CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-411

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	22411
Generic Name:	Trazodone Contramid OAD
Brand Name:	Oleptro®
Strength and Dosage Forms:	150 mg and 300mg Extended Release Tablets
Indication:	Treatment of Major Depressive Disorder
Sponsor:	Labopharm Pharm / CanReg Inc (USA Agent)
Submission Type:	Original NDA (505 (b)(2))
Submission Date:	9/18/08, 11/26/08, 4/16/09
OCP Division:	DCP1 (HFD-860)
OND Division:	DPP (HFD-130)
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

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1. Executive Summary

1.1. Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the data submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 22-411 and finds the data acceptable. OCP supports approval of Trazodone Contramid OAD (Oleptro) 150 mg and 300 mg extended release tablets. OCP recommends that Oleptro® be taken once daily on an empty stomach at bedtime.

1.2. Phase IV Commitments

The sponsor should conduct studies to investigate dose dumping in the presence of alcohol
To fulfill this request, the sponsor should perform in vitro dissolution studies for all Trazodone Contramid Extended Release strengths using the accepted dissolution conditions with the addition of the following alcohol concentrations for the in vitro dissolution studies (using 12 units each): 0 %, 5 %, 10 %, 20 %, and 40 %.

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Regulatory Background: This application was filed as a 505 (b)(2) NDA. Trazodone Contramid OAD is submitted for the treatment of Major Depressive Disorder (MDD), which is the same indication approved for the reference product, Trazodone Hydrochloride IR from Apotex. All clinical trial materials (CTM) were manufactured at Labopharm. The sponsor intends to manufacture commercial batches at a different site, (b) (4)

Proposed Therapeutic Indication and Dosage Regimen: Oleptro™ is indicated for the treatment of major depressive disorder. The recommended starting dose of Oleptro™ is 150 mg/day in adults. The usual dose is 300 mg/day. The maximum daily dose should not exceed 375 mg.
Oleptro™ tablets should be taken orally at the same time every day, in the late evening.
Dosage during prolonged maintenance therapy should be kept at the lowest effective level.
Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.

Bioavailability and Bioequivalence of Trazodone Extended Release and Trazodone IR (Apotex):

Single Dose
Following a total daily dosage of 300 mg trazodone, bioequivalence between Trazodone Contramid OAD and trazodone IR (300 mg total daily dose administered 100 mg three times a day) was not demonstrated. The following table contains the statistical analysis for the single dose bioequivalence study between Trazodone Contramid OAD and Trazodone Hydrochloride IR (Apotex)

Table 1: Summary of Statistical Analysis of Pharmacokinetic Parameters Following Administration of a 300 mg Daily Dose of Trazodone Contramid ER Caplets and IR Trazodone Tablets Under Fasting Conditions in Healthy Volunteers

Parameter	Trazodone Contramid	IR Trazodone (Apotex Corp.)	Least Squares Mean Ratio (%) (90% CI)	Intra CV (%)
	LSMean			
Cmax (ng/mL)	1137.22	2859.53	40.0 (34 – 46)	29.0
AUC (0-t) (ng*h/mL)	26620.67	32894.73	81.0 (74 – 88)	17.3
AUC(0-∞)(ng*h/mL)	28260.28	33861.63	83.0 (76 – 91)	17.4
T ½ (h)	11.32	8.02	-	23.5
Tmax[*] (h)	9.00 (2 – 16)	8.33 (8.3 – 16.3)	-	-

[#]Median (range)

The sponsor stated that Trazodone IR reference product administered at morning was 2-fold higher than following doses administered in the evening and at night. The higher AUC for the IR product was probably a result of diurnal effect on trazodone pharmacokinetics. However, in another study to evaluate the effect of time of administration, taking Trazodone Contramid at night (10 p.m.) compared to the morning (10 a.m) resulted in about a 47% increase in Cmax of Trazodone and mCPP. The extent of absorption (AUC) does not significantly change with time of administration. Therefore the decrease in AUC may not be due to diurnal effect.

Multiple Dose

Steady state AUC of trazodone is equivalent after administration of trazodone 100 mg three times a day and Trazodone Contramid 300 mg once daily for one week. Cmax,ss and Cmin,ss were not equivalent. There are lower fluctuations in concentrations after administration of the OAD formulation. The following table is the statistical analysis after administration of multiple doses of Trazodone Contramid and Trazodone IR.

Table 2: Summary of Statistical Analysis of Pharmacokinetic Variables for Trazodone

Parameter	LS Mean		Mean Ratio (Test/Ref) (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone 100 mg IR (Reference)	Trazodone 300 mg ER (Test)			
AUCss (ng*h/mL)	32159.53	27568.60	85.72	81.05; 90.67	12.1
Cmax,ss (ng/mL)	3023.39	1709.18	56.53	49.99; 63.94	26.9
Cmin,ss (ng/mL)	801.29	585.74	73.10	64.75; 82.52	26.5
Tmax[#] (h)	8.33	8.00	p-value = 0.0359		

[#]Medians and p-value according to Wilcoxon signed rank test

The extent of absorption (AUC) after administration of Trazodone Contramid OAD was equivalent to that after administration of Trazodone IR. However, Cmax was not equivalent after the administration of the once a day formulation compared to the IR. This is consistent with

expectation that Cmax would not be equivalent after administration of both formulations. Cmin of trazodone was not equivalent after administration of the once a day (OAD) formulation and IR formulation.

Bioequivalence between batches manufactured at the commercial versus clinical trial manufacturing sites

Trazodone Contramid manufacture at the commercial site (b) (4) is not bioequivalent to the clinical trial batches manufactured at Labopharm. Following administration of tablets manufactured at the two sites, bioequivalence criteria was met for trazodone AUC. However, a bioequivalence criterion was not met for Cmax for both trazodone and mCPP. The following table contains the statistical analysis for the comparison of batches manufactured at (b) (4) versus Labopharm.

Table 3: Statistical Evaluation of Trazodone Pharmacokinetic Parameters

Parameter	Least-Squares (LS) Mean		Mean Ratio (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone Contramid (b) (4) (Test)	Trazodone Contramid (Labopharm) (Reference)			
Cmax (ng/mL)	1167.762	960.627	121.56	105.53 – 140.03	30.4
AUC (0-t) (ng*h/mL)	29311.87	26608.29	110.39	102.43 – 118.96	15.8
AUC(0-∞) (ng*h/mL)	31136.57	28323.01	109.93	102.53 – 117.88	14.7
#Tmax (h)	9.50	8.50			

Median

OCP simulated, by the method of superposition, multiple dose conditions and estimated the concentrations at steady state. The following table contains the statistical analysis of pharmacokinetic parameters at steady state and the 90% confidence intervals. Trazodone Contramid manufactured at (b) (4) is not equivalent to that manufactured at Labopharm under steady state conditions. Trazodone Cmax was 15% higher when Trazodone Contramid was manufactured at (b) (4) compared to that manufactured at Labopharm. However, AUC of trazodone was similar when a product from (b) (4) site is compared to that from Labopharm.

Table 4: Statistical Analysis of Trazodone Pharmacokinetic Parameters at Steady State based on Simulated Concentrations

Parameter	Point Estimate	90% CI
Cmax	1.15	105 - 126
AUC(0-24)	1.13	104 -123

From a Clinical Pharmacology perspective, the difference in Cmax when Trazodone Contramid is manufactured at the (b) (4) (commercial site) compared to that Labopharm (Clinical Trial Material site) would not be expected to be clinically relevant.

Effect of food on the Pharmacokinetics of Trazodone after administration Trazodone Contramid
Following administration of Trazodone Contramid under fed conditions, Cmax for trazodone increased by 86%. AUCt and AUC∞ increased by 15% and 11%, respectively, under fed conditions. The 90% CI for fed/fasting mean ratios of AUCt and AUC∞ were contained within the 80% to 125% range.

Dose Proportionality

The assessment of dose proportionality by the power method demonstrated that the concentration of trazodone was proportional to dose from 75 to 375 mg. Half 150 mg caplet is proportional to the intact 150 mg caplet and that the lowest dose (75 mg) and the highest dose (375 mg) evaluated in the study are proportional to the reference dose (300 mg). Half 300 mg caplet is proportional to the intact 300 mg caplet with respect to AUC of trazodone. However, the dose-normalized Cmax was 19.7% higher for the half 300 mg caplet compared with the intact 300 mg caplet.

2. Question Based Review (QBR)

The QBR section of the review has used a deductive approach (i.e. starts with conclusions followed with supportive details) as instructed by CDER Review Template MaPP 4000.4.

2.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

This application was filed as a 505 (b)(2) NDA. Trazodone Contramid OAD is submitted for the treatment of Major Depressive Disorder (MDD), which is the same indication approved for the reference product, Desyrel (Trazodone immediate release formulation). Desyrel was discontinued in 2006 and the reference listed drug in the orange book now is Trazodone Hydrochloride from Apotex (ANDA 71-196). Therefore, the reference product in the pivotal bioavailability and bioequivalence studies was Trazodone Hydrochloride from Apotex. Trazodone Hydrochloride is an IR product that is administered 3 times a day. Trazodone Contramid is an extended release (ER) tablet that is to be administered once a day (OAD). All clinical trial materials (CTM) were manufactured at Labopharm. The sponsor intends to manufacture commercial batches at a different site, (b) (4)

The application contains one randomized, double-blind, placebo-controlled, two arm, safety and efficacy study of Trazodone Contramid ER against placebo. The application also contains biopharmaceutics studies, literature review on nonclinical aspects of trazodone and Chemistry, Manufacturing and Controls information. The sponsor is seeking a waiver for pediatric studies for children aged less than 7 years old and a request for deferral for older children (7 years and up).

2.1.1. What is the proposed therapeutic indication for Trazodone Contramid (Oleptro®)?

Oleptro™, a Serotonin 2A Antagonist Reuptake Inhibitor, is indicated for the treatment of major depressive disorder (MDD).

2.1.2. What are the proposed dosage and route of administration?

The recommended starting dose of Oleptro™ is 150 mg/day in adults. The usual dose is 300 mg/day. The maximum daily dose should not exceed 375 mg.
Oleptro™ tablets should be taken orally at the same time every day, in the late evening.
Dosage during prolonged maintenance therapy should be kept at the lowest effective level.
Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response. Oleptro is to be administered orally.

2.2. General Clinical Pharmacology and Biopharmaceutics

2.2.1. What are the design features of the pivotal bioequivalence studies used to support dosing or claims?

The two pivotal pharmacokinetic studies to demonstrate equivalence of the Trazodone Contramid OAD to Trazodone IR formulations were single and multiple dose trials. The single dose study was an open-label, randomized, two-way crossover study performed under fasting conditions that compared 300 mg Trazodone Contramid administered once a day to the 100 mg immediate-release reference product administered 3 times a day in a 24 hour period.

In the pivotal multiple dose study, the subjects were titrated to the 300 mg IR dose (100 mg on day 1, 100 mg bid on day 2 and 100 mg tid on 3 and after) and then administered Trazodone 100 mg tid for 7 days and compared to 300 mg once daily for 7 days. After 7 days, there was a down titration over two days. The two treatment phases were separated by 7 days.

The food effect study was a single-center, open-label, randomized, single dose, 2-way crossover study comparing 300 mg Trazodone Contramid administered under fed and fasting conditions.

The dose proportionality study was a single center, open-label, randomized, single dose, 5-way crossover study that evaluated under fasting conditions doses from 75 to 375 mg.

2.2.2. Are the active moieties in the plasma (or biological fluid) appropriately identified and measured to assess pharmacokinetic parameters

Yes, the active moieties in the plasma have been adequately identified and measured (Refer to section on Analytical Methods

2.2.3 Exposures

2.2.3.1. Are the exposures after administration of equal daily doses of Trazodone Contramid Extended Release Tablets and Trazodone Immediate Release Tablets (Apotex) similar?

2.2.3.1.1. Are the exposures equivalent after single dose administration

Following a total daily dosage of 300 mg Trazodone, bioequivalence between Trazodone Contramid and Trazodone IR (300 mg total daily dose administered 100 mg three times a day) was not demonstrated. Trazodone total exposures (AUCs) after administration of Contramid were 20% lower than the immediate release (IR) reference product. Cmax was 60% lower for Trazodone Contramid compared to the IR reference product. Lower Cmax after Trazodone Contramid was to be expected for comparison of the extended release to IR formulation.

The sponsor conducted an open-label, laboratory-blind, two-way crossover study under fasting conditions to evaluate whether Trazodone Contramid administered as single 300 mg extended release tablets is bioequivalent to the reference product, Trazodone 100 mg IR administered three times daily. There was a 7 to 14 day washout period between treatments. For the reference product, on day 1 of the clinical stay subject received 100 mg Trazdone IR in the evening, on day 2, 100 mg Trazodone IR was administered 2 times. For the test product, 300 mg Trazodone Contramid extended release was administered once daily. Blood samples were taken for the determination of Trazodone and its active metabolite, m-chlorophenylpiperazine (mCPP). The following is plasma concentration time profile for Trazodone.

The following table contains the statistical summary of pharmacokinetic parameters after administration of the two formulations.

Table 5: Statistical Analysis of Trazodone Following Administration of a 300 mg Daily Dose of Trazodone Contramid ER Caplets and IR Trazodone Tablets Under Fasting Conditions in Healthy Volunteers

Parameter	Trazodone Contramid	IR Trazodone (Apotex Corp.)	Least Squares Mean Ratio (%) (90% CI)	Intra CV (%)
	LSMean			
Cmax (ng/mL)	1137.22	2859.53	40.0 (34 – 46)	29.0
AUC (0-t) (ng*h/mL)	26620.67	32894.73	81.0 (74 – 88)	17.3
AUC(0-∞)(ng*h/mL)	28260.28	33861.63	83.0 (76 – 91)	17.4
T ½ (h)	11.32	8.02	-	23.5
Tmax[*] (h)	9.00 (2 – 16)	8.33 (8.3 – 16.3)	-	-

[#]Median (range)

m-chlorophenylpiperazine (mCPP)

Following a total daily dose of 300 mg trazodone, AUC for the active metabolite, mCPP, was 14% to 20% lower after administration of Trazodone Contramid than after IR product. In addition, Cmax of mCPP was 37% lower after administration of Contramid relative to the reference IR product. The mean pharmacokinetic parameters are provided in the following table.

Table 6: Statistical Analysis of mCPP Following Administration of a 300 mg Daily Dose of Trazodone Contramid OAD Extended Release Caplets and Immediate Release Trazodone Tablets Under Fasting Conditions in Healthy Volunteers (n=23; dose = 300 mg)

Parameter	Trazodone Contramid	IR Trazodone (Apotex Corp.)	Least Squares Mean Ratio (%) (90% CI)	Intra CV (%)
	LSMean			
Cmax (ng/mL)	12.55	20.07	63 (54 – 72)	28.5
AUC (0-t) (ng*h/mL)	334.16	415.73	80 (73 – 89)	20.2
AUC(0-∞)(ng*h/mL)	384.98	447.39	86 (78 – 94)	18.5
T ½ (h)	13.64	8.88	-	25.0
Tmax[*] (h)	10.0 (4.0 – 36.0)	9.0 (8.3 - 20)	-	-

[#]Median (range)

2.2.3.1.2. Are the exposures equivalent after multiple dose administration

The 90% Confidence Interval (CI) criteria for declaring equivalent exposures were met for AUCss but not Cmax or Cmin. Based on AUCss, the extent of absorption at steady state was similar after Trazodone Contramid and immediate release trazodone administered over the 24 hour profile period. The mean Cmax and Cmin at steady state were about 44% and 27% lower, respectively for Trazodone Contramid compared to the IR Trazodone reference product. Variations in maximum and minimum trazodone concentrations, as measured by %PTF was about 41.6% lower for Trazodone Contramid compared to Trazodone IR.

The sponsor conducted a study to compare the pharmacokinetics at steady state of 300 mg Trazodone Contramid extended release tablets administered once daily and the reference product, 100 mg Trazodone HCl IR tablets (Apotex) when administered 3 times a day for one week. The study was an open-label, laboratory-blind, multiple dose, randomized, two period crossover study under fasting conditions. The study consisted of two treatment phases, each of which included a multiple dose run in period of 8 days. The treatment phases were separated by a washout period of 7 to 14 days. The multiple dose run period were as follows: 1) reference product: day 1, 100 mg once in the evening, day 2, 100 mg twice a day, days 3 to 9, 100 mg 3 times a day. A 24 hour blood samples were collected after the last dose. The dose of Trazodone IR was tapered down on days 10 and 11 after the blood collection. For the test product, Trazodone Contramid, on day 1 subjects received 75 mg Trazodone Contramid (1/2 * 150 mg tablet) in the night, on day 2 subjects received 150 mg trazodone at night, on day 3 to 9 subjects received 300 mg trazodone contramid once daily in the evening. Blood samples were drawn for 24 hours after the last dose on day 9. On days 10 and 11 after the blood collection, the dose was tapered down. The figure is the 24 hour figure for Trazodone

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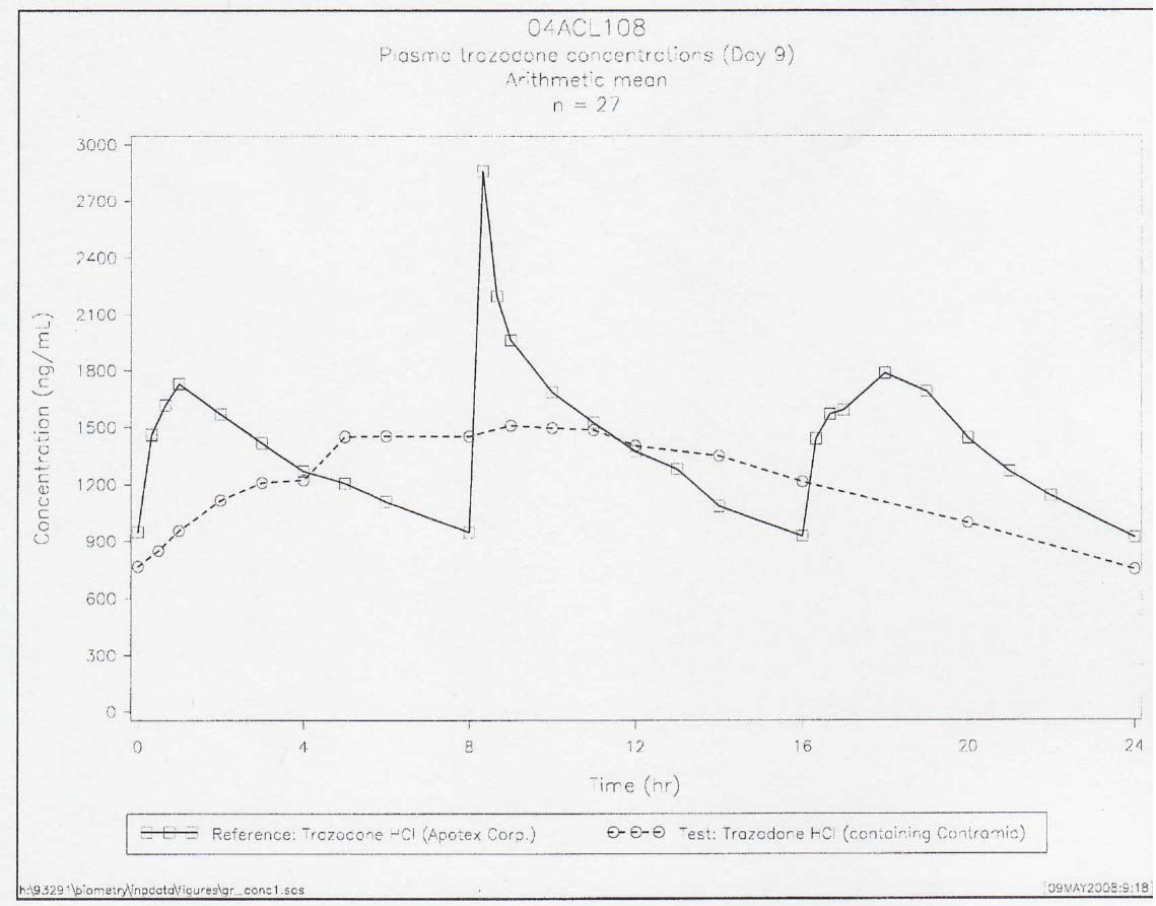


The following table contains the statistical analysis for trazodone after administration of Trazodone Contramid and IR Trazodone.

Table 7: Summary of Statistical Analysis of Pharmacokinetic Variables for Trazodone

Parameter	LS Mean		Mean Ratio (Test/Ref) (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone 100 mg IR (Reference)	Trazodone 300 mg ER (Test)			
AUCss (ng*h/mL)	32159.53	27568.60	85.72	81.05; 90.67	12.1
Cmax,ss (ng/mL)	3023.39	1709.18	56.53	49.99; 63.94	26.9
Cmin,ss (ng/mL)	801.29	585.74	73.10	64.75; 82.52	26.5
%PTF	159.75	93.34	58.43	49.64; 68.78	
Tmax# (h)	8.33	8.00	p-value = 0.0359		

Medians and p-value according to Wilcoxon signed rank test; PTF = Peak trough fluctuation

mCPP

mCPP concentrations were not equivalent after administration of Trazodone 100 mg IR three times a day and Trazodone Contramid 300 mg daily for 7 days. The following is a summary of the statistical analysis for mCPP.

Table 8: Summary of Statistical Analysis of Pharmacokinetic Parameters for mCPP

Parameter	LS Mean		Mean Ratio (Test/Ref) (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone 100 mg IR (Reference)	Trazodone 300 mg ER (Test)			
AUCss (ng*h/mL)	434.57	333.89	76.83	71.89; 82.11	14.4
Cmax,ss (ng/mL)	27.39	19.67	71.81	65.11; 79.21	21.3
Cmin,ss (ng/mL)	12.11	7.75	63.96	57.40; 71.27	23.6
%PTF	80.80	81.21	100.51	89.49; 112.89	25.4
Tmax# (h)	8.67	8.00	p-value = .5606		

Medians and p-value according to Wilcoxon signed rank test; PTF = Peak trough fluctuation

2.2.3.2. Are the exposures after administration of 300 mg Trazodone Contramid Extended Release Tablets manufactured at the Clinical Trial Site (Labopharm) bioequivalent to that manufactured at the commercial site (b) (4)

Trazodone contramid manufactured at (b) (4) is not bioequivalent to Trazodone Contramid manufactured at Labopharm after single dose administration. Following administration of tablets manufactured at the two sites, bioequivalence criteria was met for AUC of trazodone and mCPP. However, a bioequivalence criterion was not met for Cmax for both trazodone and mCPP. The 90% confidence interval around the mean ratio for trazodone Cmax was 105% - 140%, which exceeds the regulatory limit of 80% to 125%.

OCP simulated, by the method superposition, multiple dose concentrations. Trazodone Contramid manufactured at (b) (4) is not equivalent to that manufactured at Labopharm under steady state conditions. Trazodone Cmax was 15% higher when administered Trazodone Contramid that was manufactured at (b) (4) compared to that manufactured at Labopharm (90% CI: 105% - 126%). However, AUC of trazodone was similar when product from (b) (4) site is compared to that from Labopharm. From a Clinical Pharmacology perspective, the difference in Cmax when Trazodone Contramid is manufactured at the (b) (4) (commercial site) compared to that Labopharm (Clinical Trial Material site) would not be clinically relevant because:

1) The extent of exposure (AUC) are equivalent when batches manufactured at (b) (4) are compared to that from Labopharm.
2) The Cmax is within the range of Cmax observed in other studies
3) No major differences in the adverse events profile were reported during the study when batches manufactured at the two sites were administered.
4) The sponsor intends to manufacture all commercial batches at the (b) (4) site

The sponsor conducted an open-label, laboratory-blind, single-dose, randomized, two-period crossover study under fasting conditions to determine whether 300 mg Trazodone Contramid manufactured at the two different sites are bioequivalent. The study consisted of two treatment phases of 72 hours each which were separated by a wash-out period of 7 to 14 days. Blood samples were collected for a specified time period for 72 hours. The following are summary of statistical analysis for the pharmacokinetic parameters.

Table 9: Statistical Evaluation of Trazodone Pharmacokinetic Parameters

Parameter	Least-Squares Mean		Mean Ratio (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone Contramid (b) (4) (Test)	Trazodone Contramid (Labopharm) (Reference)			
Cmax (ng/mL)	1167.762	960.627	121.56	105.53 – 140.03	30.4
AUC (0-t) (ng*h/mL)	29311.87	26608.29	110.39	102.43 – 118.96	15.8
AUC(0-∞) (ng*h/mL)	31136.57	28323.01	109.93	102.53 – 117.88	14.7
#Tmax (h)	9.500	8.500			

Median

OCP simulated steady state concentrations using the method of superposition of concentrations. The following table contains the summary of statistical results after simulation of steady state conditions.

Table 10: Statistical Analysis of Trazodone Pharmacokinetic Parameters at Steady State (All Subjects)

Parameter	Point Estimate	90% CI
Cmax	1.15	105 - 126
AUC(0-24)	1.13	104 -123

The following figure depicts the range of Cmax in the pivotal single dose bioavailability and bioequivalence studies.

Figure 2

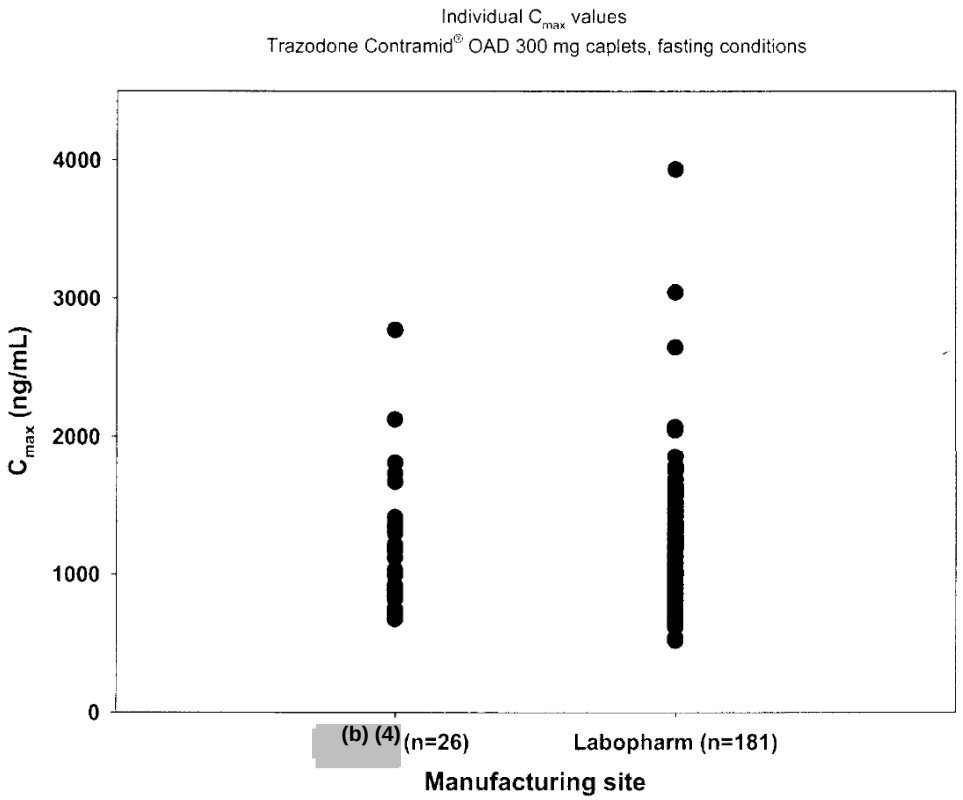


Figure 11-9 Plasma Trazodone C_{max} Values Across Studies Following Single-dose Administration of Trazodone Contramid® OAD 300 mg Caplets Under Fasting Conditions

Data source: Study reports 04ACL101, 04ACL102, 04ACL103, 04ACL104, 04ACL105, 04ACL107, 04ACL109

The following table contains dissolution profile similarity comparisons between batches manufacture at the commercial site (b) (4) and the clinical trial material site (Labopharm)

Table 11: Dissolution Profile Comparisons for Batches Manufactured at (b) (4) and LaboPharm

Dissolution conditions	type II, 150 rpm over 24 hrs			
	std condition	pH 1.2	pH 4.0	pH 6.0
150mg strength, whole caplets				
Labopharm Batch 04A19503 (b) (4) 112366	f_2= 95.8	f_2 = 99.3	f_2 = 92.5	f_2 = 99.1
150mg strength, half caplets				
Labopharm Batch 04A19503 (b) (4) Batch 112366	f_2 = 78.6	f_2= 92.3	f_2 = 92.9	f_2 = 86.5

Dissolution conditions	type II, 150 rpm over 24 hrs			
	std condition	pH 1.2	pH 4.0	pH 6.0
300mg strength, whole caplets				
Labopharm. Lot 04A19602 (b) (4) Lot 112365	f_2 = 80.3	f_2 = 74.9	f_2 = 85.1	f_2 = 70.1
300mg strength, half caplets				
Labopharm. Lot 04A19602 (b) (4) Lot 112365	f_2 = 98.6	f_2 = 91.9	f_2 = 89.6	f_2 = 92.1

The dissolution profiles for the batches manufactured at (b) (4) compared to that at Labopharm are similar.

2.2.3.3. Are the concentrations of Trazodone proportional after administration of Trazodone Contramid from 75 mg to 375 mg dose?

Results of the assessment of dose proportionality by the power method demonstrated that the concentration of trazodone was proportional to dose between 75 to 375 mg.

The sponsor conducted a randomized, five-way crossover dose-proportionality study (Doses Ranging from 75 mg to 375 mg) of Trazodone Hydrochloride Extended Release Caplets (containing Contramid) Under Fasting Conditions. The study was open-label, laboratory-blind, single-dose, randomized, 5-way crossover. There was 7 days washout period between treatments. Subjects received each treatment once. The following figure contains Box plots of dose normalized (normalized to 300 mg) Cmax and AUC.

Fig 3: Box and Whisker Plot of Dose Normalized Cmax versus Dose

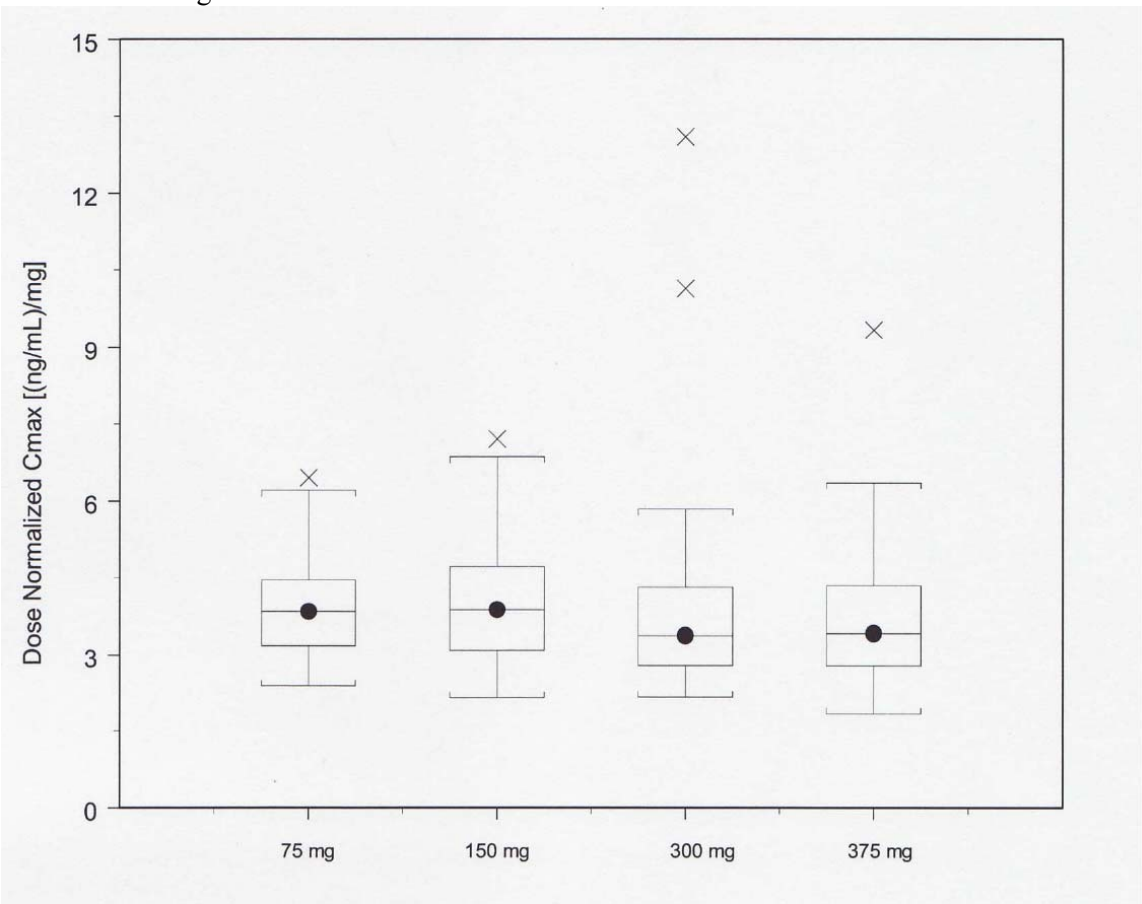
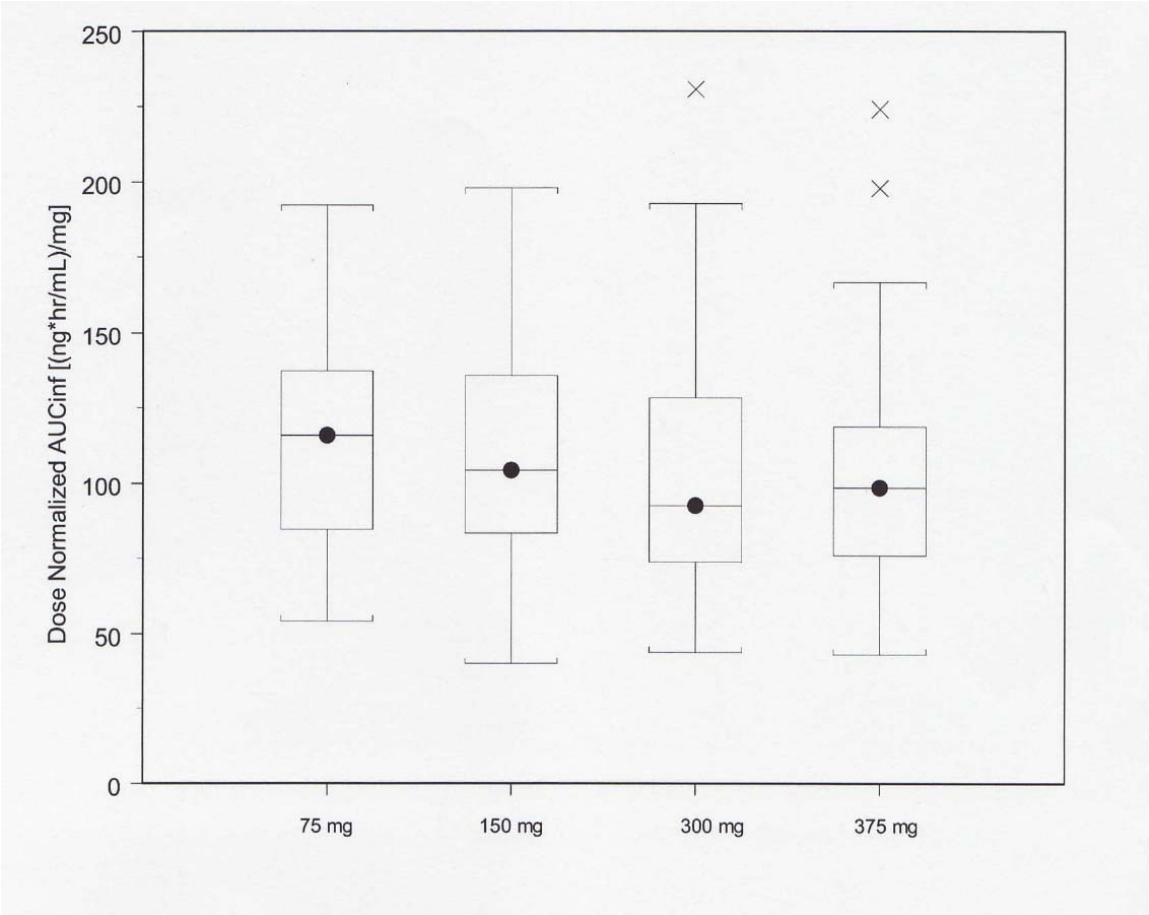
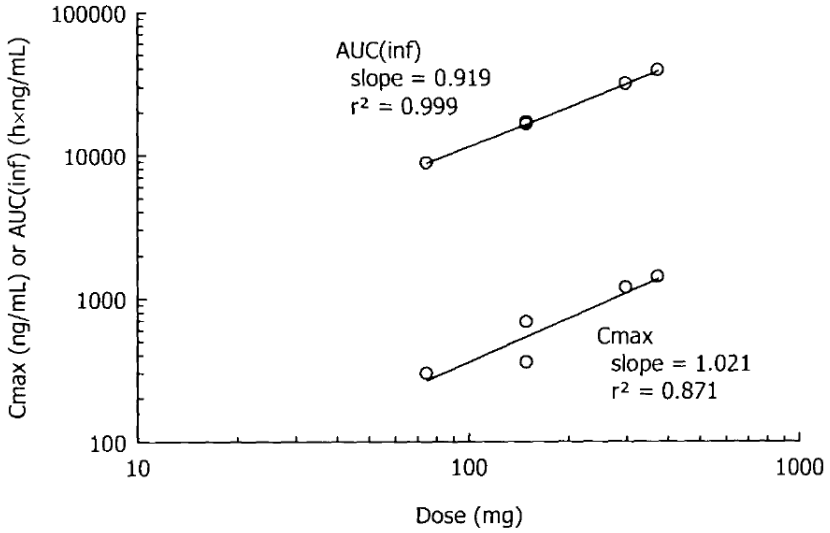


Fig 4: Box and Whisker Plot of Dose Normalized AUC versus Dose



The following figure contains the relationship between AUC, Cmax and dose.

