CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022370Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-370
	Complete Response to NDA (b) (4)
Submission Dates	4/14/2008; 6/27/2008
Brand Name	TRADENAME ER
Generic Name	Tramadol Hydrochloride
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Applicant	Cipher Pharmaceuticals, Ltd.
Relevant IND	IND (b) (4)
Relevant NDA	(b) (4) (Approvable in May 2007)
Type of Submission; Code	505 (b)(2); 5S
Reference Drugs	Ultram (Immediate Release), Ortho McNeil Pharmaceuticals, Inc. (NDA 20-281)
	Ultram ER (Extended Release), Ortho McNeil Pharmaceuticals, Inc. (NDA 21-692)
Formulation; Strength(s)	Extended Release Capsules; 100, 200, and 300 mg
Indication	Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time
Proposed Dosing Regimen	(b) (4)

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1 EXECUTIVE SUMMARY

1.1 Recommendations

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding language in the package insert.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

This NDA is a 505 (b)(2) application for a new extended-release (ER) once-a-day product of tramadol hydrochloride capsules, CIP-Tramadol ER. The listed drugs are Ultram® (tramadol hydrochloride tablets), an immediate-release (IR) product that is marketed under approved NDA

20-281 and Ultram ER® tablets, a once-a-day extended-release tramadol HCl product that is marketed under approved NDA 21-692.

The proposed indication for CIP-Tramadol ER is for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. This indication is the same as Ultram® ER. There are three dosage strengths: 100, 200 and 300 mg capsules. The intended dosing regimen is 100 to 300 mg once daily titrate to effect (the same as Ultram ER).

Initially, there was no listed drug for the tramadol ER formulation, the Sponsor submitted NDA (b) (4) in July 2006 that referenced to the Ultram IR product (NDA 20-281). The Sponsor conducted 3 double-blinded, placebo-controlled studies (b) (4) and additional open-label study and double-blinded study to support safety. Six pharmacokinetic studies were conducted to characterize the PK performance of the new ER formulation. NDA (b) (4) was deemed approvable (letter dated 5/2/07) (b) (4).

The first tramadol ER product (Ultram ER, NDA 21-692) was approved in September 2005. The Sponsor resubmitted the NDA for their tramadol ER product referencing Ultram ER in addition to Ultram IR in April 2008 (Complete response to NDA (b) (4)). A new NDA number, 22-370, was assigned administratively to reflect the change of listed drug for NDA (b) (4). To support NDA 22-370 (complete response to NDA (b) (4)), the Sponsor conducted new bioequivalence studies to Ultram ER (200 and 300 mg) and an *in vitro* comparative dissolution study.

Previously, NDA (b) (4) has addressed the following Clinical Pharmacology items and was deemed acceptable:

(1) Extended release characteristics.
(2) Dose proportionality
(3) The drug product's steady-state performance relative to a currently marketed IR product
(4) Effect of food on the formulation
(5) Effect of alcohol on the formulation

No special population or drug interaction studies were conducted. The Sponsor is relying on Agency's previous findings for Ultram (IR or ER) to construct their labeling for special populations (e.g., renal and hepatic impairment patients, elderly patients) and drug-drug interactions. Refer to Clinical Pharmacology review by Dr. Zhang for NDA (b) (4) dated 03/26/2007 for details.

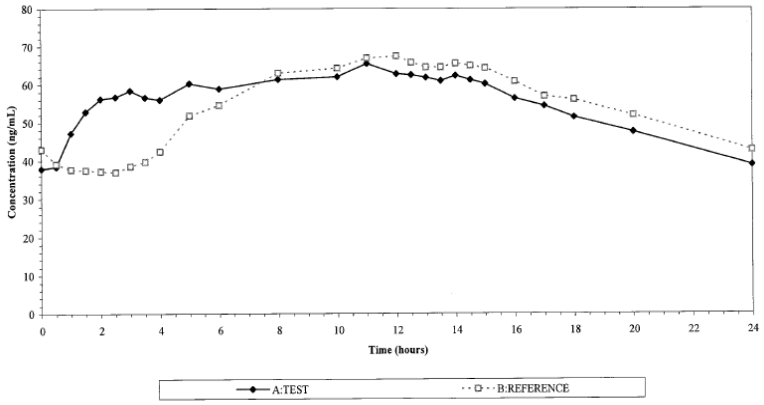
This review focuses on the new studies that Sponsor conducted and the results are summarized below.

Relative Bioavailability to Ultram ER products

The Sponsor conducted 4 new BE studies to compare their 200 or 300 mg ER capsules to Ultram ER 200 or 300 mg tablets.

200 mg (Study TRAMPK.08.02):
Study TRAMPK.08.02 was a multi-dose, randomized, two-period, two-sequence, two treatment, crossover relative bioavailability study conducted under steady-state fasting conditions. Results showed that compared to steady-state PK profile of Ultram ER (200 mg QD for 7 days), CIP-Tramadol ER (200 mg QD for 7 days) showed equivalent C_{max}, C_{min} and AUC (Figure 1 and Tables 1 and 2) for both tramadol and its active O-desmethylated metabolite, M1.

(b) (4)



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations (0-24 hr) on Day 7 for 200-mg CIP-Tramadol ER Capsules QD (♦) or 200-mg Ultram® ER Tablets QD (□) (N=38).

Table 1. Relative Bioavailability for Tramadol at Steady State (on Day 7) (A: 200 mg CIP-Tramadol ER vs. B: 200 mg Ultram ER).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Tramadol N=38				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
$AUC_{0-\tau}$ (ss) (ng-hr/mL)	5504.67	5299.33	103.87	(97.36, 110.82)
$C_{max\ (ss)}$ (ng/mL)	322.74	334.96	96.35	(90.29, 102.83)
$C_{min\ (ss)}$ (ng/mL)	120.04	112.98	106.25	(96.25, 117.29)

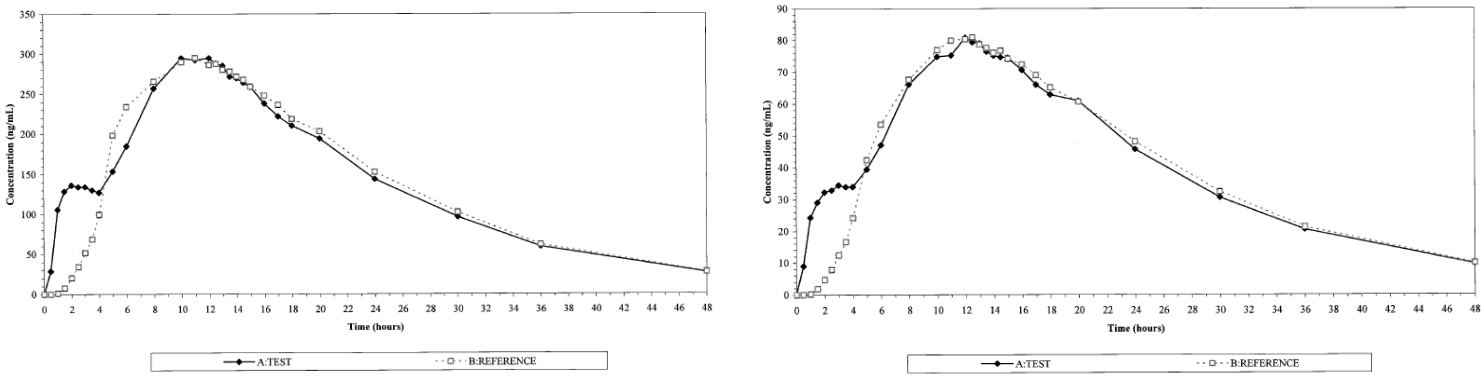
Table 2. Relative Bioavailability for M1 at Steady State (on Day 7) (A: 200 mg CIP-Tramadol ER vs. B: 200 mg Ultram ER).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data O-desmethyltramadol N=38				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
$AUC_{0-\tau}$ (ss) (ng-hr/mL)	1229.02	1191.10	103.18	(97.66, 109.01)
$C_{max\ (ss)}$ (ng/mL)	65.75	67.53	97.36	(92.08, 102.94)
$C_{min\ (ss)}$ (ng/mL)	32.72	29.93	109.31	(100.82,118.52)

300 mg:

The Sponsor conducted three single-dose BE studies to determine bioequivalence between a 300 mg CIP-Tramadol ER capsule and a 300 mg Ultram ER tablet: one was considered a pilot study (Study TRAMPK.07.01), one had 4 arms including both fed and fasting conditions (Study TRAMPK.07.04), and one had 2 arms under fasting conditions (Study TRAMPK.08.01).

Results from Study TRAMPK.08.01 showed equivalent C_{max} and AUC (Figure 2 and Tables 3 and 4) for both tramadol and M1.



a. Tramadol b. M1

Figure 2. Mean Plasma Tramadol (a) and M1 (b) Concentrations (0-48 hr) Following a Single Dose of 300-mg CIP-Tramadol ER Capsule (♦) or a 300-mg Ultram® ER Table (□) (N=30).

Table 3. Relative Bioavailability for Tramadol after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER) (N=27).

	B	A		90% CI Lower Level	90% CI Upper Level
	Geometric Means		Ratio		
AUCt (ng*hr/mL)	6445.77	6346.607	98.46	94.45	102.64
AUCinf (ng*hr/mL)	6796.14	6736.87	99.13	95.17	103.25
Cmax (ng/mL)	330.47	302.21	91.45	85.17	98.19

Table 4. Relative Bioavailability for M1 after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER) (N=27).

	B	A		90% CI Lower Level	90% CI Upper Level
	Geometric Means		Ratio		
AUCt (ng*hr/mL)	1742.24	1749.48	100.42	96.47	104.52
AUCinf (ng*hr/mL)	1877.59	1904.72	101.44	96.93	106.17
Cmax (ng/mL)	81.00	77.13	95.22	88.43	102.53

A Division of Scientific Investigation (DSI) inspection was performed for Study TRAMPK.07.04. Even though Form 483 was issued at the analytical site, the identified issues were not thought by DSI as having an adverse effect on the acceptance of data. DSI recommends that data are accepted for review. Refer to DSI review dated 10/06/08 for details.

CIP-Tramadol ER contains a tramadol HCl immediate release (IR) tablet and tramadol hydrochloride (HCl) ER beads. The *in vivo* concentration-time profiles for tramadol and its metabolite, M1, showed that there was a lower Cmax peak (Peak 1) at around 2 hours and a higher Cmax peak (Peak 2) at around 10-12 hours. Peak 1 mainly represents the release of tramadol from the IR tablet and Peak 2 mainly represents the release of tramadol from the ER beads. Overall, peak 2 corresponds to the Cmax of the product. The sponsor in their pharmacokinetic analysis focused only on the major peak corresponding to the overall Cmax of the product. For example, in the studies comparing CIP-Tramdol ER to Ultram IR (Study 02-549), CIP-Tramadol to Ultram ER tablets under single dose (Study TRAMPK.08.01) and multiple dose (Study TRAMPK.08.02) conditions, only the peak corresponding to overall peak (Cmax of the product) was assessed relative to the Cmax of the comparator products. The Clinical Pharmacology review for NDA (b) (4) contained a discussion related to the potential lack of dose-proportionality (Studies 02-406 and 02-556) and a potentially different food effect (Study 02-405) as compared to the main peak of the product based on an independent assessment by this reviewer. However, assessment of the entire data (both submitted under NDA (b) (4)

and NDA 22-370) shows that this peak is just a part of the overall pharmacokinetic profile and can be seen on a consistent basis mainly under single dose conditions and is not reproducibly seen under multiple dose conditions. Based on overall assessment of the entire database, there is no evidence to suggest that this first peak is associated with any specific safety concern. (b) (4) In the Medical Team Leader memo dated 4/25/07, Dr. Mwango Kashoki concluded that the use of CIP-Tramadol ER is associated with adverse events that have been reported with other tramadol products. Further, in the Action Letter dated 5/2/07, there were no safety-related deficiencies identified. As such, this first peak is considered a part of the overall pharmacokinetic profile of CIP-Tramadol ER product and its contribution to the efficacy and safety is already captured in terms of (a) CIP-Tramadol ER being bioequivalent to Ultram ER tablets at the 300 mg strength under single dose conditions and to the 200 mg Ultram ER tablets under multiple dose conditions and (b) CIP-Tramadol being associated with adverse events that have been reported with other tramadol products.

100 mg:
The Sponsor did not conduct an *in vivo* BE study for 100 mg dose strength. Based on the demonstrated bioequivalence between 300 mg strengths of CIP-Tramadol and Ultram ER under single dose conditions, demonstrated bioequivalence between the 200 mg strengths of CIP-Tramadol and Ultram ER under multiple dose conditions, formulation similarity between 100 and 200 mg CIP-Tramadol ER capsules, dose-proportionality across the three strengths (100, 200, and 300 mg) based on dose-normalized Cmax and AUC (Studies 556 and 406), *in vitro* dissolution similarity between 100 and 200 mg CIP-Tramadol ER capsules (Study LES-096), and approximate dose-proportionality for Ultram ER tablets (as stated in the Ultram ER package insert), it is reasonable to conclude that 100 mg CIP-Tramadol ER capsules and 100 mg Ultram ER tablets will have similar exposure.

In vitro comparative dissolution data (Study LES-096)
In vitro comparative dissolution data (Table 5) from Study LES-096 suggested that overall dissolution profiles among 100, 200 and 300 mg of CIP-Tramadol ER capsules were similar to each other (F2>50) although 300 mg ER capsule contains less IR in the formulation and shows lower dissolution levels at initial time points (Figure 3).

(b) (4)

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2 QUESTION BASED REVIEW

Reviewer's Note: This review will cover the newly submitted information that rely on Ultram ER as the reference. Refer to review for NDA (b) (4) *for other aspects of this product.*

CIP-Tramadol ER was also referred to as Tramadol ER in the review.

2.1 General Attributes

2.1.1 What are the highlights of the formulation of the drug product?

CIP- TRAMADOL ER CAPSULES are sustained release capsules containing tramadol hydrochloride (HCI) ER beads and a tramadol HCl immediate release (IR) tablet (Figure 2.1.1.1). The ER beads are manufactured by starting with IR beads which are then coated with a controlled release coating.

Capsule Strength	IR Tablet Strength	ER Beads Strength
100 mg	25 mg	75 mg
200 mg	50 mg	150 mg
300 mg	50 mg	250 mg

Figure 2.1.1.1. Schematic Graph of 100, 200 and 300 mg Capsules.

Dose strengths are 100, 200 and 300 mg (tramadol hydrochloride). The ratio of the amount of tramadol HCl in the IR tablet and the ER beads are 1/3 for 100 and 200 mg capsules, and 1/5 for 300 mg capsules. Therefore, the tramadol content in IR tablet and ER beads is proportional (1:3) between 100 and 200 mg capsules, and 300 mg capsules have more tramadol in ER beads (1:5, IR tablet: ER beads). The inactive components for the capsules are not proportional for 100, 200 and 300 mg capsules.

2.1.2 What is the proposed therapeutic indication?

The proposed indication for CIP-Tramadol ER is for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. This indication is the same as Ultram® ER tablets (NDA 21-692).

2.1.3 What are the proposed dosage recommendations and route of administration of CIP-Tramadol ER for the proposed indication?

CIP-Tramadol ER is taken orally.

The following language is proposed by the sponsor regarding dosage and administration (the same as Ultram ER tablets):

(b) (4)

(b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are new clinical pharmacology studies used to support dosing or claims?

The Sponsor conducted 4 new BE studies to compare their 200 and 300 mg ER capsules to Ultram ER 200 and 300 mg tablets: one for 200 mg (steady-state) and three for 300 mg (single dose study).

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

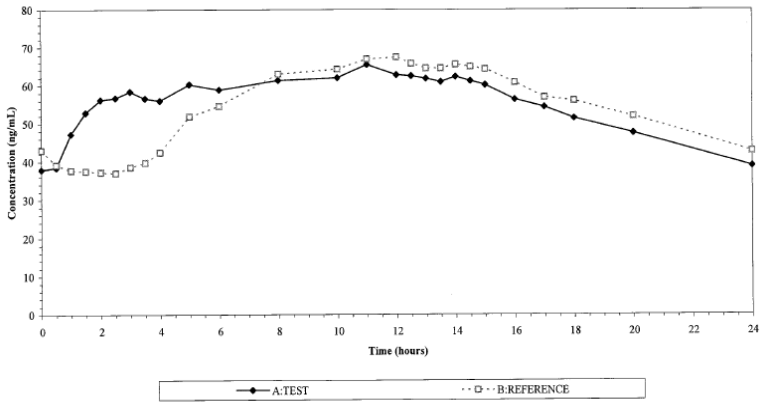
Yes. Tramadol and its active metabolite, M1 (O-desmethyltramadol), were measured in human plasma. Please refer to Section 2.6 Analysis for analytical details.

2.2.3 What is the relative bioavailability of CIP-Tramadol ER 200 mg capsules vs. Ultram ER 200 mg tablets following multiple doses?

200 mg (Study TRAMPK.08.02):

Study TRAMPK.08.02 was a multi-dose, randomized, two-period, two-sequence, two treatment, crossover relative bioavailability study conducted under steady-state fasting conditions. Results showed that compared to steady-state PK profile of Ultram ER (200 mg QD for 7 days), CIP-Tramadol ER (200 mg QD for 7 days) showed equivalent C_{max}, C_{min} and AUC (Figure 2.2.3.1 and Tables 2.2.3.1 and 2.2.3.2) for both tramadol and its active O-desmethylated metabolite, M1.

(b) (4)



a. Tramadol b. M1

Figure 2.2.3.1. Mean Plasma Tramadol (a) and M1 (b) Concentrations (0-24 hr) on Day 7 for 200-mg CIP-Tramadol ER Capsules QD (♦) or 200-mg Ultram® ER Tablets QD (□) (N=38).

Table 2.2.3.1. Relative Bioavailability for Tramadol at Steady State (on Day 7) (A: 200 mg CIP-Tramadol ER vs. B: 200 mg Ultram ER).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Tramadol N=38				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
$AUC_{0-\tau}$ (ss) (ng-hr/mL)	5504.67	5299.33	103.87	(97.36, 110.82)
$C_{max\ (ss)}$ (ng/mL)	322.74	334.96	96.35	(90.29, 102.83)
$C_{min\ (ss)}$ (ng/mL)	120.04	112.98	106.25	(96.25, 117.29)

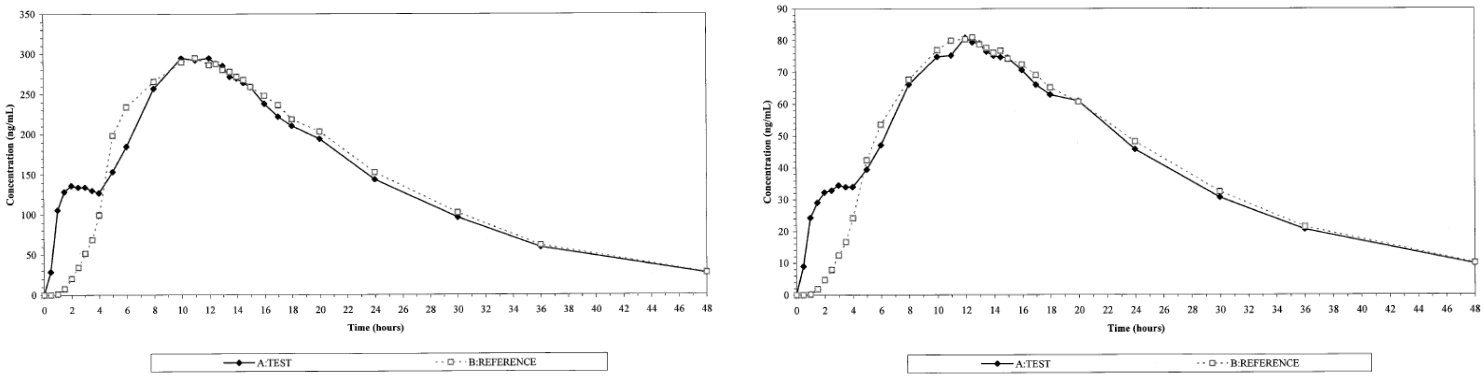
Table 2.2.3.2. Relative Bioavailability for M1 at Steady State (on Day 7) (A: 200 mg CIP-Tramadol ER vs. B: 200 mg Ultram ER).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data O-desmethyltramadol N=38				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
$AUC_{0-\tau}$ (ss) (ng-hr/mL)	1229.02	1191.10	103.18	(97.66, 109.01)
$C_{max\ (ss)}$ (ng/mL)	65.75	67.53	97.36	(92.08, 102.94)
$C_{min\ (ss)}$ (ng/mL)	32.72	29.93	109.31	(100.82,118.52)

2.2.4 What is the relative bioavailability of CIP-Tramadol ER 300 mg capsules vs. Ultram ER 300 mg tablets following a single dose?

The Sponsor conducted three single-dose BE studies to determine bioequivalence between a 300 mg CIP-Tramadol ER capsule and a 300 mg Ultram ER tablet: one was considered a pilot study (Study TRAMPK.07.01), one had 4 arms including both fed and fasted conditions (Study TRAMPK.07.04), and one had 2 arms under fasted conditions (Study TRAMPK.08.01).

Results from Study TRAMPK.08.01 showed equivalent C_{max} and AUC (Figure 2.2.4.1 and Tables 2.2.4.1 and 2.2.4.2) for both tramadol and M1.



a. Tramadol b. M1

Figure 2.2.4.1. Mean Plasma Tramadol (a) and M1 (b) Concentrations (0-48 hr) Following a Single Dose of 300-mg CIP-Tramadol ER Capsule (♦) or a 300-mg Ultram® ER Table (□) (N=30).

Table 2.2.4.1. Relative Bioavailability for Tramadol after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER) (N=27).

	B	A		90% CI Lower Level	90% CI Upper Level
	Geometric Means		Ratio		
AUCt (ng*hr/mL)	6445.77	6346.607	98.46	94.45	102.64
AUCinf (ng*hr/mL)	6796.14	6736.87	99.13	95.17	103.25
Cmax (ng/mL)	330.47	302.21	91.45	85.17	98.19

Table 2.2.4.2. Relative Bioavailability for M1 after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER) (N=27).

	B	A		90% CI Lower Level	90% CI Upper Level
	Geometric Means		Ratio		
AUCt (ng*hr/mL)	1742.24	1749.48	100.42	96.47	104.52
AUCinf (ng*hr/mL)	1877.59	1904.72	101.44	96.93	106.17
Cmax (ng/mL)	81.00	77.13	95.22	88.43	102.53

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the bioavailability of the drug from the dosage form?

Food effect was evaluated in Study 0704 with 300 mg capsules. A high fat breakfast had little effect on PK of CIP-tramadol ER 300 mg, and the confidence intervals for tramadol Cmax and AUC were slightly outside of the 80.00% to 125.00% range (90% CI: 76.1%-100.2% and 79.5%-111%, respectively). (Table 2.5.1.1).

Table 2.5.1.1. Relative Bioavailability for Tramadol after a Single Dose Administration of 300 mg Tramadol ER under Fasting and Fed Conditions (N=25).

	Fed	Fast		90% CI Lower Level	90% CI Upper Level
	Geometric Means		Ratio		
AUCt (ng*hr/mL)	7854	8402	93.5	80.0	109.2
AUCinf (ng*hr/mL)	8432	8980	93.9	79.5	111.0
Cmax (ng/mL)	346	396	87.3	76.1	100.2

The results obtained are similar to previous food effect study, Study 02-405, where food showed little effect on PK for CIP-Tramadol ER formulation (see NDA (b) (4) review).

2.5.2 What is in vitro comparative dissolution data for different strengths of CIP-Tramadol capsules vs. Ultram ER tablets?

CIP-Tramadol ER capsules and Ultram ER tablets did not show comparative dissolution profiles for all three strengths under all pH conditions (pH 1.2, 4.5 and 6.8) due to formulation differences (CIP-Tramadol had an earlier peak) (Table 2.3.2.1 and Figure 2.5.2.1). The Sponsor demonstrated *in vivo* bioequivalence between CIP-Tramadol ER and Ultram ER for 200 and 300

mg strengths. Further, since CIP-Tramadol ER capsules exhibited dose-proportionality across the 100 mg, 200 mg, and 300 mg strengths and Ultram ER showed dose-proportionality (based on the information in the package insert) across the 100 mg, 200 mg, 300 mg strengths, it is reasonable to expect that 100 mg strength of CIP-Tramadol ER would have similar bioavailability to that of 100 mg Ultram ER despite the differences seen in dissolution data.

(b) (4)

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2.5.3 What are in vitro comparative dissolution data for different strengths of CIP-Tramadol capsules?

