CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-123

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21-123	**SUBMISSION DATES:**	8/31/1999
PRODUCT:	Tramadol HCl and Acetaminophen Tablets 37.5 mg/325 mg		1/13/00, 1/31/00, 3/17/00, 3/30/00, 4/3/00, 4/20/00, 5/3/00
SPONSOR:	R.W. Johnson Route 202, P.O. Box 300, Raritan, NJ 08869		
TYPE OF SUBMISSION:	Original	**REVIEWER:**	Sue-Chih Lee, Ph.D.

I. Background

The proposed product is a combination of tramadol and acetaminophen. Tramadol is a centrally acting synthetic analgesic compound that is not derived from natural sources or chemically related to opiates and is currently marketed as ULTRAM® tramadol HCl tablets. It appears that at least two complementary mechanisms are involved in producing analgesia: inhibition of the reuptake of norepinephrine and serotonin and binding to μ-opioid receptors. In animal models metabolite M1 is up to six times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid receptor binding affinity. Acetaminophen is another centrally acting analgesic and appears to produce analgesia by elevation of the pain threshold.

Indication:
Treatment of [redacted] acute [redacted] pain.

Recommended dose:
One to two tablets every 4 to 6 hours as needed with no more than eight tablets in a 24-hour period (corresponding to maximum daily dose of 300 mg tramadol and 2.6 g APAP).

In treating long term painful conditions, initiate with 1 tablet/day and titrate every three days by 1-tablet increments as tolerated to reach a dose of 4 per day, after which 1-2 tablets may be administered every 4-6 hours as needed for pain relief up to a maximum of 8 tablets per day.

For the treatment of acute pain, full therapeutic doses (1-2 tablets every 4-6 hours) may be initiated as needed up to a maximum of 8 tablets per day.

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval be increased not to exceed 2 tablets every 12 hours

Provided in the Human Pharmacokinetics and Biopharmaceutics section are four studies (single dose BA, food effect, single dose drug interaction study, and a multiple dose drug interaction study), two population pharmacokinetic analysis, one PK/PD analysis and several published literature articles. The to-be-marketed formulation was used in all Phase 1 studies. Tramadol was administered as a racemate. Pharmacokinetics of acetaminophen and the (+) and (-) enantiomers of tramadol and its active metabolite M1 were characterized in all human PK

studies. Since the formation of M1 is known to be dependent on CYP2D6 isozyme, genotyping of CYP2D6 was performed to identify poor metabolizers in three Phase 1 PK studies.

II. Synopsis (QUESTION BASED)

1. What was the rationale for combining tramadol with acetaminophen (APAP)?

Acetaminophen is generally absorbed quickly, produces a quick onset of analgesia but has a short half-life leading to short duration. Tramadol on the other hand has a delayed onset but longer duration. In addition, the two drugs produce analgesic activities through different mechanisms with tramadol having opiate-like properties and acetaminophen having prostaglandin inhibition properties. It was thought that the two drugs would be at least complementary to each other. The goal was to provide analgesia equal to or greater than the sum of the components with a resultant reduction in the required dose of each agent, possibly leading to reduced incidences of side effects.

2. Were the assay methods adequate for characterizing the pharmacokinetics of the components in the combination tablets?

Yes, the assay methods were adequate. Tramadol was present in the combination tablet as racemate.

These methods were validated.

3. Has the pharmacokinetics of APAP and tramadol in the combination tablets been adequately characterized?

The PK of APAP and tramadol in the combination tablets was adequately characterized. The individual components (APAP and tramadol) have been marketed separately, therefore, no extensive PK studies were necessary.

PK under Fasted conditions (based on single dose administration of 3 combination tablets)

Acetaminophen was absorbed quickly and peak plasma concentration was reached approximately 1 hour postdose. Plasma acetaminophen concentrations then followed a monoexponential decay with a half-life of approximately 2.5 hours.

For tramadol, both stereoisomers reached a peak plasma concentration at approximately 2 hours postdose. However, the (+)- stereoisomer had a (~15%) higher peak plasma concentration and a (~30%) higher AUC compared to the (-)-isomer. The half-life of tramadol was 5- 6 hours (5.8 hr for (+)-isomer and 5.2 hr for (-)-isomer).

Peak plasma concentrations of the active metabolite M1 was achieved at approximately 3 hours postdose for both stereoisomers. (+)-M1 had a (~20%) lower Cmax but a similar AUC compared to (-)-M1. The half-life (~6.5 hrs) was similar for both isomers. The PK variability of M1 is high partly because the formation of M1 is dependent on CYP2D6 which exhibits genetic polymorphism.

Food effect

Food has no significant effect on the pharmacokinetics of tramadol. Following a high fat meal, mean tramadol AUC increased 5-6%, while mean Cmax remained the same with Tmax delayed for about 0.6 hours for both enantiomers. As for M1 enantiomers, the increase in either mean Cmax or AUC was less than 5% after a high fat meal.

Following a high fat breakfast, the bioavailability of acetaminophen decreased (mean Cmax: -16.0%, AUC: -5.2%) while Tmax was prolonged to 1.9 hrs (vs. 1.1 hrs under fasted conditions). Based on the 90% confidence interval of 70-143% for Cmax and 80-125% for AUC, however, the food effect is considered insignificant.

Interactions between acetaminophen and tramadol

Following a single dose administration, the interaction between acetaminophen and tramadol, if any, was found to be minimal. Upon multiple dosing to steady state, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14.0% for (+)-tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-M1 and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear.

4. Have the effects of certain intrinsic/extrinsic factors on APAP and/or tramadol PK been evaluated to address possible need for dosage adjustment?

Two population PK analyses were performed to identify covariates that affected the PK of tramadol or APAP. One of the analyses was based on Phase I studies in healthy subjects and the other [redacted] Although some factors were found to affect the PK of tramadol or APAP, none was critical enough to warrant dosage adjustment or other measures. (Note that dosage adjustment can be a complex matter for a combination product with active metabolites). The findings are summarized below.

Population PK analysis in healthy subjects

Gender: The analysis found that clearance of (+) and (-) tramadol was approximately 20% higher in female subjects. A simulation was performed which showed that the reduction in tramadol bioavailability in females was ~10% for Cmax, ~20% for Cmin and 17% for AUC based on geometric means.

Race: The analysis set 2 categories for race, i.e., white and nonwhite. Clearance of (+) and (-)-M1 in nonwhite subjects was ~20% lower compared to white subjects.

Body Weight: Clearance of APAP was roughly proportional to body weight in healthy adults. In the data set, female body weight was about 14% lower on average compared to males and, thus APAP clearance was approximately 14% lower in females.

Creatinine clearance: CL_{CR} was a significant factor for M1 clearance. The relationship was less than proportional (to the power of 0.6-0.7).
CYP2D6 genotyping: CYP2D6 poor metabolizers had a ~20% reduction in plasma clearance of (+)-tramadol resulting in a 40% reduction in the formation of metabolite M1.

[redacted]

Factors such as gender, age, weight, CL_{CR}, race and concomitant use of estrogen were evaluated. However, the analysis only identified body weight as a factor for APAP clearance and CL_{CR} as a factor for M1 clearance. CYP2D6 genotyping in these patients was not performed which could increase the unexplained variability of the data making it more difficult to identify other covariates.

5. Did the sponsor demonstrate that the combination tablets work as expected?

The sponsor conducted several clinical trials and a PK/PD analysis of analgesia in dental pain trials was carried out. The results showed that APAP contributed to quick onset while tramadol extended the duration of analgesia and that APAP helped reduce the remedication rate as compared to tramadol alone. The PK/PD modeling established the relationship between plasma concentrations of APAP/tramadol and analgesic effect as well as the consequent remedication rate. Contrary to the findings of animal studies, the modeling revealed that in humans the analgesic effect of the combination was additive and not synergistic. Increase in tramadol dose to 100 mg provides minimal improvement in pain score (i.e. increase in the percentage of patients with adequate pain relief was <5%).

III. Labeling Comments

Many parts of the Clinical Pharmacology section of the label require changes. The revised version is given in Appendix 2.

IV. Recommendation

The submission has adequately addressed the requirements of the Office of Clinical Pharmacology and Biopharmaceutics. The application is acceptable. Labeling comments should be communicated to the sponsor.

/S/ 6/7/00

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. /S/ 6/7/00

CC:
NDA 21-123
HFD-550 (Div.File)

HFD-550 (CSO/Kong)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HED-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

APPEARS THIS WAY
ON ORIGINAL

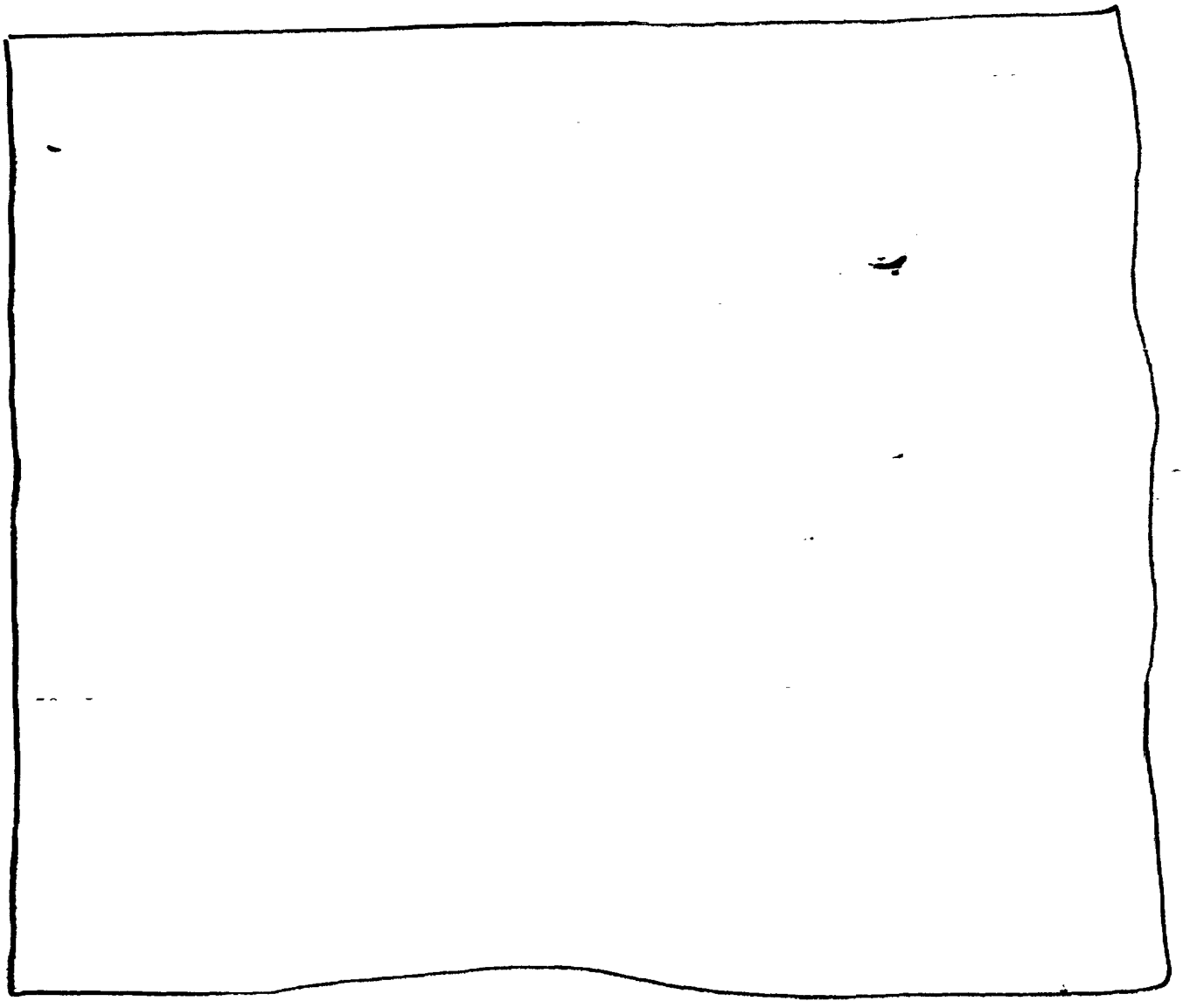
Table of Contents: Page no.

V. Formulation

The components and composition of the tramadol/APAP combination tablets are given in the table below.

Ingredient	mg/Tablet	Targeted Formulation
Tramadol Hydrochloride [redacted]	37.50	
Acetaminophen, USP	325.00	
Powdered Cellulose, NF		
Pregelatinized Starch, NF		
Sodium Starch Glycolate, NF		
Starch, NF		
Purified Water, USP[a]		
Magnesium Stearate, NF		
Total Weight of Tablet Cores		
OPADRY® Light Yellow, [redacted]		
Carnauba Wax, NF		
Total Weight of Coated Tablets	441.017	

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



VII. Summary of Bio/PK/PD Characteristics

SINGLE DOSE PHARMACOKINETICS

Study TRAM-PHI-001: A Pharmacokinetic Study of Tramadol and Acetaminophen in Healthy Subjects Following a Single Oral Administration of One Combination Tablet

This study was designed to evaluate the pharmacokinetics/bioavailability of tramadol and APAP in healthy male subjects following single oral dose administration of one Tramadol/APAP combination tablet containing 37.5 mg tramadol HCl and 325 mg APAP. The study was conducted in 12 healthy male subjects (age: 28±7.7 yrs; wt: 69.7±10.4 kg) under fasted conditions. Fourteen plasma samples were collected from each individual at various time points up to 24 hours following dosing and samples were assayed for the (+) and (-) enantiomers of

tramadol and M1 and APAP. Pharmacokinetic analysis included the determination of C_{max}, t_{max}, AUC (0-*), AUC (0-∞), CL/F, k_e, and $t_{½}$.

Results

The mean (±SD) plasma concentration-time profiles of APAP and the (+)- and (-) enantiomers of tramadol and M1 following a single oral dose of one combination tablet are shown in the figures below.