Fig 5: Relationship between AUC∞, Cmax and Dose after Oral Administration of Single Doses of Trazodone Contramid OAD (75 to 375 mg) to Healthy Volunteers Under Fasting Conditions



The results for the dose proportionality analysis of the pharmacokinetic variables Cmax, AUC(0-t) and AUC(0-∞) for trazodone and mCPP are provided in the following table. The model used is presented in the Study 105 in the Appendix.

Table 12: Summary of Statistical Analysis of Pharmacokinetic Parameters for Trazodone and mCPP using the Power Model

Parameter	Acceptance Interval	Trazodone		mCPP	
		β	90% CI	β	90% CI
AUC(0-t) (ng*h/mL)	(0.861 ; 1.139)	0.920	(0.875; 0.964)	1.024	(0.969; 1.079)
AUC (0-∞) (ng*h/mL)	(0.861 ; 1.139)	0.913	(0.867; 0.958)	0.963	(0.912; 1.013)
Cmax (ng/mL)	(0.861 ; 1.139)	0.948	(0.899; 0.997)	1.068	(1.011; 1.124)

β= estimate of proportionality constant

2.2.3.4. Are the exposures bioequivalent after administration of 300 mg Trazodone Contramid Extended Release Tablets under fed and fasting conditions?

It is recommended that Trazodone be taken under fasting conditions.
Following administration of Trazodone Contramid under fed conditions, Cmax for trazodone increased by 86%. AUCt and AUC∞ increased by 15% and 11%, respectively, under fed

conditions. The 90% Confidence Interval (CI) for fed/fasting mean ratio of Cmax fell outside the recommended criteria of 80% to 125%. The 90% CI for fed/fasting mean ratios of AUCt and AUC∞ were contained within the 80% to 125% range. The p-value indicated no significant difference in the median Tmax for trazodone under fed and fasting conditions.

Following administration of Trazodone Contramid under fed conditions, Cmax for mCPP increased by 94%. AUCt and AUC∞ for mCPP increased by 24% and 15%, respectively under fed conditions. There was no significant difference in Tmax under fed and fasting conditions.

The sponsor conducted a single center, open-label, randomized, single dose, 2-way crossover study performed under fasting and fed conditions. Two treatment phases of 72 hours each were separated by a washout period of 7 days. Subjects were administered study medication after fasting overnight or following a standardized, high-fat, high calorie breakfast. Blood samples were collected over 72 hours following dosing. The following is summary of statistical analysis of the pharmacokinetic parameters

Table 13: Summary of Statistical Analysis of Pharmacokinetic Parameters for Trazodone (n=34)

Parameter	LS Mean		Mean Ratio (%)	90% CI	Intra-individual CV (%)
	Fed (Test B)	Fasting (Test A)			
Cmax (ng/mL)	2113.28	1137.42	185.80	167.37; 206.25	25.8
AUCt (ng*h/mL)	30463.03	26471.64	115.08	108.21; 122.38	15.0
AUC∞ (ng*h/mL)	31259.93	28061.71	111.40	105.21; 117.94	13.9
T ½ (h)	7.92	9.96	79.59	72.82;87.00	21.9
Tmax* (h)	8.50	9.00	P = 0.8504		

*Medians and p-value according to Wilcoxon signed rank test

Table 14: Summary of Statistical Analysis of Pharmacokinetic Parameters for mCPP (n=34)

Parameter	LS Mean		Mean Ratio (%)	90% CI	Intra-individual CV (%)
	Fed (Test B)	Fasting (Test A)			
Cmax (ng/mL)	28.663	14.78	193.89	173.48; 216.71	27.5
AUCt (ng*h/mL)	514.38	414.11	124.21	115.70; 133.36	17.4
AUC∞ (ng*h/mL)	546.48	476.00	114.81	107.71; 122.37	15.6
T ½ (h)	8.58	12.71	67.51	59.41; 76.71	31.8
Tmax* (h)	9.52	12.00	P = 0.1984		

*Medians and p-value according to Wilcoxon signed rank test

2.2.3.5. Are the exposures equivalent after administration of 300 mg Trazodone Contramid Extended Release Tablets at different times?

Administration of Trazodone Contramid at night compared to the morning resulted in about a 47% increase in Cmax of Trazodone and mCPP. The extent of absorption (AUC) does not change with time of administration.

The sponsor conducted an open-label, randomized, single dose, 3-way crossover study. Three treatments phases of 72 hours each were separated by washout periods of 7 days. In each period, subjects were randomly assigned to receive 300 mg Trazodone Contramid at either 10:00 a.m. or 10:00 p.m. four hours after a light meal or at 6:15 p.m., fifteen minutes after administration of a high fat, high calorie meal. The following table contains statistical analysis of the pharmacokinetic parameters for trazodone and mCPP in subjects who received Trazodone Contramid at 10 a.m. (Treatment A) and at 10 p.m. (Treatment B).

Table 15: Summary of Statistics of Pharmacokinetic Parameters for Trazodone and mCPP-Treatment B (Test) vs Treatment A (Reference)

Treatment B vs Treatment A - Trazodone					
Variable *(unit)*	**LSMean**		**Mean Ratio (%)**	**90% Confidence Interval of Ratio (%)**	**Intra-individual CV (%)**
	Treatment B (Test)	**Treatment A (Reference)**			
C_{max} *(ng/mL)*	1544.144	1050.220	147.03	(128.90 ; 167.71)	27.5
AUC(0-t_{last}) *(h·ng /mL)*	29863.59	27859.90	107.19	(97.95 ; 117.30)	18.7
AUC(0-∞) *(h·ng/mL)*	31093.89	29698.78	104.70	(95.73 ; 114.51)	18.6
AUC(0-24) *(h·ng/mL)*	21425.15	17128.52	125.08	(114.46 ; 136.69)	18.4
λ_z *(1/h)*	0.070	0.060	116.48	(107.44 ; 126.29)	16.7
$t_{½,z}$ *(h)*	9.891	11.524	85.83	(79.14 ; 93.08)	16.8
T_{max}♣ *(h)*	9.000	9.000	p-value: 0.7232		
Treatment B vs Treatment A – mCPP					
C_{max} *(ng/mL)*	17.707	11.960	148.05	(131.29 ; 166.95)	25.1
AUC(0-t_{last}) *(h·ng /mL)*	397.475	353.712	112.37	(101.44 ; 124.48)	21.3
AUC(0-∞) *(h·ng/mL)*	443.799	411.770	107.78	(98.43 ; 118.02)	18.8
AUC(0-24) *(h·ng/mL)*	262.852	205.637	127.82	(115.68 ; 141.25)	20.7
λ_z *(1/h)*	0.058	0.052	112.46	(101.82 ; 124.21)	20.6
$t_{½,z}$ *(h)*	11.846	13.333	88.85	(80.44 ; 98.14)	20.6
T_{max}♣ *(h)*	11.000	13.000	p-value: 0.4056		

Treatment A: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 10:00, 4 hours after light meal

Treatment B: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 22:00, 4 hours after light meal

♣Medians and p-value according to Wilcoxon signed rank test.

Table 16: Summary of Statistics of Pharmacokinetic Parameters for Trazodone and mCPP-Treatment C (Test) vs Treatment A (Reference)

Treatment C vs Treatment A - Trazodone					
Variable *(unit)*	**LSMean**		**Mean Ratio (%)**	**90% Confidence Interval of Ratio (%)**	**Intra-individual CV (%)**
	Treatment C (Test)	**Treatment A (Reference)**			
C_{max} *(ng/mL)*	1588.738	1050.220	151.28	(132.67 ; 172.50)	27.5
AUC(0-t_{last}) *(h·ng /mL)*	32720.13	27859.90	117.45	(107.35 ; 128.49)	18.7
AUC(0-∞) *(h·ng/mL)*	34464.15	29698.78	116.05	(106.13 ; 126.89)	18.6
AUC(0-24) *(h·ng/mL)*	22811.20	17128.52	133.18	(121.90 ; 145.50)	18.4
λ_z *(1/h)*	0.065	0.060	108.36	(99.97 ; 117.46)	16.7
$t_{½,z}$ *(h)*	10.641	11.524	92.34	(85.16 ; 100.12)	16.8
T_{max}♣ *(h)*	12.000	9.000	p-value: 0.0463		
Treatment C vs Treatment A – mCPP					
C_{max} *(ng/mL)*	17.138	11.960	143.29	(127.11 ; 161.54)	25.1
AUC(0-t_{last}) *(h·ng /mL)*	419.375	353.712	118.56	(107.06 ; 131.30)	21.3
AUC(0-∞) *(h·ng/mL)*	461.287	411.770	112.03	(102.33 ; 122.64)	18.8
AUC(0-24) *(h·ng/mL)*	260.686	205.637	126.77	(114.75 ; 140.05)	20.7
λ_z *(1/h)*	0.061	0.052	116.77	(105.75 ; 128.94)	20.6
$t_{½,z}$ *(h)*	11.390	13.333	85.43	(77.36 ; 94.33)	20.6
T_{max}♣ *(h)*	14.000	13.000	p-value: 0.5052		

Treatment A: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 10:00, 4 hours after light meal

Treatment C: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 18:15, 15 minutes after a standardized high-fat, high-calorie meal

♣Medians and p-value according to Wilcoxon signed rank test.

Table 17: Summary of Statistics of Pharmacokinetic Parameters for Trazodone and mCPP-Treatment C (Test) vs Treatment B (Reference)

Treatment B vs Treatment C - Trazodone					
Variable *(unit)*	**LSMean**		**Mean Ratio (%)**	**90% Confidence Interval of Ratio (%)**	**Intra-individual CV (%)**
	Treatment B (Test)	**Treatment C (Reference)**			
C_{max} *(ng/mL)*	1544.144	1588.738	97.19	(85.24 ; 110.83)	27.5
AUC(0-t_{last}) *(h·ng /mL)*	29863.59	32720.13	91.27	(83.42 ; 99.86)	18.7
AUC(0-∞) *(h·ng/mL)*	31093.89	34464.15	90.22	(82.51 ; 98.65)	18.6
AUC(0-24) *(h·ng/mL)*	21425.15	22811.20	93.92	(85.97 ; 102.61)	18.4
λ_z *(1/h)*	0.070	0.065	107.50	(99.17 ; 116.52)	16.7
$t_{½,z}$ *(h)*	9.891	10.641	92.95	(85.73 ; 100.79)	16.8
T_{max}* *(h)*	9.000	12.000	p-value: 0.0011		
Treatment B vs Treatment C– mCPP					
C_{max} *(ng/mL)*	17.707	17.138	103.32	(91.65 ; 116.47)	25.1
AUC(0-t_{last}) *(h·ng /mL)*	397.475	419.375	94.78	(85.58 ; 104.96)	21.3
AUC(0-∞) *(h·ng/mL)*	443.799	461.287	96.21	(87.88 ; 105.32)	18.8
AUC(0-24) *(h·ng/mL)*	262.852	260.686	100.83	(91.27 ; 111.39)	20.7
λ_z *(1/h)*	0.058	0.061	96.31	(87.22 ; 106.35)	20.6
$t_{½,z}$ *(h)*	11.846	11.390	104.01	(94.19 ; 114.85)	20.6
T_{max}* *(h)*	11.000	14.000	p-value: 0.0057		

Treatment B: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 22:00, 4 hours after light meal

Treatment C: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 18:15, 15 minutes after a standardized high-fat, high-calorie meal

* Medians and p-value according to Wilcoxon signed rank test.

2.2.3.6. What are the overall adverse events profile in Phase 1 studies reported by the sponsor?

The sponsor reported that Trazodone Contramid was generally well tolerated and the adverse event profile was typical of trazodone as previously reported in studies with other formulations. The sponsor reported that the most common adverse events reported for Desyrel in USPI are: drowsiness, headache, dry mouth, dizziness/light headiness, nausea and blurred vision. In the Phase I studies, the sponsor reported Trazodone Contramid OAD were tolerated at doses ranging from 75 to 375 mg. Overall, in Phase 1 studies, 62.3% of subjects reported at least one Treatment Emergence Adverse Event (TEAE), with 1.6% of subjects reporting at least one severe TEAE, and 4.8% subjects who discontinued the study prematurely due to a TEAE. The most commonly observed TEAEs (≥5% overall, all casualties) reported by the sponsor were dizziness, headache, nausea, somnolence and nasal congestion. The incidence of TEAEs by dose was assessed in the dose proportionality study (Study 105). The most commonly TEAE reported were headache, dizziness and syncope. Syncope was reported in patients who received the 375 mg dose as a single dose given with no titration. Overall, the sponsor reported that incidence of TEAEs increased with dose, however, the severity of the TEAE does not seem to increase with dose. The sponsor reported that at the usual recommended dose (300 mg), the most common TEAEs were dizziness, headache, nausea and somnolence which is consistent with the adverse events profile at the other doses and reported by the sponsor to be consistent to that seen in the Phase III pivotal safety and efficacy study. The sponsor reported the most common TEAE (incidence ≥ 5% in active group treatment) in Trazodone Contramid OAD in the Phase III study were headache, somnolence, dry mouth, dizziness, nausea, sedation, fatigue, diarrhea, constipation, back pain and blurred vision.
Refer to medical review for Agency's evaluation of the safety of Trazodone Contramid OAD.

2.2.3.7. What is the Quantitative and Qualitative Composition of Trazodone Contramid Extended Release Tablet Formulation?

The following table provides the quantitative and qualitative composition of Trazodone Contramid OAD Extended Release Tablets used in Clinical Studies

Ingredient	Quantity per Caplet		
	Trazodone Contramid® 150 mg Labopharm Inc. Batch 04A19503	Trazodone Contramid® 300 mg Labopharm Inc. Batch 04A19602	Trazodone Contramid® 300 mg (b) (4) Batch 112365
(b) (4)	(b) (4)		
Active substance			
Trazodone hydrochloride, USP	150 mg (b) (4)	300 mg (b) (4)	300 mg (b) (4)
Excipients			
Contramid® (b) (4)	(b) (4)		
Hypromellose (b) (4) (b) (4)			
Colloidal Silicon Dioxide, NF			
Sodium Stearyl Fumarate, NF			
(b) (4)			
(b) (4) Yellow (b) (4) (b) (4)			
(b) (4)			
(b) (4)			

(2.3.P.2 Pharmaceutical Development, Vol. 1, Pg. 32)
[1] Contramid® is a (b) (4) modified starch (NF).
(b) (4)

2.3. Analytical Methods

2.3.1. What bioanalytical methods are used to assess concentrations?

Quantification of trazodone, mCPP and the internal standard (b) (4) in human plasma in the pivotal pharmacokinetic studies was achieved using HPLC with MS/MS detection. The calibration range was 31 to 3965 ng/mL for trazodone and 0.935 to 120 ng/mL for mCPP. The between-run and within-run imprecision (CV) and accuracy (%Nom) for the seven QC levels for trazodone and mCPP are provided in the following table.

Table 19: Trazodone Between-Run and Within-Run Imprecision and Accuracy

Concentration (ng/mL)	Accuracy		Imprecision	
	Between-Run	Within-Run	Between-Run	Within-Run
31.48	101	100 – 103	2.7	≤ 3.4
78.70	100	99.4 – 100	2.5	≤ 3.4
155.8	98.8	97.4 – 101	3.5	≤ 4.5
400.3	101	99.6 – 103	3.0	≤ 3.6
800.5	102	101 – 103	4.4	≤ 5.1
1601	100	98.5 – 101	3.8	≤ 4.8
3202	98.4	97.8 – 99.9	3.0	≤ 3.6

Table 20: mCPP Between-Run and Within-Run Imprecision and Accuracy

Concentration (ng/mL)	Accuracy		Imprecision	
	Between-Run	Within-Run	Between-Run	Within-Run
0.94	100	98.2 – 102	3.7	≤ 4.8
2.35	99.6	98.7 – 101	3.1	≤ 3.5
4.66	98.5	97.3 – 99.4	2.2	≤ 2.6
12.0	98.3	98.3 – 99.2	2.2	≤ 2.9
23.9	98.7	98.3 – 98.7	3.4	≤ 4.3
47.8	97.5	96.9 – 97.3	2.4	≤ 3.1
95.6	97.1	96.7 – 97.6	2.2	≤ 3.1

The MS/MS/LC method for the quantitation of trazodone and mCPP met the requirements for specificity, sensitivity, accuracy, precision. Individual in process controls are contained in the study reports in the Appendix. The assay method was adequately validated and is acceptable.

3. Detailed Label Recommendations

The following statement is recommended to be added to the Dosage and Administration sections.

Oleptro caplets should be taken orally at the same time every day, in the late evening preferably at bedtime, on an empty stomach.

Additional OCP edits are provided in the proposed label (track changes) attached.

4. **Appendix**

4.1. Individual study reports

4.1. Individual Study Reports

Title (Protocol 04ACL1-010): A Randomized, Two-Way Crossover Study to Compare the Bioavailability of 300 mg Trazodone Hydrochloride Extended Release Caplets (Containing Contramid) (Administered As a Single Dose) and 100 mg Trazodone Hydrochloride Immediate-Release Tablets (Administered Three Times Daily) Under Fasting Conditions

STUDY OBJECTIVE:	To compare the pharmacokinetic profiles of the test product, 300 mg trazodone hydrochloride (HCl) extended-release caplets (containing Contramid®), when administered as a single dose, and the reference product, 100 mg trazodone HCl immediate-release tablets (Apotex Corp), when administered three times daily. For this purpose the rate and extent of absorption of trazodone and formation of *m*-chlorophenylpiperazine (mCPP) after administration of the two formulations, were compared under fasting conditions.
METHODOLOGY:	• Open-label • Laboratory-blind • Randomized • Two-way crossover • Fasting
STUDY SUBJECTS:	• Planned for completion: at least 20 • Enrolled: 26 • Drop-outs: 1 • Discontinuers: 2 • Completed as per protocol: 23
MAIN CRITERIA FOR INCLUSION:	• Healthy male and female subjects • Non-smoker or past-smoker who stopped smoking at least 3 months before entering the study • Aged 18 to < 56 years • Healthy as judged by means of relevant medical history, physical examination and laboratory test results • Body mass within 10% of the ideal mass in relation to height and age, according to the Body Mass Index, and not less than 53 kg • Signed informed consent

REFERENCE PRODUCT (A):	• Generic name:	Trazodone HCl (Apotex Corp.)
	• Manufacturer:	(b) (4)
	• Country of origin:	United States of America
	• Dosage form:	Immediate-release tablets containing 100 mg trazodone HCl equivalent to 91.07 mg trazodone
	• Dose:	100 mg trazodone HCl immediate–release tablets (one tablet per dosing time) at 23:30 on Day 1, at 07:30 and 15:30 on Day 2 of the reference product treatment period.
	• Mode/route:	Oral
	• Lot number:	302694
	• Expiry date:	28 Feb 2010
	• Assayed product content:	99.8%
TEST PRODUCT (B):	• Generic name:	Trazodone HCl (containing Contramid®)
	• Manufacturer:	Labopharm Inc.
	• Country of origin:	Canada
	• Dosage form:	Extended-release caplets containing 300 mg trazodone HCl equivalent to 273.21 mg trazodone
	• Dose:	300 mg trazodone HCl extended-release caplets (one caplet) at 23:30 on Day 1 of the test product treatment period following a fasting period of at least 4 hours.
	• Mode/route:	Oral
	• Batch number:	04A19602
	• Expiry date:	31 Dec 2008
	• Assayed product content:	102.4%
DURATION OF TREATMENT:	Two profile periods of 68 hours, each starting with a 54.5-hour clinic day at PAREXEL International (South Africa), Bloemfontein, and a wash-out period of 7 to 14 calendar days between the last administration of study medication in Treatment Period 1 and the first administration of study medication in Treatment Period 2.	

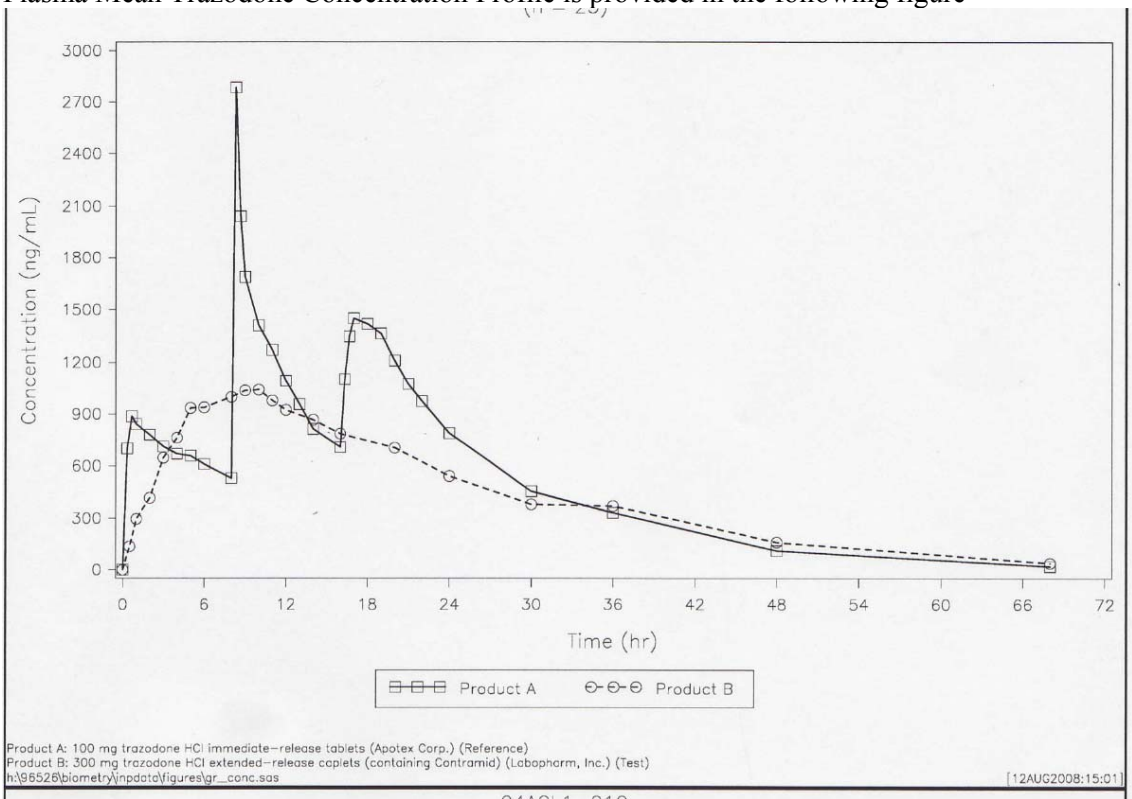
CRITERIA FOR EVALUATION	
PHARMACOKINETICS:	To compare the rate and extent of absorption of trazodone and formation of mCPP from the reference and test products, the following pharmacokinetic variables were calculated for each subject and product using the actual sampling intervals (relative to medication administration): **PRIMARY VARIABLES:** • Maximum plasma concentration (C_{max}). • Area under the plasma concentration vs. time data pairs, [AUC(0-t_{last})], where t is the time of the last quantifiable concentration. • Area under the plasma concentration vs. time data pairs, with extrapolation to infinity [AUC(0-∞)]. **SECONDARY VARIABLES:** • Area under the plasma concentration vs. time data pairs, for the first 24 hours [AUC(0-24)]. • Time to maximum plasma concentration (T_{max}). • Apparent terminal elimination rate constant (λ_z). • Apparent terminal half-life ($t_{½.z}$). The comparison was done using the overall pharmacokinetic variables for the reference product. The overall values for C_{max} and T_{max} represent the absolute maximum concentrations and the absolute T_{max} value for the entire 68-hour profile period.
SAFETY:	• Full blood count. • Clinical chemistry. • Pregnancy test results (females). • Vital signs measurements on clinic days. • Urinalysis. • Urine screen for drugs of abuse. • Post-study physical examination. • Adverse event monitoring.
STATISTICAL METHODS	
PHARMACOKINETICS:	The test product was compared to the reference product with respect to the pharmacokinetic variables C_{max}, AUC(0-t_{last}), AUC(0-∞), AUC(0-24), λ_z and $t_{½.z}$ using an analysis of variance with sequence, subject(sequence), product and period effects, after logarithmic transformation of the data. A two-sided alpha level of 0.05 was used. Point estimates and 90% confidence intervals for the "test/reference" mean ratios of these variables were calculated. The pharmacokinetic profiles of the test product and reference product were compared on the basis of the confidence intervals for the variables C_{max}, AUC(0-t_{last}) and AUC(0-∞) in relation to the conventional clinical acceptance range of 80% to 125%. In addition, a non-parametric Wilcoxon signed rank test was performed on the variable T_{max}.
SAFETY:	All full blood count, clinical chemistry and vital signs results are listed per subject for each assessment and descriptive statistics are tabulated. The number of subjects with laboratory investigations outside the reference ranges is reported, as well as individual data for all variables. Adverse events and concomitant medication are listed on an individual basis and adverse events are also summarized per system organ class. Other clinical evaluation parameters are available (see Source Data Location List) and commented on in the clinical study report.

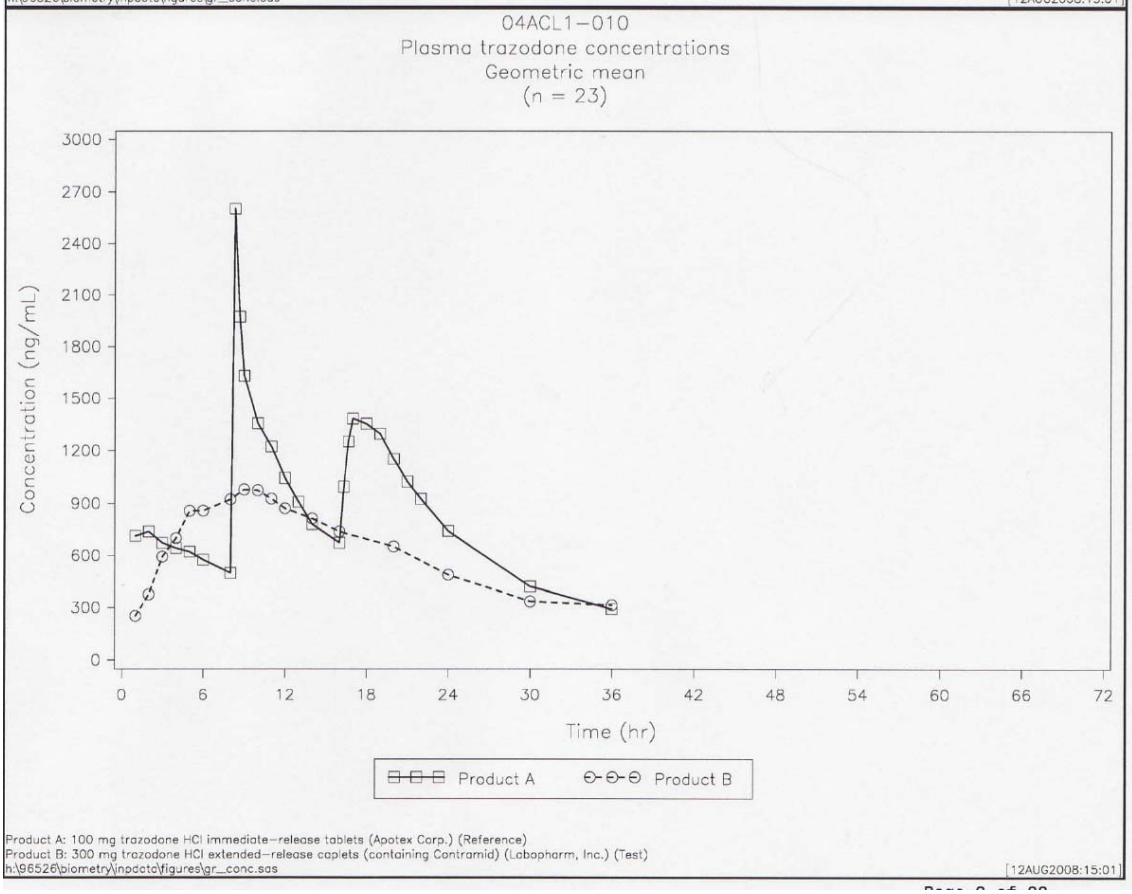
Analytical Method: Venous blood samples for the determination of trazodone and mCPP concentrations were taken at specified time periods for up to 68 hours. Plasma samples were stored at approximately -70°C until trazodone and mCPP were assayed. The calibration range for trazodone was 31 to 3965 ng/mL and for mCPP it was 0.935 to 120 ng/mL. The lower limit of quantitation (LLOQ) for trazodone was 31 ng/mL with a coefficient of variation (precision of 2.3% and a %bias (inaccuracy) of 1.4%. The LLOQ for mCPP is 0.935 ng/mL with a coefficient of variation (precision) of 4.2% and %bias (inaccuracy) of 0.1%. For each quality control level, the intra-run coefficient of variation is ≤ 5.1% and ≤ 4.8% for trazodone and mCPP, respectively for trazodone and mCPP, respectively. The intra-run accuracy falls between 97.4 and 103.3% for trazodone and between 96.7 and 101.5% for mCPP. The inter-run coefficient of variation is ≤4.4% and ≤ 3.7% for trazodone and mCPP, respectively. The inter-run accuracy is between 98.4 and 101.5% for trazodone and between 97.1 and 100.1% for mCPP. The analytical method is adequately validated and acceptable.

