X	X	X
Recent Used and Unused Medications			X		X	X		X	X	X	X	X	X
Record of Death[6]						X							X

X- Perform evaluation, V- verify that patient meets eligibility criteria related to these evaluations

[1] Days SX to S0 encompass the Period between signing of consent and enrollment in the study. The length of this time period may vary depending upon the required Wash-out time and time to obtain eligibility information for an individual patient but must not last longer than 14 days.

[2] These evaluations may be performed within 14 days prior to Visit 2 (Day S0), however, the results must be available and verified against inclusion criteria prior to enrollment at Visit 2 (S0).

[3] Sediment Microscopy is only to be done if indicated by dipstick urinalysis

[4] Open-label Early Termination Visit (OLET): If the patient stops treatment and exits the Open-Label Phase (Run-in, Taper or Wash-out Periods), the patient must be seen for an OLET Visit within 2 days of the last dose of treatment and may not receive other treatment for pain or OA prior to the Visit.

[5] Discontinuation: If the patient discontinues from the Double-Blind Phase (Titration or Maintenance Period) prior to Day M 84, the patient must be seen for a Discontinuation Visit within 2 days of the last dose of study medication and may not receive other treatment for pain or OA prior to the Visit.

[6] If the patient dies at any time during the study a Record of Death Form must be completed.

Subject Selection

Inclusion criteria

1) Males or females, 40 - 80 years of age
2) Moderate to severe OA of the knee according to the ACR criteria:
   - Current knee pain.
   - < 30 minutes of morning stiffness with or without crepitus on active motion
   - Confirmation by either arthroscopy or radiology report (X-rays showing osteophytes, joint space narrowing or subchondral sclerosis) within five years prior to entry into the study
3) Pain severity at Visit 3 (Day S0):
   - The 11-point NRS ≥ 4
   - A total increase ≥ 2 on the 11-point NRS compared to Visit 1 (Day SX)
4) History of exposure to pain treatment for the knee OA with NSAIDs, COX II inhibitors or Tramadol and taking one of the above medications on a regular basis in the 30 days prior to Visit 2 (S0)
5) ESR < 40 mm/hr
6) BMI < 38

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) On the target knee, history of bursitis, pain in the ipsilateral hip, meniscal tear (within the last 12 month), cartilage reconstruction procedure, and therapeutic arthroscopy procedure (within the last 12 months)
4) Treatment within the last 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.
5) A history of seizure disorder other than infantile febrile seizures.
6) Major illness requiring hospitalization during the 3 months before commencement of the screening period.
7) Unwillingness to stop taking pain medication other than the study medication (for arthritis or other types of pain) or unwillingness to stop taking other medications for the treatment of OA
8) Previous failure or discontinuation (due to AEs) of tramadol HCl therapy.
9) Treatment with another investigational agent within the last 30 days.
10) Corticosteroid injections in the target knee within the previous 3 months or viscous injections in the target knee within the previous 6 months.
11) Use of other opioids (e.g. codeine, oxycodone, hydromorphone, etc.) for treatment of OA or other chronic conditions.

12) Previous or current opioid dependence.
13) Current or past substance abuse or dependence, other than nicotine
14) Bowel disease causing malabsorption.
15) Pregnancy or lactating or childbearing potential and unwilling to utilize a medically approved method of contraception during participation in this clinical trial.
16) Significant liver disease (defined as active hepatitis or liver enzymes > 3x ULN)
17) Significant renal disease (defined as creatinine clearance < 30 mL/min)
18) Allergy or an adverse reaction to Tramadol or any structurally similar drugs (e.g. opiates)
19) Any other condition that, in the opinion of the Investigators, would have adversely affected the patient's ability to complete the study or its measures.

Rescue medication

No rescue medication for pain due to OA was permitted in any treatment arm or at any time during the study. Medications for chronic pain conditions were not permitted. Pain medications for acute pain were allowed but with the following conditions:

- Only short-acting analgesics (e.g. acetaminophen, *dosage was not specified*)
- Only for up to three consecutive days
- Stop this analgesic at least 3 days before any study visit; if not, the visit was to be delayed by 3-7 days
- Carefully record name, dose duration and indication in the source documents and CRF.
- Patients with intolerable pain could be withdrawn.