Figure 1: Mean (±SD) Plasma Concentration-Time Profiles of the *(+)- and (-) Enantiomers of Tramadol and M1* Following a Single Oral Dose of One Combination Tablet

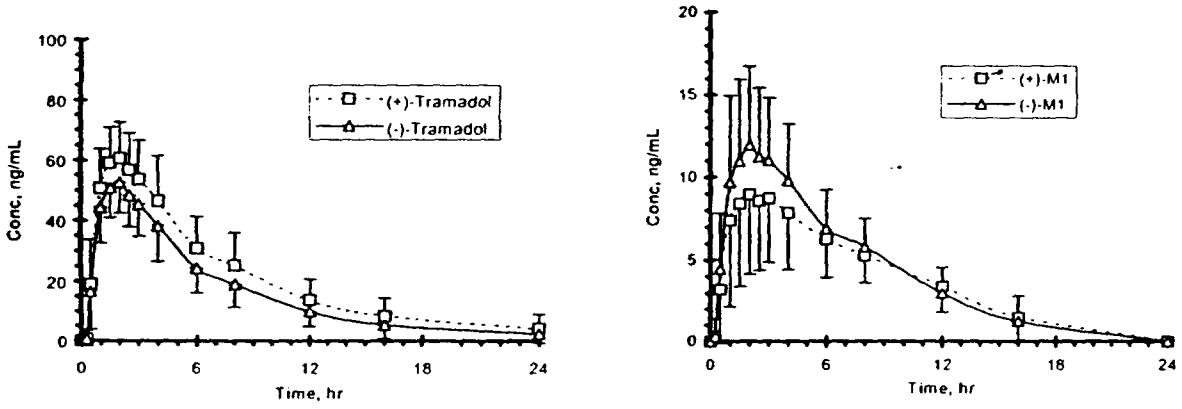
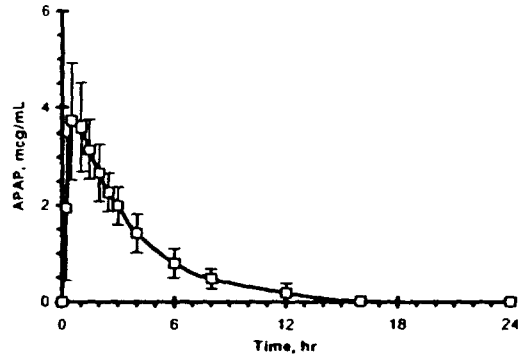


Figure 2: Mean *APAP* plasma Concentration-Time Profile Following a Single Dose of One Combination Tablet



The table below summarizes the mean (±SD) pharmacokinetic parameters for all five analytes [(+)-tramadol, (-)-tramadol, (+)-M1, (-)-M1, and APAP].

Tramadol and M1:

Peak plasma concentrations of (+) and (-)-tramadol were reached in approximately 1.8 (±0.7) hours with a Cmax of 64.3±9.3 ng/mL for (+)-tramadol and 55.5±8.1 ng/mL for (-)-tramadol, respectively. The elimination half-life for the two enantiomers was about 5 hours (5.14±1.38 hrs for (+)-tramadol; 4.67±1.20 hrs for (-)-tramadol). Compared to the parent compound, the two enantiomers of M1 had a lower Cmax (about 11-13 ng/mL), longer Tmax (about 2.1±0.7 hrs for

both enantiomers) and longer elimination half-life (6-8 hrs). The overall AUC for tramadol was approximately 4-fold that for the M1 metabolite. CYP2D6 genotyping was not performed on these subjects. However, two subjects (#106 &.109) had unmeasurable (+)-M1 concentrations, indicating these two subjects are likely to be poor metabolizers.

APAP:

The mean Cmax for acetaminophen was 4.2±0.8 µg/mL with a mean Tmax of 0.9±0.7 hours and mean elimination half-life of 2.5±0.6 hours. Compared to tramadol, acetaminophen has a rapid absorption and shorter half-life.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of Acetaminophen (APAP) and the (+) and (-) Enantiomers of Tramadol and M1 Following A Single Oral Dose Of One Combination Tablet

	Tramadol + Acetaminophen (N = 12)									
Parameter[a]	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		APAP	
C_{max} (ng/mL)	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
t_{max} (h)	1.8	(0.6)	1.8	(0.7)	2.1	(0.7)	2.2	(0.7)	0.9	(0.7)
AUC (0-*) (h·ng/mL)	488.8	(178.5)	382.5	(133.3)	79.9	(50.8)	88.9	(34.8)	14.6	(3.8)
AUC (0-∞) (h·ng/mL)	537.0	(210.4)	415.6	(149.4)	111.3	(61.4)	117.5	(33.1)	15.6	(4.1)
CL/F (mL/min)	588	(226)	736	(244)	2245	(700)	2504	(661)	365	(84)
k_e (l/h)	0.144	(0.038)	0.157	(0.037)	0.100	(0.034)	0.118	(0.026)	0.28	(0.058)
$t_{½}$ (h)	5.14	(1.38)	4.67	(1.20)	7.78	(2.98)	6.18	(1.59)	2.54	(0.63)

[a] For APAP, C_{max} measured as µg/mL and AUC measured as h·µg/mL.
[b] AUC (0-*): AUC from time 0 to the time point corresponding to the last measurable concentration.

Combination tablet vs. Solutions:

The pharmacokinetics and bioavailability data from this study were compared to historical data following single-dose administration of an oral solution of 500 mg APAP (dose normalized to 325 mg) and an oral solution of 100 mg tramadol HCl (dose normalized to 37.5 mg). Mean parameter values for all 5 analytes obtained after a single dose exposure to an oral solution are given in the table below along with the results for the Tramadol/APAP combination tablet. Comparison of this data indicates that the bioavailability of tramadol and APAP in a tablet dosage form does not appear to be appreciably different, although, as expected, the rate of absorption is somewhat slower with the tablet formulation compared to an oral solution.

Table 2: Summary of Mean (±SD) Pharmacokinetic Parameters

Parameter[a]	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		APAP	
Oral Solution										
C_{max} (ng/mL)	59.0	(5.5)	50.5	(5.5)	8.3	(4.5)	12.9	(4.2)	6.96	(2.21)
t_{max} (h)	1.73	(0.78)	1.40	(0.54)	2.81	(1.15)	1.69	(1.11)	0.31	(0.12)
AUC (h·ng/mL)	556	(118)	405	(78)	112	(47)	141	(33)	14.82	(2.28)
Combination Tablet										
C_{max} (ng/mL)	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
t_{max} (h)	1.8	(0.6)	1.8	(0.7)	2.1	(0.7)	2.2	(0.7)	0.9	(0.7)
AUC (h·ng/mL)	537.0	(210.4)	415.6	(149.4)	111.3	(61.4)	117.5	(33.1)	15.6	(4.1)

[a] For APAP, C_{max} measured as µg/mL and AUC measured as h·µg/mL.

Conclusion:

The results of this study indicate that the extent of absorption of the combination tablet did not differ appreciably from that of either component administered separately as an oral solution although, as expected, the rate of absorption was somewhat slower with the tablet formulation compared to an oral solution.

Comment: There is no information on 2D6 genotyping for subjects participated in the oral solution studies.

DRUG-DRUG INTERACTIONS (TRAMADOL/APAP INTERACTIONS)

A. Single Dose

Study #TRAMAP-PHI-002: Evaluation Of The Effect Of Tramadol HCl/Acetaminophen Combination On The Pharmacokinetics Of Tramadol And Acetaminophen Following Administration Of A Single Oral Dose In The Fasted State To Healthy Subjects (Vol. 1.039-1.040)

Study design: This study was designed to evaluate the effect of a tramadol /APAP combination on the individual pharmacokinetics of tramadol and APAP following a single oral dose administered in the fasted state to healthy subjects. It was a randomized, three-way crossover study conducted in 24 healthy subjects (12M & 12F; age: 28.7±6.2 yrs; wt: 70.2±9.9 kg) and 20 subjects completed the study. Each subject received three treatments with at least 1-week washout period between treatments. The three treatments were:

- Treatment A: 112.5 mg tramadol HCl + 975 mg APAP (3 combination tablets)
- Treatment B: 112.5 mg tramadol HCl (3 x 37.5 mg tramadol HCl capsules)
- Treatment C: 975 mg APAP (3 x 325 mg APAP tablets)

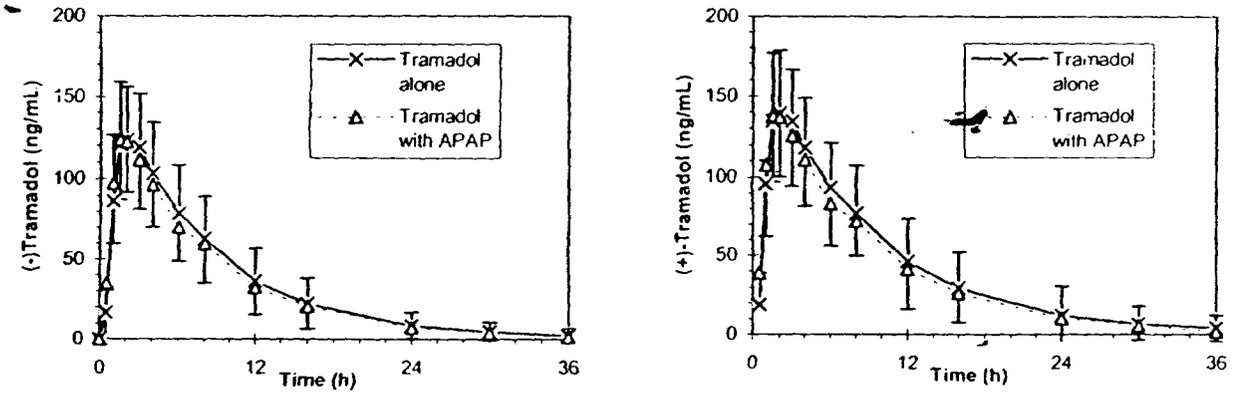
Analysis: Blood samples were collected at scheduled times up to 36 hours after dose administration. CYP2D6 genotyping was performed on each subject to identify poor metabolizers of tramadol. Pharmacokinetic analysis included the determination of C_{max}, t_{max}, AUC (0-*), AUC (0-∞), CL/F, k_e, and $t_{½}$. Pharmacokinetic parameters of tramadol and M1 with and without APAP and parameters of APAP with and without tramadol were compared using an analysis of variance (ANOVA) model and 90% confidence intervals.

Results

Tramadol

The mean (±SD) plasma concentration-time curves of (+)- and (-)-tramadol following a single dose of tramadol alone (Treatment B) or with APAP (Treatment A) are shown in Figure 1. In general, mean plasma tramadol concentrations were slightly lower for Treatment A than Treatment B.

Figure 1: The (+)- and (-)-Tramadol Mean (±SD) Plasma Concentration Profiles Following a Single Dose of Tramadol Alone or with Acetaminophen (Protocol TRAMAP-PHI-002)



The mean (±SD) pharmacokinetic parameters of the two enantiomers of tramadol following a single dose of tramadol alone (Treatment B) or with APAP (Treatment A), along with the results of the ANOVA and the 90% confidence intervals, are summarized in Table 1. The two treatments had similar Cmax (148 ng/mL; occurring at approximately 2 hours postdose) while Treatment A had a lower AUC (~8% lower for (+)-tramadol and 6% lower for (-)-tramadol). Based on the bioequivalence criteria of 90% CI within 80-125%, the two treatments were considered bioequivalent for both (+)- and (-)-tramadol.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of (+)-Tramadol and (-)-Tramadol Following a Single Dose of Tramadol Alone (Treatment B) or With Acetaminophen (Treatment A)

Parameter	Tramadol + APAP (Treatment A, N=20)		Tramadol (Treatment B, N=20)		% Difference[a]	ANOVA[b]	90% CI[c]	
(+)-Tramadol:								
C_{max} (ng/mL)	148	(32)	148	(35)	0.0	NS	EQ	94.3-107.5
t_{max} (h)	1.9	(0.6)	2.1	(0.7)	-9.5	NS	--	--
AUC (0-*) (ng h/mL)	1330	(449)	1454	(569)	-8.5	NS	EQ	86.7-100.1
AUC (0-∞) (ng h/mL)	1385	(510)	1504	(652)	-7.9	NS	EQ	88.3-100.6
CL/F (mL/min)	661	(214)	631	(230)	4.8	NS	--	--
k_e (h^{-1})	0.124	(0.022)	0.120	(0.024)	2.5	NS	--	--
$t_{½}$ (h)	5.8	(1.4)	6.1	(1.8)	-4.9	NS	--	--
(-)-Tramadol:								
C_{max} (ng/mL)	132	(32)	132	(35)	0.0	NS	EQ	94.3-108.3
t_{max} (h)	1.9	(0.6)	2.1	(0.7)	-9.5	NS	--	--
AUC (0-*) (ng h/mL)	1114	(406)	1185	(525)	-6.0	NS	EQ	90.9-103.0
AUC (0-∞) (ng h/mL)	1145	(441)	1217	(567)	-5.9	NS	EQ	91.2-103.2
CL/F (mL/min)	809	(280)	797	(307)	1.5	NS	--	--
k_e (h^{-1})	0.138	(0.026)	0.132	(0.027)	4.5	NS	--	--
$t_{½}$ (h)	5.2	(1.2)	5.5	(1.5)	-5.5	NS	--	--

[a] Reference to tramadol alone, Treatment B, (A-B)*100/B

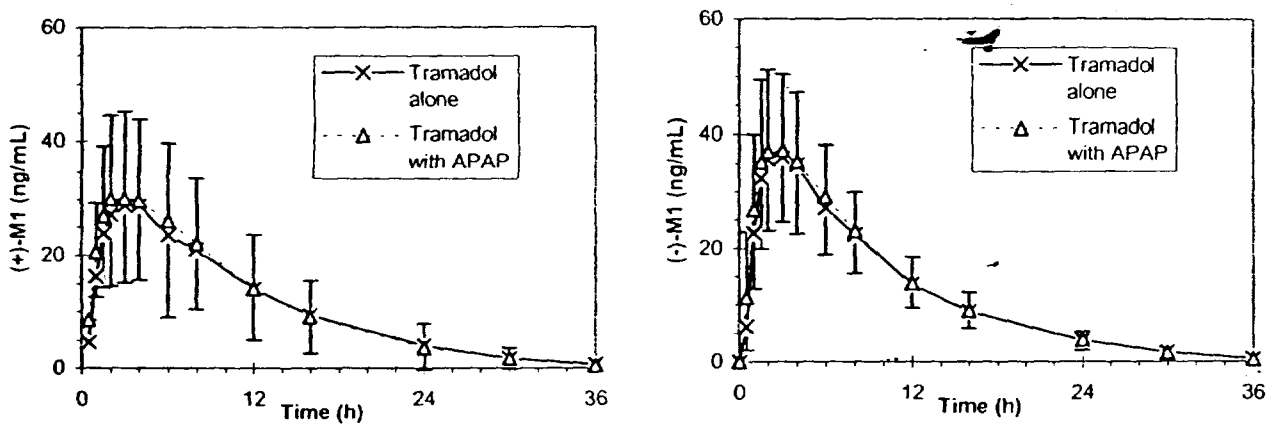
[b] ANOVA results based on log-transformed parameters; NS : p>0.05.