Data analysis: Quantitative analyses of trazodone and mCPP in the plasma samples were determined using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

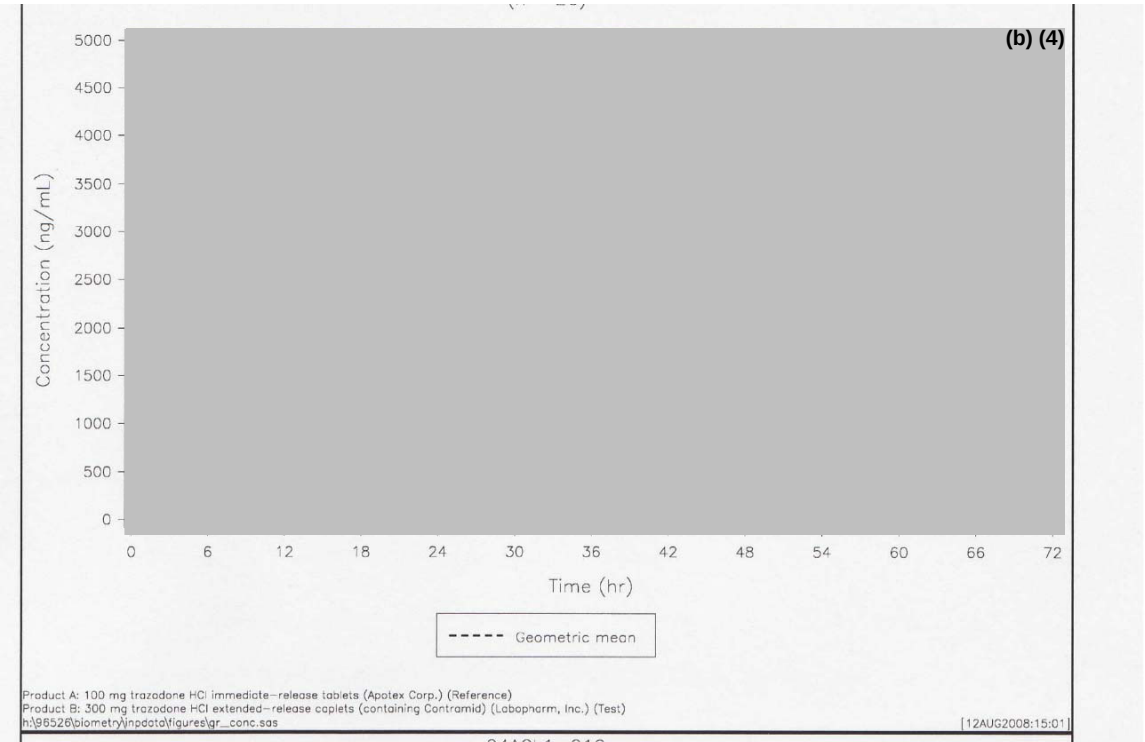
Results: The mean and combined Individual plasma concentration time profile for trazodone is provided in the following figures. Trazodone mean plasma concentrations declined in a multiexponential manner.

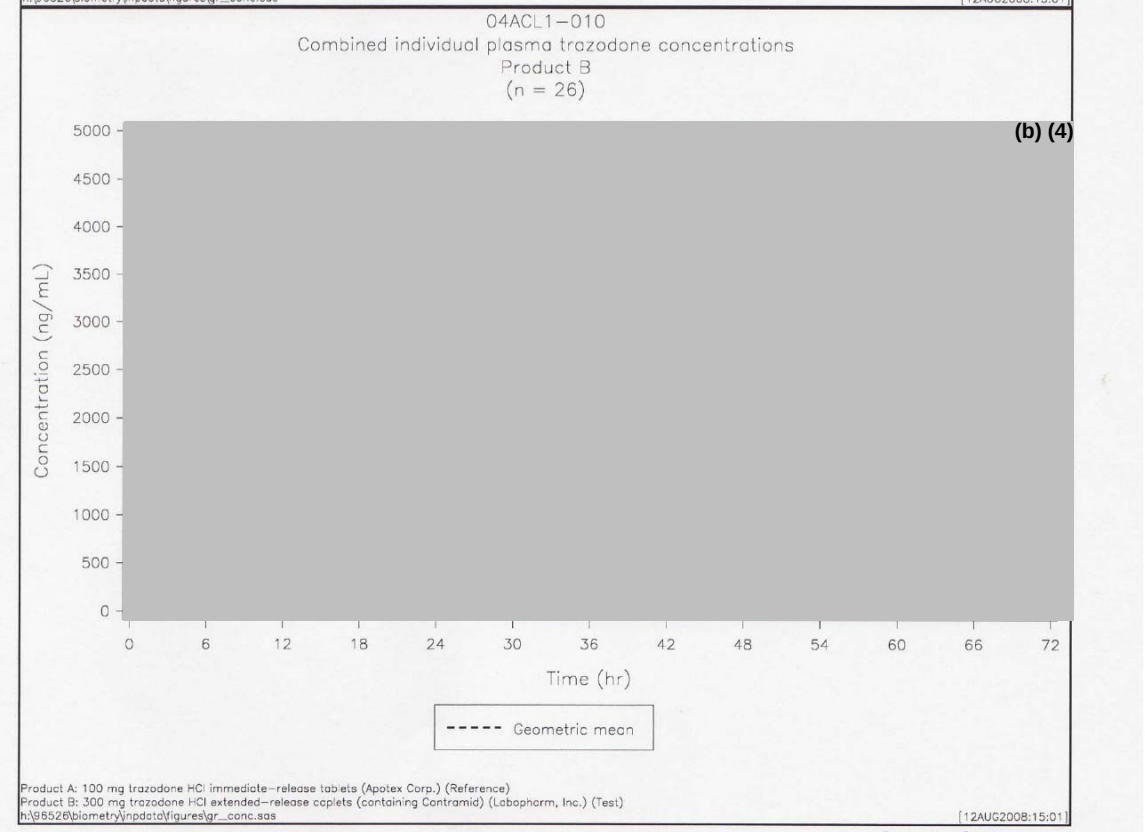
Plasma Mean Trazodone Concentration Profile is provided in the following figure





Combined Individual Plasma Trazodone Concentrations





The mean pharmacokinetic parameters with statistical analysis are summarized in the following tables.

Following administration of a total daily dosage of 300 mg trazodone, AUC for Trazodone Contramid were 20% lower than the immediate release reference product. In addition, Cmax of Trazodone Contramid was 60% lower than for the reference product.

Mean ± SD Pharmacokinetic Parameters Following Administration of a 300 mg Daily Dose of Trazodone Contramid ER Caplets and IR Trazodone Tablets Under Fasting Conditions in Healthy Volunteers

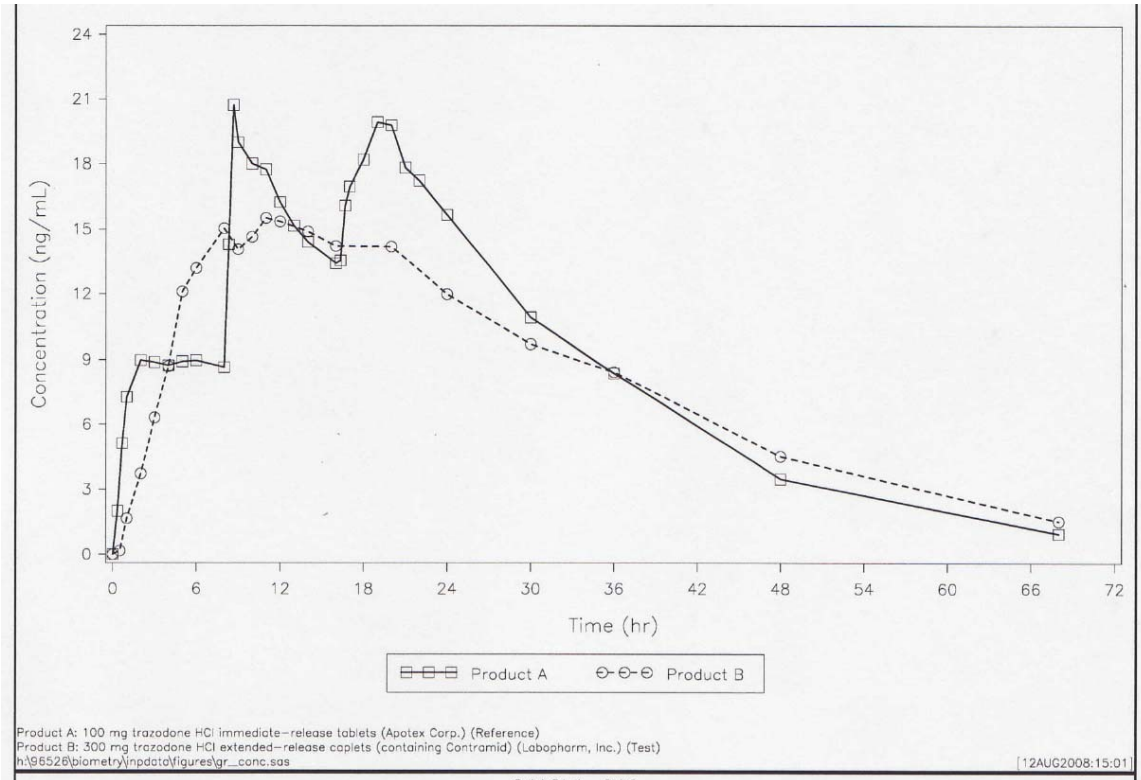
Parameter	Trazodone Contramid	IR Trazodone (Apotex Corp.)	Least Squares %Mean Ratio (90% CI)
	Mean ± SD		
Cmax (ng/mL)	1231 ± 499	2948 ± 735	40.0 (34 – 46)
AUC (0-t) (ng*h/mL)	28138 ± 8400	34272 ± 9793	81.0 (74 – 88)
AUC(0-∞)(ng*h/mL)	29672 ± 8374	35259 ± 10067	83.0 (76 – 91)
T ½ (h)	11.8 ± 3.67	8.32 ± 2.48	-
Tmax[*] (h)	9.00 (2 – 16)	8.33 (8.33 – 16.3)	-

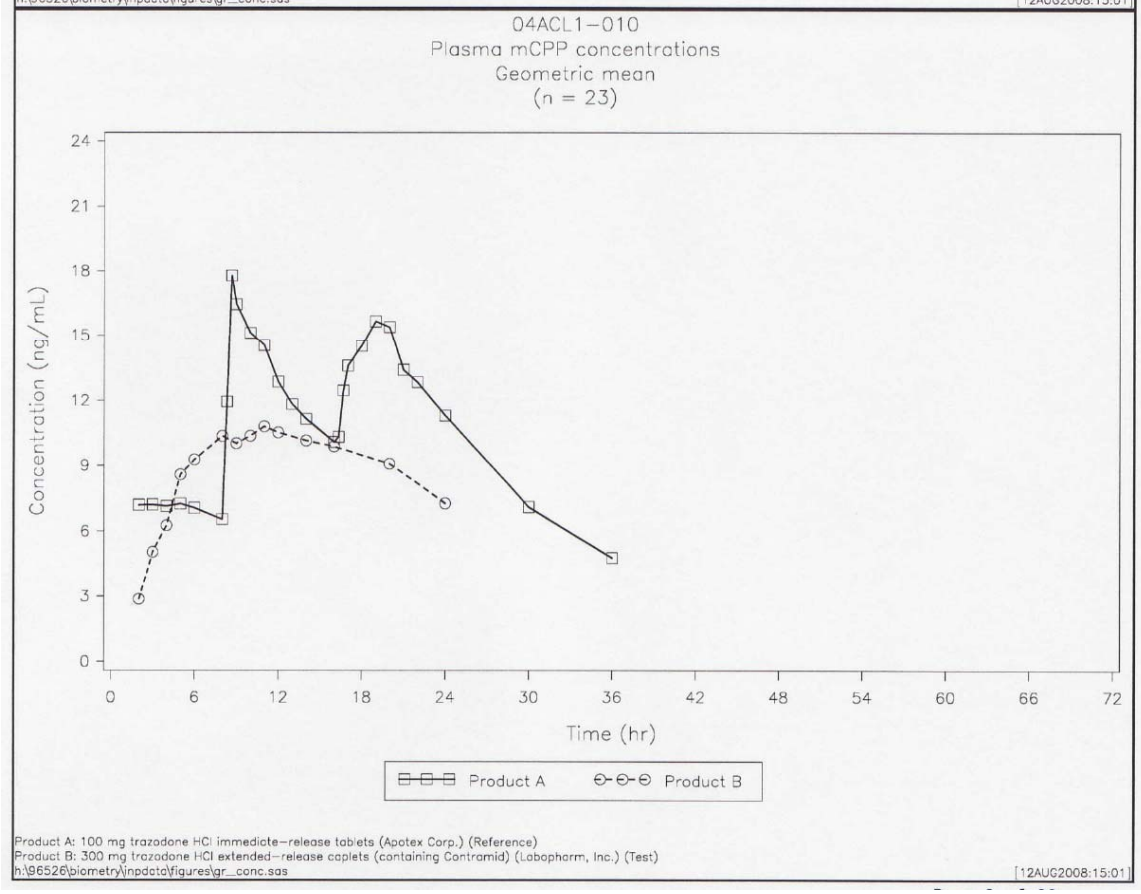
[#]Median (range)

mCPP

The mean and combined individual plasma concentration time profile are presented in the following figure. The mean plasma concentration of mCPP declined in a multi-exponential manner.

Plasma mCPP arithmetric and Geometric Mean Concentrations are provided in the following figure





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The mean pharmacokinetic parameters are provided in the following table. Following a total daily dose of 300 mg trazodone, AUC for mCPP was 14% to 20% lower after administration of Trazodone Contramid than after IR product. In addition, Cmax of mCPP was 37% lower after administration of Contramid relative to the reference IR product.

mCPP Pharmacokinetic Parameters Following Administration of a 300 mg Daily Dose of Trazodone Contramid OAD Extended Release Caplets and Immediate Release Trazodone Tablets Under Fasting Conditions in Healthy Volunteers (n=23; dose = 300 mg)

Parameter	Trazodone Contramid	IR Trazdone (Apotex)	Least Squares % Mean Ratio (90% CI)
	Mean ± SD		
Cmax (ng/mL)	18.1 ± 20.3	24.1 ± 17.3	63 (54 -72)
AUC (0 – t last) (ng*h/mL)	544 ± 735	594 ± 624	80 (73 – 89)
AUC (0 - ∞) (ng*h/mL)	607 ± 808	633 ± 665	86 (78 – 94)
T ½ (h)	14.4 ± 4.63	9.17 ± 2.57	
T max# (h)	10.0 (4.0 – 36.0)	9.0 (8.3 – 20)	

#Median (range)

Summary of Pharmacokinetics

Following a total daily dosage of 300 mg trazodone, bioequivalence between Trazodone Contramid OAD and trazodone IR (300 mg total daily dose administered 100 mg three times a day) was not demonstrated. Trazodone AUCs after administration of Contramid were lower than the IR reference product. The sponsor states that the higher AUC for the IR product was probably a result of diurnal effect on trazodone pharmacokinetics. In the present study, Trazodone Contramid was administered in the late evening, where as the IR product was administered three times a day. Trazodone IR reference product administered at morning was 2-fold higher than following doses administered in the evening and at night. Cmax was lower for Trazodone Contramid compared to the IR reference product as would be expected.

Summary of Adverse Events

The sponsor reported that Trazodone was well tolerated in this study. Dizziness, headache, nausea, vomiting, peripheral edema and nasal congestion occurred during the study. The most frequently reported adverse event was dizziness and nausea. Two subjects withdrew due to vomiting. The sponsor reported that there were no clinically significant and/or consistent drug related changes in vital signs, physical findings, safety laboratory values. Electrocardiogram evaluations were reported by the sponsor to be compatible with expectations for healthy subjects.

Reviewer Comments:

The reviewer agrees with sponsor's conclusion that 300 mg Trazodone Contramid administered as a single dose is not bioequivalent to Trazodone IR administered as 100 mg 3 times a day.

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Listing 34: Plasma trazodone pharmacokinetic variables (summary results)

---------- Product=Reference ----------

Subject/ Statistic	Cmax(0-8) (hr)	Cmax(8-16) (hr)	Cmax(16-24) (hr)	Cmax (ng/mL)	AUC(0-8) (hr*ng/mL)	AUC(8-16) (hr*ng/mL)	AUC(16-24) (hr*ng/mL)	AUC(0-24) (hr*ng/mL)	AUC(0-tlast) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	Tmax(0-8) (hr)	Tmax(8-16) (hr)	Tmax(16-24) (hr)
N	23.000	23.000	23.000	23.000	22.000	23.000	23.000	23.000	23.000	23.000	23.000	23.000	23.000
Mean	1211.361	2910.652	1767.174	2947.739	5510.979	9660.421	9405.005	24602.207	34272.429	35258.501	1.451	8.406	17.552
SD	359.401	775.814	368.686	734.656	1492.211	2388.366	2430.347	6097.496	9792.799	10067.430	1.541	0.173	1.021
Median	1264.000	2911.000	1699.000	2911.000	5525.793	9177.799	8603.714	24261.246	35486.618	36352.920	0.667	8.333	17.000
Minimum	523.800	1656.000	1065.000	1656.000	3213.571	6382.667	5930.053	15560.839	21147.490	21951.370	0.333	8.333	16.333
Maximum	1854.000	4670.000	2743.000	4670.000	10406.743	16878.649	16548.940	43887.098	58269.398	59615.273	6.033	9.000	20.000
GeomMean	1152.214	2810.405	1732.613	2860.511	5339.903	9406.150	9130.122	23954.029	32993.644	33958.639	0.938	8.404	17.524
GeomSD	404.401	785.545	353.457	734.535	1376.258	2213.068	2280.661	5643.930	9481.530	9667.856	1.083	0.169	1.005

Reference: 100 mg trazodone HCl immediate-release tablets (Apotex Corp.)

Test: 300 mg trazodone HCl extended-release caplets (containing Contramid) (Labopharm, Inc.)

*Subject not included in statistical analyses

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Listing 34: Plasma trazodone pharmacokinetic variables (summary results)

Product=Reference

Subject/ Statistic	Tmax (hr)	$t_{\frac{1}{2}}$.z (hr)	Lambda_z (1/hr)
N	23.000	23.000	23.000
Mean	8.739	8.318	0.090
SD	1.664	2.477	0.024
Median	8.333	7.466	0.093
Minimum	8.333	5.252	0.049
Maximum	16.333	14.235	0.132
GeomMean	8.639	8.000	0.087
GeomSD	1.217	2.287	0.025

Reference: 100 mg trazodone HCl immediate-release tablets (Apotex Corp.)

Test: 300 mg trazodone HCl extended-release caplets (containing Contramid) (Labopharm, Inc.)

*Subject not included in statistical analyses

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)

1: Plasma trazodone pharmacokinetic variables (summary results)

Product=Test

Subject/ Statistic	Cmax (ng/mL)	AUC(0-24) (hr*ng/mL)	AUC(0-tlast) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	Tmax (hr)	$t_{\frac{1}{2}}$.z (hr)	Lambda_z (1/hr)
N	23.000	23.000	23.000	23.000	23.000	23.000	23.000
Mean	1230.722	18331.038	28138.365	29672.459	8.962	11.775	0.064
SD	499.129	4966.408	8400.032	8373.847	3.642	3.671	0.018
Median	1203.000	18781.133	28121.097	30928.906	9.000	11.137	0.062
Minimum	542.800	9219.825	10594.255	11007.709	2.000	7.087	0.035
Maximum	2553.000	26874.344	43798.385	46109.175	16.017	19.991	0.098
GeomMean	1143.538	17621.417	26725.769	28354.672	8.109	11.280	0.061
GeomSD	463.633	5357.496	9593.063	9504.443	4.273	3.404	0.019

100 mg trazodone HCl immediate-release tablets (Apotex Corp.)
mg trazodone HCl extended-release caplets (containing Contramid) (Labopharm, Inc.)
ot included in statistical analyses

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6: Plasma mCPP pharmacokinetic variables (summary results)

---------- Product=Reference ----------

Subject/ Statistic	Tmax (hr)	$t_{\frac{1}{2}}.z$ (hr)	Lambda_z (1/hr)
N	23.000	23.000	23.000
Mean	13.377	9.167	0.080
SD	5.096	2.567	0.019
Median	9.000	8.518	0.081
Minimum	8.333	6.448	0.045
Maximum	20.000	15.426	0.107
GeomMean	12.453	8.865	0.078
GeomSD	5.017	2.326	0.021

100 mg trazodone HCl immediate-release tablets (Apotex Corp.)
ng trazodone HCl extended-release caplets (containing Contramid) (Labopharm, Inc.)
ot included in statistical analyses

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36: Plasma mCPP pharmacokinetic variables (summary results)

---------- Product=Test ----------

Subject/ Statistic	Cmax (ng/mL)	AUC(0-24) (hr*ng/mL)	AUC(0-tlast) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	Tmax (hr)	$t_{\frac{1}{2}}$.z (hr)	Lambda_z (1/hr)
N	23.000	23.000	23.000	23.000	23.000	23.000	23.000
Mean	18.131	296.353	544.461	606.599	13.092	14.383	0.055
SD	20.283	344.520	735.093	807.768	8.140	4.628	0.023
Median	10.800	189.322	289.342	315.692	10.033	13.584	0.051
Minimum	3.350	63.608	72.690	81.560	4.000	5.081	0.032
Maximum	94.600	1617.948	3349.266	3746.449	36.000	21.528	0.136
GeomMean	12.659	206.503	337.179	387.797	11.197	13.595	0.051
GeomSD	12.028	191.489	383.574	411.036	6.759	5.033	0.019

: 100 mg trazodone HCl immediate-release tablets (Apotex Corp.)

) mg trazodone HCl extended-release caplets (containing Contramid) (Labopharm, Inc.)

not included in statistical analyses

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Table 11: Parametric statistical analysis of plasma trazodone pharmacokinetic variables

	Variable	Unit	Reference N	Reference LSMean	Test N	Test LSMean	%Ratio (Test/Reference)	90% Confidence interval of ratio	Intra CV%
B vs A	Cmax	ng/mL	23	2859.528	23	1137.219	39.77	(34.42 ; 45.95)	29.0
	AUC(0-tlast)	hr*ng/mL	23	32894.73	23	26620.67	80.93	(74.18 ; 88.29)	17.3
	AUC(0-inf)	hr*ng/mL	23	33861.63	23	28260.28	83.46	(76.45 ; 91.11)	17.4
	AUC(0-24)	hr*ng/mL	23	23880.64	23	17542.83	73.46	(67.39 ; 80.08)	17.1
	$t_{½}$.z	hr	23	8.016	23	11.320	141.21	(125.51 ; 158.89)	23.5
	Lambda-z	1/hr	23	0.086	23	0.061	70.86	(62.96 ; 79.75)	23.6

A: 100 mg trazodone HCl immediate-release tablets (Apotex Corp.) (Reference)

B: 300 mg trazodone HCl extended-release caplets (containing Contramid) (Labopharm, Inc.) (Test)

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Table 12: Parametric statistical analysis of plasma mCPP pharmacokinetic variables

	Variable	Unit	Reference N	Reference LSMean	Test N	Test LSMean	%Ratio (Test/Reference)	90% Confidence interval of ratio	Intra CV%
B vs A	Cmax	ng/mL	23	20.067	23	12.549	62.53	(54.27 ; 72.06)	28.5
	AUC(0-tlast)	hr*ng/mL	23	415.727	23	334.157	80.38	(72.62 ; 88.96)	20.2
	AUC(0-inf)	hr*ng/mL	23	447.392	23	384.984	86.05	(78.38 ; 94.47)	18.5
	AUC(0-24)	hr*ng/mL	23	275.724	23	204.886	74.31	(66.17 ; 83.45)	23.1
	$t_{½}$.z	hr	23	8.878	23	13.638	153.61	(135.58 ; 174.04)	25.0
	Lambda-z	1/hr	23	0.078	23	0.051	65.19	(57.52 ; 73.88)	25.0

A: 100 mg trazodone HCl immediate-release tablets (Apotex Corp.) (Reference)

B: 300 mg trazodone HCl extended-release caplets (containing Contramid) (Labopharm, Inc.) (Test)

Title (Protocol 04ACL108): A randomized, two-way crossover study to compare the bioavailability of 300 mg trazodone hydrochloride extended release caplets (containing Contramid) (administered once daily) and 100 mg trazodone hydrochloride immediate release tablets (administered three times a day) at steady state

STUDY OBJECTIVE:	To compare the pharmacokinetic profiles at steady state of the test product, 300 mg trazodone hydrochloride (HCl) extended-release caplets (containing Contramid®), when administered once daily, and the reference product, 100 mg trazodone HCl immediate-release tablets (Apotex Corp.), when administered three times daily, for one week. For this purpose the rate and extent of absorption of trazodone and formation of *m*-chlorophenylpiperazine (mCPP) after administration of multiple doses of up to 300 mg of each of the two formulations, were compared.
METHODOLOGY:	• Open-label • Laboratory-blind • Multiple-dose • Randomized • Two-period crossover
STUDY SUBJECTS:	• Planned for completion: at least 24 • Enrolled and randomized: 30 • Drop-outs: None • Discontinuers: 3 • Completed as per protocol: 27
MAIN CRITERIA FOR INCLUSION:	• Healthy male and female subjects • Non-smoker or past-smoker who stopped smoking at least 3 months before entering the study • Aged 18 to <56 years • Healthy as judged by means of relevant medical history, physical examination and laboratory test results • Body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 60 kg • Signed informed consent

REFERENCE PRODUCT:	• Generic name:	Trazodone HCl
	• Manufacturer:	(b) (4)
	• Country of origin:	United States of America
	• Dosage form:	Immediate-release tablet containing 100 mg trazodone HCl equivalent to 91.07 mg trazodone
	• Dose regimen:	100 mg trazodone HCl (one immediate-release tablet) once (at 23:30) on Days 1 and 11, 100 mg trazodone HCl (one immediate-release tablet) twice (at 23:30 and 11:30) on Days 2 and 10, 100 mg trazodone HCl (one immediate-release tablet) three times daily (at 23:30, 07:30 and 15:30) on Days 3 to 9. Evening doses were administered after a fast of at least 4 hours.
	• Mode/route:	Oral
	• Lot number:	302694
	• Expiry date:	February 2010
	• Assayed product content	No data were available.
TEST PRODUCT:	• Generic name:	Trazodone HCl
	• Manufacturer:	Labopharm Inc.
	• Country of origin:	Canada
	• Dosage form:	Extended-release caplets containing 300 mg trazodone HCl equivalent to 273.21 mg trazodone and extended-release caplets containing 150 mg trazodone HCl equivalent to 136.61 mg trazodone (the 150 mg dosage form was only used for the up and down titration, and was not evaluated in the study).
	• Dose regimen:	75 mg trazodone HCl (½ x 150 mg extended-release caplet) on Days 1 and 11, 150 mg trazodone HCl (one extended-release caplet) on Days 2 and 10, 300 mg trazodone HCl (one extended-release caplet) on Days 3 to 9, each at 23:30 after a fast of at least 4 hours.
	• Mode/route:	Oral
	• Lot number:	300 mg extended-release caplet: 04A19602P6
	• Expiry date:	300 mg extended-release caplet: January 2009
	• Assayed product content:	300 mg extended-release caplet: 102.4%
DURATION OF TREATMENT:	Two treatment phases, each starting with a run-in period of 8 days (Days 1 to 8) and a profile period of 24 hours (Days 9 and 10) at the research clinic. Subjects received study medication until Day 11, and stayed at the research clinic until 30.5 hours after the last administration of study medication on Day 11. A drug-free period of 7 calendar days separated the last administration of study medication in Phase 1 and the first administration of study medication in Phase 2.	

CRITERIA FOR EVALUATION	
PHARMACOKINETICS:	Following a 2-day titration, subjects received a 300 mg daily dose of the study medication for 7 days. The pharmacokinetic profile was evaluated on Day 9. To compare plasma concentration profiles (the rate and extent of absorption of trazodone and formation of mCPP), from the reference and test products, the following pharmacokinetic variables (over a 24-hour profile period) were calculated for each subject and product after multiple doses, using the actual sampling intervals (relative to medication administration): **PRIMARY VARIABLES:** • Maximum plasma concentration ($C_{max,ss}$). • Area under the plasma concentration vs. time data pairs, (AUC_{ss}). **SECONDARY VARIABLES:** • Minimum plasma concentration ($C_{min,ss}$). • Plasma concentration at 24 hours post-evening dose (C_{24h}). • Time to peak exposure (T_{max}). • Percentage peak-trough fluctuation (%PTF) – calculated as $[100*(C_{max}-C_{min})/C_{av}]$. • %SWING – calculated as $[100*(C_{max}-C_{min})/C_{min}]$. For the reference product, $C_{max,ss}$, $C_{min,ss}$ and T_{max} were presented over each 8-hour dosing interval, and overall. The overall values represent the absolute maximum and minimum concentrations and absolute T_{max} value for the entire 24-hour profile period. The overall $C_{max,ss}$ and $C_{min,ss}$ were used for the calculation of %PTF and %SWING.
SAFETY:	• Physical examination. • Full blood count. • Clinical chemistry. • Urinalysis. • Vital signs measurements. • ECG (standard 12-lead). • Pregnancy test. • Serology tests at screening. • Drugs of abuse. • Adverse event monitoring.
STATISTICAL METHODS	
PHARMACOKINETICS:	The test product was compared to the reference product with respect to the pharmacokinetic variables $C_{max,ss}$, $C_{min,ss}$, AUC_{ss}, %PTF and %SWING using an analysis of variance with sequence, subject(sequence), product and period effects after logarithmic transformation of the data. The comparison was done using the overall pharmacokinetic variables for the reference product. The overall values for $C_{max,ss}$, $C_{min,ss}$ and T_{max} represent the absolute maximum and minimum concentrations and the absolute T_{max} value for the entire 24-hour profile period. Point estimates and 90% confidence intervals for the "test/reference" mean ratios of these variables were calculated. The pharmacokinetic profiles of the test product and the reference product were compared on the basis of the confidence intervals, in relation to a clinical acceptance range of 80% to 125%. In addition, a non-parametric Wilcoxon signed rank test was performed on the variable T_{max}. Trough plasma concentrations were analyzed statistically to determine whether steady state was reached.

STATISTICAL METHODS	
SAFETY:	All full blood count, clinical chemistry and vital signs results are listed per subject for each assessment and descriptive statistics are tabulated. ECG and pregnancy results are listed per subject and product. The number of subjects with laboratory investigations outside the reference ranges is reported, as well as individual data for all variables. Adverse events are listed on an individual basis and are coded with the Medical Dictionary for Regulatory Activities (MedDRA) and summarized per system organ class. Other clinical evaluation parameters are available and commented on in the clinical study report.

Analytical Method: Blood samples for trough plasma trazodone and mCPP levels were collected immediately before administration of study medication. Venous blood samples for the determination of trazodone and mCPP concentrations were taken at the following time points

(b) (4)

Quantitative analysis of trazodone and mCPP in plasma were performed using LC-MS/MS.

Results:

Trazodone

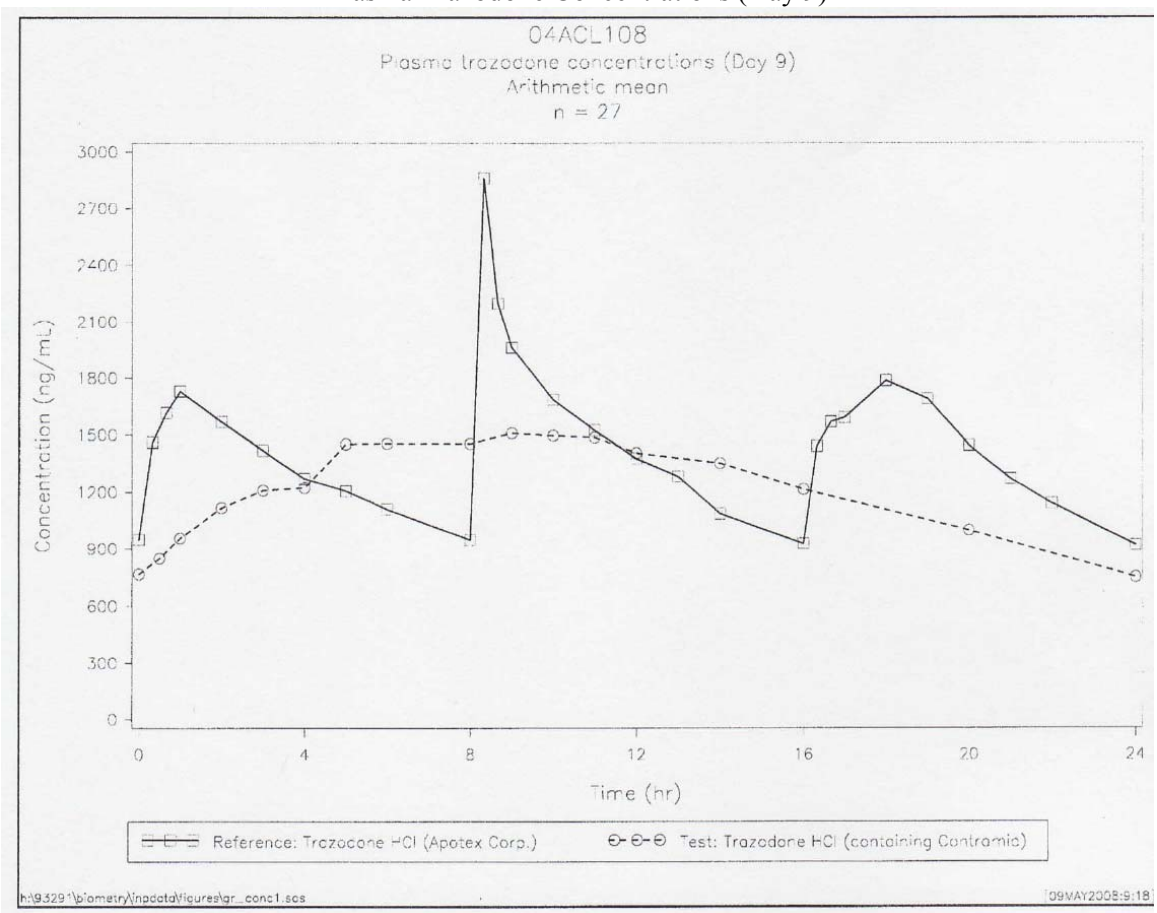
The mean values and ranges of the demographic data of all subjects who were analyzed are provided in the following table

Summary of Demographic Data of Subjects Who Completed the Study

		Age (yrs)	Height (cm)	Body Mass (kg)	Body Mass Index (kg/m^2)
All Subjects N=27	Mean Range	25.9 18 – 48	175.0 162 -186	71.57 60.0 – 82.9	23.41 19.15- 27.96
Males N=20	Mean Range	23.5 18 -39	177.6 170 – 186	74.01 66.0 – 82.9	23.51 19.51 – 25.96
Females N=7	Mean range	32.7 21 - 48	167.6 162 - 177	64.59 60.0 – 73.4	23.13 19.15 – 27.97

The mean plasma concentration time profile of trazodone after administration of the test and reference formulations are provided in the following figure.

Plasma Trazodone Concentrations (Day 9)



The mean pharmacokinetic parameters for trazodone after administration of the test and reference formulations are provided in the Appendix. The following table summarizes the statistical analysis with mean ratios and 90% confidence intervals (CI) of selected pharmacokinetic parameters.