In vitro comparative dissolution data (Table 2.5.3.1) from Study LES-096 suggested that overall dissolution profiles among 100, 200 and 300 mg of CIP-Tramadol ER capsules were similar to each other (F2>50) although 300 mg ER capsule contains less IR in the formulation and shows lower dissolution levels at initial time points (Figure 2.5.3.1).

(b) (4)

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2.6 Analytical

2.6.1 Were the analytical methods used to determine Tramadol and M-1in biological fluids adequately validated?

Yes, concentrations of tramadol and its metabolite, M1, were adequately measured in human plasma by a validated LC/MS/MS assay (Method AP LC/MS/MS 308.100) and summarized in Table 2.6.1.1. The assays are sensitive and selective for the analytes.

Briefly, the method uses an API 3000 LC/MS/MS system. The interface used with the API 3000 LC/MS/MS was a Turbo Ionspray. The positive ions were measured in MRM mode. The analytes were quantitated using a solid phase extraction procedure. Linear regression, with $1/x^2$ weighting, was used to obtain the best fit of the data for the calibration curves.

Long-term stability of tramadol and M1 in frozen human plasma at -20°C was at least (b) (4) days. The stability was long enough to cover the time span from sample collection to sample analysis. The mean recovery from plasma was 96.4% and 104% for tramadol and O-desmethyltramadol, respectively.

Table 2.6.1.1. Analytical Methods used for the Determinations of Tramadol and M1 in Each Study.

Analytes	Internal Standard	LOQ (ng/ml)	Linear Range (ng/ml)	Intra-Day Precision (%CV)	Intra-Day Accuracy (% bias)	Inter-Day Precision (%CV)	Inter-Day Accuracy (% bias)	QC Samples (ng/mL)
Tramadol	(b) (4)							
M1								

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4.2 Individual Study Review

4.2.1 Study TRAMPK07.04 (PIGD07002): An Open-Label, Single-Dose, Randomized, Four-Way, Comparative Bioavailabilty Study of Cipher Tramadol ER Capsules 300 mg Versus Biovail Ultram® ER Tablets 300 mg, in Normal, Healthy Subjects, Under Fed and Fasting Conditions

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Study Period:	Oct 9, 2007 to Nov 26, 2007
Sample Analysis Period:	December 15, 2007 to January 4, 2008
Principle Investigator:	Deepen Patel, M.D., C.C.F.P., Senior Medical Director, Allied Research International - Cetero Research
Study Center:	Allied Research International - Cetero Research, 4520 Dixie Rd. Mississauga, ON, Canada, L4W 1 N2
Analytical Site:	(b) (4)

Objective: To evaluate the relative bioavailability of Tramadol ER Capsules 300 mg (Cipher Pharmaceuticals Limited) and Biovail Ultram® ER Tablets 300 mg (PriCara ™ /Ortho-McNeil Inc) in normal, healthy male and female subjects, under high-fat fed and fasting conditions.

Study Design: This study was an open label, randomized, single dose, four-treatment, four-period, four-sequence crossover design. A two week washout period was observed between doses.

A single 300 mg dose of the assigned formulation was administered according to the randomization scheme with 240 mL of room temperature potable water, following a high-fat, high calorie breakfast for subjects in the fed group, or after an overnight fast for subjects in the fasting group. For the fed group, the breakfast was served following an overnight fast of at least 10 hours. Subjects were instructed not to chew, break or touch the study drug.

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	D	B	C
Sequence 2	B	A	C	D
Sequence 3	C	B	D	A
Sequence 4	D	C	A	B

Treatment A: Cipher Tramadol ER Capsule 300 mg (1 capsule administered after a high-fat, high calorie breakfast)
Treatment B: Biovail Ultram ER Tablet 300 mg (1 tablet administered after a high-fat, high calorie breakfast)
Treatment C: Cipher Tramadol ER Capsule 300 mg (1 capsule administered after an overnight fast of at least 10 hours)
Treatment D: Biovail Ultram ER Tablet 300 mg (1 tablet administered after an overnight fast of at least 10 hours)

All subjects were healthy non-smoking male and female volunteers between the ages of 18 and 55 years old (inclusive).

A total of 32 subjects were enrolled in the study as planned. 16 subjects dropped out during the course of the study (Table 1). Dropouts were not replaced. Data from all subjects who completed either the two fasting periods or two fed periods of the study and did not experience any emesis during the dosing interval for these periods were analyzed. A total of 16 subjects completed all 4 periods of the study. An additional 9 subjects completed at least 2 periods that allowed for a comparison of the Test and Reference formulations under either fasting or fed conditions to be made. A total of 25 subjects were included in the pharmacokinetic and statistical analyses for tramadol and O-desmethyltramadol. These included Subjects 01, 02, 04-10, 14-18, 20-22, 24, and 26-32. In the two-way fed comparison (Treatments A vs. B), Subjects 02, 04-07, 09, 10, 14-16, 20-22, 24, 26-32 were included in the analysis (N=21). In the two-way fasting comparison (Treatments C vs. D), Subjects 01, 02, 04, 06-10, 15-18, 20-22, 24, 26-29 were included in the analysis (N=20). In the two-way comparison of the Test under fed versus fasting conditions (Treatments A vs. C), Subjects 02, 04, 06, 07, 09, 10, 15, 16, 20-22, 24, 26-29 were included in the analysis (N=16). All 25 subjects were included in the 4-way analysis, but only subjects 02, 04, 06, 07, 09, 10, 15, 16, 20-22, 24, and 26-29 were analyzed for all 4 treatments.

The 32 subjects admitted had an age range (mean ± SD) of 23 to 55 (40 ± 8) years, a height range (mean ± SD) of 150.5 to 194.2 (170.6 ±10.1) cm, a weight range (mean ± SD) of 50.0 to 101.2 (75.0± 14.5) kg, and a BMI range (mean ± SD) of 19.0 to 29.9 (25.6 ± 3.1) kg/m^2. The above ranges met the criteria established for acceptable demographic information stated in the protocol. 22 were Caucasians, 6 were African American, 1 was Caucasian/African American, 1 was Asian, 1 was native Hawaiian, 1 was Caucasian/Arabic/North Africa.

Test Articles:
Test Product (A): Tramadol ER Capsules, 300 mg, Lot No. 14B05

Reference Product (B): Biovail Ultram® ER Tablets, 300 mg, Lot No. 07A013P

Sample Collection:
Blood samples were collected according to the following sampling schedule: 1 x 4 mL at 0 hours pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 11, 12, 12.5,13, 13.5, 14, 14.5, 15, 16,17,18, 20, 24, 30, 36 and 48 (± 1) hours post-dose.

Sample Analysis: Samples were analyzed at the (b) (4) Tramadol and O-desmethyl-tramadol in human plasma was analyzed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) method (Validation Method AP LC/MS/MS 308.100). The lower limit of quantitation (LLOQ) was 2.000/1.000 ng/mL and the upper limit of quantitation (ULOQ) was 500.0/250.0 ng/mL for tramadol/

O-desmethyltramadol. (b) (4) was used as an internal standard. For statistical analysis, subject sample values below the lower limit of quantitation (BLQ) were reported as zero.

The long term freezer stability has been established for (b) (4) days at -20°C ± 10°C in the First Addendum to the Method Validation and covers the required (b) (4) days freezer storage period from (b) (4) at -20°C ± 10°C. Plasma calibration curve standard and QC data demonstrated the acceptable performance of the assay method during the analysis of the study samples.

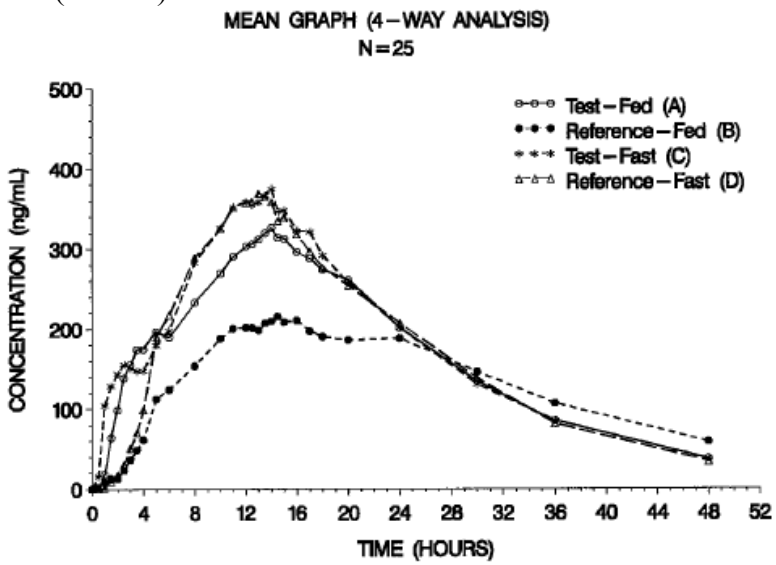
Table 1. Total Dose Consumed for withdrawn or early-terminated subjects.

Subject	Period	Reason	Participated in subsequent Periods	Total Dose Consumed (mg)	Treatment Administered (A, B, C, or D)
01	Prior to Period 4	Withdrew Voluntarily due to personal reasons	N/A	900	D, C, A
03	Prior to Period 2	Withdrew Voluntarily due to personal reasons	No	300	A
05	Prior to Period 2	By the Investigator due to AE-Emesis	Participated in Period 3 & 4	1200	All
08	Prior to Period 4	Withdrew Voluntarily due to personal reasons	N/A	900	D, C, A
11	1	By the Investigator due to AE-Emesis	No	300	A
12	1	By the Investigator due to AE-Emesis	No	300	A
13	3	As per protocol due to positive drug screen for opiates at check-in	No	600	A, D
14	Prior to Period 3	Withdrew Voluntarily due to personal reasons	Participated in Period 4	900	B, A, D
17	Prior to Period 4	Withdrew Voluntarily due to personal reasons	N/A	900	D, C, A
18	4	By the Investigator due to AE- Emesis	N/A	1200	All
19	Prior to Period 2	Withdrew Voluntarily due to personal reasons	No	300	D
23	2	By the Investigator due to AE – Emesis, subject was asked to return for subsequent periods, however subject voluntarily withdrew	No	600	D, C
25	Prior to Period 3	Withdrew Voluntarily due to personal reasons	No	600	C, B
30	2	By the Investigator due to AE-Emesis	Participated in Period 3 & 4	1200	All
31	Prior to Period 4	Withdrew Voluntarily due to ongoing AE	N/A	900	A, D, B
32	Prior to Period 3	Withdrew Voluntarily due to ongoing AE-Cold	Participated in Period 4	900	B, A, D
	4	By the Investigator due to AE-Emesis during Period 4			

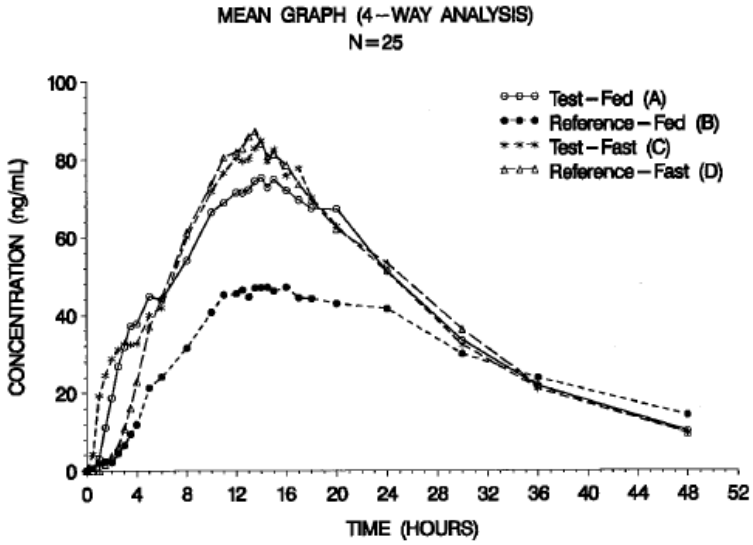
Statistical Analysis:
A four-way analysis was conducted, in which all four periods of the study were analyzed in the same statistical model. However, a significant effect of food on the plasma concentration profile of tramadol and O-desmethyltramadol was observed for the Reference formulation. This difference likely introduced bias into the calculation of the ratios and 90% confidence intervals. Thus, the Sponsor deemed that a four-way analysis was inappropriate for comparing the treatments. The pharmacokinetic and statistical analyses were also conducted using a two-way statistical approach, i.e. the data from the treatments of interest alone were treated as a two-way study and analyzed as such.

Reviewer's Note: If the sponsor did a 4-way cross-over study then it should be analyzed as such due to the model and estimation of RMSE(root means square error) which is required to estimate intra-subject variability and the 90% CI. It is not appropriate for the sponsor to "artificially" convert a four-way crossover study into a "two-way" crossover study. It will change the underlying statistical model for BE analysis. The Sponsor repeated the BE study with a 2-way crossover study design (Study TRAMPK08.01, under fasting conditions for both test and reference drugs) and obtained new results (see Section 4.2.2).

Pharmacokinetic Results:
PK Profiles
The mean plasma concentration-time profiles of tramadol and M1 metabolite from 25 subjects are shown in Figure 1 (a and b).



a. Tramadol



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations after administration of a single dose of 300 mg CIP-Tramadol ER Capsule (*, ○) or 300 mg of Ultram® ER Tablet (Δ, ●) under Fasting and Fed Conditions (N=25).

Mean PK Parameters and Comparisons (Four-Way)

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) from 25 subjects are summarized in Tables 3 and 4.

Table 3. Summary of Mean Pharmacokinetic Parameters of Tramadol Using a Four-Way Analysis Untransformed Data (N=25).

Parameter	Least Square Means				Ratio of Means (90% Confidence Interval)			Intra-subject Variability (%)
	A	B	C	D	A/B	C/D	A/C	
AUC_T (ng·h/mL)	7932.791	6360.069	8592.527	8064.539	124.7 (118.4 – 131.1)	106.5 (101.2 – 111.9)	92.3 (87.1 – 97.6)	9.9
AUC_{inf} (ng·h/mL)	8601.399	7629.415	9269.021	8622.453	112.7 (105.9 – 119.6)	107.5 (101.6 – 113.4)	92.8 (87.0 – 98.6)	10.5
C_{max} (ng/mL)	353.768	297.491	408.939	408.449	118.9 (106.4 – 131.4)	100.1 (90.6 – 109.7)	86.5 (76.4 – 96.6)	19.4
T_{max} (h)	14.52	15.19	13.68	11.63	95.6 (80.9 – 110.2)	117.6 (97.6 – 137.6)	106.1 (88.9 – 123.4)	31.4
λ (h^{-1})	0.0779	0.0727	0.0754	0.0897	107.2 (93.0 – 121.4)	84.0 (72.9 – 95.2)	103.4 (89.4 – 117.3)	22.3
$t_{1/2}$ (h)	9.63	12.05	9.82	8.47	80.0 (65.8 – 94.1)	115.9 (96.3 – 135.5)	98.1 (80.6 – 115.7)	31.4

Treatment A: Cipher Tramadol ER Capsule 300 mg (1 capsule administered after a high-fat, high calorie breakfast)

Treatment B: Biovail Ultram ER Tablet 300 mg (1 tablet administered after a high-fat, high calorie breakfast)
Treatment C: Cipher Tramadol ER Capsule 300 mg (1 capsule administered after an overnight fast of at least 10 hours)
Treatment D: Biovail Ultram ER Tablet 300 mg (1 tablet administered after an overnight fast of at least 10 hours)

Table 4. Summary of Mean Pharmacokinetic Parameters of M1 Using a Four-Way Analysis Untransformed Data (N=25).

Parameter	Least Square Means				Ratio of Means (90% Confidence Interval)			Intra-subject Variability (%)
	A	B	C	D	A/B	C/D	A/C	
AUC_T (ng·h/mL)	2038.182	1484.668	2075.565	2018.516	137.3 (127.3 – 147.3)	102.8 (95.0 – 110.7)	98.2 (90.2 – 106.2)	15.5
AUC_{inf} (ng·h/mL)	2220.581	1849.039	2299.431	2236.811	120.1 (108.6 – 131.6)	102.8 (93.5 – 112.1)	96.6 (87.0 – 106.1)	18.14
C_{max} (ng/mL)	89.971	66.981	92.651	94.074	134.3 (120.3 – 148.3)	98.5 (88.1 – 108.9)	97.1 (85.9 – 108.3)	21.3
T_{max} (h)	15.47	15.63	14.83	12.99	99.0 (89.0 – 108.9)	114.2 (101.7 – 126.6)	104.3 (93.2 – 115.5)	20.7
λ (h^{-1})	0.0679	0.0646	0.0672	0.0778	105.0 (91.0 – 119.1)	86.4 (75.1 – 97.6)	101.0 (87.2 – 114.7)	22.2
$t_{1/2}$ (h)	10.90	14.18	11.26	9.99	76.9 (61.6 – 92.2)	112.8 (91.4 – 134.1)	96.8 (77.5 – 116.2)	35.6

Table 5. Summary of Mean Pharmacokinetic Parameters of Tramadol Using a Four-Way Analysis Ln-transformed Data (N=25).

Parameter	Least Square Means				Ratio of Means (90% Confidence Interval)			Intra-subject Variability (%)
	A	B	C	D	A/B	C/D	A/C	
AUC_T (ng·h/mL)	7853.522	5477.381	8401.692	7554.051	143.4 (124.6 – 164.9)	111.2 (95.8 – 129.2)	93.5 (80.0 – 109.2)	27.0
AUC_{inf} (ng·h/mL)	8431.709	6380.361	8979.875	7981.459	132.2 (112.3 – 155.5)	112.5 (95.9 – 131.9)	93.9 (79.5 – 111.0)	28.8
C_{max} (ng/mL)	345.605	257.290	395.758	385.436	134.3 (118.5 – 152.2)	102.7 (90.1 – 117.0)	87.3 (76.1 – 100.2)	24.1

Table 6. Summary of Mean Pharmacokinetic Parameters of M1 Using a Four-Way Analysis Ln-transformed Data (N=25).

Parameter	Least Square Means				Ratio of Means (90% Confidence Interval)			Intra-subject Variability (%)
	A	B	C	D	A/B	C/D	A/C	
AUC_T (ng·h/mL)	1911.995	1281.228	1963.411	1873.206	149.2 (131.0 – 169.9)	104.8 (91.2 – 120.4)	97.4 (84.2 – 112.6)	25.0
AUC_{inf} (ng·h/mL)	2098.000	1563.723	2166.148	2044.404	134.2 (114.6 – 157.0)	106.0 (90.8 – 123.6)	96.9 (82.4 – 113.9)	27.7
C_{max} (ng/mL)	83.452	57.262	85.012	86.566	145.7 (128.0 – 166.0)	98.2 (85.7 – 112.5)	98.2 (85.0 – 113.4)	25.1

Safety: There were 93 non-serious adverse events during the conduct of the study. The occurrences of mild and moderate adverse events in each treatment are shown in table below. An Investigator judged each adverse event with respect to seriousness, severity, and causality. All adverse events were followed until resolution.

	Mild	Moderate
A: Test + Fed	27	8
B: Ref + Fed	17	2
C: Test +Fast	11	3
D: Ref + Fast	20	5

Conclusions: Based on four-way analysis, CIP-Tramadol ER and Ultram ER 300 mg did not show equivalent AUC after a singe dose for tramadol (90% CI 95.9%-131.9%). In addition, food had little effect on PK of CIP-tramadol ER 300 mg, consistent with previous findings, the confidence intervals for tramadol Cmax and AUC were slightly outside of the 80.00% to 125.00% range (90% CI: 76.1%-100.2% and 79.5%-111%, respectively). In contrast, Ultram ER had a more profound food effect. The two products were not equivalent under fed conditions (CIP-Tramadol ER was ~30-40% higher for C_{max} and AUC).

<u>Reviewer's Note:</u> The Sponsor repeated the BE study with a 2-way crossover study design (Study TRAMPK08.01, under fasting conditions for both test and reference drugs) and new results showed bioequivalence for test and reference products (see Section 4.2.2).

4.2.2 Study TRAMPK08.01 (PRACS R08-0197): An Open-Label, Single-Dose, Randomized, Two-Way, Relative Bioavailabilty Study of Cipher Tramadol ER Capsules 300 mg Versus Biovail Ultram® ER Tablets 300 mg, in Normal, Healthy Subjects, Under Fasting Conditions

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Study Period:	March 8, 2008 to March 17, 2008
Sample Analysis Period:	March 26, 2008 to April 16, 2008
Principle Investigator:	Gregory M. Haugen, M.D. PRACS Institute, Ltd. - Cetero Research, 4801 Amber Valley Parkway, Fargo, ND 58104, USA
Study Center:	PRACS Institute, Ltd. - Cetero Research, 4801 Amber Valley Parkway, Fargo, ND 58104, USA
Analytical Site:	(b) (4)

Objective: To evaluate the relative bioavailability of Tramadol ER Capsules 300 mg (Cipher Pharmaceuticals Limited) and Biovail Ultram® ER Tablets 300 mg (PriCara ™ /Ortho-McNeil Inc) in normal, healthy male and female subjects, under fasting conditions.

Study Design: This study was an open label, randomized, single dose, two-treatment, two-period, two-sequence crossover design. In each study period, a single 300 mg dose (l x 300 mg extended-release tablet or 1 x 300 mg extended-release capsule) was administered to all subjects following an overnight fast of at least 10 hours. The test formulation was Cipher Pharmaceuticals Inc.' s Tramdol ER 300 mg Capsules and the reference formulation was Ultram ER 300 mg Tablets. The subjects received the test product in one study period and the reference product in the other study period. There was a 7-day washout interval between treatments.

Blood samples were collected prior to dosing and at intervals over 48 hours after each dose. The plasma samples were sent to (b) (4) for determination of tramadol and its active metabolite, M1, concentrations. As per protocol, plasma samples from thirty (30) subjects who completed the study and did not experience any emesis within the 24-hour dosing interval were analyzed.

A total of 36 subjects (15 females and 21 males) were enrolled in the study as planned. All subjects were healthy non-smoking male and female volunteers between the ages of 18 and 55 years old (inclusive). 32 subjects completed the study and 4 subjects discontinued (Table 1). Three of them were due to adverse event (vomiting). All three were on Treatment A in Period I. The other one withdrew due to violation of protocol.

Summary demographic data for all 36 subjects are listed in Table 2. Thirty-three (91.7%) were White, 1 was Black or African American, 1 was Asian, and 1 was White Asian.

Table 1. Discontinued Subjects.

Subject No.	Reason for Dropout / Replacement	Period	Replaced?	Replaced With
11	Adverse event (vomiting). within 24 hours post-dosing interval.	Period I	No	N/A
20	Positive cotinine test	Period II check-in	No	N/A
22	Adverse event (vomiting) within 24 hours post-dosing interval.	Period I	No	N/A
36	Adverse event (vomiting) within 24 hours post-dosing interval.	Period I	No	N/A

Table 2. Summary of Mean Demographic Data (± SD).

	All Subjects (N=36)	Females (N=15)	Males (N=21)
Age	29.4 (±11.4)	34.7 (±13.8)	25.7 (±7.6)
Weight (lbs)	173.9 (±31.6)	146.1 (±20.7)	193.9 (±21.3)
Height (in.)	69.0 (±3.8)	65.3 (±1.9)	71.6 (±2.4)
BMI	25.5 (±3.0)	24.1 (±3.2)	26.6 (±2.4)

Test Articles:
Test Product (A): Tramadol ER Capsules, 300 mg, Lot No. 14B05

Reference Product (B): Biovail Ultram® ER Tablets, 300 mg, Lot No. P07J024

Sample Collection:
In each study period, blood samples were collected within 45 minutes prior to dosing (0 hour) and post-dose at study hours 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 11, 12, 12.5, 13, 13.5, 14, 14.5, 15, 16, 17, 18, 20, 24, 30, 36, and 48.

Sample Analysis: Samples were analyzed at the [redacted] (b) (4). Tramadol and O-desmethyl-tramadol in human plasma was analyzed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) method (Validation Method AP LC/MS/MS 308.100). The lower limit of quantitation (LLOQ) was 2.000/1.000 ng/mL and the upper limit of quantitation (ULOQ) was 500.0/250.0 ng/mL for tramadol/ O-desmethyltramadol. [redacted] (b) (4) was used as an internal standard. For statistical analysis, subject sample values below the lower limit of quantitation (BLQ) were reported as zero.

The long term freezer stability has been established for [redacted] (b) (4) days at -20°C ± 10°C in the First Addendum to the Method Validation and covers the required [redacted] (b) (4) days freezer storage period from [redacted] (b) (4) at -20°C ± 10°C. Plasma calibration curve standard and QC data demonstrated the acceptable performance of the assay method during the analysis of the study samples.