[c] 90% CI results based on log-transformed parameters; Reference: Treatment B.
EQ: bioequivalent.

Metabolite M1

The mean (±SD) plasma concentration-time profiles of (+)-M1 and (-)-M1 following a single dose of tramadol alone (Treatment B) or with APAP (Treatment A) are shown in Figure 2. In general, the two treatments had similar M1 concentration profiles.

Figure 2: The (+)-M1 and (-)-M1 Mean (±SD) Plasma Concentration Profiles Following a Single Dose of Tramadol Alone (Treatment B) or with Acetaminophen (Treatment A)



Mean (±SD) pharmacokinetic parameters of the two M1 enantiomers following a single dose of tramadol alone (Treatment B) or with APAP (Treatment A), as well as the statistical results, are summarized in Table 2. Treatment A had slightly (3-4%) higher mean Cmax and AUC for M1 but the two treatments had a similar Tmax (2.9 hrs.). Based on the 90% CI, the two treatments were considered bioequivalent with respect to the two M1 enantiomers.

Table 2: Summary of Mean (±SD) Pharmacokinetic Parameters of (+)-M1 and (-)-M1 Following a Single Dose of Tramadol Alone (Treatment B) or With Acetaminophen (Treatment A)

	Tramadol + APAP (Treatment A, N=20)		Tramadol (Treatment B, N=20)		% Difference[a]	ANOVA[b]	90% CI[c]	
(+)-M1:								
C_{max} (ng/mL)	32	(15)	31	(15)	6.7	NS	EQ	97.1-114.4
t_{max} (h)	2.9	(1.2)	2.9	(0.8)	0.0	NS	--	-
AUC (0-*) ng h/mL)	380	(173)	377	(166)	0.8	NS	EQ	91.6-109.8
AUC (0-∞)(ng h/mL)	407	(166)	393	(168)	3.6	NS	EQ	99.4-109.8
CL/F (mL/min)	2172	(872)	2299	(1030)	-5.5	NS	--	-
k_e (h^{-1})	0.110	(0.021)	0.108	(0.017)	1.9	NS	--	-
$t_{½}$ (h)	6.5	(1.5)	6.6	(1.3)	-1.5	NS	--	-
(-)-M1:								
C_{max} (ng/mL)	40	(13)	39	(14)	2.6	NS	EQ	96.3-111.1
t_{max} (h)	2.8	(1.5)	2.8	(1.1)	0.0	NS	--	-
AUC (0-*)(ng h/mL)	426	(126)	410	(114)	3.9	NS	EQ	98.1-108.3
AUC (0-∞)(ng h/mL)	445	(119)	430	(113)	3.5	NS	EQ	99.4-107.6
CL/F (mL/min)	1983	(544)	2059	(593)	-3.7	NS	--	-
k_e (h^{-1})	0.112	(0.022)	0.109	(0.020)	2.8	NS	--	-
$t_{½}$ (h)	6.5	(1.6)	6.6	(1.8)	-1.5	NS	--	-

[a] Reference to tramadol alone, Treatment B, (A-B)*100/B

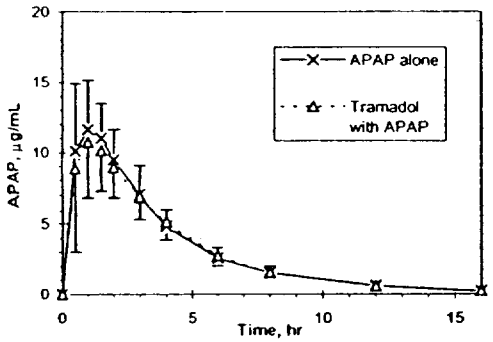
[b] ANOVA results based on log-transformed parameters; NS = not significant, p>0.05.

[c] 90% CI results based on log-transformed parameters; Reference: Treatment B; EQ: bioequivalent

Acetaminophen

Mean (±SD) plasma concentration-time profiles of APAP following a single dose of APAP alone (Treatment C) or with tramadol (Treatment B) are shown in Figure 3. Peak plasma concentrations of acetaminophen occur at about one hour postdose and are not affected appreciably by coadministration with tramadol.

Figure 3: Mean (±SD) APAP Plasma Concentration Profiles Following a Single Dose of APAP Alone (Treatment C) or with Tramadol (Treatment A)



The mean (±SD) pharmacokinetic parameters of APAP and the results of the ANOVA and the 90% confidence intervals are summarized in Table 3. The two treatments had similar AUC values although Cmax was 6.8% lower for the combination tablets as compared to APAP alone. Based on the 90% confidence interval for Cmax and AUC, the two treatments are considered bioequivalent with respect to acetaminophen.

Table 3: Summary of Arithmetic Mean (±SD) Pharmacokinetic Parameters of Acetaminophen Following a Single Dose of Acetaminophen Alone (Treatment C) or With Tramadol (Treatment A)

Parameter	Tramadol + APAP (Treatment A, N=21)		APAP (Treatment C, N=21)		% Difference[a]	ANOVA[b]	90% CI[c]	
Acetaminophen:								
C_{max} (µg/mL)	12.3	(3.5)	13.2	(3.1)	-6.8	NS	EQ	84.9-100.6
t_{max} (h)	1.1	(0.8)	1.0	(0.5)	10.0	NS	--	-
AUC (0-*) (µg h/mL)	49.2	(11.0)	50.0	(11.9)	-1.6	NS	EQ	93.9-103.9
AUC (0-∞) (µg h/mL)	50.8	(11.1)	51.7	(12.0)	-1.7	NS	EQ	93.9-103.7
CL/F (mL/min)	337	(85)	332	(86)	1.5	NS	--	-
k_e (h^{-1})	0.258	(0.048)	0.253	(0.041)	2.0	NS	--	-
$t_{½}$ (h)	2.8	(0.5)	2.8	(0.4)	0.0	NS	--	-

[a] Reference to APAP alone, Treatment C, (A-C)*100/C

[b] ANOVA results based on log-transformed parameters; NS = not significant, p>0.05.

[c] 90% CI results based on log-transformed parameters; Reference: Treatment B.
EQ: bioequivalent

CYP2D6 Poor Metabolizers

Four subjects (101, 105, 106 and 112) were identified as poor metabolizers, however, Subject 112 withdrew from the study for non-drug related reasons. These subjects had peak plasma M1 concentrations much lower (with one below LOQ) than the mean Cmax for all subjects. The Cmax of (+)- and (-)-tramadol in these subjects were within the range of that observed from all

subjects. (*Reviewer's note*: Some subjects not identified as poor metabolizers were seen to have low M1 Cmax comparable to the poor metabolizers. However, these subjects tended to have low Cmax of tramadol as well. The ratio of M1/tramadol would be a better indicator of poor metabolizers.) Out of the four subjects who withdrew from the study, two were due to adverse events (vomiting and dizziness) but both were extensive metabolizers.

Conclusion:
The pharmacokinetic parameters of tramadol, M1 and APAP following single-dose administration of the Tramadol/APAP combination tablet were in close agreement with those observed following single-dose administration of tramadol and APAP alone. The results of this study indicate that the single dose pharmacokinetics of tramadol, M1, or APAP was not significantly altered when tramadol and acetaminophen were given separately or in combination.

B. Multiple Dose Study

Protocol #TRAMAP-PHI-001:
Evaluation of the Effect of Tramadol Hydrochloride/Acetaminophen Combination on the Pharmacokinetics of Tramadol and Acetaminophen

This study was designed to evaluate the effect of a tramadol/APAP combination on the pharmacokinetics of tramadol and APAP at steady state. This was an open-label, randomized, two-way crossover study conducted in 32 healthy men and women (16 M and 16 F; mean age: 29.9±6.6 yrs; mean wt: 68.5±11.7 kg). The dosage forms for the three treatments were:

Treatment A: 325 mg APAP tablet
Treatment B: 37.5 mg tramadol HCl capsule
Treatment C: 37.5 mg tramadol HCl + 325 mg APAP combination tablet

Study design: The subjects were assigned to one of two groups, with the first eight male and eight female subjects being assigned to Group I (15 completed the study) and the next set of eight male and eight female subjects being assigned to Group II (12 completed the study). Within each group, equal numbers of subjects were randomly assigned to one of two treatment sequences (see the randomization schedule below). To minimize the side effects of tramadol, a 2-day of gradual dose titration at the beginning of each period was administered according to the following schedule: Subjects received an oral dose of one tablet/capsule at 1:00 a.m., 7:00 a.m., and 1:00 p.m. and two tablets/capsules at 7:00 p.m. on Study Days 1 and 8. Subjects received an oral dose of two tablets/capsules at 1:00 a.m., 7:00 a.m. and 1:00 p.m. and three tablets/capsules at 7:00 p.m. on Study Days 2 and 9. Immediately following the dose titration in each period, subjects received multiple oral dose regimen of alternating 2 and 3 tablets/capsules every 6 hours for 5 days. Note that subjects were genotyped for CYP2D6.

Table 1: Randomization Schedule

Group	Sequence	Treatment
I	1	APAP [Treatment A] q6 h for 7 days, followed by tramadol + APAP [Treatment C] q6h for 7 days
	2	Tramadol + APAP [Treatment C] q6h for 7 days followed by APAP [Treatment A] q6h for a 7-day period.
II	3	Tramadol [Treatment B] q6h for 7 days followed by tramadol + APAP [Treatment C] q6h for 7 days
	4	Tramadol + APAP [Treatment C] q6h for 7 days followed by tramadol [Treatment B] q6h for 7 days

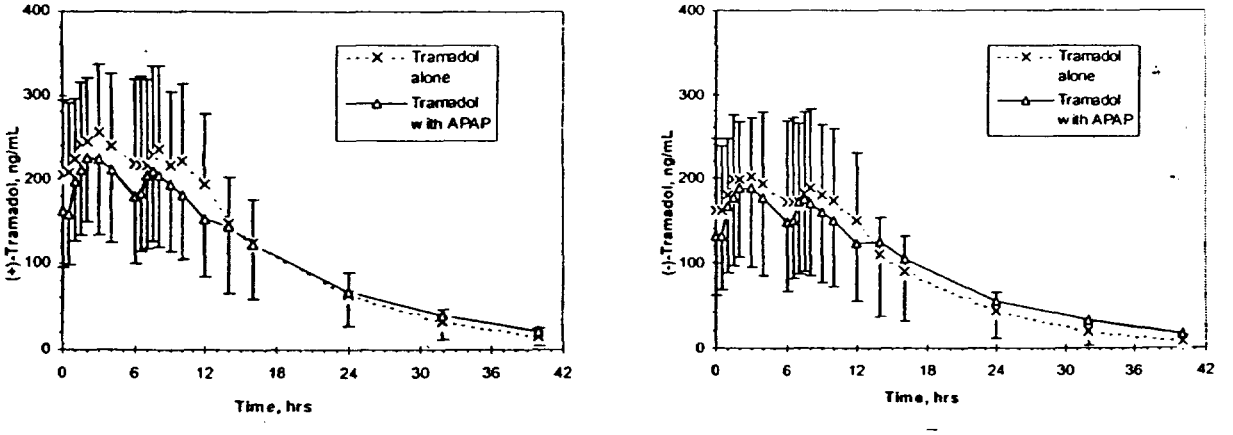
Blood samples were collected prior to the first dose (1:00 a.m.) on Day 1, and immediately prior to the second dose (7:00 a.m.) on Days 4 to 6 and 11 to 13. On Day 7, blood samples were collected prior to the 7:00 a.m. dose and at scheduled times up to 12 hours after dose administration. On Day 14, blood samples were collected prior to the 7:00 a.m. dose and at scheduled times up to 40 hours postdose. Plasma concentrations of APAP and the (+)- and (-)-enantiomers of tramadol and M1 were determined. Pharmacokinetic analysis included the determination of: C_{max1}, C_{max2}, t_{max1}, t_{max2}, C_{min1}, C_{min2}, AUC (0-12h), CL/F, k_e, and $t_{½}$.

Results

Tramadol

The mean (±SD) plasma concentration-time profiles of (+)- and (-)-tramadol at steady state following 7-day, multiple-dose treatment with tramadol + APAP were lower relative to that observed for tramadol alone through 12 hours postdose (see Figure 1; for subjects in Group II).

Figure 1: Mean (±SD) Steady-State Plasma Concentration-Time Profiles of (+)-Tramadol and (-)-Tramadol Following Seven-Day, Multiple-Dose Treatment With Tramadol + Acetaminophen or Tramadol Alone



The mean (±SD) pharmacokinetic parameters of the two enantiomers of tramadol following 7-day, multiple-dose treatment with tramadol + APAP or tramadol alone, along with the results of the ANOVA and the 90% confidence intervals, are summarized in the table below.