Summary of Statistical Analysis of Pharmacokinetic Variables for Trazodone

Parameter	LS Mean		Mean Ratio (Test/Ref) (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone 100 mg IR (Reference)	Trazodone 300 mg ER (Test)			
AUCss (ng*h/mL)	32159.53	27568.60	85.72	81.05; 90.67	12.1
Cmax,ss (ng/mL)	3023.39	1709.18	56.53	49.99; 63.94	26.9
Cmin,ss (ng/mL)	801.29	585.74	73.10	64.75; 82.52	26.5
%PTF	159.75	93.34	58.43	49.64; 68.78	
Tmax[#] (h)	8.33	8.00	p-value = 0.0359		

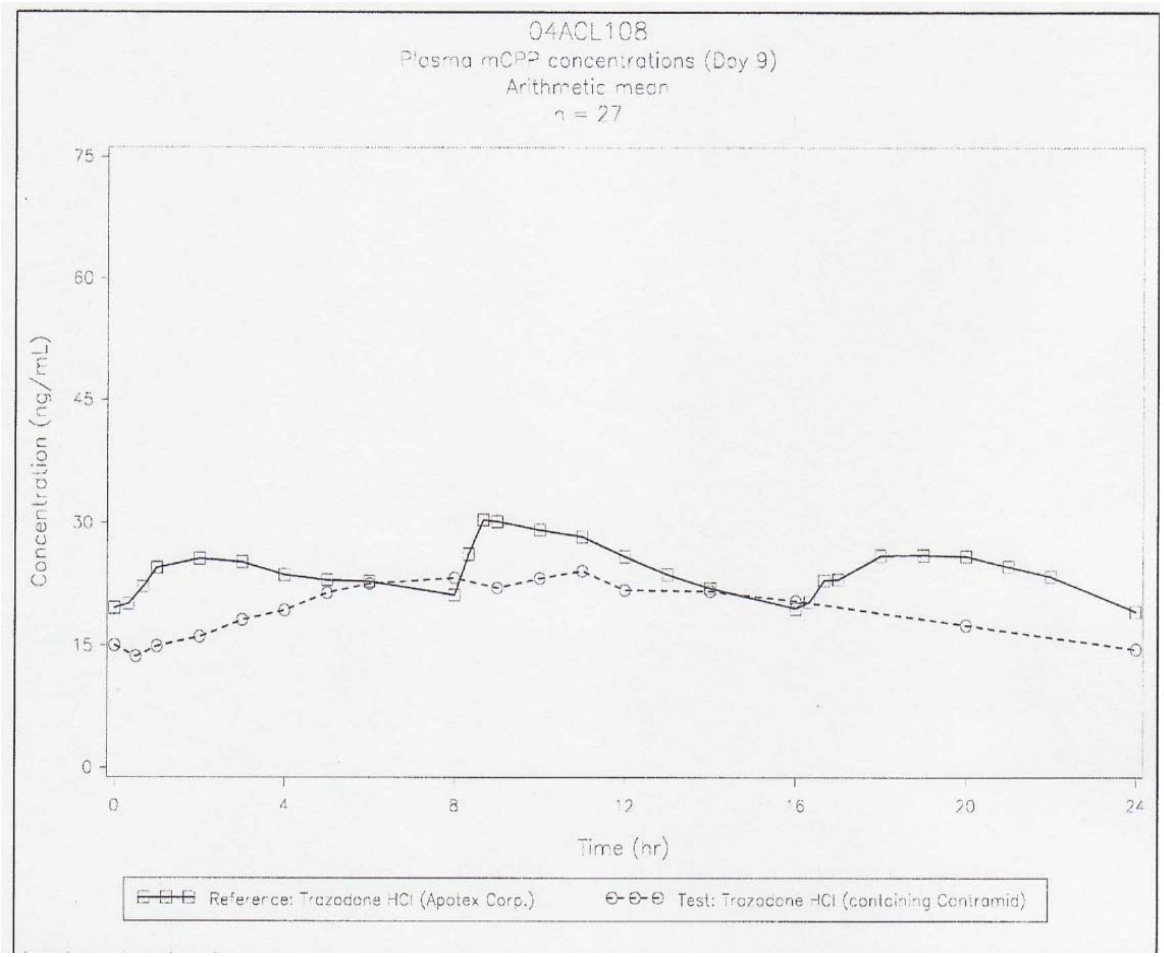
[#]Medians and p-value according to Wilcoxon signed rank test; PTF = Peak trough fluctuation

Steady state AUC of trazodone is equivalent after administration of trazodone 100 mg three times a day and trazodone contramid 300 mg once daily. Cmax,ss and Cmin,ss were not equivalent.

mCPP

The mean plasma concentration time profile of mCPP after administration of trazodone IR three times a day and trazodone contramid once daily is provided in the following tables.

Plasma mCPP concentrations



The following summarizes the statistical analysis with mean ratios and 90% CI of selected pharmacokinetic parameters

Summary of Statistical Analysis of Pharmacokinetic Parameters for mCPP

Parameter	LS Mean		Mean Ratio (Test/Ref) (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone 100 mg IR (Reference)	Trazodone 300 mg ER (Test)			
AUCss (ng*h/mL)	434.57	333.89	76.83	71.89; 82.11	14.4
Cmax,ss (ng/mL)	27.39	19.67	71.81	65.11; 79.21	21.3
Cmin,ss (ng/mL)	12.11	7.75	63.96	57.40; 71.27	23.6
%PTF	80.80	81.21	100.51	89.49; 112.89	25.4
Tmax# (h)	8.67	8.00	p-value = .5606		

Medians and p-value according to Wilcoxon signed rank test; PTF = Peak trough fluctuation

mCPP concentrations were not bioequivalent after administration of Trazodone 100 mg IR and Trazodone Contramid 300 mg.

Summary of Pharmacokinetics

Trazodone:
Steady state concentrations for trazodone were achieved on day 4 of dosing. Bioequivalence criteria were met for AUCss but not Cmax or Cmin. Based on AUCss, the extent of absorption at steady state was similar for Trazodone Contramid and for the immediate release trazodone over the 24 hour profile period. The mean Cmax and Cmin at steady state were about 44% and 27% lower, respectively for Trazodone Contramid compared to the IR reference product. Variations in maximum and minimum trazodone concentrations, as measured by %PTF and %Swing, were about 41.6% and 31.5% lower, respectively for Trazodone Contramid compared to Trazodone IR.

mCPP:
Bioequivalence criteria were not met for AUCss or Cmax,ss. The mean AUCss, Cmax and Cmin were about 23%, 28% and 36% lower, respectively, for Trazodone Contramid compared to Trazodone IR. Variations in maximum and minimum mCPP concentrations, as measured by %PTF and %Swing were 0.5% and 20.7% higher, respectively for Trazodone Contramid.

Safety Summary

The sponsor reported that one subject (subject 16) had abnormal QTc. The QTc was prolonged and varied considerably between successive predose ECGs and exceeded 450 ms. The subject was withdrawn from the study due to intercurrent illness (influenza) after receiving a single dose of study medication (Refer to medical review for evaluation).

The sponsor reported that study medications were well tolerated for 11 days at dose of 300 mg daily. The sponsor reported that 22 adverse events were reported in 11 subjects following administration of Trazodone Contramid, compared with 11 adverse events in 9 subjects following administration of the IR product. Headache, dizziness and nasal congestion were the predominant treatment related adverse events reported.

Reviewer comments

The extent of absorption after administration Trazodone Contramid OAD was equivalent to that after administration of Trazodone IR. However, Cmax was not equivalent after the administration of the once a day formulation compared to the IR. This is consistent with expectation that Cmax would not be equivalent after administration of both formulations. Cmin of trazodone was not equivalent after administration of the once a day (OAD) formulation and IR formulation. There are lower fluctuations in concentrations after administration of the OAD formulation. Equal daily doses of Trazodone Contramid OAD are equivalent to trazodone IR for AUC after multiple dose administration.

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Table 12: Plasma trazodone pharmacokinetic variables

Treatment	Variable	Unit	N	Mean	SD	Median	Minimum	Maximum	Geometric Mean	Geometric SD
Trazodone HCl (Apotex Corp.)	Cmax,ss	ng/mL	27	3117.778	757.508	3171.000	1799.000	4383.000	3025.653	779.181
	Cmin,ss	ng/mL	27	842.763	273.592	786.000	368.300	1560.000	800.482	272.864
	C24h	ng/mL	27	919.111	289.382	861.400	438.900	1560.000	876.425	284.175
	Tmax	hr	27	10.087	3.564	8.333	8.333	19.000	9.634	2.833
	AUC,ss	hr*ng/mL	27	33058.024	8006.118	32513.919	19025.812	50805.346	32136.264	7946.569
	%PTF	%	27	174.768	69.648	171.288	60.645	285.797	160.260	74.328
	%SWING	%	27	302.805	144.467	274.942	86.708	551.412	268.076	150.505
	Cmax,ss (0h - 8h)	ng/mL	27	2061.148	413.960	2030.000	1487.000	2941.000	2021.475	410.940
	Cmax,ss (8h - 16h)	ng/mL	27	3023.222	794.948	3160.000	1780.000	4383.000	2922.138	795.603
	Cmax,ss (16h - 24h)	ng/mL	27	2084.296	659.272	1913.000	1276.000	3666.000	1993.392	611.174
	Cmin,ss (0h - 8h)	ng/mL	27	869.726	315.298	813.500	368.300	1845.000	819.410	297.854
	Cmin,ss (8h - 16h)	ng/mL	27	924.626	295.376	848.000	418.900	1622.000	878.517	299.898
	Cmin,ss (16h - 24h)	ng/mL	27	890.015	265.388	858.000	438.900	1560.000	852.308	264.188
	Tmax (0h - 8h)	hr	27	1.407	1.214	1.000	0.333	5.000	1.032	0.968
	Tmax (8h - 16h)	hr	27	8.507	0.447	8.333	8.333	10.000	8.496	0.417
	Tmax (16h - 24h)	hr	27	17.852	1.067	18.000	16.333	19.000	17.821	1.075
Trazodone HCl (containing Contramid)	Cmax,ss	ng/mL	27	1812.026	620.625	1661.000	803.900	3174.000	1711.954	613.219
	Cmin,ss	ng/mL	27	673.889	354.647	617.800	126.800	1724.000	588.154	356.555
	C24h	ng/mL	27	747.270	329.025	654.800	367.600	1724.000	690.859	280.803
	Tmax	hr	27	8.222	3.468	8.000	3.000	16.000	7.540	3.393
	AUC,ss	hr*ng/mL	27	29131.374	9930.767	27656.963	12965.452	54322.691	27605.087	9519.995
	%PTF	%	27	97.090	28.357	93.090	46.524	180.487	93.277	27.606
	%SWING	%	27	210.769	127.806	169.823	62.560	604.980	182.416	104.777

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04ACL108

Listing 40: Plasma mCPP pharmacokinetic variables (summary results Trazodone HCl (Apotex Corp.))

Subject/ statistic	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	C24h (ng/mL)	Tmax (hr)	AUCss (hr*ng/mL)	%PTF	%SWING	Cmax,ss		
								Cmax,ss (0h - 8h) (ng/mL)	Cmax,ss (8h - 16h) (ng/mL)	Cmax,ss (16h - 24h) (ng/mL)
N	27	27	27	27	27	27	27	27	27	27
Mean	34.011	17.583	19.073	9.099	579.063	85.543	131.532	28.174	33.467	28.185
SD	31.803	24.408	25.078	4.133	672.849	27.791	52.091	29.542	31.892	30.063
Median	23.600	10.500	12.500	8.667	383.793	84.547	131.373	20.400	23.400	18.000
Minimum	13.300	5.160	6.620	1.000	209.197	27.372	31.092	11.300	12.000	11.600
Maximum	156.000	119.000	119.000	19.000	3244.155	155.479	267.698	140.000	156.000	144.000
GeomMean	27.574	12.204	13.636	7.588	437.642	80.705	120.583	22.019	27.000	21.860
GeomSD	16.941	9.748	10.307	6.779	304.295	30.602	57.525	14.531	16.742	14.701

*: Subjects not used in calculation of statistics

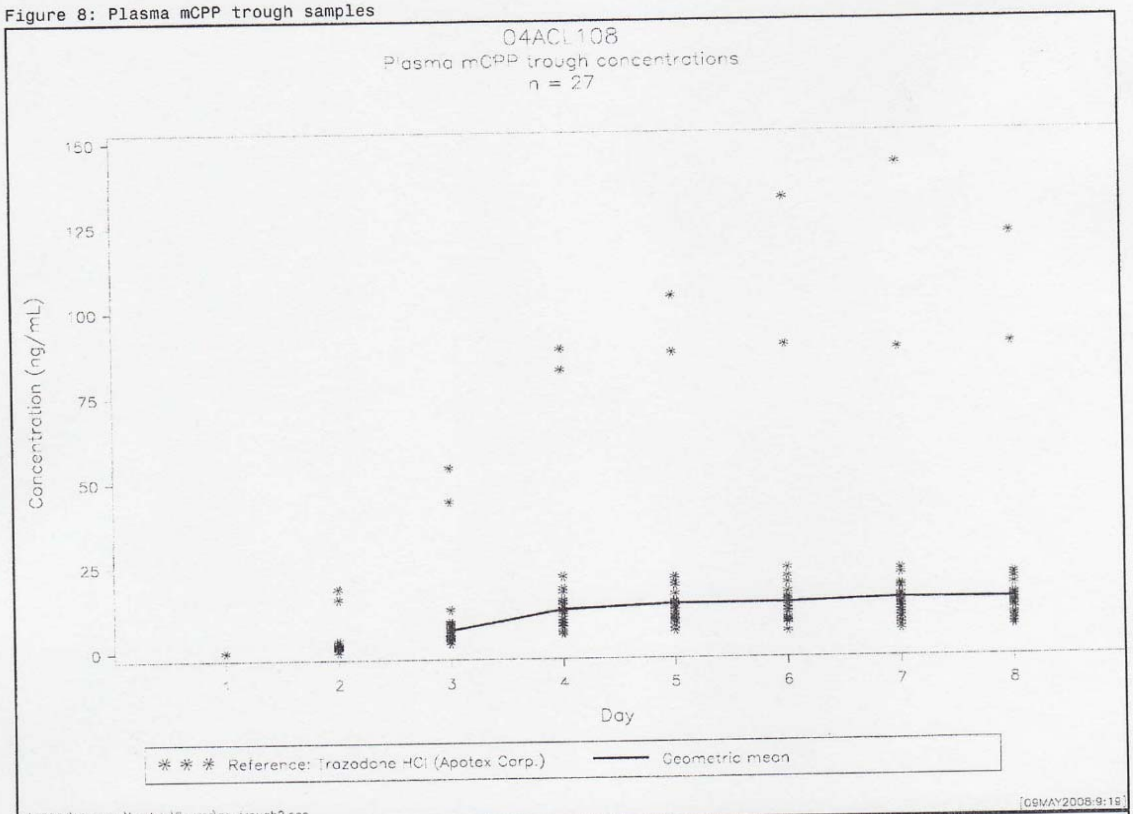
04ACL108

Listing 42: Plasma mCPP pharmacokinetic variables (summary results Trazodone HCl (containing Contramid))

Subject/ statistic	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	C24h (ng/mL)	Tmax (hr)	AUCss (hr*ng/mL)	%PTF	%SWING
N	27	27	27	27	27	27	27
Mean	26.239	12.761	14.566	8.556	470.845	85.046	164.271
SD	29.194	20.021	22.738	3.423	604.550	25.375	78.451
Median	16.700	6.810	7.960	8.000	287.380	81.039	148.575
Minimum	6.340	1.540	3.330	4.000	108.438	31.301	37.858
Maximum	130.000	94.300	105.000	16.000	2737.320	128.732	329.054
GeomMean	19.786	7.814	9.319	7.907	336.080	81.013	145.186
GeomSD	14.413	8.059	8.332	3.385	262.596	27.596	82.641

*: Subjects not used in calculation of statistics

Figure 8: Plasma mCPP trough samples



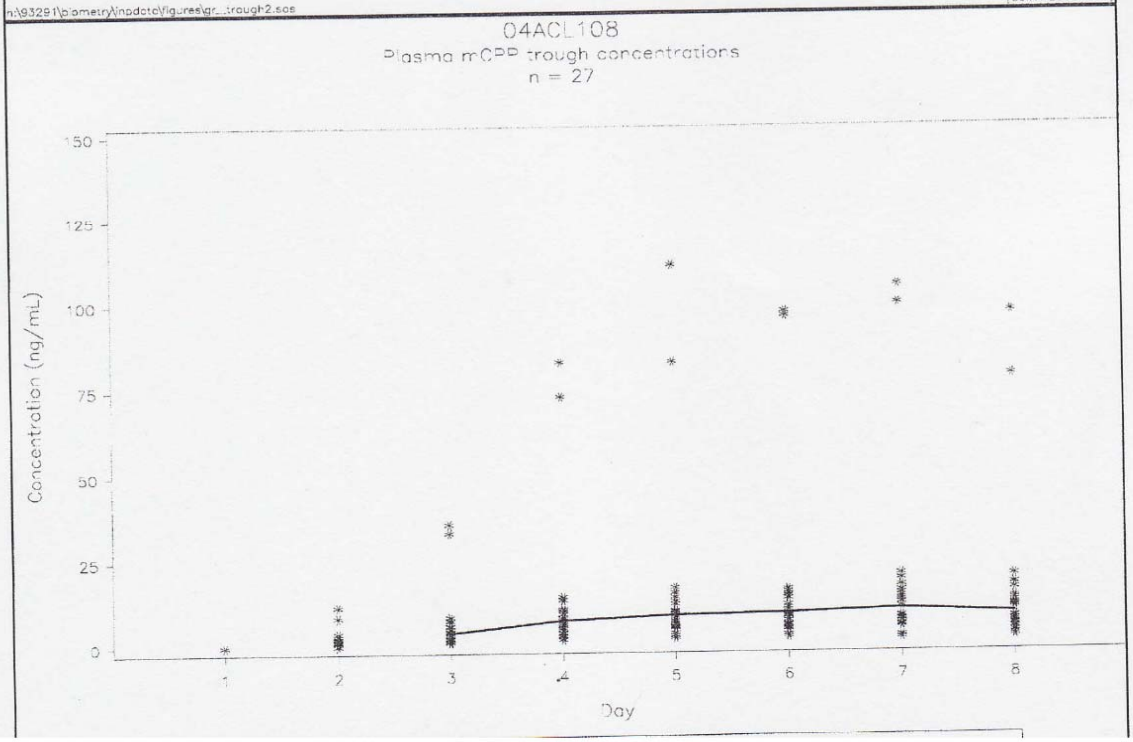
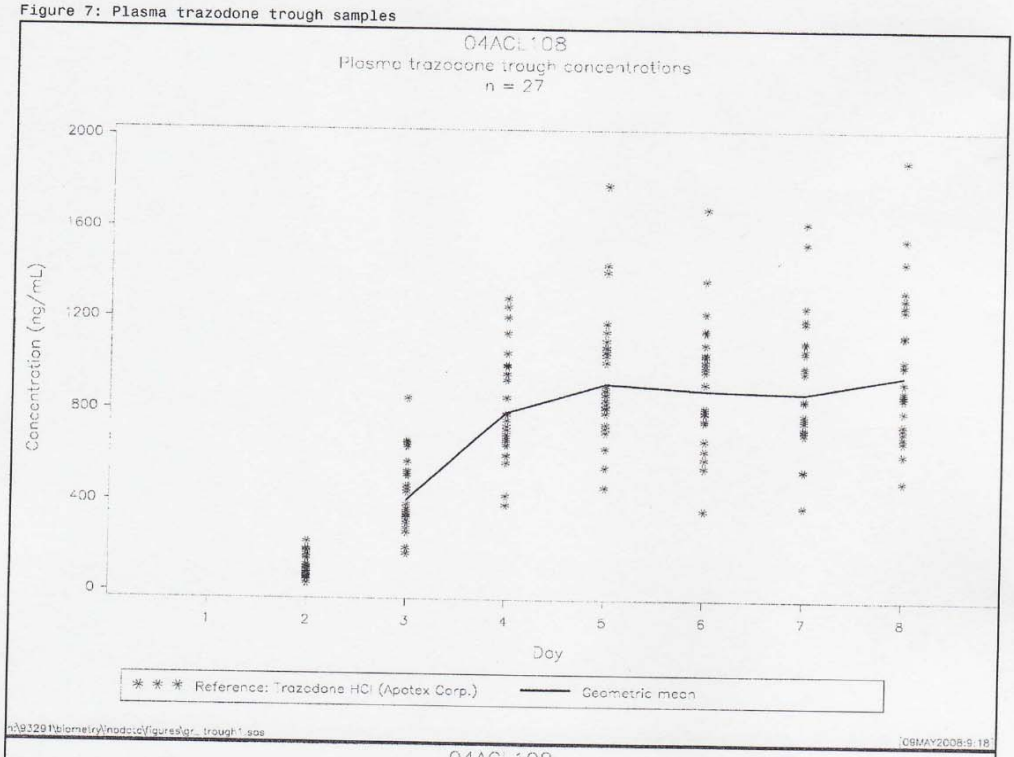
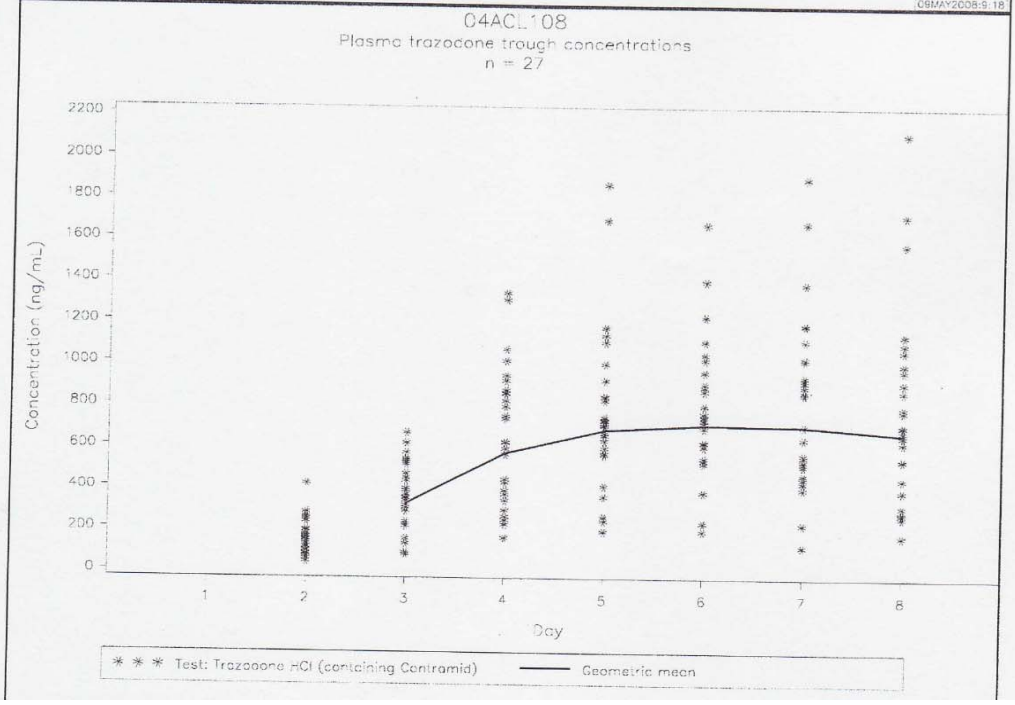


Figure 7: Plasma trazodone trough samples





Title (Protocol 04ACL104): A Randomized, Two-Way Crossover Comparative Bioavailability Study of 300 mg Trazodone Hydrochloride Extended Release Caplets (Containing Contramid) Under Fasting and Fed Conditions.

STUDY OBJECTIVE:	To assess the effect of food on 300 mg trazodone HCl extended-release caplets (containing Contramid®) following a single-dose administration under fasting and fed conditions.
METHODOLOGY:	• Open-label • Laboratory-blind • Single-dose • Randomized • Two-period crossover • Fasting and fed conditions
STUDY SUBJECTS:	• Planned for completion: at least 30 • Enrolled and randomized: 36 • Drop-outs: 1 • Discontinuers: 1 • Completed as per protocol: 34
MAIN CRITERIA FOR INCLUSION:	• Healthy male and female subject • Non-smoker or past-smoker who stopped smoking at least 3 months before entering the study • Aged 18 to < 56 years • Healthy as judged by means of relevant medical history, physical examination and laboratory test results • Body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 60 kg • Signed informed consent

TEST PRODUCT:	• Generic name:	Trazodone HCl
	• Manufacturer:	Labopharm Inc.
	• Country of origin:	Canada
	• Dosage form:	Extended-release, film-coated caplet containing 300 mg trazodone HCl equivalent to 273.21 mg trazodone. Caplet contains Contramid®.
	• Dose:	300 mg trazodone HCl extended- release caplet per treatment phase under fasting and under fed conditions
	• Route:	Oral
	• Lot number:	04A19602P3
	• Expiry date:	January 2009
	• Assayed product content:	102.4 %
DURATION OF TREATMENT:	Two profile periods of 72 hours, each starting with a 48-hour clinic day at FARMOVS-PAREXEL, and a wash-out period of 7 calendar days between clinic days.	
CRITERIA FOR EVALUATION		
PHARMACOKINETIC VARIABLES:	To compare the rate and extent of absorption of trazodone and formation of *m*-chlorophenylpiperazine (mCPP) from the test product (under fasting and fed conditions), the following pharmacokinetic variables were calculated for each subject and product using the actual sampling intervals (relative to medication administration) **PRIMARY VARIABLES:** • Maximum plasma concentration (C_{max}). • Area under the plasma concentration vs. time data pairs, AUC(0-t), where t is the time of the last quantifiable concentration. • Area under the plasma concentration vs. time data pairs, with extrapolation to infinity [AUC(0-∞)]. **SECONDARY VARIABLES:** • Area under the plasma concentration vs. time data pairs, from 0 to 24 hours [(AUC(0-24)]. • Time to maximum plasma concentration (T_{max}). • Apparent terminal elimination rate constant (λ_z). • Apparent terminal half-life ($t_{1/2}$).	
SAFETY:	• Full blood count. • Clinical chemistry. • Vital signs measurements on clinic days and post-study. • ECG (standard 12-lead) on clinic days and post-study. • Post-study physical examination. • Post-study urinalysis. • Pregnancy test (females). • Adverse event monitoring.	

STATISTICAL METHODS	
PHARMACOKINETICS:	The test product administered under fed conditions (B) was compared to the test product administered under fasting conditions (A) with respect to the pharmacokinetic variables C_{max}, AUC(0-t), AUC(0-∞), AUC(0-24), λ_z, and $t_{½,z}$ using an analysis of variance with sequence, subject(sequence), condition and period effects, after logarithmic transformation of the data. The effect of food on the bioavailability of the test product was assessed on the basis of the confidence intervals for the variables C_{max}, AUC(0-t) and AUC(0-∞) relative to the conventional acceptance range of 80% to 125%. In addition, a non-parametric Wilcoxon signed rank test was performed on the variable T_{max}.
SAFETY:	Full blood count, clinical chemistry, vital signs, 12-lead ECG, physical examination, urinalysis and pregnancy test (females) results are listed per subject for each assessment and descriptive statistics for full blood count, clinical chemistry, vital signs and 12-lead ECG results are tabulated. The number of subjects with laboratory investigations outside the reference ranges is reported, as well as individual data for all variables. Adverse events and concomitant medication are listed on an individual basis and adverse events are also summarized per system organ class. Other clinical evaluation parameters are available as source documents and commented on in the clinical study report.

Analytical Method: Quantitative analyses of trazodone and mCPP in the plasma samples were determined using LC-MS/MS. The intra-run coefficient of variation (imprecision) of each quality control level were ≤ 3.2% and ≤ 5.4% for trazodone and mCPP, respectively. The intra-run accuracy of each quality control level falls between 96.0 and 103% for trazodone and between 97.2 and 103% for mCPP. The calibration ranges were 31.22 – 3994 ng/mL for trazodone and 0.927 – 119 ng/mL for mCPP. The lower limits of quantitation was 31.22 ng/mL for trazodone and 0.927 ng/mL for mCPP. For the study sample runs, the coefficients of variation (imprecision) are ≤ 3.1% and ≤ 6.5% for trazodone and mCPP, respectively. The inaccuracies varies between -1.9 and 2% for trazodone and between -0.7% and 0.8% for mCPP. The assay method is acceptable.

Data Analysis: The effect of food on the bioavailability of the test product was assessed on the basis of the confidence intervals for the variables Cmax, AUC(0-t) and AUC(0-∞) relative to the acceptance range of 80% to 125%.

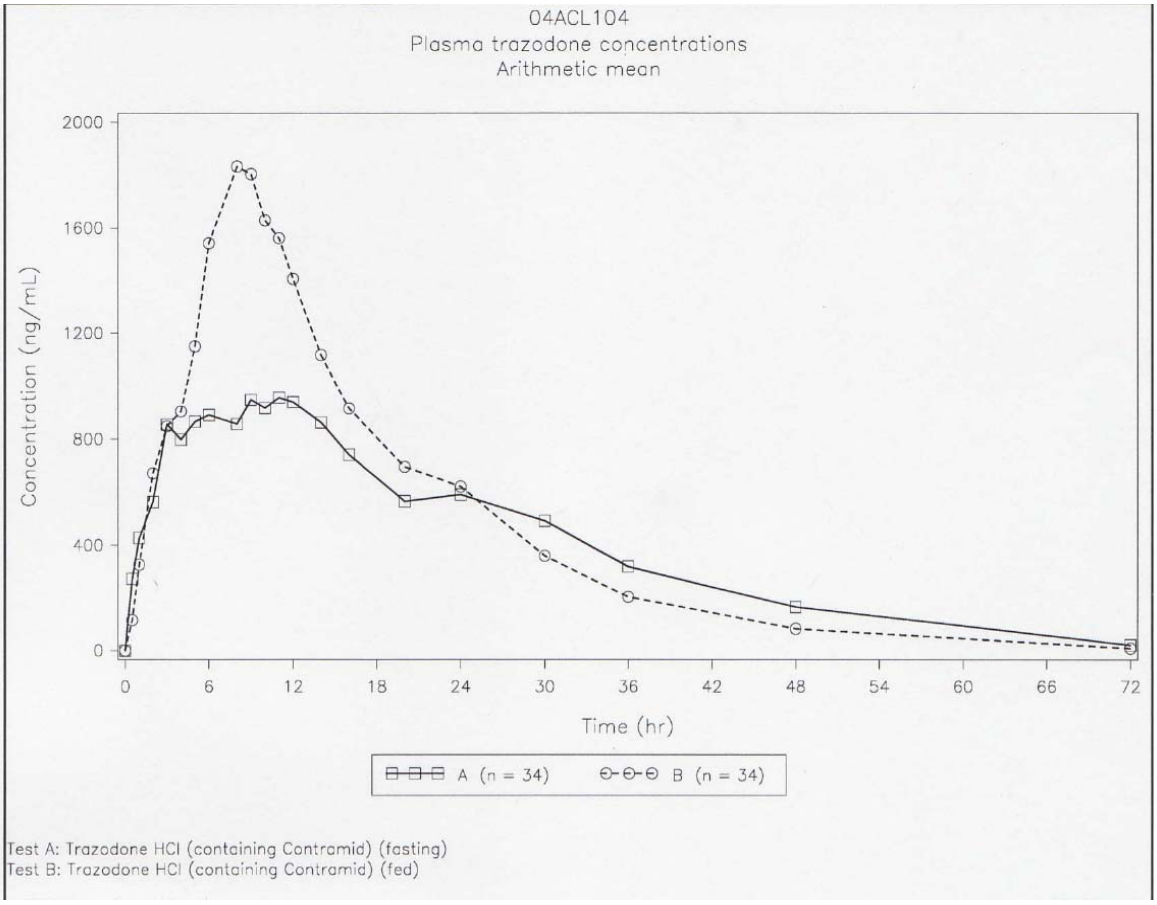
Results: The mean values and ranges of the demographic data of subjects who completed the study is provided in the following table

Summary of Demographic Data of Subjects Who Completed the Study

		Age (years)	Height (cm)	Body mass (kg)	Body Mass Index (kg/m^2)
All Subjects (n=34)	Mean Range	22.81 18.39 – 46.24	177.9 164 – 187	73.25 60.6 – 88.6	23.13 19.13 – 28.06
Males (n=25)	Mean Range	22.32 18.39 – 34.35	179.7 168 – 187	75.16 61.3 – 88.6	23.25 19.13 – 25.89
Females (n=9)	Mean Range	24.18 18.42 – 46.24	172.7 164 - 179	67.92 60.6 – 79.2	22.81 19.44 – 28.06

The mean plasma concentration time profile for trazodone is provided in the following figure.

Mean Plasma Concentration-Time Profile of Trazodone



The following tables summarizes the statistical analysis of the pharmacokinetic parameters.