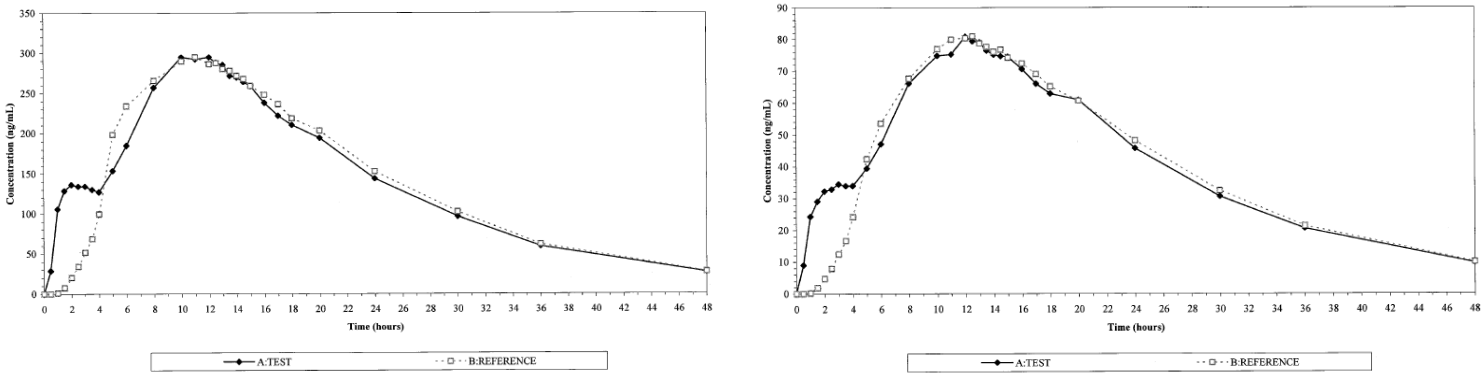
Plasma concentration data from 30 of 36 subjects were used in the statistical analysis for tramadol and O-desmethyltramadol (M1). Subjects 34 and 35 were not analyzed by the bioanalytical laboratory per the protocol. The following samples were not received for analysis (missing data points).

Subject	Period	Hour(s)
16	2	11.0
30	1	2.5, 30
30	2	15, 17, 18, 20

Pharmacokinetic Results:

PK Profiles

The mean plasma concentration-time profiles of tramadol and M1 metabolite from 30 subjects are shown in Figure 1 (a and b).



a. Tramadol b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations (0-48 hr) Following a Single Dose of 300-mg CIP-Tramadol ER Capsule (♦) or a 300-mg Ultram® ER Table (□) (N=30).

PK Comparison Between CIP-Tramadol ER and Ultram ER (300 mg)

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) from 30 subjects are summarized in Tables 3 and 4. C_{max} values for CIP-Tramadol ER in the tables refer to Peak 2. Results showed C_{max} and AUC for both tramadol and M1 were bioequivalent between CIP-Tramadol ER 300 capsules (Treatment A) and Ultram ER 300 mg tablets (Treatment B). Tmax and $T_{1/2}$ values were similar between test and reference.

Table 3. Relative Bioavailability for Tramadol after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER).

Test Product A vs. Reference Product B Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Tramadol N=30				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	6394.21	6383.52	100.17	(95.81, 104.72)
AUC_{0-inf} (ng-hr/mL)	6776.94	6808.59	99.54	(95.77, 103.45)
C_{max} (ng/mL)	307.71	320.85	95.90	(88.27, 104.20)

Non-transformed data:

PK Variable	Least Squares Mean			90% Confidence Interval	P-values for Product Effects	Power of ANOVA
	Test	Reference	% Ratio	(Lower Limit, Upper Limit)		
C_{max}	322.62	333.41	96.76	(88.29, 105.24)	0.5214	0.9721
AUC_{0-t}	6631.17	6594.44	100.56	(96.28, 104.83)	0.8262	1.0000
AUC_{0-inf}	7051.30	7043.48	100.11	(96.09, 104.13)	0.9635	1.0000
T_{max}	11.57	11.92	97.12	(83.72, 110.53)	0.7179	0.6881
Kel	0.0790	0.0866	91.24	(83.65, 98.83)	0.0638	0.9910
$T_{1/2}$	9.57	8.81	108.54	(98.53, 118.55)	0.1647	0.9066

Table 4. Relative Bioavailability for M1 after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER).

Test Product A vs. Reference Product B Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data M1 (O-Desmethyltramadol) N=30				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	1826.33	1790.09	102.02	(97.87, 106.36)
AUC_{0-inf} (ng-hr/mL)	1981.83	1944.83	101.90	(97.58, 106.42)
C_{max} (ng/mL)	80.38	82.16	97.83	(90.89, 105.31)

Non-transformed data:

PK Variable	Least Squares Mean			90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA
	Test	Reference	% Ratio			
C_{max}	86.00	90.24	95.30	(86.74, 103.86)	0.3582	0.9697
AUC_{0-t}	1934.27	1914.82	101.02	(96.94, 105.09)	0.6746	1.0000
AUC_{0-inf}	2097.52	2085.69	100.57	(96.9, 104.24)	0.7978	1.0000
T_{max}	12.67	13.67	92.68	(81.35, 104.02)	0.2814	0.8258
Kel	0.0703	0.0775	90.72	(83.18, 98.26)	0.0492	0.9916
$T_{1/2}$	10.65	9.83	108.36	(98.87, 117.85)	0.1517	0.9332

Because several plasma samples were missing for Subject 30 in both periods, the sample at Tmax was missing for Subject 16 in one of periods, and AUCinf could not be calculated for Subject 2 in one of periods, the reviewer recalculated 90% confidence intervals for the remaining 27 subjects to determine whether bioequivalence still held. The results showed that reference and test products were bioequivalent for AUC and Cmax for both tramadol and M1 (Tables 5 and 6).

Table 5. Relative Bioavailability for Tramadol after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER) (N=27).

	B	A	Ratio	90% CI Lower Level	90% CI Upper Level
	Geometric Means				
AUCt (ng*hr/mL)	6445.77	6346.607	98.46	94.45	102.64
AUCinf (ng*hr/mL)	6796.14	6736.87	99.13	95.17	103.25
Cmax (ng/mL)	330.47	302.21	91.45	85.17	98.19

Table 6. Relative Bioavailability for M1 after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER) (N=27).

	B	A	Ratio	90% CI Lower Level	90% CI Upper Level
	Geometric Means				
AUCt (ng*hr/mL)	1742.24	1749.48	100.42	96.47	104.52
AUCinf (ng*hr/mL)	1877.59	1904.72	101.44	96.93	106.17
Cmax (ng/mL)	81.00	77.13	95.22	88.43	102.53

Safety: Seventeen (17) subjects experienced a total of 45 adverse events (AEs) over the course of the study. The AEs were mild to moderate in severity including nausea and vomiting. One SAE was reported during the course of the study (Subject 7, Chondrosarcoma).

Conclusions: Based on the ln-transformed data, AUC and Cmax were equivalent between the Tramadol ER Capsules, 300 mg and Ultram® ER Tablets, 300 mg after a single dose for both analytes (tramadol and O-desmethyltramadol, M1), the 90% confidence intervals were within the 80-125% range.

4.2.3 Study TRAMPK.08.02 (PRACS R08-0364): A Open-Label, Multi-Dose, Randomized, Two-Way, Relative Bioavailability Study of Cipher Tramadol ER Capsules, 200 mg versus Ultram® ER Tablets 200 mg, in Normal, Healthy Subjects, under Fasting Steady State Conditions

Study Period:	**Period I:** April 15, 2008 - April 22, 2008 **Period II:** May 6, 2008 –May 13, 2008
Sample Analysis Period:	May 16, 2008 to June 04, 2008
Principle Investigator:	Gregory M. Haugen, M.D. PRACS Institute, Ltd. - Cetero Research, 4801 Amber Valley Parkway, Fargo, ND 58104, USA
Study Center:	PRACS Institute, Ltd. - Cetero Research, 4801 Amber Valley Parkway, Fargo, ND 58104, USA
Analytical Site:	(b) (4)

Objective: To evaluate the relative bioavailability of Tramadol ER Capsules 200 mg (Cipher Pharmaceuticals Inc.) versus the Biovail Ultram® ER Tablets 200 mg (PriCara™/Ortho-McNeil Inc.) after multiple-doses in healthy subjects under steady-state fasting conditions.

Study Design: This study was a multi-dose, randomized, two-period, two-sequence, two treatment, crossover relative bioavailability study conducted under steady-state fasting conditions. In each study period, a single 200 mg dose (1 x 200 mg extended-release tablet or capsule) was administered for 7 consecutive days to all subjects following an overnight fast of at least 10 hours. The test formulation was Cipher Pharmaceuticals Inc.'s Tramadol ER Capsules and the reference formulation was Biovail Ultram ER Tablets. The subjects received the test product in one study period and the reference product in the other study period. There was a 14-day washout interval between treatments.

Blood samples were collected prior to dosing on Days 1, 3, 4, 5, 6, and 7 and at intervals over 24 hours following the day 7 dose. The plasma samples were sent to (b) (4) for determination of tramadol and O-desmethyltramadol concentrations.

A total of 50 subjects (17 females and 33 males) were enrolled in the study as planned. All subjects were healthy non-smoking male and female volunteers between the ages of 18 and 55 years old (inclusive). 38 subjects completed the study and were included in PK and statistical analysis. Ten (10) subjects (Numbers 01, 02, 03, 12, 22, 26, 32, 33, 39 and 48) were withdrawn from the study during Period I and two (2) subjects (Numbers 17 and 24) were withdrawn from the study during Period II due to an adverse event (vomiting) (Table 1). Three subjects received Treatment A and 9 subjects received Treatment B.

Summary demographic data for all 50 subjects are listed in Table 2. In terms of race, 72% were White, 2% were White or African American, 8% were African American, 10% were American Indian or Alaskan Native subjects, and 8% were Hispanic subjects.

Table 1. Discontinued Subjects.

Subject No.	Reason for Dropout / Replacement	Period	Replaced?	Replaced With
01	Subject 01 was dropped per protocol on Period I day 1, post dose, due to adverse event (vomiting).	I	No	N/A
02	Subject 02 was dropped per protocol on Period I day 1, post dose, due to adverse event (vomiting).	I	No	N/A
03	Subject 03 was dropped per protocol on Period I day 3, post dose, due to adverse event (vomiting).	I	No	N/A
12	Subject 12 was dropped per protocol on Period I day 8, post dose, due to adverse event (vomiting).	I	No	N/A
17	Subject 17 was dropped per protocol on Period II day 22, post dose, due to adverse event (vomiting).	II	No	N/A
22	Subject 22 was dropped per protocol on Period I day 1, post dose, due to adverse event (vomiting).	I	No	N/A
24	Subject 24 was dropped per protocol on Period II day 28, post dose, due to adverse event (vomiting).	II	No	N/A
26	Subject 26 was dropped per protocol on Period I day 1, post dose, due to adverse event (vomiting).	I	No	N/A
32	Subject 32 was dropped per protocol on Period I day 1, post dose, due to adverse event (vomiting).	I	No	N/A
33	Subject 33 was dropped per protocol on Period I day 2, post dose, due to adverse event (vomiting).	I	No	N/A
39	Subject 39 was dropped per protocol on Period I day 1, post dose, due to adverse event (vomiting).	I	No	N/A
48	Subject 48 was dropped per protocol on Period I day 1, post dose, due to adverse event (vomiting).	I	No	N/A

Table 2. Summary of Mean Demographic Data (± SD).

	All Subjects (N=50)	Females (N=17)	Males (N=33)
Age	33.1 (±12.3)	37.8 (±13.5)	30.7 (±11.0)
Weight (lbs)	169.9 (±30.2)	149.2 (±26.1)	180.5 (±26.6)
Height (in.)	68.5 (±3.5)	65.1 (±2.5)	70.2 (±2.5)
BMI	25.4 (±3.4)	24.8 (±3.9)	25.7 (±3.1)

Test Articles:
Test Product (A): Tramadol ER Capsules, 200 mg (Manufactured by Galephar P.R. Inc.), Lot No: Lot# 8I04

Reference Product (B): Ultram® ER Tablets, 200 mg (Manufactured by Biovail Corporation), LOT P07L017

Sample Collection: In each study period, blood samples were collected within 45 minutes prior to dosing (0 hour) on days 1, 3, 4, 5, 6, and 7. Blood samples were collected post-dose on day 7 only at study hours 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 11, 12, 12.5, 13, 13.5, 14, 14.5, 15, 16, 17, 18, 20, and 24. The subjects were allowed to leave the clinical facility after the 24 hour blood sample collection.

Sample Analysis: Samples were analyzed at the [redacted] (b) (4). Tramadol and O-desmethyl-tramadol in human plasma was analyzed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) method (Validation Method AP LC/MS/MS 308.100). The lower limit of quantitation (LLOQ) was 2.000/1.000 ng/mL and the upper limit of quantitation (ULOQ) was 500.0/250.0 ng/mL for tramadol/ O-desmethyltramadol. (b) (4) [redacted] was used as an internal standard. For statistical analysis, subject sample values below the lower limit of quantitation (BLQ) were reported as zero.

The long term freezer stability has been established for [redacted] (b) (4) days at -20°C ± 10°C in the First Addendum to the Method Validation and covers the required [redacted] (b) (4) days freezer storage period from (b) (4) [redacted] at -20°C ± 10°C. Plasma calibration curve standard and QC data demonstrated the acceptable performance of the assay method during the analysis of the study samples.

Pharmacokinetic Results:

Steady-state Assessment
To assess the time that steady-state was reached, an ANOVA model containing factors for product, subject, period, day, and day*product was utilized to determine if the Helmert Contrasts could be performed on the test and reference products together. Since the term day*product was not significant at the 5% level, the analysis using the Helmert Contrasts were performed on the test and reference products together. An ANOVA model containing factors for product, subject, period, and day was utilized on Ln-transformed Cmin (ss) (Days 3, 4, 5, 6, and 7). With a 5%

significance level, it was determined that steady-state was reached on Day 4 for both tramadol and M1.

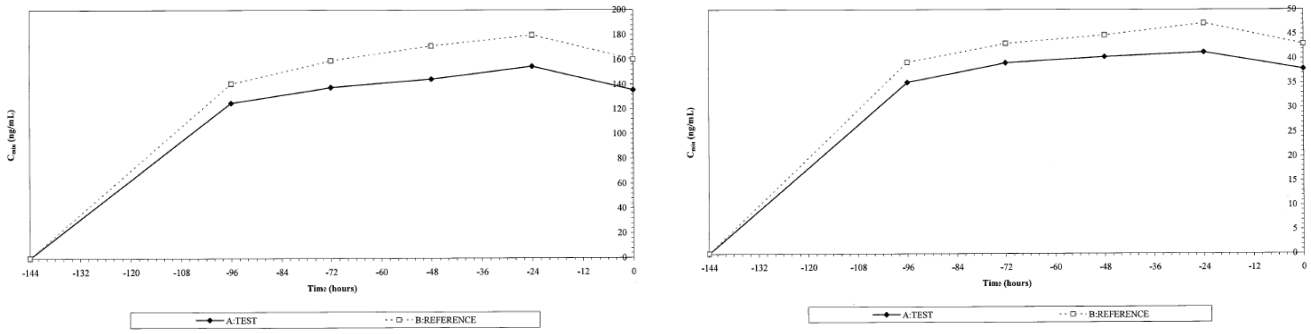
Through concentrations of tramadol and M1 were comparable from Day 3 through Day 7, suggesting that steady state was reached on Day 4 for both Tramadol ER and Ultram ER (Tables 3 and 4, Figure 1).

Table 3. Though Concentrations of Tramadol and M1 (ng/mL) on Days 3-7 Following Administration of Treatment A (Test).

	Day 3	Day 4	Day 5	Day 6	Day 7
Tramadol	125 ± 53	138 ± 47	144 ± 54	155 ± 59	136 ± 49
M1	35 ± 13	39 ± 14	40 ± 14	41 ± 14	38 ± 14

Table 4. Though Concentrations of Tramadol and M1 (ng/mL) on Days 3-7 Following Administration of Treatment B (Reference).

	Day 3	Day 4	Day 5	Day 6	Day 7
Tramadol	141 ± 62	159 ± 64	171 ± 76	180 ± 76	160 ± 58
M1	39 ± 16	43 ± 14	45 ± 17	47 ± 19	43 ± 17



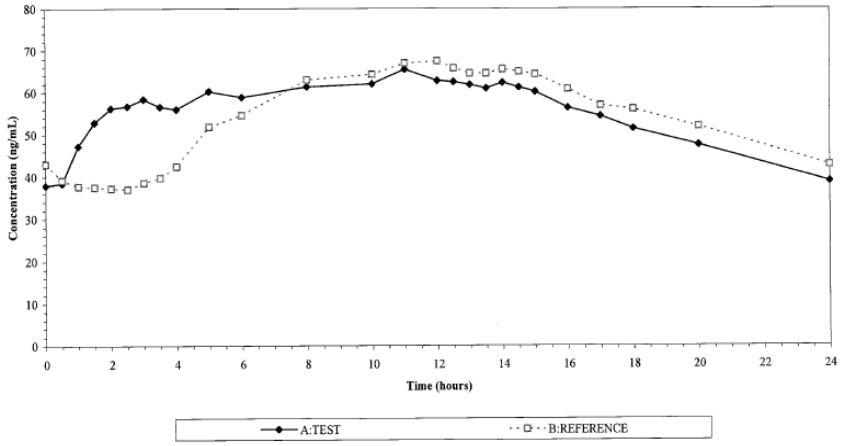
(a) Tramadol **(b) M1**

Figure 1. Mean Trough Plasma Tramadol (a) and M1 (b) Concentrations (0-24 hr) on Days 0-7 for 200-mg CIP-Tramadol ER Capsules QD (♦) or 200-mg Ultram® ER Tablets QD (□) (N=38).

PK Profiles

The mean plasma concentration-time profiles of tramadol and M1 metabolite from 38 subjects who completed both Periods I and II of the study are shown in Figure 1 (a and b). Mean PK parameters are shown in Tables 5 and 6.

(b) (4)



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations (0-24 hr) on Day 7 for 200-mg CIP-Tramadol ER Capsules QD (♦) or 200-mg Ultram® ER Tablets QD (□) (N=38).

Table 5. Mean PK Parameters (± SD) for Tramadol Following Administration of Treatment A (Test) and Treatment B (Reference) on Day 7 (N=38).

	Test (CIP-Tramadol ER)	Reference (Ultram ER)
AUCτ (ng*hr/mL)	5678 ± 1524	5563 ± 1713
Cmax (ng/mL)	332 ± 82	350 ± 107
Tmax (hr) **(Range)**	5.9 ± 3.9 (1.5-14)	10 ± 3 (0-15)
Cmin (ng/mL)	128 ± 50	125 ± 56
FLUX1	88 ± 17	101 ± 30
FLUX2	176 ± 64	219 ± 136

FLUX1 = [(Cmax $_{(SS)}$ - Cmin $_{ss}$)/Cav ss] * 100
FLUX2 = [(Cmax $_{(SS)}$ - Cmin $_{ss}$)/Cmin ss] * 100

Table 6. Mean PK Parameters (± SD) for M1 Following Administration of Treatment A (Test) and Treatment B (Reference) on Day 7 (N=38).

	Test (CIP-Tramadol ER)	Reference (Ultram ER)
AUCτ (ng*hr/mL)	1319 ± 443	1032 ± 520
Cmax (ng/mL)	70 ± 24	74 ± 30
Tmax (hr) **(Range)**	10.5 ± 3.9 (2-14.5)	13 ± 3.8 (0-18)
Cmin (ng/mL)	35 ± 13	33 ± 14
FLUX1	64 ± 14	76 ± 23
FLUX2	104 ± 33	136 ± 75

PK Comparison at Steady-State (Day 7)

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) from 38 subjects who completed both Period I and II are summarized in Tables 7 and 8.

Table 7. Relative Bioavailability for Tramadol at Steady State (on Day 7) (A: 200 mg CIP-Tramadol ER vs. B: 200 mg Ultram ER).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Tramadol N=38				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
$AUC_{0-\tau}$ (ss) (ng-hr/mL)	5504.67	5299.33	103.87	(97.36, 110.82)
$C_{max\ (ss)}$ (ng/mL)	322.74	334.96	96.35	(90.29, 102.83)
$C_{min\ (ss)}$ (ng/mL)	120.04	112.98	106.25	(96.25, 117.29)

Table 8. Relative Bioavailability for M1 at Steady State (on Day 7) (A: 200 mg CIP-Tramadol ER vs. B: 200 mg Ultram ER).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data O-desmethyltramadol N=38				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
$AUC_{0-\tau}$ (ss) (ng-hr/mL)	1229.02	1191.10	103.18	(97.66, 109.01)
$C_{max\ (ss)}$ (ng/mL)	65.75	67.53	97.36	(92.08, 102.94)
$C_{min\ (ss)}$ (ng/mL)	32.72	29.93	109.31	(100.82,118.52)

Safety: Thirty (30) subjects experienced a total of 131 adverse events (AEs) over the course of the study. The AEs were mild to moderate in intensity. No SAEs were reported.

Table 9. Disposition for All Dosed Subjects by Treatment.

	Treatment	
	A	B
Number of subjects who received study treatment	43	47
Number of subjects who withdrew consent	0	0
Number of subjects who withdrew due to AEs	0	0
Number of subjects who were dropped per Investigator due to AEs*	5	9
Number of subjects with AEs	18	25
Number of total number of AEs	50	81

Treatment A: Tramadol ER Capsules 200 mg (Lot No.: 8I04)
Treatment B: ULTRAM® ER Tablets 200 mg (Lot No.: P07L017)
*Totals represent all subjects dosed with the specific treatment.

Conclusions: Based on the ln-transformed data, AUC and Cmax were equivalent between the Tramadol ER Capsules, 200 mg and Ultram® ER Tablets, 200 mg on Day 7 for both analytes (tramadol and O-desmethyltramadol, M1), the 90% confidence intervals were within the 80-125% range. In addition, Cmin values were also equivalent between the two products.