Mean AUC_{0-12h} values were approximately 14% and 10% lower for (+)-tramadol and (-)-tramadol, respectively, following combination treatment compared to tramadol alone. A similar trend was found for Cmax as well. Mean Cmin was approximately 20% lower with the combination treatment. (*Reviewer's note:* As listed in Table 1, mean half-life of tramadol for the combination tablets was longer compared to tramadol alone, however, these values were obtained from different subjects since T1/2 was only determined in the second treatment period for each subject.)

The 90% CI for (-)-tramadol were found to be within the limits of 80 to 125% for AUC (0-12h) (81 to 95%) and C_{max1} (81 to 99%). The 90% CI for the remaining bioavailability parameters for (-)-tramadol and for all parameters for (+)-tramadol were outside the limits. (*Reviewer's note:* The sample size (n=12) in this study was only half of that in a regular BE study.)

Table 1: Summary of Mean (±SD) Steady-State Pharmacokinetic Parameters of (+)-Tramadol and (-)-Tramadol Following Seven-Day, Multiple-Dose Treatment With Tramadol + Acetaminophen or Tramadol Alone

Parameter	Tramadol + APAP (Treatment C, N=12)		Tramadol (Treatment B, N=12)		% Difference[a]	ANOVA[b]	90% CI[c]	
(+)-Tramadol								
C_{max1} (ng/mL)[d]	241	(80)	278	(87)	-13.3	S	78.2-95.9	NEQ
C_{max2} (ng/mL)[e]	222	(83)	258	(98)	-14.0	S	75.4-96.4	NEQ
t_{max1} (h)[d]	2.7	(1.3)	2.4	(1.7)	12.5	NS	-	--
t_{max2} (h)[e]	1.6	(1.1)	2.1	(1.2)	-23.8	NS	-	--
C_{min1} (ng/mL)[d]	162	(66)	205	(89)	-21.0	S	69.0-89.8	NEQ
C_{min2} (ng/mL)[e]	153	(68)	195	(84)	-21.5	S	68.7-89.8	NEQ
AUC (0-12h) (ng h/mL)	2333	(897)	2713	(1003)	-14.0	S	77.7-91.4	NEQ
CL/F (mL/min)	660	(235)	555	(160)	18.9	S	-	--
k_e (h^{-1})	0.082	(0.022)	0.091	(0.022)	-10.0	--	-	--
$t_{½}$ (h)	8.9	(1.8)	8.0	(1.8)	11.3	--	-	--
(-)-Tramadol								
C_{max1} (ng/mL)[d]	204	(87)	225	(81)	-9.3	NS	81.3-99.2	EQ
C_{max2} (ng/mL)[e]	184	(84)	205	(91)	-10.2	NS	79.1-100.3	NEQ
t_{max1} (h)[d]	2.7	(1.3)	2.4	(1.7)	12.5	NS	-	--
t_{max2} (h)[e]	1.6	(1.1)	2.3	(0.9)	-30.4	NS	-	--
C_{min1} (ng/mL)[d]	131	(71)	161	(85)	-18.6	S	71.4-93.0	NEQ
C_{min2} (ng/mL)[e]	123	(69)	150	(81)	-18.0	S	72.7-92.8	NEQ
AUC (0-12h) (ng h/mL)	1935	(957)	2160	(969)	-10.4	S	81.2-94.7	EQ
CL/F (mL/min)	826	(316)	718	(236)	15.0	S	-	--
k_e (h^{-1})	0.082	(0.011)	0.102	(0.021)	-20.0	--	-	--
$t_{½}$ (h)[f]	8.6	(1.2)	7.0	(1.3)	22.9	--	-	--

[a] Reference to tramadol alone, Treatment B, (C-B)*100/B

[b] ANOVA result:: S = statistically significant, $p \leq 0.05$; NS: $p > 0.05$.

[c] EQ = 90% CI is within the 80 to 125% limits; NEQ = 90% CI is outside the 80 to 125% limits.

[d] Following 7:00 a.m. dose on seventh day of treatment.

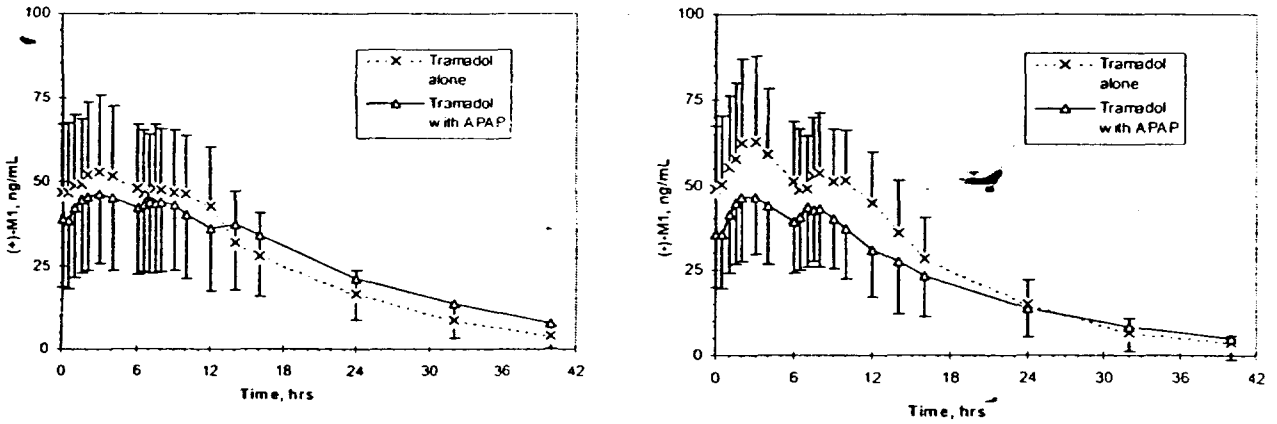
[e] Following 1:00 p.m. dose on seventh day of treatment.

[f] Determined for the 2nd treatment period only

M1

The mean (±SD) plasma concentration-time profiles of (+)- and (-)-M1 at steady state following 7-day, multiple-dose treatment with tramadol + APAP were lower relative to that observed for tramadol alone through 12 hours postdose (see Figure 2).

Figure 2: Mean (±SD) Steady-State Plasma Concentration-Time Profiles for (+)-M1 and (-)-M1 Following Seven-Day, Multiple-Dose Treatment with Tramadol + Acetaminophen or Tramadol Alone



Mean (±SD) pharmacokinetic parameters of the two M1 enantiomers following 7-day, multiple-dose treatment with tramadol + APAP or tramadol alone, as well as the statistical comparison results, are summarized in Table 2. The mean $AUC_{0\text{-}12h}$ values were 12% lower for (+)-M1 and 24% lower for (-)-M1 following treatment with the combination tablet compared to treatment with tramadol alone. Mean Cmax values were 12.5-19% lower for (+)-M1 and 27% lower for (-)-M1. Tmax (~3hrs) for M1 was similar between the two treatments. Cmin values were 14-17% lower for (+)-M1 and 30-31% lower for (-)-M1 following treatment with combination tablets compared to tramadol alone. (The elimination half-life of M1 as listed in Table 2 was longer after treatment with the combination tablets. However, as mentioned in the above section, the mean T1/2 values came from different groups of subjects as the half-life was determined in Period 2 only for each subject.) The 90% CI for bioavailability parameters of (+)-M1 and (-)-M1 were found to be outside the limits of 80 to 125%.

Table 2: Summary of Mean (±SD) Steady-State Pharmacokinetic Parameters of (+)-M1 and (-)-M1 Following Seven-Day, Multiple-Dose Treatment With Tramadol + Acetaminophen or Tramadol Alone

	Tramadol + APAP (Treatment C, N=12)		Tramadol (Treatment B, N=12)		% Difference[a]	ANOVA[b]	90% CI[c]	
(+)-M1								
C_{max1} (ng/mL)[d]	49	(22)	56	(24)	-12.5	NS	72.7-101.3	NEQ
C_{max2} (ng/mL)[e]	47	(20)	58	(34)	-19.0	NS	71.4-102.5	NEQ
t_{max1} (h)[d]	3.3	(1.1)	3.0	(1.8)	10.0	NS	-	--
t_{max2} (h)[e]	1.2	(0.9)	2.5	(1.4)	-52.0	S	-	--
C_{min1} (ng/mL)[d]	39	(20)	47	(20)	-17.0	NS	67.7-96.7	NEQ
C_{min2} (ng/mL)[e]	36	(18)	42	(18)	-14.3	NS	75.2-98.8	NEQ
AUC (0-12h) (ng h/mL)	510	(239)	579	(226)	-11.9	NS	75.1-99.5	NEQ
CL/F (mL/min)	3289	(1561)	2837	(1337)	15.7	NS	-	--
k_e (h^{-1})	0.065	(0.021)	0.076	(0.011)	-15.0	--	-	--
$t_{½}$ (h)	11.6	(3.3)	9.2	(1.2)	25.5	--	-	--
(-)-M1								
C_{max1} (ng/mL)[d]	50	(17)	68	(28)	-26.5	S	62.5-86.7	NEQ
C_{max2} (ng/mL)[e]	46	(17)	63	(31)	-27.0	S	66.4-90.0	NEQ
t_{max1} (h)[d]	3.1	(1.3)	2.9	(1.8)	6.9	NS	-	--
t_{max2} (h)[e]	1.5	(0.9)	2.5	(1.8)	-40.0	NS	-	--
C_{min1} (ng/mL)[d]	35	(16)	50	(19)	-30.0	S	57.5-85.3	NEQ
C_{min2} (ng/mL)[e]	31	(14)	45	(16)	-31.1	S	58.9-83.5	NEQ
AUC (0-12h) (ng h/mL)	489	(185)	645	(215)	-24.2	S	64.9-85.6	NEQ
CL/F (mL/min)	3141	(1025)	2371	(838)	32.5	S	-	--
k_e (h^{-1})	0.080	(0.019)	0.094	(0.017)	-15.7	--	-	--
$t_{½}$ (h)	9.1	(2.2)	7.5	(1.3)	21.3	--	-	--

[a] Reference to tramadol alone, Treatment B, (C-B)*100/B

[b] ANOVA result:; S = significant, $p \leq 0.05$; NS: $p > 0.05$

[c] EQ = 90% CI is within the 80 to 125% limits; NEQ = 90% CI is side the limits.

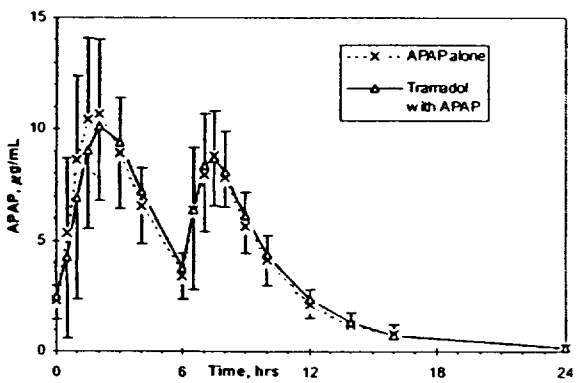
[d] Following 7:00 a.m. dose on seventh day of treatment.

[e] Following 1:00 p.m. dose on seventh day of treatment.

Acetaminophen

Mean (±SD) plasma concentration-time profiles of APAP following 7-day, multiple-dose treatment with tramadol /APAP combination (Treatment C) and APAP alone (Treatment A) were similar (Figure 3).

Figure 3: Mean (±SD) Steady-State Plasma Concentration-Time Profiles of Acetaminophen Following Seven-Day, Multiple-Dose Treatment with Tramadol + Acetaminophen (Treatment C) or Acetaminophen Alone (Treatment A)



The mean (±SD) pharmacokinetic parameters of APAP at steady state following 7-day, multiple-dose treatment with tramadol + APAP (Treatment C) or APAP alone (Treatment A) and the results of statistical comparison are summarized in Table 3. Mean AUC was 1.1% higher and mean Cmax 3-5% higher for the combination tablets compared to APAP alone. There was a slight delay in Tmax for the combination tablets. The 90% CI for the ratio of the means of the tramadol + APAP treatment (Treatment C) to the APAP treatment (Treatment A) were calculated for C_{max1}, C_{max2}, C_{min1}, C_{min2}, and AUC (0-12h) of APA. and were found to be within the limits of 80 to 125% (89.46 to 120.42%) with the exception of C_{min2} (99 to 126%).

Table 3: Summary of Mean (±SD) Steady-State Pharmacokinetic Parameters of Acetaminophen Following Seven-Day, Multiple-Dose Treatment With Tramadol + Acetaminophen (Treatment C) or Acetaminophen Alone (Treatment A)

Parameter	Tramadol + APAP (Treatment C, N=15)		APAP (Treatment A, N=15)		% Difference[a]	ANOVA[b]	90% CI[c]	
Acetaminophen:								
C_{max1} (µg/mL)[d]	12.0	(3.5)	11.6	(3.1)	3.4	NS	94.1-113.4	EQ
C_{max2} (µg/mL)[e]	9.7	(2.3)	9.2	(1.9)	5.4	NS	98.6-111.4	EQ
t_{max1} (h)[d]	2.1	(0.9)	1.7	(0.5)	23.5	NS	-	--
t_{max2} (h)[e]	1.4	(0.7)	1.2	(0.4)	16.7	NS	-	--
C_{min1} (µg/mL)[d]	2.5	(1.0)	2.3	(0.7)	8.7	NS	89.5-120.4	EQ
C_{min2} (µg/mL)[e]	2.4	(0.9)	2.1	(0.7)	14.3	NS	99.0-126.2	NEQ
AUC (0-12h) µg h/mL)	76.2	(16.9)	75.4	(19.3)	1.1	NS	97.3-105.9	EQ
CL/F (mL/min)	373	(90)	382	(99)	-2.4	NS	-	--
k_e (h^{-1})	0.300	(0.057)	0.294	(0.070)	-2.0	--	-	--
$t_{½}$ (h)	2.4	(0.4)	2.5	(0.5)	-4.5	--	-	--

[a] Reference to APAP alone, Treatment A, (C-A)*100/A
[b] ANOVA results: NS = not statistically significant, p>0.05.
[c] EQ = 90% CI is within the 80-125% limits. NEQ = 90% CI is outside the limits.
[d] Following the 7:00 a.m. dose on the seventh day of treatment.
[e] Following the 1:00 p.m. dose on the seventh day of treatment.