Summary of Statistical Analysis of Pharmacokinetic Parameters for Trazodone (n=34)

Parameter	LS Mean		Mean Ratio (%)	90% CI	Intra-individual CV (%)
	Fed (Test B)	Fasting (Test A)			
Cmax (ng/mL)	2113.28	1137.42	185.80	167.37; 206.25	25.8
AUCt (ng*h/mL)	30463.03	26471.64	115.08	108.21; 122.38	15.0
AUC∞ (ng*h/mL)	31259.93	28061.71	111.40	105.21; 117.94	13.9
AUC (0-24h) (ng*h/mL)	24305.72	17315.34	140.37	131.55; 149.79	15.9
T ½ (h)	7.92	9.96	79.59	72.82;87.00	21.9
Tmax* (h)	8.50	9.00	P = 0.8504		

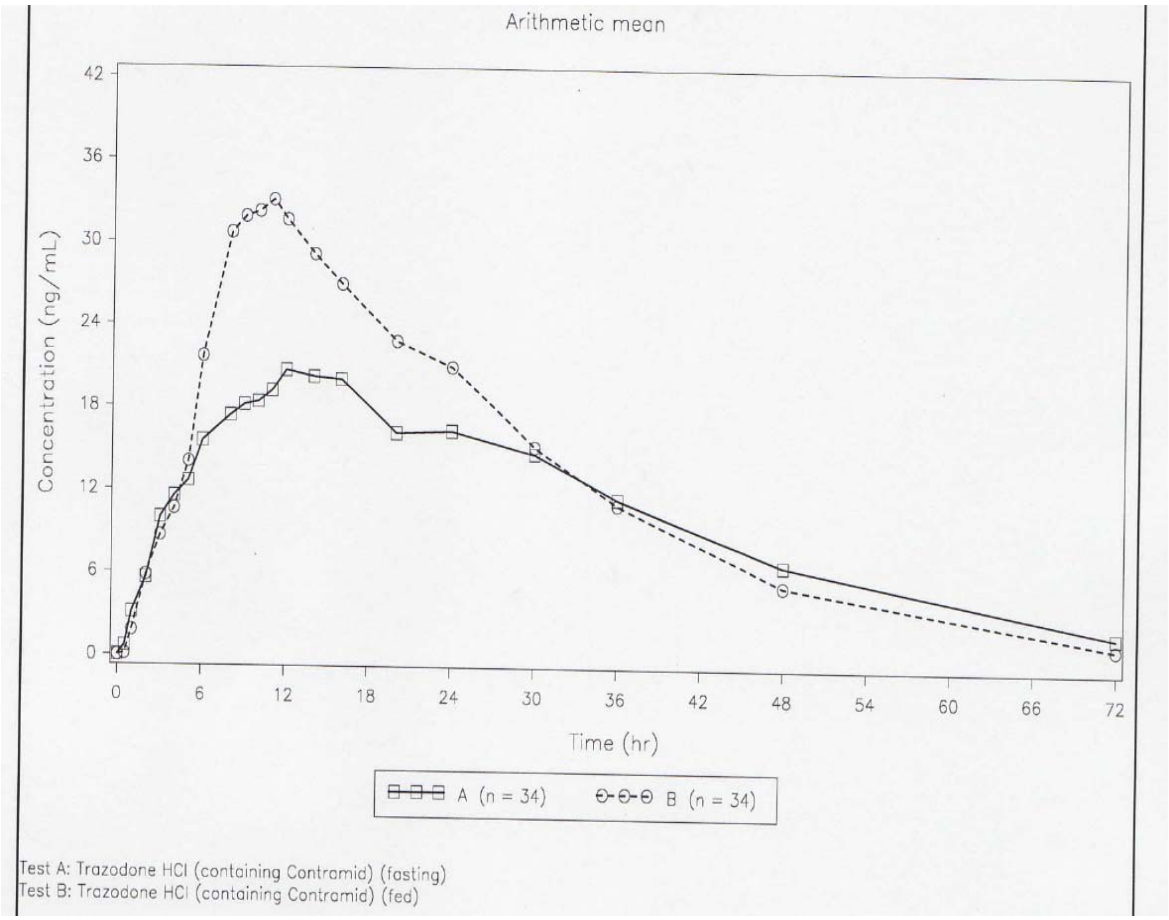
*Medians and p-value according to Wilcoxon signed rank test

Following administration of Trazodone Contramid under fed conditions, Cmax for trazodone increased by 86%. AUCt, AUC∞ and AUC24 increased by 15%, 11% and 40%, respectively, under fed conditions. The 90% Confidence Interval (CI) for fed/fasting mean ratios of Cmax and AUC24 fell outside the recommended criteria of 80% to 125%. The 90% CI for fed/fasting mean ratios of AUCt and AUC∞ were contained within the 80% to 125% range. The p-value indicated no significant difference in the median Tmax for trazodone under fed and fasting conditions.

mCPP

The following figure contains the mean plasma concentration time profile for the metabolite mCPP

Mean Plasma Concentration-Time Profile of mCPP



Summary of Statistical Analysis of Pharmacokinetic Parameters for mCPP (n=34)

Parameter	LS Mean		Mean Ratio (%)	90% CI	Intra-individual CV (%)
	Fed (Test B)	Fasting (Test A)			
Cmax (ng/mL)	28.663	14.78	193.89	173.48; 216.71	27.5
AUCt (ng*h/mL)	514.38	414.11	124.21	115.70; 133.36	17.4
AUC∞ (ng*h/mL)	546.48	476.00	114.81	107.71; 122.37	15.6
AUC (0-24h) (ng*h/mL)	372.02	249.13	149.33	138.83; 160.62	17.8
T ½ (h)	8.58	12.71	67.51	59.41; 76.71	31.8
Tmax* (h)	9.52	12.00	P = 0.1984		

*Medians and p-value according to Wilcoxon signed rank test

Following administration of Trazodone Contramid under fed conditions, Cmax for mCPP increased by 94%. AUCt, AUC∞ and AUC(0-24) for mCPP increased by 24%, 15% and 49%, respectively under fed conditions. The 90% CI for Cmax, AUCt and AUC(0- 24) were outside the recommended limits of 80% to 125%. The 90% CI for AUC∞ was contained with the limit of 80% to 125%. There was not statistically significant difference in Tmax under fed and fasting conditions.

Safety Summary

The sponsor reported that generally, trazodone was well tolerated. The sponsor reported that no serious adverse events were reported during the study. The sponsor reported twenty-two adverse events considered at least possibly related to the study drug in 15 subjects under fed conditions compared to 5 adverse events in 5 subjects under fasting conditions. The predominant adverse event reported was dizziness and headache. Other adverse events considered at least possibly related to study drug were nausea, vomiting, orthostatic hypotension and tachycardia. One subject (subject 17) vomited and experienced sinus tachycardia. The sponsor reported that the subject was followed up until adverse event resolved. The principal investigator assessed the relationship of the tachycardia as probably related to the study drug.

Reviewer Comments: After administration of Trazodone Contramid 300 mg under fed and fasting conditions, Cmax for trazodone was increased by about 87% after administration under fed conditions compared to administration under fasting conditions. Cmax for mCPP also increased about 94% after administration of Trazodone contramid under fed conditions compared fasting conditions. AUC∞ was not significantly affected after administration of Trazodone under fed compared to fasting conditions. There were more adverse events reported when Trazodone Contramid was administered under fed conditions. It is recommended Trazadone Contramid be administered under fasting conditions

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Table 10: Plasma trazodone pharmacokinetic variables

Treatment	Variable	Unit	N	Mean	SD	Median	Minimum	Maximum	Geometric Mean	Geometric SD
Test A	Cmax	ng/mL	34	1188.353	361.986	1179.500	693.600	2054.000	1138.221	344.700
	Tmax	hr	34	8.914	4.704	9.000	2.000	24.050	7.648	4.980
	AUC(0-tlast)	hr*ng/mL	34	27577.458	7959.253	27759.408	13457.045	52269.070	26500.833	7815.303
	AUC(0-inf)	hr*ng/mL	34	29230.378	8311.257	29281.217	14028.224	54254.886	28096.196	8308.644
	AUC(0-24)	hr*ng/mL	34	17785.213	4012.180	17897.250	9945.000	24594.650	17327.978	4135.419
	$t_{\frac{1}{2}}$.z	hr	34	10.436	3.075	9.924	4.974	16.488	9.990	3.113
	Lambda-z	1/hr	34	0.073	0.023	0.070	0.042	0.139	0.069	0.022
Test B	Cmax	ng/mL	34	2221.824	688.507	2079.000	1141.000	3845.000	2124.357	659.547
	Tmax	hr	34	8.619	2.387	8.500	2.000	14.000	8.206	2.967
	AUC(0-tlast)	hr*ng/mL	34	31844.653	9378.737	29494.985	20610.880	52875.485	30634.522	8671.371
	AUC(0-inf)	hr*ng/mL	34	32648.706	9486.544	30264.870	21335.580	53282.689	31433.470	8812.119
	AUC(0-24)	hr*ng/mL	34	25039.863	6035.805	23990.038	16574.725	44572.750	24409.563	5554.389
	$t_{\frac{1}{2}}$.z	hr	34	8.197	2.156	7.968	4.894	15.133	7.947	2.012
	Lambda-z	1/hr	34	0.090	0.022	0.087	0.046	0.142	0.087	0.022

Test A: Trazodone HCl (containing Contramid) (fasting)
Test B: Trazodone HCl (containing Contramid) (fed)

04ACL104

Table 12: Parametric statistical analysis of plasma trazodone pharmacokinetic variables

	Variable	Unit	Test A N	Test A LSMean	Test B N	Test B LSMean	%Ratio (Test/Reference)	90% Confidence interval of ratio	Intra CV%
B vs A	Cmax	ng/mL	34	1137.423	34	2113.283	185.80	(167.37 ; 206.25)	25.8
	AUC(0-tlast)	hr*ng/mL	34	26471.64	34	30463.03	115.08	(108.21 ; 122.38)	15.0
	AUC(0-inf)	hr*ng/mL	34	28061.71	34	31259.93	111.40	(105.21 ; 117.94)	13.9
	AUC(0-24)	hr*ng/mL	34	17315.34	34	24305.72	140.37	(131.55 ; 149.79)	15.9
	$t_{½}$.z	hr	34	9.956	34	7.924	79.59	(72.82 ; 87.00)	21.9
	Lambda-z	1/hr	34	0.070	34	0.088	125.84	(115.14 ; 137.52)	21.8

Test A: Trazodone HCl (containing Contramid) (fasting)

Test B: Trazodone HCl (containing Contramid) (fed)

04ACL1Q4

Table 11: Plasma mCPP pharmacokinetic variables

Product	Variable	Unit	N	Mean	SD	Median	Minimum	Maximum	Geometric Mean	Geometric SD
Test A	Cmax	ng/mL	34	22.619	22.000	11.600	2.990	87.600	14.757	17.447
	Tmax	hr	34	12.207	5.879	12.000	3.000	30.033	10.971	5.572
	AUC(0-tlast)	hr*ng/mL	34	747.548	861.730	365.932	55.200	3115.016	413.426	638.988
	AUC(0-inf)	hr*ng/mL	34	834.728	973.699	400.088	82.678	3463.653	474.605	681.522
	AUC(0-24)	hr*ng/mL	34	376.838	357.373	200.395	55.200	1401.110	248.801	289.060
	$t_{½}$.z	hr	34	13.862	7.856	11.985	7.712	50.564	12.672	5.047
	Lambda-z	1/hr	34	0.058	0.018	0.058	0.014	0.090	0.055	0.022
Test B	Cmax	ng/mL	34	39.088	31.286	25.450	6.520	138.000	28.759	27.652
	Tmax	hr	34	10.589	4.243	9.517	5.000	24.000	9.960	3.484
	AUC(0-tlast)	hr*ng/mL	34	881.888	1019.900	478.208	123.149	4069.073	514.950	708.117
	AUC(0-inf)	hr*ng/mL	34	925.448	1067.500	490.454	135.403	4142.356	547.151	729.367
	AUC(0-24)	hr*ng/mL	34	535.784	485.261	349.927	94.286	2124.773	372.702	389.628
	$t_{½}$.z	hr	34	8.922	2.617	8.125	5.101	15.482	8.581	2.451
	Lambda-z	1/hr	34	0.084	0.023	0.086	0.045	0.136	0.081	0.023

Test A: Trazodone HCl (containing Contramid) (fasting)
Test B: Trazodone HCl (containing Contramid) (fed)

04ACL104

Table 13: Parametric statistical analysis of plasma mCPP pharmacokinetic variables

	Variable	Unit	Test A N	Test A LSMean	Test B N	Test B LSMean	%Ratio (Test/Reference)	90% Confidence interval of ratio	Intra CV%
B vs A	Cmax	ng/mL	34	14.783	34	28.663	193.89	(173.48 ; 216.71)	27.5
	AUC(0-tlast)	hr*ng/mL	34	414.108	34	514.382	124.21	(115.70 ; 133.36)	17.4
	AUC(0-inf)	hr*ng/mL	34	476.005	34	546.480	114.81	(107.71 ; 122.37)	15.6
	AUC(0-24)	hr*ng/mL	34	249.125	34	372.017	149.33	(138.83 ; 160.62)	17.8
	$t_{½}$.z	hr	34	12.708	34	8.578	67.51	(59.41 ; 76.71)	31.8
	Lambda-z	1/hr	34	0.055	34	0.081	147.90	(130.21 ; 168.00)	31.7

Test A: Trazodone HCl (containing Contramid) (fasting)

Test B: Trazodone HCl (containing Contramid) (fed)

[07AP

19.2 MENU

HIGH-FAT AND HIGH-CALORIE RECIPE CONSTITUENTS					
Food	**Amount (g)**	**Energy (cal)**	**Carbohydrate (g)**	**Protein (g)**	**Fat (g)**
Bacon fried, 4 strips	40.0	223.7	0.2	12.2	19.6
Eggs fried, 2	104.0	193.1	1.2	13.4	15.2
Potato chips - oven heated	100.0	206.2	31.2	3.2	7.6
Bread roll, brown 1x	30.0	77.3	15.2	2.6	0.6
Butter	20.0	144.8	0.0	0.2	16.4
Milk - whole fresh	200.0	124.8	9.6	6.4	6.8
Tomato - raw	100.0	21.7	4.0	0.9	0.2
TOTAL **% ENERGY**		**991.6**	**61.4** **25**	**38.9** **15.7**	**66.4** **60**

(In accordance with the United States Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Food-Effect Bioavailability and Bioequivalence Studies. Center for Drug Evaluation and Research [CDER] December 2002 BP)
(Test meal: approximately 150, 250 and 500-600 calories from protein, carbohydrate, and fat, respectively)

Title (Study 04ACL105): A Randomized, Five-Way Crossover Dose-Proportionality Study (Doses Ranging from 75 mg to 375 mg) of Trazodone Hydrochloride Extended Release Caplets (containing Contramid) Under Fasting Conditions.

STUDY OBJECTIVES	• To assess the dose-proportionality of trazodone HCl extended-release caplets (containing Contramid®) following single dose administration of doses ranging from 75 mg to 375 mg. • To assess the dose-proportionality of 150 mg and 300 mg trazodone HCl extended-release caplets (containing Contramid®). • To assess the dose-proportionality of 300 mg trazodone HCl extended-release caplets (containing Contramid®) administered as a whole-caplet (300 mg) dose and as a half-caplet (150 mg) dose. • To assess the dose-proportionality of 150 mg trazodone HCl extended-release caplets (containing Contramid®) administered as a whole-caplet (150 mg) dose and as a half-caplet (75 mg) dose.
METHODOLOGY:	• Open-label • Laboratory-blind • Single-dose • Randomized • Five-way crossover • Fasting
STUDY SUBJECTS:	• Planned for completion: at least 30 • Enrolled: 45 • Drop-outs: 0 • Discontinuers: 2 • Completed as per protocol: 43
MAIN CRITERIA FOR INCLUSION:	• Healthy male and female subjects. • Non-smoker or past-smoker who stopped smoking at least 3 months before entering the study. • Aged 18 to < 56 years. • Healthy as judged by means of relevant medical history, physical examination and laboratory test results. • Body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 65 kg. • Signed informed consent.

TEST PRODUCTS:	Generic name:	Trazodone HCl (containing Contramid®)
	Manufacturer:	Labopharm Inc.
	Country of origin:	Canada
	Dosage form:	Extended-release caplet containing 150 mg trazodone HCl equivalent to 136.61 mg trazodone Extended-release caplet containing 300 mg trazodone HCl equivalent to 273.21 mg trazodone
	Treatments:	A: A single oral ½ x 150 mg trazodone HCl extended-release caplet (containing Contramid®) (dose: 75 mg). B: A single oral 1 x 150 mg trazodone HCl extended-release caplet (containing Contramid®) (dose: 150 mg). C: A single oral ½ x 300 mg trazodone HCl extended-release caplet (containing Contramid®) (dose: 150 mg). D: A single oral 1 x 300 mg trazodone HCl extended-release caplet (containing Contramid®) (dose: 300 mg). E: A single oral ½ x 150 mg + 1 x 300 mg trazodone HCl extended-release caplet (containing Contramid®) (dose: 375 mg).
	Mode/route:	Oral
	Batch numbers:	150 mg trazodone HCl - 04A19503 300 mg trazodone HCl - 04A19602
	Expiry dates	150 mg trazodone HCl - January 2009 300 mg trazodone HCl - January 2009
	Assayed product content:	150 mg trazodone HCl - 100.8% 300 mg trazodone HCl - 102.4%
DURATION OF TREATMENT:	Five profile periods of 72 hours, each starting with a 48-hour clinic stay at FARMOVS-PAREXEL, and a wash-out period of 7 calendar days between clinic days.	
CRITERIA FOR EVALUATION		
PHARMACOKINETICS:	To compare the rate and extent of absorption of trazodone and the formation of *m*-chlorophenylpiperazine (mCPP) from the different doses of the test product, the following pharmacokinetic variables were calculated for each subject and treatment using the actual sampling intervals (relative to medication administration): **PRIMARY VARIABLES:** • Normalized maximum plasma concentration (C_{max}norm). • Normalized area under the plasma concentration vs time data pairs [AUC(0-t)norm], where t is the time of the last quantifiable concentration. • Normalized area under the plasma concentration vs time data pairs, with extrapolation to infinity [AUC(0-∞)norm]. **SECONDARY VARIABLES:** • Normalized area under the plasma concentration for the first 24 hours [AUC(0-24)norm]. • Time to maximum plasma concentration (T_{max}). • Apparent terminal half-life ($t_{½,z}$). • Apparent terminal elimination rate constant (λ_z). • AUC(0-t)norm/AUC(0-∞)norm. • AUC(0-24)norm/AUC(0-∞)norm.	

SAFETY:	• Full blood count. • Clinical chemistry. • Vital signs. • Electrocardiogram (ECG) (standard 12-lead). • Urinalysis. • Pregnancy test. • Post-study physical examination. • Adverse event monitoring.
STATISTICAL METHODS	
PHARMACOKINETICS:	The treatments were compared with respect to the pharmacokinetic variables C_{max}norm, AUC(0-t)norm, AUC(0-∞)norm, AUC(0-t)norm/AUC(0-∞)norm, AUC(0-24)norm, AUC(0-24)norm/AUC(0-∞)norm, λ_z and $t_{1/2}$ using an analysis of variance with sequence, subject(sequence), treatment and period effects, after logarithmic transformation of the data. Dose-proportionality of the treatments was assessed on the basis of the confidence intervals for the variables C_{max}norm, AUC(0-t)norm, AUC(0-∞)norm and AUC(0-24)norm in relation to the clinical acceptance range (dose-proportionality) of 80% to 125% (bioequivalence approach). In addition, a non-parametric Wilcoxon signed rank test was performed on the variable T_{max}. The power method, combined with confidence interval criteria, was also used to evaluate the dose-proportionality of the pharmacokinetic variables C_{max}, AUC(0-t) and AUC(0-∞).
SAFETY:	All full blood count, clinical chemistry, vital signs results are listed per subject for each assessment and descriptive statistics are tabulated. The number of subjects with laboratory investigations outside the reference ranges is reported, as well as individual data for all variables. Laboratory investigations (full blood count, clinical chemistry and urinalysis) physical examination results, adverse events, concomitant medication, pregnancy tests, ECG and vital signs results are listed on an individual basis and adverse events are also summarized per system organ class. Other clinical evaluation parameters are available and commented on in the clinical study report.

Analytical Method: Venous blood samples for the determination of trazodone and mCPP concentrations were taken specified times. Quantitative analyses of trazodone and mCPP in the plasma samples were performed using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS). The method was accurate and precise showing a coefficient of variation (precision) and bias within 20% at the limit of quantitation and within 15% at the higher levels. For each quality control level, the inter-run coefficient of variation is ≤ 5.5% and ≤ 10.4% for trazodone and mCPP, respectively. The validated calibration ranges were 7.754 – 3969 ng/mL for trazodone and 0.234 – 120 ng/mL for mCPP. The lower limits of quantitation (LLOQ) of this method are 7.754 ng/mL for trazodone and 0.234 ng/mL for mCPP. The inter run accuracy is between 97.4 and 102.8% for trazodone and between 97.4% and 102.8% for mCPP.
The analytical method is acceptable.

Data Analysis: Dose proportionality was determined using the power model in addition to using confidence intervals on the dose normalized Cmax and AUC.

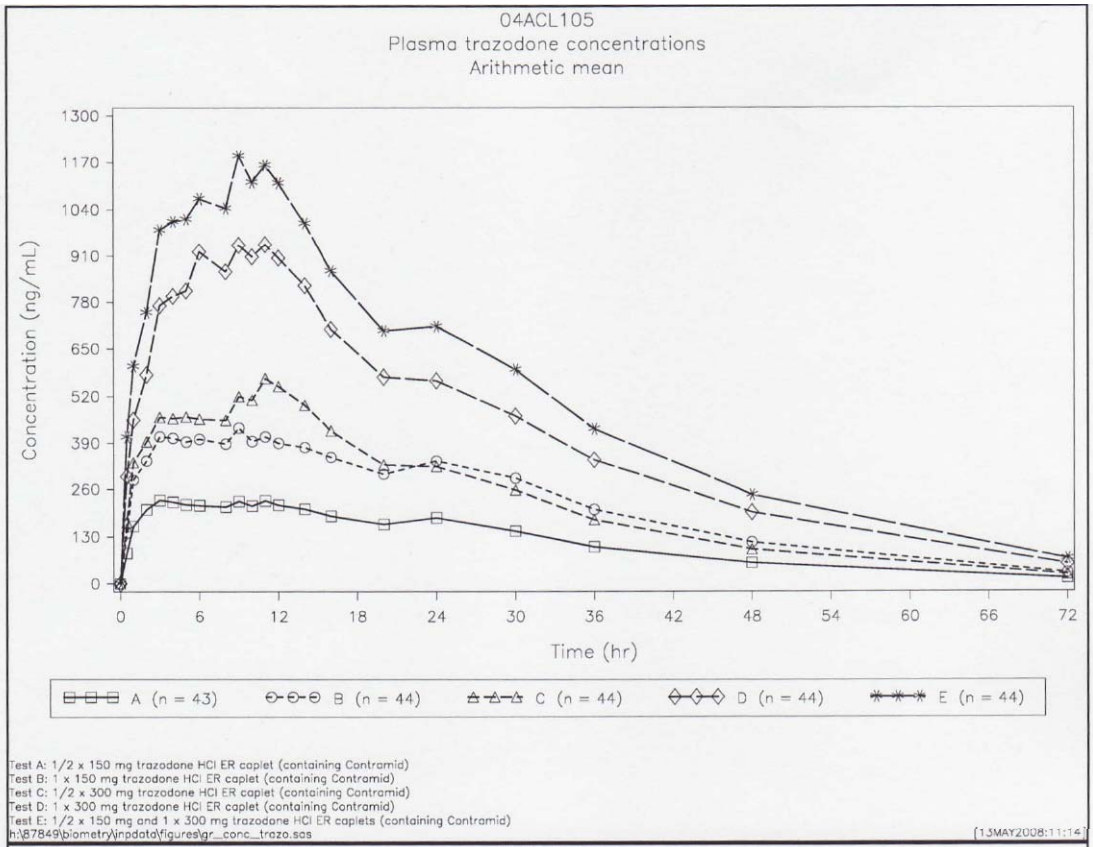
Results: Forty three subjects (23 males and 20 females) completed the study. The demographics of subjects who completed the study are provided in the following table.

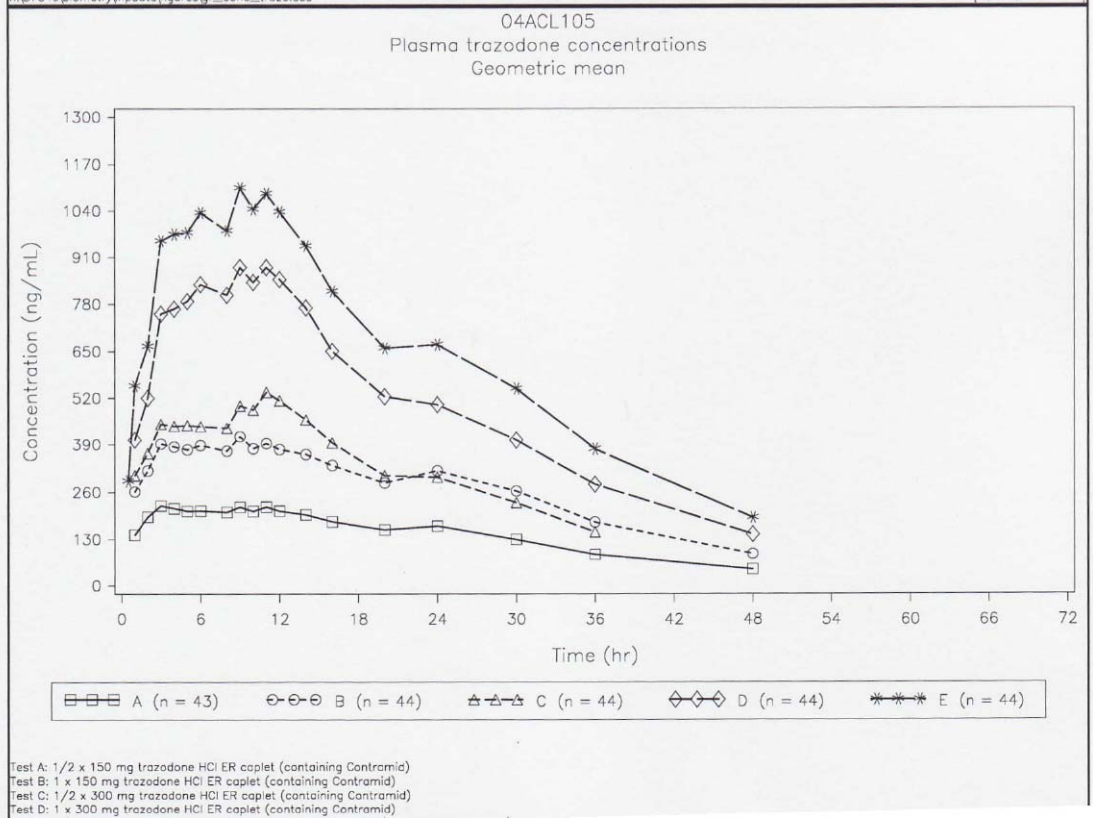
Summary of Demographic Data of Subjects who Completed the Study

		Age (years)	Height (cm)	Body Mass (kg)	Body Mass Index (kg/m^2)
All Subjects (n=43)	Mean Range	29.9 (19.7– 52.7)	175.6 (162 – 200)	75.2 (65.0 – 103.4)	24.4 (19.8 – 28.6)
Males (n=23)	Mean Range	24.9 (19.7 – 52.7)	181.9 (171 – 200)	78.5 (67.5 – 103.4)	23.7 (19.8 – 28.4)
Females (n = 20)	Mean Range	35.6 (19.9 – 48.8)	168.3 (162 – 178)	71.3 (65.0 – 80.7)	25.2 (23.2 – 28.6)

The treatments were compared with respect to the pharmacokinetic variables. The dose dependent variables were normalized to a 300 mg dose. The following figure contains the mean plasma concentration time profiles for the different treatments.

Plasma Trazodone Concentration Profiles for the various Treatments





The mean pharmacokinetic variables before dose normalization are summarized in the following table.

Summary of Mean (SD) Pharmacokinetic Parameters (before dose-normalization) of Trazodone

Parameter	½ x 150 mg (Test A)	1 x 150 mg (Test B)	½ x 300 mg (Test C)	1 x 300 mg (Test D)	½ x 150 mg + 300 mg (Test E)
AUC (0-t) (ng*h/mL)	8124 (2502)	15505 (4764)	16161 (4834)	29200 (10426)	36251 (11345)
AUC (0-∞) (ng*h/mL)	8658 (2833)	16388 (5419)	16911 (5384)	30983 (12522)	38291 (13893)
Cmax (ng/mL)	294 (71.4)	531 (143)	677 (171)	1179 (583)	1401 (522)
Tmax (h)**	8.00 (2.00-30.00)	6.00 (2.00 – 30.00)	7.00 (1.00 – 14.00)	7.00 (2.00 – 14.00)	8.00 (1.00 – 16.00)
T ½ (h)	12.7 (5.25)	12.4 (5.98)	12.0 (5.21)	13.2 (7.89)	12.5 (5.70)

The point estimates and the confidence intervals for the test/reference mean ratios of the pharmacokinetic parameters are provided in the following table.

Statistical Analysis of Plasma Trazodone Pharmacokinetic variables

	Variable	Unit	Reference N	Reference LSMean	Test N	Test LSMean	%Ratio (Test/Reference)	90% Confidence interval of ratio	Intra CV%
B vs D	Cmax,norm	ng/mL	44	1096.145	44	1029.855	93.95	(86.68 ; 101.83)	23.1
	AUC(0-tlast)norm	hr*ng/mL	44	26871.33	44	28848.87	107.36	(100.66 ; 114.51)	18.4
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.956	44	0.955	99.88	(98.58 ; 101.20)	3.7
	AUC(0-24)norm	hr*ng/mL	44	16792.72	44	16583.70	98.76	(93.06 ; 104.79)	16.9
	AUC(0-24)norm/AUC(0-inf)norm		44	0.597	44	0.549	91.85	(87.72 ; 96.17)	13.1
	AUC(0-inf)norm	hr*ng/mL	44	28106.21	44	30213.23	107.50	(100.69 ; 114.77)	18.7
	$t_{½}$.z	hr	44	11.237	44	10.863	96.67	(90.74 ; 102.98)	18.1
	Lambda-z	1/hr	44	0.062	44	0.064	103.32	(96.99 ; 110.06)	18.1
A vs B	Cmax,norm	ng/mL	44	1029.855	44	1146.036	111.28	(102.61 ; 120.69)	23.1
	AUC(0-tlast)norm	hr*ng/mL	44	28848.87	44	30149.38	104.51	(97.94 ; 111.52)	18.4
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.955	44	0.947	99.13	(97.83 ; 100.45)	3.7
	AUC(0-24)norm	hr*ng/mL	44	16583.70	44	18258.71	110.10	(103.71 ; 116.88)	16.9
	AUC(0-24)norm/AUC(0-inf)norm		44	0.549	44	0.573	104.46	(99.73 ; 109.42)	13.1
	AUC(0-inf)norm	hr*ng/mL	44	30213.23	44	31849.97	105.42	(98.69 ; 112.60)	18.7
	$t_{½}$.z	hr	44	10.863	44	11.143	102.58	(96.25 ; 109.33)	18.1
	Lambda-z	1/hr	44	0.064	44	0.062	97.53	(91.52 ; 103.94)	18.1
C vs D	Cmax,norm	ng/mL	44	1096.145	44	1312.564	119.74	(110.48 ; 129.79)	23.1
	AUC(0-tlast)norm	hr*ng/mL	44	26871.33	44	30143.87	112.18	(105.18 ; 119.65)	18.4
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.956	44	0.962	100.63	(99.31 ; 101.96)	3.7
	AUC(0-24)norm	hr*ng/mL	44	16792.72	44	19623.93	116.86	(110.13 ; 124.01)	16.9
	AUC(0-24)norm/AUC(0-inf)norm		44	0.597	44	0.626	104.81	(100.09 ; 109.75)	13.1
	AUC(0-inf)norm	hr*ng/mL	44	28106.21	44	31334.72	111.49	(104.43 ; 119.03)	18.7
	$t_{½}$.z	hr	44	11.237	44	10.678	95.02	(89.19 ; 101.23)	18.1
	Lambda-z	1/hr	44	0.062	44	0.065	105.23	(98.79 ; 112.09)	18.1
A vs D	Cmax,norm	ng/mL	44	1096.145	44	1146.036	104.55	(96.40 ; 113.39)	23.1
	AUC(0-tlast)norm	hr*ng/mL	44	26871.33	44	30149.38	112.20	(105.15 ; 119.72)	18.4
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.956	44	0.947	99.02	(97.71 ; 100.34)	3.7
	AUC(0-24)norm	hr*ng/mL	44	16792.72	44	18258.71	108.73	(102.42 ; 115.43)	16.9
	AUC(0-24)norm/AUC(0-inf)norm		44	0.597	44	0.573	95.95	(91.60 ; 100.50)	13.1

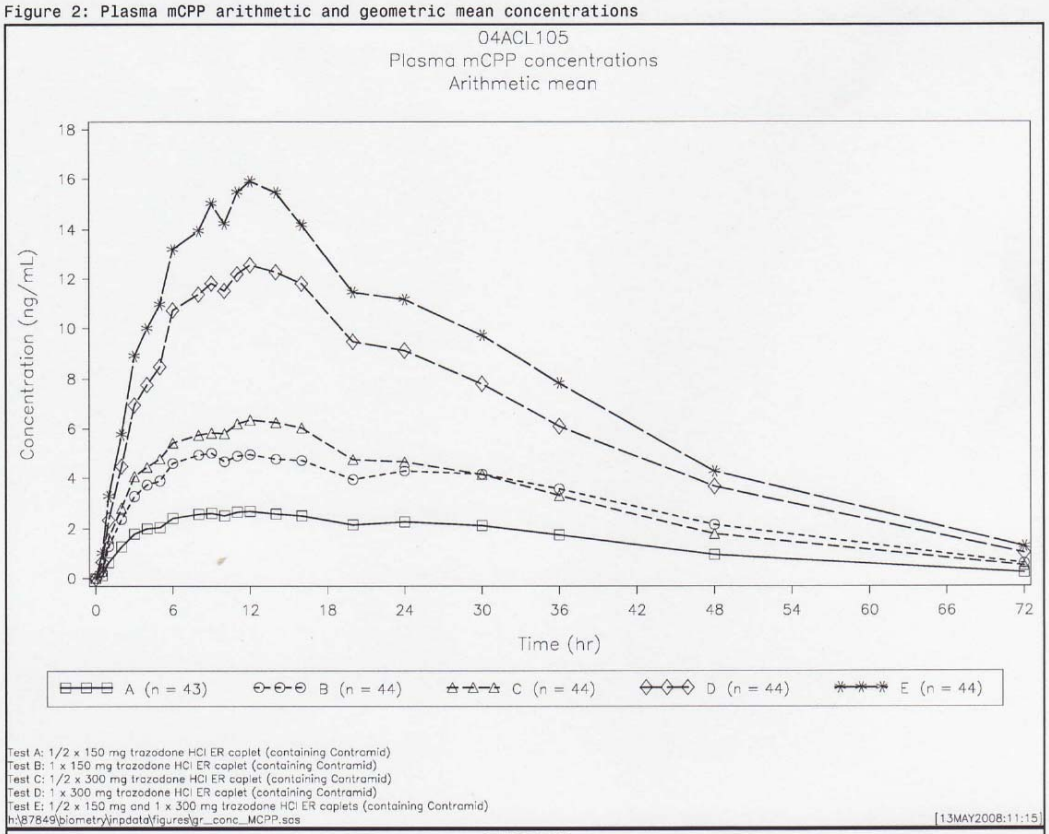
Test A: ½ x 150 mg trazodone HCl ER caplet (containing Contramid)
Test B: 1 x 150 mg trazodone HCl ER caplet (containing Contramid)
Test C: ½ x 300 mg trazodone HCl ER caplet (containing Contramid)
Test D: 1 x 300 mg trazodone HCl ER caplet (containing Contramid)
Test E: ½ x 150 mg and 1 x 300 mg trazodone HCl ER caplets (containing Contramid)

