CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-692

MEDICAL REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	September 8, 2005
DRUG:	Ralivia ER, (tramadol hydrochloride extended-release tablets, 100, 200- and 300-mg)
NDA:	21-692
NDA Code:	Type 3S NDA
SPONSOR:	Biovail Laboratories, Inc.
INDICATION:	For the treatment of moderate to moderately severe around-the-clock pain requiring treatment for an extended period of time

Biovail Laboratories, Inc. (Biovail) originally submitted their application for Ralivia ER on December 30, 2003. The reference listed drug (RLD) for this 505(b)(2) application was Ultram. The sponsor noted that there were fourteen generic immediate-release tramadol produets currently on the market at that time. Ralivia ER was formulated with the intention of providing once-daily dosing. The Division took an Approvable action on this application on October 29, 2004. The approvable letter cites the following deficiencies:

1. "The proposed indication...is not supported by the data..."

This determination was based on the fact that the indication, "...for the treatment of moderate to moderately severe pain," was not supported by the data in the application. This assessment was noted to be due to the fact that the application did not contain data from clinical trials that were similar to the trials submitted in support of the approved referenced listed drug product Ultram, and that Ralivia ER was not bioequivalent to Ultram. Additionally, the Division noted that the

pivotal studies submitted in support of efficacy of Ralivia ER did not actually demonstrate a treatment effect when appropriate methodologies were used to impute missing data in the analyses. Additionally, the pharmacokinetic profile of Ralivia ER suggested that the product would not be appropriate for the treatment of acute pain, which is included in the indication for the RLD.

2. The analyses of the safety data submitted in the application were inadequate.

All events were not included in the ISS, and an apparent increase in serious thromboembolic events was noted in the flexible-dosing groups compared to the placebo groups in the flexible-dosing trials.

In order to resolve these deficiencies, the letter states that the sponsor must:

1. Conduct an additional clinical trial in osteoarthritis or chronic low back pain patients that demonstrates efficacy and that supports the doses proposed in their draft product insert.

2. Provide additional information regarding the apparent increased thromboembolic events

3. Submit an appropriately revised package insert.

The sponsor has responded to the approvable letter with updated safety data and a rationale for why an additional clinical study to evaluate efficacy should not be necessary.

Efficacy:

Four clinical trials were submitted in the original application in support of the efficacy of Ralivia ER.

Studies B00.CT3.014 (14) and B00.CT3.015 (15) were double-blind, randomized, placebo-controlled, 12-week trials of Ralivia ER in chronic low back pain and osteoarthritis of the knee, respectively. In Study 14, subjects were titrated to 300 mg of study drug per day during a run-in period, and those without adequate pain relief, or with intolerable side effects, were discontinued. The remaining subjects were then randomized to placebo, or Ralivia ER 200 mg or 300 mg. The sponsor's efficacy analysis for the primary outcome measure, average change in pain intensity using a VAS scale and employing a last-observation-carried-forward (LOCF) imputation methodology for missing data, demonstrated a statistically significant treatment effect for the 300-mg dose ($p = 0.009$) and a treatment effect that approached significance ($p = 0.052$) for the 200-mg dose. An analysis using a landmark outcome, change from baseline to endpoint, again demonstrate a statistically significant treatment effect for the 300-mg dose, but the results for the 200-mg dose were not statistically significant ($p=0.197$). The Division

reanalyzed the data using a baseline-observation-carried-forward (BOCF) imputation methodology. Neither the change over the 12-week period, nor the change at 12 weeks compared to baseline demonstrated a statistically significant treatment effect with these more conservative, and more appropriate analyses.

In Study 15, subjects were randomized to treatment with Ralivia ER or placebo and were permitted to titrate to a dose ranging from 200 to 400 mg per day. Patients not tolerating at least 200 mg per day were discontinued from the study. The sponsors analyses, employing a LOCF imputation methodology for missing data, demonstrated a statistically significant treatment effect ($p < 0.001$) for average change in pain intensity using both a time-weighted analysis from baseline over the 12 weeks and a landmark analysis of change from baseline to endpoint, employing a VAS scale. The Division reanalyzed the data using the more conservative BOCF imputation methodology and found that only the time-weighted analysis retained statistical significance ($p = 0.021$).

Study B02.CT3.021 (21) was a randomized, double-blind, placebo- and active-controlled, dose-ranging, 12-week trial in patients with osteoarthritis of the knee and/or hip. Subjects were randomized to Ralivia ER 100, 200, or 300 mg, or celecoxib 200 mg or placebo. The sponsor's analysis of the primary outcome measure, change in pain from baseline to endpoint employing the WOMAC pain subscale and a LOCF imputation methodology for missing data demonstrated a statistically significant treatment effect celecoxib ($p = 0.004$). The effect for Ralivia ER 300 mg approached statistical significance ($p = 0.058$). The Division's analysis employing the BOCF imputation methodology demonstrated a statistically significant treatment effect only for celecoxib.

Study B02.CT3.023 (23) was a randomized, double-blind, placebo-controlled, 12-week trial in patients with osteoarthritis of the knee or hip. Subjects were randomized to Ralivia ER 100, 200, 300 or 400 mg, or placebo. The sponsor's analysis of the primary outcome measure, change in pain from baseline to endpoint employing the WOMAC pain subscale and a LOCF imputation methodology for missing data demonstrated a statistically significant treatment effect for all four Ralivia dose groups (p-values ranged from 0.002 to 0.012). The Division's analysis employing the BOCF imputation methodology demonstrated a statistically significant treatment effect only for the Ralivia ER 100-mg and 200-mg doses ($p = 0.013$ and 0.007, respectively).

The sponsor submitted a number of new analyses of these studies in their response to the approvable letter. They proposed that these analyses demonstrated clear evidence of efficacy for their product, and that no new studies should be necessary.

***Clinical Safety*:**

The sponsor submitted a complete reanalysis of the safety data. This reanalysis was reviewed by Lourdes Villalba, M.D. Dr. Villalba has concluded that the safety profile of Ralivia ER is typical for an opioid analgesic, and that there are no outstanding safety

concerns that would preclude approval of the product. Based on my own reading of the numerous safety reviews for this product, as well as the secondary and tertiary reviews, I have been unable to find a basis for the concern regarding an increased risk of cardiothrombotic events that was noted in the approvable letter.

Biopharmaceutics:

The review team expressed concern in the first review cycle that the pharmacokinetic profile of Ralivia ER would not allow for an appropriately early onset of action

of their response to the approvable letter.

An appropriate IV/IVC model was also requested in the approvable letter. While the Division and the sponsor have still not reached agreement on this model, Drs. Patrick Marroum and Lei Zhang have provided reviews indicating that the product may be approved without this agreement, as long as the sponsor agrees to tighten the dissolution specifications to an appropriate degree in the interim.

Discussion:

The sponsor has provided adequate evidence of efficacy in support of their marketing application for Ralivia ER. I disagree with the clinical review team on this issue. Drs. Villalba and Schiffenbauer's filing memo (for the original application) dated December 31, 2003, concludes that "At no time did the DAAODP agree to file an application for the treatment of moderate to moderately severe pain, or any other than [sic] the signs and symptoms of OA." They recommended that the application should not be filed. Clearly, the application was filed. Nevertheless, I think it is important to clarify that the Agency need not reach agreement with a sponsor on the indication for a new drug prior to filing of that application. This concern on the part of the review team was more appropriately dealt with during the review of the application. Thus, their recommendation that the application not be filed was inappropriate, and would not have been supported by current regulations or practices.

Dr. Schiffenbauer's secondary review (page 2) of the response to the approvable letter states that, "This reviewer believes that the response should not have been considered nor filed as a complete response because the Division requested additional studies, and these were not provided." However, the sponsor's reanalysis and contention that the available studies provide adequate evidence of efficacy does, indeed, constitute a complete response. The adequacy of their proposal and data to allow for a determination of efficacy was a matter for review.

On page 4 of his review, Dr. Schiffenbauer states:

> Although "treatment of chronic pain" is the claim that the Division would grant, this reviewer believes that it is not an appropriate indication to be granted, based on the data in the NDA submission. Tramadol has demonstrated at best, marginal efficacy for only osteoarthritis and has not provided any evidence of efficacy for other forms of chronic pain. Indeed, it is unlikely that tramadol would be effective in chronic pain syndromes such as neuropathic pain or pain associated with malignancy or fibromyalgia (although admittedly this has not been tested). The fact that this is a 505b2 submission does not bear on the discussion since the indication for Ralivia is not the same as the original Ultram indication. This afforded the Division the opportunity to request additional efficacy studies for this new formulation. If any claim is appropriate here, it should be for the treatment of the signs and symptoms of osteoarthritis. However, the efficacy of Ralivia ER for the treatment of OA has not been robustly demonstrated. One flexible dose study (015) was successful (interpretation of flexible dose studies is problematic interms of appropriate dosing) but two well designed trials (021 and 023) failed to show adequate evidence of efficacy for this indication, at least based on the use of 3 co-primary endpoints. Even if pain is the only endpoint required for approval (for the indication of treats moderate to moderately severe chronic pain), only study 023 is positive using LOCF, but the results are not supported by a number of sensitivity analyses (see below section 2.3).

Dr. Schiffenbauer's contention that the fact that this is a 505(b)(2) application "does not bear" on the discussion of the indication, since it is different from that of the RLD, is incorrect. The Agency previously determined that tramadol is a safe and effective analgesic when used appropriately. The only reason that new clinical data should have been requested was to assure that this new extended-release formulation would continue to provide effective analgesia, and would not be associated with any unexpected side effects. The very fact that this is a 505(b)(2) application allows the sponsor to rely on the Agency's previous determination regarding the drug substance. The change in indication would only require further clinical support if there was reason to believe that an analgesic of this type would not work in the population for which it was proposed, or that it might be unsafe in that population. Neither of these are the case for tramadol in the chronic pain population. The fact that the product might not work in one part of that population, (e.g., neuropathic pain patients per Dr. Schiffenbauer), is not a compelling argument to disallow the indication or deny the use of the 505(b)(2) route of application. (In point of fact, opioids are frequently used with significant success in chronic neuropathic pain patients.)

An indication for the treatment of the signs and symptoms of osteoarthritis (OA) would not have been appropriate for a product expected to treat only the pain associated with OA. I also disagree with Dr. Schiffenbauer's conclusion that only Study 23 showed a statistically significant treatment effect, no matter what imputation methodology was employed in the analyses. In fact, using the conservative BOCF imputation methodology

in Study 23, Dr. Yongman Kim has demonstrated a statistically significant treatment effect for the 100 and 200-mg doses. In Study 15, Dr. Kim again found a statistically significant treatment effect for the Ralivia ER group. The clinical review team has argued that this study is inadequate to support efficacy due to its titration-to-effect design. While I agree that fixed-dose studies are more likely to provide compelling evidence, this type of study does document that the product is effective and, additionally, provides supportive "actual use" information. The average dose used in Study 15 was 270 mg, which is strongly indicative of efficacy for the 300 mg product.

Dr. Schiffenbauer notes in the Conclusion section of his review (page 13), that "...negative trials should not be ignored." While I agree that the totality of the evaluations performed during a product's development must be considered, it is not at all uncommon to see unsuccessful outcomes in treatment studies for symptomatic indications. The studies in this application were not "negative." The data did not trend in the opposite direction from what would be expected. They simply did not reach statistical significance, a not unusual finding in opioid analgesic trials.

On page 6 of his review, Dr. Schiffenbauer writes:

> Imputation of large amounts of missing data is problematic in these circumstances, and there is no "ideal" method of imputation. Missing data is just that. We do not know how individuals would have performed in response to the drug had they remained in the trial until the end. Indeed, large numbers of dropouts tell us a great deal about the drugs tolerability and AE profile and should be weighed into the decision for approval. While this is clearly the case for an NME, even for a 505b2 application for a new formulation whose unique PK characteristics impact the use of the product (such as for various forms of pain), it seems prudent to consider all the data including that for safety as well as efficacy. In a marginally effective drug with high dropout rate, the risk benefit ratio may not be considered favorable.

Indeed, for most opioid product clinical trials we see a high rate of dropouts, especially in trials that study patient populations with less severe pain, such as the OA population. I disagree that we don't know how individuals "would have performed..." We know that their lack of ability to tolerate the drug rendered its efficacy moot. I agree that this is important information; but I do not agree that all of the data has not been considered. I also do not agree that the risk benefit ratio may not be considered favorable under these circumstances. While many patients may not be able to tolerate tramadol, there is clearly a population for which it is safe and effective. To withhold the product from that population, because of the existence of less-tolerant patients, is hardly in the interest of the public health.

Thus, based on the sponsor's demonstration that Ralivia ER is safe and effective when used according to the product labeling, I will approve this application.

Action: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
9/8/2005 04:44:40 PM
MEDICAL OFFICER

Safety Review
PREMATURE TERMINATIONS DUE TO ADVERSE EVENTS

Application Type	NDA
Submission Number	21-692
Submission Code	000
PDUFA Goal Date	October 31st, 2004
Reviewer Name	Tatiana Oussova, M.D., M.P.H.
Review Completion Date	October 29, 2004
Established Name	Tramadol Extended Release
(Proposed) Trade Name	Ralivia
Therapeutic Class	Analgesic
Applicant	Biovail
Dosing Regimen	100 mg tablets
Indication	Moderate to moderately severe pain
Intended Population	Adults
Additional clinical reviews:	Lourdes Villalba, M.D. Carolyn Yancey, M.D. Julia Castle, M.D., M.P.H.

Introduction

Biovail Laboratories, Inc. (Biovail) submitted NDA 21-692 as a 505(b)(2) application for an extended-release formulation of tramadol hydrochloride (Tramadol HCl ER) intended for once-a-day (once-daily) dosing for the management of moderate to moderately severe pain in adults.

The immediate-release formulation of tramadol HCl was approved in the United States on March 3, 1995 with the tradename of Ultram® (NDA 20-281) for the "management of moderate to moderately severe pain in adults."

This part of the review would concentrate on the analysis of premature terminations due to adverse events related to Tramadol HCl ER and attempt to determine whether there is any significant difference between Tramadol HCl ER and Ultram in terms of premature terminations due to adverse events. ISS was used to conduct this part of the review. Individual studies safety data were not reviewed.

For the easier comparison of adverse events related to Tramadol HCl ER and Ultram presented in this review, below is an Ultram label that reads:

ADVERSE REACTIONS

ULTRAM was administered to 550 patients during the double-blind or open-label extension periods in U.S. studies of chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. Table 2 reports the cumulative incidence rate of adverse reactions by 7, 30 and 90 days for the most frequent reactions (5% or more by 7 days). The most frequently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are felt to be probably related to ULTRAM administration, the reported rates also include some events that may have been due to underlying disease or concomitant medication. The overall incidence rates of adverse experiences in these trials were similar for ULTRAM and the active control groups, TYLENOL® with Codeine #3 (acetaminophen 300 mg with codeine phosphate 30 mg), and aspirin 325 mg with codeine phosphate 30 mg however the rates of withdrawals due to adverse events appeared to be higher in the ULTRAM groups.

Table 2 Cumulative Incidence of Adverse Reactions for ULTRAM in Chronic Trials of Nonmalignant Pain. (N=427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation"[1]	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

[1] "CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

Incidence 1% to less than 5%, possibly causally related: the following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with ULTRAM exists.

Body as a Whole: Malaise.

Cardiovascular: Vasodilation.

Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.

Gastrointestinal: Abdominal pain, Anorexia, Flatulence.

Musculoskeletal: Hypertonia.

Skin: Rash.

Special Senses: Visual disturbance.

Urogenital: Menopausal symptoms, Urinary frequency, Urinary retention.

Incidence less than 1%, possibly causally related: the following lists adverse reactions that occurred with an incidence of less than 1% in clinical trials and/or reported in post-marketing experience.

Body as a Whole: Accidental injury, Allergic reaction, Anaphylaxis, Death, Suicidal tendency, Weight loss, Serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).

Cardiovascular: Orthostatic hypotension, Syncope, Tachycardia.

Central Nervous System: Abnormal gait, Amnesia, Cognitive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Seizure (see WARNINGS), Tremor.

Respiratory: Dyspnea.

Skin: Stevens-Johnson syndrome/Toxic epidermal necrolysis, Urticaria, Vesicles.

Special Senses: Dysgeusia.

Urogenital: Dysuria, Menstrual disorder.

Other adverse experiences, causal relationship unknown: A variety of other adverse events were reported infrequently in patients taking ULTRAM during clinical trials and/or reported in post-marketing experience. A causal relationship between ULTRAM and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.

Cardiovascular: Abnormal ECG, Hypertension, Hypotension, Myocardial ischemia, Palpitations, Pulmonary edema, Pulmonary embolism.

Central Nervous System: Migraine, Speech disorders.

Gastrointestinal: Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure.

Laboratory Abnormalities: Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria.

Sensory: Cataracts, Deafness, Tinnitus.

I. Single-Dose Studies

For the subjects in Phase I Studies 2287-2, 2375, 2667, and 99105, the data collected did not indicate which adverse event caused the subject to discontinue from the study, therefore all adverse events reported by the subjects who prematurely terminated are included in the section.

The table below presents pooled data from completed single-dose studies.

Table 1.

Incidence of Adverse Events Identified and Not Identified in the Ultram® Label Leading to Premature Termination: Healthy Volunteers, Single-Dose Studies

MedDRA Preferred Term	Tramadol HCl ER 100 mg QD (N=56) n (%)	Tramadol HCl ER 200 mg QD (N=98) n (%)	Tramadol HCl ER 300 mg QD (N=56) n (%)	Ultram 100 mg/day (N=32) n (%)	Ultram 200 mg/day (N=15) n (%)
Total subjects who prematurely terminated due to an adverse event	4 (7.1)	2 (2.0)	4 (7.1)	0 (0.0)	1 (6.7)
Identified in the Ultram® Label					
Constipation	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Nausea	1 (1.8)	1 (1.0)	2 (3.6)	0 (0.0)	1 (6.7)
Vomiting NOS	0 (0.0)	1 (1.0)	3 (5.4)	0 (0.0)	1 (6.7)
Dizziness (exc vertigo)	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Headache NOS	1 (1.8)	1 (1.0)	0 (0.0)	0 (0.0)	1 (6.7)
Sweating increased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hot flushes NOS	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood pressure decreased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Identified in the Ultram® Label					
Electrocardiogram T wave inversion[a]	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram QT corrected interval prolonged[a]	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Label is not specific for this event.

Source: ISS Appendix F.1, Table 1.4.4.1.1.

With the exception of electrocardiogram T wave inversion and electrocardiogram QT corrected interval prolonged, adverse events which resulted in premature termination from the single-dose studies in healthy volunteers are identified in the Ultram® label. The conduction abnormalities electrocardiogram T wave inversion and electrocardiogram QT corrected interval prolonged are not specifically identified in the label, although abnormal ECG is included.

II. Multiple-Dose Studies

The tables below present a list of multiple- dose controlled clinical trials conducted with the formulation intended for commercialization. All studies for the Tramadol HCl ER program have been completed and there have been no publications of the data from these trials.

Table 2. Controlled clinical trials

Report (Protocol) Number/ Start Date – Location Report/Listings/ CRFs	Investigator	Study Design	Treatment Group	Unit Dose (mg)	Regimen	Duration	Formulation	Participants E/R	S	C	P	Age (yrs) Mean±SD Range	Gender (N) Male/ Female
I. ADEQUATE AND WELL-CONTROLLED STUDIES: MODERATE TO SEVERE CHRONIC PAIN													
B00.CT3.014.TRA.P03 November 8, 2000	Segar Multicenter	DB, PC, R, PG, LBP	Run-in period Tramadol HCl ER 100-300 mg	100	100 mg QD Days 1 to 3 200 mg QD Day 4 to Week –2 300 mg QD Weeks -2 to -1 300 mg QD Weeks –2 to 0	3 Weeks	000103	619	385	386	233	47.6±14.8 18-80	294/325
Item 11 Item 12			All Safety					616	616				
			Double-blind period Total entering double-blind					387	385				
			Tramadol HCl ER 200 mg	100	200 mg QD	12 Weeks	000103	129	129	87	42	47.4±13.8 20-80	60/69
			Tramadol HCl ER 300 mg	100	300 mg QD	12 Weeks	000103	129	129	86	42	48.5±13.7 19-79	68/60
			Placebo	NAP	3 placebo tablets QD	12 Weeks	000201	130	128	68	61	47.6±15.5 20-79	64/63
B00.CT3.015.TRA.P03 November 2, 2000	Multicenter (16) study	DB, R, DT, PG, PC, OA	Tramadol HCl ER 100-400 mg	100	100 mg QD Days 1-3 200 mg QD Days 4-7 Flexible dosing 200 mg QD 300 mg QD 400 mg QD	12 Weeks	000103	124	124	61	63	61.2±10.0 32-85	42/82
Item 11 Item 12													
			Placebo	NAP	NA	12 Weeks	000201	122	122	63	59	61.5±10.2 30-82	53/69

Report (Protocol) Number/ Start Date – Location Report/Listings/ CRFs	Investigator	Study Design	Treatment Group	Unit Dose (mg)	Regimen	Duration	Formulation	Participants E/R	S	C	P	Age (yrs) Mean±SD Range	Gender (N) Male/ Female
B00.CT3.015.TRA.P03 November 2, 2000	Multicenter (16) study	DB, R, DT, PG, PC, OA	Tramadol HCl ER 100-400 mg	100	100 mg QD Days 1-3 200 mg QD Days 4-7 Flexible dosing 200 mg QD 300 mg QD 400 mg QD	12 Weeks	000103	124	124	61	63	61.2±10.0 32-85	42/82
Item 11 Item 12													
			Placebo	NAP	NA	12 Weeks	000201	122	122	63	59	61.5±10.2 30-82	53/69

References:

Babul N, Noveck R, Chipman HN, Roth SH, Gana T, Albert K. A double-blind, randomized, 12-week placebo-controlled trial of tramadol ER in osteoarthritis of the knee. [Poster] 2002 Annual Scientific Meeting of the American College of Rheumatology; October 24-29, 2002; New Orleans, Louisiana, USA.

Babul N, Gana T, Pascual L, Albert K. Rapid titration with tramadol ER in chronic pain of osteoarthritis: a randomized, placebo-controlled clinical trial. [Poster] 22nd Annual Scientific Meeting of the American Pain Society; March 20-23, 2003; Chicago, Illinois, USA

Report (Protocol) Number/ Start Date – Location Report/Listings/ CRFs	Investigator	Study Design	Treatment Group	Unit Dose (mg)	Regimen	Duration	Formulation	Participants E/R	S	C	P	Age (yrs) Mean±SD Range	Gender (N) Male/ Female
I. ADEQUATE AND WELL-CONTROLLED STUDIES: MODERATE TO SEVERE CHRONIC PAIN													
802.CT3.021.TRA.P03 September 6, 2002	Multicenter trial (72 investigators)	DB, R, DR, PC, EP, PG, OA	All patients					1011	1002				
Item 11 Item 12			Tramadol HCl ER 100 mg	100	100 mg QD	12 Weeks	010208 02C139 010705	202	201	107	94	59.5±10.17 31-79	84/117
			Tramadol HCl ER 200 mg	100	100 mg QD Days 1-4 200 mg QD	12 Weeks	010208 02C139 010705	203	199	109	90	62.0±9.87 36-80	75/124
			Tramadol HCl ER 300 mg	100	100 mg QD Days 1-4 200 mg QD Days 5-9 300 mg QD	12 Weeks	010208 02C139 010705	201	199	101	98	59.7±11.41 21-79	78/123
			Celecoxib 200 mg	200	200 mg, QD	12 Weeks	34567-043 34567-050 34567-065	203	202	135	67	60.0±11.28 20-80	71/131
			Placebo	NAP	NA	12 Weeks	Tramadol: 020807 Celecoxib: 34567-042 34567-049 34567-064	202	201	103	97	58.9±11.63 20-80	63/137

Report (Protocol) Number/ Start Date – Location Report/Listings/ CRFs	Investigator	Study Design	Treatment Group	Unit Dose (mg)	Regimen	Duration	Formulation	Participants E/R	S	C	P	Age (yrs) Mean±SD Range	Gender (N) Male/ Female
802.CT3.023.TRA.P03 August 21, 2002	Multicenter (69 investigators)	DB, R, DR, PC, PG, OA	All patients					1020	1011				
Item 11 Item 12			Tramadol HCl ER 100 mg	100	100 mg QD	12 Weeks	02C139	203	202	120	82	58.4±10.9 22-74	76/126
			Tramadol HCl ER 200 mg	100	100 mg QD Days 1-4 200 mg QD	12 Weeks	02C139	203	201	116	85	59.1±9.9 33-74	73/128
			Tramadol HCl ER 300 mg	100	100 mg QD Days 1-4 200 mg QD Days 5-9 300 mg QD	12 Weeks	02C139	204	201	104	97	58.5±9.4 28-74	82/119
			Tramadol HCl ER 400 mg	100	100 mg QD Days 1-4 200 mg QD Days 5-9 300 mg QD Days 10-14 400 mg QD	12 Weeks	02C139	205	202	103	99	58.4±9.7 27-74	85/117
			Placebo	NAP	NA	12 Weeks	010705 020907	205	205	115	90	58.4±9.8 25-73	64/141

Table 3.

Cumulative Incidence of Premature Discontinuation Over Time Due to Adverse Events
All Double-Blind Studies

Timing	Tramadol HCl ER: Titration (N=133) n (%)	100 mg (N=403) n (%)	200 mg (N=529) n (%)	300 mg (N=528) n (%)	400 mg (N=202) n (%)	All Doses (N=1795) n (%)	Placebo (N=664) n (%)
Day 1	2 (1.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	3 (0.2%)	4 (0.6%)
Day 2	8 (6.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	10 (0.6%)	7 (1.1%)
Day 3	10 (7.5%)	2 (0.5%)	3 (0.6%)	4 (0.8%)	1 (0.5%)	20 (1.1%)	9 (1.4%)
Day 4	10 (7.5%)	3 (0.7%)	5 (0.9%)	7 (1.3%)	2 (1.0%)	27 (1.5%)	10 (1.5%)
Day 5	14 (10.5%)	3 (0.7%)	9 (1.7%)	10 (1.9%)	3 (1.5%)	39 (2.2%)	14 (2.1%)
Day 6	16 (12.0%)	5 (1.2%)	11 (2.1%)	12 (2.3%)	6 (3.0%)	50 (2.8%)	16 (2.4%)
Day 7	16 (12.0%)	9 (2.2%)	15 (2.8%)	18 (3.4%)	7 (3.5%)	65 (3.6%)	19 (2.9%)
Day 8	20 (15.0%)	20 (5.0%)	29 (5.5%)	29 (5.5%)	9 (4.5%)	107 (6.0%)	26 (3.9%)
Day 9	24 (18.0%)	20 (5.0%)	32 (6.0%)	30 (5.7%)	9 (4.5%)	115 (6.4%)	28 (4.2%)
Day 10	24 (18.0%)	20 (5.0%)	33 (6.2%)	30 (5.7%)	9 (4.5%)	116 (6.5%)	31 (4.7%)
Day 11	24 (18.0%)	23 (5.7%)	38 (7.2%)	33 (6.3%)	10 (5.0%)	128 (7.1%)	33 (5.0%)
Day 12	26 (19.5%)	24 (6.0%)	39 (7.4%)	35 (6.6%)	10 (5.0%)	134 (7.5%)	34 (5.1%)
Day 13	26 (19.5%)	24 (6.0%)	41 (7.8%)	38 (7.2%)	11 (5.4%)	140 (7.8%)	35 (5.3%)
Day 14	26 (19.5%)	26 (6.5%)	43 (8.1%)	42 (8.0%)	12 (5.9%)	149 (8.3%)	36 (5.4%)
Day 15	26 (19.5%)	28 (6.9%)	52 (9.8%)	55 (10.4%)	19 (9.4%)	180 (10.0%)	37 (5.6%)
Day 16	26 (19.5%)	32 (7.9%)	54 (10.2%)	57 (10.8%)	20 (9.9%)	189 (10.5%)	38 (5.7%)
Day 17	26 (19.5%)	32 (7.9%)	55 (10.4%)	61 (11.6%)	21 (10.4%)	195 (10.9%)	38 (5.7%)
Day 18	28 (21.1%)	32 (7.9%)	57 (10.8%)	63 (11.9%)	23 (11.4%)	203 (11.3%)	38 (5.7%)
Day 19	29 (21.8%)	32 (7.9%)	58 (11.0%)	63 (11.9%)	25 (12.4%)	207 (11.5%)	38 (5.7%)
Day 20	29 (21.8%)	33 (8.2%)	59 (11.2%)	64 (12.1%)	25 (12.4%)	210 (11.7%)	38 (5.7%)
Day 21	29 (21.8%)	35 (8.7%)	62 (11.7%)	68 (12.9%)	27 (13.4%)	221 (12.3%)	40 (6.0%)
Day 22	29 (21.8%)	40 (9.9%)	65 (12.3%)	81 (15.3%)	33 (16.3%)	248 (13.8%)	46 (6.9%)

Note: Percentage is with respect to N, the total number of patients.

Cumulative Incidence of Premature Discontinuation Over Time Due to Adverse Events
All Double-Blind Studies

Timing	Tramadol HCl ER: Titration (N=133) n (%)	100 mg (N=403) n (%)	200 mg (N=529) n (%)	300 mg (N=528) n (%)	400 mg (N=202) n (%)	All Doses (N=1795) n (%)	Placebo (N=664) n (%)
Day 23	29 (21.8%)	41 (10.2%)	66 (12.5%)	83 (15.7%)	33 (16.3%)	252 (14.0%)	46 (6.9%)
Day 24	29 (21.8%)	42 (10.4%)	66 (12.5%)	85 (16.1%)	33 (16.3%)	255 (14.2%)	47 (7.1%)
Day 25	30 (22.6%)	42 (10.4%)	67 (12.7%)	86 (16.3%)	34 (16.8%)	259 (14.4%)	47 (7.1%)
Day 26	31 (23.3%)	42 (10.4%)	67 (12.7%)	88 (16.7%)	34 (16.8%)	262 (14.6%)	47 (7.1%)
Day 27	31 (23.3%)	42 (10.4%)	68 (12.9%)	89 (16.9%)	35 (17.3%)	265 (14.8%)	48 (7.2%)
Day 28	32 (24.1%)	43 (10.7%)	68 (12.9%)	90 (17.0%)	37 (18.3%)	270 (15.0%)	48 (7.2%)
Days 29 to 56	36 (27.1%)	53 (13.2%)	94 (17.8%)	120 (22.7%)	55 (27.2%)	358 (19.9%)	58 (8.7%)
Days 57 to 84	38 (28.6%)	54 (13.4%)	102 (19.3%)	132 (25.0%)	59 (29.2%)	385 (21.4%)	70 (10.5%)
Day 85 to End	38 (28.6%)	55 (13.6%)	103 (19.5%)	133 (25.2%)	60 (29.7%)	389 (21.7%)	70 (10.5%)

COMMENTS:

The incidence of premature discontinuation over time due to adverse events is increasing over time and appears to be dose-dependent (the higher the dose, the higher the incidence compared to placebo) however it is unclear whether this difference between placebo and any of the doses is statistically significant. It is impossible to say based on this analysis whether there is a significant difference between any of the doses.

Table 4.

Incidence of Adverse Events Leading to Premature Termination by Age
All Patients

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER 100 mg n (%)	 200 mg n (%)	 300 mg n (%)	 400 mg n (%)	 Flexible Dosing n (%)	 All Doses n (%)	 Placebo n (%)	 Placebo After Tramadol Run-in n (%)
N								
All Patients	403	400	400	202	1736	3141	552	128
< 65 years	258	248	262	143	1329	2240	376	107
>= 65 years	145	152	138	59	407	901	174	21
All Body Systems								
All Events	55 (13.6%)	88 (22.0%)	118 (29.5%)	60 (29.7%)	568 (32.7%)	889 (28.3%)	52 (9.4%)	16 (12.5%)
< 65 years	28 (10.9%)	45 (18.1%)	68 (25.2%)	37 (25.9%)	390 (29.3%)	568 (25.3%)	37 (9.8%)	10 (9.3%)
>= 65 years	27 (18.6%)	43 (28.3%)	52 (37.7%)	23 (39.0%)	178 (43.7%)	323 (35.8%)	15 (8.6%)	6 (28.6%)

COMMENTS:

For all doses, the overall incidence of adverse events leading to discontinuations is higher for patients >=65 years of age than for those < 65 years. However, placebo group shows no difference between age groups.

Table 5.

Incidence of Adverse Events Leading to Premature Termination by Gender
All Patients

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER 100 Mg n (%)	 200 Mg n (%)	 300 Mg n (%)	 400 Mg n (%)	 Flexible Dosing n (%)	 All Doses n (%)	 Placebo n (%)	 Placebo After Tramadol Run-in n (%)
N								
All Patients	403	400	400	202	1736	3141	552	128
Males	160	148	158	85	713	1264	192	64
Females	243	252	242	117	1023	1877	360	64

COMMENTS:

The rates of discontinuations due to adverse events appears to be slightly higher among females than males

III. Premature Terminations: All Patients

Of the 3141 patients who received Tramadol HCl ER, 876 (27.9%) had an adverse event leading to premature termination in the studies in pain. A patient could have prematurely terminated for more than 1 adverse event.

The incidence of adverse events leading to premature termination for all patients was greater in the Tramadol HCl ER flexible dose treatment group compared to any other Tramadol HCl ER dosing group.

The tables below present the incidence of different adverse events identified and not identified in the Ultram label comparing different doses of Tramadol HCl ER, placebo and Ultram.

The number and percentage of all patients who had a gastro-intestinal adverse event which was identified in the Ultram® label leading to premature termination are presented in table 6 below.

Table 6.

Incidence of Gastrointestinal-Related Adverse Events Identified in the Ultram® Label Leading to Premature Termination: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	Tramadol HCl ER 100 mg QD (N=403) n (%)	Tramadol HCl ER 200 mg QD (N=400) n (%)	Tramadol HCl ER 300 mg QD (N=400) n (%)	Tramadol HCl ER 400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo[a] (N=128) n (%)
Patients reporting at least 1 adverse event leading to premature termination	568 (32.7)	55 (13.6)	88 (22.0)	118 (29.5)	60 (29.7)	52 (9.4)	16 (12.5)
Abdominal distension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain NOS	7 (0.4)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Abdominal pain upper	7 (0.4)	1 (0.2)	1 (0.3)	3 (0.8)	1 (0.5)	1 (0.2)	0 (0.0)
Abdominal tenderness	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	48 (2.8)	4 (1.0)	7 (1.8)	10 (2.5)	10 (5.0)	1 (0.2)	0 (0.0)
Constipation aggravated	2 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea NOS	12 (0.7)	2 (0.5)	3 (0.8)	2 (0.5)	1 (0.5)	1 (0.2)	1 (0.8)
Dry mouth	5 (0.3)	0 (0.0)	1 (0.3)	5 (1.3)	2 (1.0)	0 (0.0)	0 (0.0)
Dyspepsia	1 (0.1)	1 (0.2)	2 (0.5)	5 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia aggravated	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fecal impaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Flatulence	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal upset	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	167 (9.7)	16 (4.0)	29 (7.3)	47 (11.8)	19 (9.4)	5 (0.9)	3 (2.3)
Nausea aggravated	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting aggravated	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting NOS	80 (4.6)	7 (1.7)	9 (2.3)	18 (4.5)	6 (3.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Source: ISS Appendix F.7, Table 7.11.1

Nausea, vomiting and constipation were the most frequently reported adverse events leading to premature termination that were related to gastrointestinal disorders.

The number and percentage of all patients who had a gastro-intestinal adverse event leading to premature termination which were not identified in the Ultram® label are

presented in the table below.

Table 7.

Incidence of Gastrointestinal-Related Adverse Events Not Identified in the Ultram® Label Leading to Premature Termination: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo[a] (N=128) n (%)
Patients reporting at least 1 adverse event leading to premature termination	568 (32.7)	55 (13.6)	88 (22.0)	118 (29.5)	60 (29.7)	52 (9.4)	16 (12.5)
Appendicitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aptyalism	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric ulcer	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis NOS	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastro-esophageal reflux disease	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ileus	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Esophageal reflux aggravated	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pancreatitis NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Source: ISS Appendix F.7, Table 7.11.1

COMMENTS:

More gastro-intestinal unexpected adverse events not identified in the Ultram label occurred in the flexible dose group.

Table 8.

Incidence of Adverse Events Identified in the Ultram® Label Leading to Premature Termination, General and Administration Site Disorders: All Patients

MedDRA Preferred Term	Tramadol HCl ER						Tramadol Placebo[a]
	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	(N=128) n (%)
Patients reporting at least 1 adverse event leading to premature termination	568 (32.7)	55 (13.6)	88 (22.0)	118 (29.5)	60 (29.7)	52 (9.4)	16 (12.5)
Feeling hot	2 (0.1)	1 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling jittery	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lethargy	7 (0.4)	0 (0.0)	2 (0.5)	1 (0.3)	0 (0.0)	2 (0.4)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Mental status changes	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rigors	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Shivering	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sluggishness	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.4)	0 (0.0)
Weakness	12 (0.7)	0 (0.0)	4 (1.0)	4 (1.0)	5 (2.5)	3 (0.5)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Source: ISS Appendix F.7, Table 7.11.1

Lethargy and weakness were the most frequently reported adverse events leading to premature termination identified in the Ultram® label.

The number and percentage of all patients who had an adverse event leading to premature termination which were not identified in the Ultram® label are presented in Table 9 for general and administration site disorders.

Table 9.

Incidence of Adverse Events Not Identified in the Ultram® Label Leading to Premature Termination, General and Administration Site Disorders: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo[a] (N=128) n (%)
Patients reporting at least 1 adverse event leading to premature termination	568 (32.7)	55 (13.6)	88 (22.0)	118 (29.5)	60 (29.7)	52 (9.4)	16 (12.5)
Chest pain NEC	6 (0.3)	1 (0.2)	1 (0.3)	1 (0.3)	2 (1.0)	2 (0.4)	0 (0.0)
Chest tightness	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Fall	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Feeling abnormal	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Feeling hot and cold	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
General symptom NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza like illness	2 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint swelling	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Oedema lower limb	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain exacerbated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pain NOS	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral swelling	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pitting edema	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Source: ISS Appendix F.7, Table 7.11.1.

Fatigue was the most frequently reported adverse event in all dose groups leading to premature termination for general and administration site disorders.

The number and percentage of all patients who had an adverse event leading to premature termination which were not identified in the Ultram® label are presented in Table 10 for infections and infestations.

Table 10.

Incidence of Adverse Events Not Identified in the Ultram® Label Leading to Premature Termination, Infections and Infestations: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=562) n (%)	Tramadol/ Placebo[a] (N=128) n (%)
Patients reporting at least 1 adverse event leading to premature termination	568 (32.7)	55 (13.6)	88 (22.0)	118 (29.5)	60 (29.7)	52 (9.4)	16 (12.5)
Cellulitis	2 (0.1)	0 (0.0)	2 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis helicobacter	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis NOS	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis viral NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gingivitis infection NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Herpes zoster	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Influenza	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteomyelitis NOS	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Otitis media NOS	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pneumonia mycoplasmal	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia NOS	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Scabies infestation	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis NOS	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Upper respiratory tract infection NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection NOS	3 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Source: ISS Appendix F.7, Table 7.11.1.

Cellulitis and urinary tract infection NOS were the most frequently reported adverse events leading to premature termination that were related to infections or infestations.

The number and percentage of all patients who had an adverse event leading to premature termination which were identified in the Ultram® label are presented in Table 11 for cardiac disorders.

Table 11.

Incidence of Adverse Events Identified in the Ultram® Label Leading to Premature Termination, Cardiac Disorders: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Patients reporting at least 1 adverse event leading to premature termination	568 (32.7)	55 (13.6)	88 (22.0)	118 (29.5)	60 (29.7)	52 (9.4)	16 (12.5)
Angina pectoris	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angina unstable	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Coronary artery disease NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Palpitations	5 (0.3)	0 (0.0)	2 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Tachycardia NOS	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1.

Palpitations was the most frequently reported adverse event resulting in premature termination for cardiac disorders.

The number and percentage of all patients who had an adverse event leading to premature termination which were not identified in the Ultram® Label are presented in Table 12 for cardiac disorders.

Table 12.
Incidence of Adverse Events Not Identified in the Ultram® Label Leading to Premature Termination, Cardiac Disorders: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Patients reporting at least 1 adverse event leading to premature termination	568 (32.7)	55 (13.6)	88 (22.0)	118 (29.5)	60 (29.7)	52 (9.4)	16 (12.5)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bradycardia NOS	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Mitral valve incompetence	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1.

A total of 6 adverse events were reported for cardiac disorders leading to premature terminations which were not identified in the Ultram® label including 2 cases of MI in flexible dose group.

The number and percentage of all patients who had an adverse event leading

to premature termination which were identified in the Ultram® label are presented in Table 13 for nervous system disorders.

Table 13.

Incidence of Adverse Events Identified in the Ultram® Label Leading to Premature Termination, Nervous System Disorders: All Patients

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Placebo (N=128) n (%)
Amnesia NEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Balance impaired NOS	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Convulsions NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Disturbance in attention NEC	4 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness (exc vertigo)	114 (6.6)	13 (3.2)	25 (6.3)	30 (7.5)	14 (6.9)	6 (1.1)	1 (0.8)
Dizziness aggravated	4 (0.2)	0 (0.0)	1 (0.3)	2 (0.5)	2 (1.0)	0 (0.0)	0 (0.0)
Dizziness postural	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Formication	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gait abnormal NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grand mal convulsion	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache NOS	26 (1.5)	5 (1.2)	8 (2.0)	14 (3.5)	3 (1.5)	2 (0.4)	2 (1.6)
Hypersomnia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoaesthesia	3 (0.2)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Increased activity	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Initial insomnia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia exacerbated	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia NEC	15 (0.9)	1 (0.2)	1 (0.3)	3 (0.8)	3 (1.5)	0 (0.0)	1 (0.8)
Jerky movement NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Memory impairment	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mental impairment NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Migraine aggravated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Migraine NOS	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Myoclonic seizure	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paraesthesia NEC	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Paraesthesia tongue	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Petit mal epilepsy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Restless leg syndrome	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Sedation	8 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	45 (2.6)	4 (1.0)	8 (2.0)	10 (2.5)	12 (5.9)	3 (0.5)	1 (0.8)
Syncope	3 (0.2)	0 (0.0)	1 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Tremor NEC	7 (0.4)	0 (0.0)	1 (0.3)	3 (0.8)	0 (0.0)	1 (0.2)	0 (0.0)
Tunnel vision	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1.

Dizziness (exc vertigo), headache and somnolence were the most frequently reported adverse events related to the nervous system which resulted in premature termination.

Table 14.

Incidence of Adverse Events Not Identified in the Ultram® Label Leading to Premature Termination, Nervous System Disorders: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Hyporeflexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Lacunar infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nerve compression	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1.

The number and percentage of all patients who had an adverse event leading to premature termination which were not identified in the Ultram® label are presented in Table 15 for respiratory disorders.

Table 15.

Incidence of Adverse Events Not Identified in the Ultram® Label Leading to Premature Termination, Respiratory Disorders: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Apnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Choking sensation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Globus feeling in pharynx	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal passage irritation	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wheezing	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Yawning	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1.

The majority of respiratory-related adverse events leading to premature termination were not identified in the Ultram® label with the exception of dyspnea NOS.

The number and percentage of all patients who had an adverse event leading to premature termination which were identified in the Ultram® label are presented in Table 16 for skin disorders.

Table 16.