4.2 OCP Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-370**	**Brand Name**	**TRADENAME ER**
OCPB Division (I, II, III)	**DCP2**	**Generic Name**	**Tramadol Hydrochloride**
Medical Division	**DAARP**	**Drug Class**	**Centrally Acting Analgesic**
OCPB Reviewer	**Lei Zhang, Ph.D.**	**Indication(s)**	
OCPB Team Leader	**Suresh Doddapaneni, Ph.D**	**Dosage Form**	**Extended Release Capsules, 100, 200, and 300 mg**
		Dosing Regimen	
Date of Submission		**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review		**Sponsor**	**Cipher Pharmaceuticals, Ltd.**
PDUFA Due Date		**Priority Classification**	**New Formulation (5-S)**
Division Due Date			**IND** (b) (4) 505 b(2); References: Ultram (NDA 20-281) and Ultram ER (NDA 21-692) Related NDA: (b) (4)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
Human PK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**			
multiple dose:	**X**			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**2**	**2**	**Study TRAMPK.01.03 (02-406) (200 and 300 mg, fasting)- *Reviewed under NDA* (b) (4) Study TRAMPK.02.02 (02-556) (100 and 300 mg, fasting) - *Reviewed under NDA* (b) (4)**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**3**	**2**	**Study TRAMPK01.01 (02-403) (200 mg vs. Ultram, fasting state, single dose)-*Reviewed under NDA*** (b) (4) **Study TRAMPK01.02 (02-404) (200 mg vs. Ultram steady state) (Study was repeated and not included in analysis)** **Study TRAMPK02.02 (02-549) (200 mg vs. Ultram steady state) -*Reviewed under NDA*** (b) (4)
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**4**	**3**	**Study TRAMPK.07.01 (300 mg vs. 300 mg Ultram ER, single dose, pilot study)** **Study TRAMPK.07.04 (300 mg vs. 300 mg Ultram ER, single dose, fasting and fed conditions)** **Study TRAMPK.08.01 (300 mg vs. 300 mg Ultram ER, single dose, fasting conditions)** **Study TRAMPK.08.02 (200 mg vs. 200 mg Ultram ER, steady state)**
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**2**	**2**	**1. Study TRAMPK.01.04 (02-405) (300 mg, single dose) -*Reviewed under NDA*** (b) (4) **2. Study TRAMPK.07.04 (300 mg, single dose)**
Dissolution:	**X**			(b) (4) **If IVIVC is established, acceptance criteria will be determined based on IVIVC**

(IVIVC):				**Report is not submitted**
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Comparative Dissolution Study report (Study LES-096)	**X**	**1**	**1**	**-100 vs 200 vs 300 mg CIP-Tramadol ER capsules -100 CIP-Tramadol ER vs 100 Ultram ER -200 CIP-Tramadol ER vs 200 Ultram ER -300 CIP-Tramadol ER vs 300 Ultram ER**
Pediatric development plan	**X**	**1**	**1**	
Literature References	**X**	**1**	**1**	
Total Number of Studies		**13**	**6 (under NDA 22-370) 5 (under NDA** (b) (4)	

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?	**X**	(b) (4) you have elected to support your NDA with reliance upon the Agency's previous determination of safety and efficacy of Ultram ER (N 21-692), and demonstration of bioequivalence of your product to Ultram ER tablets. However, data from the two new submitted pharmacokinetic studies (TRAMPK.07.01 and TRAMPK.07.04) assessed bioequivalence only between the 300 mg strengths of your product and Ultram ER Tablets. Data demonstrating a similar link between the 200 mg and 100 mg strengths of your product and Ultram ER Tablets were not submitted. This information is necessary, given your current regulatory approach towards NDA approval. Provide bioequivalence data comparing the 100 mg and 200 mg strengths of your product and Ultram ER Tablets, and/or a scientific rationale demonstrating the link between the 200 mg and 100 mg strengths of the two products
QBR questions (key issues to be considered)	• **What is PK profile of 100, 200 and 300 mg CIP-TRAMADOL ER capsules? Is PK dose proportional?** • **How does exposure of the CIP-TRAMADOL ER capsules compare to Ultram or Ultram ER at steady state for both tramadol and O-desmethylated M1 metabolite at equivalent doses?** • **Is there a food effect (done with 300 mg capsules)?** • **Does PK of the new CIP-TRAMADOL ER capsule formulation support the proposed indication?** • **Is there an alcohol interaction?**	
Other comments or information not included above	**This is a 505 b(2) application. The Sponsor submitted additional dissolution and bioequivalence data during the filing to support bioequivalence of their 100 and 200 mg capsules to Ultram ER tablets.**	
Primary reviewer Signature and Date	**Lei Zhang**	
Secondary reviewer Signature and Date	**Suresh Doddapaneni**	

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

/s/

Lei K Zhang
12/2/2008 03:22:44 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
12/2/2008 03:57:51 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA	(b) (4)
Submission Dates	7/3/2006; 8/11/2006; 10/12/2006; 2/21/2007
Brand Name	CIP-TRAMADOL ER
Generic Name	Tramadol Hydrochloride
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Applicant	Cipher Pharmaceuticals, Ltd.
Relevant IND	IND (b) (4)
Type of Submission; Code	505 (b)(2); 5S
Reference Listed Drug	Ultram (Immediate Release), Ortho McNeil Pharmaceuticals, Inc. (NDA 20-281)
Formulation; Strength(s)	Extended Release Capsules; 100, 200, and 300 mg
Indication	Management of moderate to moderately severe chronic pain in adults
Proposed Dosing Regimen	(b) (4)

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

This NDA is a 505 (b)(2) application for a new extended-release (ER) once-a-day product of tramadol hydrochloride capsules, CIP-Tramadol ER. The reference product is Ultram® (tramadol hydrochloride tablets), an immediate release product that is marketed under approved NDA 20-281. Besides Ultram®, there is one approved once-a-day extended-release formulation of tramadol HCl (Ultram ER tablets, NDA 21-692, approved in September 2005).

The proposed indication for CIP-Tramadol ER is for the management of moderate to moderately severe chronic pain. This indication is the same as Ultram® except that Ultram® also manages acute pain that requires quick relief. There are three dosage strengths: 100, 200 and 300 mg capsules. The intended dosing regimen is 100 to 300 mg once daily titrate to effect.

The Sponsor conducted 3 double-blinded, placebo-controlled studies (b) (4) and additional open-label study and double-blinded study to support safety. Six pharmacokinetic studies were conducted to characterize the PK performance of the new ER formulation.

1.1 Recommendations

From a Clinical Pharmacology perspective, the Sponsor has adequately characterized the pharmacokinetic performance of this new extended-release formulation. The application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding language in the package insert.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics (CPB) Findings

This NDA submission is for a change in formulation from the currently marketed immediate release (IR) to extended release (ER) formulation, and consequently administration of dose from once every 4-6 hours (QID) to once-a-day (QD) regimen. The primary focus of the Clinical Pharmacology review was to determine whether the following aspects were studied:

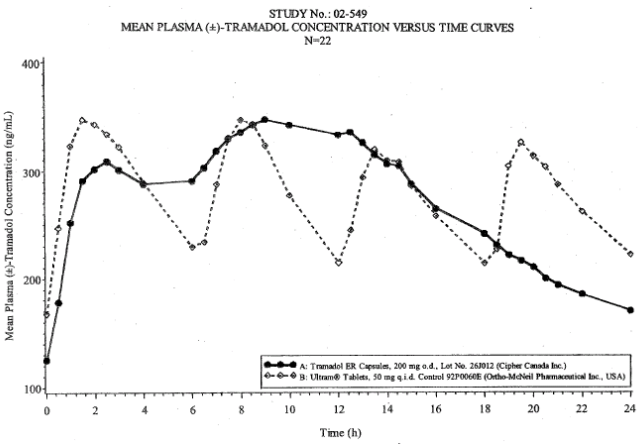
(1) The drug product meets the extended release claims made for it.
(2) Dose proportionality
(3) The drug product's steady-state performance relative to a currently marketed IR product
(4) Effect of food on the formulation
(5) Effect of alcohol on the formulation
(6) *In vitro* dissolution methodology and acceptance criterion

To support human PK and biopharmaceutics requirement, CIP-Tramadol ER was studied in a total of 6 human PK studies. Among these studies, 5 studies were reviewed in detail. These studies assessed bioequivalence of CIP-Tramadol ER compared to Ultram IR after single and multiple doses, dose proportionality, and food effect. No exposure response data was submitted in the NDA. The Sponsor is relying on Agency's previous findings for Ultram to construct their labeling for special populations (e.g., renal and hepatic impairment patients, elderly patients) and drug-drug interaction.

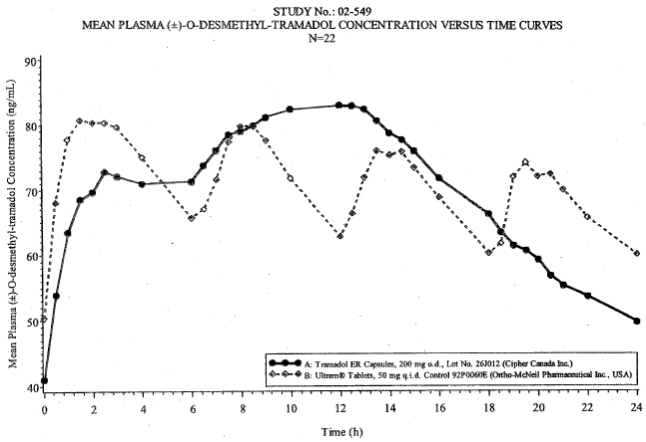
The Sponsor did not submit report on *in vitro* and *in vivo* correlation for the formulation (b) (4) Dissolution method and specification were proposed based on actual performance of capsule batches used in clinical and bioavailability studies. Interaction of the ER formulation with alcohol was investigated by the *in vitro* dissolution method. *In vitro* dissolution methodology and alcohol interaction data were reviewed in conjunction with the CMC Reviewer, Dr. Danae Christodoulou.

The extended-release capsule dosage form contains a tramadol HCI immediate release (IR) tablet and tramadol hydrochloride (HCI) ER beads. The *in vivo* concentration-time profiles for tramadol and its metabolite, M1, showed that there was a lower Cmax peak (Peak 1) at around 2 hours and a higher Cmax peak (Peak 2) at around 10-12 hours. Peak 1 mainly represents the release of tramadol from the IR tablet and Peak 2 mainly represents the release of tramadol from the ER beads.

Relative Bioavailability to Ultram (IR product) (Study 02-549)
Compared to steady-state PK profile of Ultram IR (50 mg QID), CIP-Tramadol ER (200 mg QD) showed equivalent C_{max} (Peak 2) and AUC (Figure 1 and Tables 1 and 2) for both tramadol and M1. However, C_{min} of tramadol and M1 for CIP-Tramadol ER was ~ 18-25% lower than Ultram IR at steady-state. Lower concentrations of tramadol and M1 were observed between 18 and 24 hours following CIP-Tramadol ER once a day dosing compared to Ultram every 6 hour dosing.



a. Tramadol



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations on Day 7 for 200-mg CIP-Tramadol ER Tablets QD and 50-mg Ultram® Tablets Q6h.

Table 1. Relative Bioavailability for Tramadol at Steady State (on Day 7) (A: 200 mg Tramadol ER vs. B: Ultram).

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCtau (ng·h/mL)	6392.2 6600.0 (25)	6514.0 6712.9 (26)	98.13	94.83 – 101.55	7
Cmax (ng/mL)	355.9 363.8 (21)	368.9 378.9 (24)	96.47	92.97 – 100.10	7
Cmin (ng/mL)	154.7 164.9 (35)	205.0 212.9 (29)	75.45	69.64 – 81.73	15

Table 2. Relative Bioavailability for M1 at Steady State (on Day 7) (A: 200 mg Tramadol ER vs. B: Ultram).

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCtau (ng·h/mL)	1603.8 1683.2 (31)	1617.7 1703.8 (32)	99.14	95.46 – 102.96	7
Cmax (ng/mL)	83.0 87.4 (32)	81.0 85.4 (31)	102.48	98.10 – 107.04	8
Cmin (ng/mL)	49.0 51.5 (32)	59.4 62.5 (33)	82.47	77.00 – 88.32	13

Dose Proportionality (Studies 02-406 and 02-556)

CIP-Tramadol ER is intended to be administered at doses ranging from 100 mg to 300 mg per day. Exposure of tramadol and M1 from 100, 200 and 300 mg capsules were dose proportional in terms of total AUC and Cmax (Peak 2) (Figures 2 and 3). Because the IR tablet doses in 100, 200 and 300 mg ER capsules are 25, 50 and 50 mg, respectively, Peak 1 and early AUC (e.g., $AUC_{0\text{-}4\ hour}$) were not dose proportional between 100 and 300 mg capsules, and 200 and 300 mg capsules, respectively. The clinical relevance of non-dose proportional for the early AUC between 100 and 300 mg, 200 and 300 mg capsules is not clear. The labeling needs to state that 100, 200, and 300 mg capsules are not interchangeable.

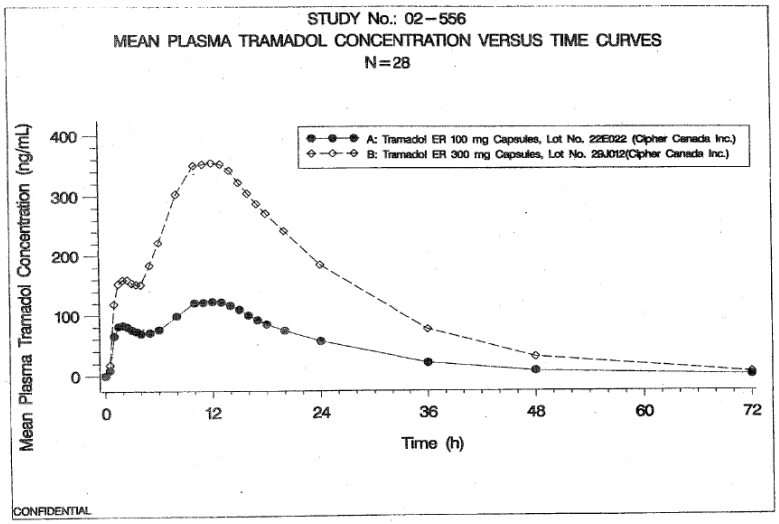


Figure 2. Mean Plasma Tramadol Concentrations Following Administration of 100 mg (●) and 300 mg (◊) ER Capsules.

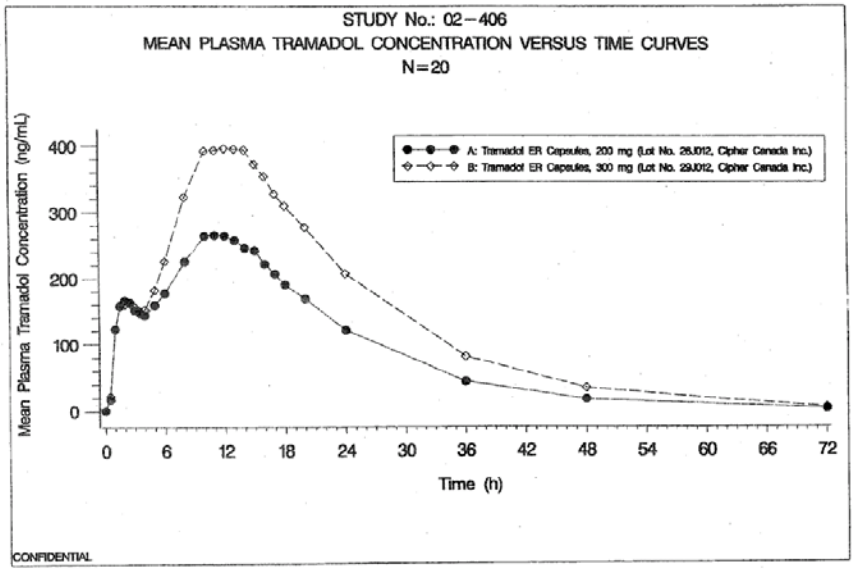


Figure 3. Mean Plasma Tramadol Concentrations Following Administration of 200 mg (●) and 300 mg (◊) ER Capsules.

Food Effect (Study 02-405)

Food does not affect C_{max} (Peaks 1 and 2) or AUC_{inf} following 300 mg CIP-Tramadol ER dosing, however, the absorption of tramadol slows down in the presence of food, there is a 1 hour and a 30 min delay in T_{max} (Peak 1) and T_{max} (Peak 2), respectively (Figure 4). In addition, AUC(0-4hr) decreased 31% in the presence of a high fat meal. Similar trend was observed for M1.

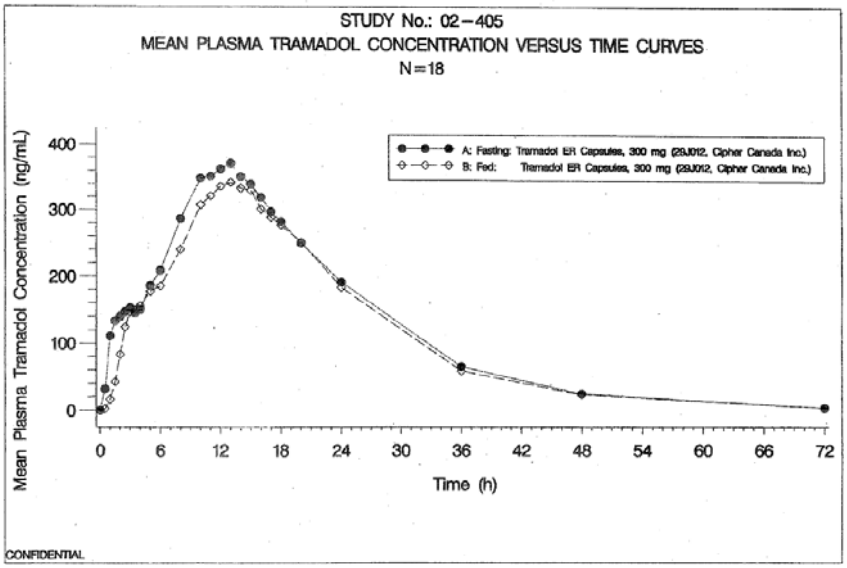


Figure 4. Mean Plasma Tramadol Concentrations under Fasting (●) and Fed (◊) Conditions.

Dissolution

The proposed dissolution method (Table 3) is adequate.

Table 3. Dissolution Method.

Parameters	**Value**
Apparatus	(b) (4)
Dissolution medium	
Dissolution medium volume	
Dissolution medium temperature	
Rotation speed	
HPLC analysis	
Sampling time	

However, the following acceptance criteria are recommended by this Reviewer. A final decision on this is pending from ONDQA.

Time	Agency's Revised Proposed Dissolution limits
1 hours	(b) (4)
4 hours	
8 hours	
16 hours	

Effect of Alcohol

The effect of alcohol on capsule dissolution performance was determined to evaluate the potential for dose dumping in the presence of alcohol. The rate of tramadol release increased in proportion to the ethyl alcohol concentrations (b) (4) so that when (b) (4) alcohol was used, complete dissolution occurred in approximately 4 hours. The effect of alcohol on the release of tramadol is similar for both 100 and 300 mg capsules (Figure 5). The effect of alcohol is anticipated because the polymer coating for the ER beads is soluble in ethanol. An *in vivo* evaluation study to determine the alcohol effect on PK of CIP-Tramadol ER is not required because previous tramadol product package inserts contain alcohol warning regardless of the formulation. For this particular product, it is anticipated that ER characteristics will be lost in the presence of alcohol

(b) (4)

Figure 5. CIP-Tramadol ER Dissolution Profile in the Presence of Alcohol (Above: 100 mg capsule; Botton: 300 mg capsule).

An OCP briefing (Optional Inter-Divisional Level) was held on March 19, 2007.

2 QUESTION BASED REVIEW

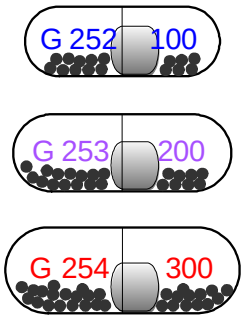
Reviewer's Note: Because this is not a new molecular entity, question-based review will focus on the aspects specific for the new formulation.

CIP-Tramadol ER was also referred as Tramadol ER in the review.

2.1 General Attributes

2.1.1 What are the highlights of the formulation of the drug product?

CIP- TRAMADOL ER CAPSULES are sustained release capsules containing tramadol hydrochloride (HCI) ER beads and a tramadol HCl immediate release (IR) tablet (Figure 2.1.1.1). The ER beads are manufactured by (b) (4)



#1 Capsule: 6.91 x 19.4 mm
(IR tablet: 25 mg)

#0 Capsule: 7.64 x 21.7 mm
(IR tablet: 50 mg)

#00 Capsule: 8.53 x 23.3 mm
(IR tablet: 50 mg)

Capsule Strength	IR Tablet Strength	ER Beads Strength
100 mg	25 mg	75 mg
200 mg	50 mg	150 mg
300 mg	50 mg	250 mg

Figure 2.1.1.1. Schematic Graph of 100, 200 and 300 mg Capsules.

Dose strengths are 100, 200 and 300 mg (tramadol hydrochloride). The ratio of the amount of tramadol HCl in the IR tablet and the ER beads are 1/3 for 100 and 200 mg capsules, and 1/5 for 300 mg capsules. For 100 mg capsules, the IR tablet contains 25 mg tramadol and ER beads contain 75 mg tramadol (See Figure 2.1.1.1 above). For 200 mg and 300 mg capsules, the IR tablet contains 50 mg tramadol. Therefore, the tramadol content in IR tablet and ER beads is proportional (1:3) between 100 and 200 mg capsules, and 300 mg capsules have more tramadol in ER beads (1:5, IR tablet: ER beads).

The inactive components for the capsules are not proportional for 100, 200 and 300 mg capsules (See Section 2.5.1).

2.1.2 What is the proposed mechanism of drug action and therapeutic indication?

Tramadol HCl is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite (M1) to μ-opioid receptors. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

The proposed indication for CIP-Tramadol ER is for the management of moderate to moderately severe chronic pain. This indication is the same as Ultram® except that Ultram® also manages acute pain that requires quick relief.

2.1.3 What are the proposed dosage recommendations and route of administration of CIP-Tramadol ER for the proposed indication?

CIP-Tramadol ER is taken orally.

The following language is proposed by the sponsor regarding dosage and administration:

(b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the clinical pharmacology and clinical studies used to support dosing or claims?

To support human PK and biopharmaceutics requirement, CIP-Tramadol ER was studied in a total of 6 human PK studies. Five studies were reviewed in detail. These studies assessed bioequivalence of CIP-Tramadol ER compared to Ultram IR after single and multiple doses, dose proportionality, and food effect.

With regard to the clinical component of the application, the Sponsor submitted 3 double-blinded, placebo-controlled studies (b) (4) (Study TRAMCT.02.01, TRAMCT.02.02 and TRAMCT.02.04), and additional open-label study (Study TRAMCT.02.03) and double-blinded study (Study TRAMCT.02.05) to support safety.

2.2.2 (b) (4)

Studies TRAMCT.02.01, TRAMCT.02.02 and TRAMCT.02.04 are pivotal trials.

All studies were conducted in osteoarthritis (OA) patients with pain in the hip or knee. The trials incorporated two pain-related efficacy measures. The Western Ontario and McMaster Universities (WOMAC) pain subscale was the primary efficacy measure, and the 100 mm Visual Analogue Scales (VAS) was a secondary measure for pain.

(b) (4)

Studies 01 and 02 are replicated trials. The following are the highlights of the studies:

- Randomized, double-blind, placebo-controlled, parallel group studies
- 12 weeks duration
  - Includes 2 week titration to fixed dose
- Patients with OA of hip and knee
  - Study 01: N=433 (>105/group) in US and Mexico
  - Study 02: N=450 (>110/group) in Canada and Argentina
- Medications:
  - Placebo QD
  - Tramadol ER 100, 200, and 300 mg QD
- Primary endpoint:
  - Change in mean WOMAC Pain score from baseline
- Secondary endpoints:
  - Change from BL in
    - mean VAS (100 mm) pain score
    - WOMAC Function score
  - Patient Global Assessment at study end
  - Responder rates

Study 04 was a long-term, double-blind, placebo-controlled safety trial. (b) (4)

- Randomized, double-blind, placebo-controlled
- 12 month duration
  - 12-week interim analysis (b) (4)

- Patients with OA of hip and knee
    - N = 856 (643 TRAM and 213 Placebo) in US and Canada (60 sites)
- Medications:
    - Placebo QD
    - Tramadol ER 300 mg QD
- Primary endpoint:
    - Change in mean WOMAC Pain score from baseline
- Secondary endpoints:
    - Week 2 WOMAC Pain
    - WOMAC Function and Total
    - Pain intensity Study Joint
    - Subject global assessment (GA) for OA and Medication
    - Investigator GA

(b) (4)

In terms of safety, no new safety signal was identified with CIP-Tramadol ER compared to other tramadol products.

Full details regarding (b) (4) safety assessment for this product can be found in Dr. Keith Burkhart (Medical Reviewer) and Dr. Joan Buenconsejo (Statistical Reviewer)'s reviews.

2.2.3 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Tramadol and its active metabolite, M1 (O-desmethyltramadol), were measured in human plasma. Please refer to Section 2.6 Analysis for analytical details.

2.2.4 What is exposure-response relationship of CIP-Tramadol ER in terms of efficacy and safety?

Exposure-response relationship of CIP-Tramadol ER in terms of efficacy and safety has not been studied by the Sponsor.

2.2.5 What are the PK characteristics of CIP-Tramadol ER?

2.2.5.1 What are single dose and multiple dose PK parameters of CIP-Tramadol ER?

Single Dose (100, 200 and 300 mg)

Table 2.2.5.1.1. Summary of PK Parameters (Mean ± SD) for Tramadol and M1 after Single Dose.

	Tramadol			M1		
	100 mg (N=27)	**200 mg (N=14)**	**300 mg (N=23)**	**100 mg (N=27)**	**200 mg (N=14)**	**300 mg (N=23)**
Cmax (Peak 2) (ng/mL)	125 ± 32	285 ± 89	379 ± 94	36 ± 11	62 ± 19	97 ± 35
AUCinf (ng·h/mL)	2776 ± 1005	6226 ± 1755	9053 ± 2952	878 ± 271	1548 ± 488	2569 ± 931
Tmax (Peak 2) (h)	11 ± 1.6	11 ± 1.6	12 ± 1.5	14 ± 1.8	13 ± 2.1	13 ± 2.5
T1/2 (h)	8.0 ± 1.5	8.5 ± 1.3	9.1 ± 1.7	8.3 ± 1.6	9.1 ± 1.4	9.7 ± 1.8

Reviewer's Note: Data for 100 and 300 mg were cited from Study 556, and data for 200 mg were cited from Study 406 (N=20). Data for subjects who vomited were excluded.

Multiple Doses (200 mg)

Table 2.2.5.1.2. Summary of PK Parameters (Mean ± SD) for Tramadol and M1 after Multiple Doses (200 mg QD) (Data were cited from Study 549).