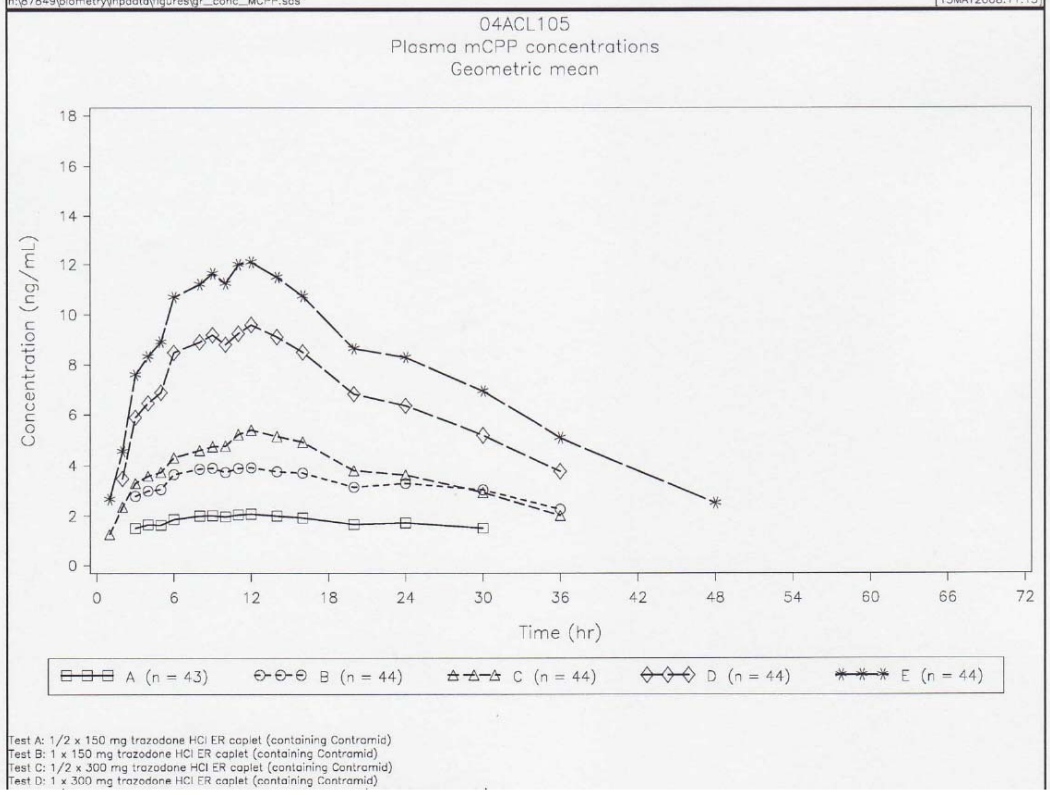
	Variable	Unit	Reference N	Reference LSMean	Test N	Test LSMean	%Ratio (Test/Reference)	90% Confidence interval of ratio	Intra CV%
A vs D	AUC(0-inf)norm	hr*ng/mL	44	28106.21	44	31849.97	113.32	(106.09 ; 121.04)	18.7
	$t_{½}$.z	hr	44	11.237	44	11.143	99.16	(93.04 ; 105.69)	18.1
	Lambda-z	1/hr	44	0.062	44	0.062	100.77	(94.56 ; 107.39)	18.1
E vs D	Cmax,norm	ng/mL	44	1096.145	44	1060.595	96.76	(89.27 ; 104.87)	23.1
	AUC(0-tlast)norm	hr*ng/mL	44	26871.33	44	27076.95	100.77	(94.48 ; 107.47)	18.4
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.956	44	0.960	100.45	(99.14 ; 101.77)	3.7
	AUC(0-24)norm	hr*ng/mL	44	16792.72	44	16671.48	99.28	(93.56 ; 105.35)	16.9
	AUC(0-24)norm/AUC(0-inf)norm		44	0.597	44	0.591	98.95	(94.50 ; 103.61)	13.1
	AUC(0-inf)norm	hr*ng/mL	44	28106.21	44	28195.29	100.32	(93.96 ; 107.10)	18.7
	$t_{½}$.z	hr	44	11.237	44	11.005	97.94	(91.93 ; 104.33)	18.1
	Lambda-z	1/hr	44	0.062	44	0.063	101.96	(95.71 ; 108.61)	18.1

Test A: ½ x 150 mg trazodone HCl ER caplet (containing Contramid)
Test B: 1 x 150 mg trazodone HCl ER caplet (containing Contramid)
Test C: ½ x 300 mg trazodone HCl ER caplet (containing Contramid)
Test D: 1 x 300 mg trazodone HCl ER caplet (containing Contramid)
Test E: ½ x 150 mg and 1 x 300 mg trazodone HCl ER caplets (containing Contramid)

The plasma concentration time profile of mCPP is provided in the figures.

Figure 2: Plasma mCPP arithmetic and geometric mean concentrations





The pharmacokinetic parameters for mCPP for the various treatments are provided in the following tablets

Summary of Mean (SD) Pharmacokinetic Parameters (before dose-normalization) of mCPP

Parameter	½ x 150 mg (Test A)	1 x 150 mg (Test B)	½ x 300 mg (Test C)	1 x 300 mg (Test D)	½ x 150 mg + 300 mg (Test E)
AUC (0-t) (ng*h/mL)	104 (108)	211 (228)	223 (231)	437(463)	539 (530)
AUC (0-∞) (ng*h/mL)	120 (118)	235 (260)	242 (263)	470(515)	576(595)
Cmax (ng/mL)	3.08 (2.48)	5.76 (4.56)	7.27 (5.12)	13.9(12.0)	18.2 (14.8)
Tmax (h)**	12.0 (3.00 – 36.00)	11.0 (3.00 – 36.0)	12.0 (4.00 – 36.00)	11.5 (4.00 – 30.0)	10.5 (4.00 – 30.00)
T ½ (h)	16.0 (9.92)	13.2 (6.49)	12.4 (5.83)	13.6 (6.69)	12.4 (4.36)

The point estimates and confidence intervals for the mean ratios of mCPP are provided in the following tables

Statistical Analysis of Plasma mCPP Pharmacokinetic Parameters

	Variable	Unit	Reference N	Reference LSMean	Test N	Test LSMean	%Ratio (Test/Reference)	90% Confidence interval of ratio	Intra CV
B vs D	Cmax,norm	ng/mL	44	11.328	44	9.705	85.67	(77.82 ; 94.31)	27.8
	AUC(0-tlast)norm	hr*ng/mL	44	322.248	44	313.888	97.41	(89.75 ; 105.72)	23.5
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.935	44	0.912	97.56	(94.68 ; 100.52)	8.5
	AUC(0-24)norm	hr*ng/mL	44	191.113	44	168.167	87.99	(81.04 ; 95.54)	23.6
	AUC(0-24)norm/AUC(0-inf)norm		44	0.554	44	0.488	88.13	(83.40 ; 93.12)	15.7
	AUC(0-inf)norm	hr*ng/mL	44	344.787	44	344.236	99.84	(92.16 ; 108.16)	23.0
	$t_{½}$.z	hr	44	11.986	44	11.742	97.97	(89.33 ; 107.44)	26.6
	Lambda-z	1/hr	44	0.058	44	0.059	102.15	(93.16 ; 112.01)	26.6
A vs B	Cmax,norm	ng/mL	44	9.705	44	10.307	106.21	(96.41 ; 117.01)	27.8
	AUC(0-tlast)norm	hr*ng/mL	44	313.888	44	311.258	99.16	(91.31 ; 107.69)	23.5
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.912	44	0.843	92.44	(89.70 ; 95.27)	8.5
	AUC(0-24)norm	hr*ng/mL	44	168.167	44	179.833	106.94	(98.43 ; 116.18)	23.6
	AUC(0-24)norm/AUC(0-inf)norm		44	0.488	44	0.487	99.67	(94.28 ; 105.37)	15.7
	AUC(0-inf)norm	hr*ng/mL	44	344.236	44	369.300	107.28	(98.97 ; 116.29)	23.0
	$t_{½}$.z	hr	44	11.742	44	13.445	114.50	(104.33 ; 125.66)	26.6
	Lambda-z	1/hr	44	0.059	44	0.052	87.48	(79.72 ; 95.98)	26.6
C vs D	Cmax,norm	ng/mL	44	11.328	44	12.750	112.55	(102.23 ; 123.90)	27.8
	AUC(0-tlast)norm	hr*ng/mL	44	322.248	44	343.484	106.59	(98.21 ; 115.69)	23.5
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.935	44	0.929	99.42	(96.49 ; 102.43)	8.5
	AUC(0-24)norm	hr*ng/mL	44	191.113	44	211.016	110.41	(101.70 ; 119.88)	23.6
	AUC(0-24)norm/AUC(0-inf)norm		44	0.554	44	0.571	102.98	(97.45 ; 108.82)	15.7
	AUC(0-inf)norm	hr*ng/mL	44	344.787	44	369.659	107.21	(98.97 ; 116.15)	23.0
	$t_{½}$.z	hr	44	11.986	44	11.113	92.72	(84.54 ; 101.68)	26.6
	Lambda-z	1/hr	44	0.058	44	0.062	108.07	(98.55 ; 118.50)	26.6
A vs D	Cmax,norm	ng/mL	44	11.328	44	10.307	90.99	(82.59 ; 100.24)	27.8
	AUC(0-tlast)norm	hr*ng/mL	44	322.248	44	311.258	96.59	(88.94 ; 104.90)	23.5
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.935	44	0.843	90.19	(87.51 ; 92.94)	8.5
	AUC(0-24)norm	hr*ng/mL	44	191.113	44	179.833	94.10	(86.61 ; 102.23)	23.6
	AUC(0-24)norm/AUC(0-inf)norm		44	0.554	44	0.487	87.83	(83.09 ; 92.85)	15.7

Test A: ½ x 150 mg trazodone HCl ER caplet (containing Contramid)
Test B: 1 x 150 mg trazodone HCl ER caplet (containing Contramid)
Test C: ½ x 300 mg trazodone HCl ER caplet (containing Contramid)
Test D: 1 x 300 mg trazodone HCl ER caplet (containing Contramid)
Test E: ½ x 150 mg and 1 x 300 mg trazodone HCl ER caplets (containing Contramid)

	Variable	Unit	Reference N	Reference LSMean	Test N	Test LSMean	%Ratio (Test/Reference)	90% Confidence interval of ratio	Intra CV%
A vs D	AUC(0-inf)norm	hr*ng/mL	44	344.787	44	369.300	107.11	(98.81 ; 116.10)	23.0
	$t_{\frac{1}{2}}$.z	hr	44	11.986	44	13.445	112.18	(102.21 ; 123.11)	26.6
	Lambda-z	1/hr	44	0.058	44	0.052	89.36	(81.43 ; 98.05)	26.6
E vs D	Cmax,norm	ng/mL	44	11.328	44	11.645	102.80	(93.38 ; 113.17)	27.8
	AUC(0-tlast)norm	hr*ng/mL	44	322.248	44	329.848	102.36	(94.31 ; 111.10)	23.5
	AUC(0-tlast)norm/AUC(0-inf)norm		44	0.935	44	0.941	100.73	(97.77 ; 103.79)	8.5
	AUC(0-24)norm	hr*ng/mL	44	191.113	44	193.838	101.43	(93.42 ; 110.12)	23.6
	AUC(0-24)norm/AUC(0-inf)norm		44	0.554	44	0.553	99.81	(94.45 ; 105.47)	15.7
	AUC(0-inf)norm	hr*ng/mL	44	344.787	44	350.370	101.62	(93.80 ; 110.09)	23.0
	$t_{\frac{1}{2}}$.z	hr	44	11.986	44	11.342	94.63	(86.28 ; 103.78)	26.6
	Lambda-z	1/hr	44	0.058	44	0.061	105.79	(96.47 ; 116.00)	26.6

Test A: ½ x 150 mg trazodone HCl ER caplet (containing Contramid)
Test B: 1 x 150 mg trazodone HCl ER caplet (containing Contramid)
Test C: ½ x 300 mg trazodone HCl ER caplet (containing Contramid)
Test D: 1 x 300 mg trazodone HCl ER caplet (containing Contramid)
Test E: ½ x 150 mg and 1 x 300 mg trazodone HCl ER caplets (containing Contramid)

Analysis of Dose proportionality

The results for the dose proportionality analysis of the pharmacokinetic variables Cmax, AUC(0-t) and AUC(0-∞) for trazodone and mCPP are provided in the following table. The model used is presented in the Appendix.

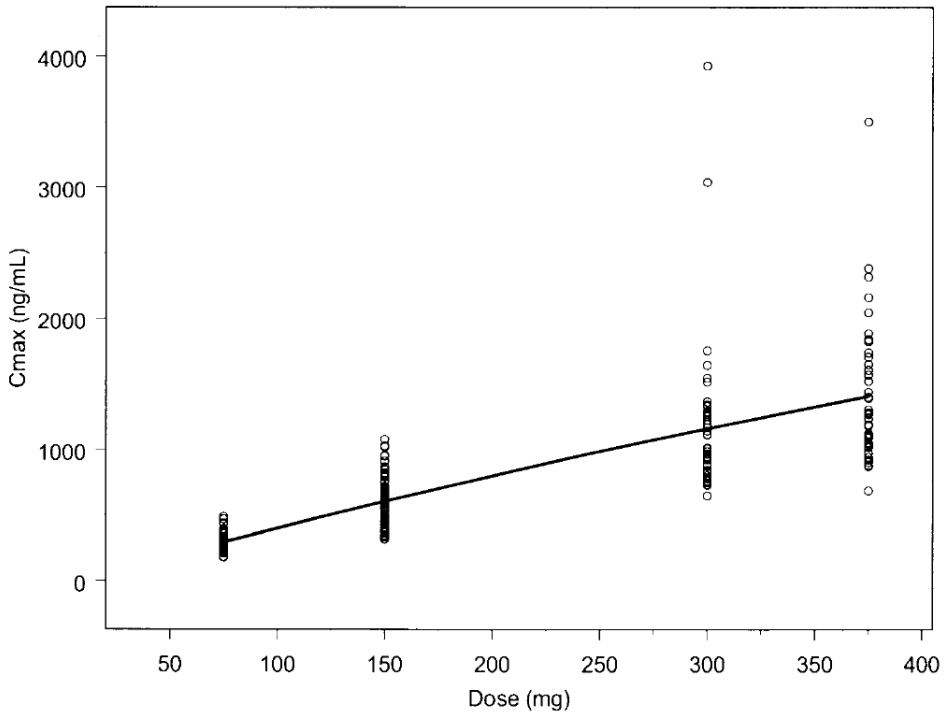
Summary of Statistical Analysis of Pharmacokinetic Parameters for Trazodone and mCPP using the Power Model

Parameter	Acceptance Interval	Trazodone		mCPP	
		β	90% CI	β	90% CI
AUC(0-t) (ng*h/mL)	(0.861 ; 1.139)	0.920	(0.875; 0.964)	1.024	(0.969; 1.079)
AUC (0-∞) (ng*h/mL)	(0.861 ; 1.139)	0.913	(0.867; 0.958)	0.963	(0.912; 1.013)
Cmax (ng/mL)	(0.861 ; 1.139)	0.948	(0.899; 0.997)	1.068	(1.011; 1.124)

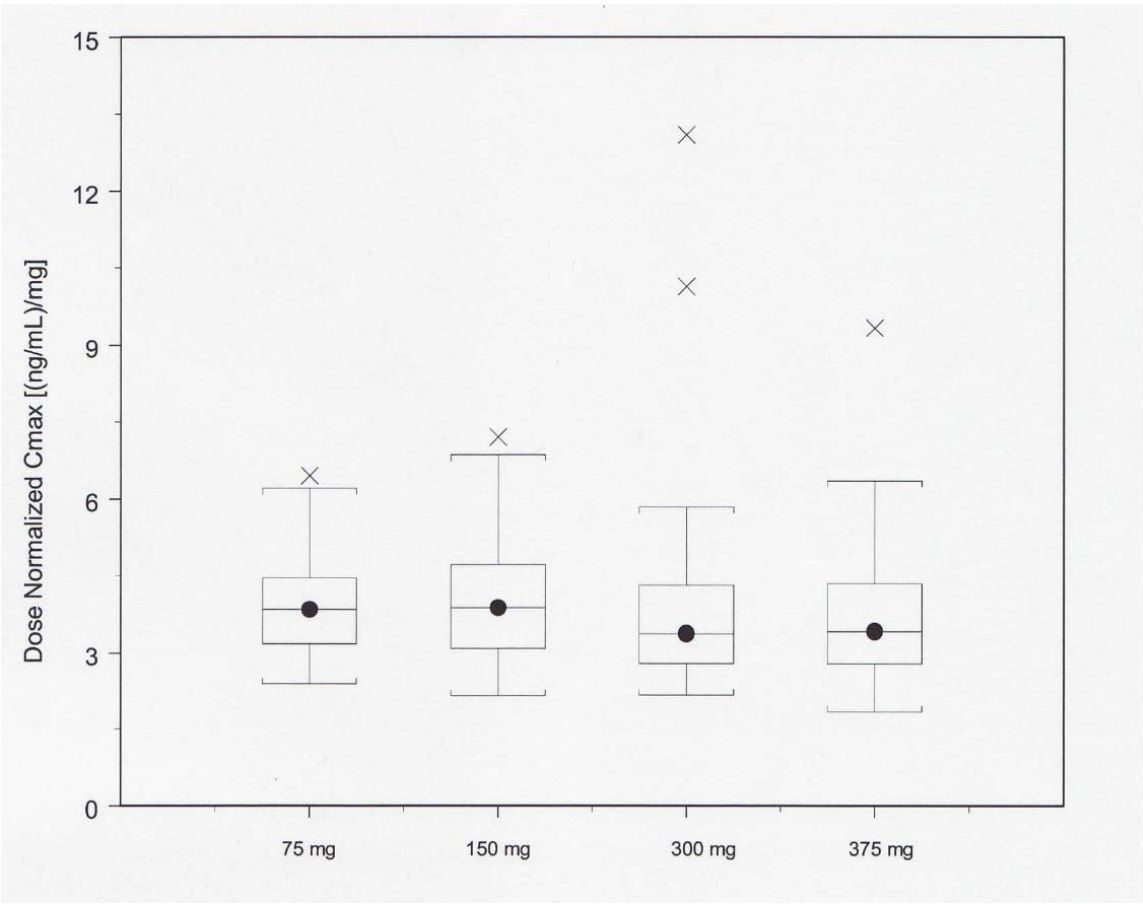
β= estimate of proportionality constant

The results of the analysis of dose proportionality using the power model indicated that the estimate of proportionality constant, and its corresponding 90% interval fall within the acceptance range. Plots for Cmax and AUC(0-∞) are provided in the following figures.

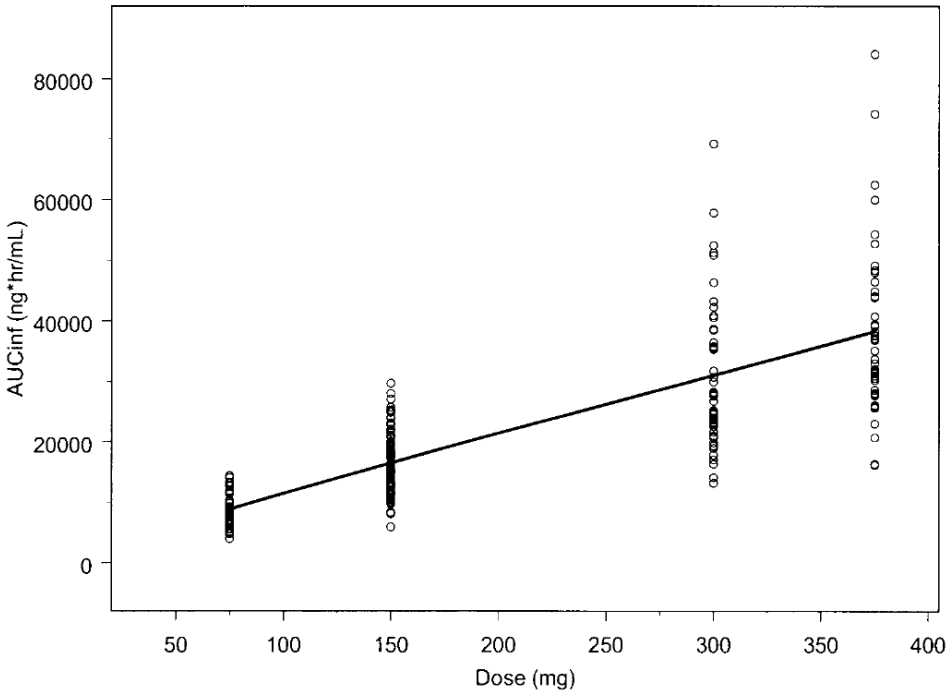
Linear Plot of Cmax versus Dose



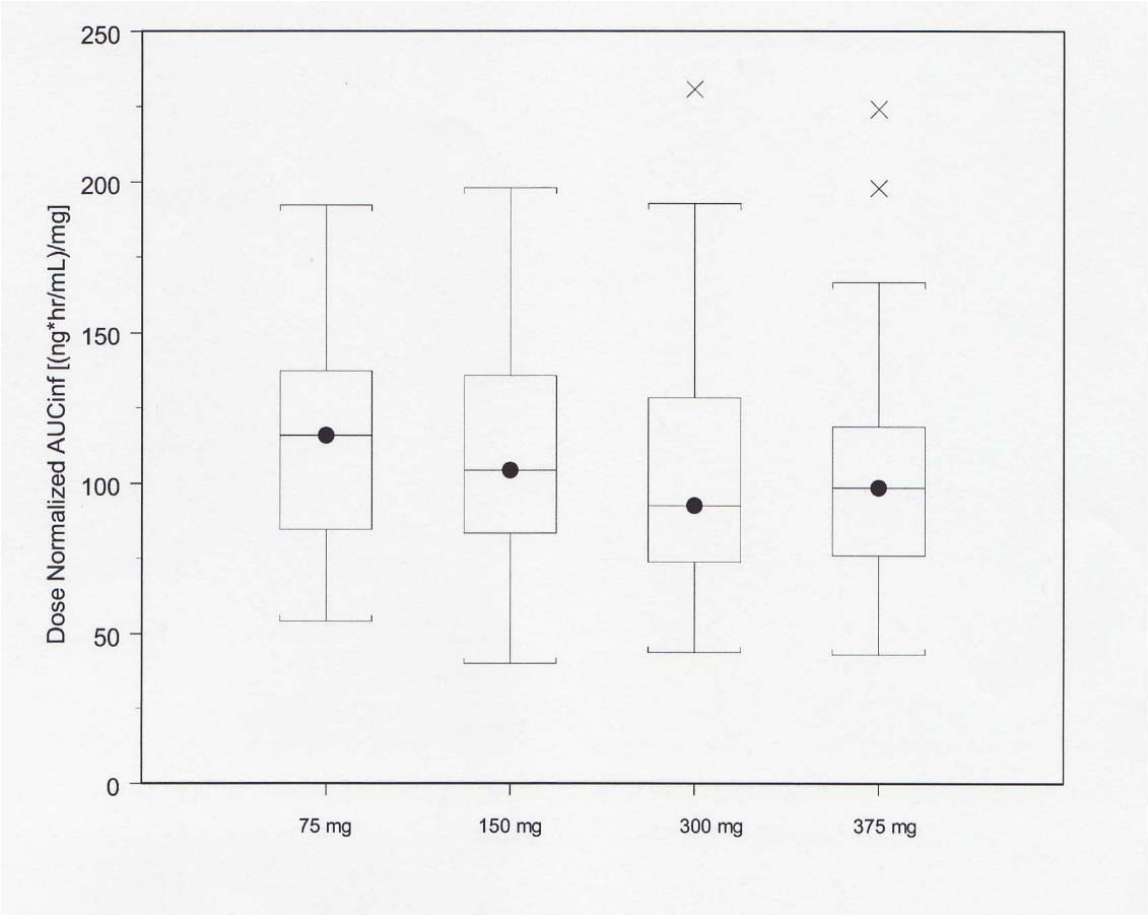
Box and Whisker Plot of Dose Normalized Cmax versus Dose



Linear Plot of AUC∞ versus Dose



Box and Whisker Plots of Dose Normalized AUC∞ versus Dose



Summary of Pharmacokinetics

Trazodone

Dose proportionality was supported by the analysis using the bioequivalence approach and power method. Results of the assessment of dose proportionality by the power method demonstrated that the concentration of trazodone was proportional to dose between 75 to 375 mg. Using the confidence interval approach, 150 mg and 300 mg intact caplets are dose proportional with respect to the rate and extent of absorption. Half 150 mg caplet is proportional to the intact 150 mg caplet and that the lowest dose (75 mg) and the highest dose (375 mg) evaluated in the study are proportional to the reference dose (300 mg). Half 300 mg caplet is proportional to the intact 300 mg caplet with respect to AUC of trazodone. However, the dose-normalized Cmax was 19.7% higher for the half 300 mg caplet compared with the intact 300 mg caplet and hence not proportional.

mCPP

It determined that half of the 150 mg and 300 mg caplets were proportional to the intact 150 mg and 300 mg caplets. Also the 75 mg and 375 mg dose were proportional with respect to rate and extent of formation of mCPP. The dose-normalized Cmax for mCPP was 14.3% lower for the 150 mg caplet compared with the 300 mg caplet.

Safety Summary

The sponsor reported that trazodone was generally well tolerated by healthy volunteers during the study. Twenty nine (29) out of 45 subjects reported 89 adverse events, of which 72 events were assessed to be at least possibly related to the study medication. The most frequently observed adverse events during the study were headache and dizziness. The sponsor reported on abnormal electrocardiograms, vital signs, physical evaluation or laboratory values after administration of Trazodone HCl (containing Contramid) ranging from 75 mg to 375 mg. Refer to medical review for Agency's evaluation of safety.

Reviewer Comments: Based on the power model used to assess dose proportionality, the reviewer agrees with the sponsor's conclusion of dose proportionality of Trazodone Contramid OAD following doses ranging from 75 mg to 375 mg.

Appendix

Table 16: Plasma trazodone pharmacokinetic variables (before normalisation)

Treatment	Variable	Unit	N	Mean	SD	Median	Minimum	Maximum	Geometric Mean	Geometric SD
Test A	Cmax	ng/mL	43	293.816	71.351	287.300	178.300	484.100	285.908	67.914
	Tmax	hr	43	10.372	7.982	8.000	2.000	30.000	7.627	7.495
	AUC(0-tlast)	hr*ng/mL	43	8124.131	2501.796	8282.310	3935.746	12867.193	7738.935	2547.820
	AUC(0-tlast)/AUC(0-inf)		43	0.945	0.052	0.967	0.752	0.988	0.944	0.056
	AUC(0-24)	hr*ng/mL	43	4674.724	1065.884	4643.746	2791.165	7698.450	4561.621	1029.980
	AUC(0-24)/AUC(0-inf)		43	0.572	0.133	0.560	0.341	0.887	0.556	0.135
	AUC(0-inf)	hr*ng/mL	43	8657.799	2832.538	8687.295	4050.307	14415.698	8200.257	2858.334
	$t_{½}$.z	hr	43	12.653	5.249	11.433	6.235	31.477	11.838	4.313
	Lambda-z	1/hr	43	0.062	0.020	0.061	0.022	0.111	0.059	0.021
Test B	Cmax	ng/mL	44	530.998	142.660	515.600	338.200	1030.000	514.452	130.307
	Tmax	hr	44	8.750	7.668	6.000	2.000	30.000	6.412	5.875
	AUC(0-tlast)	hr*ng/mL	44	15504.616	4764.266	15266.872	5907.351	24692.170	14739.507	5029.948
	AUC(0-tlast)/AUC(0-inf)		44	0.954	0.054	0.971	0.747	0.992	0.953	0.059
	AUC(0-24)	hr*ng/mL	44	8532.355	1987.798	8719.590	5014.205	13070.955	8299.798	2032.425
	AUC(0-24)/AUC(0-inf)		44	0.552	0.130	0.557	0.318	0.836	0.536	0.132
	AUC(0-inf)	hr*ng/mL	44	16387.962	5418.892	15418.016	6001.783	28069.583	15473.631	5621.137
	$t_{½}$.z	hr	44	12.392	5.982	11.052	6.165	34.344	11.385	4.650
	Lambda-z	1/hr	44	0.065	0.022	0.063	0.020	0.112	0.061	0.025
Test C	Cmax	ng/mL	44	677.466	171.167	674.700	320.800	1081.000	655.427	177.348
	Tmax	hr	44	8.477	3.738	9.000	1.000	14.000	7.363	4.899
	AUC(0-tlast)	hr*ng/mL	44	16161.196	4835.685	16068.794	5871.877	24795.960	15394.983	5163.773
	AUC(0-tlast)/AUC(0-inf)		44	0.961	0.038	0.974	0.772	0.992	0.960	0.041
	AUC(0-24)	hr*ng/mL	44	10123.702	2407.549	10342.438	5172.889	15108.145	9822.166	2552.933
	AUC(0-24)/AUC(0-inf)		44	0.625	0.124	0.624	0.364	0.878	0.612	0.126
	AUC(0-inf)	hr*ng/mL	44	16910.863	5384.454	16549.289	5995.011	29722.191	16038.552	5586.881
	$t_{½}$.z	hr	44	12.022	5.206	10.391	5.736	35.433	11.182	4.304
	Lambda-z	1/hr	44	0.066	0.023	0.067	0.020	0.121	0.062	0.024
Test D	Cmax	ng/mL	44	1179.241	583.478	1011.000	646.100	3930.000	1094.747	400.962
	Tmax	hr	44	7.410	3.909	7.000	2.000	14.033	6.243	4.371

Test A: ½ x 150 mg trazodone HCl ER caplet (containing Contramid)
Test B: 1 x 150 mg trazodone HCl ER caplet (containing Contramid)
Test C: ½ x 300 mg trazodone HCl ER caplet (containing Contramid)
Test D: 1 x 300 mg trazodone HCl ER caplet (containing Contramid)
Test E: ½ x 150 mg and 1 x 300 mg trazodone HCl ER caplets (containing Contramid)

Treatment	Variable	Unit	N	Mean	SD	Median	Minimum	Maximum	Geometric Mean	Geometric SD
Test D	AUC(0-tlast)	hr*ng/mL	44	29199.752	10425.970	26949.413	12868.170	52171.560	27434.983	10196.190
	AUC(0-tlast)/AUC(0-inf)		44	0.956	0.064	0.977	0.619	0.996	0.954	0.074
	AUC(0-24)	hr*ng/mL	44	17468.793	5221.507	16639.387	10326.750	36664.500	16800.495	4753.800
	AUC(0-24)/AUC(0-inf)		44	0.601	0.139	0.576	0.243	0.941	0.584	0.146
	AUC(0-inf)	hr*ng/mL	44	30983.135	12521.797	27813.179	13175.729	69192.251	28761.821	11575.965
	$t_{\frac{1}{2}}$.z	hr	44	13.189	7.889	11.039	5.522	50.544	11.759	5.567
	Lambda-z	1/hr	44	0.064	0.025	0.063	0.014	0.126	0.059	0.028
Test E	Cmax	ng/mL	44	1401.143	521.604	1280.000	685.400	3505.000	1324.645	446.518
	Tmax	hr	44	7.706	3.691	8.000	1.000	16.033	6.658	4.370
	AUC(0-tlast)	hr*ng/mL	44	36250.828	11345.271	34645.718	16007.733	70998.940	34570.249	11173.014
	AUC(0-tlast)/AUC(0-inf)		44	0.960	0.054	0.985	0.734	0.997	0.958	0.058
	AUC(0-24)	hr*ng/mL	44	21545.862	5503.955	21033.362	11514.275	33109.710	20846.491	5588.944
	AUC(0-24)/AUC(0-inf)		44	0.592	0.123	0.589	0.291	0.840	0.578	0.134
	AUC(0-inf)	hr*ng/mL	44	38290.766	13893.239	36954.433	16183.335	84040.488	36080.452	12935.589
	$t_{\frac{1}{2}}$.z	hr	44	12.473	5.695	10.796	5.643	34.014	11.533	4.548
	Lambda-z	1/hr	44	0.064	0.022	0.065	0.020	0.123	0.060	0.024

Test A: ½ x 150 mg trazodone HCl ER caplet (containing Contramid)
Test B: 1 x 150 mg trazodone HCl ER caplet (containing Contramid)
Test C: ½ x 300 mg trazodone HCl ER caplet (containing Contramid)
Test D: 1 x 300 mg trazodone HCl ER caplet (containing Contramid)
Test E: ½ x 150 mg and 1 x 300 mg trazodone HCl ER caplets (containing Contramid)

Table 17: Plasma mCPP pharmacokinetic variables (before normalisation)