Incidence of Adverse Events Identified in the Ultram® Label Leading to Premature Termination, Skin Disorders: All Patients

	Tramadol HCl ER						Tramadol/ Placebo
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	(N=128) n (%)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis contact	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis NOS	15 (0.9)	2 (0.5)	3 (0.8)	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Night sweats	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus NOS	21 (1.2)	6 (1.5)	4 (1.0)	6 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)
Rash generalized	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash maculopapular	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash pruritic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sweating increased	16 (0.9)	1 (0.2)	0 (0.0)	4 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)
Urticaria NOS	1 (0.1)	0 (0.0)	1 (0.3)	1 (0.3)	2 (1.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1.

Dermatitis NOS, pruritus NOS, and sweating increased were the most frequently reported adverse events related to skin disorders which resulted in premature termination.

The number and percentage of all patients who had an adverse event leading to premature termination which were not identified in the Ultram® label are presented in Table 17 for skin disorders.

Table 17.

Incidence of Adverse Events Not Identified in the Ultram® Label Leading to Premature Termination, Skin Disorders: All Patients

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Placebo (N=128) n (%)
Alopecia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clamminess	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Confusion	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema NEC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Eyelid edema	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Piloerection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1

A total of 7 adverse events leading to premature termination related to skin disorders, which were not identified in the Ultram® label, were reported.

The number and percentage of all patients who had an adverse event leading to premature termination are presented in Table 18 for vascular disorders.

Table 18.

Incidence of Adverse Events Identified in the Ultram® Label Leading to Premature Termination, Vascular Disorders: All Patients

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Placebo (N=128) n (%)
Flushing	19 (1.1)	4 (1.0)	6 (1.5)	7 (1.8)	5 (2.5)	1 (0.2)	0 (0.0)
Hot flushes NOS	7 (0.4)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension aggravated	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Postural hypotension	2 (0.1)	0 (0.0)	3 (0.8)	0 (0.0)	3 (1.5)	1 (0.2)	1 (0.8)
Vasodilatation	3 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1

Both flushing and postural hypotension were reported more frequently than any other vascular related adverse event which resulted in premature termination.

The number and percentage of all patients who had an adverse event leading to premature termination which were not identified in the Ultram® label are presented in Table 19 for vascular disorders.

Table 19.

Incidence of Adverse Events Not Identified in the Ultram® Label Leading to Premature Termination, Vascular Disorders: All Patients

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Peripheral ischemia NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombophlebitis deep	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.11.1.

Peripheral ischemia NOS and thrombophlebitis deep occurred in 1 patient each and led to premature termination.

IV. Premature Terminations: All Patients With Chronic Pain
(All Double-Blind, Placebo-Controlled Studies)

A total of 429 patients (Tramadol HCl ER, 368 patients; placebo, 61 patients) in the double-blind, placebo-controlled studies had a non-serious adverse events leading to premature termination.

The number and percentage of patients who had an adverse event leading to premature termination in ≥1% of the patients in all Tramadol dose groups in the double-blind, placebo-controlled studies are presented in Table 20 and in Appendix #1.

Table 20.

Incidence of Adverse Events Identified in the Ultram® Label Leading to Premature Termination in ≥1% of Patients: All Double-Blind, Placebo-Controlled Studies

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=133) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=529) n (%)	300 mg QD (N=528) n (%)	400 mg QD (N=202) n (%)	Placebo (N=864) n (%)
Nausea	10 (7.5)	16 (4.0)	30 (5.7)	53 (10.0)	19 (9.4)	8 (1.2)
Dizziness (exc vertigo)	21 (15.8)	14 (3.5)	29 (5.5)	36 (6.8)	16 (7.9)	7 (1.1)
Constipation	5 (3.8)	4 (1.0)	9 (1.7)	10 (1.9)	10 (5.0)	1 (0.2)
Somnolence	1 (0.8)	4 (1.0)	9 (1.7)	10 (1.9)	12 (5.9)	4 (0.6)
Asthenia (fatigue)	0 (0.0)	4 (1.0)	5 (1.0)	10 (1.9)	4 (2.0)	3 (0.5)
Flushing	1 (0.8)	4 (1.0)	6 (1.1)	7 (1.3)	5 (2.5)	1 (0.2)
Pruritus NOS	0 (0.0)	6 (1.5)	5 (1.0)	6 (1.1)	2 (1.0)	0 (0.0)
Headache NOS	2 (1.5)	5 (1.2)	8 (1.5)	15 (2.8)	3 (1.5)	4 (0.6)
Vomiting NOS	3 (2.3)	7 (1.8)	11 (2.1)	22 (4.2)	8 (3.0)	0 (0.0)

Sources: ISS Appendix F.6, Table 5.7.1.1.

Nausea, dizziness (exc vertigo), constipation, and somnolence were the most frequently reported adverse events leading to premature termination in the double-blind, placebo-controlled studies.

COMMENTS:

The incidence of the adverse events in all dose groups leading to premature discontinuation from the study appears consistent with the Ultram label

V. Open-Label Safety Study

A total of 352 (33.5%) patients who received open-label Tramadol HCl ER in Study B00.CTOL.003.TRA P03 had an adverse event leading to premature termination.

The number and percentage of patients who had an adverse event leading to premature termination which were identified in the Ultram® label are displayed in Table 21 for adverse events reported for ≥1% of all Tramadol HCl ER patients.

Table 21.

Incidence of Adverse Events Leading To Premature Termination Reported In ≥1% of Patients and Identified In the Ultram® Label: Open-Label, Chronic Low Back Pain

MedDRA Preferred Term	Tramadol HCl ER Titration (N=1052) n (%)
Patients reported at least 1 adverse event leading to premature termination	352 (33.5)
Nausea	101 (9.6)
Vomiting	49 (4.7)
Constipation	36 (3.4)
Dizziness	63 (6.0)
Flushing	13 (1.2)
Orthostasis	2 (0.2)
Syncope	1 (0.1)

Source: Final Clinical Study Report, Study B00.CTOL.003.TRA P03, Table 14.3.1.3.1.

Of the 628 AEs that resulted in withdrawal from the study; 78.2% were of mild or moderate severity. The most frequently reported adverse events leading to premature termination were gastrointestinal symptoms (166 patients): nausea (101 patients), vomiting (49 patients), and constipation (36 patients).

VI. CHANGES TO ADVERSE EVENT DATASET

1. Adverse Event Terms to be Added to the Adverse Event Dataset

Tables 6, 7, and 8 are copied directly from the Sponsor's submission therefore the numbering appears as in the Sponsor's submission.

Review of the termination comment field versus the adverse event dataset identified discrepancies where adverse events noted as reason for withdrawal

were not identified in the adverse event dataset including one patient with an SAE (hospitalization). The changes to the adverse event dataset are presented in Table 6. Two additional subjects who were identified in a comparison of the adverse event dataset versus lab abnormal or dose received comment fields are also included in Table 6.

Table 6 Adverse Event Terms to be Added to the Adverse Event Dataset

Study-Site-Subject	Reason for Withdrawal Dataset	Description of the Reason	Add Adverse Event Term to Adverse Event Dataset: Investigator Term	Add Adverse Event Term to Adverse Event Dataset: MedDRA Preferred Term
003-10-008	Patient requested withdrawal from study	Patient going onto excluded medication for Lupus	Patient going onto excluded medication for lupus	Systemic Lupus Erythmatosus
003-27-001	Investigator withdrew patient	Consistent abnormal lab values since screening	Laboratory results abnormal	Laboratory test abnormal NOS
003-71-019	Investigator withdrew patient	Protocol violation -- elevated LFT's	Elevated LFT's	Liver function tests NOS abnormal
014-35-044	Withdrawn due to AE	Patient had a Non-Serious Adverse Event	Fatigue Yeast Infection	Fatigue Fungal Infection
014-40-007	Investigator withdrew patient	Laboratory results abnormal [b]	Clinically significant LFTs Clinically significant CK level	Liver Function Tests NOS abnormal Blood Creatinine Phosphokinase Increased
014-54-024	Patient requested withdrawal from study	Pt. did not like the way the drug made him feel (he didn't give specific AE)	Feeling abnormal	Feeling abnormal
014-54-056	Withdrawal due to AE [a]	Nausea and sweating	Kidney stone	Calculus Renal NOS
021-140-014	Withdrawn Due to non-compliance	Pt. was drinking and was admitted to hospital	Intoxication	Poisoning NOS
023-207-077	Patient demonstrated renal insufficiency via lab reports	Patient demonstrated renal insufficiency via lab reports	Renal Insufficiency	Renal Insufficiency

[a] Identified in the Dose Received comment field.

[b] Identified in the Lab Abnormal comment field.

2. Changes to be Made to the Existing Adverse Event Terms in the Adverse Event Dataset

Twenty-eight patients were identified as having an adverse event corresponding to the description of the reason on the termination dataset. Additionally, one patient was identified as having a serious adverse event. Those events were not marked as causing withdrawals on the adverse event

dataset. In these cases, the reason for withdrawal was marked as "yes" on the adverse event dataset. A list of these patients is provided in Table 7.

Appears This Way
On Original

Appears This Way
On Original

Table 7 **Changes to be Made to the Existing Adverse Event Terms in the Adverse Event Dataset**

Study/ Site/ Subjects	Description of the Reason	AE Reported in the AE Database
003-06-085	Pt. unable to tolerate dose greater than 200 mg due to AE of light-headedness	Dizziness (exc Vertigo)
003-44-005	Patient had a non serious adverse event	Pain in Limb
003-12-046	Pt requested w/d from study due to prozac & amitriptyline for depr & insomnia	Depression NEC
003-76-042	"c/o feeling funny"	Influenza Like Illness
003-77-016	Pt didn't want to take study drug with septro (cipro?) for baseline UTI.	Dysuria; Urinary Tract Infection NOS
003-83-015	Took excluded medications for AE's	Muscle Injury NOS
009-01-006	Patient vomited after first dose of study medication	Vomiting NOS
014-27-020	Patient had a Non-Serious Adverse Event	Alanine Aminotransferase increased Aspartate Aminotransferase increased Blood Creatinine Phosphokinase increased Blood Lactate Dehydrogenase increased
014-29-023	Patient had a Non-Serious Adverse Event	Nausea, Dizziness (exc. vertigo)
014-30-002	Patient had a Non-Serious Adverse Event	Pruritus NOS, Vasodilatation
014-30-009	Diagnosed with ankylosing spondylitis	Joint Range of Motion decreased
014-30-019	Erectile dysfunction[a]	Erectile disturbance
014-30-020	Pt states that he couldn't tolerate side effects with bowel	Diarrhoea NOS
014-35-047	Patient had a Non-Serious Adverse Event	Anorgasmia

Study/ Site/ Subjects	Description of the Reason	AE Reported in the AE Database
014-35-044	Patient had a Non-Serious Adverse Event	Nausea
014-36-017	Pt was in a MVA 05/16/01 and started taking pain meds for his pain	Whiplash Injury; Hypoaesthesia; Paraesthesia NEC
014-36-031	Patient had a Non-Serious Adverse Event	Back Pain
014-040-016	Pt. took vicodin for migraines	Migraine NOS
014-55-009	Exclusion med Pt needed for gout	Gout
014-57-002	Pt took exclusionary meds (vicodin, skelaxin) to treat an AE	Back pain
014-57-009	Pt had a gout flare that required excluded medications.	Gout Aggravated
014-60-017	Nausea, Vomiting and Somnolence	Somnolence
015-08-020	Pt. had a SAE of chest pains and no longer wanted to participate in study	Chest pain NEC
015-10-014	Patient broke out in a rash	Dermatitis NOS
015-14-015	Patient diagnosed with scabies and was put on the excluded medications by her PCP	Scabies infestation
021-132-016	Patient non-compliant with protocol	Depression aggravated
021-135-004	Cellulitis[a]	Cellulitis
021-178-001	Subject started taking antidepressant	Anxiety NEC
021-183-072	Patient started Pamelor for depression 10 days ago	Depression aggravated
021-183-082	Non-serious AE requiring excluded con medications	Cellulitis Joint effusion Arthralgia
021-188-002	Pt took prednisone during last 3 weeks of study due to lower back pain	Back pain
023-207-026	Patient non-compliant with protocol	Pain exacerbated
023-207-074	Patient non-compliant with protocol	Plantar fasciitis
023-230-029	Medication for depression excluded	Depression aggravated
023-270-018	Patient requested withdrawal from the study	Sinusitis NOS

[a] AE is already in the Adverse Event Database but is not marked as causing withdrawal.

3. Changes to the Reason for Termination

Thirty-two patients were identified with the reason for termination as an adverse event that was not marked in the termination dataset as "Subject had a non-serious adverse event." Additionally, there are two patients who had an SAE resulting in study withdrawal. The only change to the termination dataset is the reason for withdrawal, a listing of these patients is provided in

Table 8.

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Table 8 **Changes to be Made to the Termination Dataset**

Study/ Site/ Subjects	Reason for Withdrawal Dataset	Withdrawal Date	Description of the Reason	AE Reported in the AE Database[8]	Onset Date
003-06-085	Other	09/10/01	Pt. unable to tolerate dose greater than 200 mg due to AE of light-headedness	Dizziness (exc Vertigo)	02/23/01-09/10/01
003-10-008	Patient requested withdrawal from study	04/13/01	Patient going onto excluded medication for lupus	No AE identified	NA
003-12-046	Patient requested withdrawal from study	05/02/01	Pt requested w/d from study due to prozac & amitriptyline for depr & insomnia	Depression NEC	04/20/01
003-27-001	Investigator withdrew patient	02/06/01	Consistent abnormal lab values since screening	No AE identified	NA
003-71-019	Investigator withdrew patient	03/19/01	Protocol violation – elevated LFT's	No AE identified	NA
003-76-042	Patient requested withdrawal from study	08/20/02	"c/o feeling funny"	Influenza Like Illness	08/10/02
003-77-016	Patient requested withdrawal from study	03/29/02	Pt didn't want to take study drug with septro (cipro?) for baseline UTI.	Dysuria; Urinary Tract Infection NOS	03/28/02
003-83-015	Withdrawn due to non-compliance	10/30/01	Took excluded medications for AE's	Muscle Injury NOS	10/25/01
009-01-006		03/22/03	Patient vomited after first dose of study medication	Vomiting NOS	03/22/03
014-30-009	Investigator withdrew patient	05/03/01	Diagnosed with ankylosing spondylitis	Joint Range of Motion decreased	05/03/01

Study/ Site/ Subjects	Reason for Withdrawal Dataset	Withdrawal Date	Description of the Reason	AE Reported in the AE Database[a]	Onset Date
014-30-019	Patient requested withdrawal from study	05/08/01	Study medication not effective and c/o erectile dysfunction during study	No AE reported	NA
014-30-020	Patient requested withdrawal from study	04/19/01	Pt states that he couldn't tolerate side effects with bowel	Diarrhoea NOS	04/13/01
014-36-017	Patient requested withdrawal from study	05/21/01	Pt was in a MVA 05/16/01 and started taking pain meds for his pain	Whiplash Injury; Hypoaesthesia; Paraesthesia NEC	05/20/01
014-040-007	Investigator withdrew patient	12/15/00	Elevated CK and LFTs Prior to dosing	No AE reported	NA
014-040-016	Withdrawn due to non-compliance	02/14/01	Pt. took vicodin for migraines	Migrane NOS	02/11/01
014-54-024	Patient requested withdrawal from study	04/19/01	Pt. did not like the way the drug made him feel (he didn't give specific AE)	No AE reported	NA
014-55-009	Patient non-compliant with protocol	07/27/01	Exclusion med Pt needed for gout	Gout	07/07/01
014-57-002	Withdrawn due to non-compliance	06/07/01	Pt took exclusionary meds (vicodin, skelaxin) to treat an AE	Back pain	05/24/01
014-57-009	Withdrawn due to non-compliance	05/29/01	Pt had a gout flare that required excluded medications.	Gout Aggravated	05/23/01
014-60-017	Other	06/08/01	Nausea, Vomiting and Somnolence	Somnolence	5/26/01
014-63-014		06/11/03	Vagal Response, Abdominal cramps[b]	No AE reported	06/08/03
			Nausea,	No AE reported	06/09/03
			Vomiting, Dizziness, Light headedness, Weakness, Headache,	No AE reported	06/12/03
015-08-020	Patient requested withdrawal from study	04/09/01	Pt. had a SAE of chest pains and no longer wanted to participate in study	Chest pain NEC	04/06/01

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On Original

Study/ Site/ Subjects	Reason for Withdrawal Dataset	Withdrawal Date	Description of the Reason	AE Reported in the AE Database[a]	Onset Date
015-10-014	Investigator withdrew patient	02/07/01	Patient broke out in a rash	Dermatitis NOS	05/02/01
015-14-015	Investigator withdrew patient	04/12/01	Patient diagnosed with scabies and was put on the excluded medications by her PCP	Scabies infestation	04/12/01
021-132-016	Patient non-compliant with protocol	5/22/03	From 5/14/03 patient on prozac (exclusionary medication)	Depression aggravated	5/8/03
021-140-014	Withdrawn due to non-compliance	4/15/03	PT was drinking and was admitted to hospital	No SAE reported	NA
021-178-001	Patient non-compliant with protocol	04/01/03	Subject started taking antidepressant	Anxiety NEC	03/06/03
021-183-072	Investigator withdrew patient	05/12/03	Patient started Pamelor for depression 10 days ago	Depression aggravated	02/05/03
021-183-082	Other	04/15/03	Non-serious AE requiring excluded con medications	Cellulitis Joint effusion Arthralgia	04/07/03 04/07/03 0408/03
021-188-002	Patient non-compliant with protocol	05/27/03	Pt took prednisone during last 3 weeks of study due to lower back pain	Back pain	05/22/03
023-207-026	Patient non-compliant with protocol	12/12/02	Got cortisone injection for foot pain and swelling	Pain exacerbated	12/11/03
023-207-074	Patient non-compliant with protocol	4/29/03	Patient received a steroid injection from a podiatrist on 4/5/03.	Plantar fasciitis	4/5/03
023-207-077	Investigator withdrew patient	04/04/03	Pt demonstrated renal insufficiency via lab reports	No AE identified	NA
023-230-029	Other	03/07/03	Medication for depression excluded	Depression aggravated	03/03/03
023-270-018	Patient requested withdrawal from study	6/26/03	Patient has been ill with sinus infection and low iron levels, not associated with study drug.	Sinusitis NOS	6/23/03

Conclusions

In this reviewer's opinion, the data provided with this submission showed that the incidence of adverse events leading to study discontinuation is consistent with the Ultram label. However, this is not a direct comparisons between the incidence of adverse events leading to discontinuations due to Tramadol HCl ER and Ultram and has therefore many deficiencies and cannot be viewed as a robust assessment.

Overall, the incidence of adverse events leading to premature termination was greater in the Tramadol HCl ER flexible dose group compared to any other Tramadol HCl ER dosing groups.
The number of patients who prematurely terminated due to adverse events was greater in the Tramadol HCl ER 300 mg and 400 mg groups compared to other fixed dose groups. However, no pairwise comparisons were made therefore is impossible to say whether or not those differences are statistically significant.

The incidence of premature discontinuations over time due to adverse events is increasing over time and appears to be dose-dependent. It is higher in >=65 age category than among patients less than 65 years of age.

Tatiana Oussova, M.D., M.P.H.

APPENDIX 1

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

	Tramadol HCl ER							
MedDRA Body System MedDRA Preferred Term	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=538) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
All Body System	55 (13.6%)	88 (22.0%)	118 (29.5%)	60 (29.7%)	566 (33.2%)	887 (28.5%)	52 (9.7%)	16 (12.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.5%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
ANAEMIA NOS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
LYMPHADENOPATHY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	0 (0.0%)	3 (0.8%)	2 (0.5%)	2 (1.0%)	13 (0.8%)	20 (0.6%)	1 (0.2%)	1 (0.8%)
ANGINA PECTORIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ANGINA UNSTABLE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	1 (0.8%)
ATRIAL FIBRILLATION	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
BRADYCARDIA NOS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
CORONARY ARTERY DISEASE NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
MITRAL VALVE INCOMPETENCE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
MYOCARDIAL INFARCTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
PALPITATIONS	0 (0.0%)	2 (0.5%)	1 (0.3%)	0 (0.0%)	5 (0.3%)	8 (0.3%)	0 (0.0%)	0 (0.0%)
SINUS TACHYCARDIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
TACHYCARDIA NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
CONGENITAL AND FAMILIAL/GENETIC DISORDERS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
SICKLE CELL ANAEMIA WITH CRISIS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

	Tramadol HCl ER							
MedDRA Body System MedDRA Preferred Term	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=538) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
EAR AND LABYRINTH DISORDERS	2 (0.5%)	2 (0.5%)	2 (0.5%)	0 (0.0%)	3 (0.2%)	9 (0.3%)	0 (0.0%)	0 (0.0%)
LABYRINTHITIS NOS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
TINNITUS	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
VERTIGO NEC	1 (0.2%)	2 (0.5%)	1 (0.3%)	0 (0.0%)	2 (0.1%)	6 (0.2%)	0 (0.0%)	0 (0.0%)
EYE DISORDERS	0 (0.0%)	1 (0.3%)	1 (0.3%)	2 (1.0%)	9 (0.5%)	13 (0.4%)	0 (0.0%)	0 (0.0%)
BLOODSHOT EYE	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
EYE IRRITATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
LACRIMATION INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PHOTOPHOBIA	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
VISION BLURRED	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	5 (0.3%)	7 (0.2%)	0 (0.0%)	0 (0.0%)
VISUAL DISTURBANCE NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	33 (8.2%)	57 (14.3%)	94 (23.5%)	41 (20.3%)	339 (19.9%)	564 (18.1%)	10 (1.9%)	4 (3.1%)
ABDOMINAL DISTENSION	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN NOS	1 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	7 (0.4%)	9 (0.3%)	1 (0.2%)	0 (0.0%)
ABDOMINAL PAIN UPPER	1 (0.2%)	1 (0.3%)	3 (0.8%)	1 (0.5%)	7 (0.4%)	13 (0.4%)	1 (0.2%)	0 (0.0%)
ABDOMINAL TENDERNESS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
APPENDICITIS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
APTYALISM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
CONSTIPATION	4 (1.0%)	7 (1.8%)	10 (2.5%)	10 (5.0%)	48 (2.8%)	79 (2.5%)	1 (0.2%)	0 (0.0%)
CONSTIPATION AGGRAVATED	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
DIARRHOEA NOS	2 (0.5%)	3 (0.8%)	2 (0.5%)	1 (0.5%)	12 (0.7%)	20 (0.6%)	1 (0.2%)	1 (0.8%)
DRY MOUTH	0 (0.0%)	1 (0.3%)	5 (1.3%)	2 (1.0%)	5 (0.3%)	13 (0.4%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER: 100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
DYSPEPSIA	1 (0.2%)	2 (0.5%)	5 (1.3%)	0 (0.0%)	1 (0.1%)	9 (0.3%)	0 (0.0%)	0 (0.0%)
DYSPEPSIA AGGRAVATED	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
DYSPHAGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
FAECAL IMPACTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
FLATULENCE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
GASTRIC ULCER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
GASTRITIS NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
GASTRO-OESOPHAGEAL REFLUX DISEASE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL UPSET	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ILEUS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
NAUSEA	18 (4.0%)	29 (7.3%)	47 (11.8%)	19 (9.4%)	167 (9.8%)	278 (8.9%)	5 (0.9%)	3 (2.3%)
NAUSEA AGGRAVATED	1 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
OESOPHAGEAL REFLUX AGGRAVATED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PANCREATITIS ACUTE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
PANCREATITIS NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
VOMITING AGGRAVATED	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
VOMITING NOS	7 (1.7%)	9 (2.3%)	18 (4.5%)	6 (3.0%)	78 (4.6%)	118 (3.8%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (2.5%)	17 (4.3%)	22 (5.5%)	15 (7.4%)	65 (3.8%)	129 (4.2%)	17 (3.2%)	1 (0.8%)
ASTHENIA	4 (1.0%)	5 (1.3%)	10 (2.5%)	4 (2.0%)	16 (0.9%)	39 (1.3%)	2 (0.4%)	1 (0.8%)
CHEST PAIN NEC	1 (0.2%)	1 (0.3%)	1 (0.3%)	2 (1.0%)	6 (0.4%)	11 (0.4%)	2 (0.4%)	0 (0.0%)
CHEST TIGHTNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.2%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER: 100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
FALL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
FEELING ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.3%)	5 (0.2%)	1 (0.2%)	0 (0.0%)
FEELING HOT	1 (0.2%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	5 (0.2%)	0 (0.0%)	0 (0.0%)
FEELING HOT AND COLD	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
FEELING JITTERY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.2%)	4 (0.1%)	1 (0.2%)	0 (0.0%)
GENERAL SYMPTOM NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
INFLUENZA LIKE ILLNESS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
JOINT SWELLING	1 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	3 (0.1%)	1 (0.2%)	0 (0.0%)
LETHARGY	0 (0.0%)	2 (0.5%)	1 (0.3%)	0 (0.0%)	7 (0.4%)	10 (0.3%)	2 (0.4%)	0 (0.0%)
MALAISE	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
MENTAL STATUS CHANGES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
OEDEMA LOWER LIMB	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
PAIN EXACERBATED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
PAIN NOS	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
PERIPHERAL SWELLING	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	1 (0.2%)	0 (0.0%)
PITTING OEDEMA	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PYREXIA	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
RIGORS	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.5%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
SHIVERING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
SLUGGISHNESS	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.4%)	0 (0.0%)
WEAKNESS	0 (0.0%)	4 (1.0%)	4 (1.0%)	5 (2.5%)	12 (0.7%)	25 (0.8%)	3 (0.6%)	0 (0.0%)
HEPATO-BILIARY DISORDERS	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	2 (0.1%)	1 (0.2%)	0 (0.0%)
CHOLECYSTITIS NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

	Tramadol HCl ER							
MedDRA Body System MedDRA Preferred Term	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
CHOLELITHIASIS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.2%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
SYSTEMIC LUPUS ERYTHEMATOSUS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	2 (0.5%)	6 (1.5%)	3 (0.8%)	1 (0.5%)	15 (0.9%)	27 (0.8%)	3 (0.6%)	1 (0.8%)
CELLULITIS	0 (0.0%)	2 (0.5%)	1 (0.3%)	0 (0.0%)	2 (0.1%)	5 (0.2%)	0 (0.0%)	0 (0.0%)
GASTROENTERITIS HELICOBACTER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
GASTROENTERITIS NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
GASTROENTERITIS VIRAL NOS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
GINGIVITIS INFECTION NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
HERPES ZOSTER	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.2%)	0 (0.0%)
INFLUENZA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
NASOPHARYNGITIS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
OSTEOMYELITIS NOS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
OTITIS MEDIA NOS	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PHARYNGITIS NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
PNEUMONIA MYCOPLASMAL	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PNEUMONIA NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	1 (0.2%)	0 (0.0%)
SCABIES INFESTATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
SINUSITIS NOS	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.5%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
UPPER RESPIRATORY TRACT INFECTION NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
URINARY TRACT INFECTION NOS	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

	Tramadol HCl ER							
MedDRA Body System MedDRA Preferred Term	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
INJURY AND POISONING	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	10 (0.6%)	14 (0.5%)	3 (0.6%)	0 (0.0%)
ABRASION NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ACCIDENT NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
BACK INJURY NOS	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	2 (0.1%)	2 (0.4%)	0 (0.0%)
CARTILAGE INJURY	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
HEAD INJURY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
HIP FRACTURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
INJURY NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
JOINT SPRAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
LIMB INJURY NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
MUSCLE INJURY NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
NERVE ROOT INJURY CERVICAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
WHIPLASH INJURY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
POISONING NOS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS	0 (0.0%)	6 (1.5%)	8 (2.0%)	2 (1.0%)	29 (1.7%)	45 (1.4%)	5 (0.9%)	7 (5.5%)
ALANINE AMINOTRANSFERASE INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.2%)	4 (0.1%)	1 (0.2%)	1 (0.8%)
ASPARTATE AMINOTRANSFERASE INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.2%)	4 (0.1%)	1 (0.2%)	1 (0.8%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER 100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
BLOOD ALKALINE PHOSPHATASE INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD CALCIUM INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.8%)
BLOOD CREATINE INCREASED	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD CREATINE PHOSPHOKINASE INCREASED	0 (0.0%)	1 (0.3%)	2 (0.5%)	1 (0.5%)	3 (0.2%)	7 (0.2%)	1 (0.2%)	2 (1.6%)
BLOOD CREATININE INCREASED	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.8%)
BLOOD GLUCOSE INCREASED	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.5%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
BLOOD IN STOOL	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD LACTATE DEHYDROGENASE INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	3 (0.1%)	0 (0.0%)	1 (0.8%)
BLOOD PRESSURE INCREASED	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	3 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
BLOOD UREA INCREASED	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
BODY TEMPERATURE INCREASED	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
ELECTROCARDIOGRAM P WAVE ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ENZYME ABNORMALITY NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
HEART RATE INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
LABORATORY TEST ABNORMAL NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
LIVER FUNCTION TESTS NOS ABNORMAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
RED BLOOD CELL COUNT DECREASED	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
WEIGHT DECREASED	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	3 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
WEIGHT FLUCTUATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER 100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
WHITE BLOOD CELL INCREASED	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	1 (0.2%)	4 (1.0%)	4 (1.0%)	3 (1.5%)	15 (0.9%)	27 (0.9%)	2 (0.4%)	0 (0.0%)
ANOREXIA	0 (0.0%)	0 (0.0%)	4 (1.0%)	2 (1.0%)	9 (0.5%)	15 (0.5%)	0 (0.0%)	0 (0.0%)
APPETITE DECREASED NOS	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
GOUT	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (0.1%)	4 (0.1%)	2 (0.4%)	0 (0.0%)
GOUT AGGRAVATED	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
HYPOKALAEMIA	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	9 (2.2%)	11 (2.8%)	8 (2.0%)	1 (0.5%)	25 (1.5%)	54 (1.7%)	11 (2.1%)	1 (0.8%)
ARTHRALGIA	3 (0.7%)	5 (1.3%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	9 (0.3%)	1 (0.2%)	0 (0.0%)
BACK PAIN	1 (0.2%)	0 (0.0%)	4 (1.0%)	0 (0.0%)	5 (0.3%)	10 (0.3%)	1 (0.2%)	0 (0.0%)
BACK PAIN AGGRAVATED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
BAKER'S CYST	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
BURSITIS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
COSTAL PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
FIBROMYALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
JOINT EFFUSION	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
JOINT RANGE OF MOTION DECREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
JOINT STIFFNESS	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	1 (0.2%)	0 (0.0%)
MUSCLE CRAMPS	1 (0.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

	Tramadol HCl ER							
MedDRA Body System MedDRA Preferred Term	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=538) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
MUSCLE SPASMS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	1 (0.2%)	0 (0.0%)
MUSCLE TWITCHING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
MUSCLE WEAKNESS NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
MYALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.2%)	0 (0.0%)
NECK PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	1 (0.2%)	0 (0.0%)
NECK STIFFNESS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
OSTEOARTHRITIS AGGRAVATED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
OSTEOARTHRITIS NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PAIN IN LIMB	3 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	6 (0.2%)	2 (0.4%)	0 (0.0%)
PLANTAR FASCIITIS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
SCIATICA	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	2 (0.1%)	2 (0.4%)	0 (0.0%)
TEMPOROMANDIBULAR JOINT DISORDER NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
TEMPOROMANDIBULAR JOINT SYNDROME	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
NEOPLASMS BENIGN AND MALIGNANT (INCLUDING CYSTS AND POLYPS)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	3 (0.1%)	1 (0.2%)	0 (0.0%)
BREAST CANCER NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
COLON CANCER NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
OESOPHAGEAL CARCINOMA NOS	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
UTERINE FIBROIDS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	24 (6.0%)	47 (11.8%)	70 (17.5%)	37 (18.3%)	250 (14.7%)	428 (13.8%)	16 (3.0%)	6 (4.7%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

	Tramadol HCl ER							
MedDRA Body System MedDRA Preferred Term	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=538) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
AMNESIA NEC	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
BALANCE IMPAIRED NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
CONVULSIONS NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.2%)	0 (0.0%)
DISTURBANCE IN ATTENTION NEC	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	4 (0.2%)	5 (0.2%)	0 (0.0%)	0 (0.0%)
DIZZINESS (EXC VERTIGO)	13 (3.2%)	25 (6.3%)	30 (7.5%)	14 (6.9%)	114 (6.7%)	196 (6.3%)	6 (1.1%)	1 (0.8%)
DIZZINESS AGGRAVATED	0 (0.0%)	1 (0.3%)	2 (0.5%)	2 (1.0%)	4 (0.2%)	9 (0.3%)	0 (0.0%)	0 (0.0%)
DIZZINESS POSTURAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
FORNICATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
GAIT ABNORMAL NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
GRAND MAL CONVULSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
HEADACHE NOS	5 (1.2%)	8 (2.0%)	14 (3.5%)	3 (1.5%)	28 (1.6%)	58 (1.8%)	2 (0.4%)	2 (1.6%)
HYPERSOMNIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
HYPOAESTHESIA	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	3 (0.2%)	5 (0.2%)	1 (0.2%)	0 (0.0%)
HYPOREFLEXIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
INCREASED ACTIVITY	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
INITIAL INSOMNIA	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
INSOMNIA EXACERBATED	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
INSOMNIA NEC	1 (0.2%)	1 (0.3%)	3 (0.8%)	3 (1.5%)	15 (0.8%)	23 (0.7%)	0 (0.0%)	1 (0.8%)
JERKY MOVEMENT NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
LACUNAR INFARCTION	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
MEMORY IMPAIRMENT	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
MENTAL IMPAIRMENT NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
MIGRAINE AGGRAVATED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
MIGRAINE NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	1 (0.8%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER 100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
MYOCLONIC SEIZURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
NERVE COMPRESSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PARAESTHESIA NEC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (0.1%)	3 (0.1%)	1 (0.2%)	0 (0.0%)
PARAESTHESIA TONGUE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PETIT MAL EPILEPSY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
RESTLESS LEG SYNDROME	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
SEDATION	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	8 (0.5%)	9 (0.3%)	0 (0.0%)	0 (0.0%)
SOMNOLENCE	4 (1.0%)	8 (2.0%)	10 (2.5%)	12 (5.9%)	45 (2.6%)	79 (2.5%)	3 (0.6%)	1 (0.8%)
SYNCOPE	0 (0.0%)	1 (0.3%)	2 (0.5%)	0 (0.0%)	3 (0.2%)	6 (0.2%)	0 (0.0%)	0 (0.0%)
TREMOR NEC	0 (0.0%)	1 (0.3%)	3 (0.8%)	0 (0.0%)	7 (0.4%)	11 (0.4%)	1 (0.2%)	0 (0.0%)
TUNNEL VISION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS								
PREGNANCY NOS	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PSYCHIATRIC DISORDERS	5 (1.2%)	6 (1.5%)	14 (3.5%)	7 (3.5%)	82 (4.8%)	114 (3.7%)	6 (1.1%)	1 (0.8%)
ABNORMAL DREAMS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
ACUTE STRESS DISORDER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
AGITATION	0 (0.0%)	2 (0.5%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
ANORGASMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ANXIETY AGGRAVATED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ANXIETY NEC	1 (0.2%)	1 (0.3%)	4 (1.0%)	0 (0.0%)	18 (1.1%)	24 (0.8%)	1 (0.2%)	0 (0.0%)
COMPLETED SUICIDE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER 100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
CONFUSION	1 (0.2%)	0 (0.0%)	1 (0.3%)	1 (0.5%)	5 (0.3%)	8 (0.3%)	1 (0.2%)	0 (0.0%)
CRYING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
DEPRESSION AGGRAVATED	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	2 (0.4%)	0 (0.0%)
DEPRESSION NEC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (0.6%)	10 (0.3%)	0 (0.0%)	1 (0.8%)
DISORIENTATION	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	3 (0.2%)	5 (0.2%)	0 (0.0%)	0 (0.0%)
DYSPHORIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
EMOTIONAL DISTURBANCE NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
EUPHORIC MOOD	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.5%)	5 (0.3%)	7 (0.2%)	0 (0.0%)	0 (0.0%)
GENERALISED ANXIETY DISORDER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
HALLUCINATION NOS	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.5%)	3 (0.2%)	5 (0.2%)	0 (0.0%)	0 (0.0%)
HALLUCINATION, AUDITORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
HALLUCINATION, VISUAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
HYPOACTIVE SEXUAL DESIRE DISORDER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
IRRITABILITY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
LIBIDO DECREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
LOSS OF LIBIDO	0 (0.0%)	1 (0.3%)	1 (0.3%)	1 (0.5%)	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
MOOD SWINGS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	0 (0.0%)
NERVOUSNESS	2 (0.5%)	1 (0.3%)	3 (0.8%)	2 (1.0%)	9 (0.5%)	17 (0.5%)	0 (0.0%)	0 (0.0%)
PANIC ATTACK	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
RESTLESSNESS	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	3 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
RENAL AND URINARY DISORDERS	0 (0.0%)	2 (0.5%)	3 (0.8%)	0 (0.0%)	23 (1.4%)	28 (0.9%)	2 (0.4%)	0 (0.0%)
BLADDER OBSTRUCTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 8.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER 100 mg (N=403) n (%)	 200 mg (N=400) n (%)	 300 mg (N=400) n (%)	 400 mg (N=202) n (%)	 Flexible Dosing (N=1703) n (%)	 All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
CALCULUS RENAL NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	1 (0.2%)	0 (0.0%)
DIFFICULTY IN MICTURITION	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	5 (0.3%)	7 (0.2%)	1 (0.2%)	0 (0.0%)
DYSURIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
LOIN PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
MICTURITION URGENCY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
NOCTURIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
RENAL INSUFFICIENCY	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
URINARY FREQUENCY	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
URINARY HESITATION	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
URINARY RETENTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
URINE FLOW DECREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0%)	0 (0.0%)	3 (0.8%)	3 (1.5%)	7 (0.4%)	13 (0.4%)	1 (0.2%)	0 (0.0%)
EJACULATION FAILURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ERECTILE DISTURBANCE	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	2 (0.1%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
IMPOTENCE	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	2 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
SEXUAL DYSFUNCTION NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	3 (0.2%)	5 (0.2%)	0 (0.0%)	0 (0.0%)
VAGINAL PROLAPSE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.2%)	1 (0.3%)	6 (1.5%)	2 (1.0%)	5 (0.3%)	15 (0.5%)	0 (0.0%)	1 (0.8%)
APNOEA	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
ASTHMA NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 8.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

MedDRA Body System MedDRA Preferred Term	Tramadol HCl ER 100 mg (N=403) n (%)	 200 mg (N=400) n (%)	 300 mg (N=400) n (%)	 400 mg (N=202) n (%)	 Flexible Dosing (N=1703) n (%)	 All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
CHOKING SENSATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
DYSPHOEA NOS	1 (0.2%)	0 (0.0%)	2 (0.5%)	1 (0.5%)	1 (0.1%)	5 (0.2%)	0 (0.0%)	0 (0.0%)
EPISTAXIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
GLOBUS FEELING IN PHARYNX	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
NASAL PASSAGE IRRITATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
RHINORRHOEA	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
SINUS PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
WHEEZING	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
YAWNING	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
SKIN & SUBCUTANEOUS TISSUE DISORDERS	9 (2.2%)	10 (2.5%)	14 (3.5%)	7 (3.5%)	60 (3.5%)	100 (3.2%)	0 (0.0%)	0 (0.0%)
ALOPECIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
CLAMMINESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
CONTUSION	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
DERMATITIS ALLERGIC	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
DERMATITIS CONTACT	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
DERMATITIS NOS	2 (0.5%)	3 (0.8%)	1 (0.3%)	1 (0.5%)	15 (0.9%)	22 (0.7%)	0 (0.0%)	0 (0.0%)
ERYTHEMA NEC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
EYELID OEDEMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
NIGHT SWEATS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PILOERECTION	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
PRURITUS NOS	6 (1.5%)	4 (1.0%)	6 (1.5%)	2 (1.0%)	20 (1.2%)	38 (1.2%)	0 (0.0%)	0 (0.0%)
RASH GENERALISED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)

Note: A subject can be counted in more than one column.

Table 6.5
Incidence of Adverse Events Leading to Premature Termination
All Patients With Moderate to Severe Pain
(Low Back Pain, Osteoarthritis Pain, and/or Chronic Non-Malignant Pain)

	Tramadol HCl ER							
MedDRA Body System MedDRA Preferred Term	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	Flexible Dosing (N=1703) n (%)	All Doses (N=3108) n (%)	Placebo (N=536) n (%)	Placebo After Tramadol Run-in (N=128) n (%)
RASH MACULO-PAPULAR	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
RASH PRURITIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
SWEATING INCREASED	1 (0.2%)	0 (0.0%)	4 (1.0%)	1 (0.5%)	16 (0.9%)	22 (0.7%)	0 (0.0%)	0 (0.0%)
URTICARIA NOS	0 (0.0%)	1 (0.3%)	1 (0.3%)	2 (1.0%)	1 (0.1%)	5 (0.2%)	0 (0.0%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
KNEE ARTHROPLASTY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
VASCULAR DISORDERS	4 (1.0%)	12 (3.0%)	11 (2.8%)	8 (4.0%)	32 (1.9%)	67 (2.2%)	2 (0.4%)	1 (0.8%)
FLUSHING	4 (1.0%)	6 (1.5%)	7 (1.8%)	5 (2.5%)	19 (1.1%)	41 (1.3%)	1 (0.2%)	0 (0.0%)
HOT FLUSHES NOS	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	7 (0.4%)	9 (0.3%)	0 (0.0%)	0 (0.0%)
HYPERTENSION AGGRAVATED	0 (0.0%)	1 (0.3%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
PERIPHERAL ISCHAEMIA NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
POSTURAL HYPOTENSION	0 (0.0%)	3 (0.8%)	0 (0.0%)	3 (1.5%)	2 (0.1%)	6 (0.3%)	1 (0.2%)	1 (0.8%)
THROMBOPHLEBITIS DEEP	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
VASODILATATION	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	3 (0.2%)	4 (0.1%)	0 (0.0%)	0 (0.0%)

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/s/

Tatiana Oussova
10/29/04 11:24:50 AM
MEDICAL OFFICER

Joel, please, read-if any changes or suggestions-just return it to me Thanks

Joel Schiffenbauer
10/29/04 12:04:55 PM
MEDICAL OFFICER

9/1/05

CLINICAL REVIEW

Review of Complete Response to AE letter of October 29, 2004

SAFETY

Application Type	NDA
Submission Number	21-692 —
Submission Code	CR
Letter Date	March 7, 2005
PDUFA Goal Date	September 7, 2005
Reviewer Name	Lourdes Villalba, M.D.
Review Completion Date	September 1st, 2005
Established Name	Tramadol Extended Release
(Proposed) Trade Name	Ralivia ER/ ——
Therapeutic Class	Opioid Analgesic
Applicant	Biovail
Dosing Regimen	100 mg tablets
Indication	Moderate to moderately severe pain
Intended Population	Adults

- **Scope of this review**

This review focuses on safety concerns raised during the first review cycle for NDA 21-692 (Tramadol Hydrochloride Extended Release, referred as TRAER in this review). Dr. Schiffenbauer has reviewed the responses related to efficacy.

The FDA AE letter of October 29, 2004 identified the following Safety deficiencies:

> 1. The analysis of adverse events as submitted in the Integrated Summary of Safety (ISS) is inadequate. All adverse events were not included in your analyses. As stated in your NDA submission, cases of adverse events were eliminated from the ISS.
>
> 2. An increase in serious thromboembolic events was noted in the flexible dosing group versus placebo.
>
> 3. The proposed label submitted for Ralivia ER is not adequate to address the safety concerns associated with Ralivia ER. Specifically, the label does not include serious adverse events as well as adverse events identified with Ralivia ER but not found in the Ultram® label.