N = 22	**Tramadol**	**M1**
Cmax (ng/mL)	364 ± 78	87 ± 28
Cmin (ng/mL)	165 ± 57	52 ± 17
Tmax (h)	9.7 ± 1.7	11 ± 2.4
AUCtau (ng.h/mL)	6600 ± 1658	1683 ± 518

2.2.5.2 What are the ADME (absorption, distribution, metabolism and elimination) characteristics of CIP-Tramadol ER?

Because CIP-Tramadol ER contains the same active moiety as the currently marketed immediate release (IR) drug product, the drug substance itself has a similar distribution and metabolism profile as tramadol IR products. The ER formulation has the most impact on absorption and elimination profile of the drug product which is indicative of a rate controlled or extended-release product.

Absorption

Because of both IR tablet and ER beads in the capsule, the PK profile of CIP-Tramadol ER shows 2 peaks for both tramadol and M1, one peak with lower Cmax (Peak 1) occurs about 2 hour post-dosing (mainly release of tramadol from the IR tablet) and a higher Cmax peak (Peaks 2) occurs about 10-12 hours post-dosing (mainly release of tramadol from the ER beads) (Figure 2.2.5.2.1).

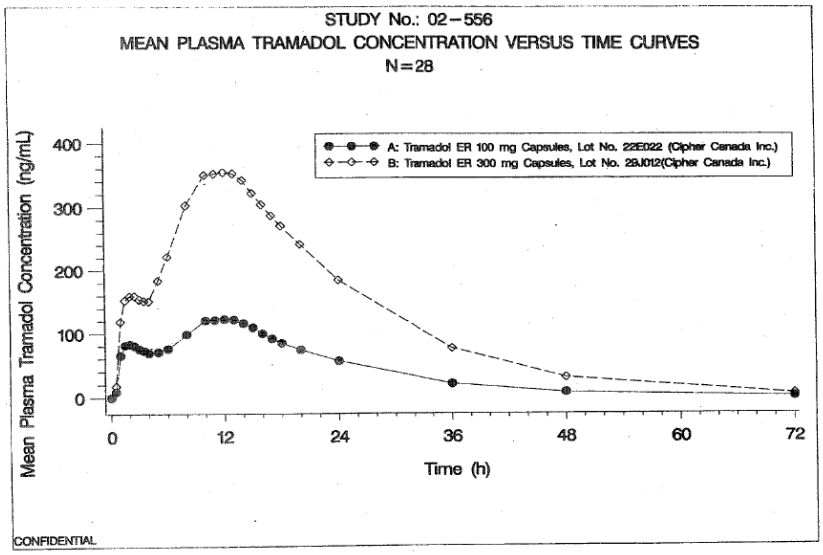


Figure 2.2.5.2.1. Mean Plasma Tramadol Concentrations Following Administration of 100 mg (●) and 300 mg (◊) ER Capsules.

Distribution (Cited from Ultram Labeling)

The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism

Tramadol is mainly metabolized by CYP2D6 and CYP3A4. The formation of the active metabolite, M1, is mediated by CYP2D6, thus susceptible to polymorphism and inhibition.

Elimination

The mean terminal plasma elimination half-lives of tramadol and M1 after administration of CIP-Tramadol ER are approximately 8-9 hours, similar to that of Ultram.

2.2.5.3 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

CIP-Tramadol ER is intended to be administered at doses ranging from 100 mg to 300 mg per day. Dose proportionality was evaluated in two single-dose studies (Study 406 and Study 556) in which one 100-mg, 200-mg, and 300-mg capsules were administered under fasting conditions. PK parameters for tramadol and M1 at different doses are listed in Tables 2.2.5.1.1. Dose corrected pharmacokinetic data indicated that AUC_{inf} and C_{max} (Peak 2) of tramadol and M1 increased proportionally with dose within the investigated dose range (Tables 2.2.5.3.1 and 2.2.5.3.2).

Table 2.2.5.3.1. AUC and Cmax (Peak 2) Comparison for Tramadol Excluding PK data from 6 Emesis Incidences (Dose-Normalized) (A: 100 mg vs. B: 300 mg).

	Ratio	90% CI lower	90% CI upper
AUCt	89.28	88.31	97.06
AUCinf	89.82	88.84	97.66
Cmax (Peak 2)	96.31	95.15	105.7

Table 2.2.5.3.2. AUC and Cmax (Peak 2) Comparison for Tramadol Excluding PK data from 21 Emesis Incidences (Dose-Normalized) (A: 200 mg vs. B: 300 mg).

	Ratio	90% CI lower	90% CI upper
AUCt	93.42	86.86	100.49
AUCi	93.52	87.15	100.36
Cmax (Peak 2)	96.38	89.34	103.98

2.2.6 What is the relative bioavailability of CIP-Tramadol ER vs. Ultram following single and multiple doses?

Single Dose

After a single daily dose of CIP-Tramadol ER 200 mg capsules and Ultram® 50 mg Tablets (Q6h) under fasting conditions, the 90% confidence intervals (CIs) of geometric mean ratio (GMR) (CIP-Tramadol ER/Ultram) of $AUC_{0\text{-}inf}$ and C_{max} for tramadol and its active metabolite, M1, were within 80.00% to 125.00% boundary for bioequivalence (Table 2.2.6.1).

Table 2.2.6.1. AUC and Cmax Comparison for Tramadol and M1 Excluding PK data from 5 Emesis Incidences (A: 200 mg CIP-Tramadol ER vs. B: Ultram).

	A	B		90% CI	90% CI
	Geometric Mean		Ratio	lower	upper
	Tramadol				
AUCt (ng*h/mL)	5551	5999	92.53	88.11	97.17
AUCi (ng*h/mL)	5616	6036	93.04	88.63	97.68
Cmax (ng/mL)	280.1	309.7	90.45	83.82	97.61
	M1				
AUCt (ng*h/mL)	1782	1893	94.15	90.80	97.63
AUCi (ng*h/mL)	1827	1932	94.57	91.27	98.00
Cmax (ng/mL)	80.7	87.3	92.38	86.52	98.64

Multiple Dose

At steady state, the 90% CIs of geometric mean ratio (GMR) (CIP-Tramadol ER/Ultram) of AUC_{τ} and C_{max} for tramadol and M1 were within 80.00% to 125.00% boundary for equivalence (Tables 2.2.6.2 and 2.2.6.3). The lower limit of 90% CI of test/reference ratio of Cmin,ss for tramadol and M1 are lower than 80% (69.64% and 77.00%, respectively).

Table 2.2.6.2. Summary of PK Result Comparison for Tramadol at Steady State (on Day 7) (A: 200 mg Tramadol ER vs. B: Ultram).

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCtau (ng·h/mL)	6392.2 6600.0 (25)	6514.0 6712.9 (26)	98.13	94.83 – 101.55	7
Cmax (ng/mL)	355.9 363.8 (21)	368.9 378.9 (24)	96.47	92.97 – 100.10	7
Cmin (ng/mL)	154.7 164.9 (35)	205.0 212.9 (29)	75.45	69.64 – 81.73	15
Tmax [a] (h)	9.70 (18)	6.98 (68)		-	
DF [a] (%)	75.33 (29)	60.56 (17)		-	

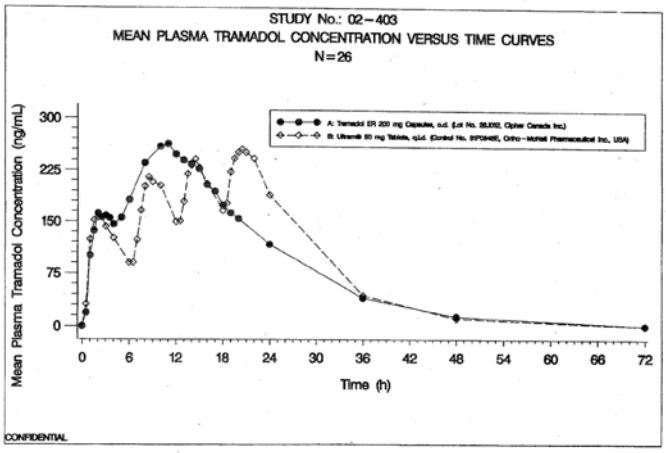
[a] Presented as arithmetic mean (CV%) only.

Table 2.2.6.3. Summary of PK Result Comparison for M1 at Steady State (on Day 7) (A: 200 mg Tramadol ER vs. B: Ultram).

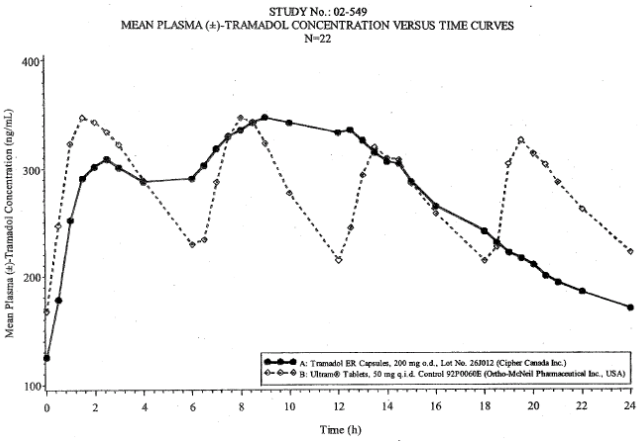
Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCtau (ng·h/mL)	1603.8 1683.2 (31)	1617.7 1703.8 (32)	99.14	95.46 – 102.96	7
Cmax (ng/mL)	83.0 87.4 (32)	81.0 85.4 (31)	102.48	98.10 – 107.04	8
Cmin (ng/mL)	49.0 51.5 (32)	59.4 62.5 (33)	82.47	77.00 – 88.32	13
Tmax [a] (h)	10.84 (22)	6.73 (71)		-	
DF [a] (%)	50.60 (33)	32.20 (23)		-	

[a] Presented as arithmetic mean (CV%) only.

PK profiles of tramadol following CIP-Tramadol ER vs. Ultram dosing are different (Figure 2.2.6.1). Low concentrations of tramadol and M1 (not shown) were observed in terminal phase (18-24 hr) following ER QD dosing compared to Ultram QID dosing.



a. Single-Dose



b. Multiple-Dose

Figure 2.2.6.1. Mean Plasma Tramadol Concentrations on Day 1 (a) and Day 7 (b) for 200-mg CIP-Tramadol ER Tablets QD and 50-mg Ultram® Tablets Q6h.

2.3 Intrinsic Factors

Not Applicable. The Sponsor did not conduct new studies.

2.4 Extrinsic Factors

Not Applicable. The Sponsor did not conduct new studies.

2.5 General Biopharmaceutics

2.5.1 What is formulation (quantitative composition) of CIP-Tramadol ER 100, 200 and 300 mg capsules?

CIP- TRAMADOL ER capsules are sustained release capsules containing tramadol hydrochloride (HCI) ER beads and a tramadol HCl immediate release (IR) tablet (Figure 2.1.1.1). The ER beads are manufactured by [redacted] (b) (4)

Dose strengths are 100, 200 and 300 mg (tramadol hydrochloride). The ratio of the amount of tramadol HCl in the IR tablet and the ER beads are 1/3 for 100 and 200 mg capsules, and 1/5 for 300 mg capsules. For 100 mg capsules, the IR tablet contains 25 mg tramadol and ER beads contain 75 mg tramadol (See Figure 2.1.1.1 above). For 200 mg and 300 mg capsules, the IR tablet contains 50 mg tramadol. Therefore, the tramadol content in IR tablet and ER beads were proportional (1:3) between 100 and 200 mg. 300 mg capsules have more tramadol in ER beads (1:5, IR tablet: ER beads).

Quantitative composition for 100, 200 and 300 mg capsules are listed in Table 2.5.1.1.

Table 2.5.1.1. Quantitative Composition of 100, 200 and 300 mg CIP-Tramadol ER Capsules.

Ingredient (and Test Standard)	Amount per Capsule (mg)		
	100 mg Strength	200 mg Strength	300 mg Strength
Tramadol HCl (EP)	100.0	200.0	300.0
Microcrystalline Cellulose (NF), (b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucrose Stearate (b) (4)			
Hydroxypropyl Methylcellulose (b) (4) (USP)			
Talc (USP)			
Magnesium Stearate (NF)			
Polysorbate 80 (NF)			
Simethicone Emulsion (USP)			
Eudragit NE30D (EP)			
Lactose Monohydrate 200 mesh (NF)			
Povidone K30 (USP)			
Starch (NF)			
Sodium Starch Glycolate (NF)			
Gelatin Capsule (NF)	White Opaque Cap & Body ("G 252" on cap, "100" between lines on body, in blue ink)	White Opaque Cap & Body, ("G 253" on cap, "200" between lines on body, in violet ink)	White Opaque Cap & Body ("G 254" on cap, "300" between lines on body, in red ink)
Titanium dioxide (USP)	(b) (4)	(b) (4)	(b) (4)
Gelatin (NF) (b) (4)			
(b) (4)			
Shellac (NF)	Present	Present	Present
(b) (4)	y	y	y
	y	y	y
	y	y	y
	Present	Present	Present
	y	y	y
Titanium Dioxide (USP) (b) (4)	Present	Present	Present
D&C Red #7 Calcium Lake E-180	no	Present	Present
D&C Yellow #10 Aluminium Lake	no	no	Present
FD&C Blue #2 Aluminium Lake E-132	Present	Present	no
Size	1	0	00
Total Fill Weight	**324**	**517**	**770**

Table 2.5.1.2. The Functions of the Components.

Ingredient	Function
Tramadol HCl, EP	(b) (4)
Microcrystalline Cellulose, NF (b) (4)	
Microcrystalline Cellulose, NF (b) (4)	
Sucrose Stearate	
Hydroxypropyl Methylcellulose (b) (4) USP	
Talc, USP	
Magnesium Stearate, NF	
Polysorbate 80, NF	
Simethicone Emulsion, USP	
Eudragit NE30D, EP	
Lactose Monohydrate 200 mesh, NF	
Povidone K30, USP	
Corn Starch, NF	
Sodium Starch Glycolate, NF	
Gelatin Capsule	
Titanium dioxide, USP	
Gelatin, NF	
(b) (4)	

2.5.2 Do the three dose strength capsules demonstrate dosage form equivalence?

Based on IR/ER ratio and formulation composition, 100 and 200 mg capsules are likely to be dosage form equivalent (Figure 2.1.1.1 and Table 2.5.1.1). However, 100 and 300 mg, and 200 and 300 mg are not dosage form equivalent as confirmed by results from Studies 556 and 406.

Results from these 2 studies indicated that dose-normalized AUCt, AUCi, and Cmax (Peak 2) for tramadol and M1 are equivalent (Tables 2.2.5.3.1 and 2.2.5.3.2). However, because 100 and 300 mg, and 200 and 300 mg capsules have different IR to ER ratio, the Cmax of Peak 1 and early

AUC (AUC_{0-4}) are not dose proportional between 100 and 300 mg, and 200 and 300 mg (Tables 2.5.2.1 and 2.5.2.2 and Figures 2.5.2.1 and 2.5.2.2).

Table 2.5.2.1. AUC(0-4), Cmax (Peak 1), and Tmax (Peak 1) Comparison for Tramadol (N=28) (A: 100 mg vs. B: 300 mg) (Data cited from Study 556).

	A Test	B Reference	Ratio of Geometric Means	90% CI lower	90% CI upper
	Arithmetic Mean ± SD		Dose-Normalized		
AUC(0-4) (ng*h/mL)	250 ± 54	496 ± 108	151.76	144.83	159.03
Cmax (Peak 1) (ng/mL)	86 ± 17	170 ± 35	151.84	147.26	156.55
Tmax (Peak 1) (hr)	1.9 ± 0.6	2.4 ± 1.0	-	-	-

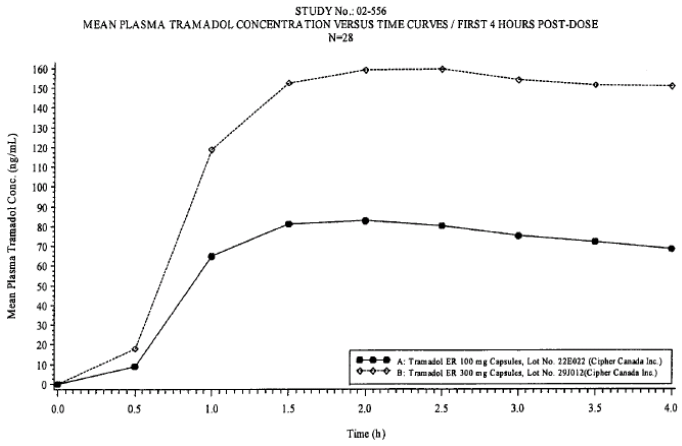


Figure 2.5.2.1. Mean Plasma Tramadol Concentrations Following Administration of 100 mg (●) and 300 mg (◊) ER Capsules.

Table 2.5.2.2. AUC(0-4), Cmax (Peak 1), and Tmax (Peak 1) Comparison for Tramadol (N=20) (A: 200 mg vs. B: 300 mg) (Data are cited from Study 406).

	A Test	B Reference	Ratio of Geometric Means	90% CI lower	90% CI upper
	Arithmetic Mean ± SD		Dose-Normalized		
AUC(0-4) (ng*h/mL)	500 ± 137	505 ± 133	147.87	138.61	157.74
Cmax (Peak 1) (ng/mL)	177 ± 48	174 ± 39	150.80	143.46	158.52
Tmax (Peak 1) (hr)	2.2 ± 0.6	2.5 ± 1.0	-	-	-

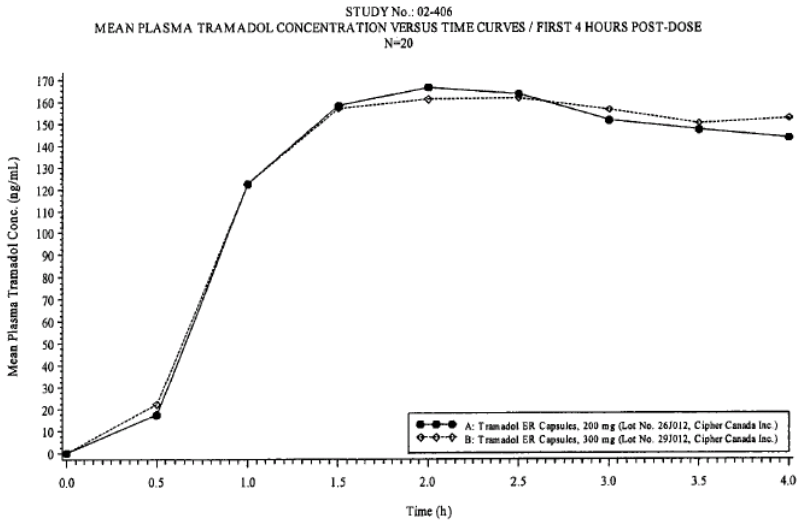


Figure 2.5.2.2. Mean Plasma Tramadol Concentrations Following Administration of 200 mg (●) and 300 mg (◊) ER Capsules.

The clinical relevance of non-dose proportional for Cmax (Peak 1) and early AUC between 100 and 300 mg, and 200 and 300 mg is not clear. The labeling needs to state that 100, 200 and 300 mg capsules are not interchangeable, i.e., the patients should not take three one 100 mg capsules nor one 100 mg and one 200 mg capsules for the 300 mg dose because higher peak 1 and early AUC will be achieved from three 100 mg capsules or one 100 mg and one 200 mg capsules vs. one 300 mg capsule.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?

Food effect was evaluated in Study 405 with 300 mg capsules. Food does not affect C_{max} (Peaks 1 and 2) nor AUC_{inf} following 300 mg CIP-Tramadol ER dosing, however, the absorption of tramadol slows down in the presence of food (Figure 2.5.3.1 and Table 2.5.3.1). There is a 1 hour and a 30 min delay in $T_{max,1}$ (Peak 1) and $T_{max,2}$ (Peak 2), respectively. In addition, AUC(0-4hr) of tramadol and M1 decreased 31% and 40%, respectively in the presence of a high fat meal (Tables 2.5.3.2 and 2.5.3.3).

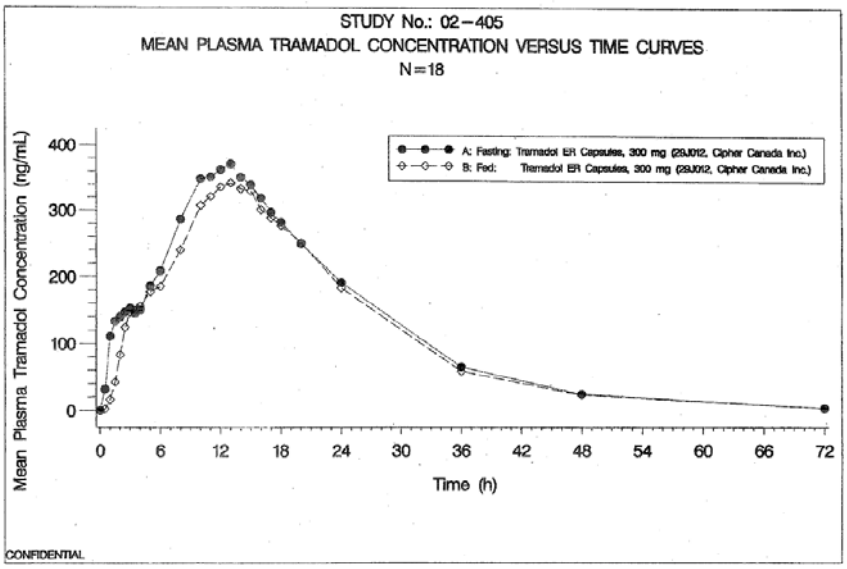


Figure 2.5.3.1. Mean Plasma Tramadol Concentrations under Fasting (●) and Fed (◊) Conditions.

Table 2.5.3.1. AUC and Cmax (Peak 2) Comparison for Tramadol and M1 Excluding PK data from 4 Emesis Incidences (N=14) (A: Fasting vs. B: Fed).

	B	A		90% CI	90% CI
	Geometric Mean		Ratio	lower	upper
	Tramadol				
AUCt (ng*h/mL)	7783	8348	93.23	89.59	97.02
AUCinf (ng*h/mL)	7713	8279	93.17	89.50	97.00
Cmax (Peak 2) (ng/mL)	349	383	91.13	87.00	95.47
	M1				
AUCt (ng*h/mL)	2145	2323	92.36	88.35	96.55
AUCinf (ng*h/mL)	2192	2378	92.18	88.40	96.11
Cmax (Peak 2) (ng/mL)	90	96	94.14	88.19	100.50

Table 2.5.3.2. AUC(0-4), Cmax (Peak 1), and Tmax (Peak 1) Comparison for Tramadol under Fasting and Fed Conditions (N=18).

	A Fasting (Reference)	B Fed (Test)	Ratio of Geometric Means	90% CI lower	90% CI upper
	Arithmetic Mean ± SD				
AUC(0-4) (ng*h/mL)	468 ± 126	321 ± 90	69.25	61.63	77.81
Cmax (Peak 1) (ng/mL)	166 ± 45	164 ± 45	99.67	93.12	106.68
Tmax (Peak 1) (hr)	2.5 ± 1.0	3.5 ± 0.6	-	-	-

Table 2.5.3.3. AUC(0-4), Cmax (Peak 1), and Tmax (Peak 1) Comparison for M1 under Fasting and Fed Conditions (N=18).

	A Fasting	B Fed	Ratio of Geometric Means	90% CI lower	90% CI upper
	Arithmetic Mean ± SD				
AUC(0-4) (ng*h/mL)	109 ± 30	70 ± 33	60.37	53.29	68.39
Cmax (Peak 1) (ng/mL)	39 ± 9	37 ± 12	91.47	85.16	98.26
Tmax (Peak 1) (hr)	3.4 ± 0.9	3.8 ± 0.4	-	-	-

2.5.4 Has the Sponsor established in vitro-in vivo correlation (IVIVC) of CIP-Tramadol ER?

No, the Sponsor did not submit report on *in vitro* and *in vivo* correlation for the formulation [redacted] (b) (4).

2.5.5 Has the Sponsor developed an appropriate dissolution method and specifications that will ensure in vivo performance and quality of the product?

Dissolution Method

Table 2.5.7.1 lists the proposed dissolution method. It is adequate.

Table 2.5.7.1. Dissolution Method.

Parameters	Value
Apparatus	(b) (4)
Dissolution medium	
Dissolution medium volume	
Dissolution medium temperature	
Rotation speed	
HPLC analysis	
Sampling time	

The dissolution method was evaluated and validated to determine the effect of media, pH, temperature, and rotation speed:

(b) (4)

Results: Changes to the dissolution media pH ((b) (4)) and baskets rotation speed (from (b) (4) rpm and (b) (4) rpm) did not affect significantly the results. However, the drug release rate is affected by changing media temperature ((b) (4)); an increase of temperature causes acceleration in the drug release rate.