Prior and Concomitant Therapy

- Patient could take Nytol (Valerian) for sleep disturbances.
- Patients could not take sedative hypnotics, topical preparations or medications, anesthetics or muscle relaxants.
- Patients could not start new physical therapies for their knees during the study; those under physical therapy had to be on a stable regimen for ≥ 3 months prior to Visit 1 (screening).
- Herbal remedies such as glucosamine sulphate and chondroitin sulphate were to be washed out (*but period was not specified*) and not taken during the trial.
- Patients under low-dose ASA for cardioprotection with stable dose >3 months were to continue at the same dose.
- Symptomatic medications for tramadol-associated AEs: dimenhydrinate for nausea and psyllium hydrophilic mucilloids, docusate sodium, sennosides for constipation. Any medications used to treat AEs were collected in CRFs.

[Reviewer's Comments: The applicant did not specify the waiting period prior to entering the study for patients with previous intra-articular corticosteroid and/or viscous injections, which would confound the analgesia outcome of Tramadol OAD.]

Treatment Compliance:

The tablet counts were recorded from Visits 3-9 (from the Run-in period during Open-label phase to end of Double-blind phase.

Efficacy Measures

Pain Intensity NRS (PI-NRS)

At each study visit, patients were asked to rate their pain on an 11-point numerical rating scale (NRS): 0 = no pain and 10 = worst possible pain.

Patient's Global Impression of Change:

Patient's impression on the effect of the treatment on pain and side effects using a 7-point categorical scale (1 = very much improved and 7 = very much worse).

Physician's Global Impression of Change:

Investigator's overall impression of the change in the patient's status from the beginning of the study to each of 4 visits during Maintenance period or at the Open-label early termination or discontinuation visits without consulting with the patient or reviewing previous ratings, based on the 7-point categorical scale

WOMAC Pain and Physical Function Subscales: using 5-point Likert scale (0 = none, 1 = slight, 3 = severe, 4 = extreme)

[Reviewer's comments: The protocol did not specify the specific time when patients were to take their dose on the visit day relative to the assessments of all efficacy parameters. The timing of the dose very likely impacted the efficacy outcome due to low plasma level of Tramadol OAD in the morning.

The applicant describes use of a 5-point Likert scale for the WOMAC Pain Subscale. However, a 100-mm VASis the commonly used for measure for the WOMAC index.]

Safety Measures

Physical examination:

- PE including specific examination of the knees at Visit 2 (the 2nd Screening visit), open-label early termination visit, visit 9 (week 12 of Maintenance period)
- Body height at Visit 2 and body weight at Visit 1 and Visit 9 to determine BMI [*the applicant did not state why to take the body weight at 2 different visits*]

Vital signs:

- At all visits and early termination visits
- Inspection, palpation and mobilization of the knee at baseline and the end of study
- Body weight at baseline and the end of study and height at baseline to determine BMI

Clinical laboratory

- At Visit 1 and Visit 9 or early termination during the Open-label or the Double-blind phases)
- Hematology, biochemistry, urinalysis and pregnancy test (also at Visit 7)
- Any clinically relevant changes occurring during the study were recorded on CRF

AE Monitoring throughout the duration of the study:

Other Measures

- Physical activity level rating scale:
  - Assessed at all visits (Visits 1-9) or at early termination visits
  - Rated using a 5-point scale (1 = no active to 5 = extremely active)
- Patient indication of treatment: Patients were asked to complete a Case Report Form indicating their opinion regarding which treatment they received after randomization (active or placebo).

Statistical Analysis

The Statistical Analysis Plan of this trial was submitted for SPA review in November 2004, which was generally acceptable, as indicated in the Division's letter to the applicant dated on December 6, 2004. Refer to the Statistician's review for detail about the final statistical analysis methodology.

Primary efficacy analysis

- The PI-NSR score at the end of study (Visit 9, or Week 12) with the 2-side superiority hypotheses:
  - H0: $\mu_t = \mu_p$ and H1: $\mu_t \neq \mu_p$; where μ_t and μ_p are the PI score at individual last visit for Tramadol OAD and for Placebo, respectively.
  - The estimated treatment difference and 95% CI for the difference were derived from an ANCOVA with "treatment" as a factor and the PI-NRS baseline as the covariate
- Responder was defined as a PI-NRS decrease $\geq$ 2 points from baseline (Visit 4, at end of the Washout period during Open-label phase), but it was changed to *post hoc* "responder curve" analysis as requested by the division.
- 2-tail/α=0.05 used for all tests; no α-adjustment applied to the primary endpoint (due to one primary efficacy criterion); there was also no multiplicity α-adjustment on the two tested dose levels (because of separate comparisons to placebo).
- Time to response was defined as the number of days between starting the Double-blind treatment and becoming a responder which was analyzed by Kaplan-Meier survival estimates with long-rank test.
- Full analysis population (FA) with LOCF imputation for missing data due to dropouts was used for primary efficacy analysis; the FA population was defined as all randomized patients who received at least one dose of the study medication regardless of the status of the post-dosing assessment; for primary efficacy analysis.