Information needed to resolve deficiencies were as follows:

> Provide additional data to support the risk/benefit ratio:
>
> 1. Conduct an additional trial in osteoarthritis (OA) or chronic lower back pain (CLBP) that demonstrates robust evidence of efficacy and that supports all doses proposed in the label. We recommend that Ultram® be included as a comparator.
>
> 2. Provide additional information regarding the increased number of serious thromboembolic events.
>
> 3. Submit a revised label that addresses the safety findings in the Ralivia ER NDA and which delineates any additional safety and efficacy findings with Ralivia ER, including a description of the carcinogenicity studies you have conducted.
>
> In addition, the Applicant was asked to provide the following information and analyses related to safety:
>
> a. Provide an analysis of outliers and dropouts due to laboratory, vital signs or ECG (including QT intervals) abnormalities, as appropriate. This should include a presentation of the extent of these abnormalities.
>
> b. Provide an analysis of the measures of central tendency as well as shifts from normal to abnormal, as appropriate.

d. For patients with renal or hepatic impairment, you relied on Ultram labeling along with your studies to develop dosing recommendations. Please provide a more detailed explanation on how final conclusions regarding dosage reduction in these patients were reached in each condition.

e. To further evaluate age effect, provide additional data on Ralivia ER exposure-response in elderly (65-75 yrs) and older (>75 yrs) subjects.

- **Review of the current submission (safety component):**

The submission contains an updated ISS, an analysis of thromboembolic events, analyses of vital signs, ECG and laboratory measurements (outliers, dropouts, central tendency and shifts) and analyses by age, as requested in the AE letter. The submission also includes a response in support of the dosing recommendation in hepatically and renally impaired patients. The data sources for these analyses are the studies submitted as part of the December 31, 2003 application. There are no new studies in this application.

On July 18, 2005 the Applicant stated that since the 120-day safety report update submitted on April 30, 2004, for the first review cycle, there have been no new safety reports.

At this time the name "Ralivia" is no longer the proposed name for this product. A new proposed tradename for this product has not been submitted.

- **Conclusions**

The current submission has addressed most of the safety concerns raised by the Agency in the October 29, 2004 AE letter.

In general, the safety profile of TRAER was consistent with that of Ultram®, although because no trial included both products except for a couple of small single dose PK studies, it is impossible to conclude with complete certainty that the safety profile of these two drugs is identical. However, this is a 505(b)(2) application that contains more safety information than most 505(b)(2) applications. If approved, Tramadol ER should carry the same WARNINGS, PRECAUTIONS and CONTRAINDICATIONS as Ultram®, including the potential for physical dependence and abuse, seizures, etc.

There are no safety findings that would preclude approval of TRAER. There were no unique events observed with TRAER that had not been observed with Ultram®.

Review of the original NDA application and additional information provided by the Applicant in the March 7, 2005 submission and subsequent responses to FDA requests for clarification indicate a clear dose response in terms of adverse events, particularly for the most common adverse events such as GI disorders (constipation, nausea, vomiting) and Nervous system disorders (dizziness in particular). This dose response in terms of toxicity needs to be placed into the context of a lack of evidence of a dose response in terms of efficacy.

The NDA database suggests a greater number of patients on TRAER had cardiovascular serious AEs as compared to placebo, but the numbers are small (five vs. two on TRAER and placebo, respectively). As is usually the case, an NDA database is not powered to adequately evaluate cardiovascular safety. Of note, Ultram® has been in the market for longer than twenty years and was never thought to be associated with cardiovascular risk. So did NSAIDs. The Applicant should not be allowed to claim superior CV safety as compared to NSAIDs.

In general, there were similar percentages for cardiac events (all, serious and non-serious) in both treatment groups. A greater rate of vascular events in the TRAER treatment group was driven by the higher rate of "flushing" and "hot flushes" (11.6% vs. 5.4% in the TRAER and placebo groups, respectively). The apparent greater risk of flushing and vasodilation with TRAER may be truly due to greater toxicity of the extended release formulation or to better ascertainment of these events in the Biovail TRAER clinical program. The cause of the "flushing" is not fully clear but appears to be of neurogenic (vasovagal) origin.

Analyses of vital signs indicate a greater incidence of orthostatic hypotension and weight decrease with TRAER as compared to placebo. The rate of orthostatic hypotension appears to be more frequent in the 400 mg dose group and open label flexible dose group (24%), as compared to the 100-300 mg groups and placebo (14%). The rate of weight decrease seems to be dose related (presented by 0.8, 1.8 and 3% of patients receiving

TRAER 200, 300 and 400 mg, respectively, in studies 023 and 021), as compared to 0% on placebo. Although relatively uncommon, it may be relevant for the elderly population.

There were no major differences in the incidence of ECG or laboratory abnormalities in the analysis of these datasets.

The rate of adverse events among the elderly and older elderly were somewhat greater than among the < 65 year population, particularly for the 300 and ~~400 m~~g doses. Events that appear to be most influenced by age were in the GI, Nervous system, Metabolic and nutrition and Vascular and skin and subcutaneous tissues disorders. Of note, tramadol immediate release's maximum recommended dose in the older elderly is 300 mg. No patients >75 were exposed to TRAER 400 mg. The exposure for the >75 year old group was limited to 36 patients at the 100, 200 or 300 mg fixed doses and 99 patients exposed to 100 to 300mg flexible doses.

No studies were conducted to support the dosages recommended in Special Populations section of the label. As per the Biopharm reviewer (Dr. Zhang Lei) information provided by the Applicant in this Complete Response is not satisfactory to support the proposed dose regimen in renally and hepatically impaired patients. There are no PK data to support the proposed dose of TRAER in the elderly . All clinical pharmacology studies were conducted in healthy and young volunteers (mean age 29 to 34 years)

1. Integrated Summary of Safety

The 3/7/05 submission includes an Integrate Summary of Safety table that involves the single dose pre-emptive pain study, four double blind placebo-controlled studies (021, 023, 015 and 014) and one open label study (003, rollover from some of the placebo-controlled studies). PK studies are not included in the table. In general, all adverse events were more frequent in the active treatment group as compared to placebo. Adverse events that occurred in at least 1% of patients in any treatment group are presented below:

Table 1. Incidence (%) of adverse events from all patients in the Ralivia ER clinical program (014, 015, 021, 023, open label safety study (003) and one single dose dental pain study (009). Source: Applicant's Table 2 of Complete Response submitted 3/7/05.

MedDRA System Organ Class Preferred Term	Tramadol ER, all doses N= 3241 n (%)	Placebo N=522 n (%)
Any AE	2563 (81.6)	325 (58.9)
Eye disorders		
Vision blurred	31 (1.0)	3 (0.5)
GI disorders		
Abdominal Pain NOS	53 (1.7)	2 (0.4)
Abdominal Pain upper	89 (2.8)	3 (0.5)
Constipation	733 (23.3)	24 (4.3)
Diarrhea	226 (6.7)	22 (4.0)
Dry mouth	209 (6.7)	7 (1.3)
Dyspepsia	70 (2.2)	7 (1.3)
Nausea	927 (29.5)	43 (7.8)
Sore throat NOS	47 (1.5)	4 (0.7)
Vomiting NOS	323 (10.3)	11 (2.0)
General Disorders & Administr		
Asthenia	231 (7.4)	8 (1.4)
Fall	43 (1.4)	3 (0.5)
Feeling hot	50 (1.6)	1 (0.2)
Influenza like illness	50 (1.6)	3 (0.5)
Lethargy	39 (1.2)	3 (0.5)
Pain NOS	85 (2.7)	10 (1.8)
Rigors	40 (1.3)	1 (0.2)
Weakness	104 (3.3)	5 (0.9)
Infections and Infestations		
Gastroenteritis Viral NOS	47 (1.5)	4 (0.7)
Influenza	78 (2.5)	3 (0.5)
Nasopharingitis	123 (3.9)	26 (4.7)
Sinusitis	90 (2.9)	12 (2.2)
Upper Respiratory Tract Infection	108 (3.4)	18 (3.3)
Urinary Tract Infection NOS	46 (1.5)	6 (1.1)
Investigations		
Blood CK increased	5.3 (1.7)	5(0.9)
Weight Decreased	49 (1.6)	0 (0)
Metabolism and nutrition disorder		
Anorexia	118 (3.8)	0
Appetite Decreased NOS	85 (2.7)	1 (0.2)

Table 1. Inclidence of AE in Ralivia ER clinical program - Continued

Applicant: Biovail

MedDRA System Organ Class Preferred Term	Tramadol ER, all doses N= 3241 n (%)	Placebo N=522 n (%)
Musculoskel., connective tissue and bone		
Arthralgia	104 (3.3)	16 (2.9)
Back Pain	62 (2.0)	10 (1.8)
Muscle Cramps	27 (0.9)	9 (1.6)
Neck Pain	34 (1.1)	6 (1.1)
Pain In Limb	52 (1.7)	12 (2.2)
Nervous system disorder		
Dizziness (exc Vertigo)	831 (26.5)	43 (7.8)
Headache NOS	451 (14.4)	67 (12.1)
Hypoaethesia	38 (1.2)	4 (0.7)
Insomnia NEC	262 (8.3)	16 (2.9)
Paraesthesia NEC	40 (1.3)	4 (0.7)
Somnolence	397 (12.6)	9 (1.6)
Tremor NEC	60 (1.9)	1 (0.2)
Psychiatric disorders		
Anxiety	83 (2.6)	2 (0.4)
Depression NEC	49 (1.6)	0
Euphoric Mood	30 (1.0)	2 (0.4)
Nervousness	111 (3.5)	4 (0.7)
Restlessness	42 (1.3)	1 (0.2)
Resp., thoracic and mediastinal disorders		
Cough	49 (1.6)	10 (1.8)
Dyspnoea NOS	30 (1.0)	2 (0.4)
Nasal congestion	48 (1.5)	4 (0.7)
Rhinorrhoea	50 (1.6)	3 (0.5)
Sinus Congestion	30 (1.0)	3 (0.5)
Sneezing	74 (2.4)	2 (0.4)
Skin and Subcutaneous tissue disorders		
Dermatitis NOS	80 (2.5)	9 (1.6)
Pruritus NOS	278 (8.9)	6 (1.1)
Sweating Increased	150 (4.8)	1 (0.2)
Flushing	361 (11.5)	24 (4.3)
Hot Flashes NOS	80 (2.5)	6 (1.1)
Postural Hypotension	139 (4.4)	11 (2.0)
Vasodilatation	36 (1.1)	4 (0.7)

As noted in Table 1, approximately one in every four patients receiving Ralivia ER had nausea, constipation or dizziness, as compared to one in every 10 or 20 patients in the placebo group. Other adverse events of interest that showed greater rates with Ralivia ER as compared to placebo were asthenia (7% and 1%, respectively), somnolence (13% and 2%), pruritus (9% and 1%) and flushing (12% and 4%).

COMMENT: In this reviewer's opinion, the strategy chosen by the Applicant to pool all the studies included in the current ISS is inappropriate. Additionally it is unclear whether the Applicant is referring to number of events or number of patients having the events. For instance, the Applicant's ISS table lists three anginal episodes under Ralivia ER (angina pectoris, angina pectoris aggravated and angina unstable) and none on placebo. It is unclear if the three anginal

episodes refer to the same patient or to three different patients. Additionally, numerically greater number of rhythm disorders (atrial fibrillation, atrioventricular block, bradycardia, bundle branch blocks, arrhythmia NOS), are listed in the Ralivia ER group, as compared to placebo. However, many of those events may have occurred in the open label study, where there was no exposure to placebo.

The following informational request was sent to the Applicant on 7/21/05:

Please provide a Table of AEs from patients included in studies 021, 023 and 015 only, by treatment group (tramadol or placebo) by MedDRA System Organ Class Preferred Term (similar to Table 2 of the ISS of the 3/7/05 response but without study 014, the dental pain study and the open-label phase of the controlled studies). In the table provide the total number of patients having the adverse event in each organ system class category.

Provide a separate table as described above, only for studies 023 and 021 together, by dose group.

Provide similar summary tables for Serious AEs and Discontinuations due to AE's.

The information was provided by the Applicant on 7/28/05. A new table was generated by the medical reviewer as follows:

Table 2. Incidence (%) of patients with adverse events rates ≥5% and greater than placebo, from studies 015, 021 and 023 of the Ralivia ER clinical program. Source: Applicant's Table 1.1 of 7/28/05 submission.

MedDRA System Organ Class Preferred Term	Tramadol ER, all doses N= 1538 n (%)	Placebo N=536 n (%)
Patients reporting at least one AE	1139 (74)	318 (59)
NERVOUS SYSTEM DISORDERS	**645 (41.9)**	**132 (24.6)**
DIZZINESS (EXC VERTIGO)	338 (22.0)	42 (7.8)
HEADACHE NOS	207 (13.5)	64 (11.9)
SOMNOLENCE	158 (10.3)	9 (1.7)
INSOMNIA NEC	124 (8.1)	16 (3.0)
GI DISORDERS	**681 (44.3)**	**91 (17.0)**
NAUSEA	339 (22.0)	42 (7.8)
CONSTIPATION	294 (19.1)	24 (4.5)
VOMITING NOS	112 (7.3)	11 (2.1)
DIARRHOEA NOS	98 (6.4)	22 (4.1)
DRY MOUTH	110 (7.2)	7 (1.3)
GENERAL DISORDERS AND ADMIN SITE	**308 (20.0)**	**61 (11.4)**
ASTHENIA	87 (5.7)	8 (1.5)
VASCULAR DISORDERS	**232 (15.1)**	**46 (8.6)**
FLUSHING	151 (9.8%)	24 (4.5)

MedDRA System Organ Class Preferred Term	Tramadol ER, all doses N=1538 n (%)	Placebo N=536 n (%)
SKIN & SUBCUTANEOUS TISSUE DISORDERS	**224 (14.6)**	**22 (4.1)**
PRURITUS NOS	122 (7.9)	6 (1.1)
SWEATING INCREASED	47 (3.1)	1 (0.2)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DIS	**155 (10.1)**	**66 (12.3)**
PSYCHIATRIC DISORDERS	**145 (9.4)**	**46 (3.0)**
NERVOUSNESS	24 (4.5%)	4 (0.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**130 (8.5)**	**30 (5.6)**
INVESTIGATIONS	**96 (6.2)**	**30 (5.6)**
METABOLISM AND NUTRITION DISORDERS	**101 (6.6)**	**13 (2.4)**
ANOREXIA	46 (3.0)	1 (0.2)
APPETITE DECREASED NOS	31 (2.0)	1 (0.2)
INJURY AND POISONING	**56 (3.6)**	**15 (2.8)**
RENAL AND URINARY DISORDERS	**52 (3.4)**	**5 (0.9)**

COMMENT: The results in Table 2 which does not include the acute pain and the open label study are consistent with Table 1. Adverse events were more frequent in the Tramadol ER groups as compared to placebo. The most common events were related to the neurologic system (dizziness (22%) and sleep disorders (18%) followed by the gastrointestinal system (nausea (22%), constipation (20%) and vomiting (7%)). These events are known to occur with Ultram® and other opioids.

Of note, other events that were more common in Ralivia as compared to placebo were asthenia, feeling hot, rigors, influenza-like illness, drug withdrawal syndrome, shivering, sweating increased. These events might be related to physical dependence and are also known to occur with Ultram® and other opioids.

Among "investigations", 1.2% of patients (n=19) presented weight decrease as compared to none on placebo. The cause of weight decrease might be related to anorexia and decreased appetite, presented by 3% and 2% of patients on Ralivia ER, as compared to 0.2% and 0.2 % of patients on placebo. This finding could be a potential concern in the elderly.

1.1 Dose Response:

Analysis of adverse events in terms of dose indicate a clear dose response, particularly for most common events such as gastrointestinal and nervous system disorders (Table 3).

Table 3. NDA 21-692. Adverse Events with clear evidence of a dose response. Studies 021 and 023 only.

MedDRA System Organ Class MedDRA Preferred Term	TRAER 100 mg (N=403)	TRAER 200 mg (N=400)	TRAER 300 mg (N=400)	TRAER 400 mg (N=202)	Placebo (N=406)
GASTROINTESTINALDISORDERS	**139 (34.5%)**	**173 (43.3%)**	**196 (49.0%)**	**109 (54.0%)**	**69 (17.0%)**
NAUSEA	61 (15.1%)	90 (22.5%)	102 (25.5%)	53 (26.2%)	32 (7.9%)
CONSTIPATION	49 (12.2%)	68 (17.0%)	85 (21.3%)	60 (29.7%)	17 (4.2%)
VOMITING NOS	20 (5.0%)	29 (7.3%)	34 (8.5%)	19 (9.4%)	11 (2.7%)
NERVOUS SYSTEM DISORDERS	**138 (34.2%)**	**168 (42.0%)**	**167 (41.8%)**	**104 (51.5%)**	**98 (24.1%)**
DIZZINESS(EXC VERTIG)	64 (15.9%)	81 (20.3%)	90 (22.5%)	57 (28.2%)	28 (6.9%)
SOMNOLENCE	33 (8.2%)	45 (11.3%)	29 (7.3%)	41 (20.3%)	7 (1.7%)
INSOMNIA NEC	26 (6.5%)	32 (8.0%)	36 (9.0%)	22 (10.9%)	13 (3.2%)
GENERAL DISORDERS AND ADMIN SITE CONDITIONS	**58 (14.4%)**	**79 (19.8%)**	**93 (23.3%)**	**50 (24.8%)**	**49 (12.1%)**
ASTHENIA	14 (3.5%)	24 (6.0%)	26 (6.5%)	13 (6.4%)	7 (1.7%)
WEAKNESS	3 (0.7%)	8 (2.0%)	14 (3.5%)	9 (4.5%)	5 (1.2%)
RIGORS	3 (0.7%)	2 (0.5%)	9 (2.3%)	7 (3.5%)	1 (0.2%)
INFLUENZA LIKE ILLN	1 (0.2%)	6 (1.5%)	7 (1.8%)	4 (2.0%)	2 (0.5%)
VASCULAR DISORDERS	**43 (10.7%)**	**64 (16.0%)**	**58 (14.5%)**	**46 (22.8%)**	**36 (8.9%)**
FLUSHING	31 (7.7%)	40 (10.0%)	35 (8.8%)	32 (15.8%)	18 (4.4%)
POSTURAL HYPOTENSION	7 (1.7%)	17 (4.3%)	8 (2.0%)	11 (5.4%)	9 (2.2%)
HOT FLUSHES NOS	4 (1.0%)	8 (2.0%)	11 (2.8%)	4 (2.0%)	2 (0.5%)
SKIN & SUBCUTANEOUS TISSUE	**43 (10.7%)**	**57 (14.3%)**	**61 (15.3%)**	**39 (19.3%)**	**17 (4.2%)**
PRURITUS NOS	25 (6.2%)	34 (8.5%)	30 (7.5%)	24 (11.9%)	4 (1.0%)
SWEATING INCREASED	6 (1.5%)	8 (2.0%)	15 (3.8%)	13 (6.4%)	1 (0.2%)
PSYCHIATRIC DISORDERS	**20 (5.0%)**	**38 (9.5%)**	**49 (12.3%)**	**27 (13.4%)**	**14 (3.4%)**
NERVOUSNESS	7 (1.7%)	13 (3.3%)	18 (4.5%)	8 (4.0%)	3 (0.7%)
ANXIETY NEC	2 (0.5%)	6 (1.5%)	14 (3.5%)	2 (1.0%)	2 (0.5%)
DEPRESSION NEC	2 (0.5%)	4 (1.0%)	7 (1.8%)	3 (1.5%)	0
INVESTIGATIONS					
WEIGHT DECREASED	0	3 (0.8%)	7 (1.8%)	6 (3.0%)	0
METABOLISM AND NUTRITION	13 (3.2%)	19 (4.8%)	36 (9.0%)	25 (12.4%)	10 (2.5%)
ANOREXIA	3 (0.7%)	7 (1.8%)	21 (5.3%)	12 (5.9%)	1 (0.2%)
APPETITE DECREASED	5 (1.2%)	9 (2.3%)	8 (2.0%)	7 (3.5%)	0

1.2 Serious Adverse Events and Discontinuations due to Adverse Events

Summary tables of serious AEs and discontinuations due to AE from studies 015, 021 and 023 are presented in Table 4 and Table 5.

There were no substantial differences in the percentages of AEs in both treatment groups. Adverse events in study 014 are difficult to interpret, since there was a run-in period that selected out patients who did not tolerate Ralivia. Findings in the open-label study are difficult to interpret because of the lack of controls.

This NDA database is relatively small to adequately address safety. However, this is a 505 (b)(2) application. No additional safety studies will be required at this juncture.

Table 4. NDA 21-692 - Patients with serious AEs by treatment group in studies 015, 021 and 023.

MedDRA System Organ MedDRA Preferred Term	Tramadol HCl ER (N=1538)	Placebo (N=536)
GASTROINTESTINAL DISORDERS	6 (0.4%)	1 (0.2%)
PANCREATITIS NOS	2 (0.1%)	0
ABDOMINAL PAIN NOS	1 (<0.1%)	0
APPENDICITIS	1 (<0.1%)	0
ILEUS	1 (<0.1%)	0
INGUINAL HERNIA NOS	1 (<0.1%)	0
PANCREATITIS ACUTE	0	1 (0.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (0.3%)	2 (0.4%)
CHEST PAIN NEC	3 (0.2%)	1 (0.2%)
CHEST TIGHTNESS	0	1 (0.2%)
DRUG WITHDRAWAL SYNDROME	1 (<0.1%)	0
PAIN NOS	1 (<0.1%)	0
HEPATO-BILIARY DISORDERS	7 (0.5%)	0
CHOLELITHIASIS	4 (0.3%)	0
CHOLECYSTITIS NOS	2 (0.1%)	0
CHOLECYSTITIS ACUTE NOS	1 (<0.1%)	0
INFECTIONS AND INFESTATIONS	4 (0.3%)	0
CELLULITIS	1 (<0.1%)	0
GASTROENTERITIS NOS	1 (<0.1%)	0
OSTEOMYELITIS NOS	1 (<0.1%)	0
URINARY TRACT INFECTION NOS	1 (<0.1%)	0
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	4 (0.3%)	0
PAIN IN LIMB	2 (0.1%)	0
BAKER'S CYST	1 (<0.1%)	0
NECK PAIN	1 (<0.1%)	0
OSTEOARTHRITIS AGGRAVATED	1 (<0.1%)	0
CARDIAC DISORDERS	2 (0.1%)	1 (0.2%)
ATRIAL FIBRILLATION	1 (<0.1%)	0
BRADYCARDIA NOS	1 (<0.1%)	0
CORONARY ARTERY DISEASE NOS	0	1 (0.2%)
VASCULAR DISORDERS	3 (0.2%)	0
HYPERTENSION AGGRAVATED	2 (0.1%)	0
THROMBOPHLEBITIS DEEP	1 (<0.1%)	0
NEOPLASMS BENIGN AND MALIGNANT (INCLUDING CYSTS AND POLYPS)	2 (0.1%)	0
OESOPHAGEAL CARCINOMA NOS	1 (<0.1%)	0
TERATOMA NOS	1 (<0.1%)	0
NERVOUS SYSTEM DISORDERS	1 (<0.1%)	1 (0.2%)
CONVULSIONS NOS	0	1 (0.2%)
LACUNAR INFARCTION	1 (<0.1%)	0
PSYCHIATRIC DISORDERS	2 (0.1%)	0
ANXIETY NEC	1 (<0.1%)	0
CONFUSION	1 (<0.1%)	0
DEPRESSION NEC	1 (<0.1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.1%)	0
DYSPNOEA NOS	1 (<0.1%)	0
PLEURAL EFFUSION	1 (<0.1%)	0
SURGICAL AND MEDICAL PROCEDURES	0	2 (0.4%)
GASTRIC OPERATION NOS	0	1 (0.2%)
KNEE ARTHROPLASTY	0	1 (0.2%)
CONGENITAL AND FAMILIAL/GENETIC DISORDERS	1 (<0.1%)	0
SICKLE CELL ANAEMIA WITH CRISIS	1 (<0.1%)	0
INJURY AND POISONING	0	1 (0.2%)
LIMB INJURY NOS	0	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (<0.1%)	0
POISONING NOS	1 (<0.1%)	0
INVESTIGATIONS	1 (<0.1%)	0
RED BLOOD CELL COUNT DECREASED	1 (<0.1%)	0
METABOLISM AND NUTRITION DISORDERS	1 (<0.1%)	0
GOUT	1 (<0.1%)	0
RENAL AND URINARY DISORDERS	0	1 (0.2%)

Table 5. NDA 21-692. AE's that lead to discontinuation in at least 0.5% of patients (studies 015, 021 and 023).

MedDRA System Organ Class MedDRA Preferred Term Number of Patients Reporting at	Tramadol HCl ER (N=1538)	Placebo (N=536)

Least 1 Adverse Event	359 (23.3%)	52 (9.7%)
GASTROINTESTINAL DISORDERS	176 (11.4%)	7 (1.3%)
NAUSEA	121 (7.9%)	5 (0.9%)
VOMITING NOS	43 (2.8%)	0
CONSTIPATION	36 (2.3%)	1 (0.2%)
DIARRHOEA NOS	8 (0.5%)	1 (0.2%)
ABDOMINAL PAIN UPPER	7 (0.5%)	1 (0.2%)
DRY MOUTH	8 (0.5%)	0
DYSPEPSIA	8 (0.5%)	0
NERVOUS SYSTEM DISORDERS	157 (10.2%)	13 (2.4%)
DIZZINESS (EXC VERTIGO)	98 (6.4%)	6 (1.1%)
SOMNOLENCE	35 (2.3%)	3 (0.6%)
HEADACHE NOS	32 (2.1%)	2 (0.4%)
INSOMNIA NEC	8 (0.5%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE COND	59 (3.8%)	15 (2.8%)
ASTHENIA	23 (1.5%)	2 (0.4%)
WEAKNESS	13 (0.8%)	3 (0.6%)
PSYCHIATRIC DISORDERS	33 (2.1%)	6 (1.1%)
NERVOUSNESS	8 (0.5%)	0
SKIN & SUBCUTANEOUS TISSUE DISORDERS	38 (2.5%)	0
PRURITUS NOS	18 (1.2%)	0
DERMATITIS NOS	10 (0.7%)	0
SWEATING INCREASED	7 (0.5%)	0
VASCULAR DISORDERS	33 (2.1%)	2 (0.4%)
FLUSHING	23 (1.5%)	1 (0.2%)
POSTURAL HYPOTENSION	6 (0.4%)	1 (0.2%)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	26 (1.7%)	8 (1.5%)
ARTHRALGIA	9 (0.6%)	1 (0.2%)
METABOLISM AND NUTRITION DIS	15 (1.0%)	2 (0.4%)
ANOREXIA	7 (0.5%)	0
INFECTIONS AND INFESTATIONS	13 (0.8%)	3 (0.6%)
INVESTIGATIONS	13 (0.8%)	3 (0.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	11 (0.7%)	0
CARDIAC DISORDERS	8 (0.5%)	1 (0.2%)

As expected, there were more discontinuations due to adverse events in the tramadol hydrochloride ER group as compared to placebo.

2. Cardiovascular adverse events

In response to the AE letter of October 29, 2004, the Applicant provided additional information from 18 patients with cardiovascular serious adverse events (CV SAEs) as well as 36 patients with non-serious AEs identified in the ISS tables. The term "Serious" refers to the regulatory definition of seriousness (events that cause death, hospitalization, prolong hospitalization, are life threatening or associated with congenital malformation). A summary of the CV serious and non-serious AEs in the Ralivia clinical program as presented by the Applicant is shown in the following table:

Table 6. Summary of Cardiovascular serious and non-serious events in NDA 21-692 as presented by the Applicant in the 3/7/05 complete response.

	n	Placebo-controlled studies (12 wks)		Open-label study (up to 58 wks). All Ralivia ER
CV Serious AE	**18[1]**	**7**		**11**
		TRAER	Placebo	
		5	2	
CV Non-serious AE	**36**	**21**		**15**
Hypertension aggravated	25	16		9
		TRAER	Placebo	
		12	4	
Non-hypertension aggrav[2]	11	5		6
		TRAER	Placebo	
		4	1	9

1. One patient with MI is counted under CV serious and non-serious. 2. CV non-serious non-hypertension aggravated includes cases such as bradycardia, atrial fibrillation and coronary artery disease. Source, section 4.1 and 4.2 of 3/7/05 ISS.

In some parts of the submission the Applicant refers to 18 patients with CV serious AE and in others refers to 17 patients with CV serious AE and one non-serious AE. This apparent discrepancy is because of patient 023-206-009, who had a non-serious "myocardial infarction NOS" and appears counted as serious and non-serious.

> *COMMENT: The numbers are small but suggest a greater risk of cardiovascular serious and non-serious adverse events in the Ralivia ER group as compared to placebo in the 12-week placebo-controlled studies.*

2.1 CV Serious adverse events

Of the 18 patients with CV SAEs, 16 were on TRAER and two were on placebo at the time of the event. These events are presented in Table 3.

Of the 18 patients, 12 had the condition pre-existing at screening/baseline before study medication were started and 6 had risk factors present at screening/baseline, which continued through the study treatment period.

Eleven of the 16 CV SAEs on TRAER occurred in the one-year open label safety study, which was a flexible dose study with less stringent entry criteria than the randomized studies and no placebo comparison. Two patients had been rolled over from the placebo-controlled studies (one from 014 and 0ne from 015); the rest had entered directly into the open label study.

Of note most patients with CV serious AEs discontinued from the study due to the listed CV adverse event. However, some patients are listed as withdrawn due to another adverse event (003-83-015, a 44 year old woman who had a pulmonary embolism is listed as discontinued due to muscle injury; 003-02-035, a 65 year old man who had angina pectoris aggravated is listed as discontinued due to anxiety and nervousness). Additionally, patient 003-31-002, a 34 year old woman who developed thromboembolism is listed as discontinued due to non-compliance with the protocol (took Darvocet).

COMMENT: Altogether, there were more CV serious events on TRAER (n=16) as compared to placebo (n=2). Eleven of the 16 occurred in the open label study. Still, five occurred during the placebo-controlled phase of the trials, as compared to two in the placebo group. The listing of patients with CV serious events is presented in Table 3. The lack of a control arm in study 003 precludes definitive conclusions regarding the cardiovascular safety of TRAER.

The size and duration of this NDA database is inadequate to rule out an increased risk of cardiovascular events with TRAER as compared to placebo.

2.2 CV non-serious AEs

In addition to the analysis of CV serious AEs, the Applicant presented analyses of CV non-serious AEs, separated into two categories: "hypertension aggravated" (25 cases) and "non-hypertension aggravated" (11 cases).

2.2.1 CV Non-serious, hypertension related events

COMMENT: It is unclear why the Applicant chose "hypertension aggravated" as a category instead of "hypertension NOS" or all hypertension related events to conduct these analyses.

Adverse events related to changes in blood pressure selected from the Applicant's 3/7/05 ISS table are listed in Table 8 of this review. Of note, these events are included under two different MedDRA System Organ Classes: Investigations and Vascular disorders. There were 26 and 5 cases of blood pressure increased under Investigations. There were also 23 cases of HTN aggravated and 22 of HTN NOS under Vascular disorders. It unclear whether these are the same of different patients but it is likely that some of the patients with HTN aggravated are also listed under HTN NOS.

Table 8. Listing of adverse events related to increases in blood pressure in studies 021, 023, 014, 015, open label study and one single dose dental pain study.

MedDRA Organ System Class Preferred Term	Tramadol ER, all doses N= 3241 n (%)	Placebo N=522 n (%)
Investigations		
Blood Pressure Diastolic Increased	1 (0.0)	1 (0.2)
Blood Pressure Increased)	26 (0.8)	5 (0.9)
Vascular disorders		
Hypertension aggravated	23 (0.7)	4 (0.7)
Hypertension NOS	22 (0.7)	2 (0.4)

Source, Table 2 of the 3/7/05 ISS.

There does not appear to be a substantial difference in the incidence of hypertension related events between Ralivia ER and placebo in this table. A similar analysis was conducted upon receipt of the request for information submitted 7/28/05, for studies 021, 023 and 015 only (straightforward, randomized, placebo-controlled, 12-week studies). Again, there does not seem to be a greater risk of hypertension related events with Ralivia ER as compared to placebo.

2.2.2 CV Non serious, non- hypertension related events

The Applicant analyses submitted on 3/7/05 included four cases of atrial fibrillation (all in Ralivia ER, in the open label study), three cases of bradycardia (all on Ralivia ER, two in the controlled phase, one in the open label study), three cases of coronary artery

disease (all on Ralivia ER, two in the controlled phase, one in the open-label study) and one MI (on placebo, who is also included under the analysis of CV serious AEs).

COMMENT: It is unclear why the Applicant chose to include atrial fibrillation, bradycardia and coronary artery disease as the only non-serious non-hypertension related CV events in these analyses, since there were many more listed in the updated ISS.

The following table summarizes all serious and non-serious cardiac and vascular events in studies 021, 023 and 015, as provided by the Applicant on 7/28/05:

Table 9. NDA 21-692. Serious and non-serious Cardiovascular events with TRAER as compared to placebo. Studies 021, 023 and 015.

MedDRA System Organ Class MedDRA Preferred Term	**Tramadol HCl ER** (N=1538)	**Placebo** (N=536)
CARDIAC DISORDERS	**22 (1.4%)**	**6 (1.1%)**
PALPITATIONS	10 (0.7%)	0
TACHYCARDIA NOS	3 (0.2%)	2 (0.4%)
SINUS BRADYCARDIA	1 (<0.1%)	2 (0.4%)
BRADYCARDIA NOS	2 (0.1%)	0
ATRIAL FIBRILLATION	1 (<0.1%)	0
ATRIOVENTRICULAR BLOCK NOS	1 (<0.1%)	0
CONDUCTION DISORDER NOS	1 (<0.1%)	0
CORONARY ARTERY DISEASE NOS	0	1 (0.2%)
EXTRASYSTOLES NOS	0	1 (0.2%)
MYOCARDIAL INFARCTION	0	1 (0.2%)
PERICARDIAL EFFUSION	1 (<0.1%)	0
PERICARDITIS NOS	1 (<0.1%)	0
SINUS ARRHYTHMIA	1 (<0.1%)	0
SINUS TACHYCARDIA	1 (<0.1%)	0
VASCULAR DISORDERS	**232 (15.1%)**	**46 (8.6%)**
FLUSHING	151 (9.8%)	24 (4.5%)
POSTURAL HYPOTENSION	46 (3.0%)	11 (2.1%)
HOT FLUSHES NOS	27 (1.8%)	5 (0.9%)
HYPERTENSION AGGRAVATED	13 (0.8%)	4 (0.7%)
VASODILATATION	12 (0.8%)	3 (0.6%)
HYPERTENSION NOS	5 (0.3%)	2 (0.4%)
FLUSHING AGGRAVATED	2 (0.1%)	1 (0.2%)
HAEMATOMA NOS	2 (0.1%)	0
HYPOTENSION NOS	2 (0.1%)	0
PHLEBITIS NOS	1 (<0.1%)	0
THROMBOPHLEBITIS DEEP	1 (<0.1%)	0
VARICOSE VEINS NOS	1 (<0.1%)	0
VENOUS THROMBOSIS DEEP LIMB	1 (<0.1%)	0
VENOUS THROMBOSIS NOS	0	1 (0.2%)

By this table, there were no difference in the rate of cardiac events between TRAER and placebo. However, there was a higher rate of vascular disorders such as flushing, postural hypotension and hot flushes.

In summary: The NDA database suggests a greater number of patients on TRAER had CV serious AEs as compared to placebo, but the numbers are small (two versus five). In general, there were similar percentages for cardiac events in both treatment groups. The difference in "vascular events" was driven by the higher rate of "flushing" and "hot flushes" in the TRAER group as compared to placebo (11.6% vs. 5.4%). The cause of the "flushing" is unclear.

COMMENT: Increased cardiovascular risk is rarely detected in NDA databases and requires long-term, controlled studies. For Vioxx, for instance, a 5000-patient NDA database did not allow adequate assessment of cardiovascular safety. In fact, the cardiovascular safety of Vioxx in the NDA looked similar to the active NSAID comparators (ibuprofen and diclofenac for up to one year). The cardiovascular signal for Vioxx was first observed in a one-year, 8000 patient study (VIGOR) and later confirmed in a 3-year, placebo controlled study (APPROVe). The Ralivia ER safety database is limited to 3108 subjects who received Ralivia ER at doses of 100 to 400 mg daily, of whom only 475 were exposed for ≥6 months. This database is inadequate to address cardiovascular safety.

Tramadol immediate release (Ultram and fifteen generics) has been in the market for many years and was never thought to carry an increased cardiovascular risk. So did NSAIDs. Recent events have lead to the understanding that all drugs in the NSAID class have an increased CV risk, but the risk was unknown because large and long trials were never conducted. A similar situation might apply to tramadol hydrochloride. Unless adequate studies are conducted, the true cardiovascular risk of this drug will never be known.

If approved, the Applicant should not be allowed to claim superior cardiovascular safety of TRAER as compared to NSAIDs.

3. Outliers for Vital signs, ECG and Clinical Laboratory parameters

3.1 Vital signs

Table 10. Criteria for identifying Vital Sign values of potential clinical importance (source: Table 1., Applicant's outliers report 3/7/05).

Variable	Criterion Value[a]		Change Relative to Baseline
Systolic Blood Pressure	180	mm Hg	Increase of ≥20 mm Hg
	90	mm Hg	Decrease of ≥20 mm Hg
Diastolic Blood Pressure	105	mm Hg	Increase of ≥15 mm Hg
	50	mm Hg	Decrease of ≥15 mm Hg
Heart Rate	120	bpm	Increase of ≥15 bpm
	50	bpm	Decrease of ≥15 bpm

[a] In order to be identified as an abnormality of potential clinical importance, a value would need to meet the criterion value and also represent a change of at least the magnitude noted in the change column.

The values chosen as outlier values appear way above normal, for both the value and the absolute change. It has been recently recognized that changes in blood pressure as little as a few mmHg may have a great long-term impact in cardiovascular risk. A change of 20 mmHg to achieve the Applicant's definition of outlier implies a huge increase in blood pressure.

Sitting BP

There was no clear dose response in terms of increase in systolic blood pressure when looking at patients with increase in sitting SPB of ≥ 20 mmHg: 15.1%, 15.6% 17.1%, 14.9%, 21.1% and 20.4%, for placebo, TRAER100, 200, 300, 400 and Ralivia flexible dose, respectively.

There seems to be a trend for a dose-response in terms of decrease in sitting diastolic BP ≥ 15 mmHg was 12.2%, 14.1%, 15.8%, 17.9% and 19.4% for placebo, TRAER 100, 200, 300, 400 and flexible dose, respectively.

Standing BP

For standing SBP again, there was no evidence of increased BP, with 15.6 % and 16 to19% of patients having increases of ≥20mmHg on placebo and TRAER groups, respectively.

There was no clear dose response for a decrease in standing diastolic BP ≥15 mmHg: 13.8%, 14.6%, 13.6%, 15.8%, 23% and 19.4%, for placebo, TRAER 100, 200, 300, 400 and flexible dose, respectively.

Orthostatic hypotension

Postural hypotension and weight decreased were the only vital sign-related adverse events that were reported in greater than 1% of patients. In the 3/7/05 ISS, the incidence of postural hypotension was 5.5%, 1.7%, 4.3%, 2.0%, and 5.4% in the TRAER flexible, 100, 200, 300, and 400 mg/day dose groups, respectively, compared to 2.1% and 3.1% in the placebo and Tramadol/Placebo groups, respectively. A dose-response was not observed in the TRAER dose groups.

The Applicant notes the following:

"Postural hypotension has been reported previously in studies conducted with Tramadol (Ultram). The higher incidence observed in this clinical program (4.4% in the combined TRAER group; n=3,108) compared to that for Ultram (<1%) may be due to (a) increased reporting from active solicitation of orthostasis along with syncope, fainting, passed out, etc., in this clinical program at the request of the Division; (b) the longer duration of exposure to TRAER in this clinical program – treatment was for a total duration of 12 weeks in studies 015, 021 and 023; 15 weeks in study 014; and 1 year and at up to 400 mg/day in study 003. In the Ultram clinical program, 3 chronic pain studies were conducted, 2 for a total duration of treatment of 1 month each and the third study for a duration of 3 months; and (c) the larger number of patients exposed to TRAER – 3,108 compared to 550 patients in the Ultram clinical program".

> *COMMENT: In an early phase I study conducted under the IND, three patients presented with syncope while receiving TRAER 400 mg dose, as compared to none on placebo. Moreover, there was also a higher incidence of dizziness and vasodilation as compared to placebo in all of the early trials. The opening IND was placed on Clinical Hold, until the Applicant provided additional data on the patients with syncope and amended the proposed protocol to include adequate monitoring for potential syncope and orthostatic hypotension. Moreover, the Applicant proposed that in further trials all patients would follow a dose titration regimen starting with the 100 mg daily dose instead of 300 or 400 mg given at once.*
>
> *It is possible that a greater incidence of postural hypotension with TRAER as compared to tramadol immediate release (4.4% vs <1%, respectively) be related to better ascertainment and larger and longer exposure. However, since there are no direct comparisons between TRAER and Ultram in any of these studies, this difference needs to be noted in the label.*

A request for analyses of orthostatic hypotension was sent to the Applicant as follows:

> Syncopal episodes were observed in early clinical trials in the Tramadol Hydrochloride development program. Please provide a summary table and the listing of patients who developed (symptomatic or asymptomatic) orthostatic hypotension in studies 015, 021 and 023, by treatment group.

> We suggest you use the definition of orthostatic hypotension by the American Autonomic Society and the American Academy of Neurology: a systolic blood pressure decrease of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within three minutes of standing.

The Applicant provided the requested information on 8/8/05. Evaluation of these tables suggests that the incidence of orthostatic hypotension with TRAER, at the doses of 100, 200 and 300 mg daily (14-16%) was not substantially different from placebo (14%) in the three-month, placebo-controlled studies (015, 021 and 023). However, TRAER 400 mg daily was associated with 24% of patients having symptomatic or asymptomatic OH at least once during the study. The rate of OH in 003, the open label study, was also 24% (data not shown).

3.2 ECG

ECG results were categorized to show changes between baseline and the end of treatment. The categories used and their definitions are provided in the following table.

Table 11. ECG analysis categories (Source. Applicant's Table 4, 3/7/05 submission)

Category	Baseline Result	End of Treatment Result
No Change	Normal	Normal
	Abnormal, NCS[a]	Abnormal, NCS
	Abnormal, CS	Abnormal, CS
Improved	Abnormal, NCS	Normal
	Abnormal, CS	Normal
	Abnormal, CS	Abnormal, NCS
Worsened	Normal	Abnormal, NCS
	Normal	Abnormal, CS
	Abnormal, NCS	Abnormal, CS

[a] NCS = Not clinically significant; CS = Clinically significant.

Baseline was defined as the last measurement prior to the first dose of study drug. Endpoint was defined as the last measurement among the values captured after the first dose to the last date of study drug plus 2 days.

Table 12. NDA 21-692. Incidence of ECG-related Adverse Events (studies 015, 014, 021, 023 and 003)

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1703) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=536) n (%)	Placebo (N=128) n (%)
Arrhythmia NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial fibrillation	4 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial flutter	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial hypertrophy	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block NOS	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bundle branch block left	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bundle branch block NOS	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bundle branch block right	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Conduction disorder NOS	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sinus bradycardia	6 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Sinus tachycardia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Electrocardiogram abnormal NOS	6 (0.3)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.8)

Table 13. cont. NDA 21-692. ECG related Adverse Events.