The robustness of the proposed dissolution method was used in the formulation development and determined that Eudragit excipients and thickness of the coating of the ER beads were important for the release rate. In addition, 300 mg which contains a greater percentage of the ER component showed a slower drug release profile.

Please refer to the CMC review for detail results of method validation.

Specifications:

Typical dissolution data and profiles for 100 and 300 mg capsules under the proposed dissolution method were shown in Tables 2.5.7.2 and 2.5.7.3 and Figures 2.5.7.1 and 2.5.7.2.

Table 2.5.7.2 Dissolution Data for 100 mg Capsules.

(b) (4)

Table 2.5.7.2 Dissolution Data for 300 mg Capsules.

(b) (4)

(b) (4)

In the absence of IVIVC data, the Sponsor proposed the following acceptance criteria for 100, 200 and 300 mg capsules (Table 2.5.7.4). Different dissolution acceptance criteria were proposed for 100/200 mg and 300 mg reflecting slower release rate of the 300 mg strength.

Table 2.5.7.4. Sponsor's Proposed Dissolution Acceptance Criteria for Each Capsule Strength.

Time	100 and 200 mg	300 mg
1 hours	(b) (4)	
7 hours		
8 hours		
24 hours		

However, there were several concerns with the proposal:

(b) (4)

Recommended acceptance criteria by this Reviewer are as follows:

Time	Agency's Revised Proposed Dissolution limits
1 hours	(b) (4)
4 hours	
8 hours	
16 hours	

A final decision is pending from ONDQA.

2.5.6 What is effect of alcohol on the dissolution of the drug product?

The effect of alcohol on capsule dissolution performance was determined *in vitro* to evaluate the potential for dose dumping in the presence of alcohol (Study Report LES-073). The rate of tramadol release increased in proportion to the ethyl alcohol concentrations ((b) (4) ethanol) so that when (b) (4) alcohol was used, complete dissolution occurred in approximately 4 hours. The effect of alcohol on the release of tramadol is similar for both 100 and 300 mg capsules (Figure 2.5.6.1). The effect of alcohol is anticipated because the polymer coating for the ER beads is soluble in ethanol. An *in vivo* evaluation study to study the alcohol effect is not required because previous tramadol product package inserts contain alcohol warning regardless of the formulation. For this particular product, it is anticipated that ER characteristics will be lost in the presence of alcohol.

(b) (4)

Figure 2.5.6.1. CIP-Tramadol ER Dissolution Profile in the Presence of Alcohol (Above: 100 mg capsule; Botton: 300 mg capsule).

2.6 Analytical

2.6.1 Were the analytical methods used to determine Tramadol and M-1in biological fluids adequately validated?

Yes, concentrations of tramadol and its metabolite, M1, were adequately measured in human plasma by validated LC/MS/MS assays and summarized in Table 2.6.1.1. The assays are sensitive and selective for the analytes. Project No. (b) (4)-557-02-01 quantifes (+)-tramadol, (-)-tramadol, (+)-M1 and (-)-M1 separately.

Long-term stability of tramadol and M1 in frozen human plasma at -20°C was at least (b) (4) days. The stability was long enough to cover the time span from sample collection to sample analysis.

Table 2.6.1.1. Analytical Methods used for the Determinations of Tramadol and M1 in Each Study.

Studies	Reference Validation Method	Analytes	Internal Standard	LOQ (ng/ml)	Linear Range (ng/ml)	Between Batch Precision (%CV)	Between Batch Accuracy (% nominal values)	QC Samples (ng/mL)
Study 403	Project No. (b) (4) 524-00-01	Tramadol M1	(b) (4)					
Study 405								
Study 406								
Study 556	Project No. (b) (4) 524-00-02	Tramadol M1						
Study 549	Project No. (b) (4) 557-02-01	(+)-Tramadol (+)-M1 (-)-Trmadol (-)-M1						

3 LABELING RECOMMENDATIONS

The labeling recommendation will be provided in a separate document. The following items would need to be paid attention to during labeling review:

- 100 and 300 mg, and 200 and 300 mg capsules are not interchangeable.
- Warning of safety concern due to dose dumping in the presence of alcohol

8 Page(s) have been Withheld in Full as b4 (Draft Labeling) immediately following this page

4.2 Individual Study Review

4.2.1 Study 02-403 (TRAMPK.01.01): A Two-Way Study to Compare the Bioavailability of Tramadol ER 200 mg Capsules (o.d.) versus Ultram® 50 mg Tablets (q.i.d.), in Normal, Healthy Subjects, under Fasting Conditions

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Study Period:	Period I: February 28, 2002 Period II: March 14, 2002
Sample Analysis Period:	March 23, 2002 to April 04, 2002
Principle Investigator:	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Study Center:	Pharma Medica Research Inc., 1410 Warden Avenue. Toronto, Ontario, Canada M1R 5A3
Analytical Site:	(b) (4) [redacted]

Objective: To compare the bioavailability of Cipher's Tramadol ER 200 mg Capsules (o.d.) versus Ultram® 50 mg Tablets (q.i.d.) in healthy, non-smoking subjects under fasting conditions.

Study Design: This was an open-label, single-dose, randomized, two-treatment, two-period, two-sequence, crossover comparative bioavailability study, with a washout period of at least 14 days between the two study period drug administrations.

A single 200 mg dose of the test product (l capsule) was administered to each subject as Regimen A. A 50 mg dose of the reference product (1 tablet) was given to each subject at 0, 6, 12 and 18 hours as Regimen B for a total dose of 200 mg. All subjects fasted for at least 10 hours before until 4 hours after the first (0 hour) drug administration. For the subsequent drug administrations in Regimen B, subjects also fasted from approximately 1 hour before until 2 hours after dosing.

Twenty-eight (28, including 2 alternates) healthy non-smoking subjects (15 males and 13 females) were dosed in Period I on February 28, 2002. Subject 13 withdrew from the study prior to Period II dosing due to personal reasons. Therefore, 27 subjects were dosed in Period II on March 14, 2002 and all completed the study. Subject 28 was considered an alternate and was not included in the analysis.

The 26 subjects (15 males and 11 females) who were included in the pharmacokinetic/statistical analysis of the study had a mean age of 33 ± 7 yr (range 18-43 yr), a mean height of 67.3 ± 3.3 in (63-76 in), and a mean weight of 155.7 ± 22.3 lb (113-197 lb). 17 were Caucasians, 6 were African American and 3 were Asian.

Test Articles:
Test Product (A): Tramadol ER Capsules, 200 mg (Cipher Canada Inc., Manufactured by Galephar P.R. Inc.), Lot No: 26J012

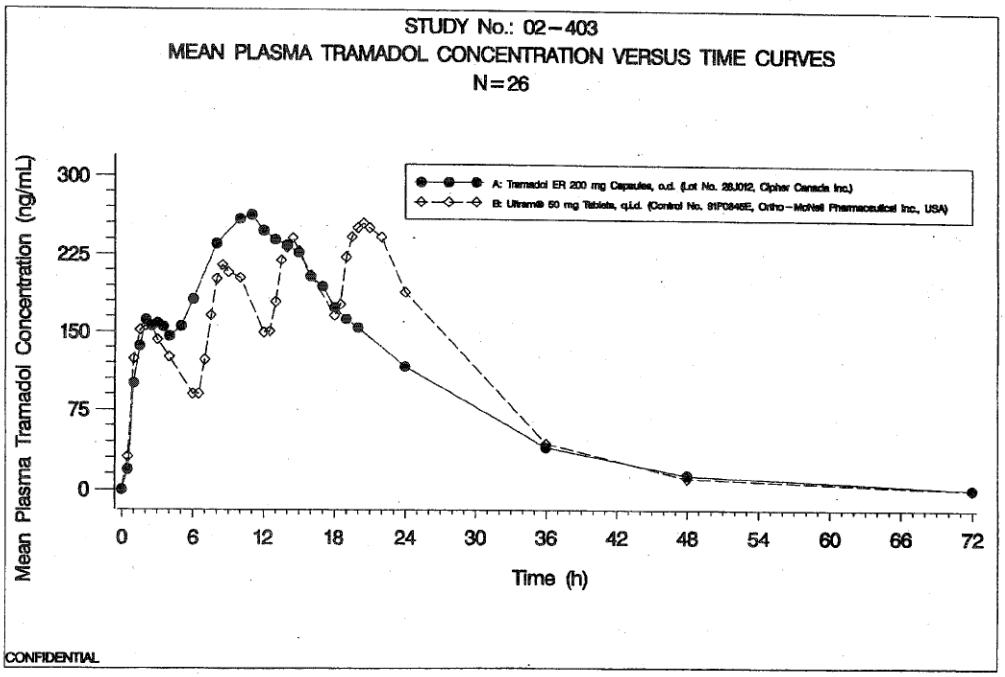
Reference Product (B): Ultram® Tablets, 50 mg (Manufactured by Ortho- McNeil Pharmaceutical, Inc., U.S.A.), Control: 91P0845E, Expiry Date: 7-03

Sample Collection:
Regimen A: Venous blood samples were collected pre-dose (2 x 7 mL), and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 36, 48, and 72 hours post-dose (1 x 7 mL) in each period.

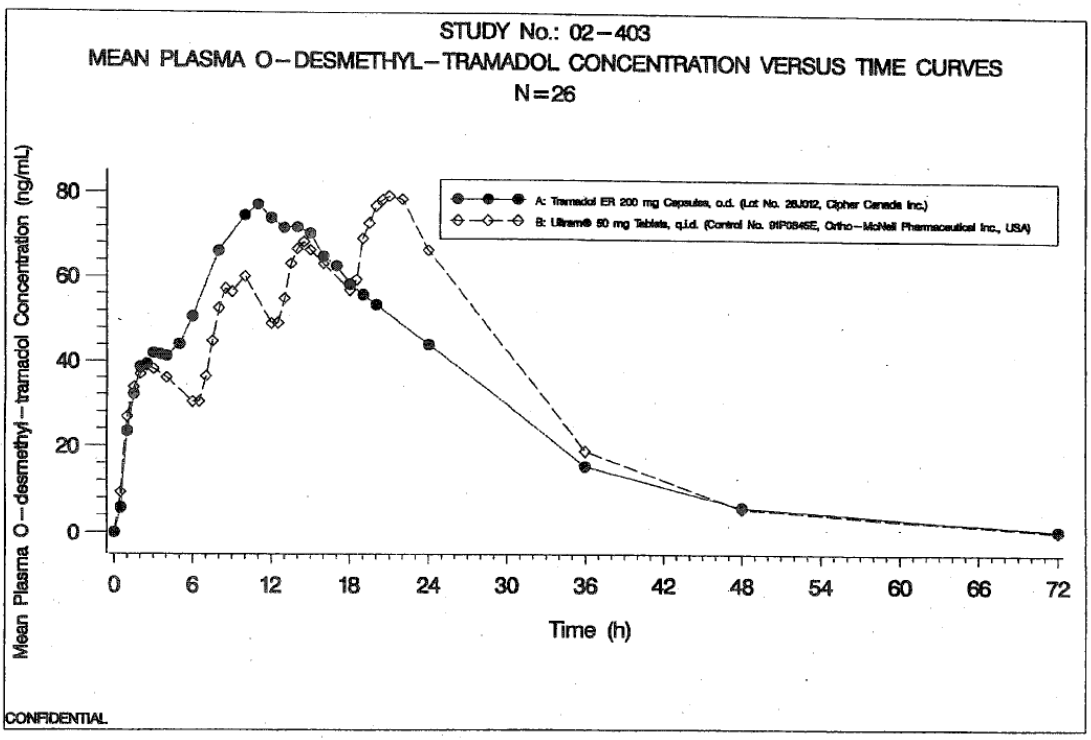
Regiment B: venous blood samples were collected pre-dose (2 x 7 mL), and 0.5, 1, 1.,2, 2.5, 3, 4, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 16, 18, 18.5, 19, 19.5, 20, 20.5, 21, 22, 24, 36, 48, and 72 hours post-dose (l x 7 mL) in each period.

Sample Analysis: Samples were analyzed at the bioanalytical laboratory of (b) (4) Analysis for tramadol and O-desmethyl-tramadol in human plasma was performed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) method (Project No. (b) (4)-524-00-01) with a calibration range of (b) (4) for tramadol and (b) (4) for O-desmethyl-tradol (M1). (b) (4) was used as an internal standard. The laboratory was blinded regarding the randomization scheme and treatment plan.

Pharmacokinetic Results:
PK Profiles
The mean plasma concentration-time profiles of tramadol and M1 metabolite from 26 subjects are shown in Figure 1 (a and b).



a. Tramadol



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations after administration of a single dose of 200 mg Tramadol ER (●) or a single daily dose (50 mg qid) of Ultram® (◊).

PK Comparison Between CIP-Tramadol ER and Ultram after a single daily dose

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) from 26 subjects are summarized in Tables 1 and 2. Cmax and Tmax values for CIP-Tramadol ER in the tables refer to Peak 2.

Table 1. Summary of PK Result Comparison for Tramadol (A: 200 mg Tramadol ER vs. B: Ultram).

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval (%)	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCt (ng·h/mL)	5552.83 5816.06 (35)	5985.41 6125.96 (26)	92.77	88.53 – 97.22	9.86
AUCi (ng·h/mL)	5618.95 5883.56 (35)	6021.32 6160.70 (26)	93.32	89.10 – 97.74	9.75
Cmax (ng/mL)	269.42 279.96 (31)	312.32 318.27 (23)	86.26	79.53 – 93.57	17.21
Tmax[a] (h)	10.00 (8.00-15.00)	19.50 (13.50-22.00)		-	
Kel (h^{-1})	0.0893 (17)	0.1187 (25)		-	
Thalf (h)	7.98 (17)	6.18 (24)		-	

[a]Tmax is expressed as median (range).

Table 2. Summary of PK Result Comparison for M1 (A: 200 mg Tramadol ER vs. B: Ultram).

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval (%)	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCt (ng·h/mL)	1789.18 1861.94 (29)	1895.05 1970.14 (27)	94.41	91.58 – 97.33	6.40
AUCi (ng·h/mL)	1833.13 1904.64 (28)	1935.65 2009.71 (27)	94.70	91.90 – 97.59	6.32
Cmax (ng/mL)	78.05 81.39 (29)	88.46 91.67 (23)	88.23	81.86 – 95.09	15.84
Tmax* (h)	11.00 (10.00-15.00)	20.00 (13.50-22.00)		-	
Kel (h^{-1})	0.0850 (15)	0.1072 (18)		-	
Thalf (h)	8.36 (17)	6.67 (18)		-	

*Tmax is expressed as median (range).

Six incidents of emesis were reported during the confinement of subjects at the clinic. Four incidents involved 4 subjects (01, 04, 09 and 26) in association with Regimen A (test product) and ranged in time of onset from approximately 2 to 13 hours post-dose. Two incidents involved Subjects 15 and 28 following the last dose of Regimen B (reference product), and the times of onset were, approximately 20 hours and 6.5 hours, respectively. Subject 28 was considered an alternate and was not included in the analysis.

Vomiting can be considered as detrimental to the integrity of the pharmacokinetic data. The Sponsor did not exclude these subjects from the study in order to preserve the necessary sample size.

PK data for Subject 4 and 9 under Regimen A showed exposure at low end. Emesis may have an effect on the PK. This Reviewer evaluated 90% confidence interval excluding tramadol PK data from these subjects (Subjects 1, 4, 9 and 26 for regiment A and Subject 15 for regimen B) who had emesis incidences (N=22 for Regimen A and N=25 for Regimen B). The data suggest that AUC and Cmax for both tramadol and M1 were bioequivalent between Tramadol ER and Ultram (Tables 3 and 4). Relative Cmax of tramadol and M1 for CIP-Tramadol ER were slightly higher when excluding subjects who had emesis compared to data obtained without exclusion.

Table 3. AUC and Cmax Comparison for Tramadol Excluding PK data from 5 Emesis Incidences (A: 200 mg CIP-Tramadol ER vs. B: Ultram).

	A	B	Ratio	90% CI lower	90% CI upper
	Geometric Mean				
AUCt (ng*h/mL)	5551	5999	92.53	88.11	97.17
AUCi (ng*h/mL)	5616	6036	93.04	88.63	97.68
Cmax (ng/mL)	280.1	309.7	90.45	83.82	97.61

Table 4. AUC and Cmax Comparison for M1 Excluding PK data from 5 Emesis Incidences (A: 200 mg Tramadol ER vs. B: Ultram).

	A	B	Ratio	90% CI lower	90% CI upper
	Geometric Mean				
AUCt (ng*h/mL)	1782	1893	94.15	90.80	97.63
AUCi (ng*h/mL)	1827	1932	94.57	91.27	98.00
Cmax (ng/mL)	80.7	87.3	92.38	86.52	98.64

Conclusions: Based on the ln-transformed data, AUC and Cmax were equivalent between the Tramadol ER Capsules, 200 mg o.d. and the Ultram® Tablets, 50 mg administered every 6 hours (q.i.d.) for both analytes (tramadol and O-desmethyltramadol, M1), the 90% confidence intervals were within the 80-125% range. In terms of overall PK profile, CIP-Tramadol ER showed lower exposure after approximately 18 hours compared to Ultram.

With the extended-release capsules, the tramadol levels reached their maximum concentration approximately 10 hours after dosing.

4.2.2 Study 02-549 (TRAMPK.02.01): A Multiple-Dose, Two-Way Study to Compare the Bioavailability of a Formulation of Tramadol ER Capsules, 200 mg (o.d.), with Ultram® 50 mg Tablets (q.i.d.) at Steady State, in Healthy, Male Subjects

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Study Period: Period I: September 7-14, 2002
Period II: September 28-October 5, 2002
Sample Analysis Period: April 10 to May 12, 2003

Objective: To compare the bioavailability between Tramadol ER Capsules 200 mg, o.d. (Cipher Canada Inc.), and Ultram® Tablets 50 mg, q.i.d. (Ortho-McNeil Pharmaceutical, Inc.), in healthy, male subjects, at steady state under fasting conditions.

Study Design: This was an open-label, multiple-dose, randomized, two-treatment, two-sequence, two-period, crossover, bioavailability study, with a washout period of at least 14 days between drug administrations.

The test drug (200 mg extended-release capsules) was administered once a day (o.d.) for 7 days as Treatment A and the reference drug (50 mg immediate-release tablets) was given four times daily (q.i.d.) for 7 days as Treatment B. For Treatment A, subjects were dosed once in the morning at approximately 08:00 hour on each day of the study. For Treatment B, subjects were dosed at approximately 08:00, 14:00, 20:00 and 02:00 hours on Days 1-7. Subjects fasted overnight for at least 9 hours prior to the morning drug administration and for at least 4 hours post morning drug administration on Days 1 - 7 for both treatments in both periods. In addition, for Treatment B, subjects fasted for 1 hour before and until at least 2 hours after all drug administrations.

Twenty-nine (29) healthy, non-smoking male subjects were dosed in Period I. Subjects 01, 06, 09, and 23 were dismissed from the study during Period I by a physician due to adverse events. Subject 18 was dismissed from the study due to a positive alcohol breath test result during Period II check-in. After completing Period I, Subject 21 withdrew prior to Period II check-in due to personal reasons. Therefore, 23 subjects were dosed in Period II. Subject 16 was withdrawn from the study by the Principal Investigator during Period II due to adverse events. Therefore, 22 subjects completed both Period I and Period II.

Demographic information for the 22 subjects who completed the study and were analyzed is as follows, mean ± SD (range):

- Age: 30 ± 6 yrs (21 - 46 yrs)
- Height: 175.4 ± 7.6 cm (164.5 - 190.5 cm)
- Weight: 75.9 ± 9.4 kg (60.0 - 94.5 kg)

16 were Caucasians, 4 were African American and 2 were Asian.

Test Articles:
Test Product (A): Tramadol ER Capsules, 200 mg (Cipher Canada Inc., Manufactured by Galephar P.R. Inc.), Lot No: 26J012

Reference Product (B): Ultram® Tablets, 50 mg (Manufactured by Ortho-McNeil Pharmaceutical, Inc., U.S.A.), Control: 92P0060E, Expiry Date: 12-03

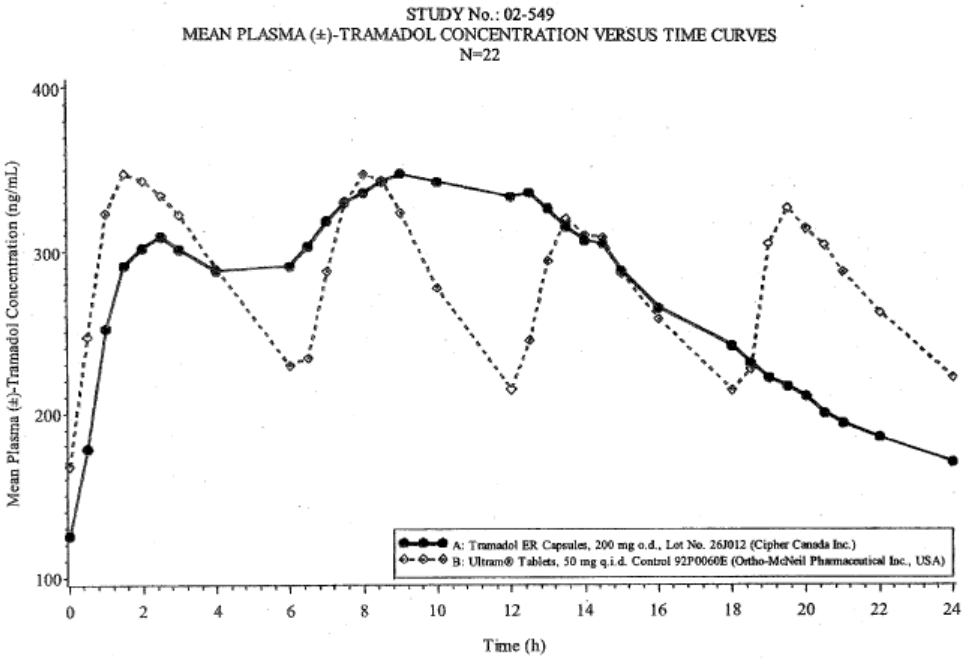
Sample Collection: Venous blood samples were collected pre-dose (0 hour) on Day 1 (2 x 5 mL), pre-dose (0 hour) on Days 5, 6, and 7 (l x 5 mL), and on Day 7 at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 16, 18, 18.5, 19, 19.5, 20, 20.5, 21, 22 and 24 hours post-dose (l x 5 mL) in each period.

Sample Analysis: Samples were analyzed at the bioanalytical laboratory of (b) (4) [redacted]. Analyses for (+)-tramadol, (-)-tramadol, (+)-O-desmethyl-tramadol and (-)-O-desmethyl-tramadol in human plasma were performed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) method (Project No. (b) (4) [redacted]-557-02-01) with a calibration range of (b) (4) [redacted] ng/mL for both enantiomers of tramadol and (b) (4) [redacted] ng/mL for both enantiomers of O-desmethyl-tramadol (M1). (b) (4) [redacted] was used as an internal standard for (+)-tramadol and (+)-O-desmethyl-tramadol. (b) (4) [redacted] was used as an internal standard for (-)-tramadol and (-)-O-desmethyl-tramadol. The laboratory was blinded regarding the randomization scheme and treatment plan.

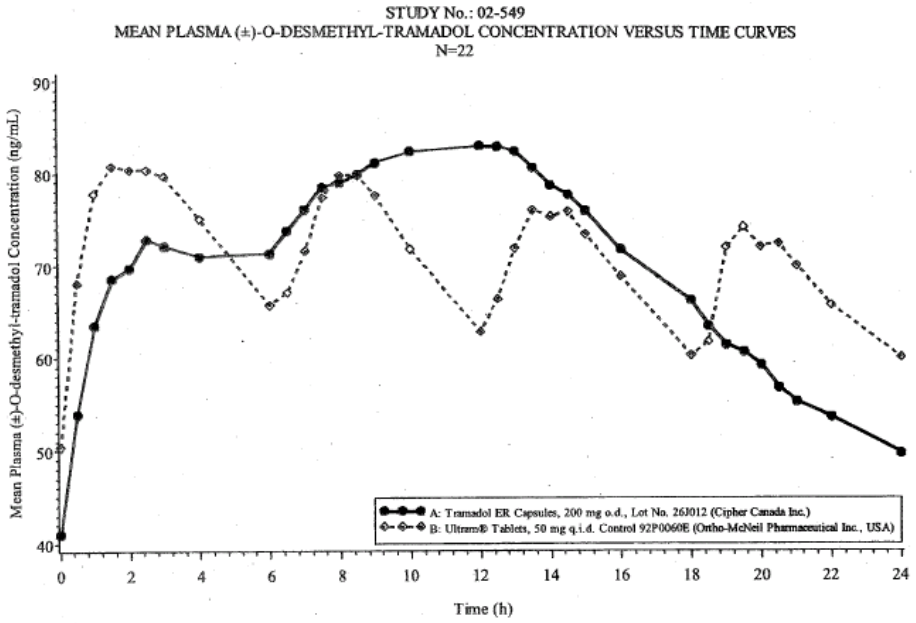
Pharmacokinetic Results:

PK Profiles

The mean plasma concentration-time profiles of tramadol and M1 metabolite from 22 subjects who completed both Periods I and II of the study are shown in Figure 1 (a and b). Plot for tramadol (Figure 1a) combines the concentration versus time data for (+)-tramadol with (-)-tramadol, and plot for M1 (Figure 1b) combines the concentration versus time data for (+)-O-desmethyl-tramadol with (-)-O-desmethyl-tramadol.



a. Tramadol



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations after Multiple Dose Administration of 200 mg Tramadol ER (●) (qd) or of Ultram® (◊) (qid) for 7 Days.