CYP2D6 Genotyping

Only one subject (#108; in Group I) was identified as a poor metabolizer. This subject did have a low (+)- and (-)-M1 plasma concentrations.

Conclusion

The results of this study indicate that the steady-state pharmacokinetics of APAP was not significantly altered following multiple oral dose administration of Tramadol/APAP tablets for 7 days.

Following multiple-dose oral administration of Tramadol/APAP tablets with a 2-day of gradual dose titration, lower steady-state plasma concentrations of (+)- and (-)-enantiomers of tramadol and M1 were found following the treatment with the Tramadol/APAP combination tablet relative to tramadol alone. For (+)- and (-)-tramadol, the differences in Cmax and AUC_{0-12h} ranged from [redacted] (18 -21% for Cmin). For (+) and (-)-M1, greater differences in Cmax, Cmin and AUC were observed (12-19% for (+)-M1 and 24-31% for (-)-M1). The sponsor indicated that the extent of absorption for tramadol might be reduced following combination treatment and considered that the observed differences were modest and not of clinical significance. However,

the cause is really not clear as the reduction in M1 AUC was more than that in tramadol AUC which is not consistent with the applicant's theory.

Reviewer's comment:
In this multiple dose study, differences in the pharmacokinetics of tramadol and M1 metabolite were observed between the combination tablets and tramadol capsules. This information has been communicated to Dr. Chang Lee, Medical Officer of HFD-550. Possible factors that contributed to the observed differences were formulation differences and drug interaction between tramadol and acetaminophen. There was no clear indication that the formulation difference is a factor from the single dose study in which the same lots of combination tablets and tramadol capsules were used since the differences in pharmacokinetics of tramadol (including Cmax, AUC and T1/2) between the two treatments was small. To study the drug-drug interactions, it is best to use the same formulations so that formulation differences would not be a confounding factor.

FOOD EFFECT

Study #TRAMAP-PHI-003: Effect of Food on the Bioavailability of Tramadol and Acetaminophen Following Administration of a Single Oral Dose of Three Tablets to Healthy Subjects

This study was designed to evaluate the effect of food on the bioavailability of tramadol and APAP following administration of a single oral dose of three Tramadol/APAP combination tablets to healthy subjects. This was an open-label, randomized, complete two-way crossover study. Twenty-four healthy subjects (12 M and 12 F; age: 28.3±6.8 yrs; wt: 70.8±10.6 kg) enrolled to receive a single oral dose of three combination tablets following a 10-hour overnight fast and within 10 minutes of finishing a high-fat breakfast on two occasions with at least a 7-day washout. Twenty-three subjects completed the study.

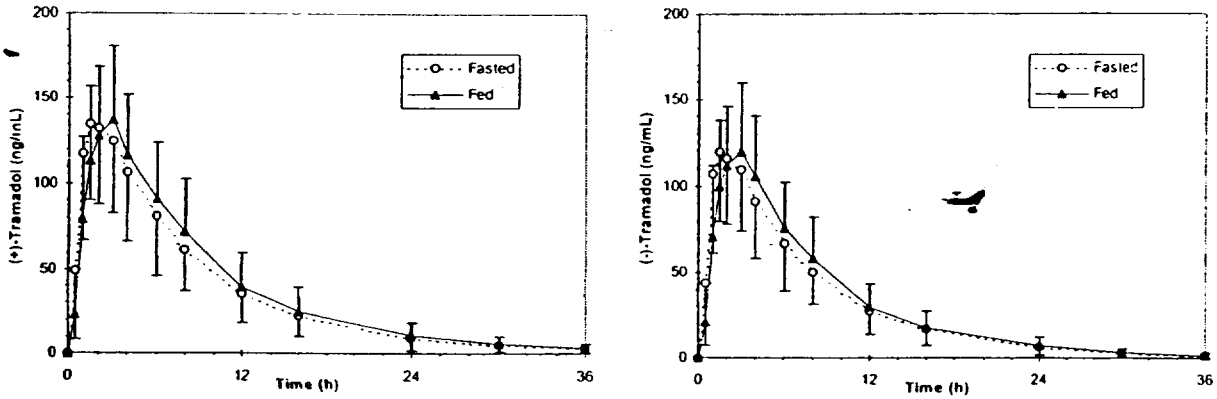
Blood samples were collected at scheduled times for up to 36 hours after dose administration for assay of plasma concentrations of APAP and the (+) and (-) enantiomers of tramadol and M1.

CYP2D6 genotyping was performed on each subject to identify poor metabolizers of tramadol. Pharmacokinetic analysis included the determination of C_{max}, t_{max}, AUC (0-*), AUC (0-∞), CL/F, k_e, and $t_{½}$. Tramadol, M1, and APAP PK parameters under fasted and fed conditions were compared using an analysis of variance (ANOVA) model and 90% confidence intervals.

Results

(+)- and (-)-Tramadol
The mean (±SD) plasma concentration-time profiles of the (+)- and (-)- enantiomers of tramadol following a single oral dose of three tramadol + APAP combination tablets under fasted and fed conditions are shown in Figure 1.

Figure 1: Mean (±SD) Plasma Concentration-Time Profiles for *(+)-Tramadol and (-)-Tramadol* Following a Single Dose of Three Combination Tablets Under Fasted and Fed Conditions



The mean (±SD) plasma pharmacokinetic parameters of the two enantiomers of tramadol are summarized in Table 1. Under fed conditions, AUC increased 5-6%, while Cmax remained the same with Tmax delayed for about 0.6 hours for both enantiomers. The 90% CI for the ratio of the means under fed conditions (Treatment B) to those under fasted conditions (Treatment A) for C_{max}, AUC (0-*), and AUC (0-∞) of (+)-tramadol and (-)-tramadol (Table 1) were found to be within the limits of 80 to 125%.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of (+)-Tramadol and (-)-Tramadol Following a Single Dose of Three Combination Tablets Under Fasted and Fed Conditions

Parameter	Fed (Treatment B) (N=23)		Fasted (Treatment A) (N=23)		% Difference[a]	ANOVA[b]	90% CI[c]	
(+)-Tramadol:								
C_{max} (ng/mL)	148	(41)	148	(45)	0.0	NS	EQ	93.8-111.0
t_{max} (h)	2.5	(0.9)	1.9	(0.9)	31.6	S	--	-
AUC (0-*) (ng h/mL)	1338	(482)	1262	(508)	6.0	S	EQ	102.9-114.0
AUC (0-∞) (ng h/mL)	1369	(503)	1294	(530)	5.8	S	EQ	102.8-113.5
CL/F (mL/min)	711	(366)	793	(518)	-10.3	S	--	-
k_e (h^{-1})	0.123	(0.028)	0.124	(0.031)	-0.8	NS	--	-
$t_{1/2}$ (h)	5.9	(1.2)	5.9	(1.4)	0.0	NS	--	-
(-)-Tramadol:								
C_{max} (ng/mL)	132	(36)	131	(39)	0.8	NS	EQ	93.6-110.4
t_{max} (h)	2.5	(0.9)	1.9	(0.9)	31.6	S	--	-
AUC (0-*) (ng h/mL)	1079	(370)	1024	(395)	5.4	S	EQ	102.3-112.7
AUC (0-∞) (ng h/mL)	1095	(378)	1042	(406)	5.1	S	EQ	102.2-112.3
CL/F (mL/min)	863	(381)	944	(490)	-8.6	S	--	-
k_e (h^{-1})	0.136	(0.025)	0.135	(0.027)	0.7	NS	--	-
$t_{½}$ (h)	5.3	(0.9)	5.4	(1.1)	-1.9	NS	--	-

[a] Reference to fasted state, Treatment A, (B-A)*100/A.

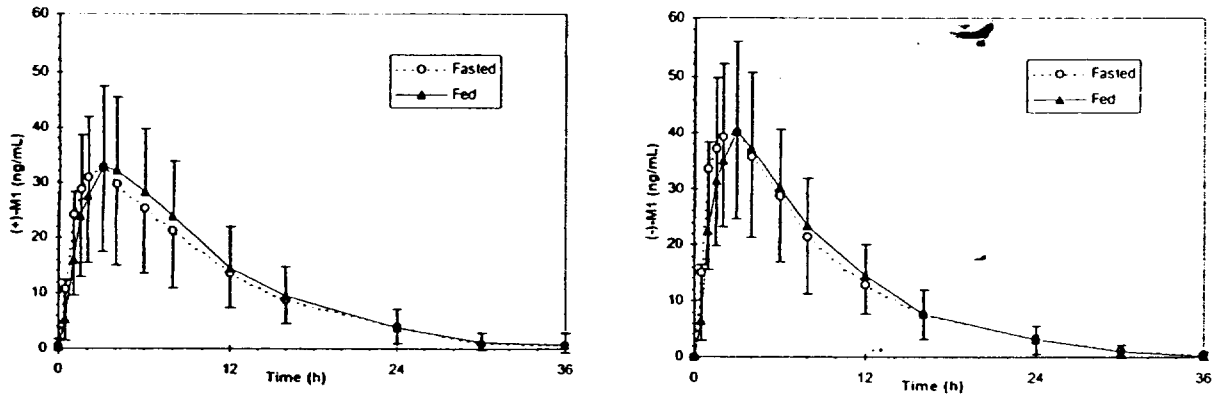
[b] ANOVA results based on log-transformed C_{max}, AUC (0-*), AUC (0-∞), and CL/F, on ranked values for t_{max}, and on raw data for k_e and $t_{½}$. NS = not significant, $p>0.05$; S = statistically significant, $p\leq0.05$.

[c] 90% CI results based on log-transformed parameters. EQ: bioequivalent

(+)- and (-)-M1

The mean (±SD) plasma concentration-time profiles of the (+)- and (-)-M1 enantiomers following a single oral dose of three tramadol + APAP combination tablets under fasted and fed conditions are shown in Figure 2.

Figure 2: Mean (±SD) Plasma Concentration-Time Profiles for (+)-M1 and (-)-M1 Following a Single Dose of Three Combination Tablets Under Fasted and Fed Conditions



Arithmetic mean (±SD) plasma pharmacokinetic parameters of the two M1 enantiomers following administration of a single oral dose of three combination tablets under both fasted and fed conditions, as well as the statistical results, are summarized in Table 2. Under fed conditions, Cmax and AUC increased less than 10% for both enantiomers of M1 based on geometric mean. The 90% CI for the ratio of the means under fed conditions (Treatment B) to fasted conditions (Treatment A) were calculated for C_{max}, AUC (0-∞), and AUC (0-*) of (+)-M1 and (-)-M1 and were found to be within the limits of 80 to 125% (Table 2).

Table 2: Summary of Mean (±SD) Plasma Pharmacokinetic Parameters of (+)-M1 and (-)-M1 Following a Single Dose of Three Combination Tablets Under Fasted and Fed Conditions

	Fed (Treatment B) (N=23)		Fasted (Treatment A) (N=23)		% Difference[a]	ANOVA[b]	Ratio[c]	90% CI[c]
(+)-M1:								
C_{max} (ng/mL)	35	(15)	34	(16)	2.9	NS	104.71	95.3-115.1
t_{max} (h)	3.2	(1.2)	2.6	(0.8)	23.1	S	-	-
AUC (0-*) (ng h/mL)	400	(168)	376	(162)	6.4	NS	106.88	98.7-115.8
AUC (0-∞) (ng h/mL)	448	(173)	438	(183)	2.3	NS	103.61	97.1-110.5
CL/F (mL/min)	2130	(1047)	2251	(1120)	-5.4	NS	--	-
k_e (h^{-1})	0.117	(0.025)	0.108	(0.029)	8.3	S	--	-
$t_{1/2}$ (h)	6.2	(1.1)	6.8	(1.6)	-8.8	S	--	-
(-)-M1:								
C_{max} (ng/mL)	43	(16)	43	(16)	0.0	NS	101.49	92.9-110.9
t_{max} (h)	2.6	(0.9)	2.5	(1.1)	4.0	NS	-	-
AUC (0-*) (ng h/mL)	401	(145)	399	(164)	0.5	NS	102.88	97.0-109.1
AUC (0-∞) (ng h/mL)	451	(145)	447	(163)	0.9	NS	101.89	96.2-108.0
CL/F (mL/min)	2124	(1108)	2287	(1271)	-7.1	NS	--	-
k_e (h^{-1})	0.120	(0.032)	0.117	(0.032)	2.6	NS	--	-
$t_{½}$ (h)	6.3	(1.9)	6.4	(1.9)	-1.6	NS	--	-

[a] Reference to fasted state, Treatment A, (B-A)*100/A.

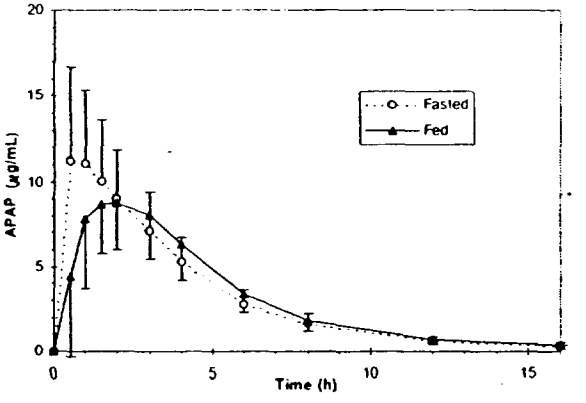
[b] ANOVA results based on log-transformed C_{max}, AUC (0-*), AUC (0-∞), and CL/F, on ranked values for t_{max}, and on raw data for k_e and $t_{½}$. NS = not significant, $p>0.05$; S = statistically significant, $p\leq0.05$.

[c] 90% CI results based on log-transformed parameters.

APAP

Mean (±SD) plasma concentration-time profiles of APAP following administration of the tramadol + APAP combination tablets under fasted (Treatment A) differed from that seen under fed (Treatment B) conditions (Figure 3).