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1703) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=536) n (%)	Placebo (N=128) n (%)
Electrocardiogram P wave abnormal	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram QRS complex abnormal	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram QT corrected interval prolonged	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Electrocardiogram QT prolonged	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram ST segment abnormal	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram ST-T change NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram T wave abnormal	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Extrasystoles NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Right Ventricular Hypertrophy	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NOS = Not Otherwise Specified

Source, Table 1.2 of 3/7/05 submission.

ECG related CV events were rare. They were more common in the flexible dose group. This may be in part because of the larger number of patients and the longer average duration of exposure (up to 1 year) on the highest dose of TRAER tested (400 mg).

There were 5 cases of QT or QTc interval prolongation. The magnitude of the QT intervals were not listed in the patient profiles and their ECG parameters were not provided by the sites. Three cases were receiving Tramadol HCl ER (two flexible dose, one TRAER 400 mg) and two were receiving placebo (in study 021) at the time of the finding. None of the cases was considered by the investigator to be clinically significant. All but one patient receiving placebo completed the study. Treatment with TRAER does not appear to be related to QT prolongation.

3.3 Clinical Laboratory Test Results

The number and percentage of subjects with new laboratory abnormalities at endpoint compared to baseline were identified. Baseline and endpoint laboratory values were compared using the standard laboratory normal ranges. Missing values were characterized as abnormal, to be conservative.

Laboratory ranges used to identify results of potential clinical importance are presented in Table 14.

Table 14. NDA 21-692. Laboratory ranges used to identify results of potential clinical importance. Source: Applicant's Table 9, 3/7/05 submission.

Laboratory Parameter (units)	Less Than or Equal To[a]	Greater Than or Equal To
Hematology		
Hemoglobin (g/dL)		
Male	11.5	-
Female	9.5	-
Hematocrit (%)		
Male	37	-
Female	32	-
WBC ($x10^3/\mu L$)		
Neutrophils	15%	-
Eosinosphils	-	10%
Platelets ($x10^3/\mu L$)	75.0	700.0
Clinical Chemistry		
Renal Function		
Creatinine (mg/dL)	ND	2.0
Electrolytes		
Sodium (mEq/L)	125	155
Potassium (mEq/L)	3.0	5.9
Chloride (mEq/L)	92	115
Bicarbonate (mEq/L)	16.0	40.0
Liver Function		
SGPT (ALT) (U/L)	ND	3x Upper Limit of Normal
SGOT (AST) (U/L)	ND	3x Upper Limit of Normal
Total bilirubin (mg/dL)	ND	2.0
Alkaline phosphatase (U/L)	ND	3x Upper Limit of Normal
Other		
Calcium (mg/dL)	7.0	12.0
Phosphorus (mg/dL)	2.0	6.0

[a] ND = Not done.

Hematology: The number of patients with Hemoglobin/Hematocrit test results of potential clinical importance pre dose and on drug were low (<4%) in all dose groups. There were no major differences between the Tramadol HCl ER dose groups and placebo in the hematology results of potential clinical importance pre dose and on drug. Post dose hematology test results of potential clinical importance were rare (data not shown) Changes in WBC and platelet count changes were low in all treatment groups, as well, with no obvious trends. The group with greater changes was the flexible dosing group, and even in this group, the changes were mild and occurred in approximately 10% of patients. WBC counts of potential clinical importance were rare pre dose, on drug and post dose in all dose groups. No trends were obvious (data not shown).

Chemistry:
Renal function test results of potential clinical importance were rare pre dose, on drug and post dose (<1.2%). The incidence of renal function test result-related adverse events were rare. Blood creatinine increased showed no trend and there was only 1 case of renal insufficiency in the Tramadol HCl ER 200 mg/day dose group.

Liver function tests. Increase in ALT and or AST was observed in some patients on TRAER and on placebo. In general, the incidence of increased LFT's was greater on TRAER than placebo, but the rates varied with the doses. Of note, the criteria for determination of increased LFT's used by the Applicant was Grade 1 = >50% increase and Grade 2 = >100 % increase. Therefore, the rate of ALT x2 was 3% in the flexible dosing and 300 mg groups, but similar to placebo for the other doses. There was no clear evidence of a dose response in this dataset that included studies 015, 021, 023, 014 and 003 (see Table 12).

Table 12. NDA 21-692. Changes in AST and ALT. Studies 015, 021, 023, 014 and 003.

Parameter/ Treatment Group	Grade Change					
	Total	-2	-1	No Change	+1	+2
ALT (SGPT)						
Flexible Dosing	1299	-	-	1197 (92.1)	63 (4.8)	39 (3.0)
100 mg	374	-	-	348 (93.0)	19 (5.1)	7 (1.9)
200 mg	366	-	-	345 (94.3)	18 (4.9)	3 (0.8)
300 mg	367	-	-	340 (92.6)	16 (4.4)	11 (3.0)
400 mg	189	-	-	181 (95.8)	7 (3.7)	1 (0.5)
Placebo	508	-	-	480 (94.5)	20 (3.9)	8 (1.6)
Tramadol/Placebo	113	-	-	105 (92.9)	5 (4.4)	3 (2.7)
AST (SGOT)						
Flexible Dosing	1299	-	-	1212 (93.3)	59 (4.5)	28 (2.2)
100 mg	374	-	-	320 (85.6)	46 (12.3)	8 (2.1)
200 mg	366	-	-	320 (87.4)	42 (11.5)	4 (1.1)
300 mg	367	-	-	323 (88.0)	39 (10.6)	5 (1.4)
400 mg	189	-	-	170 (89.9)	15 (7.9)	4 (2.1)
Placebo	508	-	-	461 (90.7)	41 (8.1)	6 (1.2)
Tramadol/Placebo	113	-	-	107 (94.7)	4 (3.5)	2 (1.8)

Source: Applicant's Table 19, 3/7/05 submission. Grade 1 = increase of >50%. Grade 2= increase of >100 %.

There were very few liver function test results related adverse events. Again, most events appear to be in the flexible dose group (Table 13). Liver function test results of potential clinical importance were rare pre dose, on drug and post dose, and showed no trends (data not shown).

Table 15. NDA 21-692. Liver function tests-related events. Studies 015, 014, 021, 023 and 003. Source: Applicant's Table 21, 3/7/05 submission.

	Tramadol HCl ER						
MedDRA Preferred Term	Flexible (N=1703) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=536) n (%)	Tramadol/ Placebo (N=128) n (%)
Alanine aminotransferase increased	21 (1.2)	2 (0.5)	1 (0.3)	1 (0.3)	0 (0.0)	4 (0.7)	2 (1.6)
Aspartate aminotransferase increased	18 (1.1)	1 (0.2)	1 (0.3)	1 (0.3)	0 (0.0)	3 (0.6)	2 (1.6)

Electrolytes. The incidence of serum electrolyte-related adverse events (sodium, potassium, glucose) were very small (0 to 0.2% for most doses). The greater incidence of hypokalemia was observed for the 300 mg qd dose (0.5%). The numbers are small and preclude meaningful interpretations. Similarly, the incidence of other serum electrolyte-related adverse events were generally rare. Blood creatine phosphokinase increased and blood glucose increased were the most frequently occurring other clinical laboratory test result-related adverse events. The incidence rates for glucose increased adverse events was similar between the Tramadol HCl ER dose groups (up to 1%) and placebo (0.9%). The incidence of creatine phosphokinase increased was slightly greater for Tramadol ER (1.5-2% at different doses) as compared to placebo (0.9%). The clinical significance of this small difference is unknown.

In summary, analyses of vital signs indicate a greater incidence of orthostatic hypotension and weight decrease with TRAER as compared to placebo. The rate of weight decrease seems to be dose related (presented by 0.8, 1.8 and 3% of patients receiving TRAER 200, 300 and 400 mg, respectively, in studies 023 and 021), as compared to 0% on placebo. The rate of orthostatic hypotension appears to be more frequent in the 400 mg dose group and open label flexible dose group (24%), as compared to the 100-300 mg groups and placebo (14%).

There were no major differences in the incidence of ECG or laboratory abnormalities in the analysis of these datasets.

4.0 Analyses by Age

The Applicant analysis of age group distribution (<65, elderly: 65-75 and older elderly: >75 years) Tramadol Hydrochloride ER clinical trials is presented in Table 14.

Table 16. NDA 21-692. Tramadol Hydrochloride Extended Release.
Age distribution (studies 015, 021, 023, and 003).

Age group	100 mg	200 mg	300 mg	400 mg	Flexible dose	All doses	Placebo	Tramadol/ Placebo
All patients	403 (100.0)	400 (100.0)	400 (100.0)	202 (100.0)	1703 (100.0)	3108 (100.0)	536 (100.0)	128 (100.0)
< 65 years	258 (64.0)	248 (62.0)	262 (65.5)	143 (70.8)	1296 (76.1)	2207 (71.0)	362 (67.5)	107 (83.6)
65-75 years	139 (34.5)	137 (34.2)	123 (30.8)	59 (29.2)	308 (18.1)	766 (24.6)	151 (28.2)	15 (11.7)
> 75 years	6 (1.5)	15 (3.8)	15 (3.8)	0	99 (5.8)	135 (4.3)	23 (4.3)	6 (4.7)

Source: Applicant's Table 2, Age analyses submitted 3/7/05.

As seen in Table 16, approximately 25%-30% of patients exposed to TRAER were 65 years or older. There seems to be a substantial exposure among elderly patients in this application, except for the >75 year old. A greater number of elderly patients were exposed to the lower doses of TRAER (up to 38% of patients on the 100 and 200 mg doses were elderly) as compared to the higher doses (<30% of patients on the 400 mg dose were elderly). The number of patients >75 years is small and precludes definitive conclusions about the safety of TRAER in this group.

COMMENT: An analysis of the placebo-controlled fixed dose studies (021 and 023) separated from the open label, flexible dose studies would be more appropriate than the current analysis presented by the Applicant (all chronic studies). However, the results of these two approaches were very consistent when performed in the general population (all ages) as seen in Tables 1 and 2-4 of this review. Therefore, additional analyses will not be requested at this point.

4.1 Adverse events by organ system category.

In general, adverse events tended to be higher in the 65 to 75 and >75 years groups as compared to the < 65 years group, for both the active and the placebo treatment groups. This was more evident for the "all adverse events" category, the most common organ system events (GI disorders, Nervous system disorders) and the metabolism and nutrition disorders categories . For instance, for metabolism and nutrition disorders, the rate of adverse events with TRAER was approximately 2 to 11% among the <65 years population (as compared to 2.8% on placebo) and 6 to 17% among the elderly (0% on placebo).

For other organ system categories, the frequency of AEs in the <65 and ≥65 years grups were about the same but varied with the specific category and the dose. The rate of AEs in the 65-75 years group was also about the same as the >75 year olds except for the "vascular" and "skin and subcutaneous tissue disorders" systems, in which the rate was greater in the older elderly as compared to the 65 to 75 years age. (Source: Table 3, Age analysis submitted 3/7/05, data not shown).

4.2 Individual adverse events with greater frequency among elderly and older elderly.

Table 15 presents some adverse events that were more frequent in the elderly and older elderly.

Dizziness was present in approximately one third of all older elderly patients (33%) regardless of dose as compared to a dose-related 15 to 30 % in the <75 years groups.

Dose-related *constipation* was almost twice as common in the 65-75 years group as compared with the <65 years population (approximately 42% and 24% respectively, for the two higher doses).

Asthenia also showed a greater incidence among the elderly, in a dose response manner.

Table 17. Ralivia ER. Selected AEs by age. Studies 015, 021, 023, 014 and 003.

MedDRA Preferred Term All Patients Age <65 years Age 65 to 75 years Age >75 years	R 100 mg (N=403) (N=258) (N=139) (N=6) n (%)	R 200 mg (N=400) (N=248) (N=137) (N=15) n (%)	R 300 mg (N=400) (N=262) (N=123) (N=15) n (%)	R 400 mg (N=202) (N=143) (N=59) (N=0) n (%)	R Flexible (N=1703) (N=1296) (N=308) (N=99) n (%)	Placebo (N=536) (N=362) (N=151) (N=23) n (%)
Dizziness						
All patients	64 (15.9)	81 (20.3)	90 (22.5)	57 (28.2)	532 (31.2)	42 (7.8)
< 65 years	41 (15.9)	46 (18.5)	52 (19.8)	39 (27.3)	410 (31.6)	34 (9.4)
65-75 years	21 (15.1)	30 (21.9)	33 (26.8)	18 (30.5)	93 (30.2)	7 (4.6)
> 75 years	2 (33.3)	5 (33.3)	5 (33.3)	0	29 (29.3)	1 (4.3)
Constipation						
All patients	49 (12.2)	68 (17.0)	85 (21.3)	60 (29.7)	471 (27.7)	471 (27.7)
< 65 years	30 (11.6)	40 (16.1)	36 (13.7)	35 (24.5)	299 (23.1)	299 (23.1)
65-75 years	18 (12.9)	26 (19.0)	46 (37.4)	25 (42.4)	127 (41.2)	127 (41.2)
> 75 years	1 (16.7)	2 (13.3)	3 (20.0)	0	45 (45.5)	45 (45.5)
Asthenia						
All patients	14 (3.5)	24 (6.0)	26 (6.5)	13 (6.4)	154 (9.0)	8 (1.5)
< 65 years	5 (1.9)	13 (5.2)	14 (5.3)	7 (4.9)	115 (8.9)	6 (1.7)
65-75 years	8 (5.8)	10 (7.3)	12 (9.8)	6 (10.2)	27 (8.8)	1 (0.7)
> 75 years	1 (16.7)	1 (6.7)	0	0	12 (12.1)	1 (4.3)
				0		

(Source: Applicant's Table 4, Age analyses, submitted 3/7/05)

In summary, as expected, the rate of adverse events among the elderly and older elderly were somewhat greater than among the < 65 year population. Events that appear to be most influenced by age were in the GI disorder, Nervous system, Metabolic and nutrition, Vascular and Skin and subcutaneous tissues disorders.

5.0 Safety in single and short-term multiple dose studies

Safety results from acute pain and PK studies were submitted with the original application of December 31, 2003 but were not mentioned in the original FDA review. The application included one study in acute dental pain, one pre-emptive pain study and seven clinical pharmacology studies. The kinds of adverse events were similar to those in the chronic pain studies: dizziness, nausea, vomiting, constipation, etc. Of note, the mean age of these normal volunteers in these trials was 22 to 34 years.

Table 18. NDA 21-692. TRAER. Non-chronic pain studies.

Study #	Description	N	number of AEs
1968	Four way, fasting comparative biovailability study of three tablet formulations of TRAER 200 mg vs Ultram® tablets (2x50 mg bid) in healthy non-smoking male volunteers. Mean age: 34 years (range: 22 to 41)	11	1 / 4 / 3
2015	A pilot two-way fasting comparative bioavailability study of TRAER 400 mg and Ultram® tablets (100 mg qid) in healthy non-smoking male and female volunteers. Mean age 31 years (range 20-43)	12	10 T [1] 12 Ultram
2016	A pilot single and multiple dose, open label fasting PK study of TRAER 2x200 mg in healthy non-smoking male and female. Mean age: 28 years (range 18 to 44))	12	64 [2]
2017	A pilot two-way single dose, fasting dosage strength proportionality study of TRAER (100 and 200 mg) in healthy non-smoking male and female volunteers. Mean age: 29 years (range 19 to 41):	12	21 T 100mg 25 T 200 mg
407	A three-way, multiple dose, open label fasting dose proportionality study of TRAER (1x 100, 2x 100 and 4x 100 mg tablets) in healthy non smoking male and female. Mean age: 31 years (range 20 to 45)	28	[3]
408	A two-way multiple dose open label comparative bioavailability of TRAER (2x 100 mg tablets) vs. Ultram ® (50 mg qid) in healthy non-smoking subjects. Mean age: 30 (range 21 to 43)	28	[3]
992208	A three-way single dose open label fasting and food effect comparative bioavailability study of TRAER 100 mg in healthy non-smoking male volunteers. Mean age:29 years (range 21 to 43)	27	[3]
002	A pilot study of TRAER in the preemptive prevention of acute dental pain following third molar extraction Mean age: 22 years (18 to 29)	T200/100=15 Placebo= 16	9 3
009[4]	A pilot study of two presurgical dosing regimens of TRAER vs. placebo in the preemptive prevention of acute dental pain after third molar extraction. Mean age: 23 years (range 18 to 35)	T200/100=17 T100/100=16 Placebo= 16	15 11 7

1. Two subjects had syncope and one had symptomatic orthostatic hypotension in the TRAER group. No cases of syncope were reported from any of the other non-chronic studies.
2. All 12 subjects had dizziness. Half of them had nausea.
3. Most subjects had adverse events. The format of listing provided by applicant in these crossover studies does not allow adequate analysis of dose response. In general, the nature of adverse events is similar to that of the chronic studies.
4. For detailed safety results see Table 19.

Table 19. NDA 21-962. Study 009. Number of subjects with adverse events in most frequently affected body systems (at least 5% in any treatment group).

	Total	Tramadol HCl ER			Placebo	p-value[a]
		Total	200/100 mg	200/200 mg		
	n = 49	n = 33	n = 17	n = 16	n = 16	
All Body Systems, n (%)	33 (67.3)	26 (78.8)	11 (64.7)	15 (93.8)	7 (43.8)	0.007
Gastrointestinal disorders	18 (36.7)	17 (51.5)	5 (29.4)	12 (75.0)	1 (6.3)	<0.001
Nausea	17 (34.7)	16 (48.5)	5 (29.4)	11 (68.8)	1 (6.3)	0.001
Vomiting	11 (22.4)	11 (33.3)	3 (17.6)	8 (50.0)	0 (0.0)	0.002
General disorders and administration site conditions	3 (6.1)	3 (9.1)	1 (5.9)	2 (12.5)	0 (0.0)	0.528
Weakness	3 (6.1)	3 (9.1)	1 (5.9)	2 (12.5)	0 (0.0)	0.528
Musculoskeletal, connective tissue, and bone disorders	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0.653
Neck Pain	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0.653
Nervous system disorders	20 (40.8)	16 (48.5)	7 (41.2)	9 (56.3)	4 (25.0)	0.224
Dizziness	8 (16.3)	7 (21.2)	3 (17.6)	4 (25.0)	1 (6.3)	0.400
Headache	9 (18.4)	6 (18.2)	3 (17.6)	3 (18.8)	3 (18.8)	1.000
Somnolence	8 (16.3)	8 (24.2)	3 (17.6)	5 (31.3)	0 (0.0)	0.053
Tremor	1 (2.0)	1 (3.0)	0 (0.0)	1 (6.3)	0 (0.0)	0.653
Psychiatric disorders	4 (8.2)	4 (12.1)	3 (17.6)	1 (6.3)	0 (0.0)	0.306
Anxiety	1 (2.0)	1 (3.0)	1 (5.9)	0 (0.0)	0 (0.0)	1.000
Euphoric mood	2 (4.1)	2 (6.1)	1 (5.9)	1 (6.3)	0 (0.0)	1.000
Nervousness	1 (2.0)	1 (3.0)	1 (5.9)	0 (0.0)	0 (0.0)	1.000
Sleep disorder	1 (2.0)	1 (3.0)	1 (5.9)	0 (0.0)	0 (0.0)	1.000
Renal and urinary disorders	2 (4.1)	2 (6.1)	1 (5.9)	1 (6.3)	0 (0.0)	1.000
Dysuria	2 (4.1)	2 (6.1)	1 (5.9)	1 (6.3)	0 (0.0)	1.000
Respiratory, thoracic, and mediastinal disorders	1 (2.0)	1 (3.0)	1 (5.9)	0 (0.0)	0 (0.0)	1.000
Rhinorrhea	1 (2.0)	1 (3.0)	1 (5.9)	0 (0.0)	0 (0.0)	1.000
Skin and subcutaneous tissue disorders	2 (4.1)	2 (6.1)	0 (0.0)	2 (12.5)	0 (0.0)	0.204
Pruritus	2 (4.1)	2 (6.1)	0 (0.0)	2 (12.5)	0 (0.0)	0.204
Vascular disorders	3 (6.1)	1 (3.0)	0 (0.0)	1 (6.3)	2 (12.5)	0.306
Hot flushes	2 (4.1)	1 (3.0)	0 (0.0)	1 (6.3)	1 (6.3)	0.537
Vasodilation	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0.653

Source: Table 12.1. 009 CSR submitted 12/31/03.

COMMENT: Most common AEs are again those of the GI system and Nervous system. There is some evidence of a dose response between the 200/100 and 200/200 mg dosings. There were no deaths and no serious AEs. Two subjects discontinued due to severe vomiting, one in each treatment group. The study failed to show efficacy.

6. Special Populations

Information submitted by the Applicant does not satisfactorily address the lack of clinical pharmacology information to support proposed dose labeling in the Special Populations section of the label. (See review by Zhang Lei, PhD., Biopharm reviewer).

No elderly subjects (> 65 years) were included in any of the seven clinical pharmacology studies. The mean age in these studies was 29 to 34 years (See Table 18). Of note, the target population for this drug will likely be older, will have comorbidities and will be taking concomitant medications.

Appears This Way
On Original

7.0 Conclusions

The current submission has addressed most of the safety concerns raised by the Agency in the October 29, 2004 AE letter.

In general, the safety profile of TRAER was consistent with that of Ultram®, although because no trial included both products except for a couple of small single dose PK studies, it is impossible to conclude with complete certainty that the safety profile of these two drugs is identical. However, this is a 505(b)(2) application that contains more safety information than most 505(b)(2) applications. If approved, Tramadol ER should carry the same WARNINGS, PRECAUTIONS and CONTRAINDICATIONS as Ultram®, including the potential for physical dependence and abuse, seizures, etc.

There are no safety findings that would preclude approval of TRAER. There were no unique events observed with TRAER that had not been observed with Ultram®.

Review of the original NDA application and additional information provided by the Applicant in the March 7, 2005 submission and subsequent responses to FDA requests for clarification indicate a clear dose response in terms of adverse events, particularly for the most common adverse events such as GI disorders (constipation, nausea, vomiting) and Nervous system disorders (dizziness in particular). This dose response in terms of toxicity needs to be placed into the context of a lack of evidence of a dose response in terms of efficacy.

The NDA database suggests a greater number of patients on TRAER had cardiovascular serious AEs as compared to placebo, but the numbers are small (five vs. two on TRAER and placebo, respectively). As is usually the case, an NDA database is not powered to adequately evaluate cardiovascular safety. Of note, Ultram® has been in the market for longer than twenty years and was never thought to be associated with cardiovascular risk. So did NSAIDs. The applicant should not be allowed to claim superior CV safety as compared to NSAIDs.

In general, there were similar percentages for cardiac events (all, serious and non-serious) in both treatment groups. A greater rate of vascular events in the TRAER treatment group was driven by the higher rate of "flushing" and "hot flushes" (11.6% vs. 5.4% in the TRAER and placebo groups, respectively). The apparent greater risk of flushing and vasodilation with TRAER may be truly due to greater toxicity of the extended release formulation or to better ascertainment of these events in the Biovail TRAER clinical program. The cause of the "flushing" is not fully clear but appears to be of neurogenic (vasovagal) origin.

Analyses of vital signs indicate a greater incidence of orthostatic hypotension and weight decrease with TRAER as compared to placebo. The rate of orthostatic hypotension appears to be more frequent in the 400 mg dose group and open label flexible dose group (24%), as compared to the 100-300 mg groups and placebo (14%). The rate of weight decrease seems to be dose related (presented by 0.8, 1.8 and 3% of patients receiving

TRAER 200, 300 and 400 mg, respectively, in studies 023 and 021), as compared to 0% on placebo. Although relatively uncommon, it may be relevant for the elderly population.

There were no major differences in the incidence of ECG or laboratory abnormalities in the analysis of these datasets.

The rate of adverse events among the elderly and older elderly were somewhat greater than among the < 65 year population, particularly for the 300 and 400 mg doses. Events that appear to be most influenced by age were in the GI, Nervous system, Metabolic and nutrition and Vascular and skin and subcutaneous tissues disorders. Of note, tramadol immediate release's maximum recommended dose in the older elderly is 300 mg. No patients >75 were exposed to TRAER 400 mg. The exposure for the >75 year old group was limited to 36 patients at the 100, 200 or 300 mg fixed doses and 99 patients exposed to 100 to 300mg flexible doses.

No studies were conducted to support the dosages recommended in Special Populations section of the label. As per the Biopharm reviewer (Dr. Zhang Lei) information provided by the Applicant in this Complete Response is not satisfactory to support the proposed dose regimen in renally and hepatically impaired patients. There are no PK data to support the proposed dose of TRAER in the elderly . All clinical pharmacology studies were conducted in healthy and young volunteers (mean age 29 to 34 years)

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/s/

Maria Villalba
9/1/2005 12:22:54 PM
MEDICAL OFFICER

Joel Schiffenbauer
9/1/2005 12:27:18 PM
MEDICAL OFFICER
Agree, Please also see my review of the complete response.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel:(301) 827-2040

MEMO TO FILE

DATE:	August 29, 2005
DRUG:	Ralivia ER (tramadol
NDA:	21—— (30-Dec-2003, 07-Mar-2005)
SPONSOR:	Biovail Laboratories, Inc.

In my Deputy Director Memo dated October 26, 2004, I described the results of four efficacy studies submitted in support of the original NDA. This data and my prior memo were reviewed in the context of the response to approvable letter submitted March 7, 2005. I am writing this memo to file to correct an error in the Deputy Director Memo. In describing the results of a reanalysis of the data from Study 015 using BOCF by Dr. Kim, I notice that I reported the p-value as p=0.21. The correct p-value from this reanalysis is 0.021.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Hertz
8/29/2005 04:11:15 PM
MEDICAL OFFICER

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HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel: (301) 827-2040

ACTING DIVISION DIRECTOR CONCURRANCE OF APPROVABLE ACTION

DATE: October 29, 2004

DRUG: Ralivia ER (tramadol hydrochloride extended release)

NDA: 21-692 (December 31, 2003); 505(b)(2)

SPONSOR: Biovail Laboratories, Incorporated

DOSAGE FORM: Oral

DOSAGE STRENGTHS: 100, 200, and 300 mg tablets

INDICATIONS: Management of moderate to moderately severe pain in adults.

ACTION RECOMMENDED BY THE DIVISION: Approvable

I CONCUR WITH THE RECOMMENDATIONS OF THE DEPUTY DIVISION DIRECTOR AND WITH THE APPROVABLE ACTION

ADDITIONAL CLINICAL INFORMATION REQUIRED FOR APPROVAL:

Provide additional data to support the risk/benefit ratio:

1. Conduct an additional trial in osteoarthritis (OA) or chronic lower back pain (CLBP) that demonstrates robust evidence of efficacy and that supports all doses proposed in the label. We recommend that Ultram® be included as a comparator.

2. Provide additional information regarding the increased number of serious thromboembolic events.

3. Submit a revised label that addresses the safety findings in the Ralivia ER NDA and which delineates any additional safety and efficacy findings with Ralivia ER, including a description of the carcinogenicity studies you have conducted.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nancy Clark
10/29/04 04:24:24 PM
CSO

Brian Harvey
10/29/04 04:32:11 PM
MEDICAL OFFICER

10/29/04

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-692
Submission Code	000
Letter Date	December 31, 2003
Stamp Date	December 31, 2003
PDUFA Goal Date	October 31st, 2004
Reviewer Name	Lourdes Villalba, M.D.
Review Completion Date	October 29, 2004
Established Name	Tramadol Extended Release
(Proposed) Trade Name	Ralivia
Therapeutic Class	Analgesic
Applicant	Biovail
Priority Designation	S
Dosing Regimen	100 mg tablets
Indication	Moderate to moderately severe pain
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Sponsor has not adequately demonstrated that Biovail Tramadol ER (TRAER) is safe and effective for the treatment of moderate to moderately severe pain at the doses of 100 to — daily. This claim implies that TRAER may — chronic pain conditions as the immediate release formulation is. TRAER was not studied in — and failed to show efficacy in the chronic pain setting. Additionally, the use of TRAER in the — setting raises safety concerns.

TRAER also failed to demonstrate adequate evidence of efficacy for the treatment of moderate to moderately severe chronic pain, a claim that the FDA was willing to grant if the application supported it. Three out of four studies included in the application succeeded the primary analyses using the last observation carried forward (LOCF) approach for imputation of missing data. However, results were not supported by sensitivity analyses using different methods of imputation.

Additionally, data presentation, particularly safety analyses were not presented in a clear format. Some tables in the ISS (integrated summary of safety) do not reflect the adverse events as reported in the individual study reports. There were some discrepancies in the analyses conducted by the sponsor in different tables. Some safety analyses, such as analysis of laboratory outliers are missing from the application.

Based on the lack of adequate evidence of efficacy, this application should not be approved.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No recommendations at this point.

1.2.2 Required Phase 4 Commitments

No recommendations at this point.

1.2.3 Other Phase 4 Requests

No recommendations at this point.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Product name: Tramadol Extended Release is a dual μ-opioid agonist and serotonine/ norepinephrine reuptake inhibitor analgesic.
Route of administration is oral. The proposed indication is for the management of moderate to moderately severe pain.

The application includes four efficacy studies in chronic pain conditions, one pre-emptive pain study and one chronic safety study, involving approximately 3100 patients exposed to TRAER in doses of 100 to 400 mg daily. In addition to the exposure in the NDA database, extensive data exist from post-marketing experience with Tramadol immediate release (ULTRAM ® and generic products). The reader is referred to section 4, Data sources, for more details.

1.3.2 Efficacy

Of the four efficacy studies in chronic pain conditions, three were in patients with osteoarthritis (OA) (B02.CT3.021.TRA.PO3, B02.CT3.023.TRA.PO3 and B00.CT3.015.TRA.PO3) and one in patients with chronic low back pain (B00.CT3.014.TRA.P03).

Of the three OA studies, two were adequate and well controlled: protocols 021 and 023. Both were originally designed to support an indication for the "treatment of the signs and symptoms of OA".

- ❖ B02.CT3.021.TRA.PO3: 12 week, randomized, placebo and active controlled (celecoxib) study of Tramadol ER 100, 200 and 300 mg, in patients with OA of the knee and hip, using three co-primary endpoints: Pain, Function and Patient Global assessment. This study will be referred to as study 021.

- ❖ B02.CT3.023.TRA.PO3: 12 week, randomized, placebo-controlled of Tramadol ER 100,200, 300 and 400 mg. Same population and primary endpoints as 021. This study will be referred to as study 023.

The third OA study (B00.CT3.015.TRA.PO3) was a 12 week, randomized, double blind, placebo controlled, of Tramadol ER flexible dose (100 to 400 mg daily) in patients with OA of knee (no hip). Primary endpoint was Pain VAS (only). Secondary endpoints included WOMAC questionnaire and Patient Global assessments. This study will be referred to as study 015.

B00.CT3.014.TRA.P03 was a 12 week, double blind, placebo-controlled study of Tramadol ER 200 and 300 mg. The study had a 3-week, open-label run-in period preceding randomization. The primary efficacy endpoint was Pain VAS (only). This study will be referred to as study 014.

Studies 021 and 023 failed to show efficacy for the "signs and symptoms of OA" indication at daily doses of 100 mg, 200 mg, 300 mg, or 400 mg of TRAER. In these studies, one or more of co-primary endpoints - pain, physical function, and patient global assessment - failed at each dose level.

None of the studies succeeded in demonstrating robust evidence of efficacy for the "treatment of moderate to moderately severe chronic pain" indication.

Study 023 showed efficacy for the WOMAC Pain subscale endpoint at each dose (100 mg, 200 mg, 300mg, and 400 mg daily) based on LOCF analyses. However, efficacy was not supported by other methods for imputation of missing data (BOCF and BOCF/LOCF combined), indicating that the successful response was driven by patients that eventually dropped from the study.

Study 021 failed to show efficacy for the WOMAC Pain variable with LOCF and BOCF. Moreover, TRAER 200 and 100 did worse than placebo for the WOMAC Pain and Function subscales.

Study 015 (knee OA) succeeded in showing efficacy for the Pain variable at flexible daily doses ranging from 100 mg to 400 mg of TRAER, over the 12-week treatment period, in the Sponsor's defined modified ITT population, using LOCF as the method of imputation. However, efficacy was not supported by analyses at the 12-week landmark endpoint, in the ITT population and using BOCF as the method of imputation, again suggesting that the response was driven by patients who eventually dropped from the study. Additionally, the flexible dose design did not allow adequate characterization of a dose response.

Study 014 in chronic low back pain (CLBP) showed worsening of pain scores in all treatment arms (TRAER 200 and 300 mg and placebo), although active treatment did less bad than placebo. The primary analysis was not supported by alternative methods of imputation of missing data. Efficacy and safety assessments from this study are problematic, since a substantial number of patients dropped out of the study during the open run-in period, mostly due to adverse events.

1.3.3 Safety

The safety profile of Ralivia ER was in general similar to that of Ultram®. However, claims of similarity to Ultram® can not be made because none of the chronic pain studies included Ultram® as one of the treatment arms. There were deficiencies in the way the data was presented in the integrated summary of safety (ISS), since not all adverse events that occurred during individual trials were incorporated into this summary.

There was evidence of a dose-response in terms of efficacy, with more adverse events associated to the 400 mg dose as compared to the 300 mg and lower doses.

1.3.4 Dosing Regimen and Administration

Clinical data in this application does not support the dosing of 100, 200, 300 [redacted] mg daily, as proposed by the Sponsor. No adequate dose response determination has been provided. Primary efficacy analyses showed inconsistent results for different doses among trials, although all doses failed sensitivity analyses, therefore no dose showed robust evidence of efficacy. However, there was a trend for a dose response in terms of safety that does not seem to justify the use of the [redacted] dose over the 300 mg dose.

1.3.5 Drug-Drug Interactions

The proposed label carries the same drug-drug interaction sections than the immediate release formulation of tramadol.

1.3.6 Special Populations

For patients with renal or hepatic impairment, the Sponsor relied on Ultram® labeling along with studies to develop dosing recommendations. However, it is unclear how the Sponsor arrived to the final conclusions regarding dosage reduction in these patients.

There was no evaluation of exposure-response in the elderly.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Tramadol Extended Release (TRAER) is a dual μ-opioid agonist and serotonine/norepinephrine reuptake inhibitor (SNRI) analgesic.
Proposed trade name: Ralivia®
Route of administration: oral.
Proposed indication: for the management of moderate to moderately severe pain in adults
Proposed dose: 100 to — mg daily
Dosage forms: 100, 200 and 300 mg tablets

2.2 Currently Available Treatment for Indications

Although no perfect or optimal analgesic currently exists for the treatment of chronic pain, several products are available in the market, including opioid and non-opioid analgesics.

2.3 Availability of Proposed Active Ingredient in the United States

Tramadol hydrochloride, the active moiety in Ralivia®, has been marketed in the U.S. since 1995 (Ultram®) at the dose of 50 to 100 mg up to 4 times a day not to exceed 400 mg daily. At least 15 generic tramadol hydrochloride immediate release products are also approved.

There are no approved tramadol extended release formulations in the U.S, although there are several available in other parts of the world.

2.4 Important Issues with Pharmacologically Related Products

Main safety concerns with tramadol hydrochloride are the risk of seizures, hypersensitivity reactions, CNS depression, physical dependence and abuse potential. All these events have been part of the Ultram® label since approval. However, after post-marketing reviews conducted by the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug products and the Office of Drug Safety (April 21, 2000), the label was updated and strengthened in August 2001. Changes included a statement that Tramadol is an opioid product and emphasized the risks of adverse events associated with Tramadol, including potential for death

Of note, despite being an opioid product, Tramadol is not scheduled under the Controlled Substances Act and is therefore promoted as having "less potential for abuse" and as a "non-narcotic" analgesic. Several FDA attempts to schedule Tramadol, have been unsuccessful. The

FDA has recently conducted an updated Eight Factor Analysis that is currently under evaluation by the DEA.

Other labeling changes for Ultram® implemented over the years include the addition of two slow titration schedules to improve tolerability, starting at 25 mg daily with titration up to 300 - 400 mg daily over a 10 day period or a 14-day period. Of note, the proposing starting dose of TRAER is 100 mg daily.

2.5 Presubmission Regulatory Activity

NDA 21-692 (Ralivia ®), proposes the use of Tramadol Extended Release (ER) Tablets for the **treatment of moderate to moderately severe pain.** This is the same indication that Tramadol Hydrochloride immediate release tablets currently has, although this extended release formulation **is not suitable for the treatment of acute pain.**

Ultram® was approved based on several efficacy studies in acute pain models and two chronic pain studies: one was a 4 week study in cancer patients and the other was a 12-week study in a very heterogeneous population of patients with nonmalignant pain including low back pain, cancer, neuropathic pain, rheumatoid arthritis and "fibrositis". Both studies used flexible dosing. None of them was placebo-controlled. Neither study today would be considered adequate to evaluate chronic pain. However, at the time of approval, it was considered that these two studies along with the evidence of efficacy in acute pain were adequate to support the "treatment of moderate to moderately severe pain" indication.

As per the attached regulatory history and meeting minutes (*Section 10. Appendix 3*), over the years, the intended indications for Ralivia® have evolved.

Throughout the drug development program, the Division consistently advised the Sponsor that the treatment of moderate to moderately severe pain was not an appropriate indication to pursue since it was not informative for labeling to prescribers. Instead, a more specific claim, such as the treatment of the signs and symptoms of OA, or the treatment of chronic low back pain, would be more appropriate indications (February 12, 2002, EOP2/Guidance meeting). For additional support to the approach taken by the DAAODP - granting specific indications versus a general chronic pain claims - the reader is referred to the transcripts of the Arthritis/Analgesia Advisory Committee Meeting on Pain, held in July 2002.

As per the PreNDA briefing document submitted by Biovail in August 19, 2003 to the PreNDA meeting to be held in September 22, 2003, (IND 59,023 SN 049) the Sponsor intended to submit an NDA under 505(b)1, . However,

after unblinding one of the pivotal OA studies and upon receipt of draft answers provided by the Division in advance to the meeting, the Sponsor cancelled the PreNDA meeting. Then, in December 31, 2003, an NDA application was submitted for the **treatment of moderate to moderately severe pain**, under 505(b)(2).

Efficacy trials included in the current application

In addition to PK studies, the current application includes:

- Three OA efficacy studies:

  Two of them were adequate and well controlled: protocols 021 and 023:
  Study 021 was a 12 week, randomized, placebo and active controlled (celecoxib) study of Tramadol ER 100, 200 and 300 mg, in patients with OA of the knee and hip, using three co-primary endpoints: Pain, Function and Patient Global assessment.
  Study 023 was a 12 week, randomized, placebo-controlled of Tramadol ER 100,200, 300 and 400 mg. It involved identical population and primary endpoints as 021.

  The third study was study 015. This was a 12 week, randomized, double blind, placebo controlled, of Tramadol ER flexible dose (100 to 400 mg daily) in patients with OA of knee (only). Primary endpoint was Pain VAS (only). Secondary endpoints included WOMAC questionnaire and Patient Global assessments. The flexible dose design does not allow adequate characterization of a dose response.

- One chronic low back pain (LBP) efficacy study (study 014) was a 12 week, double blind, placebo-controlled study of Tramadol ER 200 and 300 mg. The study had a 3-week, open label run in period preceding randomization. Primary endpoint was Pain VAS (only). Efficacy and safety assessments from this study are problematic, since it highly selects patients who tolerated Tramadol during the run in period.

- A one-year, safety, open-label study in chronic non-malignant pain (B00.CTOL.003.TRA. PO3).

- One pilot pre-emptive pain study in an acute surgical dental pain model (B00.CT2PC.009.TRA. PO3)

2.6 Other Relevant Background Information

Ralivia® is not approved in other countries.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Based on preliminary discussions with the corresponding reviewers, there do no seem to be any relevant chemistry or pharmacology/toxicology issues that would affect approvability of this drug.

3.1 CMC (and Product Microbiology, if Applicable)

No issues significant issues have been identified that would render this application not approvable.

3.2 Animal Pharmacology/Toxicology

No issues significant issues have been identified that would render this application not approvable. The Sponsor conducted several non-clinical studies but does not plan to include these in the Ralivia® label.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Complete study reports were available electronically and reviewed by the medical officers involved in this application. (\\Cdsesub1\N21692\N_000\2003-12-31)

4.2 Tables of Clinical Studies

Table 1 summarizes all clinical studies submitted in the current application. For clinical pharmacology studies see reviewer by Dr. Li, Biopharmacology reviewer.

Table 1. NDA 21-629 Clinical Studies included in the application.

Study	Design	Treatment						Primary outcome
		TR 400	TR 300	TR 200	TR 100	Placebo	Cele 200	
Osteoarthritis (OA)								
021*	12-week, R, PC, AC Randomized	-	**199**	**199**	**201**	**202**	**200**	WOMAC Pain subscale, WOMAC Function Patient Global Assessment of Disease Activity,
023*	12-week, R, PC Randomized	**202**	**201**	**201**	**202**	**205**	-	Landmark at 12 weeks, MITT, LOCF
015[1,2]	12-week, R, PC Randomized	Flexible dose 100 to 400 mg/d **124**				**122**	-	Pain VAS Average over 12 weeks, MITT
Chronic Low Back Pain (CLBP)								
014	3 wk run-in, OL, then, 12-week PC Entered DB	Screened = **619** (Dropped during run-in = 233) -	**128**	**129**	-	**129**	-	Pain VAS Average at 12 wks, MITT
Open label Safety up to one year								
003	Enrolled	**1067** Dose titration to 300-400 mg daily.				-	-	Safety Descriptive stats for pain
Pilot, Pre-emptive, dental pain								
009	One dose night before One dose right before			17	16		16	Pain intensity VAS Time to re-medication

* studies received special protocol assessments). Original Pivotal trials for the OA indication. DB: double-blind. PC: placebo controlled. AC: Active comparator controlled. Scales: WOMAC Pain 0-500 mm VAS; WOMAC Physical Function (0-1700 mm VAS); Patient Global (0-100 VAS). [1] Efficacy analyses for 014 exclude site 01. [2] MITT population includes 101 and 118 patients only.

4.3 Review Strategy

Individual complete study reports (CSR) as well the integrated summary safety (ISS) were reviewed by the medical officer. This application did not include an integrated summary of efficacy. Emphasis was put on tables summarizing efficacy and adverse events. Tables were checked for correlation with CRTs (case report tabulations). Selected case report forms (CRFs) were also reviewed. The safety review of this application was split among several medical officers: Dr. Schiffenbauer evaluated deaths; Dr. Yancey evaluated serious adverse events; Dr. Oussova evaluated discontinuations due to adverse events and Dr. Castle evaluated common adverse events observed in the TRAER program. The controlled substance staff (CSS) evaluated the potential for physical dependence, withdrawal and abuse.

4.4 Data Quality and Integrity

Standard procedures for handling and processing records are described in the application and appear adequate. Meetings with investigators and site monitoring visits were conducted by personnel from [redacted] and Biovail laboratories, Inc. [redacted] audited 3 of the 16 study sites. Site 01 [redacted] was performed because of data inconsistencies. The FDA was notified of the inconsistencies and this investigator is currently en the process of being disqualified. Analyses have been performed with and without data from this study site.

FDA conducted two site inspections [redacted]. No significant problems have been identified that would change the overall efficacy results of these multi-center studies.

Regarding data quality, the information in this application was not presented in a clear and organized way, particularly in reference to the safety analyses. Some tables in the ISS (integrated summary of safety) do not reflect the adverse events as reported in the individual study reports. Some safety analyses, such as analysis of laboratory outliers are missing from the application. This application does not contain an integrated summary of efficacy (ISE).