- Alternative methods to handle the missing data due to early dropouts were use to test the sensitivity of primary LOCF method, including BOCF, Repeated Measures (with LOCF) and Time-Weighted Average
- No imputation methods applied to the secondary efficacy analysis using the PP population
- Statistical models were not adjusted for center effects due to too few patients enrolled per center.

Interim Analysis:

- An administrative interim analysis was performed when 175 patients had completed 6 weeks of the Maintenance period to verify the assumptions regarding sample size determination (SD and drop-out rates).
- There was no α-adjustment on the interim analysis.

Safety Evaluation

- Based on Safety Population, defined as all patients who received at least one dose of the study medication
- The number of days exposed to treatment:
  - Open-label Phase: one plus date of last dose minus date of first dose
  - Double-blind phase: one plus data of last dose minus data of first dose minus number of days during which a patients stopped the study medication
- Safety data from the Open-label and double-blind phases were summarized separately, and stratified by treatment group.
- TEAEs were summarized as number and % of AES in exposed patients, duration/time to onset of AEs, including abnormal lab values, with Chi-Squared test or Fisher's exact test.

Sample size

A total of 550 patients were planned for enrollment and 465 patients were expected to enter the randomized Double-blind phase at the randomization ratio of 2:1 (Tramadol OAD vs. Placebo). The sample size calculation was based on the following assumptions:

- Minimal between-group difference in the PI-NRS score = 1 (considered clinically significant)
- SD = 2.25
- Power = 90%
- Overall α = 0.05 (adjustment for 1 extra comparison)
- Expected dropout rate: 15% during the Run-in Period (Open-label Phase), 5% during the Titration Period and 25% during the Maintenance Period.

The actual enrollment was 1028 patients (see below Amendment #3)

Protocol Amendment

- Amendment #1: dated Oct-7-2004, PE could be done by certified PA or Nurse practitioner instead of a medical doctor.
- Amendment #2: dated on Dec-15-2004, increase the maximum BMI from 35 to 37.
- Amendment #3: dated on June-08-2005, with the following two amendments:

- Increase sample size from 550 to 800 patients (thus increased the study centers) based in a pre-planned administrative interim analysis. However, the actual enrollment was 1028 patients in the Open-label phase because the applicant permitted all patients with analgesic-washout being enrolled due to "ethical" concern.
- Permit subjects to be consented in language other than those in the original protocol.

Change in Planned Analyses

Following changes were discussed and documented prior to unblinding:

- Subgroup analysis as requested by the division (Dec 6, 2004): 200 mg Tramadol OAD vs. placebo and 300 mg Tramadol OAD vs. placebo without multiplicity adjustment in addition to Tramadol OAD overall response (200 and 300 mg) vs. placebo as originally planned.
- Sensitivity analysis for imputation for missing data as requested by the division: time-weighted average, repeated measure with LOCHF, BOCF.
- Change in definition of responder: using responder curve with PI changes from ≥ 1 up to ≥ 5, instead of ≥ 2 points change from baseline in average pain.

RESULTS

Subject Disposition

Open-label Phase:
A total of 1028 patients were enrolled during the Open-label phase and 1027 entered the Run-in Period; 646 patients completed the Open-label Phase (dropout rate: 37% of 1028) and were randomized into the Double-blind Phase.

The main reasons for dropout during the Open-label phase were adverse events, followed by patient request and protocol deviation; only a small proportion of dropouts was due to lack of efficacy (likely because of flexible dosing) (Table 2). Across subgroups, slightly more Caucasian (41%) than non-Caucasian (30%) dropped out; otherwise, the dropout rates were similar across group

[*The applicant did not compare demographic characteristics between the dropouts and the non-dropouts; the comparison would be valuable to assess if the patients enriched through the open-label treatment were similar to the target population.*]

Double-blind Phase:
A total of 646 patients who completed the Open-label Phase were randomized at a ratio of 2:1 into Tramadol OAD (n=432) and Placebo (n=214) groups followed by 2-week titration and 12-week maintenance treatment.

The overall dropout rate during the Double-blind Phase was 24% (Table 2). About 9% of patients dropped out during the Titration period and 23% during the 12-week maintenance

period. The main reasons for dropout were AEs (42% on Tramadol OAD vs. 22% on Placebo) and treatment failure (34% on Tramadol OAD and 49% on Placebo) (Table 2).