Treatment	Variable	Unit	N	Mean	SD	Median	Minimum	Maximum	Geometric Mean	Geometric SD
Test A	Cmax	ng/mL	43	3.079	2.481	2.320	0.539	11.800	2.408	1.891
	Tmax	hr	43	13.767	9.000	12.000	3.000	36.000	11.195	8.377
	AUC(0-tlast)	hr*ng/mL	43	104.243	108.316	61.620	15.101	567.403	73.926	69.323
	AUC(0-tlast)/AUC(0-inf)		43	0.850	0.117	0.882	0.422	0.963	0.840	0.142
	AUC(0-24)	hr*ng/mL	43	52.811	42.122	40.800	10.325	199.655	41.765	31.671
	AUC(0-24)/AUC(0-inf)		43	0.496	0.141	0.492	0.219	0.821	0.475	0.149
	AUC(0-inf)	hr*ng/mL	43	119.910	118.118	82.784	25.399	634.826	87.993	76.359
	$t_{\frac{1}{2}}$.z	hr	43	15.962	9.920	13.239	6.645	57.934	14.088	6.945
	Lambda-z	1/hr	43	0.054	0.021	0.052	0.012	0.104	0.049	0.024
Test B	Cmax	ng/mL	44	5.755	4.563	4.460	0.961	25.100	4.601	3.362
	Tmax	hr	44	14.614	9.438	11.000	3.000	36.000	11.905	8.828
	AUC(0-tlast)	hr*ng/mL	44	210.872	228.166	141.038	23.638	1320.872	150.734	138.279
	AUC(0-tlast)/AUC(0-inf)		44	0.912	0.070	0.930	0.616	0.990	0.909	0.078
	AUC(0-24)	hr*ng/mL	44	98.715	77.493	77.326	17.428	432.172	79.418	56.907
	AUC(0-24)/AUC(0-inf)		44	0.498	0.135	0.499	0.202	0.796	0.479	0.143
	AUC(0-inf)	hr*ng/mL	44	234.606	260.443	155.040	28.576	1507.494	165.748	153.486
	$t_{\frac{1}{2}}$.z	hr	44	13.201	6.493	11.404	6.992	44.021	12.180	4.760
	Lambda-z	1/hr	44	0.060	0.019	0.061	0.016	0.099	0.057	0.022
Test C	Cmax	ng/mL	44	7.266	5.117	6.095	2.040	27.500	6.044	3.961
	Tmax	hr	44	11.842	5.698	12.000	4.000	36.000	10.837	4.719
	AUC(0-tlast)	hr*ng/mL	44	223.288	230.540	135.059	47.732	1339.443	164.875	137.719
	AUC(0-tlast)/AUC(0-inf)		44	0.928	0.048	0.940	0.725	0.978	0.927	0.052
	AUC(0-24)	hr*ng/mL	44	120.521	85.517	93.747	31.082	431.643	99.676	66.310
	AUC(0-24)/AUC(0-inf)		44	0.575	0.123	0.574	0.273	0.839	0.560	0.132
	AUC(0-inf)	hr*ng/mL	44	242.421	262.837	145.229	53.819	1581.006	177.843	147.921
	$t_{\frac{1}{2}}$.z	hr	44	12.430	5.833	10.826	4.991	41.620	11.517	4.478
	Lambda-z	1/hr	44	0.064	0.023	0.064	0.017	0.139	0.060	0.023
Test D	Cmax	ng/mL	44	13.931	11.970	10.400	3.420	54.700	10.745	8.520
	Tmax	hr	44	11.500	4.364	11.500	4.000	30.000	10.770	4.131

Test A: ½ x 150 mg trazodone HCl ER caplet (containing Contramid)
Test B: 1 x 150 mg trazodone HCl ER caplet (containing Contramid)
Test C: ½ x 300 mg trazodone HCl ER caplet (containing Contramid)
Test D: 1 x 300 mg trazodone HCl ER caplet (containing Contramid)
Test E: ½ x 150 mg and 1 x 300 mg trazodone HCl ER caplets (containing Contramid)

Table 17: Plasma mCPP pharmacokinetic variables (before normalisation)

Treatment	Variable	Unit	N	Mean	SD	Median	Minimum	Maximum	Geometric Mean	Geometric SD
Test D	AUC(0-tlast)	hr*ng/mL	44	436.908	463.256	300.790	75.708	2132.940	309.645	283.956
	AUC(0-tlast)/AUC(0-inf)		44	0.935	0.061	0.958	0.701	0.992	0.933	0.066
	AUC(0-24)	hr*ng/mL	44	233.214	200.706	167.858	56.298	905.433	180.610	140.968
	AUC(0-24)/AUC(0-inf)		44	0.559	0.130	0.539	0.263	0.898	0.544	0.135
	AUC(0-inf)	hr*ng/mL	44	469.782	514.646	311.338	79.130	2547.556	331.967	301.147
	$t_{½}$.z	hr	44	13.565	6.692	11.374	5.062	37.585	12.402	5.271
	Lambda-z	1/hr	44	0.060	0.023	0.061	0.018	0.137	0.056	0.024
Test E	Cmax	ng/mL	44	18.162	14.816	13.900	2.470	61.200	13.831	11.928
	Tmax	hr	44	10.683	4.236	10.500	4.000	30.000	9.999	3.781
	AUC(0-tlast)	hr*ng/mL	44	538.676	530.395	428.487	86.245	2971.567	396.741	351.800
	AUC(0-tlast)/AUC(0-inf)		44	0.941	0.050	0.957	0.809	0.996	0.939	0.051
	AUC(0-24)	hr*ng/mL	44	289.499	218.439	231.443	48.079	1039.267	229.210	179.269
	AUC(0-24)/AUC(0-inf)		44	0.556	0.119	0.573	0.301	0.772	0.543	0.127
	AUC(0-inf)	hr*ng/mL	44	576.122	595.221	435.860	106.647	3452.651	422.367	368.569
	$t_{½}$.z	hr	44	12.410	4.355	11.121	7.005	23.243	11.759	3.921
	Lambda-z	1/hr	44	0.062	0.019	0.062	0.030	0.099	0.059	0.020

Test A: ½ x 150 mg trazodone HCl ER caplet (containing Contramid)
Test B: 1 x 150 mg trazodone HCl ER caplet (containing Contramid)
Test C: ½ x 300 mg trazodone HCl ER caplet (containing Contramid)
Test D: 1 x 300 mg trazodone HCl ER caplet (containing Contramid)
Test E: ½ x 150 mg and 1 x 300 mg trazodone HCl ER caplets (containing Contramid)

Figure 4 **Log-Log Plot of AUClast versus Dose**

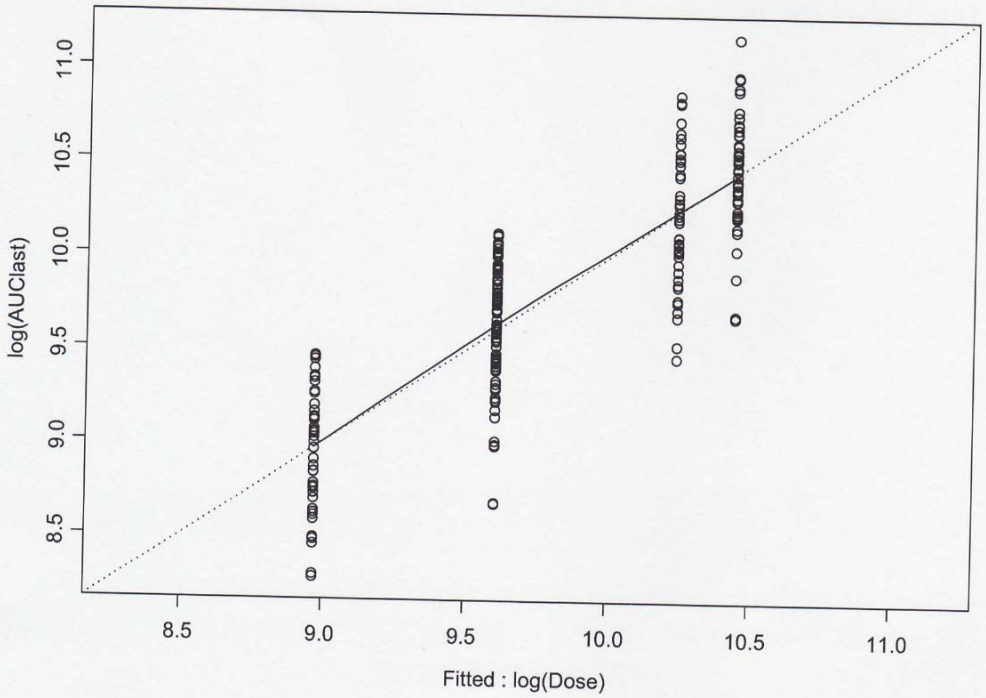


Figure 5 Linear Plot of AUClast Versus Dose

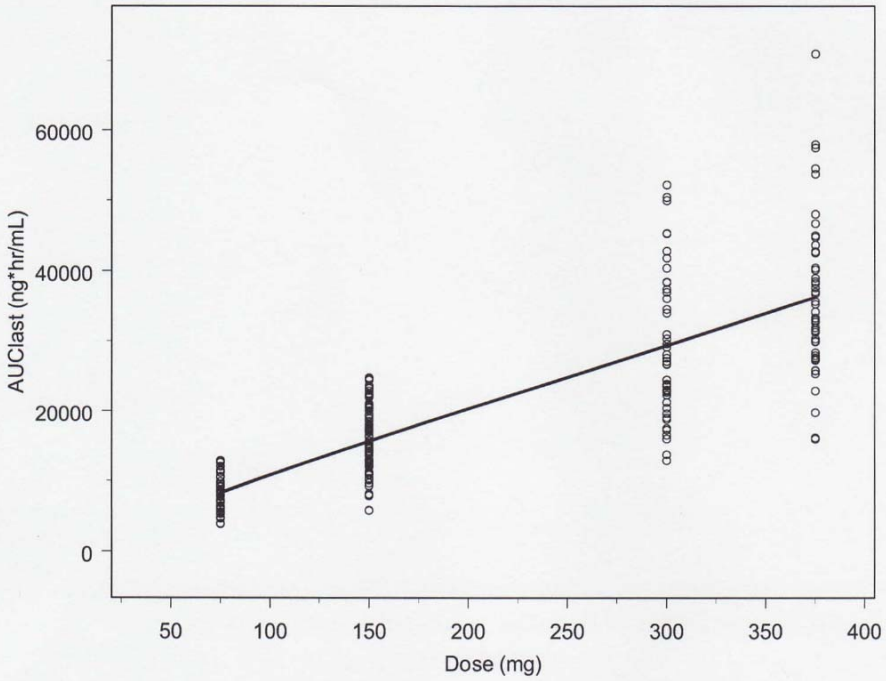
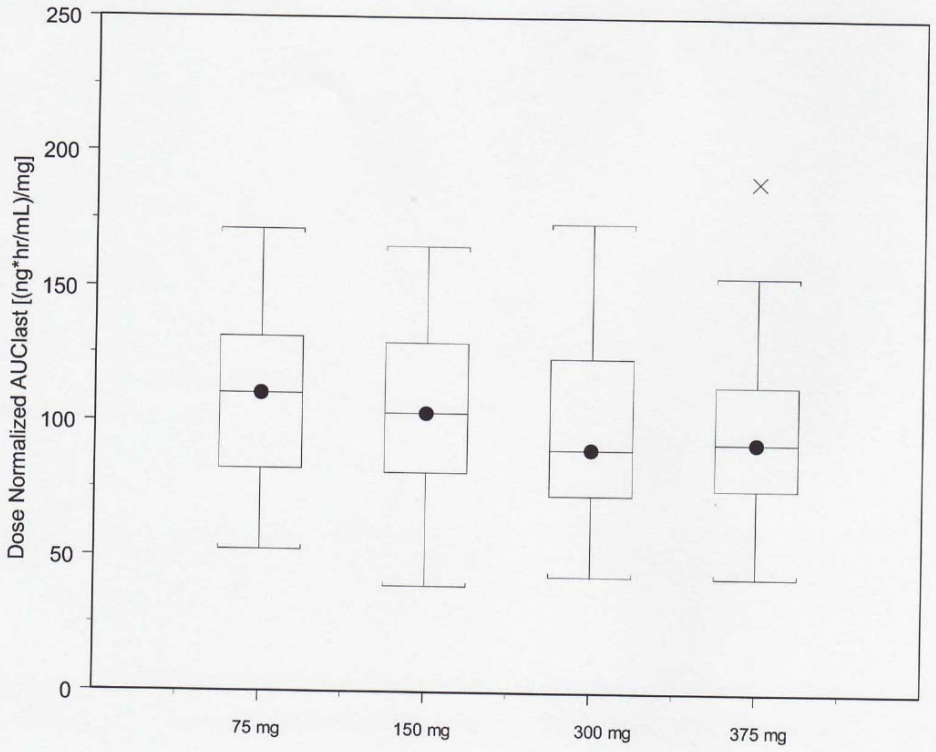


Figure 6 **Box and Whisker Plot of Dose Normalized AUClast Versus Dose**



1. BACKGROUND

When drug concentrations remain within the range in which pharmacokinetics are linear, key pharmacokinetic parameters can be divided into two groups; those that change with changing dose and those that are independent of dose (Table 1).

Table 1 Pharmacokinetic Parameters By Dependence on Dose

Change with Dose	Independent of Dose
C_{max}	T_{max}
AUC_t	$t_{1/2}$
AUC	k_{el}
C_{min}	CL
$C_{av,ss}$	F
Ae	V

Parameters that increase proportionally with dose can be converted into dose independent parameters by normalization (dividing the parameter by dose). Thus, the parameters of a drug that exhibits proportional behavior, when normalized, should be consistent across the range of doses being examined.

The power method for evaluating dose proportionality, combined with confidence interval criteria to identify proportionate and disproportionate ranges of doses for the drug under consideration, is recommended as the primary analysis for AUC and C_{max} [1].

The method assumes the following relationship between the pharmacokinetic parameter (Y) and dose:

$$Y = \alpha * Dose^{\beta}, \qquad \text{where } Y = AUC \text{ or } C_{max}$$

The proportionality constant is estimated byβ. For dose proportionality, $\beta = 1$. In this case a doubling of the dose will result in a doubling of the dependent variable (AUC or C_{max}).

The maximal dose ratio (r) for the study is defined as:

$$r = h/\ell, \qquad \text{where } h = \text{highest dose administered in study}, \quad \ell = \text{lowest dose administered in study}$$

Dose proportionality exists if, for the relevant pharmacokinetic parameters (e.g. AUC or C_{max}), the ratio of the geometric mean values corresponding to

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the highest and lowest doses, equals 1, i.e. if the ratio of the dose-normalized geometric mean values equals 1.

The predicted geometric mean of Y at the highest dose is αh^{β} and the corresponding value at the lowest dose is $\alpha \ell^{\beta}$. Since dose proportionality exists if the ratio of the geometric mean pharmacokinetic parameter values equals $r = h/\ell$, dose proportionality corresponds to $(\alpha h^{\beta}/\alpha \ell^{\beta}) = h/\ell$, which can be rewritten as:

$(h^{\beta-1}/\ell^{\beta-1}) = 1.$

Given the pre-specified lower and upper limits of the acceptance interval, θ_L and θ_H (where $\theta_L = 0.8$ and $\theta_H = 1.2$), the acceptance intervals are defined:

$$\theta_L < r^{\beta-1} < \theta_H$$

and are modified as:

$$1 + (\log(\theta_L)/\log(r)) < \beta < 1 + (\log(\theta_H)/\log(r))$$

A mixed effects statistical model, allowing for random between-subject variability in the intercept and slope parameters, was implemented to estimate β and its corresponding 90% confidence interval. The following procedures were applied using a purpose written script in Splus Version 6.2:

- Fit log(Y) versus log(Dose), where Y = C_{max}, AUClast and AUCinf. The statistical model included terms for subject and dose. If necessary, the dose term can be separated into a linear component and a term representing deviations from linearity (lack of fit) [2].
- Provide an estimate of β with its associated 90% confidence interval (L, U).
- Compare the 90% confidence intervals with the modified acceptance intervals using the decision rules below.

The following decision rules were applied:

- Dose proportionality will be declared if the calculated 90% confidence interval for β lies completely within the acceptance region $[1 + (\log(\theta_L)/\log(r)), 1 + (\log(\theta_H)/\log(r))]$. This criterion is equivalent to having the ratio of the dose-normalized geometric mean pharmacokinetic parameter values contained completely within the interval (θ_L, θ_H).
- If the calculated 90% confidence interval lies completely outside the acceptance region, lack of proportionality will be concluded.
- If the calculated 90% confidence interval spans the acceptance region, then the results with respect to dose proportionality will be determined to be inconclusive.

Title (Protocol 04ACL107): Comparison of the Bioavailability of 300 mg Trazodone Hydrochloride Extended Release Caplets (Containing Contramid®) After Oral Administration At Different Times of the Day.

STUDY OBJECTIVE:	To assess the effect of the time of day and the effect of food on the bioavailability of 300 mg trazodone hydrochloride (HCl) extended-release caplets (containing Contramid®) following single-dose administration.
METHODOLOGY:	• Open-label • Laboratory-blind • Single-dose • Randomized • Three-period crossover • Fasting and/or fed conditions
STUDY SUBJECTS:	• Planned for completion: at least 24 • Enrolled and randomized: 30 • Drop-outs: 2 • Discontinuers: 4 • Completed as per protocol: 24
MAIN CRITERIA FOR INCLUSION:	• Healthy male and female subject. • Non-smoker or past smoker who stopped the use of any form of tobacco, including snuff or similar products, at least 3 months before entering the study. • Aged 18 to < 56 years. • Healthy as judged by means of relevant medical history, physical examination, electrocardiogram (ECG), vital signs and laboratory test results. • Body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 55 kg. • Signed informed consent.

TEST PRODUCT:	• Generic name:	Trazodone HCl (containing Contramid®)
	• Manufacturer	Labopharm, Inc.
	• Country of origin:	Canada
	• Dosage form:	Extended-release, film-coated caplet containing 300 mg trazodone HCl equivalent to 273.21 mg trazodone
	• Dose:	300 mg trazodone HCl (one extended-release caplet) per treatment phase
	• Mode/route	Oral
	• Times administered:	Treatment A: administered at 10:00, 4 hours after light meal Treatment B: administered at 22:00, 4 hours after light meal Treatment C: administered at 18:15, 15 minutes after a standardized high-fat, high-calorie meal
	• Batch number:	04A19602 P2
	• Expiry date:	January 2009
	• Assayed product content:	102.4% trazodone per caplet
DURATION OF TREATMENT:	Three profile periods of 72 hours, each starting with a 48-hour clinic day at FARMOVS-PAREXEL, and two wash-out periods of 7 calendar days between clinic days (except for one subject who had a wash-out period of 14 calendar days after Treatment phase II).	
CRITERIA FOR EVALUATION		
PHARMACOKINETICS:	To compare the rate and extent of absorption of trazodone and formation of *m*-chlorophenylpiperazine (mCPP) from the test product, the following pharmacokinetic variables were calculated for each subject and treatment using the actual sampling intervals (relative to medication administration): **PRIMARY VARIABLES:** • Maximum plasma concentration (C_{max}). • Area under the plasma concentration vs time data pairs, AUC(0-t_{last}), where t_{last} is the time of the last quantifiable concentration. • Area under the plasma concentration vs time data pairs, with extrapolation to infinity [AUC(0-∞)]. **SECONDARY VARIABLES:** • Area under the plasma concentration vs time data pairs for the first 24 hours [AUC(0-24)]. • Time to maximum plasma concentration (T_{max}). • Apparent terminal rate constant (λ_z). • Apparent terminal half-life ($t_{1/2}$).	
SAFETY:	• Full blood count. • Clinical chemistry. • Urinalysis. • Vital signs measurements on clinic days. • ECG (standard 12-lead) on clinic days. • Physical examination. • Pregnancy tests (female subjects) on clinic days. • Adverse event monitoring.	

STATISTICAL METHODS	
PHARMACOKINETICS:	Treatments were compared with respect to the pharmacokinetic variables C_{max}, AUC(0-t_{last}), AUC(0-∞), AUC(0-24), λ_z and $t_{½,z}$ using an analysis of variance with sequence, subject(sequence), treatment and period effects, after logarithmic transformation of the data. A two-sided alpha level of 0.05 was used. Point estimates and 90% confidence intervals for the "test/reference" mean ratios of these variables were calculated. The effect of the time of day and the effect of food on the bioavailability of trazodone were assessed on the basis of the confidence intervals for the variables C_{max}, AUC(0-t_{last}), AUC(0-∞) and AUC(0-24) relative to the conventional acceptance range of 80% to 125%. In addition, a non-parametric Wilcoxon signed rank test was performed on the variable T_{max} and the calculated p-value is reported. The comparisons of interest are as follows: • Treatment B (test) vs Treatment A (reference) • Treatment C (test) vs Treatment A (reference) • Treatment B (test) vs Treatment C (reference)
SAFETY:	All hematological, clinical chemistry and vital signs results are listed per subject for each assessment and descriptive statistics are tabulated. The number of subjects with laboratory investigations outside the reference ranges is reported, as well as individual data for all variables. Adverse events, concomitant medication, physical examination, urinalysis, 12-lead ECG and pregnancy tests are listed on an individual basis and adverse events are also summarized per system organ class. Other clinical evaluation parameters are available as source documents and commented on in the clinical study report.

The 3 treatments were separated by two washout periods of 7 calendar days, except for Subject 29 who had a wash-out period of 14 calendar days between Treatment phases II and III.

Analytical Method: Analyses of trazodone and mCPP in the plasma samples were determined using liquid chromatography with tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation (LLOQ) value as 31.00 ng/mL for Trazodone and 0.935 ng/mL for mCPP.

Data Analysis: The effect of time of day and the effect of food on the bioavailability of the test product were assessed on the basis of the confidence intervals for variables Cmax and AUC relative to the conventional acceptance range of 80% to 125%.

Results

The mean values and ranges of the demographic data of subjects who completed the study as follows. All the subjects who participated were Caucasian.

Summary of Demographic Data of Subjects Who Completed the Study

		Age (years)	Height (cm)	Body Mass (kg)	Body Mass Index (kg/m^2)
All Subjects (n=24)	Mean Range	31.05 18.45 – 55.37	176.8 159 – 200	73.85 55.4 – 103.2	23.60 19.06 – 28.74
Males (n=16)	Mean Range	27.99 18.45 – 53.54	180.3 168 – 200	74.36 58.8 – 103.2	22.78 19.06 – 28.47
Females (n=8)	Mean Range	37.17 20.99 – 55.37	169.8 159 – 180	72.85 55.4 – 86.0	25.23 21.91 – 28.74

The mean plasma concentration time profiles are provided in the following figures.

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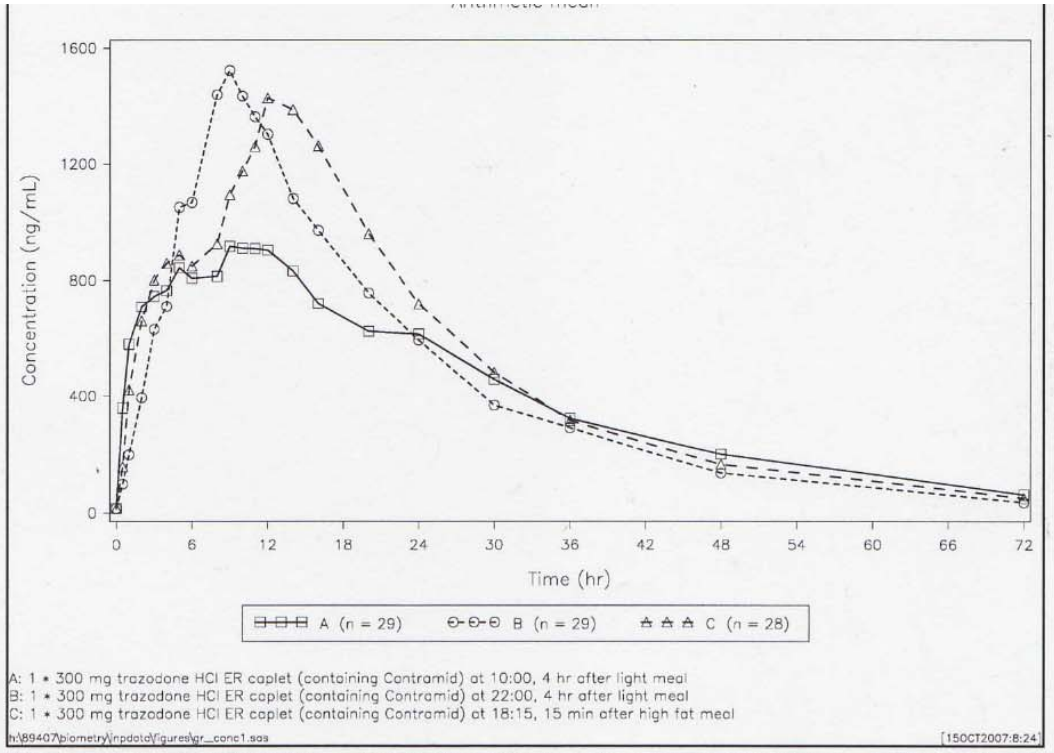

Figure 11-1 Graphical Representation of Trazodone Concentrations – Arithmetic Mean
Data source: Section 14.2, Figure 1

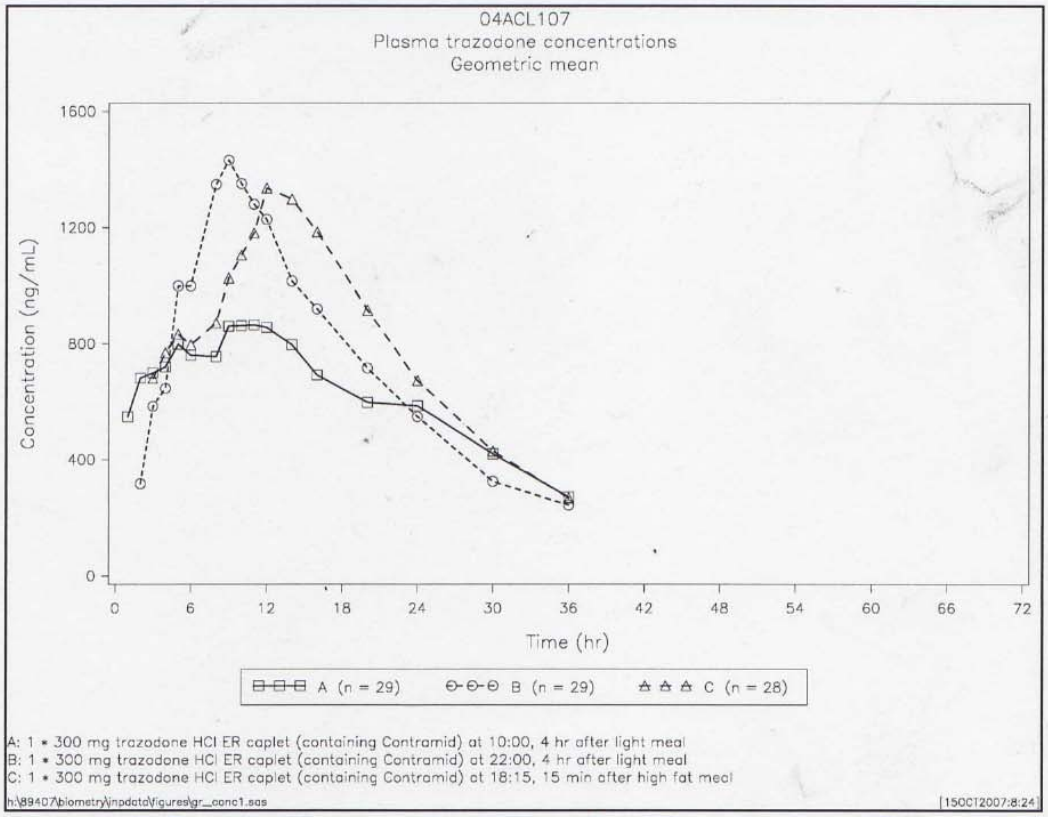

Figure 11-2 Graphical Representation of Trazodone Concentrations – Geometric Mean

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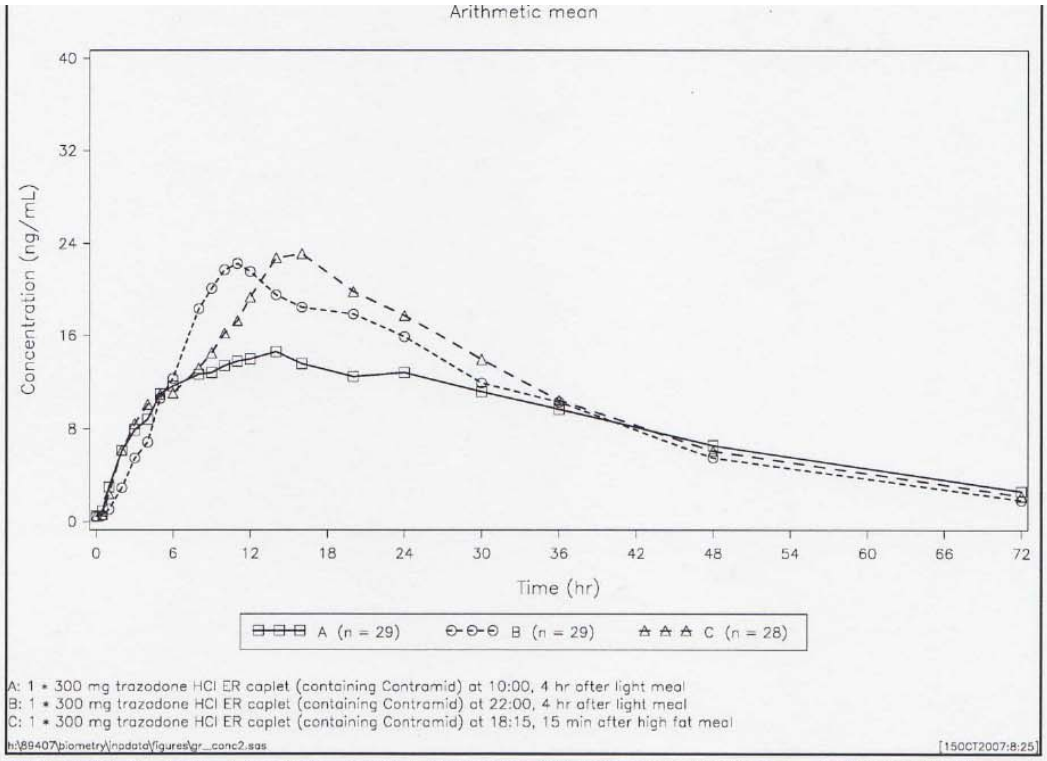

Figure 11-3 Graphical Representation of mCPP Concentrations – Arithmetic Mean
Data source: Section 14.2, Figure 2

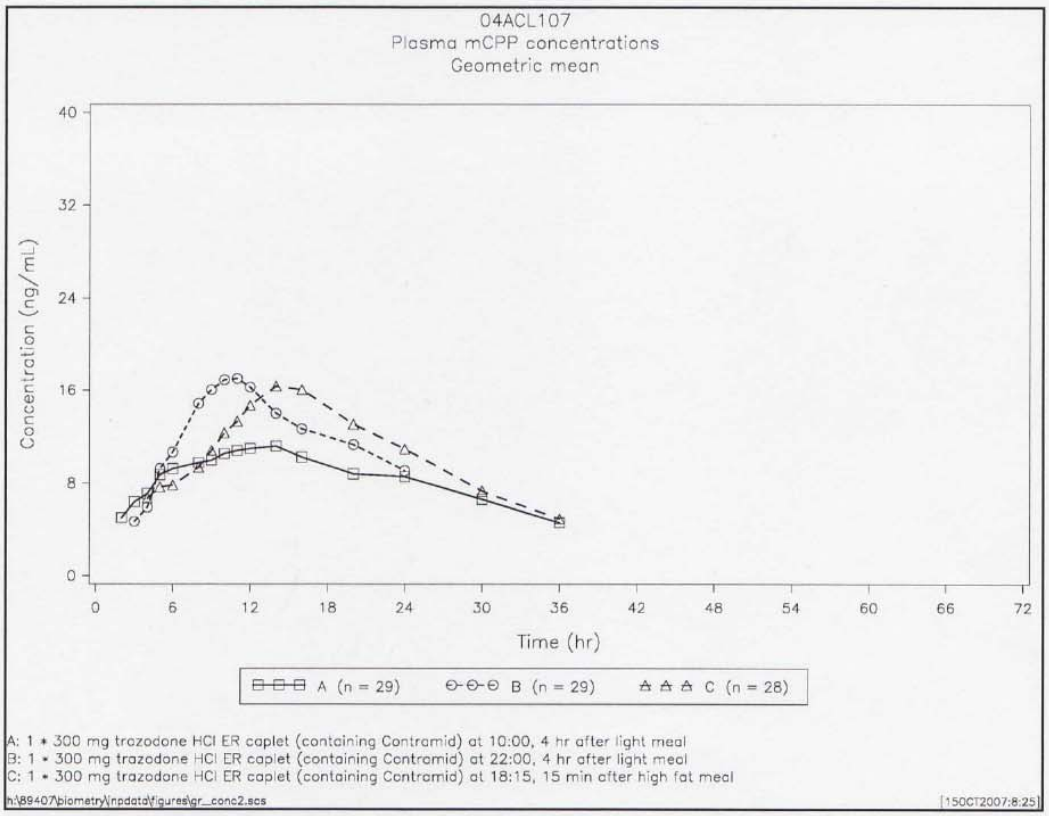

Figure 11-4 Graphical Representation of mCPP Concentrations – Geometric Mean

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The mean pharmacokinetic parameters for the three treatments are provided in the Appendix. The statistical analysis of the pharmacokinetic parameters for trazodone and mCPP for the treatment comparisons are provided in the following tables.

Summary of Statistical Analysis of Pharmacokinetic Parameters for Trazodone and mCPP-Treatment B (Test) vs Treatment A (Reference)

Treatment B vs Treatment A - Trazodone					
Variable *(unit)*	**LSMean**		**Mean Ratio (%)**	**90% Confidence Interval of Ratio (%)**	**Intra-individual CV (%)**
	Treatment B (Test)	**Treatment A (Reference)**			
C_{max} *(ng/mL)*	1544.144	1050.220	147.03	(128.90 ; 167.71)	27.5
AUC(0-t_{last}) *(h·ng /mL)*	29863.59	27859.90	107.19	(97.95 ; 117.30)	18.7
AUC(0-∞) *(h·ng/mL)*	31093.89	29698.78	104.70	(95.73 ; 114.51)	18.6
AUC(0-24) *(h·ng/mL)*	21425.15	17128.52	125.08	(114.46 ; 136.69)	18.4
λ_z *(1/h)*	0.070	0.060	116.48	(107.44 ; 126.29)	16.7
$t_{½,z}$ *(h)*	9.891	11.524	85.83	(79.14 ; 93.08)	16.8
T_{max}♣ *(h)*	9.000	9.000	p-value: 0.7232		
Treatment B vs Treatment A – mCPP					
C_{max} *(ng/mL)*	17.707	11.960	148.05	(131.29 ; 166.95)	25.1
AUC(0-t_{last}) *(h·ng /mL)*	397.475	353.712	112.37	(101.44 ; 124.48)	21.3
AUC(0-∞) *(h·ng/mL)*	443.799	411.770	107.78	(98.43 ; 118.02)	18.8
AUC(0-24) *(h·ng/mL)*	262.852	205.637	127.82	(115.68 ; 141.25)	20.7
λ_z *(1/h)*	0.058	0.052	112.46	(101.82 ; 124.21)	20.6
$t_{½,z}$ *(h)*	11.846	13.333	88.85	(80.44 ; 98.14)	20.6
T_{max}♣ *(h)*	11.000	13.000	p-value: 0.4056		

Treatment A: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 10:00, 4 hours after light meal

Treatment B: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 22:00, 4 hours after light meal

♣Medians and p-value according to Wilcoxon signed rank test.