4.5 Compliance with Good Clinical Practices

The studies are compliant with Good Clinical Practices.

4.6 Financial Disclosures

It does not appear to be any financial disclosures that could cast doubt on the integrity of the findings. Biovail states it has not entered into any financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study (Form 3454).

5 CLINICAL PHARMACOLOGY

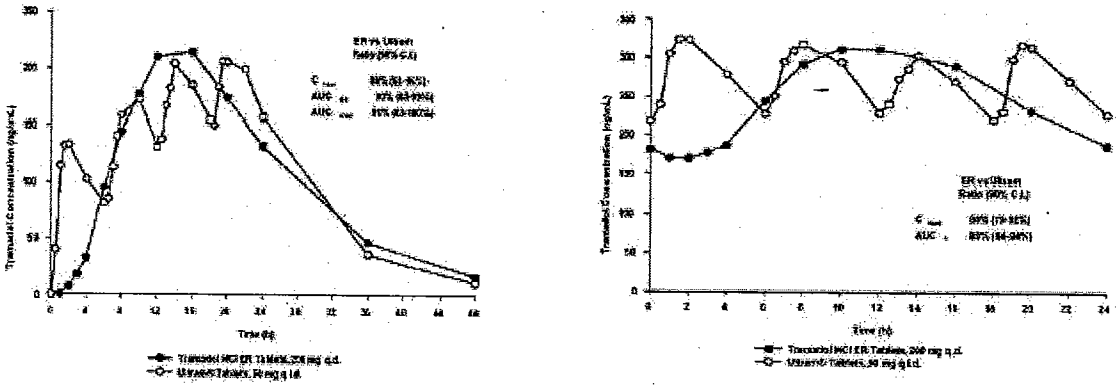
To support human PK and biopharmaceutics requirement, TRAER was studied in a total of 17 *in vivo* PK studies. Among these studies, 8 studies were considered pivotal and were reviewed in detail. These studies included the assessment of bioequivalence of TRA ER compared to Ultram® (tramadol immediate release) after single and multiple doses, dose proportionality, dosage form equivalence, food effect, morning dosing vs. evening dosing, the potential for a drug interaction with quinidine in healthy subjects, and studies in patients with renal and hepatic impairments.

The Sponsor did not conduct exposure-response studies with TRAER.

Pharmacokinetic studies demonstrated differences in the PK profile of TRAER and Ultram®. Low concentrations of tramadol and M1 were observed in the absorption phase (0-6 hr) and terminal

phase (18-24 hr) following TRAER QD dosing compared to Ultram® QID dosing. Therefore, PK characteristics of TRAER do not support the same indication as Ultram® (moderate to moderately severe pain, which implies use in acute pain). Additionally, it is unclear whether this extended release formulation is a "once daily" drug (see Figure 1.)

Figure 1.



Single Dose Multiple Dose

Tramadol concentration after single and multiple dose TRAER 200 mg and Ultram 50 mg Q6H.
Source: Dr. Zhang's Biopharmacology review.

5.1 Pharmacokinetics

Please refer to Dr. Zhang, biopharmacology reviewer.

5.2 Pharmacodynamics

Please refer to Dr. Zhang, biopharmacology reviewer.

5.3 Exposure-response Relationships

There was no adequate exploration of exposure-response relationships.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor's proposed indication is the treatment of moderate to moderately severe pain, which implies use in acute and chronic pain settings. However, because of PK characteristics (Time to maximum concentration after single dose is approximately 12 hours), and poor tolerability (particularly of doses above 100 mg if not adequately titrated), this extended release formulation is not suited for use in acute pain settings. The application does not include any trial to support an acute pain indication. The Division evaluated this product for the treatment of moderate to moderately severe chronic pain. Of note, the current application does not contain an Integrated Summary of Efficacy.

6.1.1 Methods

Four efficacy trials (three in osteoarthritis and one in chronic low back pain) were reviewed with attention to the Pain variable. One pilot study of pre-emptive analgesia in a surgical dental pain model and a one-year open label study in chronic pain conditions were also reviewed. These studies were submitted to provide additional safety data to support the proposed indication.

6.1.2 General Discussion of Endpoints

Four efficacy trials were included in this application (021, 023, 015 and 014). Three of them in osteoarthritis (OA) and one in chronic low back pain (LBP). Two of the OA studies (021 and 023) were adequate and well controlled and included the three co-primary endpoints currently recommended in the FDA OA Guidance document (WOMAC pain, WOMAC physical function and a patient global assessment). These two studies were the product of special protocol assessments and originally identified as pivotal studies in the pre-NDA package. However, the studies failed the pre-specified primary endpoint.

Studies 015 and 014- which preceded the design and conduction of the pivotal studies - used only Pain as the single primary efficacy endpoint. Evaluation of physical function and patient global assessments were done as part of the secondary efficacy endpoints. It should be noted that the study design for studies 015 and 014 are problematic for use as pivotal studies (see below).

The Sponsor proposed that the two studies and 014 in LBP would be sufficient to support "Treatment of moderate to moderately severe pain" indication under a 505(b)2 application.

The optimal endpoint for chronic pain studies is still under discussion within the scientific pain community and within the FDA. Some experts feel that since a statistically significant difference with placebo in a single pain endpoint may sometimes be clinically irrelevant and since there is no widely accepted minimally clinically important difference (MCID) for the pain outcome, an effective analgesic should be able to demonstrate superiority to placebo for the physical function

and patient global assessment variables as well as the pain variable. Other experts feel that demonstration of analgesic efficacy should require demonstration of a clinically substantial and statistically significant superiority to placebo for the pain variable, while improvement or lack of worsening on other variables could be secondary endpoints. For detailed discussions about primary endpoints in analgesic trials the reader is referred to the AAC (July 29 and 30, 2002).

For the purpose of this review, and given the fact that this application is filed under a 505(b)(2) provision, Pain was considered as the single primary endpoint while physical function and patient global assessments are considered secondary endpoints.

that the Division never agreed that Pain VAS alone was adequate for chronic pain trials.

As noted above, this sustained release formulation is not suited for use in acute pain settings. Only the chronic pain indication is being considered for this application.

6.1.3 Study Design

Studies 021 and 023 were 12-week, randomized, double blinded, placebo-controlled studies using three co-primary endpoints, in patients with OA of the knee and hip, as recommended by the FDA. These trials were the product of SPAs. They were adequate and well controlled. Study 021 also included celebrex as an active comparator.

Studies 015 (OA) and 014 (LBP) included only Pain VAS as the primary efficacy endpoint. In addition to the endpoint issues, studies 015 and 014 had problematic study designs. For instance, 015 was a flexible-dose study. Patients were started on 100 mg daily dose and titrated up to 300 or 400 mg as needed and tolerated. If the dose was not tolerated, the patient could bring the dose down. All analyses from this study were done with pooled doses 100 to 400 mg doses, therefore the study does not allow an adequate analysis of dose response in terms of efficacy or safety. Study 014 was a 12-week randomized, placebo controlled study preceded by a 3-week active run-in period. During the run-in period approximately 37% of patients dropped from the study, most of them because of adverse events. Therefore, this study highly selects the population who tolerated tramadol.

Studies 015 and 14 could be used as supportive studies, but they are no pivotal studies for an analgesic indication.

The initial dose of Tramadol HCl ER was 100 mg daily in all of these studies, with slow titration over two or three weeks up to 300-400 mg daily.

6.1.4 Efficacy Findings

6.1.4.1 Demographics and baseline characteristics:

In the OA studies, mean age was approximately 60 years, with 60 to 76% of patients younger than 65 years. There were slightly more females than males (56 - 68%). Most patients were Caucasian (80-86%), with a mean weight of 92 to 99 Lbs. Duration of disease was ≥ 5 years in 50 to 60% of patients.

In general, demographics and baseline characteristics were balanced among treatment groups in each study. However, some characteristics were exactly balanced such as the weight in study 015 in which the placebo group had a mean weight of 97 Lbs as compared to 93 Lbs in the TRAER (flexible dose) treatment group.

For demographic characteristics in each study the reader is referred to Dr. Yongman Kim's review (statistical reviewer).

6.1.4.2 Efficacy results

Two pivotal studies (021 and 023) failed primary analyses for treatment of the signs and symptoms of osteoarthritis indication (see Dr Kim's review and Appendices for individual studies). Of note, the active comparator in 021 (Celebrex 200mg daily) was successful in all co-primary endpoints. As shown in Table 2, when looking at the Pain variable alone, three out of four studies succeeded in the primary analysis with LOCF imputation (023, 014 and 015). However, when using BOCF (baseline observation carried forward) in the intent to treat population, and at the 12 week landmark (end of study time point) all three failed the efficacy analyses

Table 2. NDA 21-692. TRAER. - Summary of efficacy for Pain variable only in chronic pain conditions.

	021 (OA)	023 (OA)	015 (OA)	014 (CLBP)
	WOMAC pain subscale	WOMAC pain subscale	Pain intensity VAS	Pain intensity VAS
	T 100, 200 & 300	T 200, 300 & 400	T 100-400 Flexible dose	T 200 & 300
LOCF*	-	+ 100, 200 and 300 mg doses	+ flexible dose	+ 300 mg dose only
BOCF** ITT 12-week landmark	-	-	-	-

T: TRAER dose (mg/day)
* LOCF : last observation carried forward. Done on ITT (intent to treat population) at 12 week landmark in studies 021 and 023. Done on Modified ITT averaged over 12-week period in studies 015 and 014.
** BOCF: baseline observation carried forward
(+) Statistically different from placebo. (–) Not statistically different from placebo
OA: osteoarthritis. LBP: chronic low back pain

Modified ITT: all randomized, ≥ 1 dose, primary efficacy variable at baseline visit and first post randomization visit, and any patient who dropped out of the study before the week 1 visit due to lack of treatment efficacy.

6.1.5 Clinical Microbiology
Not applicable

6.1.6 Efficacy Conclusions

The current application does not support the efficacy of Biovail TRAER (Ralivia™) 100 to — mg daily for the "management of moderate to moderately severe pain", — or "the management of moderately to moderately severe chronic pain". Results of primary efficacy analyses are inconsistent among studies and not supported by sensitivity analyses.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review of this application was split among several reviewers. The ISS was reviewed along with individual study reports. Adverse events tables were evaluated and checked for consistency with individual study reports and listings.

The following table provides a summary of the subject exposure across the NDA in clinical studies in osteoarthritis and chronic low back pain.

Table 3. Exposure to TRAER in patients with osteoarthritis and chronic low back pain in this NDA

Tramadol HCl ER Dose Group	Treatment Exposure			
	Any Length[1]	<6 months	≥6 months[2]	≥1 year[3]
Any dose (excluding placebo)	3108	2633	475	185
Flexible dose[4]	1703	1228	475	185
100 mg[4]	403	403	0	0
200 mg[4]	400	400	0	0
300 mg[4]	400	400	0	0
400 mg[4]	202	202	0	0
Placebo[5]	505	505	0	0

1Source: ISS Table 29, first row, excluding patients (33 Flexible dose, 16 Placebo) from the acute dental pain Study 009 and 31 Placebo patients from Study 015 who rolled over to Study 003, and, therefore, received Tramadol HCl ER.
2Source: ISS Table 11 (Study 003).
3Source: ISS Table 34 (Study 003).
4Includes all patients from Study 014, patients from Study 015 who were randomized to Tramadol HCl ER, and all patients from Study 003.
5Includes patients from Study 015 who were randomized to Placebo and all patients from Studies 021 and 023.
Note: Patients who rolled over from Study 014 or 015 to Study 003 underwent dose titration of Tramadol HCl ER in Study 003, regardless of the dose they were on at the end of Study 014 or 015. Only their treatment exposure during Study 003 is included in this
Source of this Table: 10/26/04 sponsor's response to FDA informational request.

As noted in this table, approximately 3,100 patients were exposed to Ralivia ER in osteoarthritis and chronic low back pan clinical trials. Of those, 202 patients received TRAER at the maximum recommended dose for at least six months. Additionally, 475 and 185 patients received TRAER (flexible doses 100 to 400 mg daily) for at least six months and one year, respectively. However, it is unclear what dose of TRAER those patients on "flexible dosing" actually received. Therefore, as presented, the size of the safety database does not seem to support the use of the doses proposed by the Sponsor. Additional analyses will be needed to tease out how many patients received long-

term treatment at the 300 and 400 mg daily doses in the flexible dose studies. Those analyses are pending at the time of this review.

7.1.1 Deaths

Review of deaths was conducted by Dr. Schiffenbauer

No deaths or serious adverse events were reported for any of the Phase I studies. No deaths or adverse events leading to death were reported in the 5 double blind, placebo-controlled studies (Studies B00.CT2PC.009.TRA P03, B00.CT3.014.TRA P03, B00.CT3.015 TRA.P03 B02.CT3.021.TRA P03, and B02.CT3.023.TRA P03).

A total of 2 patients on open-label Tramadol HCl ER had an adverse event leading to death. Both of these patients were in Study B00.CTOL.003.TRA P03.

Patient 09-005 in Study B00.CTOL.003.TRA P03 died from a head injury sustained during a motor vehicle accident.

Patient 34-012 in Study B00.CTOL.003.TRA P03 died as a result of an apparent intentional overdose of venlafaxine, citalopram, and tramadol. The patient had no known prior history of depression or suicidal ideation. The source of the antidepressant medication was unknown to the investigator but suggested the possibility of depressive illness.

> *COMMENT: There were only 2 deaths in the entire database. However the first death occurred while the subject was operating a motor vehicle. This accident could have been secondary to Ralivia® induced seizure, dizziness, hypotension, syncope etc and so may be related to the drug. The second death was a suicide that included the use of tramadol.*
>
> *The current label for Ultram® states the following:*
>
> *Ultram may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.*
>
> *The label also mentions "suicidal tendency" under the ADVERSE REACTIONS section, and "fatalities have been reported in post marketing in association with both intentional and unintentional overdose" in the OVERDOSAGE section.*

The patient narratives are provided below:

Study B00.CTOL.003.TRA P03, Patient 003-34-012

Patient 003-34-012, a 37-year-old White female (height 170.2 cm; weight 64.5 kg at study entry) with a medical history of ankle fracture, ankle operation, bone operation, femur fracture, osteoarthritis, and pain was randomized to Tramadol HCl ER flexible dosing and began

treatment on March 6, 2002. The patient's suicide was reported as a serious adverse event which caused withdrawal from the study.

The patient prematurely terminated from the study due to this adverse event. The patient received the last dose of study medication on September 18, 2002. On [redacted] the patient committed suicide after [redacted] days of treatment with Tramadol HCl ER; the dose at the onset of this adverse event was 400 mg. The Medical Examiner verbally indicated to the site that the patient had Tramadol HCl ER in her system at the time of her death. On [redacted], the Department of Health, Office of Medical Examiners, [redacted] listed the cause of death as acute intoxication by the combined effects of citalopram, venlafaxine, and tramadol. The adverse event was considered severe and reported as serious. The patient's death was not considered by the Investigator to be related to study drug. Other adverse events reported for this patient included disturbance in attention and irritability.

Study B00.CTOL.003.TRA P03, Patient 003-09-005

Patient 003-09-005, a 45-year-old White female (height 159.5 cm; weight 93.1 kg at study entry) with a medical history of appendicitis, back pain, cardiac murmur, drug hypersensitivity, dysmenorrhea, facial bones fracture, hypothyroidism, infertility, insomnia, osteoarthritis, and tonsillitis was randomized to Tramadol HCl ER flexible dosing and began treatment on January 19, 2001. The patient had head injury reported as a serious adverse event which resulted in withdrawal from the study. The patient had head injury on [redacted] after [redacted] days of treatment with Tramadol HCl ER; the dose at the onset of this adverse event was 400 mg. The adverse event was considered severe and study medication was discontinued. The patient died and it was not considered by the Investigator to be related to study drug. The patient was driving to work at 0900 on [redacted] when she lost control of her car, hit a tree, and was killed due to severe head injuries sustained during the motor vehicle accident. The patient was cremated and no autopsy was performed. The patient received the last dose of study medication on [redacted]

Other adverse events reported for this patient included blood pressure increased, foot fracture, nasopharyngitis, sinus congestion, sinusitis, and upper respiratory tract infection.

7.1.2 Other Serious Adverse Events

Review of serious adverse events was conducted by Dr. Carolyn Yancey.
Her conclusions are as follows:

- The sponsor reports SAE by "Adverse Events known to be associated with Tramadol HCl" and by "Adverse Events not listed in the Ultram label". The number of patient reported SAE is too small across all the labeled and non-labeled SAE to draw firm conclusions about the SAE and safety risk with Tramadol HCl ER in fixed doses of 100mg, 200mg, 300mg and 400mg. Though the overall incidence of any SAE was less than 1%, the incidence of SAE for all patients was greater in the Tramadol HCl ER flexible dose compared to the other Tramadol HCl ER fixed-dose groups. This higher incidence of SAEs in the flexible dosing group may be due to the longer

duration of the open-label safety study (flexible dose) compared to the 12-week duration of the randomized, double-blind, fixed-dose studies.

- All SAEs not in the current Ultram label, yet reported as new SAEs in this review, must be included in the proposed label ADVERSE EVENT section. For example, it should be noted that there are two cases of myocardial infarctions and one case of unstable angina in the Tramadol group and none in the placebo group. All events occurred after 180 days of exposure. In the absence of a comparator treatment arm beyond 12 weeks, it is impossible to determine whether these events are drug related. The Sponsor has not addressed this issue.

For a detailed review of serious adverse events, see Dr. Yancey's review.

7.1.3 Dropouts and Other Significant Adverse Events

Review of dropouts due to adverse events was conducted by Dr. Tatiana Oussova.
Her conclusions are as follows:

"In this reviewer's opinion, the data provided with this submission showed that the incidence of adverse events leading to study discontinuation is consistent with the Ultram label. However, this is not a direct comparison between the incidence of adverse events leading to discontinuations due to Tramadol HCl ER and Ultram and has therefore many deficiencies and cannot be viewed as a robust assessment.

Overall, the incidence of adverse events leading to premature termination was greater in the Tramadol HCl ER flexible dose group compared to any other Tramadol HCl ER dosing groups.

The number of patients who prematurely terminated due to adverse events was greater in the Tramadol HCl ER 300 mg and 400 mg groups compared to other fixed dose groups. However, no pairwise comparisons were made therefore is impossible to say whether or not those differences are statistically significant.

The incidence of premature discontinuations over time due to adverse events is increasing over time and appears to be dose-dependent. It is higher in >=65 age category than among patients less than 65 years of age".

For a detailed review of dropouts due to adverse events, see Dr. Oussova's review.

Other significant adverse events

Although not considered serious, based on the observation of syncopal episodes during the initial pharmacokinetic studies, special attention was placed on documentation of syncope and "vasodilation" during the drug development program. These were reviewed by Dr. Castle (see below).

7.1.4 Other Search Strategies

Not applicable

7.1.5 Common Adverse Events

Review of common adverse events was conducted by Dr. Julia Castle. Her conclusions are as follows:

"For single-dose studies the incidence of common adverse events reported in >=2% of patients overall was higher for Tramadol HCl ER compared to Ultram.

In double-blind, placebo-controlled trials, adverse events overall were reported with a higher incidence for Tramadol HCl ER than for placebo. Comparing the incidence of adverse events for Tramadol HCl ER with rates reported in the Ultram label is not a valid comparison. The sponsor needs to include Ultram as an active comparator in the double-blind, placebo-controlled trials.

The sponsor needs to provide an analysis of the outliers and mean changes for labs and EKG findings. Also the sponsor needs to provide details for the EKGs from the seven patients listed in the single-dose studies with QTc prolongation.

The Adverse Reactions section in the Tramadol HCl ER label, proposed by the sponsor, has many deficiencies. There are many adverse events listed in Table 5.5.1.1 at greater than 2% incidence, which were not included in the proposed label, such as "chest pain", "cough", "muscle spasms", and "pain in the limb". Some adverse events even had an incidence more than 2 % above placebo, for example "feeling hot", and "rigors". The sponsor needs to provide adequate justification for excluding these adverse events from the proposed label, or include them.

There are also rare but potentially clinically significant adverse events that are not listed in the label, such as "blood glucose increased", "hypertension aggravated", "vision blurred", and "AST increased". "Hepatomegaly", "pericarditis", and "small intestine obstruction" were each reported in one patient treated with Tramadol HCl ER. The sponsor also needs to include a section on significant adverse events reported with an incidence less than 2%, regardless of causality".

7.1.6 Less Common Adverse Events.

See previous section, last paragraph.

7.1.7 Laboratory Findings

The sponsor provided the following tables that are presented here. For the laboratory findings the sponsor did not provide an analysis of outliers as part of the ISS. This information should be

requested in the deficiency letter. The sponsor however did provide a table (see below) that defined laboratory tests of potential clinical importance (the subsequent analyses do not provide for example the extent of the increase in LFTs, bilirubin etc).

Table 4: **Laboratory Ranges Used to Identify Results of Potential Clinical Importance**
(From ISS, Table 164)

Laboratory Parameter (units)	Less than or Equal To[a]	Greater Than or Equal To
Hematology		
Hemoglobin (g/dL)		
Male	11.5	-
Female	9.5	-
Hematocrit (%)		
Male	37	-
Female	32	-
WBC ($x10^3/\mu L$)		
Eosinosphils	-	10%
Neutrophils	15%	-
Platelets ($x10^3/\mu L$)	75.0	700.0
Clinical Chemistry		
Electrolytes		
Sodium (mEq/L)	125	155
Potassium (mEq/L)	3.0	5.9
Chloride (mEq/L)	92	115

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Laboratory Parameter (units)	Less than or Equal To[a]	Greater Than or Equal To
Bicarbonate (mEq/L)	16.0	40.0
Liver Function		
Alkaline phosphatase (U/L)	ND	3x Upper Limit of Normal
SGOT (AST) (U/L)	ND	3x Upper Limit of Normal
SGPT (ALT) (U/L)	ND	3x Upper Limit of Normal
Total bilirubin (mg/dL)	ND	2.0
Renal Function		
Creatinine (mg/dL)	ND	2.0
Other		
Calcium (mg/dL)	7.0	12.0
Phosphorus (mg/dL)	2.0	6.0

[a] ND = Not done.

Table 5: Incidence of Hematology-Related Adverse Events: All Patients
(From Table 168, ISS)

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	Tramadol HCl ER						
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
RBC Related							
Red blood cell count decreased	3 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	2 (1.0)	1 (0.2)	1 (0.8)
Hemoptysis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin decreased	4 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.5)	2 (0.4)	1 (0.8)
Hematocrit decreased	4 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	2 (1.0)	1 (0.2)	1 (0.8)
Anemia NOS	3 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Hematemesis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal hemorrhage	9 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood in stool	1 (0.1)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin increased	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hematocrit increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Red blood cell count increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
WBC Related							
White blood cell increased	9 (0.5)	0 (0.0)	2 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count increased	6 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Band neutrophil count increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophil count increased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Monocyte count increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet Count Related							
Thrombocythemia	3 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.5.1

Reviewer comments: The only difference appears to be in the "WBC increased" category with 0.5% seen in flexible dosing protocol. However, this finding is not reproduced consistently at the other doses. Other categories have too few cases to allow firm conclusions.

Table 6 : **Incidence of Electrolyte-Related Adverse Events: All Patients**
(From Table 171 ISS)

	Tramadol HCl ER						
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Sodium-Related							
Blood sodium decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blood sodium increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Potassium-Related							
Blood potassium increased	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)
Hyperkalemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Blood potassium decreased	0 (0.0)	0 (0.0)	3 (0.8)	3 (0.8)	1 (0.5)	0 (0.0)	0 (0.0)
Hypokalemia	4 (0.2)	0 (0.0)	1 (0.3)	2 (0.5)	2 (1.0)	1 (0.2)	0 (0.0)
Chrloride-Related							
Hyponatremia	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.7, Table 7.5.1

Table 7 : **Incidence of Renal Function-Related Adverse Events: All Patients**
(FROM Table 173, ISS)

	Tramadol HCl ER						
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Blood creatinine increased	4 (0.2)	1 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

Source: ISS Appendix F.7, Table 7.5.1

Reviewer comments: there are too few cases to draw any firm conclusions about either renal or electrolyte AEs associated with the use of Ralivia.

Table 8 : **Incidence of Liver Function-Related Adverse Events: All Patients**
(FROM Table 175, ISS)

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Liver function tests NOS abnormal	12 (0.7)	0 (0.0)	2 (0.5)	1 (0.3)	0 (0.0)	1 (0.2)	1 (0.8)
Alanine aminotransferase increased	21 (1.2)	2 (0.5)	1 (0.3)	1 (0.3)	0 (0.0)	4 (0.7)	2 (1.6)
Aspartate aminotransferase increased	18 (1.0)	1 (0.2)	1 (0.3)	1 (0.3)	0 (0.0)	3 (0.5)	2 (1.6)
Blood alkaline phosphatase NOS increased	9 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Blood bilirubin increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.8)

Source: ISS Appendix F.7, Table 7.5.1.

Reviewer comments: there appears to be a trend for more liver related AEs with Ralivia than with placebo. There is no active comparator in these studies to provide additional comparisons. No outlier analyses were provided in the NDA. However, the Ultram label does include liver failure, elevated liver enzymes, and hepatitis in the AE section.

Table 9 : **Incidence of Other Clinical Chemistry-Related Adverse Events: All Patients**
(FROM Table 177 ISS)

MedDRA Preferred Term	Tramadol HCl ER Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Calcium Related							
Blood calcium decreased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood calcium increased	3 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.4)	1 (0.8)
Hypercalcemia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Phosphorus Related							
Hypophosphatemia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other							
Blood lactate dehydrogenase increased	7 (0.4)	1 (0.2)	0 (0.0)	2 (0.5)	2 (1.0)	0 (0.0)	1 (0.8)

Source: ISS Appendix F.7, Table 7.5.1.

COMMENT: the clinical significance of the increase in LDH is not clear. This may be related to liver affects but can also be derived from muscle. There are no reports of elevated CPK so the source is most likely liver.

7.1.8 Vital Signs

See common adverse events. Additional analyses will be requested.

7.1.9 Electrocardiograms (ECGs)

See serious adverse events. Additional analyses will be requested.

7.1.10 Immunogenicity

Immunogenicity studies were not conducted in this application.

7.1.11 Human carcinogenicity

For human carcinogenicity studies see Dr. Chen's, Pharmacology-Toxicology review.

7.1.12 Special safety studies

Special safety studies were not conducted in this application

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The results of abuse potential analyses are summarized here. The reader is referred to the Controlled Substance Staff review by Dr. M. Klein for more details. In short, the CSS staff has determined that data from the NDA demonstrates that TRAER produces responses that are similar to those of other opiates and tramadol products. The Ultram® label describes withdrawal symptoms, psychic and physical dependence of the morphine type.

The Physical Dependence Questionnaire and Addiction Research Center Inventory were evaluated in the studies in patients with moderate to moderately severe pain.

Table 10: Physical Dependence Questionnaire and Addiction Research Center Inventory

	Physical Dependence Questionnaire (PDQ)		Addiction Research Center Inventory (ARCI)	
Dosing/Population	Study	Time Points[a]	Study	Time Points
Fixed Dosing				
Chronic Low Back Pain	B00.CT3.014.TRA.P03	Baseline (on) Week 12 (on) Week 13 (off)	B00.CT3.014.TRA.P03	Baseline (on) Weeks 1, 2, 4, 8, and 12 (on) Week 13 (off)
Osteoarthritis	B02.CT3.021.TRA.P03	Baseline (off) Week 12 (on) Week 13 (off)	B02.CT3.021.TRA.P03	Baseline (off) Week 12 (on)
	B02.CT3.023.TRA.P03	Baseline (off) Week 12 (on) Week 13 (off)	B02.CT3.023.TRA.P03	Baseline (off) Week 12 (on)
Flexible Dosing				
Osteoarthritis	B00.CT3.015.TRA.P03	Baseline (off) Week 12 (on) Week 13 (off)	B00.CT3.015.TRA.P03	Baseline (off) Weeks 1, 2, 4, 8, and 12 (on)
Dental Pain	B00.CT2PC.009.TRA.P03	Screening (off) Post surgery (off)	Not done	-
	B99.CT2PC.002.TRA.P03[b]	Baseline Post surgery	Not done	-
Open-Label Safety Study	B00.CTOL.003.TRA.P03	Baseline (off) End of study[c] (off)	B00.CTOL.003.TRA.P03	Baseline (off) Weeks 1, 2, 3, 6, 12, 18, 24, 30, 36, 38, 42, 48, 54, and 58 (on)

[a] On = On study drug; Off = Off study drug.

[b] A different formulation of Tramadol HCl was used in Study B99.CT2PC.002.TRA.P03. Results from the PDQ were not reported for this study.

[c] Endpoint was defined as 1 week after the last dose of study medication (the Week 39 visit for roll-over patients and Week 55 or 59 for direct enrollment patients) and at variable times past the last dose for early termination patients.

Withdrawal:

The following statements appear in the Ultram® label:

Withdrawal symptoms may occur if Ultram is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

The following statements appear in the Ultram® label:

Ultram may induce psychic and physical dependence of the morphine-type (μ-opioid). Ultram should not be used in opioid-dependent patients. Ultram has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are not limited to those patients with prior history of opioid dependence.

To evaluate for possible physical dependence and abuse potential, patients in the Phase II and III studies completed the PDQ after the end of treatment with their assigned study medication. This questionnaire asked patients to grade the severity (mild, moderate, severe) of the following 16 symptoms they may have experienced: body aches, diarrhea, fever, gooseflesh, increased heart rate, increased sweating, increased yawning, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, stomach cramps, tremors or shivering, trouble with sleeping, and weakness. Each symptom severity was scored as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The analyses of the PDQ included in the trial reports were based on the average score of all symptoms for each patient, and on the proportions of patients with each symptom. The PDQ previously has been used in addiction research.

All the symptoms recorded on the PDQ are known pharmacological effects of Tramadol HCl.

Table 11 : Physical dependence questionnaire

Symptom/ Time Point	Tramadol HCl ER 100 mg QD n (%) N[a]	n (%)	200 mg QD n (%) N	n (%)	300 mg QD n (%) N	n (%)	Placebo n (%) N	n (%)	Between-Treatment p-Value[b]
Body aches									
Week 12	189	159 (84.1)	186	144 (77.4)	189	140 (74.1)	189	150 (79.4)	0.184
Week 13	146	111 (76.0)	147	110 (74.8)	140	100 (71.4)	152	107 (70.4)	0.802

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Symptom/ Time Point	Tramadol HCl ER 100 mg QD n (%) N[a]	n (%)	200 mg QD n (%) N	n (%)	300 mg QD n (%) N	n (%)	Placebo n (%) N	n (%)	Between-Treatment p-Value[b]
Diarrhea									
Week 12	188	23 (12.2)	188	31 (16.5)	189	21 (11.1)	189	27 (14.3)	0.598
Week 13	146	12 (8.2)	147	17 (11.6)	140	25 (17.9)	152	14 (9.2)	0.042
Fever									
Week 12	189	6 (3.2)	188	14 (7.4)	189	13 (6.9)	190	6 (3.2)	0.054
Week 13	146	3 (2.1)	147	6 (4.1)	140	6 (4.3)	152	2 (1.3)	0.379
Gooseflesh									
Week 12	188	7 (3.7)	187	18 (9.6)	189	25 (13.2)	188	9 (4.8)	0.002
Week 13	145	6 (4.1)	147	17 (11.6)	139	22 (15.8)	151	2 (1.3)	<0.001
Increased heart rate									
Week 12	189	6 (3.2)	187	19 (10.2)	188	19 (10.1)	190	13 (6.8)	0.054
Week 13	145	4 (2.8)	147	16 (10.9)	139	8 (5.8)	152	3 (2.0)	0.004
Increased sweating									
Week 12	189	30 (15.9)	188	50 (26.6)	189	38 (20.1)	190	22 (11.6)	<0.001
Week 13	146	12 (8.2)	147	18 (12.2)	140	20 (14.3)	152	10 (6.6)	0.201
Increased yawning									
Week 12	189	33 (17.5)	188	29 (15.4)	189	26 (13.8)	190	18 (9.5)	0.081
Week 13	146	15 (10.3)	146	25 (17.1)	139	16 (11.5)	152	8 (5.3)	<0.001
Loss of appetite									
Week 12	189	23 (12.2)	188	50 (26.6)	189	66 (34.9)	190	17 (8.9)	<0.001
Week 13	146	9 (6.2)	147	18 (12.2)	140	27 (19.3)	152	5 (3.3)	<0.001
Nausea									
Week 12	189	25 (13.2)	187	43 (23.0)	189	54 (28.6)	190	15 (7.9)	<0.001
Week 13	146	9 (6.2)	146	15 (10.3)	140	21 (15.0)	161	8 (5.3)	<0.001
Nervousness or restlessness									
Week 12	189	58 (30.7)	188	62 (33.0)	189	58 (30.7)	190	42 (22.1)	0.010
Week 13	146	40 (27.4)	147	44 (29.9)	140	40 (28.6)	152	21 (13.8)	<0.001
Runny nose									
Week 12	189	47 (24.9)	188	62 (33.0)	189	44 (23.3)	190	43 (22.6)	0.134
Week 13	146	36 (24.7)	147	45 (30.6)	140	37 (26.4)	152	28 (18.4)	0.024
Sneezing									
Week 12	189	42 (22.2)	188	44 (23.4)	189	42 (22.2)	190	45 (23.7)	0.649
Week 13	146	52 (35.6)	146	60 (41.1)	140	61 (43.6)	152	25 (16.4)	<0.001
Stomach cramps									
Week 12	189	22 (11.6)	188	35 (18.6)	189	27 (14.3)	190	18 (9.5)	0.004
Week 13	146	12 (8.2)	147	16 (10.9)	140	20 (14.3)	152	11 (7.2)	0.033

Symptom/ Time Point	Tramadol HCl ER 100 mg QD n (%) N[a]	n (%)	200 mg QD n (%) N	n (%)	300 mg QD n (%) N	n (%)	Placebo n (%) N	n (%)	Between-Treatment p-Value[b]
Tremors or shivering									
Week 12	189	11 (5.8)	188	23 (12.2)	189	24 (12.7)	190	12 (6.3)	0.003
Week 13	146	9 (6.2)	146	19 (13.0)	140	22 (15.7)	152	3 (2.0)	<0.001
Trouble with sleeping									
Week 12	189	91 (48.1)	187	100 (53.5)	189	98 (51.9)	189	98 (51.9)	0.563
Week 13	146	77 (52.7)	147	79 (53.7)	140	77 (55.0)	152	47 (30.9)	<0.001
Weakness									
Week 12	189	54 (28.6)	188	56 (29.8)	189	53 (28.0)	190	47 (24.7)	0.274
Week 13	146	30 (20.5)	145	35 (24.1)	140	31 (22.1)	151	19 (12.6)	0.117

[a] N is the maximum number of patients who answered any of the 16 questions.

[b] Pearson's Chi-Square test.

Source: Final Study Report, Study B02.CT3.021.TRA P03, Table 6.9.1

For study 021, at the Week 13 visit, significant treatment group differences were observed for 12 symptoms (diarrhea, gooseflesh, increased heart rate, increased yawning, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, stomach cramps, tremors or shivering, and trouble with sleeping). For these symptoms, the proportions of patients in the Tramadol HCl ER 200 and 300 mg groups who experienced the symptoms were generally 1.3 to 12.2 times greater than those in the placebo group. The rates in the Tramadol HCl ER 100 mg group were either comparable to placebo or up to twice as high as placebo.

For study 023, at the Week 13 visit, significant treatment group differences were observed for 12 symptoms (gooseflesh, increased sweating, increased yawning, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, trouble with sleeping, and weakness). For these symptoms, the proportions of patients in the Tramadol HCl ER 300 and 400 mg groups who experienced the symptoms were generally 1.6 to 11 times greater than those in the placebo group.

It does appear from these results that patients who were treated with Tramadol HCl ER for extended periods of time experienced symptoms upon abrupt cessation of chronic Tramadol HCl ER therapy that appears to be consistent with opioid withdrawal. These findings are consistent with those reported for Ultram®.

The ARCI shortened form (49 questions) has been widely used for over 30 years in abuse liability studies to evaluate psychological dependence.[2] The ARCI consists of 49 questions which are

answered by either yes (scored as +1) or no (scored as -1). The ARCI questions were combined as specified in the statistical analysis plans for each study to form the following 5 subscales:3

- PCAG: pentobarbital-chlorpromazine-alcohol group scale (range, -15 to +15). This scale provides a measure of sedation effects.
- MBG: morphine-benzedrine group scale (range, -16 to +16). This scale provides a measure of euphoric effects.
- LSD: lysergic acid di-ethyl group scale (range, -14 to +14). This scale provides a measure of psychotomimetic (dysphoric) effects.
- BG: benzedrine group scale (range, -13 to +13). This scale is a measure of stimulant-like effects.
- A: amphetamine scale (range, -11 to +11). This scale is an empirically-derived scale sensitive to the stimulant-like effects of d-amphetamine.

Morphine-Benzedrine Group Scale: Euphoric Effects

The MBG scale provides a measure of euphoric effects. The mean results for the MBG scale of the ARCI are presented for safety populations in the 3-month, fixed dosing studies, Studies B00.CT3.014.TRA P03, B02.CT3.021.TRA P03, and B02.CT3.023.TRA P03 are presented in the following table:

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Table 12 : The mean results for the MBG scale of the ARCI from studies 014, 021 and 023.

Study/ Variables[a]	Tramadol HCl ER					Between-Treatment p-Value[b]
	100 mg QD	200 mg QD	300 mg QD	400 mg QD	Placebo	
Baseline						
B00.CT3.014.TRA.P03						
n	-	129	128	-	127	-
Mean±SD	-	5.06±4.428	4.91±3.823	-	4.78±4.199	-
Median	-	4.0	4.0	-	3.0	-
Range	-	0.0-16.0	0.0-15.0	-	0.0-16.0	-
p-Value	-	-	-	-	-	0.723
B02.CT3.021.TRA.P03						
N	201	199	199	-	200	-
n	199	198	199	-	197	-
Mean±SD	5.5±3.89	5.4±3.59	5.5±3.68	-	4.8±3.21	-
Median	5.0	4.8	5.0	-	4.0	-
Range	0-15	0-15	0-15	-	0-15	-
p-Value	-	-	-	-	-	0.182
B02.CT3.023.TRA.P03						
N	202	201	201	202	205	-
n	202	200	198	201	205	-
Mean±SD	4.8±3.54	5.1±3.58	4.7±3.73	5.3±3.56	5.2±3.67	-
Median	4.0	4.0	4.0	5.0	4.0	-
Range	0-16	0-15	0-15	0-15	0-15	-
p-Value	-	-	-	-	-	0.363
Change from Baseline to Week 12						
B00.CT3.014.TRA.P03						
n	-	88	93	-	74	-
Mean±SD	-	-0.45±3.793	-0.13±3.760	-	-0.96±4.176	-
Median	-	0.0	0.0	-	-1.0	-
Range	-	-14-14	-13-10	-	-13-12	-
p-Value[c]	-	0.175	0.706	-	0.011	0.163

Study/ Variables[a]	Tramadol HCl ER 100 mg QD	Tramadol HCl ER 200 mg QD	Tramadol HCl ER 300 mg QD	Tramadol HCl ER 400 mg QD	Placebo	Between-Treatment p-Value[b]
B02.CT3.021.TRA.P03						
n	187	186	189	-	188	-
Mean±SD	0.4±3.81	0.3±4.26	0.3±3.79	-	0.2±3.59	-
Median	0.0	0.0	0.0	-	0.0	-
Range	-10-14	-12-14	-8-14	-	-10-10	-
p-Value[c]	0.297	0.530	0.338	-	0.487	0.037
B02.CT3.023.TRA.P03						
n	187	184	180	191	190	-
Mean±SD	0.6±4.44	0.6±3.61	0.6±4.00	0.3±3.90	0.2±3.66	-
Median	0.0	0.0	0.0	0.0	0.0	-
Range	-12-14	-10-11	-10-14	-11-15	-15-14	-
p-Value[c]	0.142	0.075	0.138	0.427	0.910	0.739
Change from Baseline to Week 13						
B00.CT3.014.TRA.P03						
n	-	86	84	-	68	-
Mean±SD	-	-0.59±3.179	-1.04±3.974	-	-1.47±4.155	-
Median	-	0.0	-1.0	-	-1.0	-
Range	-	-12-12	-12-13	-	-12-12	-
p-Value[c]	-	0.027	0.001	-	<0.001	0.264

[a] Response range: -16 (all 'no') to +16 (all 'yes').

[b] Kruskal-Wallis test for between-treatment change.

[c] Wilcoxon signed-rank test for within-treatment change.

Source: Final Clinical Study Report, Study B00.CT3.014.TRA.P03, Table 14.3.7.2.1; Final Clinical Study Report, Study B02.CT3.021.TRA.P03, Table 6.8.1; Final Clinical Study Report, Study B02.CT3.023.TRA.P03, Table 6.8.1.

The results of the studies demonstrate that the PDQ effects for Tramadol HCl ER 100 mg are comparable to placebo. The results for Tramadol HCl ER 200 mg, 300 mg, and 400 mg are higher than those for placebo, but no dose response was demonstrated. Although ARCI results from the long-term, open-label safety study are significant, no comparisons can be made to a control due the design of the study. The results for the ARCI subscales do not demonstrate a clear, reproducible drug effect. The results of the studies conducted with Tramadol HCl ER are consistent with the information provided in the Ultram® label.

7.1.14 Human Reproduction and Pregnancy data

No data on pregnant subjects are available.

7.1.15 Assessment of Effect on Growth

Not applicable.

7.1.16 Overdose Experience

Please see Controlled Substances Staff's review (Dr. Klein).

7.1.17 Postmarketing Experience

As noted above, Ralivia ER is not approved in any part of the world.

7.2 Adequacy of Patient Exposure and Safety Assessments

To date, it is unclear how many patients have been exposed to the highest recommended doses of TRAER in this application. The original NDA provided several exposure tables none of which showed data beyond 84 days of exposure. A summary table was requested by FDA reviewers. This table, submitted on October 26, 2004 demonstrated that a substantial number of patients in this application were exposed to the flexible dose regimen. Relatively few patients appear to be exposed to the 300 and 400 mg daily dose for 6 months and one year. These numbers would not support the use of TRAER at the doses proposed by the Sponsor (100 to — mg daily). Additional analyses are pending regarding number of patients exposed to each dose.

The Sponsor has not robustly demonstrated efficacy of any of the proposed doses of TRAER 100, 200, 300 — mg daily. Regarding efficacy, study 021 showed efficacy for the WOMAC pain variable for the 300 mg dose with LOCF. The 100 and 200 mg doses failed to show efficacy with LOCF and actually showed worsening. Regarding study 023, all doses were effective by the LOCF analyses but the effect size of the different treatment groups was very similar. (Both studies failed the BOCF analyses).

Although there was no evidence of a dose-response in terms of efficacy, there was evidence of a dose response in terms of safety.

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

Minimum ICH (International Conference for Harmonization) guidelines call for a minimum of 1500 patients, with 300 to 600 exposed for six months and at least 100 patients exposed for one year at clinically relevant doses. Because of the "dose-creep" phenomenon so commonly observed with analgesic products, the DAAODP has consistently requested that sponsors provide minimum ICH guideline numbers at the maximum dose proposed in the label. Therefore, the size of the database is relatively large. A summary of the studies included in this NDA is presented in Table xx. The following tables provide summaries of the subject exposure across the NDA.