PK Comparison Between Tramadol ER and Ultram at steady-state

There were five (5) occurrences of emesis reported during the confinement of subjects at the clinic.

Subject	Treatment	Time of Occurrence				Number of episodes
		Period	Day	Dose	Time after dosing (hours)	
01	B	I	1	4	1.65	1
05	A	I	7	1	49.5	1
06	A	I	1	1	0.83	5
09	A	I	1	1	9.5	9
23	B	I	2	1	0.48	1

Vomiting can be detrimental to the integrity of the pharmacokinetic data. All subjects except Subject 05 were dismissed during Period 1. Subject 05 was not excluded from the analysis due to the lengthy time interval between the last drug administration (Day 7) and emesis.

Steady-state

Predose exposure of tramadol and M1 were comparable from Day 5 through Day 7, suggesting that steady state was reached on Day 5 for both Tramadol ER and Ultram (Tables 1 and 2).

Table 1. Predose Tramadol and M1 Concentrations (ng/mL) on Days 5, 6, and 7 Following Administration of Treatment A.

	Day 5	Day 6	Day 7
(+)-Tramadol	97 ± 34	94 ± 31	97 ± 35
(-)-Tramadol	73 ± 27	70 ± 25	71 ± 26
Tramadol	**170 ± 61**	**164 ± 55**	**167 ± 60**
(+)-M1	27 ± 9	26 ± 10	25 ± 9
(-)-M1	31 ± 10	28 ± 10	28 ± 10
M1	**58 ± 18**	**54 ± 19**	**52 ± 18**

Table 2. Predose Tramadol and M1 Concentrations (ng/mL) on Days 5, 6, and 7 Following Administration of Treatment B.

	Day 5	Day 6	Day 7
(+)-Tramadol	128 ± 38	125 ± 38	125 ± 36
(-)-Tramadol	101 ± 35	98 ± 35	96 ± 31
Tramadol	**228 ± 72**	**224 ± 72**	**220 ± 66**
(+)-M1	33 ± 11	31 ±11	30 ± 10
(-)-M1	39 ± 11	35 ± 11	35 ± 11
M1	**72 ± 21**	**66 ± 22**	**64 ± 21**

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) from 22 subjects who completed both Period I and II are summarized in Tables 3 and 4. (+)-Tramadol in general showed higher levels than (-)-tramadol, and (+)-M1 showed lower levels than (-)-M1 indicating setero-difference in terms of metabolism. Cmax and Tmax values for CIP-Tramadol ER in the tables refer to Peak 2.

Table 3. Summary of PK Result Comparison for Tramadol at Steady State (on Day 7) (A: 200 mg Tramadol ER vs. B: Ultram).

Note: (+) and (-)-Tramadol concentration data were combined at each timepoint for each subject to generate the PK data for total (±) tramadol listed in Table 3.

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCtau (ng·h/mL)	6392.2 6600.0 (25)	6514.0 6712.9 (26)	98.13	94.83 – 101.55	7
Cmax (ng/mL)	355.9 363.8 (21)	368.9 378.9 (24)	96.47	92.97 – 100.10	7
Cmin (ng/mL)	154.7 164.9 (35)	205.0 212.9 (29)	75.45	69.64 – 81.73	15
Tmax [a] (h)	9.70 (18)	6.98 (68)		-	
DF [a] (%)	75.33 (29)	60.56 (17)		-	

[a] Presented as arithmetic mean (CV%) only.

Table 4. Summary of PK Result Comparison for M1 at Steady State (on Day 7) (A: 200 mg Tramadol ER vs. B: Ultram).
Note: (+) and (-)-M1 concentration data were combined at each timepoint for each subject to generate the PK data for total (±) M1 listed in Table 4.

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCtau (ng·h/mL)	1603.8 1683.2 (31)	1617.7 1703.8 (32)	99.14	95.46 – 102.96	7
Cmax (ng/mL)	83.0 87.4 (32)	81.0 85.4 (31)	102.48	98.10 – 107.04	8
Cmin (ng/mL)	49.0 51.5 (32)	59.4 62.5 (33)	82.47	77.00 – 88.32	13
Tmax[a] (h)	10.84 (22)	6.73 (71)		-	
DF[a] (%)	50.60 (33)	32.20 (23)		-	

[a] Presented as arithmetic mean (CV%) only.

Conclusions: The two formulations (ER and Ultram) exhibited equivalent AUCtau and Cmax (Peak 2) over a 24-hour interval at steady state for both tramadol and its metabolite, M1 at equivalent daily doses (200 mg and 50 mg qid). The average Cmin exhibited by the Tramadol ER Capsules 200 mg was lower than the mean Cmin demonstrated by the immediate-release tablets over a 24-hour interval. Accordingly, the extended-release drug product exhibited larger changes in the concentration levels over a 24-hour period than the immediate-release tablets.

4.2.3 Study 02-556 (TRAMPK.02.02): An Open-Label, Single-Dose, Two-Way Study to Determine the Dose Proportionality of Tramadol ER 100 mg and 300 mg Capsules, in Healthy Subjects, Under Fasting Conditions

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Study Period: Period I: September 14, 2002
Period II: September 28, 2002
Sample Analysis Period: October 28, 2002 to November 7, 2002

Objective: To assess the dose proportionality between two new formulations of tramadol 100 mg and 300 mg once a day capsules in healthy, non-smoking male and female subjects, under fasting conditions.

Study Design: This study was designed as an open-label, single-dose, randomized, two-treatment, two-sequence, two-period, crossover, bioavailability study, with a washout period of at least 14 days between drug administrations.

Twenty-eight subjects (14 males and 14 females) entered the study. All completed the study. Demographic information for the 28 subjects who completed the study is as follows, mean ± SD (range): age of 33 ± 7.3 yrs (18 - 47 yrs), a height of 67.0 ± 3.3 in (60.0 -73.4 in) and a weight of l49.4 ± 22.1lbs (109.8 - 183.6 lbs). 24 were Caucasians, 3 were African American and 1 was Asian.

A single dose of either Treatment A (1 x 100 mg capsules) or Treatment B (l x 300 mg capsules) was administered after an overnight fast of at least 10 hours.

Test Articles:
Treatment A: Tramadol ER Capsules, 100 mg (1 x 100 mg) (Manufactured by Galephar P.R. Inc. on behalf of Cipher Canada Inc.), Lot No. 22E022; Manufacturing Date: Not Specified.

Treatment B: Tramadol ER Capsules, 300 mg (1 x 300 mg) (Manufactured by Galephar P.R. Inc. on behalf of Cipher Canada Inc.), Lot No. 29J012; Manufacturing Date: Not Specified.

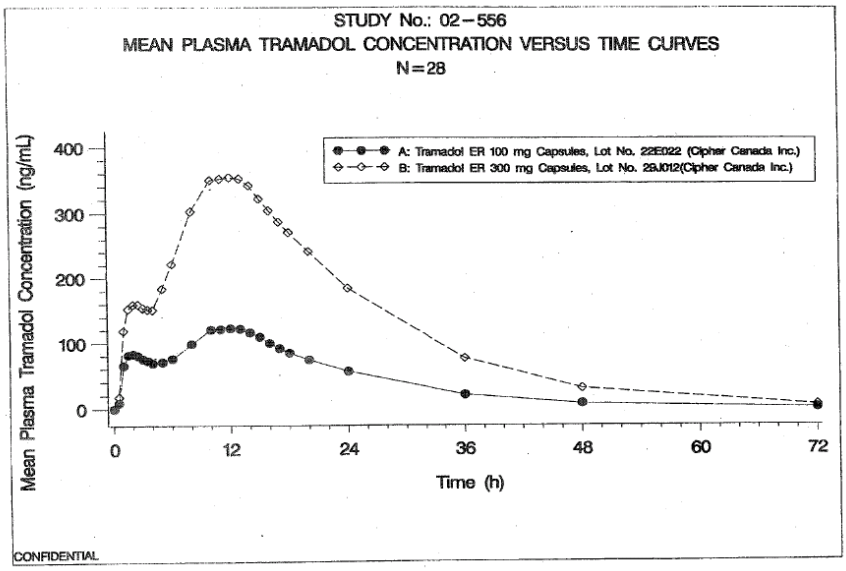
Sample Collection: Venous blood samples were collected pre-dose (2 x 7 mL), and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 36, 48, and 72 hours post-dose (1 x 7 mL) in each period.

Sample Analysis: Samples were analyzed at the bioanalytical laboratory of (b) (4) [redacted]. Analysis for tramadol and O-desmethyl-tramadol in human plasma was performed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) method (Project No. (b) (4)-524-00-02) with a calibration range of (b) (4) [redacted] ng/mL for tramadol and (b) (4) [redacted] ng/mL for O-desmethyl-tradol (M1). (b) (4) [redacted] was used as an internal standard. The laboratory was blinded regarding the randomization scheme and treatment plan.

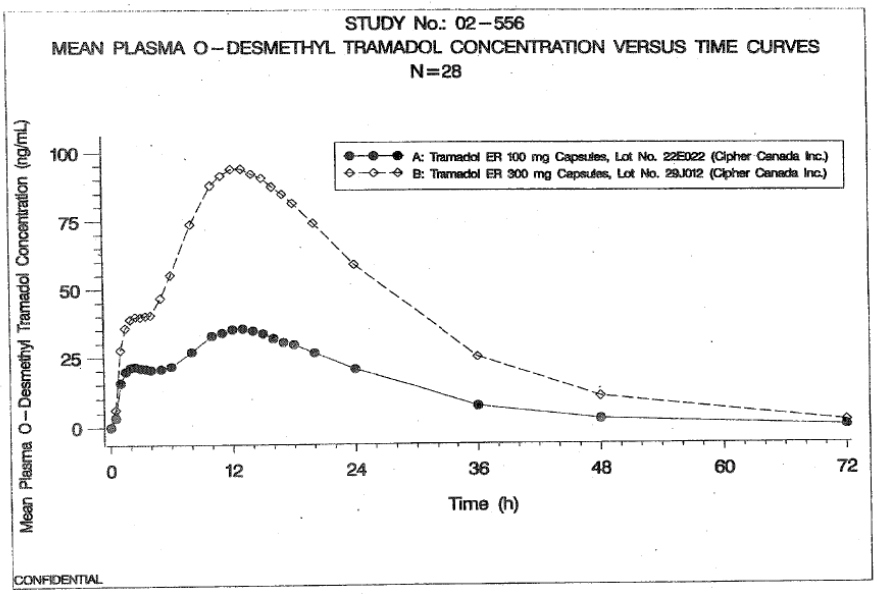
Pharmacokinetic Results:

PK Profiles

The extended-release capsule dosage form contains a tramadol HCI immediate release (IR) tablet and tramadol hydrochloride (HCI) ER beads. The *in vivo* concentration-time profiles for tramadol and its metabolite, M1, showed that there was a lower Cmax peak (Peak 1) at around 2 hours and a higher Cmax peak (Peak 2) at around 10-12 hours (Figure 1a and b). Peak 1 mainly represents the release of tramadol from the IR tablet and Peak 2 mainly represents the release of tramadol from the ER beads.



a. Tramadol



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations Following Administration of 100 mg (●) and 300 mg (◊) ER Capsules.

Relative Bioavailability

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) from the 28 subjects who completed the study are summarized in Tables 1 and 2. Cmax and Tmax values in the tables refer to Peak 2.

Table 1. Summary of PK Result Comparison for Tramadol (A: 100 mg vs. B: 300 mg).

Parameter	Test (A)	Reference (B)	Ratio of Geometric Means[b] (%)	90% Geometric Confidence Interval[b]	Intra-Subject CV (%)
	Geometric Mean[b] Arithmetic Mean (CV%)				
From Measured Data:					
AUCt (ng·h/mL)	26.00 2779.81 (36)	27.45 8639.51 (32)	94.69	89.95 – 99.69	11
AUCi (ng·h/mL)	26.44 2826.81 (36)	27.74 8733.87 (32)	95.32	90.46 – 100.44	12
Cmax (ng/mL)	1.23 128.23 (28)	1.20 369.82 (24)	103.00	97.25 – 109.10	13
Tmax[a] (h)	11.36 (14)	11.79 (12)		-	
Kel[a] (h^{-1})	0.0896 (20)	0.0802 (17)		-	
Thalf[a] (h)	8.00 (18)	8.90 (18)		-	

[a]Presented as arithmetic mean (CV%) only.
[b] Geometric Means were estimated from dose-normalized AUCs and Cmax parameters.

Table 2. Summary of PK Result Comparison for M1 (A: 100 mg vs. B: 300 mg).

Parameter	Test (A)	Reference (B)	Ratio of Geometric Means[b] (%)	90% Geometric Confidence Interval[b]	Intra-Subject CV (%)
	Geometric Mean[b] Arithmetic Mean (CV%)				
From Measured Data:					
AUCt (ng·h/mL)	8.21 869.27 (32)	7.85 2494.22 (33)	104.54	99.53 – 109.81	11
AUCi (ng·h/mL)	8.50 896.88 (32)	8.02 2546.63 (33)	105.99	100.96 – 111.27	11
Cmax (ng/mL)	0.35 37.05 (32)	0.31 98.00 (32)	113.46	107.74 – 119.49	11
Tmax[a] (h)	13.71 (14)	13.00 (20)		-	
Kel[a] (h^{-1})	0.0862 (19)	0.0748 (17)		-	
Thalf[a] (h)	8.32 (19)	9.53 (18)		-	

[a] Presented as arithmetic mean (CV%) only.
[b] Geometric Means were estimated from dose-normalized AUCs and Cmax parameters.

Because the IR tablet doses in 100 and 300 mg ER capsules are 25 and 50 mg, respectively, Peak 1 and early AUC (e.g., $AUC_{0\text{-}4\ hour}$) were not dose proportional between 100 and 300 mg capsules as anticipated (Table 3 and Figure 2). Exposure to tramadol were about 2-times from 300 mg capsule compared to 100 mg capsule proportional to the IR tablet dose in the ER capsule. The data indicated that most if not all IR tablet dose contributed to Peak 1 and early AUC. Similar relationship between 100 and 300 capsules were demonstrated for M1. Data for M1 were not shown.

Table 3. AUC(0-4), Cmax (Peak 1), and Tmax (Peak 1) Comparison for Tramadol (N=28) (A: 100 mg vs. B: 300 mg).

	A Test	B Reference	Ratio of Geometric Means	90% CI lower	90% CI upper
	Arithmetic Mean ± SD		Dose-Normalized		
AUC(0-4) (ng*h/mL)	250 ± 54	496 ± 108	151.76	144.83	159.03
Cmax (Peak 1) (ng/mL)	86 ± 17	170 ± 35	151.84	147.26	156.55
Tmax (Peak 1) (hr)	1.9 ± 0.6	2.4 ± 1.0	-	-	-

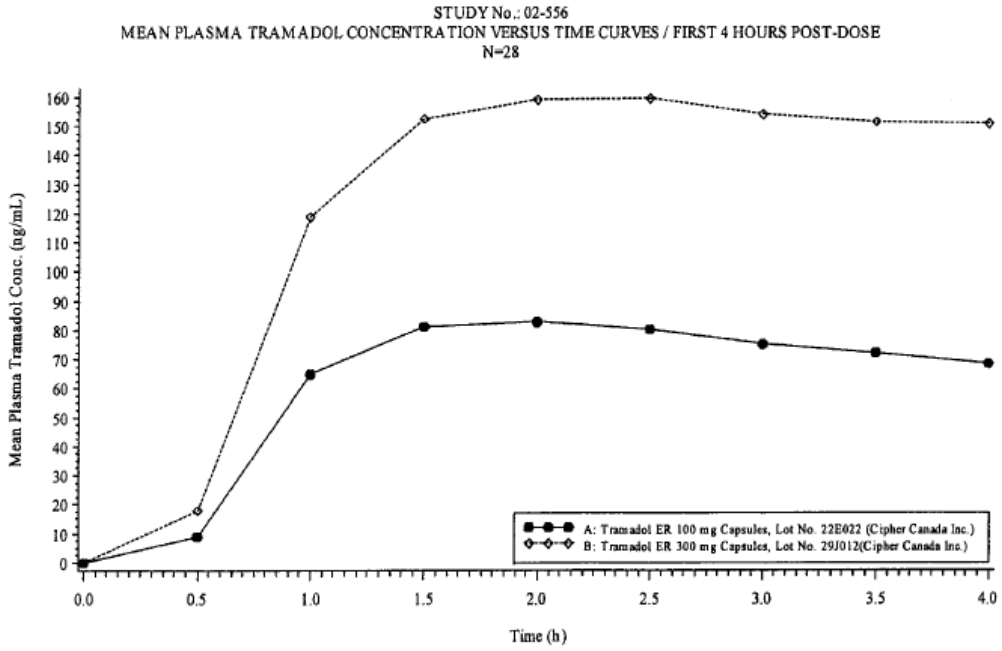


Figure 2. Mean Plasma Tramadol Concentrations Following Administration of 100 mg (●) and 300 mg (◊) ER Capsules.

Impact of emesis on AUC and Cmax
Six (6) incidents of emesis were reported during the confinement of subjects at the clinic. They involved Subjects 07, 09, 11, 12, and 13 in association with treatments B, B, A/B, B, and B, respectively, and ranged in time of onset from approximately 2 hours post-dose to 15.5 hour post-dose.

Vomiting can be considered detrimental to the integrity of the pharmacokinetic data depending on the time elapsed since dosing. However, the Sponsor chose not to exclude these subjects from the study in order to preserve the necessary sample size.

Overall CV of PK parameters including all subjects is about 30-40%. PK data obtained from these subjects when emesis happened were within the range of other subject data indicating the likely impact of emesis on PK was small (data not shown). This Reviewer further evaluated 90% confidence interval excluding tramadol PK data from these 6 incidences. The data suggest that dose-normalized AUC and Cmax,2 (Peak 2) for tramadol data between 100 and 300 mg were bioequivalent (Table 4), the same conclusion when including all the data.

Table 4. AUC and Cmax Comparison for Tramadol Excluding PK data from 6 Emesis Incidences (Dose-Normalized to 100 mg) (A: 100 mg vs. B: 300 mg).

	A Test	B Reference	Ratio	90% CI lower	90% CI upper
	Geometric Mean				
AUCt (ng*h/mL)	2552	2756	92.58	88.31	97.06
AUCi (ng*h/mL)	2594	2785	93.14	88.84	97.66
Cmax (ng/mL)	121	120	100.29	95.15	105.7

Conclusions: Dose-normalized AUCt, AUCi, and Cmax,2 (Peak 2) for tramadol and M1 are equivalent between 100 and 300 mg capsules. However, because 100 and 300 mg capsules are not proportional in terms of IR and ER ratio, the Cmax of Peak 1 is not proportional between 100 and 300 mg. The clinical relevance of non-dose proportional for Cmax (Peak 1) and early AUC between 100 and 300 mg is not clear. The labeling needs to state that 100 and 300 mg capsules are not interchangeable, i.e., the patients should not take three 100 mg capsules for the 300 mg dose because higher peak 1 and early AUC will be achieved from three 100 mg capsules vs. one 300 mg capsule.

4.2.4 Study 02-406 (TRAMPK.01.03): An Open-Label, Single-Dose, Two-Way Study to Determine the Dose Proportionality of Tramadol ER 200 mg and 300 mg Capsules, in Healthy Subjects, Under Fasting Conditions

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Study Period: Period I: January 29, 2002
Period II: February 12, 2002
Sample Analysis Period: March 11, 2002 to April 02, 2002

Objective: To assess the dose proportionality between two new formulations of tramadol 200 mg and 300 mg once a day capsules in healthy, non-smoking male and female subjects, under fasting conditions.

Study Design: This was an open-label, single-dose, randomized, two-treatment, two-sequence, two-period, crossover, bioavailability study, with a washout period of at least 14 days between drug administrations.

Twenty-two subjects (including 2 alternates) entered the study. Twenty-one (21) subjects completed the study. Subject 22 refused to take the treatment in Period II. The first 20 subjects who completed the study had a mean age of 37 ± 8 yrs (range 18 - 48 yrs), a mean height of 66.4 ± l 4.1 in (range 59.3 -75.6 in), and a mean weight of 154.5 ± 26.6 lbs (range 116.6 - 225.3 lbs). 16 were Caucasians, 2 were African American and 2 were Asian.

A single dose of either Treatment A (1 x 200 mg capsules) or Treatment B (l x 300 mg capsules) was administered after an overnight fast of at least 10 hours.

Test Articles:
Treatment A: Tramadol ER Capsules, 200 mg (Cipher Canada Inc., Manufactured by Galephar P.R Inc.), Lot No. 26J012, GF-038, Expiry Date: Not applicable.

Treatment B: Tramadol ER Capsules, 300 mg (Cipher Canada Inc., Manufactured by Galephar P.R. Inc.), Lot No, 29J012, GF-040, Expiry Date: Not applicable.

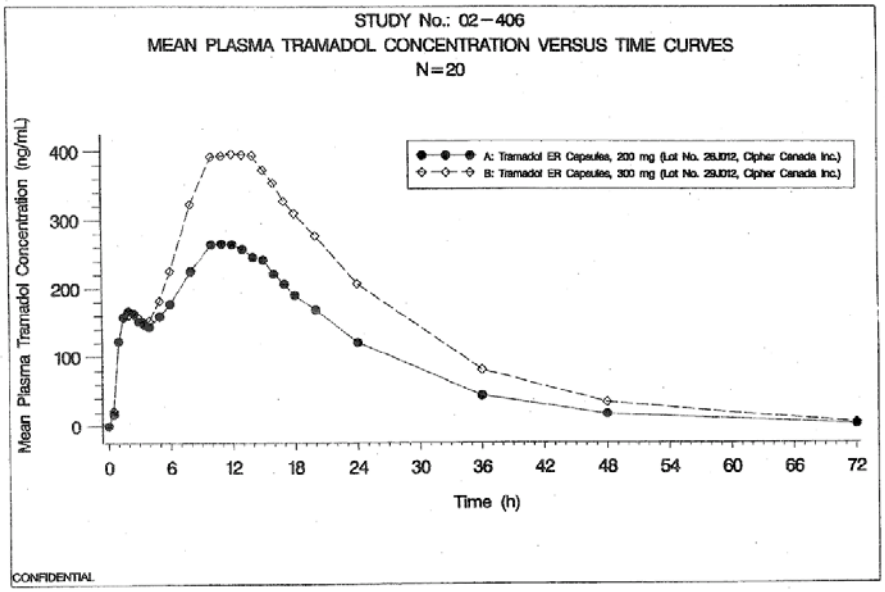
Sample Collection: Venous blood samples were collected pre-dose (2 x 7 mL), and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 36, 48, and 72 hours post-dose (1 x 7 mL) in each period.

Sample Analysis: Samples were analyzed at the bioanalytical laboratory of (b) (4) Analysis for tramadol and O-desmethyl-tramadol in human plasma was performed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) method (Project No. (b) (4)-524-00-01) with a calibration range of (b) (4) ng/mL for tramadol and (b) (4) ng/mL for O-desmethyl-tradol (M1). (b) (4) was used as an internal standard. The laboratory was blinded regarding the randomization scheme and treatment plan.