Figure 3: Mean (±SD) Plasma Acetaminophen Plasma Concentration-Time Profiles Following a Single Dose of Three Combination Tablets Under Fasted and Fed Conditions



Under fed conditions, (geometric) mean AUC was similar but mean Cmax was 12% lower than under fasted conditions. The time to peak plasma acetaminophen concentration was prolonged from 1.1 hrs under fasted conditions to 1.9 hrs under fed conditions. The 90% CI for both AUC parameters were within 80 to 125%; for Cmax, the 90% CI was 77.9-99.6%.

Table 3: Summary of Mean (±SD) Plasma Pharmacokinetic Parameters of Acetaminophen Following a Single Dose of Three Combination Tablets Under Fasted and Fed Conditions

Parameter	Fed (Treatment B) (N=23)		Fasted(Treatment A) (N=23)		% Difference[a]	ANOVA[b]	Ratio[c]	90% CI[c]
Acetaminophen:								
C_{max} (µg/mL)	11.0	(2.9)	13.1	(4.5)	-16.0	NS	88.0	77.9-99.6
t_{max} (h)	1.9	(1.1)	1.1	(0.6)	72.7	S	-	-
AUC (0-*) (µg h/mL)	51.2	(13.3)	53.5	(18.6)	-4.3	NS	99.0	91.8-106.8
AUC (0-∞) (µg h/mL)	52.7	(13.4)	55.6	(20.5)	-5.2	NS	98.4	90.7-106.7
CL/F (mL/min)	328	(86)	335	(142)	-2.1	NS	-	--
k_e (h^{-1})	0.271	(0.051)	0.268	(0.042)	1.1	NS	-	--
$t_{½}$ (h)	2.6	(0.4)	2.6	(0.4)	0.0	NS	-	--

[a] Reference to fasted conditions, Treatment A, (B-A)*100/A, based on arithmetic means.

[b] ANOVA results based on log-transformed C_{max}, AUC (0-*), AUC (0-∞), and CL/F, on ranked values for t_{max}, and on raw data for k_e and $t_{½}$. NS = not significant, $p>0.05$; S = significant, $p\leq0.05$.

[c] Ratio and 90% CI results based on log-transformed parameters.

CYP2D6 Genotyping

Two subjects (#104 and 212) were identified as poor metabolizers of tramadol. Both subjects had very low ratios of (+)-M1/(+)-tramadol plasma concentrations compared to other subjects.

These two subjects reported no adverse events following administration of the combination tablets under fasted or fed conditions.

Conclusions
The results of this study indicate that administration of a single oral dose of three Tramadol/APAP combination tablets following a high-fat breakfast did not appreciably alter the Cmax and AUC of either component relative to administration under fasted conditions. As expected, the rate of absorption of tramadol and APAP were delayed (with a delay in Tmax of 0.6hr and 0.8 hr, respectively) under fed conditions compared to fasted conditions.

POPULATION PK ANALYSIS

In Healthy Volunteers

Objective: A NONMEM analysis was performed to determine whether any demographic covariates might significantly affect the pharmacokinetics of tramadol/M1 and APAP given as a combination.

Data: Acetaminophen, tramadol, and its metabolite M1 plasma concentration data collected in four Phase I PK studies of Tramadol/APAP tablet were analyzed. There were 84 subjects (50 M & 34 F; age:19-40 yrs; body weight:49-94 kg) (see Table 1 for demographic summary). The data set included complete pharmacokinetic profiles after a single oral dose of Tramadol/APAP (112.5 mg/975 mg) or after multiple oral doses to steady state.

Table 1: Demographic Summary for Subjects Included in the NONMEM Analysis

Covariate	No. of Sub.	Age (yr)		Body Weight (kg)		CL_{CR} (mL/min)	
		Range	Mean (±SD)	Range	Mean (±SD)	Range	Mean (±SD)
All	84	19-40	28.8 (6.8)	49-94	70.2 (10.0)		114.6 (15.5)
Gender							
Male	50	19-40	29.0 (7.3)	56-94	74.4 (9.7)		114.0 (16.4)
Female	34	21-40	28.6 (6.0)	49-82	63.9 (6.8)		114.9 (14.7)
Race							
White	43	19-40	28.8 (7.1)	54-94	70.0(10.2)		117.1 (14.6)
Nonwhite[a]	41	19-40	28.9 (6.5)	49-90	70.3(10.0)		111.5 (16.3)
Smoker	11	19-39	27.3 (8.1)	58-94	74.5(11.8)		116.9 (12.9)
Poor[b] Metabolizer	8	19-38	29.8 (5.9)	56-79	65.1 (7.4)		102.8 (16.9)

[a]16 Black, 21 Hispanic, and 4 other
[b]Six identified by CYP2D6 genotyping and 2 identified by metabolite ratio

Model: A one-compartment PK model with first-order input was used in the analysis. Covariates investigated were gender, race, body weight, creatinine clearance, smokers, and CYP2D6 genotyping. The NONMEM analysis focused on the contribution of the various covariates on the apparent oral clearance (CL) and apparent volume of distribution (Vd). Exponential error models were employed for the interindividual variability of k_a, CL, and Vd. A multiple stepwise

procedure was used to determine which covariates should be included in the optimal model describing the population pharmacokinetics.

Results:

The parameter estimates from the population PK analysis is given in Appendix 1.

Body weight: APAP: Body weight was the most significant covariate on CL and Vd.
Tramadol: Body weight was not a significant covariate on CL or Vd (Table 2).

Creatinine clearance: Creatinine clearance was not a significant covariate on CL of APAP or (+)- and (-)-tramadol as expected, but was found to be a significant covariate on CL of (+)- and (-)-M1 indicating the significant contribution of renal excretory pathway to the elimination of M1.

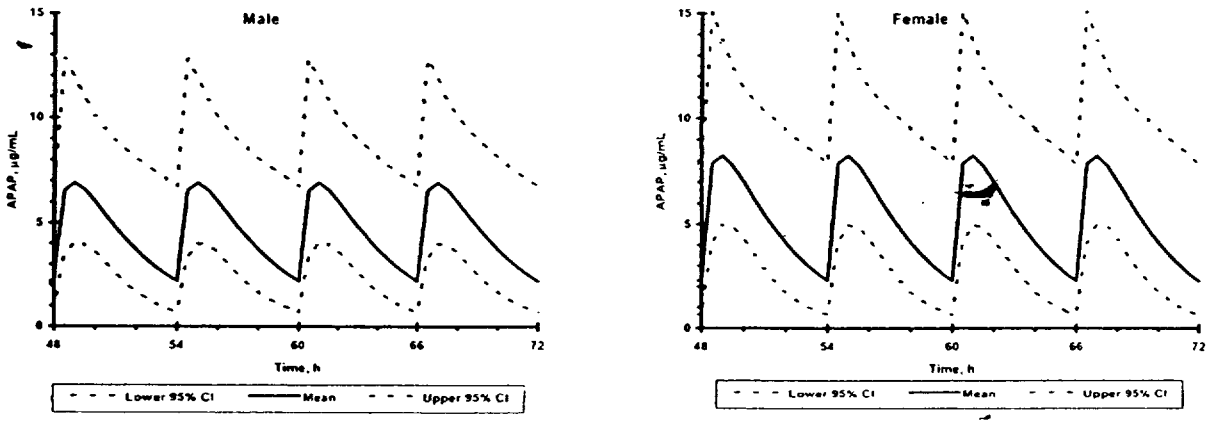
Table 2: The Covariate Effects on Clearance and Vd of APAP, Tramadol, and M1

Covariate Effect on CL/F	APAP	(+)-Tramadol	(-)-Tramadol	(+)-M1	(-)-M1
Gender	-	M: 34.5 L/hr F: 19.6%↑	M: 40.6 L/hr F: 19.7%↑	-	-
Race	-	-	-	+	+
Body Weight	+	-	-	-	-
CL_{CR}	-	-	-	+	+
Smoking	-	-	-	-	-
CYP2D6 genotyping	-	PM: 19.6%↓	-	+	+
Covariate Effect on Vd/F	**APAP**	**(+)-Tramadol**	**(-)-Tramadol**	**(+)-M1**	**(-)-M1**
Gender	F: 12%↓	-	-	-	-
Race	-	-	-	-	-
Body Weight	+	-	-	-	-
CL_{CR}	-	-	-	-	-
Multiple dose	-	MD: 30% ↑	+	+	+
Smoking	-	-	-	-	-
CYP2D6 genotyping	-	-	-	-	+
+ = Significant;	- = Not significant: Δobjective function <8				

Gender:

APAP: The population PK analysis indicated that there was no gender effect on the apparent APAP clearance but females had a 12% lower Vd/F. As stated above, body weight was found to be a factor for both CL/F and V/F. Since female body weight is about 14% lower on average compared to male, the APAP concentration will be higher in female patients receiving the same dose. Because of this, the sponsor performed Monte Carlo simulations of APAP plasma concentrations at steady state using NONMEM for 1000 male and 1000 female subjects. The mean plasma APAP concentration profiles and 95% population confidence intervals following a 650 mg APAP q6h regimen were compared between male and female subjects. From these simulations, the sponsor concluded that the difference in steady-state APAP concentrations between male and female were marginal (see Figure 1).

Figure 1: Monte Carlo Simulations of *APAP* Steady-state Plasma Concentrations for Male and Female Subjects Following Oral Administration of 650 mg APAP q6h Regimen



Solid line: mean concentrations (N=1000); Dashed lines : 95% CI intervals of the population.

Tramadol: Clearance of the (+)- and (-)-tramadol was (19.6% and 19.7%, respectively) higher in females than males. There was no gender effect on the volume of distribution of the (+)- and (-)-tramadol. There was no gender effect on the clearance and volume of distribution of the (+)- and (-)-M1. Monte Carlo simulations of tramadol plasma concentrations at steady state were performed by NONMEM for 1000 male and 1000 female subjects. The mean plasma tramadol concentration profiles and 95% population confidence intervals following a 75-mg q6h regimen was compared between male and female subjects. Female subjects had lower steady state plasma concentrations resulting in a 13% lower Cmax, 20% lower Cmin and 17% lower AUC in (+)-tramadol and a 11% lower Cmax, 19% lower Cmin and 17% lower AUC in (-)-tramadol compared to males (Table 3).

Table 3: Comparison of Steady State Mean Parameters Between Male and Female Subjects Following Oral Administration of a 75-mg q6h Regimen

Steady State Parameter	Male	Female	Ratio (F/M)
(+)-Tramadol			
Cmax (ng/mL)	382	333	0.872
Cmin (ng/mL)	250	199	0.796
AUC (ng.h/mL)	1909	1591	0.833
(-)-Tramadol			
Cmax (ng/mL)	326	291	0.893
Cmin (ng/mL)	205	166	0.810
AUC (ng.h/mL)	1622	1352	0.834

Race:

No race effect was noted on the clearance and volume of distribution of APAP and (+)- and (-)-tramadol. The clearance of the (+)- and (-)-M1 in nonwhite subjects is about 20% higher than that in white subjects. No race effect on the volume of distribution of the (+)- and (-)-M1 was found.

CYP2D6 Genotype:
There were eight CYP2D6 poor metabolizers identified in the Phase I studies of Tramadol/APAP combinations.

There was no CYP2D6 genotype effect on pharmacokinetics of APAP.

CYP2D6 poor metabolizers were found to have a 20% decrease in (+)-tramadol clearance and a 40% decrease in M1 formation. The slight decrease of tramadol clearance in CYP2D6 poor metabolizers is expected since the contribution of CYP2D6 metabolic pathway is only a small fraction of tramadol total body clearance. (Increased tramadol and decreased M1 concentrations following oral administration of tramadol in poor metabolizers has been reported in a study of 12 poor metabolizers and 15 extensive metabolizers of sparteine by Poulsen et al. The median AUC (0-10 h) values increased from 1143 to 1401 h·ng/mL (equivalent to a 22.6% increase) for (+)-tramadol and from 953 to 1192 h·ng/mL (equivalent to a 25.1% increase) for (-)-tramadol in poor metabolizers as compared to extensive metabolizers.)

Smoker:
There were 11 smokers (out of 84 subjects) included in this analysis. The pharmacokinetics of APAP and the (+)- and (-)-tramadol and M1 in smokers were not significantly different from those of nonsmokers.

Conclusion
The population pharmacokinetic analysis evaluated the effect of demographic covariates on the pharmacokinetics of APAP and tramadol when administered as a combination. None of the covariates were considered to have an effect on the pharmacokinetics of APAP or tramadol requiring a dose adjustment. Due to the narrow range of body weight and creatinine clearance in healthy subjects typically enrolled in Phase I studies, the effect of body weight and creatinine clearance on the pharmacokinetics of APAP and tramadol cannot be extrapolated outside the observed range.

Reviewer's comments:
1. Age was not included as a covariate in this analysis. In view of the age range (19-40 yrs) in the dataset, this is considered reasonable.
2. The number of smokers or poor metabolizers was low and, therefore, it would be identified as a significant covariate only when its effect is rather large and consistent.

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS

Objective

A population pharmacokinetic-pharmacodynamic (PK/PD) model was developed that characterized the relationship of analgesic activity with plasma drug concentrations in patients receiving an oral dose of tramadol in combination with APAP for the treatment of pain from oral surgery.

Data

A total of 1652 patients were included from six clinical trials. Patients had moderate to severe pain after extraction of one or more impacted third molars and were given a single dose of placebo, tramadol, APAP or tramadol/APAP. At any time, patients were allowed to remedicate but were encouraged to wait at least 1 hour after dosing before taking a rescue medication. Pain relief was measured periodically with the use of a five-category ordinal scale (0=none to 4=complete pain relief) up to 10 hours. No pain relief score was determined after remedication. In these trials, tramadol dose ranged from (0, 25, 50, 75, 100 and 150 mg) with and without APAP at the fixed dose of 650 mg to characterize the PK/PD relationship. Table 1 gives an overview of all doses and dose combinations evaluated in the six clinical trials.