Table 13 : Number of Patients Exposed to Tramadol HCl ER: Integrated Summary of Safety (From Table 12 ISS)

	Tramadol HCl ER (mg QD)						
Population	Flexible[a]	100	200	300	400	Placebo	Tramadol/ Placebo
Healthy volunteers							
Single dose	-	56	98	56	-	-	-
Multiple dose	30	-	52	47	-	-	-
Special populations							
Renal impairment	-	18	-	-	-	-	-
Hepatic impairment	-	18	-	-	-	-	-
All patients	1736	403	400	400	202	552	128[b]
All patients with chronic pain[c]	1703	403	400	400	202	536	128[b]
Double-blind studies	133	403	529	528	202	664[b]	-
Chronic low back pain	616[d]	-	129[e]	128[e]	-	-	128[b]

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Population	Tramadol HCl ER (mg QD)						Tramadol/ Placebo
	Flexible[a]	100	200	300	400	Placebo	
Osteoarthritis pain	133	403	400	400	202	536[f]	-
Open-label safety study	1056[g]	-	-	-	-	-	-
Long-term safety[h]	475	-	-	-	-	-	-
Pre-emptive Treatment of Acute Dental Pain	-	17[e,i]	16[e]	-	-	16	-

[a] Tramadol HCl ER 100 to 500 mg QD.

[b] Includes 128 patients in Study B00.CT3.014.TRA.P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo. A total of 127 of these patients are included in the safety population in the Clinical Study Report for Study B00.CT3.014.TRA.P03. One additional patient was later identified and was included in the ISS safety data analyses for all patients and all double-blind studies (see Appendix D).

[c] This population does not include the dental pain patients from Study B00.CT2PC.009.TRA.P03.

[d] Of the 619 patients enrolled in Study B00.CT3.014.TRA.P03, 615 patients received at least 1 dose of study drug. One additional patient was later identified and was included in the ISS safety data analyses for all patients (see Appendix D).

[e] Patients are included in the flexible dosing group for the all patients population (see Appendix D).

[f] Includes placebo patients from Studies B00.CT3.015.TRA.P03, B02.CT3.021.TRA.P03, and B02.CT3.023.TRA.P03 , plus 1 additional patient who was later identified and was included in the ISS analyses for all patients, all double-blind studies, and all osteoarthritis patients (see Appendix D).

[g] Includes 1052 patients identified in the Clinical Trial Report for Study B00.CTOL.003.TRA.P03 plus 4 additional patients who were later identified. A total of 1056 patients is included in the ISS safety data analyses for all patients (see Appendix D).

[h] Patients from Study B00.CTOL.003.TRA.P03 who were treated with Tramadol HCl ER for ≥6 months.

[i] Patients received 1 dose of Tramadol HCl ER 200 mg followed by 1 dose of Tramadol HCl ER 100 mg.

Source: ISS Appendix F.1, Tables 1.1.1, and 1.1.2; F2, Table 2.1; F3, Table 3.1; Appendix F.4, Table 4.1; Appendix F.5, Table 5.1.1; Appendix F.6, Table 6.1, and Appendix F.7, Table 7.1, 7.6.3, and 7.14.2.

The following table provides subject exposure in the double blind placebo controlled studies. The greatest number of subjects exposed occurred for longer than 2 months (with a maximum of up to 513 days).

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Table 14 : Treatment Exposure: All Double-Blind, Placebo-Controlled Studies (From Table 30 ISS)

	Tramadol HCl ER					
Variable	Flexible (N=133)	100 mg QD (N=403)	200 mg QD (N=529)	300 mg QD (N=528)	400 mg QD (N=202)	Placebo[a] (N=664)
Total Patient Days of Exposure	6779	23403	31405	30074	10950	37555
Mean Daily Dose (mg)						
n	133	403	528	528	202	664
Mean±SD	247.6±93.61	98.3±9.82	183.9±29.10	255.9±63.90	299.4±96.62	0.0±0.0
Median	256	100	195	285	354	0
Range	50.0 - 381.2	29.9 - 150.0	50.0 - 296.9	18.8 - 444.3	5.0 - 513.6	0.0 - 0.0
Duration of Treatment (days)						
n	133	403	529	528	202	664
Mean±SD	51.0±36.58	58.1±34.21	59.4±34.17	57.0±34.04	54.2±33.47	56.6±34.48
Median	78	84	84	83	80	83
Range	1 - 94	1 - 105	1 - 134	1 - 101	1 - 94	1 - 116
Number of Patients Dosed [n (%)]						
1 - 7 days	26 (19.5)	51 (12.7)	65 (12.3)	59 (11.2)	21 (10.4)	78 (11.7)
8 - 14 days	17 (12.8)	29 (7.2)	43 (8.1)	48 (9.1)	19 (9.4)	61 (9.2)
15 - 21 days	4 (3.0)	35 (8.7)	30 (5.7)	40 (7.6)	20 (9.9)	52 (7.8)
22 - 28 days	7 (5.3)	17 (4.2)	19 (3.6)	29 (5.5)	12 (5.9)	34 (5.1)
29 - 56 days	9 (6.8)	26 (6.5)	44 (8.3)	41 (7.8)	22 (10.9)	52 (7.8)
57 - 84 days	29 (21.8)	82 (20.3)	140 (26.5)	141 (26.7)	60 (29.7)	168 (25.3)
> 84 days	41 (30.8)	163 (40.4)	188 (35.5)	170 (32.2)	48 (23.8)	219 (33.0)

[a] Includes 128 patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Sources: ISS Appendix F.5, Table 5.2.1.

For a summary table of exposure in all chronic pain studies included in this application the reader is referred to section 7.1 (Safety).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary datasources were used to evaluate the safety of TRAER (Ralivia ER). A PubMED search for "tramadol extended release" generated only two documents: one clinical trial in patients with OA of the knee (study 015) and one review that provides estimates of the total market size of tramadol, both sponsored by Biovail Corporation.

Although other tramadol extended and sustained release formulations are approved outside the U.S., Ralivia ER is not approved in other parts of the world and therefore there is no relevant post-marketing safety information for this product.

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience with TRAER is limited to those patients who are known to have an acceptable safety profile with tramadol immediate release. This NDA excluded patients who had any of the contraindications and precautions recommended in the tramadol label.

There was no adequate characterization of a dose-response in terms of efficacy. Studies 021 and 023 provided some evidence of a dose response in terms of safety with more discontinuations due to adverse events in the 300 and 400 mg daily doses as compared to the 100 and 200 mg daily doses. However, there was no clear evidence of a dose response in terms of efficacy. Study 021 failed the primary analysis of the WOMAC Pain endpoint for all doses. Moreover, TRAER 200 and 100 did worse than placebo in terms of WOMAC Pain and Function. Study 023 succeeded the primary analysis of the WOMAC Pain endpoint for all doses (100, 200, 300 and 400 mg/day) but sensitivity analyses did not support the primary analyses. Additionally, the effect size for these four doses was very similar and actually, the 200 mg daily dose was the one with the larger effect size. The design of studies 014, 015 and 003 did not allow adequate characterization of dose-response.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This application was submitted under 505(b)2.

No significant non-clinical issues were raised on these studies. For a detailed review of non clinical studies the reader is referred to Dr. Chen, Pharmacology-toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

Testing of study subjects conducted in the application appears to be adequate. However, several safety analyses, such as the analyses of outliers for laboratory parameters are missing from the application.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

For detailed analyses of in vitro and in vivo testing carried out by the applicant the reader is referred to the Clinical Pharmacology review by Dr. Zhang.

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

In general, the safety profile of Ralivia® appears to be similar to that of Ultram® (tramadol hydrochloride immediate release). However, TRAER is not bioequivalent to Ultram® and none of the studies in OA or CLBP included Ultram® as comparator, therefore, safety or efficacy comparisons would be inappropriate.

7.2.8 Assessment of Quality and Completeness of Data

Overall, data presentation was confusing, particularly for the evaluation of safety. The following are some of the problems:

The ISS provides numbers of adverse events that do not match the numbers in the individual study reports.

It is difficult to discern whether some patients in study 014 discontinued during the run-in period or during the double-blind period.

Five patients in study 015 were listed as protocol violators because of total knee replacement. When additional information was requested, the sponsor clarified that three of those patients, who were on placebo, actually had not undergone total knee replacement before, during or after the study. It is unclear whether those patients were discontinued from the study and whether they were included or not in the ITT analyses.

7.2.9 Additional Submissions, Including Safety Update

The SUR was submitted to the Agency in paper copy only, on April 30, 2004. The Sponsor stated that there was no safety information to add at that time and that all safety data had been included in the December, 2003 submission.

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

Again, the use of an open label run-in period and of a flexible dose design limits the interpretation of safety results. However, studies 021 and 023 provide some evidence of a dose response in terms of safety. Single doses of TRAER demonstrated greater incidence of adverse events than tramadol immediate release in single dose studies. Multiple dose and long term efficacy studies did not include the Ultram® formulation as a comparator. Conclusions of comparability to the immediate release formulation are inappropriate.

7.4 General Methodology

Safety review was conducted by reviewing deaths, serious adverse events, discontinuation due to adverse events and all adverse events in the integrated summary of safety and in individual trials. Due to time constrains, deaths were reviewed by Dr. Schiffenbauer, Serious adverse events were reviewed by Dr. Yancey, discontinuations due to adverse events were reviewed by Dr. Oussova and common adverse events were reviewed by Dr. Castle. Potential for abuse and dependence was reviewed by the Controlled Substances staff.

This medical officer conducted a summary of overall safety of TRAER based on individual reviewer's evaluations as well as a review of adverse events in the acute post-surgical dental pain study.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Only data from studies 021 and 023 should be pooled for safety or efficacy purposes. The different study design for the other studies (one flexible dose, one open label safety and one with a 3-week open-label run-in before randomization) precludes pooling data from these studies.

7.4.2 Explorations for Predictive Factors

Predictive factors for adverse events such as dose dependency, time-dependency and drug-drug interaction were not adequately explored.

7.4.3 Causality Determination

Causality determination was conducted by the reporting investigators. This medical officer believes that causality determination is of limited value, since it rarely identifies adverse events that had not been previously associated with the drug or class of drugs.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There was no adequate evidence of a dose response in terms of efficacy. There was a trend for a dose response in terms of adverse events. Proposed dosing was extrapolated from the immediate release formulation.

Dosing in the elderly was also extrapolated from the IR formulation.

8.2 Drug-Drug Interactions

No new drug-drug interaction studies were conducted. The sponsor plans to use the information on drug-drug interaction in the Ultram® label.

8.3 Special Populations

Adverse events in the elderly were analyzed and compared to those in adults younger than 65 years. In general, TRAER was associated with greater number of AE's than in the adult non-elderly. Exposure-response studies were not conducted in the elderly population.

Dosing in renal impaired and hepatic impaired populations was based mostly on the prior Ultram® experience. The Sponsor conducted some PK studies to address these issues as well, however, the PK reviewer commented that it is unclear how the Sponsor arrived to the final dosing recommendations in these populations.

8.4 Pediatrics

A request for a waiver to conduct pediatric studies was requested by the Sponsor. A deferral was granted. If this drug were to be approved for the osteoarthritis indications a waiver could be granted. However, if indications other than osteoarthritis and chronic low pain are approved, the need for pediatric studies should be reconsidered.

8.5 Advisory Committee Meeting

No Advisory committee meeting was held for this application.

8.6 Literature Review

Only two reports were available through a literature search on tramadol extended release. Both of them were sponsored by Biovail.

8.7 Postmarketing Risk Management Plan

No Postmarketing Risk Management plan was included in this application.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Ralivia has not demonstrated adequate evidence of efficacy and safety for the proposed indication at the proposed doses.

9.2 Recommendation on Regulatory Action

Tramadol ER (Ralivia®) should not be approved.

An additional single trial in osteoarthritis (OA) or chronic lower back pain (CLBP) that provides robust evidence of efficacy that is durable and supports all doses proposed in the label may provide adequate evidence of efficacy. It is recommended that Ultram be included as a comparator.

9.3 Recommendation on Postmarketing Actions

No recommendations at this point.

9.3.1 Risk Management Activity

No recommendations at this point

9.3.2 Required Phase 4 Commitments

None at this point.

9.3.3 Other Phase 4 Requests

None at this point.

9.4 Labeling Review

No labeling review at this point.

9.5 Comments to Applicant

See action letter issued on October 29, 2004.

10 APPENDICES

10.1 Review of Individual Study Reports

1) Study B02.CT3.021.TRA P03 (021 in OA)

1. Protocol

a. Protocol Title: Double-Blind, Randomized, Dose-ranging, Parallel-group Comparison of the Efficacy and Safety of Extended Release Tramadol Hydrochloride (Tramadol HCl ER) 100 mg, 200 mg and 300 mg, Celecoxib 200 mg and Placebo in the Treatment of Osteoarthritis of the Knee and/or Hip

b. Design/objective: A 12-week, multicenter (n=), randomized, placebo- controlled study to evaluate analgesic efficacy (primary objective) and safety (secondary objective) of TRAER in patients with OA of the knee or hip.

c. Patients/eligibility: Planned: 1000. Enrolled: 1011 patients, approximately 200 per group.

Inclusion: Males or females at least 18 years of age, able to provide informed consent
Pain Intensity of at least 40 mm following 2-7 day washout from analgesics for treatment of pain, at the baseline visit.
Fulfilling ACR clinical and radiologic criteria and Functional Class I-III OA of the Knee or hip. At least one knee joint was involved and warranted treatment NSAIDs, APAP or opioid analgesics for at least 75 to 90 days preceding the screening visit.
Women of childbearing potential were to practice abstinence or adequate contraception.

Exclusion: Medical condition not well controlled
Arthritis other than OA; prior joint replacement at the index joint
Chronic pain syndrome or fibromyalgia
Anticipated invasive procedure on the index joint during course of the study or expected within 4 months of screening.
Use of analgesics during the washout period.
Prior history of clinically significant intolerance to Tramadol or known hypersensitivity to opioid analgesics.
Had received oral, IM, IV, IA or soft tissue administration of CS within 1 month of Screening or IA CS in the index joint within 2 months prior to the first dose, or viscosupplementation of the index joint within the past 6 months or a non-index joint within 3 months.
History of seizure disorder or a recognized risk of seizure.
History of receiving MAO inhibitors or tricyclic compounds (such as

cyclobenzaprine) within 14 days of starting the study.
Patients receiving neuroleptics, SSRI or SNRIs, carbamazepine or quinidine.
At risk in terms of the precautions, warnings and contraindications for Tramadol.
History of substance abuse, including alcohol abuse, within 6 months.
Diagnosis of cancer within the past 3 years.
Chronic respiratory insufficiency
Had received any investigational medication witin 30 days prior to first dose.
Had aspartate aminotransferase (AST [SGOT - serum glutamic-oxaloacetic transaminase]) or alanine aminotransferase (ALT [SGPT - serum glutamic-pyruvic transaminase]) > 2 times the upper limit of normal or creatinine > 1.9 mg/dL at screening, or any laboratory abnormality which, in the opinion of the investigator, would have contraindicated study participation.

Concomitant medications:
Prohibited:

- NSAID or other analgesics except for 325 mg/d aspirin for cardiovascular prophylaxis and up to 2000 mg/day APAP for no more than three consecutive days for reasons other than OA pain and/or OA symptoms. Use of APAP was to be avoided in the 24 hours before each study visit after the screening visit.
- Systemic of intra-articular CS
- Topical analgesics
- MAO inhibitors
- Tricyclic antidepressants, SSRIs. SNRIs, cycobenzaprine, promethazine, quinidine and carbamazepine.

Allowed:

- glucosamine and chondroitin were permitted provided the patient had been regularly using them for a minimum of 2 months before randomization and the daily dose was to remain constant througuht the study.
- Other complementary therapies such as herbal medicines and magnetic therapy could be continued provided that the patient had been suing them regularly for at leas one month before randomization.

d. Treatment: Following a 2 to 7 day washout period, eligible patients were randomly assigned to once daily dosing with orally administered TRAER 100 mg, 200mg, 300mg, celecoxib 200 mg or placebo. The starting dose of Tramadol HCl ER was 100 mg QD. On day 5, patients randomized to Tramadol HCl ER 200 mg QD or 300 mg QD had their dose increased to 200 mg QD. On day 10, patients randomized to Tramadol HCl ER 300 mg QD had their dose increased to 300 mg QD.

e. Evaluations (see Attachment 1, after study results):

- Efficacy:
Primary efficacy variables were:

- Western Ontario and McMaster Universities (WOMAC) OA Index Pain Subscale (with five questions, each one using 0 to 100 VAS score.

- WOMAC Function Subscale (with seventeen questions, each one using 0 to 100 VAS score.
- Patient Global Assessment of disease activity (0-100 VAS score).

Secondary efficacy variables: daily arthritis pain intensity VAS score from patient diaries; WOMAC OA Index stiffness subscale and composite index; walking on a flat surface item of the WOMAC OA Index pain subscale; physician's global assessments of disease activity; arthritis pain intensity VAS score in the index joint and non-index joints; incidence of patient withdrawal due to lack of treatment efficacy; time to withdrawal due to lack of efficacy; use of unauthorized medications; SF-36 Health Survey physical component summary (PCS) and mental component summary (MCS) scales, and the eight subscales; and, Chronic Pain Sleep Inventory (CPSI) scales including overall quality of sleep.

- Safety: include assessment of adverse events, syncope and vasodilation assessments, clinical laboratory, physical examination, ECG, vital signs, Physical Dependence questionnaire and Addiciton Research Center Inventory (ARCI).

f. Statistical methods:

Primary efficacy analyses would be in the intent to treat population, analyzed at the end of the 12-week treatment period (landmark analysis), using LOCF as the method of imputation for missing data. A sequential method would be used, starting with the highest (300 mg dose). If there was no statistically significant with placebo, further analyses would not be carried out.

The ITT population included all randomized patients who took at least one dose of study medication. The Efficacy Evaluable population included all patients who had primary efficacy information recorded at baseline, had no major protocol violations, were 80% to 120% compliant with their dosing regimen, and completed the 12-week treatment period. Efficacy analyses were based on actual values and last observation carried forward (LOCF) values. If there were no postbaseline values, the baseline value was carried forward. The LOCF analyses were the primary analyses. Baseline variables were compared using a 1-way analysis of variance (ANOVA) with treatment as the factor for continuous variables and Pearson's chi-square for categorical variables.

Mean changes from baseline to Weeks 1, 2, 3, 6, 9, and 12 (primary time point) and to the average of Weeks 1, 2, 3, 6, 9, and 12 for arthritis pain intensity score VAS for index joint, non-index joints; WOMAC OA Index pain, stiffness, and physical function subscales, pain when walking on a flat surface item of the WOMAC OA Index pain subscale, and composite index; physician's global assessment of disease activity; patient global assessment of disease activity; the CPSI and SF-36 Health Survey variables were analyzed using analysis of covariance (ANCOVA) with treatment, index joint (knee, hip), and study site as factors and baseline value as a covariate. Daily diary arthritis pain intensity scores were analyzed using a repeated measures ANCOVA with treatment, study site, index joint, and day as factors, and the baseline pain intensity as thecovariate. Discontinuation rates due to lack of efficacy and proportions of patients using unauthorized medications were analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusting for site and index joint. Time to withdrawal due to lack of efficacy was analyzed using survival analysis methods.

COMMENT: The Division prefers the landmark analysis in the ITT population as the primary analysis, with the average or area under the curve as a confirmatory analysis. The Division also recommends that methods of imputation other than the LOCF be conducted to better assess studies in which there are substantial number of dropouts.

- Protocol amendments

The original protocol (dated 05 March 2002) underwent revision. The revised protocol (dated 24 June 2002) was amended (17 July 2002) before any patient was enrolled. The principal changes to the protocol resulting from this amendment were:

- Changed the study population from patients with OA of the knee to patients with OA of the knee and/or hip.
- Clarified the criteria for the selection of the index joint.
- Clarified the study inclusion criteria for diagnosis of OA of the knee and specified the criteria for diagnosis of OA of the hip.
- Specified that at least 25% of randomized patients were to have OA of the hip.
- Added assessments (arthritis pain intensity VAS) of the response to study medication in non-index joints.

-Post Hoc changes

The statistical analysis plan dated March 24, 2003 was amended on July 2, 2003 and on August 1, 2003. For details the reader is referred to Dr. Yongman Kim's review.

2. Results

a. Disposition.

As noted in table xx, 45 to 49% of patients discontinued from the TRAER groups, as compared to 49% from placebo and 33% from celecoxib 200 mg. More patients discontinued due to insufficient therapeutic effect from the placebo group (33%) as compared to any of the active treatment groups. There seems to be a trend for a dose response in terms of efficacy: 25, 17 and 11 % discontinued due to insufficient therapeutic effect in the TRAER 100, 200 and 300 mg daily. There is also some evidence of a dose response in terms of discontinuations due to non-serious adverse events: 12, 22 and 30% in the TRAER 100, 200 and 300 mg dose.

Table 15. Disposition of patients in study 021.

Table 15. Study 021 in OA. Disposition

	TRA 300 mg	TRA 200 mg	TRA 100 mg	Celecoxib 200 mg	Placebo
Randomized to treatment	201	203	202	203	202
Analyzed for safety and efficacy	199	199	201	202	200
Completed study, n (%)	101 (50.8)	109 (54.8)	107 (53.2)	135 (66.8)	103 (51.5)
Withdrawn, n (%)	98 (49.2)	90 (45.2)	94 (46.8)	67 (33.2)	97 (48.5)
Insufficient therapeutic effect	22 (11.1)	33 (16.6)	51 (25.4)	30 (14.9)	65 (32.5)
Serious adverse event	1 (0.5)	3 (1.5)	0 (0.0)	0 (0.0)	3 (1.5)
Non-serious adverse event	60 (30.2)	43 (21.6)	25 (12.4) [1]	20 (9.9)	12 (6.0)
Non-compliant with protocol	3 (1.5)	7 (3.5)	8 (4.0)	8 (4.0)	3 (1.5)
Patient requested withdrawal from study	7 (3.5)	1 (0.5)	4 (2.0)	2 (1.0)	4 (2.0)
Investigator withdrew patient	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	1 (0.5)
Patient lost to follow-up	3 (1.5)	2 (1.0)	6 (3.0)	2 (1.0)	3 (1.5)
Other	2 (1.0)	1 (0.5)	0 (0.0)	3 (1.5)	6 (3.0)

Source. Table 10-1 021 CSR.

b.Demographics and baseline characteristics
See statistical review by Dr. Yongman Kim.

c.Efficacy

Primary efficacy analyses

Sponsor's analyses

The study failed to show a statistically significant difference with placebo on the analysis of WOMAC Pain subscale for all three doses 100, 200 and 300 mg daily dose at the 12-week landmark. It also failed to show a statistically significant difference for WOMAC Function subscale for all doses. It did show a statistically significant difference for Patient global assessment for the 300 mg dose only. Of note, the 200 and 100 mg dose showed negative changes (were worse than placebo) for WOMAC Pain and Function subscales. All the above described analyses were on the ITT population at the 12-week landmark timepoint using LOCF as the method of imputation.

Table 16. Study 021 in OA. Primary endpoints. 12-week landmark. ITT. LOCF.

	TRAER			Celecox	Placebo
	300 N=199	200 N=199	100 N=201	N=202	N=200
WOMAC Pain (0-500 scale)					
LS Mean change from baseline (SE)	117.8 (8.9)	90.4 (8.9)	82.5 (8.9)	130.0 (9.0)	94.9 (8.9)
Difference with Placebo (95% CI)	22.8 (-0.8,46.5)	-4.5 (-28.4,19.3)	-12.4 (-36.2,11.4)	35.1 (11.2,58.9)	
P value*	.058	(.708)	(.308)	.004	
WOMAC Physical Function (0-1700 scale)					
Mean change from baseline	357.2 (29)	271.0 (29)	273.3 (29)	429.2 (29)	290.1 (29)
Difference with Placebo (95% CI)	67.1 (-10.2, 144.4)	-19.1 (-97, 58.7)	-17.8 (-95.6, 60.0)	139.1 (61.2, 217)	
P value*	.089	(.630)	(.653)	<.001	
Patient Global Assessment					
Mean change from baseline	26.4 (2.0)	20.6 (2.0)	18.8 (2.0)	28.6 (2.0)	20.2 (2.0)
Difference with Placebo (95% CI)	6.1 (8, 11.4)	0.3 (-5.0, 5.6)	-1.5 (-6.8, 3.8)	8.4 (3.0, 13.7)	
P value*	.023	.905	(.583)	0.02	

LS means and p-values calculated from ANCOVA model. *p-values by sequential testing procedure were provided by the Sponsor. The sequential testing procedure stops prior to calculating p-values in the parenthesis. ITT: intent to treat population. LOCF: Last observation carried forward. For details the reader is referred to Dr. Yongman's review.

- **FDA analyses**

Sensitivity analysis conducted by the FDA statistician (Dr. Yongman) using the Bonferroni approach for adjustment for multiple testing as well as different methods for imputation of missing data (BOCF) were consistent with the failure of the primary analyses.

Analyses of efficacy averaged over weeks 1 to 12 (which was not the primary analysis) using LOCF showed statistically superiority to placebo for the 300 mg dose only (not for the 200 and 100 mg doses). Additional sensitivity analyses were not performed for this secondary analysis.

Of note, Celebrex 200 mg daily, the active comparator, showed a statistically significant difference with placebo for all three co-primary endpoints at the 12 week landmark and averaged over weeks 1 to 12 with the ITT LOCF and preserved its superiority to placebo with the BOCF analysis.

Table 17. Study 021 in OA. LS Mean* changes in WOMAC Pain subscale at the 12-week landmark. Statistical comparisons (P value) with different methods of imputation.

	TRAER			Celecox	Placebo
	300 N=199	200 N=199	100 N=201	N=202	N=200
LOCF[1]	.058	(.708)	(.308)	.004	
BOCF[2]	.895	(.521)	(556)	.018	
BOCF/LOCF[3]	.874	(.232)	(.225)	.007	

*LS means and p-values calculated from ANCOVA model. The sequential testing procedure stops prior to calculating p-values in the parenthesis. [1] LOCF: last observation carried forward provided by Sponsor. [2] BOCF: baseline observation carried forward and [3] BOCF/LOCF (BOCF for adverse events and LOCF for other dropouts) analyses conducted by FDA reviewer, Dr. Yongman Kim.

3. Summary

Study 021 failed to show [redacted] adequate evidence of efficacy for the treatment of chronic pain, since it did not succeed on the WOMAC Pain subscale endpoint when sensitivity analyses were performed to confirm the primary analysis. Celebrex succeeded in all three co-primary endpoints for the primary and all sensitivity analyses.

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Attachment 1. Schedule of assessments in Study 021.

Table 9-3 Schedule of Assessments

Study Period	Pre-treatment Period		Treatment Period							Post-treatment Period[b]	
Visit	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	
	Screening	2-7 Days Washout[a]	Week 0 Baseline	Week 1	Week 2	Week 3	Week 6	Week 9	Week 12 End of Dosing	Week 13 Final Visit[i]	Early Termination
Medical History	X										
Vital Signs	X		X	X	X	X	X	X	X	X	X
Physical Examination	X								X		X
Clinical Laboratory Tests	X		X	X			X		X		X
Pregnancy Tests[c]	X[c]		X[c]			X	X	X	X		X
ECG[h]	X								X		X
Syncope and Vasodilation Assessment	X		X	X	X	X	X	X	X	X	X
Randomization[d]			X								
Adverse Events[e]			X	X	X	X	X	X	X	X	X
Dispense Study Medication[f]			X	X	X	X	X	X			
Drug Accountability				X	X	X	X	X	X		X
Osteoarthritis Assessments[g]	X		X	X	X	X	X	X	X		X
Patient Global Assessment[g]	X		X	X	X	X	X	X	X		X
Physician's Global Assessment	X		X	X	X	X	X	X	X		X
SF-36 Health Survey			X						X		
ARCI Questionnaire			X						X		X
Chronic Pain Sleep Inventory (CPSI[g])	X		X	X	X	X	X	X	X		X
Physical Dependence Questionnaire			X						X	X	X

[a] A 2 to 7 day washout period during which analgesic use was to be discontinued.
[b] Patients were contacted between Visits 8 and 9 to ensure that they were not taking opioid analgesics or tramadol. Visit 9 could be scheduled earlier than 1 week after Visit 8 if needed.
[c] A negative urine pregnancy test was required at the screening or baseline visits, within 7 days of first dose of study medication.
[d] Patients with pain intensity ≥ 40 mm on VAS in the index knee or hip joint were randomly assigned to receive either Tramadol HCl ER, celecoxib, or placebo.
[e] Monitored throughout the study at visits and by telephone contact.
[f] Patients assigned to Tramadol HCl ER initially received 100 mg/day. Patients who were randomized to receive 200 mg or 300 mg Tramadol HCl ER had their dose increased to
200 mg on day 5, and patients randomly assigned to receive Tramadol HCl ER 300 mg had their dose increased to 300 mg on day 10. The dose titrations were double-blinded
[g] Includes arthritis pain intensity VAS, WOMAC OA Index, and non-index joint arthritis pain intensity VAS. Starting on the day after the screening visit patients were to record their arthritis pain intensity VAS once daily in diaries. At each visit, OA assessments and patient's global assessments were to be completed before completing the CPSI andSF-36 Health Survey.
[h] ECG required in the 14 days before the first dose of study medication.
[i] In case of early termination, the visit was to be 1 week after the Early Termination visit.

Source: Table 29-3. Study 021 CSR.

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On Original

2) **Study B02.CT3.023.TRA P03 (023 in OA)**

1.Protocol
Title: Double-blind, Randomized, Dose-ranging, Parallel-group Comparison of the Efficacy and Safety of Extended Release Tramadol Hydrochloride (Tramadol HCl ER) 100 mg, 200 mg, 300 mg and 400 mg with Placebo in the Treatment of Osteoarthritis of the Knee and/or Hip.

The study design, eligibility and endpoints are identical to study 021. However, the treatment groups were different: TRAER 100 mg, 200 mg, 300 mg, 400 mg or placebo. No active comparator was included in this study.

A total of 1011 patients were enrolled, with approximately 200 per treatment group.

For amendments and Post-hoc changes the reader is referred to Dr. Yongman's review.

2. Results
a. Disposition

Table 18. Patient disposition. Source Table 10-1 023 CSR.

	Number (%) of Patients				
	TRA 400 mg	TRA 300 mg	TRA 200 mg	TRA 100 mg	Placebo
Randomized to treatment	205	204	203	203	205
Analyzed for safety and efficacy	202	201	201	202	205
Completed study	103 (51.0)	104 (51.7)	116 (57.7)	120 (59.4)	115 (56.1)
Withdrawn	99 (49.0)	97 (48.3)	85 (42.3)	82 (40.6)	90 (43.9)
Insufficient therapeutic effect	23 (11.4)	18 (9.0)	29 (14.4)	31 (15.3)	46 (22.4)
Serious adverse event	3 (1.5)	2 (1.0)	4 (2.0)	2 (1.0)	2 (1.0)
Non-serious adverse event	57 (28.2)	52 (25.9)	36 (17.9)	27 (13.4)	19 (9.3)
Non-compliant with protocol	3 (1.5)	5 (2.5)	6 (3.0)	4 (2.0)	7 (3.4)
Patient requested withdrawal from study	8 (4.0)	14 (7.0)	6 (3.0)	11 (5.4)	9 (4.4)
Investigator withdrew patient	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)
Patient lost to follow-up	1 (0.5)	5 (2.5)	2 (1.0)	3 (1.5)	3 (1.5)
Other	2 (1.0)	0 (0.0)	1 (0.5)	4 (2.0)	3 (1.5)

Of note, 40 to 50% of patients withdrew from the study, including the placebo group.

More patients on placebo discontinued due to insufficient therapeutic effect (22%) as compared to the active treatment groups (9 % to 15%), although one would expect to observe a larger difference. There seems to be a trend for a dose response in terms of efficacy among TRAER groups, since more patients discontinued due to insufficient therapeutic effect in the TRAER 100 and 200 (15 % and 14 %) as compared to the higher doses. However, the 400 mg doses had more discontinuations due to insufficient therapeutic effect than the 300 mg dose (11 % and 9%, respectively).

There seems to be a dose response in terms of discontinuations due to non-serious adverse events, with 13, 18, 26 and 28% of patients in the TRAER 100, 200, 300 and 400 mg/day groups, as compared to 9% on placebo

b. Demographics and baseline characteristics

See statistical review by Dr. Yongman Kim.

c. Efficacy

Primary:

The primary analysis was to be conducted in the ITT population, at the 12-week landmark, with LOCF. A sequential analysis was planned in the DAP, starting with the highest dose (400 mg) and proceeding to the lower doses if successful.

The study failed to support the
the "moderate to moderately severe chronic pain" indication.

The study succeeded in demonstrating superiority to placebo at 12 weeks for all doses studied using a LOCF approach for the Pain and Function variables but failed to show superiority to placebo for the Patient Global assessment endpoint (See review by Dr. Yongman). Of note, the analysis conducted over the Average 1-12 weeks (not the primary analysis), was statistically different from placebo for all three co-primary endpoints. Secondary efficacy analyses were consistent with the primary analyses.

It is unclear why study 023 was successful in all co-primary endpoints by the LOCF analysis while study 021, with identical study design and population, did not succeed and even showed worsening in the WOMAC Pain and Function endpoints as compared to placebo.

- **Sensitivity analyses conducted by FDA statistician** (Dr. Yongman Kim):

Additional analyses to take into account the substantial number of dropouts were conducted for the WOMAC Pain variable in this study. These analyses (BOCF and BOCF/LOCF combined) did not support the LOCF analyses. As seen in Table 19, the differences between TRAER and placebo

lost statistical significance for the 400 dose and therefore for all doses, since sequential testing required stopping further analyses. For detailed statistical analyses the reader is referred to Dr. Yongman's review.

Table 19. Study 023 in OA. WOMAC Pain (0-500 scale). 12-week landmark. ITT.

	TRAER			100	Placebo
	400 N=202	300 N=201	200 N=201	N=202	N=205
LOCF					
LS Mean change from baseline (SE)	107.8 (8.7)	103.9 (8.7)	111.5 (8.6)	107.2 (8.6)	94.9 (8.9)
Difference with Placebo (95% CI)	33.6 (10.5,56.6)	29.7 6.6, 52.7)	37.3 (14.2, 60.4)	32.9 (T0, 55.9)	
P value* Bonferroni	.004 .016	.012 .048	.002 .008	.005 .020	
Sensitivity analysis 1: BOCF					
Mean change from baseline	70.8 (8.4)	63.5 (8.4)	87.3 (8.5)	84.6 (8.3)	
Difference with Placebo (95% CI)	14.2 (-8.1, 36.5)	6.9 (-15.4, 29.2)	30.7 (8.3, 53.1)	28.0 (5.8, 50.3)	
P value*	.212	(.544)	(.007)	(.013)	
Sensitivity analysis 2: BOCF for AE dropouts and LOCF for other dropouts)					
Mean change from baseline	78.1 (8.7)	75.9 (8.7)	98.8 (8.8)	98.4 (8.6)	71.4 (8.5)
Difference with Placebo (95% CI)	6.7 (-16.4, 29.8)	4.6 (-18.5, 27.7)	27.5 (4.3, 50.6)	27.0 (4.0, 50.0)	
P value*	.567	(.698)	(.020)	(.021)	

LS means and p-values calculated from ANCOVA model. *p-values by sequential testing procedure were provided by the Sponsor. The sequential testing procedure stops prior to calculating p-values in the parenthesis. ITT: intent to treat population. LOCF: last observation carried forward. BOCF: baseline observation carried forward. For details the reader is referred to Dr. Yongman's review.

By looking at the effect sizes of the different doses, there is no clear evidence of a dose response. If something, the 200 mg dose has a larger effect size than the 300 and 400 mg doses, which does not make clinical sense, except, may be to suggest that the 300 and 400 mg doses were not as well tolerated as the lower doses of TRAER.

3. Summary

Study 023 failed to show robust evidence of efficacy to support the chronic pain indication, since sensitivity analyses of

the WOMAC Pain subscale score (BOCF and BOCF/LOCF) indicated that the results of the primary analysis (LOCF) were driven by patients who dropped from the study.

3) Study 015 in OA

1. Protocol (final amendment)

a. Title: Double-blind, randomized, dose-titration, parallel group comparison of the efficacy and safety of Tramadol hydrochloride ER and placebo in the treatment of osteoarthritis (OA) of the knee.

b. Design/objectives: A 12-week, multicenter (n=16), randomized, dose titration, placebo-controlled study to evaluate analgesic efficacy (primary objective) and safety (secondary objective) in 245 patients with OA of the knee.

c. Patients/ eligibility: Planned: 245, to have at least 140 completing 4 weeks. Enrolled: 246 (124 to TRAER and 122 to placebo). Eligibility criteria similar to 021 and 023 but patients with OA of the hip were not included in this study.

d. Treatment: Following a 2 to 7 day washout period, eligible patients were randomly assigned to once daily dosing with orally administered TRAER or placebo. Study medication was to be taken within 1 hour of the recommended time of 8:00 AM.

TRAER ER, 100 mg tablets, taken once daily starting with 100 mg/day for 3 days which could be increased to 200 mg/day. At the end of week 1, all patients were to have their dose increased to at least 200 mg/day. After the first week, further increases to 300 and 400 mg daily were allowed. Patients who did not tolerate at least 200 mg were to be discontinued from the study. The maximum dose for patients ≥ 75 years was 300 mg/day.

e. Evaluations:
- Efficacy: Primary efficacy variable: Arthritis Pain Intensity (PI) VAS score recorded at patient visits.
Secondary: PI from patient diaries; WOMAC questionnaire (individual subscales and composite index); Patient Global assessment of OA; Physician Global assessment of OA; incidence of patient withdrawal due to lack of efficacy; time to withdrawal due to lack of efficacy; patient sleep assessment.

- Safety: Adverse events, syncope and vasodilation assessments, clinical laboratory, physical examination, ECG, vital signs, Physical Dependence questionnaire and Addiciton Research Center Inventory (ARCI).

f. Statistical methods:

As per the protocol statistical and analysis plans, primary efficacy analyses were to be conducted in the ITT population. The ITT population was defined by the Sponsor as patients who had data

recorded for the primary efficacy variable at the baseline visit and week 1, and any patient who dropped out of the study before the week 1 visit due to lack of treatment efficacy.

Comment: A more adequate definition of an ITT population would include all patients randomized who received at least one dose of medication.

Seconday analyses would be conducted in the evaluable population, defined as all patients who were in the ITT and had data recorded at week 4, if they were using at least 200 mg/day at visit 3 (week 1).

The change from baseline to weeks 1, 2, 4, 8 and 12 and the average change over weeks 1-12 were analyzed using an analysis of covariance with treatment and site as a cofactors and baseline value of the variable analyzed as the covariate. The primary efficacy variable was the change in arthritis pain intensity score averages over the 12 weeks of study.

COMMENT: The Division prefers the landmark analysis at the end of study as the primary analysis and the average or area under the curve as a confirmatory analysis.

- Protocol Amendments

The original protocol was submitted 8/25/00. It was amended on 9/27/00 before any patients were enrolled and on 3/14/01 after 196 patients were enrolled. A relevant change to the protocol in September, 2000 was specification that patients were to achieve a minimum tolerable dose of TRAER by the end of week 1 rather than week 2 and clarified the use of concomitant medications.

The relevant change on March 2001 was the increase in the number of patients from 200 to 245, because of the higher than expected rate of discontinuations and to ensure a minimum of 140 patients completing at least 4 weeks of treatment.

- Post Hoc changes

The study was conducted according to the amended protocol and statistical analysis plan. Analyses were performed with and without study site 01. Changes from baseline to days 1 - 7 in the PI score as recorded in patients' diaries were also analyzed.

2. Results

a. Disposition

As per information submitted September 9,2004, a total of 350 patients were screened for this study. Of these, eighty seven (25%) did not enter the study (60 did not fulfill eligibility criteria - reason not specified - , six were lost to follow-up, fifteen requested withdrawal, one was not compliant and five did not enter due to "other" reasons).

COMMENT: Approximately 25% of patients screened failed to enter randomization, including fifteen who requested withdrawal and six lost to follow up. It is unclear why would they request withdrawal if they were not in the study yet.

Excluding the 17 patients enrolled in site 01, 246 patients (124 TRAER, ~~122~~ placebo) were randomized to treatment. Approximately 50 % of patients completed each treatment group. As seen in Table 20, more than twice the number of patients discontinued due to lack of efficacy from the placebo group, as compared to the TRAER 100-400 mg group, while almost four times the number of patients discontinued due to adverse events from the TRAER group as compared to placebo. Additionally, six patients were either withdrawn by the investigator or lost to follow up in the TRAER group (these patients may have potentially discontinued because of adverse events or lack of efficacy).

Table 20. 015 in OA. Patient Disposition. All randomized patients

	Tramadol HCl ER	Placebo
Randomized to treatment	124	122
Completed study	61 (49.2%)	63 (51.6%)
Withdrawn	63 (50.8%)	59 (48.4%)
Insufficient therapeutic effect	19 (15.3%)	45 (36.9%)
Serious adverse event	2 (1.6%)	2 (1.6%)
Non-serious adverse event	31 (25.0%)	7 (5.7%)
Patient requested withdrawal from study	5 (4.0%)	4 (3.3%)
Investigator withdrew patient	3 (2.4%)	0 (0.0%)
Patient lost to follow-up	3 (2.4%)	0 (0.0%)
Other	0 (0.0%)	1 (0.8%)

Source. Table 10-1 CSR.

[1] Includes patient 14-015 who was withdrawn by the Investigator because of an adverse event

There were several protocol deviations, some of them minor - such as inclusion of one patient with an X-ray obtained more than 6 months before screening or one who had a 10-day washout versus a 7-day washout before randomization - while others may have had some impact on outcomes such as the use of prohibited concomitant medications. Most of these occurred in the placebo arm, but there were some protocol violators in the TRAER arm too, such as patient 03-016 who used hydrocodone/ibuprofen and patient 13-018 who used glucosamine during the trial As per the original submission six patients underwent knee reconstruction. However, when asked to clarify whether this occurred before or after surgery, the sponsor stated that three of those six patients had not actually undergone knee replacement at any time.

b. Compliance. At weeks 1, 2, 4, 8 and 12, patients were to return all unused medications. The amount dispensed and returned at each visit is provided in a listing, however, analyses of treatment compliance were not performed.

c. Demographics and baseline characteristics

There were no major differences in the baseline characteristics of the patients randomized to either TRAER or placebo (See Dr. Yongman's review). Of note, there was a difference of approximately 3 Lbs. between the weight of TRAER and placebo patients (mean of 94 and 97 Lbs., respectively). It is unclear how this factor may have played in the results.

d. Efficacy: Primary

- Sponsor's analyses

Primary analysis:

The primary analysis was the change from baseline in the Pain VAS score in the Sponsor's defined ITT (SpITT) (which excludes patients who did not have 1 week efficacy data), analyzed over the 12-week period, with LOCF (Last observation carried forward). This analysis showed that TRAER at doses of 100 to 400 mg daily (flexible dosing) was statistically different from placebo.

Table 21. Sponsor's result. LSMean change from baseline over 12-week period.
Sponsor defined ITT population, LOCF.

	TRAER (100-400 mg/day) N= 101	Placebo N=118	Difference with placebo
Pain VAS (100 mm scale)	30.1	17.7	12.4*

*P value <0.001. LOCF (last observation carried forward)

Analyses of WOMAC Pain, WOMAC Physical function and Patient Global assessment over the 12-week period in the SpITT population with LOCF were also statistically superior to placebo, suggesting a meaningful result. Additional analyses were conducted in the true ITT population.