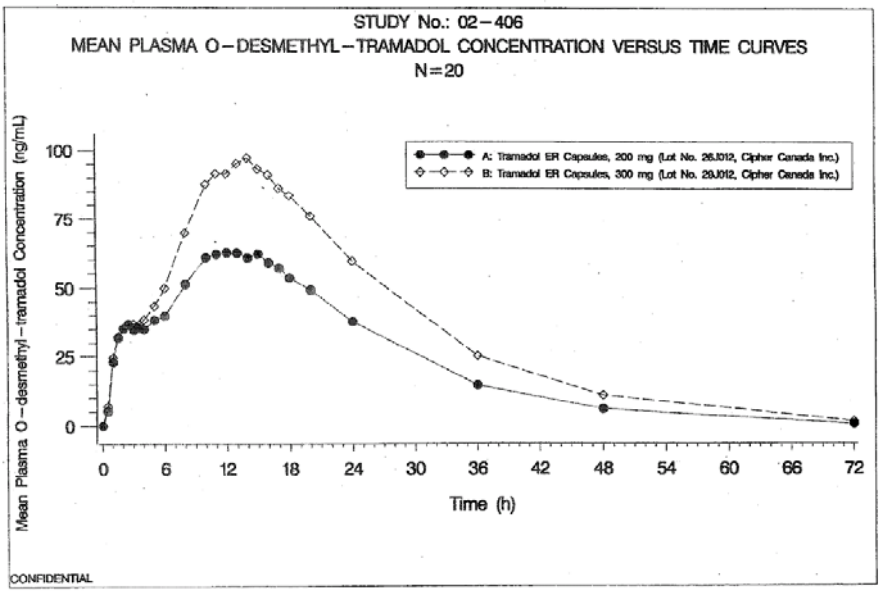
Pharmacokinetic Results:

PK Profiles

The extended-release capsule dosage form contains a tramadol HCI immediate release (IR) tablet and tramadol hydrochloride (HCI) ER beads. The *in vivo* concentration-time profiles for tramadol and its metabolite, M1, showed that there was a lower Cmax peak (Peak 1) at around 2 hours and a higher Cmax peak (Peak 2) at around 10-12 hours (Figure 1a and b). Peak 1 mainly represents the release of tramadol from the IR tablet and Peak 2 mainly represents the release of tramadol from the ER beads.



a. Tramadol



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations Following Administration of 200 mg (●) and 300 mg (◊) ER Capsules.

Relative Bioavailability

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) from the first 20 subjects who completed the study are summarized in Tables 1 and 2. Cmax and Tmax values in the tables refer to Peak 2.

Table 1. Summary of PK Result Comparison for Tramadol (A: 200 mg vs. B: 300 mg).

Parameter	Test (A)	Test (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval (%)	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean[a] Arithmetic Mean[b] (CV%)				
AUCt (ng·h/mL)	29.77 30.80 6159.10 (27)	30.71 31.72 9514.91 (28)	96.94	91.01 – 103.26	11.55
AUCi (ng·h/mL)	30.01 31.01 6202.69 (26)	31.05 32.15 9643.66 (29)	96.63	90.77 – 102.87	11.45
Cmax (ng/mL)	1.36 1.41 281.00 (28)	1.36 1.41 421.60 (28)	99.95	93.80 – 106.51	11.62
Tmax[c] (h)	11.00 (8.00-13.00)	11.99 (8.00-14.00)		-	
Kel[d] (h^{-1})	0.0837 (13)	0.0805 (17)		-	
Thalf[d] (h)	8.42 (14)	8.84 (16)		-	

[a] Based on dose normalized data.
[b] Based on measured data.
[c] Tmax is expressed as median (range).
[d] For Kel and Thalf the arithmetic mean and the inter-subject CV% are presented.

Table 2. Summary of PK Result Comparison for M1 (A: 200 mg vs. B: 300 mg).

Parameter	Test (A)	Test (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval (%)	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean[a] Arithmetic Mean[b] (CV%)				
AUCt (ng·h/mL)	7.81 8.19 1637.05 (31)	8.12 8.33 2499.15 (22)	96.19	90.21 – 102.56	11.74
AUCi (ng·h/mL)	8.04 8.39 1678.83 (30)	8.30 8.50 2550.97 (21)	96.80	91.07 – 102.90	11.18
Cmax (ng/mL)	0.323 0.336 67.22 (29)	0.326 0.337 101.14 (26)	99.22	93.56 – 105.22	10.74
Tmax[c] (h)	12.50 (10.00-17.00)	14.00 (10.00-16.00)		-	
Kel[d] (h^{-1})	0.0783 (16)	0.0741 (16)		-	
Thalf[d] (h)	9.07 (16)	9.60 (17)		-	

Because the IR tablet doses in 200 and 300 mg ER capsules are the same, 50 mg, Peak 1 and early AUC (e.g., $AUC_{0\text{-}4\ hour}$) were not dose proportional between 200 and 300 mg capsules as anticipated (Table 3 and Figure 2). Exposure to tramadol were about the same from 300 mg capsule compared to 200 mg capsule. The data indicated that most if not all IR tablet dose contributed to Peak 1 and early AUC. Similar relationship between 200 and 300 capsules were demonstrated for M1. Data for M1 were not shown.

Table 3. AUC(0-4), Cmax (Peak 1), and Tmax (Peak 1) Comparison for Tramadol (N=20) (A: 200 mg vs. B: 300 mg).

	A Test	B Reference	Ratio of Geometric Means	90% CI lower	90% CI upper
	Arithmetic Mean ± SD		Dose-Normalized		
AUC(0-4) (ng*h/mL)	500 ± 137	505 ± 133	147.87	138.61	157.74
Cmax (Peak 1) (ng/mL)	177 ± 48	174 ± 39	150.80	143.46	158.52
Tmax (Peak 1) (hr)	2.2 ± 0.6	2.5 ± 1.0	-	-	-

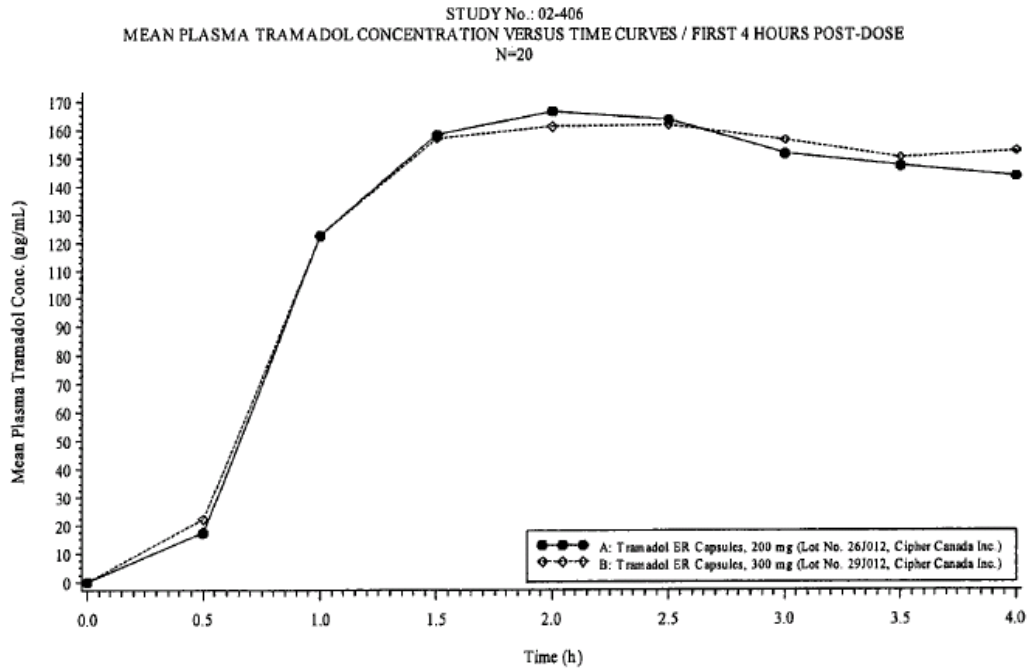


Figure 2. Mean Plasma Tramadol Concentrations Following Administration of 200 mg (●) and 300 mg (◊) ER Capsules.

Impact of emesis on AUC and Cmax

Twenty-one incidences of emesis were reported during the confinement of subjects at the clinic. They involved Subjects 02, 03, 04, 05, 08, 09, 10, 11 and 19, and were associated with treatments A, B, A/B, A/B, B, B, A, A/B and A, respectively. The emesis ranged in time of onset from approximately 8.5 hours post-dose to 32 hours post-dose.

Vomiting can be considered as detrimental to the integrity of the pharmacokinetic data. However, due to the numerous incidents of emesis, and the times of emesis (8.6 – 32 hours after dosing), the Sponsor chose not to exclude any subject from the study in order to preserve the necessary sample size.

Overall CV of PK parameters including all subjects is about 30%. PK data obtained from these subjects who had emesis incidences were within the range of other subject data indicating that the likely impact of emesis on PK was small (data not shown). This Reviewer further evaluated 90% confidence interval excluding tramadol PK data from these subjects who had vomiting (total N=28, N=14 for each treatment). The data suggest that dose-normalized AUC and Cmax (Peak 2) data between 200 and 300 mg were bioequivalent (Table 4), the same conclusion when including all data.

Table 4. AUC and Cmax Comparison for Tramadol Excluding PK data from 21 Emesis Incidences (Dose-Normalized) (A: 200 mg vs. B: 300 mg).

	A	B		90% CI	90% CI
	Geometric Mean		Ratio	lower	upper
AUCt (ng*h/mL)	6002	6424	93.42	86.86	100.49
AUCi (ng*h/mL)	6046	6465	93.52	87.15	100.36
Cmax (ng/mL)	278	289	96.38	89.34	103.98

Conclusions: Dose-normalized AUCt, AUCi, and Cmax,2 (Peak 2) for tramadol and M1 are equivalent between 200 and 300 mg capsules. However, because 200 and 300 mg capsules are not proportional in terms of IR and ER ratio, the Cmax of Peak 1 is not dose proportional between 200 and 300 mg. The clinical relevance of non-dose proportional for Cmax (Peak 1) and early AUC between 200 and 300 mg is not clear. Combined with the results from Study 556, the labeling needs to state that 100, 200 and 300 mg capsules are not interchangeable, i.e., the patients should not take one 100 mg and one 200 mg capsules for the 300 mg dose because higher peak 1 and early AUC will be achieved from one 100 mg and one 200 mg capsules vs. one 300 mg capsule.

4.2.5 Study 02-405 (TRAMPK.01.04): A Single-Dose, Two-Way Study to Compare the Bioavailability of a Formulation of Tramadol ER Capsules, 300 mg, in Normal, Healthy, Male Subjects, under Fasting and Fed Conditions

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Study Period: Period I: February 3, 2002
Period II: February 17, 2002
Sample Analysis Period: March 19, 2002 to April 5, 2002

Objective: To compare the bioavailability under fasting and fed conditions (high fat breakfast) of a new formulation of Tramadol 300 mg Capsules (Cipher Canada Inc.), in healthy, non-smoking, male subjects.

Study Design: This was an open-label, single-dose, randomized, two-treatment, two-period, two-sequence, crossover bioavailability study, with a washout period of at least 14 days between drug administrations.

Twenty subjects (including 2 alternates, all males) entered the study. Subject 12 was dismissed prior to dosing in Period II after leaving approximately 35% of his breakfast uneaten. Therefore, 19 subjects (including the two alternates) were dosed in Period II and completed the study. The first 18 subjects who completed the study had a mean age of 34 ±7 yrs (range 20 - 43 yrs), a mean height of 176.3 ±5.2 cm or 69.4 ±2.0 in, and a mean weight of77.6 ±5.9 kg or 171.0 ± 13.1 lb. 14 were Caucasians, 3 were African American and 1 was Asian.

A single dose of the test product (1 x 300 mg) was administered under the following conditions:

A: following an overnight fast of at least 10 hours.
B: after a high fat breakfast, served 30 minutes prior to drug administration, following an overnight fast of at least 10 hours.

Test Articles:
Tramadol ER Capsules, 300 mg (Cipher Canada Inc., Manufactued by Galephar P.R. Inc.), Lot No. 29J012

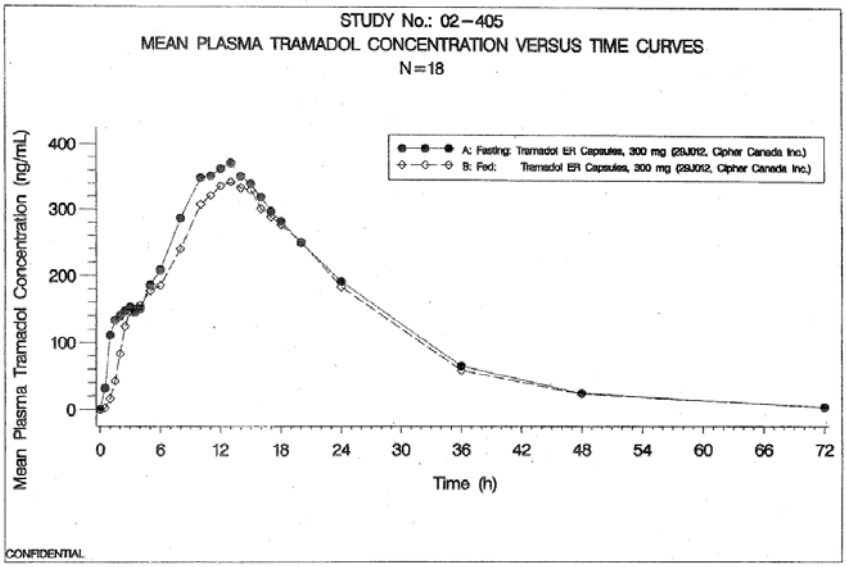
Sample Collection: Venous blood samples were collected pre-dose (2 x 7 mL), and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 36, 48, and 72 hours post-dose (1 x 7 mL) in each period.

Sample Analysis: Samples from the first 18 subjects who completed the study were analyzed at the bioanalytical laboratory of (b) (4) [redacted]. Analysis for tramadol and O-desmethyl-tramadol in human plasma was performed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) method (Project No. (b) (4) [redacted] 524-00-01) with a calibration range of (b) (4) [redacted] ng/mL for tramadol and (b) (4) [redacted] ng/mL for O-desmethyl-tradol (M1). (b) (4) [redacted] was used as an internal standard. The laboratory was blinded regarding the randomization scheme and treatment plan.

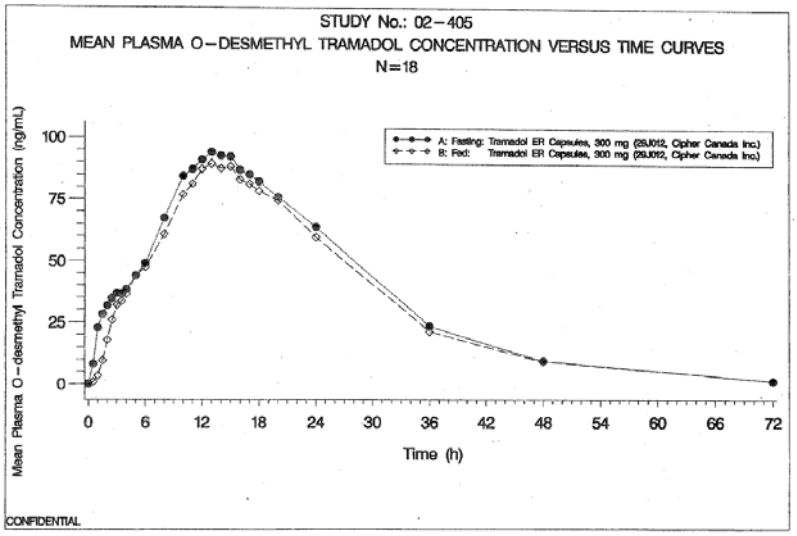
Pharmacokinetic Results:

PK Profiles

The mean plasma concentration-time profiles of tramadol and M1 metabolite under fasting and fed conditions are shown in Figure 1 (a and b).



a. Tramadol



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations under Fasting (●) and Fed (◊) Conditions.

Relative Bioavailability (Fed vs. Fasting)

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) from 18 subjects are summarized in Tables 1 and 2. Cmax and Tmax values in the tables refer to Peak 2.

Table 1. Summary of PK Result Comparison for Tramadol (A: Fast vs. B: Fed).

Parameter	Test (B)	Test (A)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval (%)	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCt (ng·h/mL)	7427.49 7832.67 (32)	8093.70 8493.73 (29)	91.77	88.17 – 95.51	6.87
AUCi (ng·h/mL)	7522.37 7928.36 (32)	8158.08 8557.91 (29)	92.21	88.82 – 95.72	6.43
Cmax (ng/mL)	337.65 352.83 (28)	370.83 387.00 (28)	91.05	87.29 – 94.98	7.27
Tmax[a] (h)	13.00 (12.00-15.00)	12.50 (8.00-15.00)		-	
Kel[b] (h^{-1})	0.0861 (22)	0.0889 (19)		-	
Thalf[b] (h)	8.41 (21)	8.08 (19)		-	

[a]Tmax is expressed as median (range).
[b]Expressed as arithmetic mean (CV%) only.

Table 2. Summary of PK Result Comparison for M1 (A: Fast vs. B: Fed).

Parameter	Test (B)	Test (A)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval (%)	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean (CV%)				
AUCt (ng·h/mL)	2183.23 2260.29 (27)	2366.85 2429.27 (23)	92.24	88.72 – 95.90	6.70
AUCi (ng·h/mL)	2239.18 2317.72 (27)	2418.89 2481.23 (23)	92.57	89.21 – 96.06	6.36
Cmax (ng/mL)	92.30 95.13 (25)	97.08 99.16 (21)	95.07	89.68 – 100.78	10.05
Tmax[a] (h)	13.00 (10.00-17.00)	14.00 (10.00-15.00)		-	
Kel[b] (h^{-1})	0.0796 (21)	0.0813 (19)		-	
Thalf[b] (h)	9.06 (20)	8.79 (18)		-	

[a]Tmax is expressed as median (range).
[b]Expressed as arithmetic mean (CV%) only.

Effect of food on Cmax (Peak 1) and AUC(0-4) were evaluated (Tables 3 and 4). Food did not have an effect on Cmax (Peak 1). However, the absorption of tramadol slowed down in the presence of food, AUC(0-4) decreased (31% and 40% for tramadol and M1, respectively) and Tmax (Peak 1) increased (1 hour and 30 min for tramadol and M1, respectively).

Table 3. AUC(0-4), Cmax (Peak 1), and Tmax (Peak 1) Comparison for Tramadol under Fasting and Fed Conditions (N=18).

	A Fasting (Reference)	B Fed (Test)	Ratio of Geometric Means	90% CI lower	90% CI upper
	Arithmetic Mean ± SD				
AUC(0-4) (ng*h/mL)	468 ± 126	321 ± 90	69.25	61.63	77.81
Cmax (Peak 1) (ng/mL)	166 ± 45	164 ± 45	99.67	93.12	106.68
Tmax (Peak 1) (hr)	2.5 ± 1.0	3.5 ± 0.6	-	-	-

Table 4. AUC(0-4), Cmax (Peak 1), and Tmax (Peak 1) Comparison for M1 under Fasting and Fed Conditions (N=18).

	A Fasting	B Fed	Ratio of Geometric Means	90% CI lower	90% CI upper
	Arithmetic Mean ± SD				
AUC(0-4) (ng*h/mL)	109 ± 30	70 ± 33	60.37	53.29	68.39
Cmax (Peak 1) (ng/mL)	39 ± 9	37 ± 12	91.47	85.16	98.26
Tmax (Peak 1) (hr)	3.4 ± 0.9	3.8 ± 0.4	-	-	-

Impact of emesis on AUC and Cmax

Four incidences of emesis were reported during the confinement of subjects at the clinic. They involved Subjects 06 and 09 in association with both treatments and ranged in time of onset from approximately 9.5 hours post-dose to 18 hour post-dose.

Vomiting can be considered as detrimental to the integrity of the pharmacokinetic data. The Sponsor did not exclude these subjects from the study. This Reviewer evaluated 90% confidence interval excluding tramadol PK data from 2 subjects (Subjects 6 and 9) who had emesis incidences (N=16 for Regimen A and Regimen B). The data suggest that AUC and Cmax (Peak 2) for both tramadol and M1 were bioequivalent between fasting and fed conditions (Tables 5 and 6).

Table 5. AUC and Cmax (Peak 2) Comparison for Tramadol Excluding PK data from 4 Emesis Incidences (A: Fasting vs. B: Fed).

	B	A	Ratio	90% CI lower	90% CI upper
	Geometric Mean				
AUCt (ng*h/mL)	7783	8348	93.23	89.59	97.02
AUCinf (ng*h/mL)	7713	8279	93.17	89.50	97.00
Cmax (Peak 2) (ng/mL)	349	383	91.13	87.00	95.47

Table 6. AUC and Cmax (Peak 2) Comparison for M1 Excluding PK data from 4 Emesis Incidences (A: Fasting vs. B: Fed).

	B	A	Ratio	90% CI lower	90% CI upper
	Geometric Mean				
AUCt (ng*h/mL)	2145	2323	92.36	88.35	96.55
AUCinf (ng*h/mL)	2192	2378	92.18	88.40	96.11
Cmax (Peak 2) (ng/mL)	90	96	94.14	88.19	100.50

Conclusions: Food does not affect C_{max} (Peaks 1 and 2) or AUC_{inf} following 300 mg CIP-Tramadol ER dosing, however, the absorption of tramadol slows down in the presence of food. There is a 1 hour and 30 min delay in $T_{max,1}$ (Peak 1) and $T_{max,2}$ (Peak 2), respectively (Figure 4). In addition, AUC(0-4hr) decreased 31% in the presence of high fat meal.

4.3 OCP Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	(b) (4)	**Brand Name**	**CIP-TRAMADOL ER**
OCPB Division (I, II, III)	**DCP2**	**Generic Name**	**Tramadol Hydrochloride**
Medical Division	**DAARP**	**Drug Class**	**Centrally Acting Analgesic**
OCPB Reviewer	**Lei Zhang, Ph.D.**	**Indication(s)**	**Management of moderate to moderately severe chronic pain in adults**
OCPB Team Leader	**Suresh Doddapaneni, Ph.D**	**Dosage Form**	**Extended Release Capsules, 100, 200, and 300 mg**
		Dosing Regimen	**The starting dose of CIP-TRAMADOL ER CAPSULES is 100 mg administered once a day. The** (b) (4)
Date of Submission	**7/3/2006**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**2/28/2007**	**Sponsor**	**Cipher Pharmaceuticals, Ltd.**
PDUFA Due Date	**5/3/2007**	**Priority Classification**	**New Formulation (5-S)**
Division Due Date	**4/3/2007**		**IND** (b) (4) 505 b(2); Reference Ultram (NDA 20-281)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
Human PK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**			
multiple dose:	**X**			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**2**	**2**	**Study TRAMPK.01.03 (02-406) (200 and 300 mg, fasting) Study TRAMPK.02.02 (02-556) (100 and 300 mg, fasting)**

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**3**	**2**	**Study TRAMPK01.01 (02-403) (200 mg vs. Ultram, fasting state, single dose)** **Study TRAMPK01.02 (02-404) (200 mg vs. Ultram steady state) (Study was repeated and not included in analysis)** **Study TRAMPK02.02 (02-549) (200 mg vs. Ultram steady state)**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**	**1**	**1. Study TRAMPK.01.04 (02-405) (300 mg, single dose)**
Dissolution:	**X**			(b) (4) **If IVIVC is established, acceptance criteria will be determined based on IVIVC**
(IVIVC):				**Report is not submitted**
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies		**6**	**5**	

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable?	**X**			
Comments sent to firm?				
QBR questions (key issues to be considered)	• **What is PK profile of 100, 200 and 300 mg CIP-TRAMADOL ER capsules? Is PK dose proportional?** • **How does exposure of the CIP-TRAMADOL ER capsules compare to Ultram at steady state for both tarmadol and O-desmethylated M1 metabolite at equivalent doses?** • **Is there a food effect (done with 300 mg capsules)?** • **Does PK of the new CIP-TRAMADOL ER capsule formulation support the proposed indication?** • **Is there an alcohol interaction?**			
Other comments or information not included above	**This is a 505 b(2) application. The sponsor did not conduct the bioequivalence study to RLD with the 300 mg capsule (highest dose strength). This is considered acceptable because tramadol has tolerability issues and the Sponsor believed that 300 mg may not be tolerated by healthy volunteers for multiple dose studies. The sponsor used 200 mg daily dose that represents the most common dose given to patients.** **Sponsor conducted in vitro study for alcohol interaction determination. The Division reached agreement with the sponsor that an in vivo study for alcohol interaction is not needed.**			
Primary reviewer Signature and Date	**Lei Zhang, 8/7/2006** **3/9/2007 revised**			
Secondary reviewer Signature and Date	**Suresh Doddapaneni**			

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

/s/

Lei K Zhang
3/26/2007 10:15:17 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/26/2007 11:04:20 AM
BIOPHARMACEUTICS