Table 1: Overview of Number of Patients Studied for Each Tramadol and APAP Dose and Dose Combination

Trial[a]	Placebo	Tramadol (mg)					APAP (mg)	Tramadol/APAP (mg)			Total
	-	25	50	75	100	150	650	25/650	50/650	75/650	
1	40	-	39	40	41	39	-	-	-	-	199
2	49	-	-	50	-	-	50	-	-	50	199
3	50	50	48	-	-	-	49	50	50	-	297
4	79	-	-	78	-	-	80	-	-	80	317
5	80	-	-	80	-	-	80	-	-	80	320
6	80	-	-	80	-	-	80	-	-	80	320
Total	378	50	87	328	41	39	339	50	50	290	1652

[a]Trial 1= study TF3, trial 2= study TRAMAP-ANAG-002, trial 3= study TRAMAP-ANAG-007, trial 4= study TRAMAP-ANAG-010, trial 5= study TRAMAP-ANAG-012, trial 6= study TRAMAP-ANAG-013

Model

The NONMEM program was used for the PK/PD analysis. Pharmacodynamic data collected in analgesic trials consists of two important response variables: pain relief at distinct time points after dosing and remedication time. The methodology developed by [redacted] and further implemented by [redacted] was applied to characterize the PK/PD relationship for Tramadol/APAP combination. Briefly, the PD model involved logistic model to characterize the probability distribution of pain relief scores as a function of plasma drug concentration and survival analysis to account for dropout due to inadequate pain relief. Model selection was made on basis of the log likelihood criterion at $p<0.01$ and visual inspection of the fits. Covariates such as gender and baseline pain intensity were investigated.

PK Model

Pharmacokinetic data of tramadol was available in the tramadol dose-ranging clinical trial (study TF3 conducted in support of the NDA for ULTRAM® tablet). The pharmacokinetics of tramadol was described by a one-compartment model with first order absorption and a lag time. However, pharmacokinetic data of APAP was not available from any of these clinical trials. Therefore, an assumption was made that the pharmacokinetics of APAP in patients is similar to healthy subjects as determined from the Phase I pharmacokinetic studies of Tramadol/APAP combination. The pharmacokinetics of APAP was described by a one-compartment model with first order absorption and no lag time. The mean parameter values are provided in Table 2.

Table 2: Tramadol and Acetaminophen PK Parameters (population mean & %CV)

Parameter	Tramadol	Acetaminophen
Ka (1/hr)	1.41 (125%)	2.18 (149%)
CL/F (L/hr)	47.2 (49.0%)	21.1 (29.4%)
V/F (L)	339 (54.2%)	69.4 (25.9%)
Tlag (hr)	0.4 (-)	0

Model for Pain Relief: P(Y\|η)

Pain relief (Y_t) is an ordered categorical variable that can take values of 0 through 4 (0=none to 4=complete pain relief). The probability that Y_t is greater than or equal to the score m (m=1, 4) is given by the following model:

$$g\{P(Y_t \geq m|\eta)\} = f_p(m,t) + f_d(Ca,Cb) + \eta_Y$$

in which f_p is the function describing the combined placebo and disease effect as a function of time, f_d is a function describing the drug effect as a function of the concentrations of APAP and tramadol, η_Y is a random individual effect determining the individual sensitivity, and g{x} denotes the logit transform of a probability.

The placebo effect was described by the following model:

$$f_p(m,t) = \sum_{k=1}^{m} \beta_k + PM \cdot (\exp(-\gamma_1 \cdot t) - \exp(-\gamma_2 \cdot t))$$

where γ_1 and γ_2 are the first order rate constants, PM determines the magnitude of placebo effect, and β_k's specify the baseline set of probabilities for the various degrees of pain relief.. This model allows the placebo effect to increase and decrease with time.

Linear, power, E_{max}, and sigmoid E_{max} models were evaluated to describe the contribution of tramadol and APAP concentrations to the probabilities of pain relief. The best model to characterize drug effect as a function of concentrations was a linear function for tramadol and a power function for APAP. A first order delay between plasma tramadol concentrations and effect site concentrations was incorporated into the model while there was a direct relationship between APAP plasma concentration and analgesic effect. The combined effect of tramadol and APAP was found to be additive.

Model for Remediation: P(T/Y, η)

The time to remediation (T) is viewed as a survival variable. A survival function S(t) is defined as the probability that a person remains in the study at least to time t and is given by the following equation:

$$P(T>t|Y,\eta) = S(t) = \exp(-\int_0^t \lambda(u)du)$$

where λ(t) is the hazard function that describes the instantaneous risk. The following model was used for the hazard function λ(t).

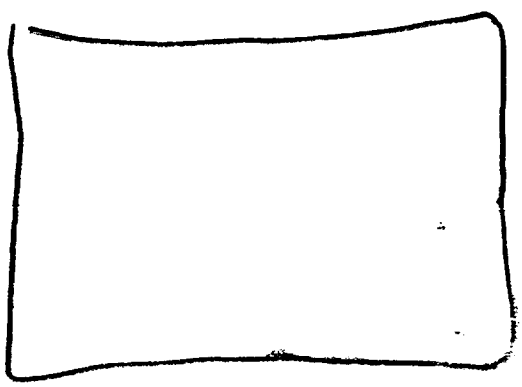
$$\lambda_k(t) = \begin{Bmatrix} \lambda_k & if & 1.5 \le t \\ fc \cdot \lambda_k & if & 0.5 \le t < 1.5 \\ 0 & if & 0 \le t < 0.5 \end{Bmatrix}$$

where λ_k is the hourly hazard for each level of pain relief k and fc is a fixed fraction by which the hazard is reduced during the time period 0.5 to 1.5 hours after medication.

Results

Pharmacodynamic parameter estimates of pain relief and remedication as well as the fit of the model to the observed data are given in Appendix 1. Neither gender nor the baseline pain intensity had significant effect on the PK/PD relationship.

Figure 1 shows the time course of the contribution of tramadol 75 mg, APAP 650 mg, and Tramadol/APAP 75/650 mg to the logit of the pain relief probabilities (f_d) as a function of time. The figure indicates that, excluding the placebo effect, 650 mg APAP contributes considerably more than 75 mg tramadol and has a faster onset. Peak contribution of APAP to pain relief is achieved at 1 hour, whereas the tramadol effect peaks at 6.5 hours. Tramadol 75 mg has a longer duration of action compared to 650 mg APAP. Based on the model that best described the data, the combined action of tramadol and APAP is the sum of the individual contributions to the logit of the pain relief probabilities.



Simulation

Monte Carlo simulation of pain relief scores at scheduled time points was performed using the pharmacokinetic/pharmacodynamic model derived from this population analysis. Figure 2 shows the probability of having adequate pain relief (defined as a pain relief score greater than or equal to 2) as a function of tramadol dose and time. The relationships are obtained after Monte Carlo simulation of 2500 patients per dose group.

Figure 2: Model Predicted Relationship between Tramadol Dose, Time, and Probability of Having Adequate Pain Relief

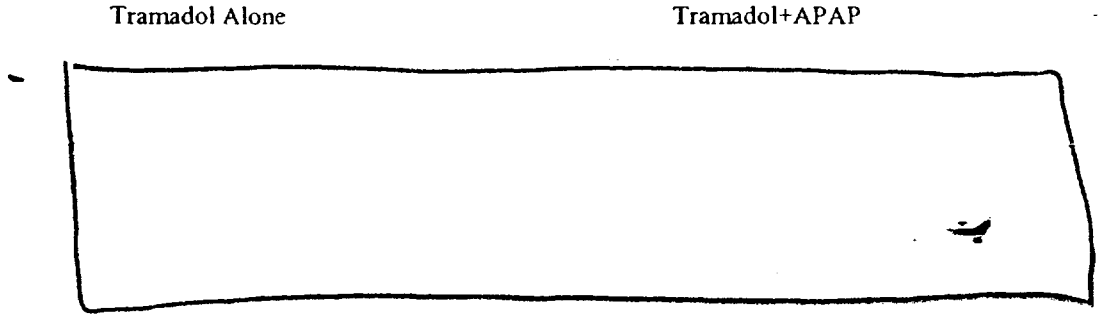
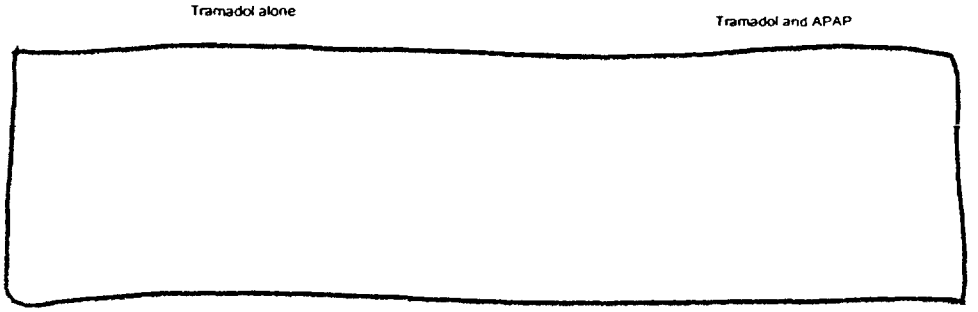


Figure 3 shows the contour plot as derived from the three-dimensional plots. The left panel shows the time course of the dose-response relationship for tramadol alone, whereas the right panel shows the relationship for tramadol combined with 650 mg APAP. The contour lines show the probability of having adequate pain relief. The tightly spaced horizontal lines near the bottom of the contour plot in the bottom panel indicated that the onset of analgesic effect, defined as the time point at which a certain percent of patients reach adequate pain relief, is similar for all doses of tramadol combined with 650 mg APAP because the quick onset of analgesic effect is due to the fixed dose of APAP component of the combination drug. The contour line for 50% of patients with adequate pain relief in the bottom panel indicated that the duration of analgesic effect increased with tramadol dose.

Figure 3: Contour Plot of Model Predicted Relationship between Tramadol Dose, Time, and Probability of Having Adequate Pain Relief



APPEARS THIS WAY
ON ORIGINAL

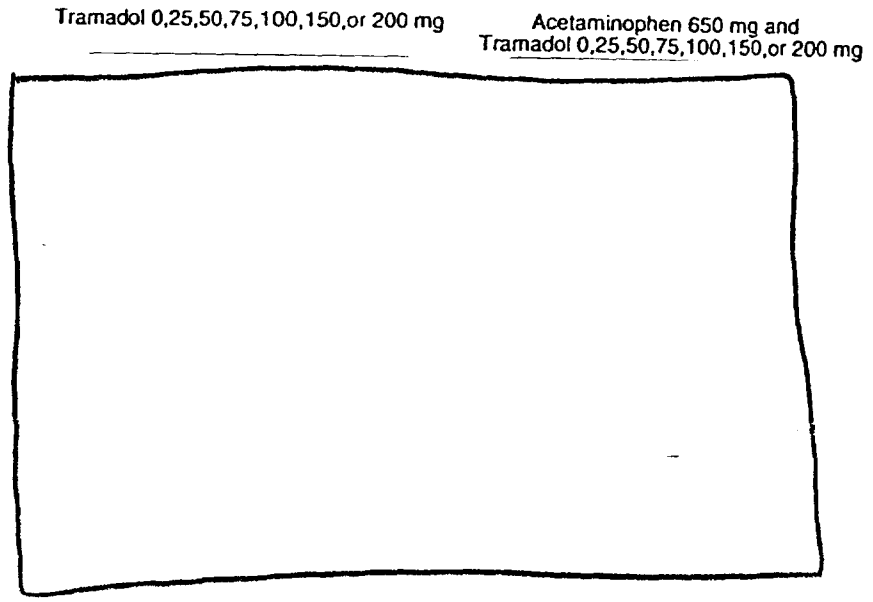
Table 3 summarizes the probability of having adequate pain relief at 1 hour, 2 hours, 4 hours, 6 hours, 10 hours, and peak effect after administration of placebo, 50 or 100 mg tramadol, APAP 650 mg, and APAP 650 mg combined with 25, 50, 75, or 100 mg tramadol. This table shows that the onset of analgesic effect is due to APAP component of the combination and the prolonged duration of analgesic effect of the combination is due to tramadol component.

Table 3: Probability of Having Adequate Pain Relief for Various Doses of Tramadol, Acetaminophen 650 mg, and Tramadol/APAP Combinations

Treatment	1 Hour	2 Hours	4 Hours	6 Hours	10 Hours	Peak
Placebo						
Tramadol 50 mg						
Tramadol 100 mg						
APAP 650 mg						
Tramadol/APAP 25/650 mg						
Tramadol/APAP 50/650 mg						
Tramadol/APAP 75/650 mg						
Tramadol/APAP 100/650 mg						

Figure 4 shows a simulation of the fraction of patients that have not remedicated as a function of time and tramadol dose. The left panel shows the relationship for tramadol alone and the right panel shows the relationship for tramadol/APAP. Comparing the two panels, it is apparent that acetaminophen helps lower the remedication rate. Increase in tramadol dose also lowers the probability of remedication.

Figure 4: Model predicted relationship between tramadol dose and the probability of remedication as a function of time (Left panel: tramadol alone; Right panel: coadministration with APAP 650 mg)



Conclusion

A population PK/PD model for the analgesic effect of tramadol/APAP combination tablets was developed to characterize the time course of the probability distribution of pain relief scores to

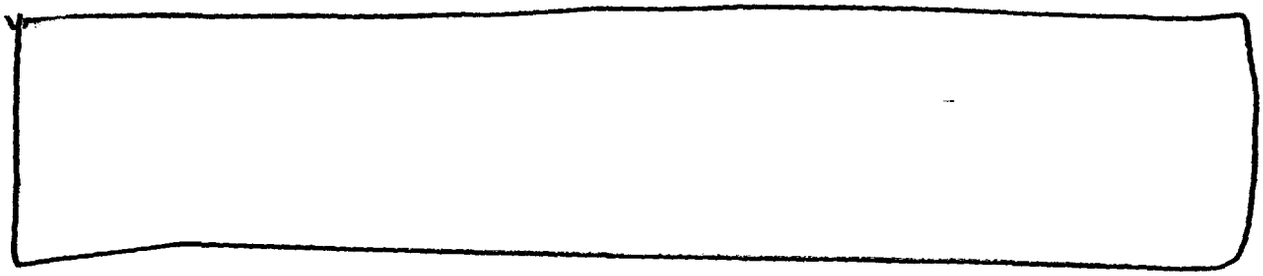
plasma concentration-time profiles of tramadol and APAP. There is a direct relationship between APAP plasma concentration and analgesic effect while the effect of tramadol is delayed. The analgesic effect of tramadol and APAP in the combination tablet is additive and complementary to each other in terms of the onset and duration of action. In addition, the model characterized the relationship between the probability of remedication and the observed pain relief scores. Based on the model derived from this population analysis, Monte Carlo simulation of pain relief scores at scheduled time points and time to remedication for patients in the placebo group and active drug groups were obtained. These simulations allow one to closely examine the onset and duration and remedication profiles for various tramadol/APAP dose combinations.