- **FDA Analyses**

Efficacy analyses in the ITT population are more adequate than those that exclude patients who dropped during the study, since in most cases, the cause of withdrawal is not unrelated to the treatment received (informative censoring). Also, the Division prefers the landmark analysis at end of study time point as the primary analysis, with the average analysis as a confirmatory analysis. Moreover, imputation of missing data is always problematic, particularly if large and if there is differential dropout such as in this study. The dropout rate due to AE in this study was 7 and 27 % for placebo and TRAER, respectively (Table xx). The FDA statistical reviewer conducted analyses in the true ITT population at the 12 weeks landmark, using both LOCF and BOCF as methods of imputation for missing data. Analyses of WOMAC Function subscale and Patient global assessment were also conducted.

Analyses in the true ITT population using LOCF

Twenty-three (19%) and four (3%) patients were excluded from the TRAER and placebo groups, respectively in the sponsor's defined ITT population (SpITT) As seen in Table 22, the majority of patients excluded from the sponsor's primary analyses had adverse events within the first week of treatment. Most common AEs were constipation, nausea and dizziness.

Table 22. Study 015. Patients excluded from Sponsor's defined ITT (SpITT)

Reason for not entering ITT	TRAER ITT = 124 SpITT= 101	Placebo ITT = 122 SpITT = 118
Completed but missed wk 1 data	1	-
Patient requested withdrawal	2	1
Early adverse event	18	3
Lost to follow up	2	-
Total excluded from SpITT	23	4

Source: Table 14.1.2 CSR. N= patients randomized

Analyses of change from baseline for Pain VAS, WOMAC Function subscale and Patient Global assessments in the true ITT population at the 12-week landmark using the LOCF method of imputation were consistent with the primary analysis in the Sponsor's defined ITT population (p value <0.001 for all three) (Table 23). However, these analyses were not supported by the BOCF method of imputation.

Table 23. Study 015 in OA. Efficacy analyses. Change from baseline to 12-week landmark. ITT. LOCF.

	TRAER (100-400 mg/day) N= 124	Placebo N=122	Difference with placebo
Pain VAS	36.6	22.1	14.5 *
WOMAC Function[1]	498.7	272.4	226.3*
Patient Global assessment[2]	32.0	18.6	13.4*

Source: FDA statistical review (Dr. Kim). [1] Scale 0-1700 mm. [2] Scale 0-100 mm.
* p<0.001 for all three variables. LOCF: last observation carried forward.

Analysis using BOCF

As mentioned above, when there is a high dropout rate, other methods of imputation are preferred to the LOCF. Table 24, shows that the change from baseline for the Pain, WOMAC function and Patient global assessment were not statistically different from placebo when using the BOCF method of imputation.

Table 24. Study 015 in OA. Pain VAS (0-100 mm). Change from baseline to 12-week landmark. ITT. BOCF.

	TRAER (100-400 mg/day) N= 124	Placebo N=122	Difference with placebo	P value
Pain VAS	23.8	18.6	5.2	0.124
WOMAC Function	336.5	242/7	93.8	0.057
Patient Global assessment	20.6	16.5	4.1	0.204

Source: FDA statistical review (Dr. Kim). [1] Scale 0-1700 mm. [2] Scale 0-100 mm.

These analyses suggest that superiority to placebo using LOCF was likely driven by a substantial number of patients who eventually dropped from the study (mostly because of adverse events). This observation reduces the robustness of the primary analysis. Another issue that limits the clinical relevance of the efficacy findings is that the study used a flexible dose regimen that did not allow adequate characterization of a dose response in terms of efficacy or safety.

In addition to the original analyses, the FDA requested the sponsor to provide efficacy analyses by TRAER dose at the time of the evaluations. As per information submitted 8/6/04, these post-hoc analyses seem to support the efficacy of doses of 200, 300 and 400 on the primary variable of Pain Intensity as well WOMAC Function and Patient Global assessment in the Sponsor's defined ITT population with LOCF. BOCF analyses in the true ITT population from different dose groups were not performed . The current submission also included an analysis of concomitant medications. It appears that there were no significant differences in the use of concomitant medications between treatment groups.

3. Efficacy Conclusions:

The study suggests that TRAER may have some efficacy in some patients with OA of the knee but it does not provide robust evidence of efficacy and does not allow identification of the subgroup of patients who may benefit from it.

Efficacy analyses using LOCF showed superiority to placebo on Pain VAS and other endpoints. However, analyses in the true ITT population using the BOCF method of imputation failed to demonstrate a statistically significant difference with placebo suggesting that results using LOCF analyses are driven by patients who dropped out of the study.

The usefulness of this product seems to be limited by the poor tolerability, particularly during early treatment. Thirty four (27 %) and nine (7 %) patients withdrew from TRAER and placebo groups due to AEs during the study. Half of the patients who withdrew from TRAER did so within the first 10 days of treatment (at the 100 or 200 mg/day dose). The "flexible dose" study design did not allow adequate characterization of a dose response in terms of efficacy or safety.

4) B00.CT3.014.TRA P03 (014 in CLBP)

1. Protocol

a. Title: Double-blind, Randomized, Placebo-controlled, Parallel-group Comparison of the Efficacy and Safety of Extended Release Tramadol (Tramadol HCl ER) 300 mg and 200 mg to Placebo in the Treatment of Chronic Low Back Pain (CLBP)

b. Design/objective:

Multicenter (n=30), 3-week open-label, active-treatment run-in period followed by a 12-week, randomized, double-blind, placebo-controlled period in patients with moderate to severe chronic (≥ 6 months) LBP.

Primary objective: to compare analgesic efficacy of oral TRAER 300 and 200 mg daily to placebo

Secondary objectives: to compare analgesic efficacy of TRAER 300 mg QD with 200 mg QD,
to evaluate safety and tolerability of TRAER

c. Patients/Eligibility:

Males or females in good health, between 18 and 80 years of age, with chronic LBP requiring daily treatment with an analgesic and a pain intensity of ≥ 40 mm on the 100 mm VAS following a 2 to 7 day washout from analgesics.

Planned: 600 patients were planned to get approximately 120 patients per treatment group in the placebo-controlled part of the study. Enrolled: 619 patients.

d. Treatment

Tramadol HCl ER 100 mg tablets taken once daily, starting with a 100 mg/day dose (Week -3) for at least three days, with increase to 200 mg/day by the beginning of the second week (Week -2) and to 300 mg/day by the beginning of Week -1. At week 0 (baseline) patients were randomized to receive Tramadol HCl ER 300 mg, Tramadol HCl ER 200 mg, or placebo (one dose daily for 12 weeks).

e. Evaluations

Efficacy:
The primary efficacy variable was the patient's pain intensity score since the previous visit, using a visual analog scale (VAS) (0 mm = no pain and 100 mm = extreme pain).

The secondary efficacy variables were the current pain intensity, patient's global assessment of study medication, Roland Disability Index, sleep assessments, and the proportion of patients who exited the study early.

Safety:

Safety was assessed through adverse events (including syncope and vasodilation); vital signs, physical examination; clinical laboratory tests; 12-lead EKG; the Addiction Research Center Inventory (ARCI); and the Physical Dependence Questionnaire (PDQ). In addition to routine safety assessments, since episodes of flushing and syncope had been observed in early trials, these adverse events were assessed at baseline and at every visit in this study.

f. Statistical analyses

Efficacy analyses were to be based on data collected during the 12- week double-blind period in the "Intent-To-Treat" (ITT) population (all patients who received at least one dose of study medication and had primary efficacy information recorded at "baseline" [Week 0, Visit 5]). LOCF were to be used for imputing missing data.

> *COMMENT: This is not the true ITT population, since patients started TRAER at week -3 and almost 40 % of patients dropped during the open-label run in period. This reviewer will call this population as the Post run-in ITT population.*
>
> *The primary efficacy was Pain Intensity VAS since the previous visit. Of note, the DAP is a bit unclear as to whether the primary analysis was to be OVER the 12 weeks period or at 12-week endpoint. However, under Efficacy hypothesis and interpretation the DAP states: "When the efficacy analysis results are interpreted, definitive conclusions from the analyses will primarily be based on the following principles, given that consistency of results will always be examined: when analyses are performed separately for the average over tinme, and for each of weeks 1, 2,4,8 and 12, the results on the average over time will be interpreted prior to that of any particular week". Therefore, it appears that the primary analysis is the outcome averaged over the 12 week period.*

Safety data were to be analyzed separately for the run-in, the double-blind, and the entire study periods. The incidence of adverse events was to be analyzed using Fisher's Exact test.

The sample size determination was based on the primary efficacy variable of patient pain intensity score since the previous visit (on a 0-100 mm VAS scale). It was assumed that the standard deviation (SD) among the patients was 30 mm and that the mean difference between Tramadol HCl ER and placebo would be at least 15 mm. It was also assumed that the significance level was 5% and that the power to detect the difference of 15 mm was 90%. For the purpose of establishing the superiority of Tramadol HCl ER over placebo, the null hypotheses of interest was tested in a conditional and pre-specified manner (*a priori* ordering of the null hypotheses of interest), the Step-down procedure (SD2) by Dunnett and Tamhane.[24] The overall 2-sided test for treatment effect was the first to be assessed. If the overall test was significant, the following comparisons

were to be done in the order indicated: Tramadol HCl ER 300 mg > Tramadol HCl ER 200 mg > placebo.

The initial hypothesis of interest was that the magnitude of response between Tramadol HCl ER 300 mg and placebo would be the same. If this null hypothesis was rejected, then the null hypothesis that the magnitude of response between Tramadol HCl ER 200 mg and placebo would be the same was to have been tested. This procedure were to stop after the first pair-wise test of Tramadol HCl ER vs. placebo yielded a nonstatistically significant result. Since statistical testing of treatment differences between Tramadol HCl ER and placebo were performed by means of *a priori* ordered hypotheses, no adjustment for the 5% significance level was needed. Based on these assumptions, it was determined that 97 patients per treatment group were required. Assuming a postrandomization dropout rate of approximately 20%, a minimum total of 120 patients per treatment group were needed. Assuming that approximately 40% of the patients would not complete the open label titration period, then approximately 600 patients would have been needed to ensure a minimum of 360 patients.

- Amendments

The protocol dated September 11, 2000 was amended on September 27, 2000 before any patients were enrolled and did not involve changes that would dramatically affect study outcomes. The final SAP dated November 21, 2001 applied to the double-blind period. Statistical analyses for the run-in period were determined AFTER unblinding and draft statistical analysis of the double-blind period had occurred, with the intention of treating the run-in data as an open label study to potentially provide additional safety.

- Post Hoc changes
As per section 9.8 (Changes in conduct of the study or planned analyses) of the CSR dated December 19, 2002 (page 46 of electronic CSR), rather than a Wilcoxon signed-rank test as specified in the protocol, a paired t-test was used to assess the statistical significance of the within-group changes from baseline to the post-baseline assessments for the primary and secondary efficacy variables, body weight, and vital signs. It is unclear why the statistical analysis was changed.

2. Results

a. Disposition

Table 25 shows disposition for all patients who entered the study.

Table 25. Study 014. All patients entered into the study

	Run-In	Double-Blind		
		Tramadol HCl ER 300 mg	Tramadol HCl ER 200 mg	Placebo
Entered	619			
Not Randomized*	233			
Randomized		128	129	129
Completed, n (%)		86 (67.2)	87 (67.4)	68 (52.7)
Withdrawn, n (%)		42 (32.8)	42 (32.6)	61 (47.3)
Lack of efficacy	41 (6.6)	13 (10.2)	11 (8.5)	21 (16.3)
Serious adverse event	3 (0.5)[b]	0 (0.0)	3 (2.3)	1 (0.8)
Non-serious adverse event[c]	125 (20.2)	13 (10.2)	10 (7.8)	17 (13.2)
Patient noncompliant with protocol	21 (3.4)	5 (3.9)	7 (5.4)	10 (7.8)
Patient requested withdrawal from study	20 (3.2)	5 (3.9)	9 (7.0)	3 (2.3)
Investigator withdrew patient[d]	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)
Other	21 (3.4)	6 (4.7)	2 (1.6)	8 (6.2)

Source. Table 10-1 CSR. * As per patient listings 16.2.1 six additional patients discontinued before randomization due to lack of efficacy and/or adverse events.

Of note, the "Other" category for withdrawal includes patients who were lost to follow up. Seventeen of all patients entering the study (2.7%) were lost to follow up during the open-label run-in period. An additional 2.5 % were lost during the 12-week placebo controlled period (five from T300, two from T200 and eight from placebo).

Protocol deviations: Most protocol deviations were related to the use of excluded medications. Some of these patients were withdrawn from the study because of protocol non-compliance during either the run in period or the randomized portion of the study, but other stayed in the trial. These patients were not excluded from the SpmITT population.

COMMENT: As an alternative to the usual treatment design and as a way of avoiding imputation of data in a large number of patients, some experts recommend a "withdrawal design" in chronic pain studies. However, if there is a high dropout rate in the active treatment, having a run in period does not solve the problem of missing data, it simply ignores or neglects to evaluate a substantial part of the population.

In this case, a total of 233 patients (38% of all patients entering the study) dropped during the active treatment run-in period. Of these, at least 128 (55%) dropped because of adverse events and 41 (18%) because of lack of efficacy. This enrichment design highly selects patients who tolerate and are likely to respond to TRAER.

Additionally, data presentation from this study was sometimes confusing. For instance, seven patients withdrew during the randomized period due to adverse events that started during the run in period but were not listed as discontinued during the randomization

period, 4 patients who withdrew due to AEs were included in both run-in and double blind period analyses and one patient who dropped during the run-in was not included in neither period.

b. Compliance

At each visit patients were to return all unused study medication. This information was presented in listings but statistical analyses of treatment compliance were not performed.

c. Baseline demographics and clinical characteristics

There were no significant differences among treatment groups with respect to their demographic characteristics (age, gender, race) among patients who entered the randomization part of the study. Overall, patients were 19 to 80 years of age (mean, 47 to 48 years), 50% were female, and 84% were Caucasian. There was a statistically significant difference among the three treatment groups with respect to weight ($p = 0.031$), with a higher mean weight in the Tramadol HCl ER 300 mg group (92 kg) compared with the Tramadol HCl ER 200 mg and placebo groups (87 kg and 86 kg, respectively). It is unclear whether this difference in weight may have affected study outcomes.

d. Efficacy

Primary- Primary efficacy outcome was mean change from baseline in Low Back Pain intensity (0-100 mm VAS) to the average over the study period (Weeks 1-12), with LOCF.

- **Sponsor's analyses**

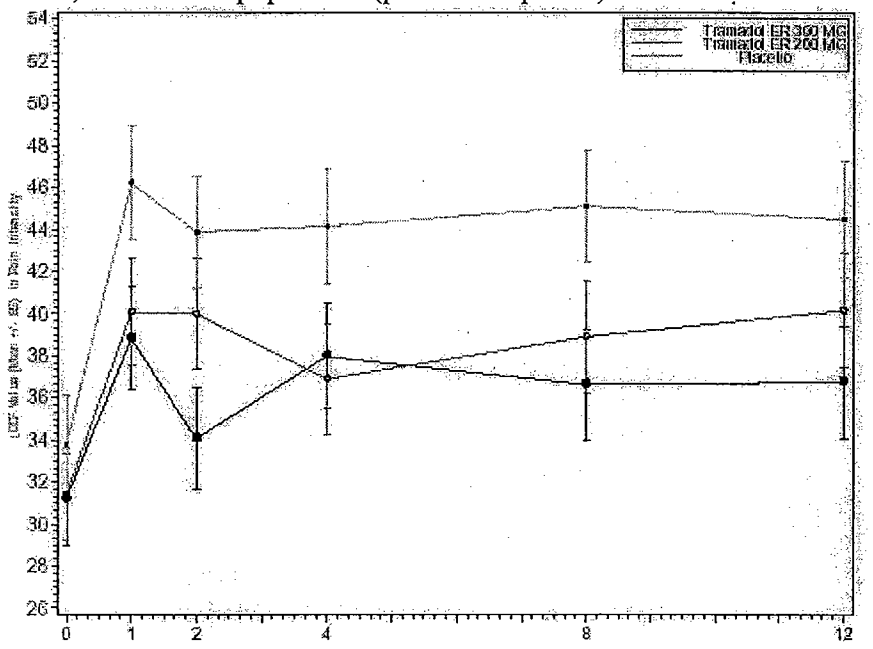
Table 26. Study 014. Low back pain. Change in Pain Intensity score (0-100 mm VAS) from baseline, since the previous visit (LOCF), Post run-in randomized population.

	T 300 [1] mean (SD) (N= 127)	T 200 [1] mean (SD) (N=129)	placebo [1] mean (SD) (N=126)	P value versus placebo T (both doses)	T 300	T 200
Baseline	31.2 (25.0)	31.4 (25.0)	33.8 (26.1)			
Weeks 1-12* avg.	-5.2 (24.2)	-7.8 (25.8)	-12.2 (25.3)	0.027	0.009	0.052
At Week 12	-5.1 (32.4)	-8.7 (30.2)	-11.9 (30.2)	0.113	0.038	0.197

- Primary analysis. [1]Within group comparisons were all statistically significantly different. T 300: TRAER 300 mg/day. T 200: TRAER 200 mg/day. (95% CI not provided). Source: Modified from Table 11-3, CSR.

Of note, there are discrepancies between Table 11-3 of the CSR and Table 14.2.1.1 in regards to the patients remaining in the study and the change from baseline at week 12. Sponsor should clarify this issue.

Figure 1: Mean (± standard error) Low Back Pain Intensity VAS (M) LOCF. Post run-in, randomized population (post run-in period).



COMMENT:

1. *What the Sponsor calls the ITT population is not a true ITT population. These are the patients who survived the open-label, run-in period, therefore, this reviewer will call it the Post run-in, randomized population.*

2. *The changes in Pain intensity score as compared to the score at the time of randomization were relatively small in all groups. All groups got worse although both TRAER groups did less bad than the placebo group. This observation is somewhat surprising. One would expect that patients randomized to continue active treatment would be stable or continue to improve over the ensuing 12 weeks rather than get worse. Additionally, if TRAER were an efficacious analgesic one would expect that those who stop and start to receive placebo would have shown a more dramatic worsening.*

3. *Although statistically significant, the effect size for the TRAER groups as compared to placebo (point estimate of approximately 5 -7 mm) was clinically irrelevant. There is no accepted MCID for pain, however, most experts agree that it should be at least a 15 to 20% of the full scale, which would be at least 15 to 20 mm difference.*

4. *The Division recommends the efficacy analysis at landmark (end of study timepoint) as the primary analysis, with the area under the curve or average analysis as a confirmatory analysis. The Sponsor used the average analysis as the primary and the landmark analysis*

as the secondary analysis. In this case, results of the efficacy analysis over 12 weeks were not confirmed by the analysis at landmark (12 weeks). Only the T300 dose was successful in this analysis.

5. *As mentioned above, since there is no widely accepted MCID, the Division currently recommends that a Functional assessment and a Patient global assessment of disease activity or response to therapy be included in all chronic pain trials. In this trial, the Roland Disability index (a measure of function) was included as a secondary variable. The sponsor also included a global assessment of study medication. Secondary endpoints in this study were successful.*

6. *A greater number of patients dropped from the placebo group due to adverse events, as compared to the TRAER groups. This differential dropout is difficult to interpret. Were patients having withdrawal symptoms? Were patients unblinded by the fact that they did not have nausea and dizziness anymore? In the opinion of this reviewer, this study design can not provide reliable efficacy or safety results.*

7. *All analyses performed by the Sponsor used the LOCF as the method of imputation for missing data. However, as noted in Table 27. the LOCF method of imputation clearly inflated negative results in the placebo group, while had little effect on the TRAER groups.*

- **FDA Analyses:**

FDA analyses are presented in Table xx.

Table 27. Study 014. Low back pain. LS Mean Change in Pain Intensity score (0-100 mm VAS) from baseline, averaged over week 12 weeks, Post-run-in ITT population with BOCF.

	T 300 [1] LS mean (SD) (N= 127)	T 200 [1] LSmean (SD) (N=129)	placebo [1] LSmean (SD) (N=126)	P value versus placebo T 300	T 200
Change from baseline	-4.4 (1.6)	- 3.5 (1.5)	- 7.0 (1.6)	.176	.106
Diff w/placebo	3.0 (-1.3, 7.2)	3.5 (-0.8, 7.8)			

Source: Statistical review, Yongman Kim.

Summary: Study 014, with an open-label run in period, succeeded in the primary analysis of change in Pain intensity score over the 12-week period. This analysis was not supported by the 12-week landmark analysis that only succeeded for the TRAER 300 mg dose. Additionally, BOCF analyses to account for 40-50% dropouts, did not confirm the primary analysis either. This study design did not allow adequate characterization of the efficacy or safety of TRAER.

10.2 Line-by-Line Labeling Review

None at this point.

10.3 **Regulatory History**

August 10, 1999: PreIND meeting:

General questions regarding Non-Clinical, Biopharm and Clinical [redacted] In reference to chronic pain, Sponsor asked whether the proposed chronic Phase III study was acceptable. The Division responded that design of the study appeared to be adequate but replication was required. In addition, a 3-month study was preferred. Sponsor inquired if replication would be required under 505b2. The Division would have internal discussions and get back to the Sponsor.

September 21, 1999: IND submission:

One acute and one chronic pain study. The IND was put on partial clinical hold to request additional information about syncopal episodes. Regarding the chronic pain study, the Division stated that the submitted study would be appropriate to assess safety but not efficacy of tramadol ER and that the Division preferred a fix-dose study instead of a titration study.

March 21, 2000: EOP2 meeting:

Division agreed to file a 505(b)2 provided the Sponsor was able to meet the requirements for such an application. Minimum ICH guidance exposure should be provided in the NDA application. A pre-emptive claim would be a new claim that would require replication. Regarding chronic pain, question 6 of the meeting package stated:

The applicant is planning to submit one pivotal clinical trial to support the efficacy, safety and tolerability of tramadol extended release in patients with chronic pan (B00.CT3.010.TRAP03). This trial compares 300 mg of tramadol ER as a single daily dose, immediate release tramadol 100 mg three times daily and placebo in an enrichment study design for a total of 11 weeks. Does the Agency concur that statistically significant results on the a priori specified primary outcome measure in this protocol will provide sufficient evidence in support of the efficacy of this product?

FDA response was: No. Replicate studies should be conducted in a chronic pain model, and a 12-week duration was recommended. Also the patient population proposed for this study was considered too heterogeneous. The Division recommended that a patient population (e.g. low back pain, cancer pain, etc.) be identified for the study and that more than one dose level of tramadol ER be evaluated. Moreover, chronic neuropathic pain was viewed by the Division as a separate indication from other chronic pain models. Safety would require minimum ICH guidance numbers, although it would require less than that if submitted under 505b2.

The Sponsor was advised to submit the phase III protocols for review.

The Sponsor did not agree with the need for replication under a 505(b)2 application.

March 29, 2000: Tcon. Special guidance.

The Division stated that the issue of bioequivalence between an extended release formulation and an immediate release product required further policy exploration and definition. Dr. Bashaw would present the issue at an internal CDER Biopharm meeting at the end of April and the Division would give a final response to the Sponsor's proposal to submit a 505(b)2 application with limited safety data.

June 15, 200: Tcon, Special guidance, continuation.

The opinion of the OCPB management team was that not enough was known about the PK/PD of tramadol to ascertain whether he difference between the ER and IR formulations would affect efficacy. Therefore, the DAAODP stated that two efficacy studies would be required in a chronic pain model. Minimum ICH guidance numbers at the maximum labeled dose should be provided in the NDA.

February 21, 2001: Division comments to three phase protocols in chronic pain, submitted in October, 2002 (SN 005).

1) B00.CT3.014.TRA PO3: "Double-blind placebo-controlled, parallel group comparison of the efficacy and safety of extended release Tramadol (Tramadol ER) 300 mg and 200 mg to placebo in the treatment of chronic low back pain".
2) B00.CT3.015.TRA PO3: "Double-blind, randomized, dose titration, parallel group comparison of the efficacy and safety of extended release Tramadol (Tramadol ER) and placebo in the treatment of osteoarthritis of the knee."
3) B00.CTOL.003.TRA PO3: "Open label assessment of the safety and effectiveness of extended release Tramadol (Tramadol ER) in the treatment of chronic non-malignant pain."

The following comments were conveyed to Biovail:

1. The three studies submitted on October 2, 2000 are safe to proceed.
2. The proposed studies do not allow determination of the minimal effective dose. The use of an open-label run-in period is problematic. At the time of the filing the application should contain clinical efficacy and safety data to support all proposed dosing regimens in the label.
3. At the time of filing the application should have the recommended ICH long term safety database: 300 to 600 patients exposed for at least 6 months and 100 patients for at least 12 months *at the highest labeled dose.*
[redacted]. Labeling would be anticipated to reflect this fact.
4. The inclusion of an opioid active control arm is recommended for the efficacy studies.
5. In view of the heightened susceptibility of the elderly to complications associated with nausea, vomiting, dizziness and somnolence, safety in this population should be addressed specifically.

March 5, 2001: Sponsor request for clarification of comments on phase III protocols (SN011).
Sponsor states that these comments had not been offered at the preIND and EOP2 meetings.

March 20, 2001: DAAODP response to March 5, 2001 Sponsor's letter

The Division advised that discussions at pre-IND are preliminary and non-binding. Formal thorough review of phase III protocols are generally not offered at the time of an EOP2 discussion. General comments had been offered and the Sponsor had been advised to submit phase III protocols for review. In the future, a 45-day protocol assessment (SPA) or alternatively, specific, focused questions about protocol dosing might be asked at the time of submission of a phase III protocol.

June 27, 2001: Submission of SPA for low back pain (B01.CT3.017.TRA P03).

Division comments to SPA provided to the Sponsor in August 14, 2001. In addition to specific comments to the protocol, the Division stated that the chronic pain indicaton had not been [adequately] discussed at the prior EOP2 meeting. The Division encouraged the Sponsor to request a meeting to discuss their development program for the chronic pain indication. This study was never conducted.

February 12, 2002: EOP2/Guidance meeting

Division clarified that appropriate indication would be the treatment [redacted] and that the designs of completed studies B00.CT3.014.TRA .P03 (low back pain) and B00.CT3.015.TRA.PO3 (OA) were not adequate to support an indication.

April 3, 2002: Submission of SPA for OA studies (B02.CT3.021.TRA.PO3 and B02.CT3.023.TRA.PO3). Division responded April 20, 2002.

July 12, 2002: Guidance meeting

Final agreement on design of OA pivotal studies.

August 19, 2003: Biovail submitted briefing document for the PreNDA meeting to be held in September 22. 2003. (IND 59,023 SN 049).

[redacted]

September 22, 2003: Biovail submitted additional information and questions for the PreNDA meeting (IND 59,063 SN 052).

After unblinding, study 021 had failed the primary analysis (a landmark analysis). The study, however, had apparently succeeded in a secondary analysis (an average analysis). The Sponsor asked for the Division's concurrence with a change in the statistical analysis plan for the second OA study (023) and for the NDA Integrated Summary of Efficacy.

October 10, 2003, the DAAODP provided Bioavail with draft responses in advance to the October 14, 2003, PreNDA meeting (see attached).

The Division advised against changing the primary analyses and noted that if one of the OA pivotal studies had failed, the NDA might be considered deficient for filing.

October 13, 2003: a voice mail was left by Biovail requesting that the October 14, 2003 PreNDA sponsor meeting be cancelled.
December 31, 2003: NDA application is submitted for the treatment of moderate to moderately severe pain.

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Maria Villalba
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Joel Schiffenbauer
10/29/04 05:13:07 PM
MEDICAL OFFICER

Brian Harvey
10/29/04 05:18:57 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-692
Reviewer Name	Joel Schiffenbauer
Trade Name	Ralivia ER
Applicant	Biovail
Priority Designation	S
Indication	pain

This review will serve as my secondary review for this NDA.

Summary:

Ralivia ER is a long acting form of tramadol developed as a once a day formulation to provide ease of use for patients. The intent was to also provide a dosing regimen with more uniform drug levels that might have an improved safety profile over short acting tramadol. However, the applicant intends for Ralivia ER to have the same labeled indications as Ultram, although it is not bioequivalent to tramadol. The recommendation for this NDA is "not approved" based on lack of efficacy in conjunction with the high rate of adverse events. A discussion of the issues is provided below:

Issues:

1) Not for acute pain: Ralivia ER is designed as a long acting alternative to the short acting tramadol. Although no studies in the acute pain setting have been performed, even if performed, it is unlikely that Ralivia ER would be effective for acute pain, presumably because of the slower time to onset of analgesia.

2) Not same indication as Ultram: Based on the above discussion in regards to acute pain, it seems apparent that Ralivia ER cannot have the same indications as Ultram. The labeled indications for Ultram are based on the clinical trials performed at the time of approval which included studies in both acute pain and chronic pain models. Ralivia ER has not provided a similar set of clinical trials and is not bioequivalent. Therefore, the indications for Ralivia ER, if approved, cannot be identical to Ultram. Furthermore, to label both drugs with identical indications would be a public health issue. Prescribers and patients would not be able to discern a difference between the drugs by reading the label. Individuals with acute pain might therefore be prescribed Ralivia ER with its potential attendant lack of efficacy for acute pain, thereby leaving patients in pain. This might also necessitate the use of alternate rescue medication compounding the problem of multiple pain medications with additional adverse effects.

3) No chronic pain indication: In pre-NDA responses (October 10, 2003) that were sent to Biovail the Division's position at that time was outlined. The following comments were provided:

   The indication that the Sponsor proposes (treatment of moderate to moderately severe pain) is no longer granted by the DAAODP and so is not a viable option under a NDA 505(b)(2) approval route. In addition, there is insufficient information in the reference product to support a chronic pain indication (also no longer granted by the DAAODP) or a chronic use pain indication such as osteoarthritis.

In the past, the Division has discussed this issue internally and concluded that in order for a drug to receive the indication "treats chronic pain" a minimum of 3 chronic pain models would need to be studied (presumably of different mechanisms). This is a high bar but one that was set because of the implication of a claim as broad as "chronic pain." The sponsor has not met this requirement and so cannot receive this indication (see also #6, below).

Even if the sponsor were to demonstrate robust evidence of efficacy in a single chronic pain model such as osteoarthritis, in this reviewer's opinion, the chronic pain indication should be reserved for drugs with proven efficacy and safety in more than one pain model. Acknowledging that studies using Ultram included subjects with multiple types of pain, those studies would not meet today's standards for demonstration of efficacy in each model in individual studies. Again, since Ralivia ER is not bioequivalent to Ultram, we can and should apply today's standards to approval of this drug for the appropriate indications recognized today.

4) No indication for the treatment of moderate to severe pain: (see also number 3) The Division in recent years has moved away from the type of analgesic indications that describe pain in this fashion, essentially because it is too difficult to clearly define what pain meets the threshold of moderate or severe pain. Pain is a subjective endpoint and one person's moderate pain may be another's severe or mild.

5) Not bioequivalent to tramadol: Clearly, Ralivia ER is not bioequivalent to Ultram. Indeed, one of the reasons for the need for clinical trials was to document the efficacy of this new formulation. Furthermore, the PK data points to a potential problem with this drug in that the levels for the first and last 6 hours of the 24 hour dosing interval fall below those of Ultram. The clinical effect of these differences in serum levels on pain management is not clear, and no studies were performed to specifically address this issue. While it is theoretically possible that the smoother rise and fall in serum levels might reduce the incidence of adverse events, the sponsor has not demonstrated this (indeed no clinical trials included Ultram as a comparator).

   In addition, the biopharm review notes that linear PK were observed following multiple doses of 100m to 200 mg Ralivia ER. However the observed tramadol AUC values for the 400 mg dose were 25.7% higher than predicted based on the AUC values for the 200 mg dose suggesting non-linear PK. The clinical significance of this has not been investigated, and may be relevant if the 400 mg dose is proposed as a potentially efficacious dose and will be used for chronic indications.

6) Efficacy not supported: The sponsor's analyses are generally "average change from baseline to endpoint over 12 weeks." It should be stated upfront that the Division prefers the landmark analysis rather than an AUC or time weighted

average because it provides efficacy at the end of the trial and supports durability of response. For OA, the Division has provided consistent advice that 3 co-primary endpoints including pain, function, and a patient global are needed to demonstrate efficacy. The following summarizes the key points of the pivotal trials (for a more complete discussion of the trial results and analyses, the reader is referred to the reviews by Drs. Villalba and Youngman).

Trial 021: Trial 021 in OA, essentially failed at the 100, 200, and 300 mg doses at all endpoints (patient global at 300 mg gave a p value of 0.023 by LOCF and 0.895 by BOCF).

Trial 023: Trial 023, in OA, gave statistically significant results at all doses (100, 200, 300, 400 mg) by LOCF for pain and function but not patient global. However, additional analyses by BOCF did not demonstrate results that were statistically significant. Furthermore, there was essentially no difference in effect between the doses (see # 7, below). Finally, if one examines the week by week assessments, it appears that the effect peaks at approximately week 6-8 and begins to taper off by week 12. Of concern (although not addressed in these trials) is if the trial were continued longer than 12 weeks one might see a greater loss of effect, than even that seen at week12.

Trial 014: Trial 014 was a trial in chronic low back pain that involved a run in period of subjects on Ralivia (only those who tolerated tramadol remained in the trial). For the change from baseline to week 12 for the pain endpoint using LOCF, the 300 mg dose is significantly different from placebo at p=0.038 although the 200 mg dose is not (p=0.197). Using BOCF the pain endpoint is not significant. This suggests that efficacy was "driven" by subjects who could not tolerate the drug and dropped out. Other concerns relate to the design of a trial with a run in period. Subjects on Ralivia for several weeks were then randomized to drug or placebo. Those randomized to placebo may have been "unblinded" because of withdrawal symptoms (which do appear to occur with tramadol).

Trial 015: This was designed as a randomized dose titration placebo controlled trial with doses ranging from 100 mg to 400 mg in knee OA subjects. Efficacy as analyzed by ITT/LOCF for change from baseline to 12 weeks was statistically significant for pain VAS and WOMAC pain for Ralivia over placebo. However, for pain VAS and WOMAC pain for ITT/BOCF the results were not significant (pain VAS p=0.124; for WOMAC pain p=0.061). Although the study suggests that Ralivia ER is efficacious, various analyses do not provide robust evidence of such. Furthermore, the appropriate dose cannot be determined because of the titration allowed during the study.

In summary, 2 trials failed (021 and 014), and 2 did not provide robust evidence of efficacy (023 and 015) as assessed by the lack of effect seen with additional sensitivity analyses. It is also not clear how to label the drug to inform the practitioner of the appropriate dosing regimen. Since 023 showed no dose-

response relationship, and 015 allowed titration of the dose, and therefore, no dose-response relationship can be identified

7) No dose response determination: examination of trial 023 did not demonstrate a dose response between the 100 mg and 400 mg dose. Furthermore, trial 015, an efficacy study which allowed dose titration, was not able to identify an efficacious dose because of the study design.

8) Safety discussion: Treatment related discontinuation rates for tramadol range up to 3-4 fold higher than placebo, throughout the studies. Adverse event rates are also consistently higher for Ralivia compared to placebo. These consist mainly of the known adverse effects of tramadol including nausea, vomiting, dizziness, and constipation among others. Even in study 015 where subjects were allowed to titrate the dose of Ralivia, there was a 4 fold discontinuation rate for subjects on Ralivia compared to placebo. Ultram was not included as a comparator in any of the chronic trials. In addition, the sponsor should provide analyses of laboratory safety that examine outliers. For a detailed discussion of the safety profile of this drug the reader is referred to the medical review.

9) Risk:benefit discussion: Based on the data provided and in light of the fact that the active ingredient is tramadol can we approve this product? It is this reviewers opinion that the answer is no. This product is not bioequivalent to Ultram. Therefore, the Division requested additional clinical trials to provide robust evidence of efficacy. Based on the above discussion, the sponsor has not provided this evidence of efficacy of. Furthermore, in light of the high rate of adverse events seen with this product, the sponsor has not provided evidence of an acceptable risk to benefit ratio for this product.

Conclusions:

In light of the above discussion, this drug should not be approved. The sponsor should provide additional evidence of efficacy. It is difficult to compare the safety profile of Ralivia ER to ULtram as Ultram was not included as a comparator in any of the chronic trials. However, in light of the relative lack of efficacy, robust evidence of efficacy needs to be provided to better understand the risk/benefit ratio, before the drug is approved. A single trial in OA or even CLBP that provides robust evidence of efficacy that is durable, may be sufficient to allow approval.

Joel Schiffenbauer, M.D.
Medical Officer

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Joel Schiffenbauer
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CLINICAL REVIEW

Application type:	NDA
Submission Number:	21-692
Submission code:	000
Letter Date:	December 31, 2003
Stamp Date:	December 31, 2003
PDUFA Goal Date:	October 31, 2004
Serious Adverse Events, Reviewer:	Carolyn L. Yancey, MD
Review Completion Date:	October 27, 2004
Established Name:	Tramadol Extended Release
(Proposed) Trade Name:	Ralivia
Therapeutic class:	Analgesic
Applicant:	Biovail
Priority Designation:	S
Dosing Regimen:	100 mg tablets
Indication:	Moderate to moderately severe pain
Intended Population:	Adults

Serious Adverse Events

No serious adverse events (SAE) were reported for any of the Phase I studies. No deaths or SAE were reported for patients in the dental pain study.

The sponsor reports SAE by "Adverse Events known to be associated with Tramadol HCl" and by "Adverse Events not listed in the Ultram label". Of the 3,141 patients who were treated with Tramadol HCl ER, the sponsor reports 91 patients reported at least 1 SAE in the studies in pain as follows:

- 65 patients in the Tramadol HCl ER flexible dose treatment group
- 5 patients in the Tramadol HCl ER100 mg QD treatment group
- 9 patients in the Tramadol HCl ER 200 mg QD treatment group
- 6 patients in the Tramadol HCl ER 300 mg QD treatment group
- 6 patients in the Tramadol HCl ER 400 mg QD treatment group

The incidence of serious adverse events across all **labeled adverse events** for all patients is described in **Table 1.** The incidence of any serious adverse event was less than 1% in any treatment group. The incidence of SAEs for all patients was greater in the Tramadol HCl ER flexible treatment group and the 400 mg treatment group compared to the 100 mg, 200 mg or 300 mg Tramadol HCl ER treatment groups.

Table 1, Incidence of Serious Adverse Events Labeled Adverse Events*: All Patients
(sponsor table 119, page 171 of 322)

MedDRA Preferred Term	Tramadol HCl ER					Placebo (N=552) n (%)	Tramadol/ Placebo[a] (N=128) n (%)
	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)		
Patients reported at least 1 SAE	65 (3.7)	5 (1.2)	9 (2.3)	6 (1.5)	6 (3.0)	9 (1.6)	1 (0.8)
Abdominal pain NOS	3 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness (exc vertigo)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gait abnormal NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grand mal convulsion	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety NEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Confusion	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression NEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Source: ISS Appendix F.7, Table 7.8.1.

*Ultram Label

The longer exposure in the open-label study compared to the 12-week exposure in the randomized, double-blind, fixed-dose studies may account for the increased incidence of SAEs in the flexible dose and 400 mg treatment groups. The number of patients exposured is too small to make firm conclusions about the overall SAE risks of treatment with Tramadol HCl ER

Tables 2 through Table 9 describe the incidence of **serious adverse events by system and/or condition (non-labeled adverse events in the Ultram label):** by all patients. The systems and/or conditions described are the cardiovascular system, gastrointestinal system, general disorders, infections or infestations, metabolism and nutrition disorders, neoplasms, vascular disorders and other serious adverse events.

In **Table 2**, SAE in the cardiovascular system for AE not listed in the Ultram label are noted for angina pectoris, unstable angina and myocardial infarction. Atrial fibrillation was reported in one patient treated with 200 mg per day; bradycardia was noted in one patient treated with 300 mg. The incidence was < 1% for all cardiovascular events; however, the flexible dose treatment group demonstrated the largest number of cardiovascular SAEs. The total number of patients exposed is too small to make firm conclusions about the cardiovascular serious adverse event risks of Tramadol HCl ER. However, it should be noted that there are 2 MIs and one case of unstable angina in the Tramadol group and none in the placebo group.

Table 2. Incidence of Serious Adverse Events Related to the **Cardiovascular System (Non-Labeled Adverse Events*)**: All Patients (sponsor table 120, page 172 of 322)

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Placebo[a] (N=128) n (%)
Angina pectoris	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angina unstable	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Coronary artery disease NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Myocardial infarction	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bradycardia NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mitral valve incompetence	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Source: ISS Appendix F.7, Table 7.8.1

*Ultram label

In **Table 3**, in the gastrointestinal system SAE demonstrate dysphagia, gastroesophageal reflux disease, oesophageal reflux disease, gastric ulcer, gastrointestinal hemorrhage NOS, appendicitis and colitis ischemic were greatest in the flexible dose treatment. The incidence of gastrointestinal adverse events was less than 1% for any treatment group. Similarly, this reviewer concludes that the number of patients treated is too small to draw conclusions about gastrointestinal SAEs. See **Table 3.**

Table 3. Incidence of Serious Adverse Events Related to the **Gastrointestinal System (Non-Labeled Adverse Events*)**: All Patients (sponsor table 121, page 173 of 322)

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Placebo[a] (N=128) n (%)
Dysphagia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastro-oesophageal reflux disease	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oesophageal reflux aggravated	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric ulcer	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal haemorrhage NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ileus	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Appendicitis	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis ischemic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pancreatitis NOS	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Inguinal hernia NOS	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

*Ultram label

The incidence of SAEs in the general disorders category (non-labeled, Ultram labeled adverse events) for all patients was again greater in the Tramadol HCl ER flexible dose treatment group compared to the other Tramadol HCl ER 100 mg, 200 mg, 300 mg or 400 mg treatment groups. See **Table 4**. The sponsor reports two patients with drug withdrawal syndrome. (See safety section, study withdrawals/drop-out). The overall incidence of SAE related to general disorders was less than 1% in any treatment group.

Table 4. Incidence of Serious Adverse Events Related to the **General Disorders (Non-Labeled Adverse Events*)**: All Patients (sponsor table 122, page 174 of 322)

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Placebo[a] (N=128) n (%)
Chest pain NEC	9 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.5)	1 (0.2)	0 (0.0)
Chest tightness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Drug withdrawal syndrome	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Fall	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hernia NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hernia pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain NOS	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weakness	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

*Ultram label

In Table 5, the incidence of SAEs related to infections or infestations (non-labeled events) for all patients was greater in the Tramadol HCl ER flexible dose treatment group compared to the fixed dose studies. Gastroenteritis, osteomyelitis, upper respiratory tract infection, pneumonia and urinary tract infection were noted in the flexible dose treatment group. There were no SAEs in the 300 mg or 400 mg fixed dose groups. Similarly, overall the incidence of any SAE related to infections or infestations is less than 1%. These patient numbers are too small to make any conclusions about the about the SAE risk profile for infections/infestations with Tramadol HCl ER.

Table 5. Incidence of Serious Adverse Events Related to **Infections or Infestations (Non-Labeled Adverse Events*):** All Patients (sponsor table 123, page 175 of 322)

	Tramadol HCl ER						
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo[a] (N=128) n (%)
Gastroenteritis NOS	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteomyelitis NOS	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia NOS	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection NOS	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

*Ultram label

SAEs reported as dehydration, gout, hypoglycemia and hyponatremia were reported in the flexible dose treatment group. Gout was reported in one patient in the 100 mg fixed dose study. The overall incidence of SAE was < 1% in the metabolism and nutrition disorder category.

Table 6. Incidence of Serious Adverse Events Related to **Metabolism and Nutrition Disorders (Non-Labeled Adverse Events*)**: All Patients (sponsor table 124, page 175 of 322)

	Tramadol HCl ER						
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo[a] (N=128) n (%)
Dehydration	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gout	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoglycemia NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

*Ultram label

As demonstrated in **Table 7**, neoplasms, diagnosed as breast cancer, colon cancer, parathyroid tumor benign, bladder neoplasm and uterine fibroids were each reported in one patient in the flexible dose group; oesophageal carcinoma was reported in one patient treated with the 200 mg fixed dose and a teratoma was diagnosed in one patient treated with the 400 mg fixed dose. The overall incidence of any SAE related to neoplasms was < 1%.

Table 7. Incidence of Serious Adverse Events Related to **Neoplasms (Non-Labeled Adverse Events*):** All Patients (sponsor table 125, page 176 of 322)

	Tramadol HCl ER						Tramadol/ Placebo[a]
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	(N=128) n (%)
Breast cancer NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colon cancer NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oesophageal carcinoma NOS	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parathyroid tumour benign	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Teratoma NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Bladder neoplasm NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine fibroids	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

Vascular disorders as atherosclerosis, carotid artery stenosis, pulmonary embolism, thromboembolism were reported in one patient each and peripheral ischemia was reported in two patients treated in the flexible dose group. One patient with hypertension and one patient with thrombophlebitis were reported in the 200 mg fixed dose group; one patient had hypertension in the 300 mg fixed dose group. Overall the incidence of SAE was < 1% in any treatment group. See **Table 8.**

Table 8. Incidence of Serious Adverse Events Related to **Vascular Disorders (Non-Labeled Adverse Events*)**: All Patients (sponsor table 126, page 177 of 322)

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Placebo[a] (N=128) n (%)
Arterial aneurysm NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arteriosclerosis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Carotid artery stenosis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral ischemia NOS	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension aggravated	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thromboembolism NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombophlebitis deep	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

*Ultram label

As demonstrated in **Table 9**, the incidence of "other" serious adverse events for all patients was similarly greater in the flexible dose treatment group than each of the fixed dose treatment groups, 100 mg, 200 mg, 300 mg or 400 mg. The number of patients is too small to draw any conclusions in these "other" categories of SAE with Tramadol HCl ER treatment. See **Table 9.**

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Table 9. Incidence of **Other** Serious Adverse Events **(Non-Labeled Adverse Events*):** All Patients (sponsor table 127, page 178 through 179 of 322)

	Tramadol HCl ER						Tramadol/
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Placebo[a] (N=128) n (%)
Anemia NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sickle cell anemia with crisis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Labyrinthitis NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo NEC	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid nodule	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute NOS	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Cholelithiasis	2 (0.1)	0 (0.0)	2 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Cellulitis	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthropod sting	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Head injury	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hip fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Limb injury NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ulnar nerve injury	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Catheterisation cardiac	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematocrit increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Red blood cell count decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baker's cyst	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neck pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis aggravated	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in limb	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Convulsions NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lacunar infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Thoracic outlet syndrome	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Completed suicide	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug dependence	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Calculus renal NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Menorrhagia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ovarian cyst	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine hemorrhage	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma NOS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea NOS	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Table 9 (continued)

Pleural effusion	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric operation NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Knee arthroplasty	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

[a] Includes patients in Study B00.CT3.014.TRA.P03 who received Tramadol HCl ER in the open-label run-in period and were later randomized to placebo.

*Ultram label

Reviewer Comments:

- The sponsor reports SAE by "Adverse Events known to be associated with Tramadol HCl" and by "Adverse Events not listed in the Ultram label". The number of patient reported SAE is too small across all the labeled and non-labeled SAE to draw firm conclusions about the SAE and safety risk with Tramadol HCl ER in fixed doses of 100mg, 200mg, 300mg and 400mg. Though the overall incidence of any SAE was less than 1%, the incidence of SAE for all patients was greater in the Tramadol HCl ER flexible dose compared to the other Tramadol HCl ER fixed-dose groups. This higher incidence of SAEs in the flexible dosing group may be due to the longer duration of the open-label safety study (flexible dose) compared to the 12-week duration of the randomized, double-blind, fixed-dose studies.

- All SAEs not in the current Ultram label, yet reported as new SAEs in this review, must be included in the proposed label ADVERSE EVENT section. For example, it should be noted that there are two cases of myocardial infarctions and one case of unstable angina in the Tramadol group and none in the placebo group.

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/s/

Carolyn L. Yancey
10/29/04 01:57:12 PM
MEDICAL OFFICER

Joel Schiffenbauer
10/29/04 02:13:47 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-692
Submission Code	000
Letter Date	December 31, 2003
Stamp Date	December 31, 2003
PDUFA Goal Date	October 31st, 2004
Reviewer Name	Julia Castle, M.D.
Review Completion Date	October 27, 2004
Established Name	Tramadol Extended Release
(Proposed) Trade Name	Ralivia
Therapeutic Class	Analgesic
Applicant	Biovail
Priority Designation	S
Formulation	
Dosing Regimen	100 mg tablets
Indication	Moderate to moderately severe pain
Intended Population	Adults

Note: Following is a review of only Common Adverse Events. For the remainder of the safety review please see reviews by Dr. Oussova, Dr. Yancey, and Dr. Schiffenbauer. For review of efficacy please see review by Dr. Villalba.

7.1.5 Common Adverse Events

The following is an excerpt from the sponsor's NDA 21692 Submission, page 47.

There are discrepancies in the number of patients included in the safety populations in the individual study reports from those included in the Table of All Studies. The sponsor added or excluded patients from the safety population based on a review of all available data. Review of the pooled safety data from the individual studies identified 39 cases for which some additional adjudication was required. The sponsor explains that in 32 cases it was determined that the safety data did not need to be added to the ISS database. However, in 7 cases, a decision to include the patients was made.

In the 32 cases where the data were not included, it was determined that, in 31 of these cases, the patient did not have an adverse event based on a review of the documentation provided and the information in the database. In one case, an adverse event was identified, but no study drug start date was recorded and no dosing information was provided. In the absence of this information, it could not be confirmed that the patient received drug and the adverse event data was not included in the ISS database.

Excluding patients as described above is not an acceptable way to complete the Integrated Summary of Safety Information (ISS). The sponsor needs to provide information regarding the 39 patients excluded.

Single Dose Studies:
The single dose studies are noted, since Ultram is reported as an active comparator, and this is a deficiency of the double-blind, placebo-controlled studies. The incidence of common adverse events reported in >=2% of subjects in single-dose studies, seen in Table (below), showed a higher percentage of subjects in the Tramadol HCl ER study drug groups (100 mg, 41%; 200 mg, 54%; and 300 mg, 66%) reported adverse events compared to the Ultram groups (100 mg, 16%; 200 mg, 7%). Dizziness, nausea, and headache were the most frequently reported adverse events. This is similar to the Ultram label, although headache was listed as the fourth most frequently reported event, with constipation being the third most common adverse event in the Ultram label.

Table Incidence of Adverse Events Reported in >=2% of Subjects: Healthy Volunteers, Single-Dose Studies (from ISS, Table 68)

	Tramadol HCl ER			Ultram	
MedDRA Preferred Term	100 mg QD (N=56) n (%)	200 mg QD (N=98) n (%)	300 mg QD (N=56) n (%)	100 mg/day (N=32) n (%)	200 mg/day (N=15) n (%)
Subjects with at least 1 adverse event	23 (41.1)	53 (54.1)	37 (66.1)	5 (15.6)	1 (6.7)
Dizziness (exc vertigo)	6 (10.7)	16 (16.3)	22 (39.3)	2 (6.3)	0 (0.0)
Nausea	3 (5.4)	14 (14.3)	20 (35.7)	0 (0.0)	1 (6.7)
Headache NOS	4 (7.1)	17 (17.3)	10 (17.9)	0 (0.0)	1 (6.7)
Vomiting NOS	0 (0.0)	9 (9.2)	14 (25.0)	0 (0.0)	1 (6.7)
Pruritus NOS	0 (0.0)	7 (7.1)	5 (8.9)	0 (0.0)	0 (0.0)
Electrocardiogram QT corrected interval prolonged	7 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	1 (1.8)	3 (3.1)	2 (3.6)	1 (3.1)	0 (0.0)
Somnolence	0 (0.0)	4 (4.1)	2 (3.6)	0 (0.0)	0 (0.0)
Dry mouth	0 (0.0)	2 (2.0)	3 (5.4)	0 (0.0)	0 (0.0)
Euphoric mood	0 (0.0)	1 (1.0)	4 (7.1)	0 (0.0)	0 (0.0)
Pallor	2 (3.6)	1 (1.0)	2 (3.6)	0 (0.0)	0 (0.0)

Source: ISS Appendix F.1, Table 1.4.1.1

Overall, there was an apparent dose response for the most frequently reported adverse events except for "electrocardiogram QT corrected interval prolonged", which was reported in 12.5% of the patients in the Tramadol HCl ER 100 mg group only. Further details about these EKG findings were not presented or obtainable from the ISS. Table 1.4.1.1 did not provide details needed to fully understand the importance of the seven patients with prolonged QTc. The sponsor needs to provide an analysis of the outliers and mean changes for EKG findings.

The number and percentage of subjects in the single-dose pharmacokinetic studies with adverse events are displayed by maximum severity in Table (below), for adverse events that were reported for 2%, for all Tramadol HCl ER doses combined, and for all reported adverse events.

Table Incidence of Adverse Events Reported in >=2% of Subjects by Maximum Severity: Healthy Volunteers, Single-Dose Studies (from ISS, Table 69)

MedDRA Preferred Term/ Study Drug	N	Total Patients With Event n (%)	Severity		
			Mild n (%)	Moderate n (%)	Severe n (%)
Subjects with at least 1 adverse event					
Tramadol HCl ER 100 mg	56	23 (41.1)	20 (35.7)	3 (5.4)	0 (0.0)
Tramadol HCl ER 200 mg	98	53 (54.1)	42 (42.9)	10 (10.2)	1 (1.0)[a]
Tramadol HCl ER 300 mg	56	37 (66.1)	24 (42.9)	13 (23.2)	0 (0.0)
Ultram 100 mg	32	5 (15.6)	5 (15.6)	0 (0.0)	0 (0.0)
Ultram 200 mg	15	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Dizziness (exc vertigo)					
Tramadol HCl ER 100 mg	56	6 (10.7)	4 (7.1)	2 (3.6)	0 (0.0)
Tramadol HCl ER 200 mg	98	16 (16.3)	14 (14.3)	2 (2.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	22 (39.3)	21 (37.5)	1 (1.8)	0 (0.0)
Ultram 100 mg	32	2 (6.3)	2 (6.3)	0 (0.0)	0 (0.0)
Nausea					

MedDRA Preferred Term/ Study Drug	N	Total Patients With Event n (%)	Severity		
			Mild n (%)	Moderate n (%)	Severe n (%)
Tramadol HCl ER 100 mg	56	3 (5.4)	3 (5.4)	0 (0.0)	0 (0.0)
Tramadol HCl ER 200 mg	98	14 (14.3)	14 (14.3)	0 (0.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	20 (35.7)	17 (30.4)	3 (5.4)	0 (0.0)
Ultram 200 mg	15	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Headache NOS					
Tramadol HCl ER 100 mg	56	4 (7.1)	4 (7.1)	0 (0.0)	0 (0.0)
Tramadol HCl ER 200 mg	98	17 (17.3)	17 (17.3)	0 (0.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	10 (17.9)	8 (14.3)	2 (3.6)	0 (0.0)
Ultram 200 mg	15	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Vomiting NOS					
Tramadol HCl ER 200 mg	98	9 (9.2)	2 (2.0)	7 (7.1)	0 (0.0)
Tramadol HCl ER 300 mg	56	14 (25.0)	2 (3.6)	12 (21.4)	0 (0.0)
Ultram 200 mg	15	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Pruritus NOS					
Tramadol HCl ER 200 mg	98	7 (7.1)	7 (7.1)	0 (0.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	5 (8.9)	5 (8.9)	0 (0.0)	0 (0.0)
Electrocardiogram QT corrected interval prolonged					
Tramadol HCl ER 100 mg	56	7 (12.5)	7 (12.5)	0 (0.0)	0 (0.0)
Fatigue					
Tramadol HCl ER 100 mg	56	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Tramadol HCl ER 200 mg	98	3 (3.1)	3 (3.1)	0 (0.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	2 (3.6)	1 (1.8)	1 (1.8)	0 (0.0)
Ultram 100 mg	32	1 (3.1)	1 (3.1)	0 (0.0)	0 (0.0)
Somnolence					
Tramadol HCl ER 200 mg	98	4 (4.1)	4 (4.1)	0 (0.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	2 (3.6)	2 (3.6)	0 (0.0)	0 (0.0)
Dry mouth					
Tramadol HCl ER 200 mg	98	2 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	3 (5.4)	3 (5.4)	0 (0.0)	0 (0.0)
Euphoric mood					
Tramadol HCl ER 200 mg	98	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	4 (7.1)	4 (7.1)	0 (0.0)	0 (0.0)
Pallor					
Tramadol HCl ER 100 mg	56	2 (3.6)	0 (0.0)	2 (3.6)	0 (0.0)
Tramadol HCl ER 200 mg	98	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Tramadol HCl ER 300 mg	56	2 (3.6)	2 (3.6)	0 (0.0)	0 (0.0)

[a] Syncope was reported by 1 patient (1.0%) in the Tramadol HCl ER 200 mg group and was reported as severe.

Source: ISS Appendix F.1, Table 1.4.2.1.

The majority of reported adverse events were more frequent in the Tramadol HCl ER groups compared with the Ultram groups. There were more subjects with at least 1 adverse event in the Tramadol HCl ER groups at 100 mg (41 %), 200 mg (54 %), 300 mg (66 %), compared to Ultram 100 mg (16 %). Headache was reported for Tramadol HCl ER 200 mg (17 %), 300 mg (18 %), and for Ultram (7 %). Vomiting was reported for Tramadol HCl ER 200 mg (9 %), 300 mg (25 %), and for Ultram 200 mg at (7 %).

Double-Blind, Placebo-Controlled Studies:

Table Incidence of Adverse Events Reported in ≥2% of Patients and Identified in the Ultram® Label: All Double-Blind, Placebo-Controlled Studies in Patients With Chronic Low Back Pain or Osteoarthritis (from ISS, Table 84)

	Tramadol HCl ER					
MedDRA Preferred Term	Flexible (N=133) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=529) n (%)	300 mg QD (N=528) n (%)	400 mg QD (N=202) n (%)	Placebo (N=664) n (%)
Patients reporting at least 1 adverse event	105 (78.9)	271 (67.2)	374 (70.7)	394 (74.6)	170 (84.2)	391 (58.9)
Nausea	33 (24.8)	61 (15.1)	102 (19.3)	128 (24.2)	53 (26.2)	51 (7.7)
Dizziness (exc vertigo)	46 (34.6)	64 (15.9)	95 (18.0)	108 (20.5)	57 (28.2)	54 (8.1)
Constipation	32 (24.1)	49 (12.2)	76 (14.4)	104 (19.7)	60 (29.7)	25 (3.8)
Headache NOS	18 (13.5)	49 (12.2)	78 (14.7)	65 (12.3)	32 (15.8)	77 (11.6)
Flushing	13 (9.8)	31 (7.7)	47 (8.9)	42 (8.0)	32 (15.8)	26 (3.9)
Somnolence	10 (7.5)	33 (8.2)	46 (8.7)	32 (6.1)	41 (20.3)	11 (1.7)
Insomnia NEC	8 (6.0)	26 (6.5)	42 (7.9)	54 (10.2)	22 (10.9)	22 (3.3)
Vomiting NOS	10 (7.5)	20 (5.0)	36 (6.8)	44 (8.3)	19 (9.4)	13 (2.0)
Pruritus NOS	9 (6.8)	25 (6.2)	36 (6.8)	31 (5.9)	24 (11.9)	6 (0.9)
Diarrhea NOS	12 (9.0)	15 (3.7)	38 (7.2)	43 (8.1)	10 (5.0)	29 (4.4)
Dry mouth	4 (3.0)	20 (5.0)	29 (5.5)	39 (7.4)	18 (8.9)	8 (1.2)
Asthenia (fatigue)	10 (7.5)	14 (3.5)	29 (5.5)	32 (6.1)	13 (6.4)	10 (1.5)
Postural hypotension	3 (2.3)	7 (1.7)	21 (4.0)	18 (3.4)	11 (5.4)	15 (2.3)
Sweating increased	5 (3.8)	6 (1.5)	9 (1.7)	18 (3.4)	13 (6.4)	1 (0.2)
Anorexia	3 (2.3)	3 (0.7)	7 (1.3)	23 (4.4)	12 (5.9)	1 (0.2)
Nervousness	0 (0.0)	7 (1.7)	13 (2.5)	20 (3.8)	8 (4.0)	5 (0.8)
Abdominal pain upper	3 (2.3)	5 (1.2)	12 (2.3)	16 (3.0)	5 (2.5)	5 (0.8)
Weakness	1 (0.8)	3 (0.7)	11 (2.1)	15 (2.8)	9 (4.5)	5 (0.8)
Dyspepsia	2 (1.5)	7 (1.7)	10 (1.9)	14 (2.7)	5 (2.5)	8 (1.2)

Source: ISS Appendix F.5, Table 5.5.1.1

Table Incidence of Adverse Events Reported in ³2% of Patients and Not Identified in the Ultram® Label: All Double-Blind, Placebo-Controlled Studies in Patients With Chronic Low Back Pain or Osteoarthritis (from ISS, Table 85)

	Tramadol HCl ER					
MedDRA Preferred Term	Flexible (N=133) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=529) n (%)	300 mg QD (N=528) n (%)	400 mg QD (N=202) n (%)	Placebo (N=664) n (%)
Patients reporting at least 1 adverse event	105 (78.9)	271 (67.2)	374 (70.7)	394 (74.6)	170 (84.2)	391 (58.9)
Nasopharyngitis	6 (4.5)	12 (3.0)	23 (4.3)	14 (2.7)	6 (3.0)	28 (4.2)
Arthralgia	1 (0.8)	11 (2.7)	20 (3.8)	11 (2.1)	8 (4.0)	21 (3.2)
Pain NOS	2 (1.5)	10 (2.5)	16 (3.0)	16 (3.0)	5 (2.5)	14 (2.1)
Upper respiratory tract infection NOS	5 (3.8)	15 (3.7)	12 (2.3)	13 (2.5)	4 (2.0)	20 (3.0)
Sinusitis NOS	3 (2.3)	7 (1.7)	13 (2.5)	12 (2.3)	5 (2.5)	12 (1.8)
Back pain	3 (2.3)	11 (2.7)	9 (1.7)	8 (1.5)	5 (2.5)	10 (1.5)
Sneezing	0 (0.0)	10 (2.5)	10 (1.9)	12 (2.3)	4 (2.0)	2 (0.3)

Source: ISS Appendix F.5, Table 5.5.1.1

Table Incidence of Adverse Events Reported in ³2% of Patients and Identified in the Ultram® Label: Osteoarthritis (from ISS, Table 91)

	Tramadol HCl ER					
MedDRA Preferred Term	Flexible (N=133) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=536) n (%)
Patients reporting at least 1 adverse event	105 (78.9)	271 (67.2)	296 (74.0)	297 (74.3)	170 (84.2)	318 (59.3)
Nausea	33 (24.8)	61 (15.1)	90 (22.5)	102 (25.5)	53 (26.2)	42 (7.8)
Dizziness (exc vertigo)	46 (34.6)	64 (15.9)	81 (20.3)	90 (22.5)	57 (28.2)	42 (7.8)
Constipation	32 (24.1)	49 (12.2)	68 (17.0)	85 (21.3)	60 (29.7)	24 (4.5)
Headache NOS	18 (13.5)	49 (12.2)	62 (15.5)	46 (11.5)	32 (15.8)	64 (11.9)
Somnolence	10 (7.5)	33 (8.2)	45 (11.3)	29 (7.3)	41 (20.3)	9 (1.7)
Flushing	13 (9.8)	31 (7.7)	40 (10.0)	35 (8.8)	32 (15.8)	24 (4.5)
Insomnia NEC	8 (6.0)	26 (6.5)	32 (8.0)	36 (9.0)	22 (10.9)	16 (3.0)
Pruritus NOS	9 (6.8)	25 (6.2)	34 (8.5)	30 (7.5)	24 (11.9)	6 (1.1)
Vomiting NOS	10 (7.5)	20 (5.0)	29 (7.3)	34 (8.5)	19 (9.4)	11 (2.1)
Dry mouth	4 (3.0)	20 (5.0)	29 (7.3)	39 (9.8)	18 (8.9)	7 (1.3)
Diarrhea NOS	12 (9.0)	15 (3.7)	27 (6.8)	34 (8.5)	10 (5.0)	22 (4.1)
Asthenia (fatigue)	10 (7.5)	14 (3.5)	24 (6.0)	26 (6.5)	13 (6.4)	8 (1.5)
Nasopharyngitis	6 (4.5)	12 (3.0)	18 (4.5)	9 (2.3)	6 (3.0)	26 (4.9)
Sweating increased	5 (3.8)	6 (1.5)	8 (2.0)	15 (3.8)	13 (6.4)	1 (0.2)
Anorexia	3 (2.3)	3 (0.7)	7 (1.8)	21 (5.3)	12 (5.9)	1 (0.2)
Nervousness	0 (0.0)	7 (1.7)	13 (3.3)	18 (4.5)	8 (4.0)	4 (0.7)
Postural hypotension	3 (2.3)	7 (1.7)	17 (4.3)	8 (2.0)	11 (5.4)	11 (2.1)
Pain NOS	2 (1.5)	10 (2.5)	14 (3.5)	14 (3.5)	5 (2.5)	10 (1.9)
Sinusitis NOS	3 (2.3)	7 (1.7)	11 (2.8)	9 (2.3)	5 (2.5)	12 (2.2)
Weakness	1 (0.8)	3 (0.7)	8 (2.0)	14 (3.5)	9 (4.5)	5 (0.9)
Abdominal pain upper	3 (2.3)	5 (1.2)	9 (2.3)	12 (3.0)	5 (2.5)	3 (0.6)
Dermatitis NOS	5 (3.8)	5 (1.2)	8 (2.0)	12 (3.0)	3 (1.5)	9 (1.7)
Dyspepsia	2 (1.5)	7 (1.7)	7 (1.8)	12 (3.0)	5 (2.5)	7 (1.3)

Source: ISS Appendix F.5, Table 5.5.2.1

Table Incidence of Adverse Events Reported in ³2% of Patients and Not Identified in the Ultram® Label: Osteoarthritis (from ISS, Table 92)

	Tramadol HCl ER					
MedDRA Preferred Term	Flexible (N=133) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=536) n (%)
Patients reporting at least 1 adverse event	105 (78.9)	271 (67.2)	296 (74.0)	297 (74.3)	170 (84.2)	318 (59.3)
Arthralgia	1 (0.8)	11 (2.7)	15 (3.8)	10 (2.5)	8 (4.0)	16 (3.0)
Upper respiratory tract infection NOS	5 (3.8)	15 (3.7)	7 (1.8)	13 (3.3)	4 (2.0)	18 (3.4)
Back pain	3 (2.3)	11 (2.7)	7 (1.8)	8 (2.0)	5 (2.5)	10 (1.9)
Sneezing	0 (0.0)	10 (2.5)	8 (2.0)	12 (3.0)	4 (2.0)	2 (0.4)
Appetite decreased NOS	2 (1.5)	5 (1.2)	9 (2.3)	8 (2.0)	7 (3.5)	1 (0.2)

Source: ISS Appendix F.5, Table 5.5.2.1

The incidence of adverse events reported in >=2% of patients, present or absent from the Ultram label, in double-blind, placebo-controlled trials for chronic low back pain or osteoarthritis, and for osteoarthritis are reported in the tables (four preceding) above. The double-blind, placebo-controlled trials have a major deficiency, as noted in the tables above, in that there is no active comparator. Comparison of the incidence rates of adverse events for Tramadol HCl ER with rates reported in the label for Tramadol is not a valid comparison.

The reviewer appreciates that the adverse events not found in the Ultram label, listed in Tables (ISS, Table 85 and 92) above, are listed in the proposed Tramadol HCl ER label. However, there are other adverse events reported with an incidence greater than 2% that are not listed in the label. Review of Table 5.5.1.1 "All adverse events by descending frequency – number of patients with events – all double-blind studies" provided more information about adverse events.

The Adverse Reactions section in the Tramadol HCl ER label, proposed by the sponsor, has many deficiencies. The sponsor lists adverse events with >= 5% incidence, in table form, and then lists adverse events with "an incidence of 2% to less than 5% of all patients". There are many adverse events listed in Table 5.5.1.1 at greater than 2% incidence, which were not included in the proposed label. For example, "chest pain" was reported in 2.3% of patients treated with Tramadol HCl ER titration, "cough" was reported for 3% of patients treated with Tramadol HCl ER 400 mg, "muscle spasms" was reported in 2.3% of patients treated with Tramadol HCl ER titration, and "pain in the limb" was reported in 2.3% of patients treated with Tramadol HCl ER titration, also not found in the proposed label. Some adverse events even had an incidence more than 2% above placebo. For example "feeling hot" was reported in 3% of patients treated with Tramadol HCl titration and 0.5% of patients on placebo, the difference being 2.5%. A second example is "rigors" reported with an incidence of 3.5% for patients treated with Tramadol HCl ER 400 mg, compared to placebo with an incidence of 0.3%, the

difference being 3.2%. The sponsor has not provided adequate justification for excluding these adverse events from the proposed label.

There are also rare but potentially clinically significant adverse events that are not listed in the label. For example, "blood glucose increased" was reported in 1.5% of patients treated with Tramadol HCl ER titration, "hypertension aggravated" was reported in 1.1% of patients treated with Tramadol HCl ER 300 mg, "vision blurred" was reported in 1.5% of patients treated with Tramadol HCl ER 400 mg, and "AST increased" in 1.5% of patients treated with Tramadol HCl ER titration. "Hepatomegaly" was reported for one patient treated with Tramadol HCl ER 400 mg, "pericarditis" was reported for one patient treated with Tramadol HCl ER 300 mg, and "small intestine obstruction" was reported for one patient treated with Tramadol HCl ER 200 mg. The sponsor also needs to include a section on significant adverse events reported with an incidence less than 2%, regardless of causality.

Of note QTc interval prolongation in all double-blind studies was reported for no patients treated with Tramadol HCl ER, and for two patients in the placebo group.

Table Incidence of Dizziness, Syncope, and Vasodilation: All Patients (from ISS, Table 107)

	Tramadol HCl ER						
MedDRA Preferred Term	Flexible (N=1736) n (%)	100 mg QD (N=403) n (%)	200 mg QD (N=400) n (%)	300 mg QD (N=400) n (%)	400 mg QD (N=202) n (%)	Placebo (N=552) n (%)	Tramadol/ Placebo (N=128) n (%)
Dizziness (exc vertigo)	539 (31.0)	64 (15.9)	81 (20.3)	90 (22.5)	57 (28.2)	43 (7.8)	13 (10.2)
Dizziness aggravated	2 (0.1)	2 (0.5)	6 (1.5)	3 (0.8)	4 (2.0)	2 (0.4)	0 (0.0)
Dizziness postural	6 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	16 (0.9)	1 (0.2)	3 (0.8)	4 (1.0)	2 (1.0)	2 (0.4)	0 (0.0)
Vasodilation	26 (1.5)	1 (0.2)	2 (0.5)	2 (0.5)	5 (2.5)	4 (0.7)	0 (0.0)

Source: ISS Appendix F.7, Table 7.5.1

The adverse events, dizziness, syncope, and vasodilation, reported in Table (ISS Table 107) above, have a higher incidence in patients treated with Tramadol HCl ER than placebo.

Comments:
Excluding patients after reviewing the data is not an acceptable way to complete the ISS. The sponsor needs to provide information regarding the 39 patients excluded from the safety data.

For single-dose studies the incidence of common adverse events reported in >=2% of patients overall was higher for Tramadol HCl ER compared to Ultram.

In double-blind, placebo-controlled trials, adverse events overall were reported with a higher incidence for Tramadol HCl ER than for placebo. Comparing the incidence of adverse events for Tramadol HCl ER with rates reported in the Ultram label is not a valid comparison. The sponsor needs to include Ultram as an active comparator in the double-blind, placebo-controlled trials.

The sponsor needs to provide an analysis of the outliers and mean changes for labs and EKG findings. Also the sponsor needs to provide details for the EKGs from the seven patients listed in the single-dose studies with QTc prolongation.

The Adverse Reactions section in the Tramadol HCl ER label, proposed by the sponsor, has many deficiencies. There are many adverse events listed in Table 5.5.1.1 at greater than 2% incidence, which were not included in the proposed label, such as "chest pain", "cough", "muscle spasms", and "pain in the limb". Some adverse events even had an incidence more than 2 % above placebo, for example "feeling hot", and "rigors". The sponsor needs to either provide adequate justification for excluding these adverse events from the proposed label, or include them.

There are also rare but potentially clinically significant adverse events that are not listed in the proposed label, such as "blood glucose increased", "hypertension aggravated", "vision blurred", and "AST increased". In addition, other potentially clinically significant events such as, "hepatomegaly", "pericarditis", and "small intestine obstruction" were each reported in a patient treated with Tramadol HCl ER. The sponsor needs to include a section on clinically significant adverse events reported with an incidence less than 2%, regardless of causality.

Julia Castle, MD, MPH, FACP

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/s/

Julia Castle
10/29/04 03:09:02 PM
MEDICAL OFFICER

Joel Schiffenbauer
10/29/04 03:35:52 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel:(301) 827-2040

DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	October 26, 2004
DRUG:	Ralivia ER (tramadol
NDA:	21-[redacted](30-Dec-2003),[redacted]
SPONSOR:	Biovail Laboratories, Inc.
DOSAGE FORM:	Oral
DOSAGE STRENGTHS:	100 mg and 200 mg
INDICATIONS:	The management of moderate to moderately severe pain in adults

ACTION RECOMMENDED BY THE DIVISION: Approvable

ADDITIONAL INFORMATION REQUIRED FOR APPROVAL:
At least one adequate and well-controlled study to support a finding of efficacy.

Summary

The sponsor has submitted a 505(b)(2) application for Ralivia ER, a modified-release formulation of tramadol hydrochloride. The reference listed product is Ultram (tramadol hydrochloride) NDA 20-281 which was approved in 1995. The sponsor notes that there are currently 14 generic immediate-release tramadol products currently on the market. Ralivia ER has been formulated with the intention of providing once daily dosing. Because this represents the first modified-release formulation of tramadol, an assessment of efficacy was requested to ensure that the change in dosage form does not reduce efficacy.

The sponsor currently seeks the indication of moderate to moderately severe pain as is held for Ultram. The potential benefit of this reformulation is with the need for less frequent dosing once steady-state is achieved. However, the result of the pharmacokinetic (PK) characteristics of the modified-release formulation is that tramadol ER is not suitable for management of acute pain,

nor for intermittent dosing. As a result, the indication would need to reflect moderate to moderately severe chronic pain. The sponsor has also requested the same language in the package insert as Ultram. The sections of the package insert that make reference to the unique PK characteristics of Ultram and that make reference to use in acute pain are not appropriate for inclusion in the package insert for tramadol ER.

As for the indication, tramadol is thought to exert its analgesic effect through low-affinity binding to mu-opioid receptors and weak inhibition of serotonin uptake. Tramadol also weakly inhibits norepinephrine uptake. There is no need to narrow the indication for tramadol beyond moderate to moderately severe chronic pain, because the effects of tramadol on the symptom of pain are generalizable enough given the proposed mechanism of action, the prior findings of efficacy made in response to the Ultram marketing application, and the many year history of clinical use of Ultram.

As a new formulation with different PK characteristics, clinical evidence of efficacy was necessary. This development program failed to provide adequate evidence of efficacy and the PK characteristics of tramadol ER may provide an answer as to why the program was unsuccessful. Tramadol, and opioids in general, often result in relatively large numbers of clinical trial subjects discontinuing study participation due to adverse effects. This effect was noted in the clinical trials presented. However, unlike other opioid and non-opioid analgesics, the effects of tramadol ER failed to sufficiently separate from placebo to reach statistical significance. The per-protocol analyses appeared to demonstrate efficacy, but when the efficacy results of patients dropping out due to adverse events (AEs) were not imputed using last observation, there was no longer any evidence of efficacy present in any consistent manner among patients able to tolerate the product. Furthermore, there was a failure to demonstrate a dose response within parallel arm trials of doses ranging from 100 mg ——— per day. It is unfortunate that a more frequent dosing interval was not evaluated, it is possible adequate evidence of efficacy might have been observed.

The safety profile reported was consistent with what is known about the effects of tramadol. There were no deaths or serious adverse events associated with overdosage reported.

CMC

The chemistry, manufacturing, and controls information was reviewed by Dr. Bart Ho. Adequate stability data was supplied from the proposed storage period. Deficiencies noted in the one of the DMFs were satisfactorily resolved. The drug substance and drug product specifications were acceptable.

Pharmacology and Toxicology

A non-clinical pharmacology and toxicology was performed by Dr. Conrad Chen. No deficiencies were noted in the pharmacology and toxicology program submitted in support of this indication.

Efficacy

A detailed review of clinical efficacy studies was performed by Dr. Lourdes Villalba and a statistical review was performed by Dr. Yongman Kim. Six clinical studies were submitted for review. The sponsor identified three studies to support efficacy, but has submitted the results of five studies that were double-blind, randomized, and placebo-controlled. One additional open-label study was submitted to provide additional safety information.

Study 014 was a double-blind, randomized, placebo-controlled, 12-week study in patients with chronic low back pain for six months or more. This study used an enrichment design that enriched for patients responsive to and able to tolerate tramadol. Patients were titrated to tramadol ER 300 mg per day during a run-in period. Those without adequate relief or with intolerable adverse events (AEs) were discontinued from the study. Patients were then randomized to placebo, tramadol ER 200 mg or Tramadol ER 300 mg. Of the 619 patients enrolled, 233 (37.6%) patients withdrew during the run-in period. Following randomization, the further withdrawals for AEs was comparable across treatment groups, 13 (10%) withdrew from the 300 mg arm, 13 (10%) withdrew from the 200 mg arm (including three SAEs) and 18 (14%) from the placebo arm. The number of patients that withdrew due to lack of efficacy was 13 (10%) from the 300 mg arm, 11 (8.5%) from the 200 mg arm, and 21 (16%) from the placebo arm. This was surprising as it might have been anticipated that as all patients were titrated to efficacy and tolerability prior to randomization, those randomized to placebo would have dropped out in much greater numbers once they were no longer receiving active drug.

The sponsor's efficacy analysis using last observation carried forward to impute missing data revealed a statistically significant average change in pain intensity over 12 weeks (a time-weighted analysis) was statistically significant for the 300 mg dose compared to placebo ($p=0.009$) and approached significance for the 200 mg dose ($p=0.52$). The results in a landmark analysis, change from baseline to endpoint was statistically significantly different from baseline for the 300 mg dose ($p=0.38$), but not the 200 mg dose ($p=0.197$). It is notable that all three treatment arms revealed worse pain at 12 weeks than at baseline, the tramadol arms were less worse than the placebo arm. Dr. Kim performed reanalysis using a more conservative imputation method, baseline observation carried forward, to assess the effects of the imputation method on the outcome. Neither the change over the 12 week period analysis, nor the change at 12 weeks compared to baseline analysis retained any statistical significance.

Study 015 was a randomized, double-blind, placebo-controlled, 12-week study in patients with osteoarthritis of the knee. Patients were randomized to treatment with tramadol ER or placebo and were permitted to titrate to a dose ranging from 200 mg to 400 mg per day. Patients not tolerating at least 200 mg per day were discontinued from the trial. Of the 246 patients randomized to treatment, nearly 50% discontinued the study early. Nineteen (15%) patients in the tramadol ER arm discontinued for lack of effect and 33 (27%) due to adverse events including three SAEs. Forty five (37%) patients withdrew from the placebo arm due to lack of efficacy, nine (8%) due to AEs including two SAEs.

The sponsor's analysis using LOCF to impute missing data revealed a statistically significant difference ($p<0.001$) in average change in pain intensity for active vs. placebo, using either a time weighted analysis from baseline over 12 weeks, or a landmark analysis of change from baseline to endpoint. Dr. Kim also performed re-analyses of these comparisons using BOCF to impute missing data revealed loss of statistical significance for the landmark analysis of change from baseline to endpoint, while the time-weighted analysis did retain statistical significance ($p=0.21$).

Study 021 was a randomized, double-blind, placebo- and active-controlled, dose-ranging, 12-week study in patients with osteoarthritis of the knee and/or hip. Patients were randomized to treatment with tramadol ER 100 mg, 200 mg, and 300 mg, celecoxib 200 mg and placebo. Patient withdrawal due to lack of efficacy was highest in the placebo arm (32.5%), followed by tramadol ER 100 mg (25.4%), tramadol ER 200 mg (16.6%), celecoxib (14.9%), and tramadol ER 300 mg (11.1%). Patient withdrawal due to non-serious adverse events was highest in the tramadol ER 300 mg arm (30.2%), followed by tramadol ER 200 mg (21.6%), tramadol ER 100 mg (12.4%), celecoxib 200 mg (9.9%), and placebo (6.0%).

The sponsor's analysis using LOCF for average change in pain from baseline to endpoint compared to placebo revealed a statistically significant difference for celecoxib ($p=0.004$), and approached significance for tramadol ER 300 mg ($p=0.058$). Dr. Kim's analysis using BOCF revealed a statistically significant difference only for celecoxib ($p=0.018$).

Study 023 was a randomized, double-blind, placebo-controlled, 12-week study in patients with osteoarthritis of the knee or hip. Patients were randomized to tramadol ER 100 mg, 200 mg, 300 mg, 400 mg, and placebo. Patient withdrawal due to lack of efficacy was highest in the placebo arm (22.4%), followed by tramadol ER 100 mg 15.3%), tramadol ER 200 mg (14.4%), tramadol 400 mg (9.0%) and tramadol ER 300 mg (9.0%). Patient withdrawal due to non-serious adverse events was highest in the tramadol ER 400 mg arm (28.2%), followed by tramadol ER 300 mg (25.9%), 200 mg (17.9%), tramadol ER 100 mg (13.4%), and placebo (9.3%).

The sponsor's analysis using LOCF for average change in pain from baseline to endpoint revealed a statistically significant difference compared to placebo for all four treatment groups. Dr. Kim's analysis using BOCF revealed the only finding to reach statistical significance was tramadol 200 mg ($p=0.28$), with tramadol 100 mg approaching significance ($p=0.52$). Additionally, no dose response was found across the four tramadol ER doses.

These efficacy studies also evaluated other endpoints, function and global assessments. These are discussed in Dr. Villalba's review.

Across these four studies, we have efficacy results that are unconvincing that this product was able to provide evidence of effectiveness in the patients studied. Consistent findings are relatively large numbers of patients who discontinue due to adverse events. In patients receiving tramadol ER 400 mg in Study 023, 28% dropped out due to AEs. In patients receiving tramadol 300 mg, 30% and 26% in Studies 021 and 023, respectively, dropped out due to AEs. In patients receiving tramadol 200 mg, 10% and 18% in Studies 021 and 023, respectively, dropped out due to AEs. On the other hand, the number of patients dropping out due to lack of efficacy was

consistently higher in the placebo treatment arms. Using LOCF to impute missing data, patients dropping out due to AEs have a relatively good value assigned even though the treatment was not tolerated, while patients dropping out due to lack of efficacy have a relative poor value assigned. When the reason for the missing data is nonrandom, as in the case of these trials with the active treatment arms have more dropouts due to AEs and the placebo arm has more dropouts due to lack of efficacy, LOCF creates a bias in favor of the active treatment arms. Using a conservative method such as BOCF, demonstrates that in the absence of good values being assigned to the dropouts due to AEs, little evidence of efficacy remains for the active treatment groups compared to placebo. This is regardless of whether patients were assigned to a specific dose of tramadol ER or permitted to titrate to the final study dose.

Safety

The review of the clinical safety data was performed by a team consisting of Dr. Julia Castle, Dr. Tatiana Oussova, Dr. Carolyn Yancey, and Dr. Joel Schiffenbauer. The extent of exposure was substantial. Nearly 1800 patients were enrolled in double-blind efficacy studies for chronic pain, with an additional 1300 patients with open-label exposure. Approximately 1700 patients were exposed to flexible dosing in studies with doses ranging from 100 mg to 500 mg including the 52-week, open-label safety study. Two hundred patients received 400 mg per day in a fixed dose chronic pain study, and there were over 400 patients who received 300 mg per day, 200 mg per day and 100 mg per day in fixed dose chronic pain studies.

There were no deaths reported. Fourteen patients with SAEs are reported including one patient who received placebo. These included two reports of abdominal pain, unstable angina, hernia pain, pneumonia, osteoarthritis, cholelithiasis, neck mass (benign cyst), grand mal convulsion, uterine hemorrhage, chest pain with congestive heart failure, chest pain with epigastric pain, arterial aneurysm with peripheral ischemia and ulnar nerve injury, chest pain with a bee sting. The absence of deaths or reports of serious overdoses is notable given the larger quantity of tramadol in the 200 mg tablet.

The most frequent adverse events were nausea, dizziness, constipation, headache, somnolence, flushing, vomiting, pruritus, insomnia, asthenia, diarrhea, and dry mouth. AEs identified as not present in the Ultram label included nasopharyngitis, upper respiratory tract infection, arthralgia, sinusitis, and decreased appetite. There were reports of myoclonus seizure (1), convulsions (1 on tramadol ER and 1 on placebo), and grand mal convulsion (1).

The sponsor did not adequately explore outliers for the laboratory data.

Abuse Liability

Assessment of abuse liability was performed by the Controlled Substance Staff. The results of the Addiction Research Center Inventory and Physical Dependence Questionnaire were consistent with responses to other opiates and tramadol products. A recommendation to schedule all tramadol products in the controlled substance act is under review.

Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology and biopharmaceutics data was reviewed by Dr. Lei Zhang and Dr. Abimbola Adebowale who note that an adequate characterization of the PK performance was established by the sponsor. It was noted in their review that the PK profiles of tramadol ER and Ultram differ. The steady-state concentrations of tramadol and the active M1 metabolite over 24 hours were lower for once daily dosing of tramadol ER than for every six hour dosing of Ultram during the 0-6 hour and 18-24 hour intervals following tramadol ER dose.

It was also noted that a lower C_{max} and AUC was achieved following dosing in the evening compared to dosing in the morning, perhaps related to slowing in gastrointestinal transit over night.

The effects of mild and moderate renal impairment differed with respect to serum tramadol levels, but the M1 active metabolite increased such that the maximum total daily dose of 200 mg was recommended in such patients. Hepatic impairment resulted in lower M1 concentrations, suggesting that dose adjustment might be needed to maintain an adequate analgesic effect. The recommended dosing in cirrhosis was not supported by data. Concurrent administration with a high fat meal resulted in reduced C_{max} and AUC, but not clearly enough to necessarily require dose adjustment.

An additional study was suggested, to evaluate the effects of age in elderly and older elderly subjects. It was also suggested there could be benefit in evaluating the product in an exposure response study compared to Ultram. Acceptance of the dissolution specifications was pending review of the in vitro-in vivo correlation results.

The differences in steady-state PK profile are important in light of the poor results from the efficacy trial. At steady-state, for roughly 12 hours out of every 24 hours, the serum concentration of tramadol and the active M1 metabolite are below what would be found with around-the-clock dosing with Ultram. It may be that tramadol ER would be more effective with every 12 hour dosing.

Sharon Hertz, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmological Drug Products
ODE V, CDER

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Sharon Hertz
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