Reviewer's comments:

1. The overall fit for pain relief data is good although greater deviation between the predicted and observed values were seen at some doses (e.g., tramadol/APAP:25/0) possibly due to small sample size.
2. At the proposed dose of Tramadol 75 mg/APAP 650 mg, the fraction of patients getting adequate pain relief appears low, (the probability that patients have not remedicated is about 0.55 at 4 hours and 0.45 at 6 hrs.) and the percentage of patients that get adequate pain relief reaches 60% for only a very brief time period. Although increase in tramadol dose to 100 mg though beneficial in increasing the percentage of patients with adequate pain relief, this increase was small.
3. When evaluated in an animal model, the combination of tramadol and acetaminophen exhibited a synergistic effect. This PK/PD analysis of analgesia in dental pain trials, however, showed that the combination yielded only additive effect.
4. Metabolite M1 is active and in some animal models more active than the parent compound. However, the PK/PD analysis did not include metabolite M1 in the model nor did it attempt to differentiate contributions of individual stereoisomers. Since the overall fitting was good, the PK/PD model is considered adequate for the purpose of the analysis. However, caution should be made when using the PK/PD relationship derived in this study for situations where the ratio of metabolite M1 to parent compound may be different from that observed for the tablets (e.g., for an injection dosage form).

DISSOLUTION

The proposed dissolution test method and specifications are given below:



Comments:

Based on the dissolution test results on 5 clinical batches, dissolution was nearly complete at 20 minutes (see Appendix 1). Therefore, it would seem reasonable to tighten the specification to Q[ ]at 20 minutes. However, stability data have to be taken into consideration as well. This issue will be discussed with the Review Chemist.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 1

Individual Studies: design & data

NDA #	NDA 21-123	Submission Date:	8-31-1999	Volume: 2,- p.46
Study Type:	Bioavailability/Dosage performance	Study #:	TRAM-PHI-001	
Study Title:	A Pharmacokinetic Study Of Tramadol And Acetaminophen In Healthy Subjects Following A Single Oral Administration Of One Combination Tablet Containing 37.5 Mg Tramadol Hcl And 325 Mg APAP.			

Clinical Investigator: Stephen Scheinman, M.D.		Analytical Investigator	
Site	South Florida Bioavailability clinic 11190 Biscayne Boulevard Miami, FL 33181	Site	[redacted]

Single Dose:	x	Multiple Dose:		Washout Period:	
Cross-over		Parallel		Other Design:	

Fasted		x	Food Study		FDA high fat breakfast	
If fasted, how long (hrs.)?		10				

Subject Breakdown							
Normal	x	Patients		Young:		Elderly	

Subject Type		Normal			Group I	N= 12	M= 12	F= 0
Weight	Mean	70	Range	56-83 kg	Treatment	N=	M=	F=
Age	Mean	28	Range	20-40 yr	Treatment	N=	M=	F=

Treatment Group	Dose	Dosage Form	Strength	Lot #	Lot size
Group I	37.5mg Tramadol HCl + 325 mg Acetaminophen	Tablet	Tramadol HCl, 37.5 mg/tab Acetaminophen, 325 mg/tab	[redacted]	

Sampling Times	
Plasma	[redacted]
Urine	None
Feces	None

Assay Method:	[redacted]
Assay Sensitivity	
Assay Accuracy	

NDA #	NDA 21-123	Submission Date:	8-31-1999	Volume: 5-6, p.1
Study Type:	Single dose PK	Study #:	TRAMAP-PHI-002	
Study Title:	Evaluation Of The Effect Of Tramadol HCl/Acetaminophen Combination On The Pharmacokinetics Of Tramadol And Acetaminophen Following Administration Of A Single Oral Dose In The Fasted State To Healthy Subjects.			

Clinical Investigator: Gary D. Anderson, M.D.		Analytical Investigator	
Site	Corning Besselaar Clinical Research Units, Inc. 309 West Washington Ave., Madison, WI 53703	Site	[redacted]

Single Dose:	x	Multiple Dose:		Washout Period:	> 1 week
Cross-over	x	Parallel		Other Design:	

Fasted	x	Food Study		FDA high fat breakfast	
If fasted, how long (hrs.)?	10				

Subject Breakdown							
Normal	x	Patients		Young:		Elderly	

Subject Type		Normal			Group I	N= 24	M= 12	F= 12
Weight	Mean	70 kg	Range	58-94 kg	Treatment A (Tramadol+APAP)	N= 24	M= 12	F= 12
Age	Mean	29 yr	Range	19-40 yr	Treatment B (Tramadol alone)	N= 24	M= 12	F= 12
					Treatment C (APAP alone)	N= 24	M= 12	F= 12

Treatment Group	Dose	Dosage	Strength	Lot #	Lot size
A (APAP alone)	975 mg Acetaminophen	Tablet	Acetaminophen, 325 mg/tab	[redacted]	
B (Tramadol alone)	112.5mg Tramadol HCl	Capsule	Tramadol HCl, 37.5 mg/cap		
C (Tramadol+APAP)	112.5mg Tramadol HCl + 975 mg Acetaminophen	Tablet	Tramadol HCl, 37.5 mg/tab Acetaminophen, 325 mg/tab		

Sampling Times	
Plasma	[redacted]
Urine	0 to 36 hr, samples not analyzed
Feces	None

Assay Method:	[redacted]
Assay Sensitivity	
Assay Accuracy	

NDA #	NDA 21-123	Submission Date:	8-31-1999	Volume: 7-8, p.1
Study Type:	Multiple dose PK	Study #:	TRAMAP-PHI-001	
Study Title:	Evaluation Of The Effect Of Tramadol HCl/Acetaminophen Combination On The Pharmacokinetics Of Tramadol And Acetaminophen At Steady State Following Multiple Dose Oral Administration In Healthy Subjects.			

Clinical Investigator: Tosca Kinchelow, M.D.		Analytical Investigator	
Site	ICCR 105 Neptune Blvd., Neptune, NJ 07754	Site	[redacted]

Single Dose:		Multiple Dose:	x	Washout Period:	None
Cross-over	x	Parallel		Other Design:	

Fasted	None	Food Study		FDA high fat breakfast	
If fasted, how long (hrs.)?					

Subject Breakdown							
Normal	x	Patients		Young:		Elderly	

Subject Type		normal			Group I	N= 16	M= 8	F= 8
Weight	Mean	69 kg	Range	49-94 kg	Treatment A (APAP alone)	N= 16	M= 8	F= 8
Age	Mean	29 yr	Range	19-38 yr	Treatment C (Tramadol+APAP)	N= 16	M= 8	F= 8
					Group II	N= 16	M= 8	F= 8
Weight	Mean	69 kg	Range	44-90 kg	Treatment B (Tramadol alone)	N= 16	M= 8	F= 8
Age	Mean	31 yr	Range	21-40 yr	Treatment C (Tramadol+APAP)	N= 16	M= 8	F= 8

Treatment Group	Dose	Dosage Form	Strength	Lot #	Lot size
A (APAP alone)	975 mg Acetaminophen	Tablet	Acetaminophen, 325 mg/tab	[redacted]	
B (Tramadol alone)	112.5mg Tramadol HCl	Capsule	Tramadol HCl, 37.5 mg/cap		
C (Tramadol+APAP)	112.5mg Tramadol HCl + 975 mg Acetaminophen	Tablet	Tramadol HCl, 37.5 mg/tab Acetaminophen, 325 mg/tab		

Sampling Times	At steady state
Plasma	[redacted]
Urine	0-12 hour at steady-state, sample not analyzed
Feces	None

Assay Method:	[redacted]
Assay Sensitivity	
Assay Accuracy	

NDA #	NDA 21-123	Submission Date:	8-31-1999	Volume: 3-4, p.210
Study Type:	Food Effect	Study #:	TRAMAP-PHI-003).	
Study Title:	Effect Of Food On The Bioavailability Of Tramadol And APAP Following Administration Of A Single Oral Dose Of Three Tablets Each Containing 37.5 Mg Of Tramadol HCl And 325 Mg Of APAP To Healthy Subjects.			

Clinical Investigator: Dennis N. Morrison, D.O.		Analytical Investigator	
Site	Bio-Kinetic Clinical Applications, inc. 1816 W. Mt. Vernon, Springfield, MO 65802	Site	[redacted]

Single Dose:	x	Multiple Dose:		Washout Period:	> 1 week
Cross-over	x	Parallel		Other Design:	

Fasted	x	Food Study	x	FDA high fat breakfast	x
If fasted, how long (hrs.)?	10				

Subject Breakdown							
Normal	x	Patients		Young:		Elderly	

Subject Type		normal			Group	N=	M=	F=
Weight	Mean	71 kg	Range	54-94 kg	Treatment A (fasted)	N= 24	M= 12	F= 12
Age	Mean	28 yr	Range	19-39 yr	Treatment B (fed)	N= 24	M= 12	F= 12

Treatment Group	Dose	Dosage Form	Strength	Lot #	Lot size
Fasted and fed	112.5mg Tramadol HCl + 975 mg Acetaminophen	Tablet	Tramadol HCl, 37.5 mg/tab Acetaminophen, 325 mg/tab	[redacted]	

Sampling Times	
Plasma	[redacted]
Urine	None
Feces	None

Assay Method:	[redacted]
Assay Sensitivity	
Assay Accuracy	

5 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-123 **SUBMISSION DATE:** 11/14/2000
PRODUCT: Ultracet
(Tramadol HCl/Acetaminophen Tablets, 37.5 mg/325 mg)
SPONSOR: R.W. Johnson
Route 202, P.O. Box 300, Raritan, NJ 08869
TYPE OF SUBMISSION: Amendment **REVIEWER:** Sue-Chih Lee, Ph.D.

Background

The review of pharmacokinetic studies as provided in the original NDA submission was completed in May 2000. In this amendment, the sponsor provided new clinical information and a new label to deal with clinical issues that were raised in the original review by the Medical Officer. As a result of this and a labeling supplement [redacted] for Ultram tablets, we have re-evaluated our proposed label and has made some modifications to it. (See the attachment.) Since these modifications are primarily explanatory in nature, they will not be identified individually.

Recommendation

From the Clinical Pharmacology and Biopharmaceutics standpoint, the application is acceptable provided that the sponsor revise their label accordingly.

/S/ 5/14/01

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. 5/14/01

ATTACHMENT:
PROPOSED LABEL FOR
PHARMACOKINETICS AND DRUG-DRUG INTERACTIONS SECTIONS

Pharmacokinetics

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one ULTRACET tablet are shown in Table 1. Tramadol has a slower absorption and longer half-life, when compared to acetaminophen.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose Of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers

Parameter[a]	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		acetaminophen	
C_{max} (ng/mL)	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
t_{max} (h)	1.8	(0.6)	1.8	(0.7)	2.1	(0.7)	2.2	(0.7)	0.9	(0.7)
CL/F (mL/min)	588	(226)	736	(244)	-	-	-	-	365	(84)
$t_{1/2}$ (h)	5.1	(1.4)	4.7	(1.2)	7.8	(3.0)	6.2	(1.6)	2.5	(0.6)

[a] For acetaminophen, C_{max} was measured as μg/mL.

A single dose pharmacokinetic study of ULTRACET in volunteers showed no drug interactions between tramadol and acetaminophen. Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The [redacted] decrease [redacted] in AUC were 14.0% for (+)-tramadol and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear. Following single or multiple dose administration of Ultracet, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

Absorption:

The absolute bioavailability of tramadol from ULTRACET tablets has not been determined. Tramadol hydrochloride has a mean absolute bioavailability of approximately 7 % following administration of a single 100 mg oral dose of ULTRAM® tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two ULTRACET tablets occur at approximately three hours post-dose. [redacted]

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol.

Food Effects: When ULTRACET was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for acetaminophen. However, peak plasma concentration or the extent of absorption of either tramadol or acetaminophen were not affected.

Distribution:

The volume of distribution of tramadol was 2.6 and 2.9 L/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.

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

Metabolism:

Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. [redacted] of M1 is dependent on [redacted] and as such is subject to [redacted] induction and inhibition which may affect the therapeutic response.

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITIORS may enhance the risk of adverse events, including seizure(see WARNINGS) and serotonin syndrome.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principle separate pathways:

a) conjugation with glucuronide;

b) conjugation with sulfate; and

c) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidney. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing.

The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Special Populations

Renal:

The pharmacokinetics of the [redacted] in patients with renal impairment have not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min, adjustment of dosing regimen in this patient population is recommended. (See DOSAGE AND ADMINISTRATION). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.

Hepatic:

The pharmacokinetics and tolerability of ULTRACET in patients with impaired hepatic function has not been studied. Since tramadol and acetaminophen are both extensively metabolized by the liver [redacted] the use of ULTRACET in patients with hepatic impairment is not recommended (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with ULTRACET which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function. (See PRECAUTIONS: Geriatric Use)

Gender:

Tramadol clearance was 20% higher in female subjects compared to males on four phase I studies of ULTRACET in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

Pediatric:

Pharmacokinetics of ULTRACET Tablets have not been studied in pediatric patients below 16 years of age.

Drug Interactions

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.