Summary of Statistical Analysis of Pharmacokinetic Parameter for Trazodone and mCPP-Treatment C (Test) vs Treatment A (Reference)

Treatment C vs Treatment A - Trazodone					
Variable *(unit)*	**LSMean**		**Mean Ratio (%)**	**90% Confidence Interval of Ratio (%)**	**Intra-individual CV (%)**
	Treatment C (Test)	**Treatment A (Reference)**			
C_{max} *(ng/mL)*	1588.738	1050.220	151.28	(132.67 ; 172.50)	27.5
AUC(0-t_{last}) *(h·ng /mL)*	32720.13	27859.90	117.45	(107.35 ; 128.49)	18.7
AUC(0-∞) *(h·ng/mL)*	34464.15	29698.78	116.05	(106.13 ; 126.89)	18.6
AUC(0-24) *(h·ng/mL)*	22811.20	17128.52	133.18	(121.90 ; 145.50)	18.4
λ_z *(1/h)*	0.065	0.060	108.36	(99.97 ; 117.46)	16.7
$t_{½,z}$ *(h)*	10.641	11.524	92.34	(85.16 ; 100.12)	16.8
T_{max}* *(h)*	12.000	9.000	p-value: 0.0463		
Treatment C vs Treatment A – mCPP					
C_{max} *(ng/mL)*	17.138	11.960	143.29	(127.11 ; 161.54)	25.1
AUC(0-t_{last}) *(h·ng /mL)*	419.375	353.712	118.56	(107.06 ; 131.30)	21.3
AUC(0-∞) *(h·ng/mL)*	461.287	411.770	112.03	(102.33 ; 122.64)	18.8
AUC(0-24) *(h·ng/mL)*	260.686	205.637	126.77	(114.75 ; 140.05)	20.7
λ_z *(1/h)*	0.061	0.052	116.77	(105.75 ; 128.94)	20.6
$t_{½,z}$ *(h)*	11.390	13.333	85.43	(77.36 ; 94.33)	20.6
T_{max}* *(h)*	14.000	13.000	p-value: 0.5052		

Treatment A: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 10:00, 4 hours after light meal

Treatment C: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 18:15, 15 minutes after a standardized high-fat, high-calorie meal

*Medians and p-value according to Wilcoxon signed rank test.

Summary of Statistical Analysis of Pharmacokinetic Parameters for Trazodone and mCPP-Treatment B (Test) vs Treatment C (Reference)

Treatment B vs Treatment C - Trazodone					
Variable *(unit)*	**LSMean**		**Mean Ratio (%)**	**90% Confidence Interval of Ratio (%)**	**Intra-individual CV (%)**
	Treatment B (Test)	**Treatment C (Reference)**			
C_{max} *(ng/mL)*	1544.144	1588.738	97.19	(85.24 ; 110.83)	27.5
AUC(0-t_{last}) *(h·ng /mL)*	29863.59	32720.13	91.27	(83.42 ; 99.86)	18.7
AUC(0-∞) *(h·ng/mL)*	31093.89	34464.15	90.22	(82.51 ; 98.65)	18.6
AUC(0-24) *(h·ng/mL)*	21425.15	22811.20	93.92	(85.97 ; 102.61)	18.4
λ_z *(1/h)*	0.070	0.065	107.50	(99.17 ; 116.52)	16.7
$t_{½,z}$ *(h)*	9.891	10.641	92.95	(85.73 ; 100.79)	16.8
T_{max}* *(h)*	9.000	12.000	p-value: 0.0011		
Treatment B vs Treatment C– mCPP					
C_{max} *(ng/mL)*	17.707	17.138	103.32	(91.65 ; 116.47)	25.1
AUC(0-t_{last}) *(h·ng /mL)*	397.475	419.375	94.78	(85.58 ; 104.96)	21.3
AUC(0-∞) *(h·ng/mL)*	443.799	461.287	96.21	(87.88 ; 105.32)	18.8
AUC(0-24) *(h·ng/mL)*	262.852	260.686	100.83	(91.27 ; 111.39)	20.7
λ_z *(1/h)*	0.058	0.061	96.31	(87.22 ; 106.35)	20.6
$t_{½,z}$ *(h)*	11.846	11.390	104.01	(94.19 ; 114.85)	20.6
T_{max}* *(h)*	11.000	14.000	p-value: 0.0057		

Treatment B: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 22:00, 4 hours after light meal

Treatment C: 300 mg trazodone HCl OAD extended-release caplet (containing Contramid®) at 18:15, 15 minutes after a standardized high-fat, high-calorie meal

* Medians and p-value according to Wilcoxon signed rank test.

Summary of Pharmacokinetics

The effect of the time of medication administration and the effect of food on the bioavailability was assessed on the basis of the confidence intervals (CI) for the variables Cmax, AUC (0-tlast), AUC(0-∞) and AUC (0-24) relative to the recommended acceptance range of 80% to 125%.

Comparison of Treatment B vs A

Trazodone

The 90% CI around trazodone Cmax mean ratio of Treatment B/A fall outside the recommended range of 80% to 125%. Cmax of Trazodone was about 47% higher after administration at night (10 p.m.) relative to administration in the morning (10 a.m.). The 90% CI around trazodone AUC(0-tlast) and AUC(0-∞) fell within the recommended range of 80% - 125%. Time of administration did not affect the extent of exposure to trazodone.

mCPP
The 90% CI around mCPP Cmax mean ratio fell outside the recommended range of 80% - 125%. mCPP Cmax increased by about 48%. The 90% CI around mCPP AUC(0-tlast) and AUC(0-∞) fell within the recommended range of 80% - 125%.

Comparison of Treatment C vs A

Trazodone
The 90% CI for the mean ratio of Cmax did not fall within the recommended 80% to 125%. Cmax increased by about 51% when administered 15 mins after a high fat meal in the evening (6 p.m.) relative to administration after 4 hours after a light meal. The 90% CI around the mean ratio for all AUC parameters fell outside the recommended interval of 80% to 125%. AUC∞ increased by 16% after administration after a fat meal in the evening compared to 4 hours after a light meal in the morning (10 a.m.). The increase seen in Cmax and AUC is confounded by time of administration and food.

mCPP
The 90% CI for the mean ratio of Cmax did not fall within the recommended 80% to 125%. Cmax of mCPP increased by about 43% when administered 15 mins after a high fat meal in the evening (6 p.m.) relative to administration after 4 hours after a light meal. The 90% CI around the mean ratio for all AUC∞ and AUC(0-tlast) fell outside the recommended interval of 80% to 125%. AUC∞ increased by 12% after administration after a fat meal in the evening compared to 4 hours after a light meal in the morning (10 a.m.). The increase seen in Cmax and AUC is confounded by time of administration and food.

Comparison of B vs C

Trazodone
The 90% CI for Treatment B/Treatment C mean ratio of pharmacokinetic parameters Cmax, AUC(0-tlast), AUC(0-∞) and AUC (0-24) all fell within the recommended interval of 80% to 125%. There was not significant difference in exposure between administration at 6 p.m and 10 p.m. The results are confounded by the fact that high fat meal was given to subjects taking Treatment C.

mCPP
The 90% CI for Treatment B/Treatment C mean ratio of pharmacokinetic parameters Cmax, AUC(0-tlast), AUC(0-∞) and AUC (0-24) all fell within the recommended interval of 80% to 125%. There was not significant difference in exposure between administration at 6 p.m and 10 p.m. The results are confounded by the fact that high fat meal was given to subjects taking Treatment C.

Safety Summary

The sponsor reported that in general, trazodone was reasonably well tolerated in the study. The sponsor reported that a total of 71 adverse events were reported by 24 (80%) of the 30 subjects. Of these, 8 were assessed as either not related or unlikely related to the study medication, and all others to be at least possibly related to the study medication. Dizziness (47%), headache (37%) and nausea (40%) were the predominant adverse events reported after dosing. The sponsor reported that the incidence events at least possibly related to study medication was similar for Treatments A (47%) and B (43%) and less in Treatment C (30%). The other adverse

events reported were musculoskeletal pain, nasal congestion, dry mouth, somnolence, syncope and vomiting. The sponsor reported that no deaths or serious adverse events were reported. Refer to medical review for Agency's evaluation of Safety.

Reviewer Comments

Administration of Trazodone Contramid at night compared to the morning resulted in about a 47% increase in Cmax of Trazodone and mCPP. The extent of absorption (AUC) does not change with time of administration. The effect of food could not be adequately evaluated in this study because the time of administration and the type of food given.

Appendix

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Listing 32: Plasma trazodone pharmacokinetic variables (summary results)

treat=A

Subject/ statistic	Cmax (ng/mL)	AUC(0-tlast) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	Tmax (hr)	AUC(0-24) (hr*ng/mL)	Lambda-z (1/hr)	$t_{½}$.z (hr)
N	24	24	24	24	24	24	24
Mean	1123.096	29143.128	31289.810	9.292	17747.423	0.068	12.669
SD	392.121	9623.474	12097.563	5.706	4510.550	0.029	6.522
Median	1109.500	27905.510	29496.978	9.000	17455.350	0.065	10.825
Minimum	511.400	16900.375	17367.412	1.000	8964.050	0.022	5.333
Maximum	2065.000	53669.675	71560.494	24.000	29219.000	0.130	31.789
GeomMean	1059.162	27819.100	29551.813	7.674	17194.128	0.061	11.336
GeomSD	386.048	8674.541	10036.879	5.914	4562.967	0.030	5.659

A: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 10:00, 4 hr after light meal
B: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 22:00, 4 hr after light meal
C: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 18:15, 15 min after high fat meal

Listing 32: Plasma trazodone pharmacokinetic variables (summary results)

treat=B

Subject/ statistic	Cmax (ng/mL)	AUC(0-tlast) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	Tmax (hr)	AUC(0-24) (hr*ng/mL)	Lambda-z (1/hr)	$t_{\frac{1}{2}}$.z (hr)
N	24	24	24	24	24	24	24
Mean	1634.104	31188.425	32329.503	8.375	22301.026	0.075	10.279
SD	520.686	9620.789	9760.627	2.464	6366.004	0.027	3.327
Median	1505.500	28644.602	30041.919	9.000	20931.099	0.070	9.944
Minimum	925.900	17511.936	17715.897	4.000	13507.900	0.040	4.543
Maximum	2721.000	50470.190	51035.925	16.000	34902.050	0.153	17.433
GeomMean	1558.991	29799.175	30931.097	8.023	21504.243	0.071	9.757
GeomSD	498.510	9433.263	9671.264	2.530	5944.689	0.025	3.374

A: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 10:00, 4 hr after light meal
B: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 22:00, 4 hr after light meal
C: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 18:15, 15 min after high fat meal

Listing 32: Plasma trazodone pharmacokinetic variables (summary results)

treat=C

Subject/ statistic	Cmax (ng/mL)	AUC(0-tlast) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	Tmax (hr)	AUC(0-24) (hr*ng/mL)	Lambda-z (1/hr)	$t_{\frac{1}{2}}$.z (hr)
N	24	24	24	24	24	24	24
Mean	1695.517	34515.240	36375.035	11.586	23776.936	0.071	11.365
SD	604.965	12494.241	13495.891	3.728	7274.627	0.026	5.098
Median	1607.000	33173.003	34799.237	12.000	23007.427	0.074	9.430
Minimum	778.100	16265.295	16666.269	3.000	12895.275	0.026	5.360
Maximum	3507.000	76789.147	78287.660	20.000	49782.367	0.129	26.932
GeomMean	1603.139	32660.882	34288.662	10.823	22896.995	0.066	10.482
GeomSD	560.684	11251.034	12263.105	4.733	6367.645	0.027	4.338

A: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 10:00, 4 hr after light meal
B: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 22:00, 4 hr after light meal
C: 1 * 300 mg trazodone HCl ER caplet (containing Contramid) at 18:15, 15 min after high fat meal

19.2 MENU

HIGH-FAT AND HIGH-CALORIE RECIPE CONSTITUENTS					
Food	**Amount (g or mL)**	**Energy (cal)**	**Carbohydrate (g)♦**	**Protein (g)**	**Fat (g)**
Margarine - medium fat, more than 50% polyunsaturated fats	16.0	71.9	0.1	0.0	8.1
Banana (raw and peeled)	70.0	63.9	14.3	0.9	0.2
Milk - whole fresh (mL)	200.0	125.2	9.6	6.4	6.8
Ham and tongue loaf	30.0	85.2	0.8	4.2	7.3
Frankfurter sausage - beef and pork	80.0	251.7	2.1	9.0	23.4
Egg chicken (boiled)	50.0	73.6	0.6	6.3	5.2
Cheese - Cheddar	25.0	98.4	0.5	6.2	8.1
Bread/Rolls - wholewheat	70.0	180.9	35.6	5.8	1.5
Total		**954.3**	**63.6**	**38.8**	**60.6**
Energy (cal)			**253.7**	**154.8**	**545.8**
FDA Guidance [13]		**800 - 1000**	**250**	**150**	**500 - 600**
% Energy			**26.7**	**16.3**	**57.4**

♦ Carbohydrate value includes fibre

Data source: FoodFundi 2 Professional - Dietary Management Software for Windows™ (b) (4) (b) (4)

Title (Protocol 04ACl109): A Randomized, two-way crossover comparative bioavailability study of 300 mg Trazodone Hydrochloride Extended Release caplets (containing Contramid®) manufactured at two different sites.

Objectives: To compare the pharmacokinetic profiles of trazodone HCl 300 mg extended release caplets (Contramid), manufactured at Labopharm Inc., Quebec and trazodone HCl 300 mg extended release caplets (Contramid) manufactured at (b) (4) For this purpose the rate and extent of absorption of trazodone and formation of mCPP were compared after administration of a single dose of 300 mg of each of the two formulations under fasting conditions.

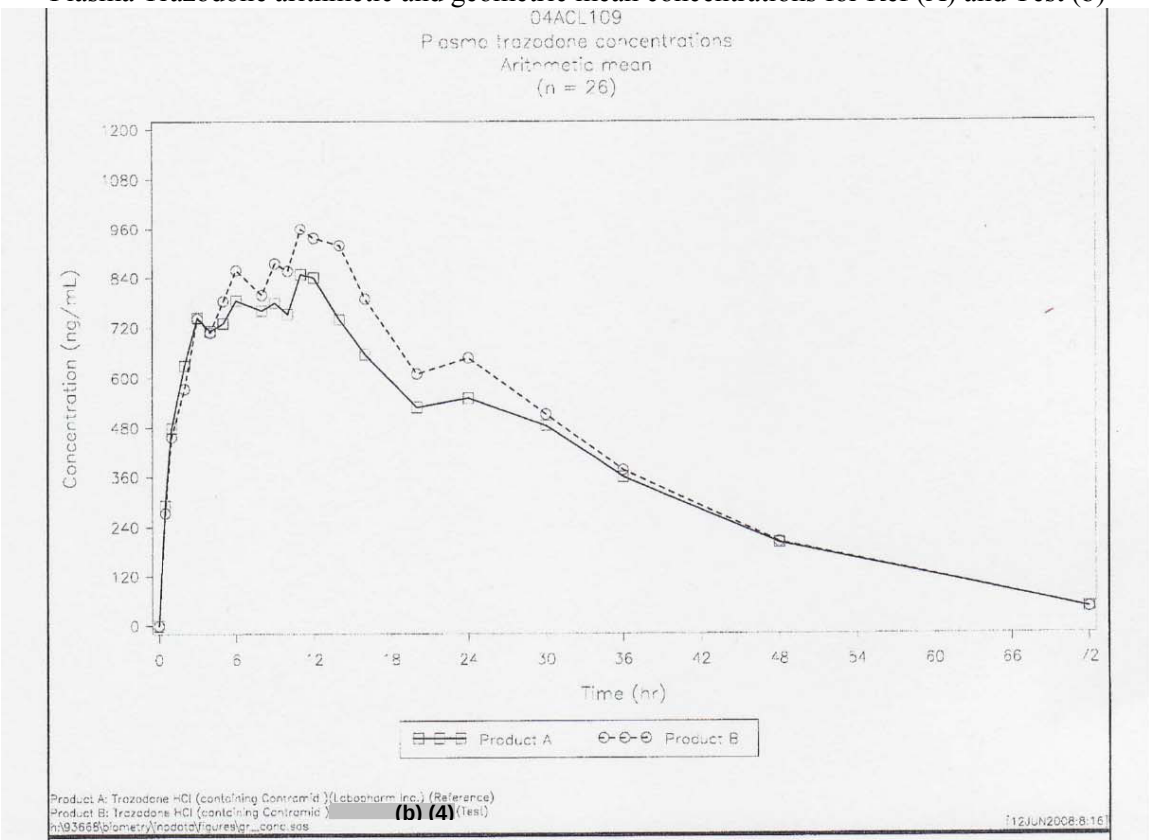
Study Design: The study was an open-label, laboratory-blind, single-dose, randomized, two-period crossover trial under fasting conditions. The study consisted of two treatment phases of 72 hours each which were separated by a wash-out period of 7 to 14 days. Thirty (30) healthy male and female subjects (non-smokers) were entered into the study and assigned to treatment sequence according to the randomization schedule. After an overnight fast of at least 10 hours, the subjects were administered 300 mg Contramid extended release tablet orally of either the test (Contramid. (b) (4) Batch no. 04A19602P7) or reference (Contramid, Labopharm Inc., Batch no. 112524BP1) with 240 mL water according to the randomization schedule. Subjects received each product once. Blood samples were collected for a specified time period for 72 hours.

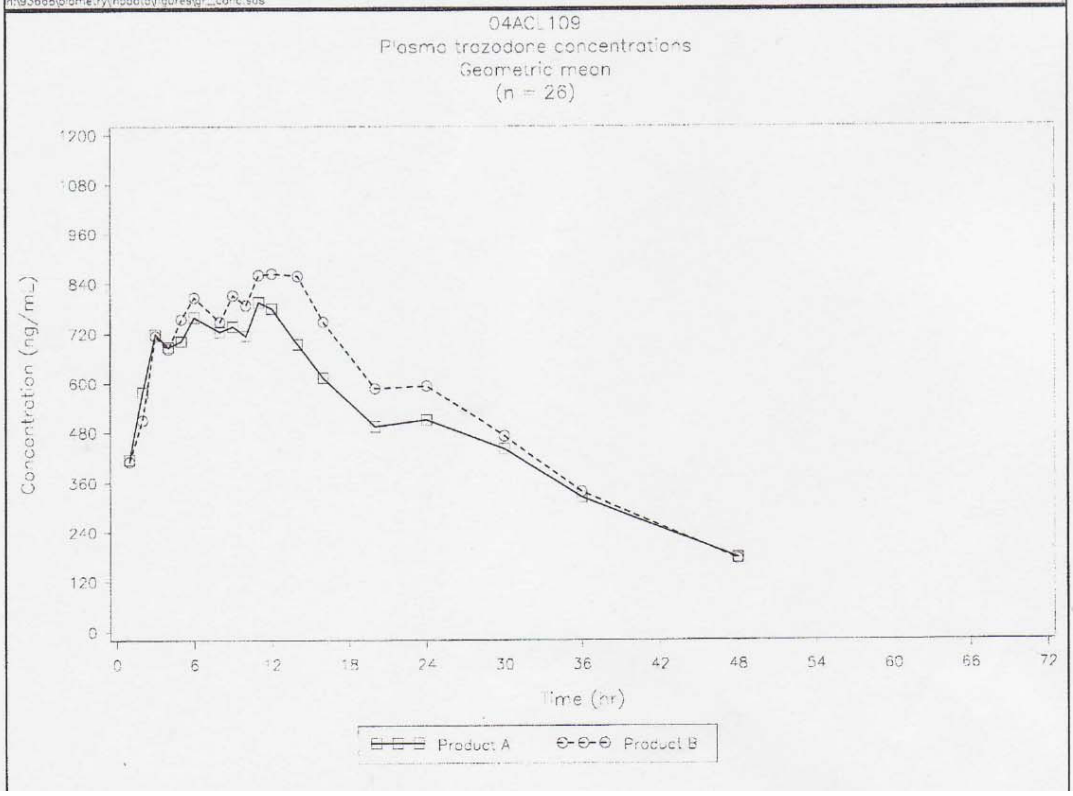
Analytical Method: Trazodone and mCPP concentrations in plasma were determined using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS). Results from the re-instatement validation indicate that intra-run coefficients of variation (imprecision) of each quality control level are ≤ 6.2% and ≤ 3.0% for trazodone and mCPP, respectively. The intra-run accuracy of each quality control level falls between -4.1% and 1.8% for trazodone and between -2.1% and 1.1% for mCPP. The calibration ranges for trazodone and mCPP were 30.98 to 3965 ng/mL and 0.938 to 120 ng/mL, respectively. The lower limits of quantitation (LLOQ) were 30.98 and 0.938 ng/nL, respectively for trazodone and mCPP. The accuracy ranged from 97.4% to 103% for trazodone and from 96.7 to 102% for mCPP. Precision (expressed as %CV) ranged from 1.6 to 5.1% and from 1.3 to 4.8% for trazodone and mCPP, respectively. The analytical method was adequately validated and is acceptable.

Data Analysis: Pharmacokinetic parameters were determined using noncompartmental pharmacokinetic method.

Results: The mean plasma concentration time profile for the test (b) (4) and reference (Labopharm) formulations are provided in the following figures. A combination of individual profiles is also provided in the following figures.

Plasma Trazodone arithmetic and geometric mean concentrations for Ref (A) and Test (b)





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The following table contains the summary of the pharmacokinetic parameters for Trazodone manufactured at (b) (4) (Test) and Trazodone manufactured at Labopharm (Reference).

Summary of Statistics of Plasma Trazodone Pharmacokinetic Parameters (Test: (b) (4)

Subject/ Statistic	Cmax (ng/mL)	AUC(0-t) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	AUC(0-24) (hr*ng/mL)	Tmax (hr)	$t_{1/2}$.z (hr)	Lambda_z (1/hr)
N	26.000	26.000	26.000	26.000	26.000	26.000	26.000
Mean	1241.427	30593.345	32237.777	18067.828	9.038	12.857	0.059
SD	492.612	9506.993	9229.816	5091.840	4.984	4.547	0.017
Median	1179.000	29117.482	30220.168	17542.563	9.500	11.680	0.060
Minimum	668.600	16512.000	18267.961	10703.525	2.000	7.036	0.026
Maximum	2766.000	50773.470	51999.777	28391.550	24.000	26.656	0.099
GeomMean	1161.134	29214.414	31009.961	17378.696	7.670	12.227	0.057
GeomSD	438.965	9294.639	8993.780	5088.285	5.223	3.913	0.018

Summary of Statistics of Plasma Trazodone Pharmacokinetic Parameters (Ref: Labopharm)

Subject/ Statistic	Cmax (ng/mL)	AUC(0-t) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	AUC(0-24) (hr*ng/mL)	Tmax (hr)	$t_{1/2}$.z (hr)	Lambda_z (1/hr)
N	26.000	26.000	26.000	26.000	26.000	26.000	26.000
Mean	990.773	27539.114	29195.951	15822.458	8.271	13.088	0.057
SD	283.889	8076.391	8011.063	4218.647	5.281	3.680	0.015
Median	884.450	24863.405	25634.025	15330.800	8.500	12.311	0.056
Minimum	611.300	13303.090	15162.601	9863.950	1.000	8.132	0.033
Maximum	1579.000	47292.867	48157.250	24018.535	24.000	20.833	0.085
GeomMean	953.929	26429.702	28170.544	15291.722	6.382	12.628	0.055
GeomSD	270.502	7942.816	7846.790	4150.245	6.318	3.470	0.015

The following table contains the statistical analyses with 90% confidence interval.

Statistical Evaluation of Trazodone Pharmacokinetic Parameters

Parameter	Least-Squares Mean		Mean Ratio (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone Contramid (b) (4) (Test)	Trazodone Contramid (Labopharm) (Reference)			
Cmax (ng/mL)	1167.762	960.627	121.56	105.53 – 140.03	30.4
AUC (0-t) (ng*h/mL)	29311.87	26608.29	110.39	102.43 – 118.96	15.8
AUC(0-∞) (ng*h/mL)	31136.57	28323.01	109.93	102.53 – 117.88	14.7
AUC (0-24) (ng*h/mL)	17458.46	15372.56	113.57	104.60 – 123.31	17.4
#Tmax (h)	9.500	8.500			

Median

Following single dose administration of test and reference products, the plasma concentrations declined in multiphasic manner with terminal half-lives of about 13 hours. Statistical evaluation of AUC indicated that the 90% confidence interval (CI) indicated that 90% CI around the point estimate (test/reference) for AUC fell within the regulatory criteria of 80 to 125%. However, the 90% CI for Cmax fell outside the regulatory criteria of 80 to 125% to declare bioequivalence. Therefore, Trazodone contramid manufactured at (b) (4) is not bioequivalent to Trazodone Contramid manufactured at Labopharm. The sponsor performed a non-parametric Wilcoxon signed rank test on Tmax. The p-value calculated was p= 0.5727.

The sponsor indicated that two subjects (12 and 13) had unusual spikes in trazodone concentration between 6 and 20 hours that was not consistent with the other subjects. Therefore, 90% interval was recalculated leaving out these two subjects. The following contains the statistical calculation without subjects 12 and 13.

Statistical Evaluation of Trazodone Pharmacokinetic Parameters Excluding Subjects 12 and 13

Parameter	Least-Squares Mean		Mean Ratio (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone Contramid (b) (4) (Test)	Trazodone Contramid (Labopharm) (Reference)			
Cmax (ng/mL)	1097.963	984.512	111.52	100.42 – 123.85	21.3
AUC (0-t) (ng*h/mL)	29199.27	26959.43	108.31	100.36 – 116.88	15.4
AUC(0-∞) (ng*h/mL)	31052.63	28669.95	108.31	100.95 – 116.21	14.2
AUC (0-24) (ng*h/mL)	16993.68	15667.20	108.47	100.73 – 115.65	12.9

Removing subjects 12 and 13 resulted in the 90% confidence interval around the point estimate for Cmax falls within the regulatory criteria for bioequivalence.

Plasma mCPP

The mean plasma concentration time profile is for the metabolite, mCPP, is provided in the following figure. The mean pharmacokinetic parameters for mCPP and statistical evaluation are provided in the following tables. Composite of individual plasma concentration time profile and individual pharmacokinetic parameters are provided in the Appendix.

Statistical Evaluation of mCPP Pharmacokinetic Parameters

Parameter	Least-Squares Mean		Mean Ratio (%)	90% CI (%)	Intra-individual CV (%)
	Trazodone Contramid (b) (4) (Test)	Trazodone Contramid (Labopharm) (Reference)			
Cmax (ng/mL)	13.317	11.835	112.53	97.16 – 130.33	30.4
AUC (0-t) (ng*h/mL)	403.576	360.816	111.85	103.38 – 121.02	15.8
AUC(0-∞) (ng*h/mL)	465.334	418.544	111.18	102.86 – 120.17	14.7
AUC (0-24) (ng*h/mL)	224.068	197.20	113.50	102.34 – 125.87	17.4
#Tmax (h)	14.000	11.50			

Median

Following single-dose administration, plasma concentrations of mCPP declined in multiphasic manner with terminal half-lives of about 15 hours. The 90% confidence interval around the point estimate for AUC fell within the regulatory criteria for bioequivalence. But the 90% confidence interval around the point estimate for Cmax was outside the regulatory criteria of 80% to 125%. The sponsor performed a non-parametric Wilcoxon signed rank test on Tmax. The p-value calculated was reported as p= 0.0.427.

Summary of Bioequivalence evaluation

Bioequivalence of test product (manufactured at (b) (4) and reference product (manufactured at Labopharm) was not demonstrated. Following administration of caplets manufactured at the two sites, bioequivalence criteria was met for AUC for both trazodone and mCPP. However, a bioequivalence criterion was not met for Cmax for both trazodone and mCPP. The 90% confidence interval around the mean ratio for Cmax for trazodone was 105% - 140%, which exceeds the regulatory limit of 80% to 125%. The 90% confidence interval around the mean ratio for mCPP Cmax also exceeded the regulatory limit.

The sponsor stated that trazodone Cmax values observed following administration of caplets manufactured at (b) (4) are within the range of Cmax values reported for 300 mg caplets manufactured at Labopharm and evaluated under fasting conditions in seven pharmacokinetic studies. The following figure illustrates the distribution of Cmax values in the seven studies that used batches manufactured at Labopharm and that at (b) (4). The sponsor states that the atypical profiles were seen in subjects 12 and 13. The sponsor stated that in past studies, these atypical profiles are generally distributed equally across treatments. But in this study atypical profiles were mainly seen in subjects dosed with caplets manufactured at (b) (4) labs. Therefore, the sponsor states that the differences in Cmax values observed in the current study appear to be due to factors other than site of manufacture (e.g. intrasubject variability).

Individual Cmax values of Trazodone Contramid OAD 300 mg caplets, fasting conditions are provided in the following figure.

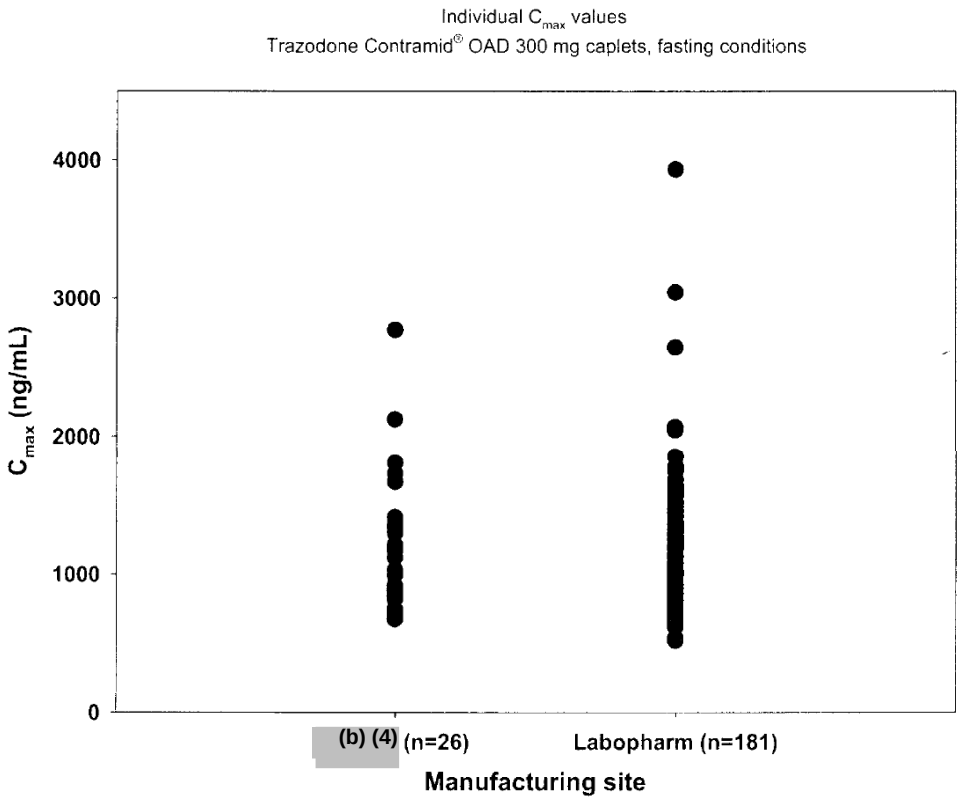


Figure 11-9 Plasma Trazodone C_{max} Values Across Studies Following Single-dose Administration of Trazodone Contramid® OAD 300 mg Caplets Under Fasting Conditions

Data source: Study reports 04ACL101, 04ACL102, 04ACL103, 04ACL104, 04ACL105, 04ACL107, 04ACL109

Summary of Safety

The sponsor reported that trazodone was generally well tolerated by healthy volunteers. No deaths or serious adverse events were reported in the study. The most frequent adverse events reported were headache, dizziness and nausea. The sponsor reported that there were no clinically significant change in vital signs, physical findings or safety laboratory values after administration of a total dose of 300 mg of trazodone per treatment phase.

Reviewer Comments
Trazodone Contramid manufacture at the commercial site (b) (4) *is not bioequivalent to the clinical trial batches manufactured at Labopharm. The sponsor contends that the differences in Cmax was due to subjects having a typical profile. It must be noted that this study was a cross over, and such atypical profile was seen only after administration of the caplets manufactured at* (b) (4)*. Also it must be noted that higher Cmax has been noticed in caplets manufactured at Labopharm. Therefore this reviewer does not agree that the differences in Cmax is due to the atypical profiles observed for the two subjects and the results for the two subjects should not be excluded*

OCP simulated by the method of superposition, multiple dose concentrations and estimated the concentrations. The following table contains the statistical analysis of pharmacokinetic parameters at steady state and the 90% confidence intervals. Trazodone Contramid manufactured at Labopharm is not equivalent to that manufactured at (b) (4) *under steady state conditions. Trazodone Cmax is 15% higher when Trazodone Contramid was manufactured at* (b) (4) *compared to that manufactured at Labopharm. However, AUC of trazodone was similar when products from* (b) (4) *site is compared to that from Labopharm.*

Statistical Analysis of Trazodone Pharmacokinetic Parameters at Steady State (All Subjects)

Parameter	Point Estimate	90% CI
Cmax	1.15	105 - 126
AUC(0-24)	1.13	104 -123

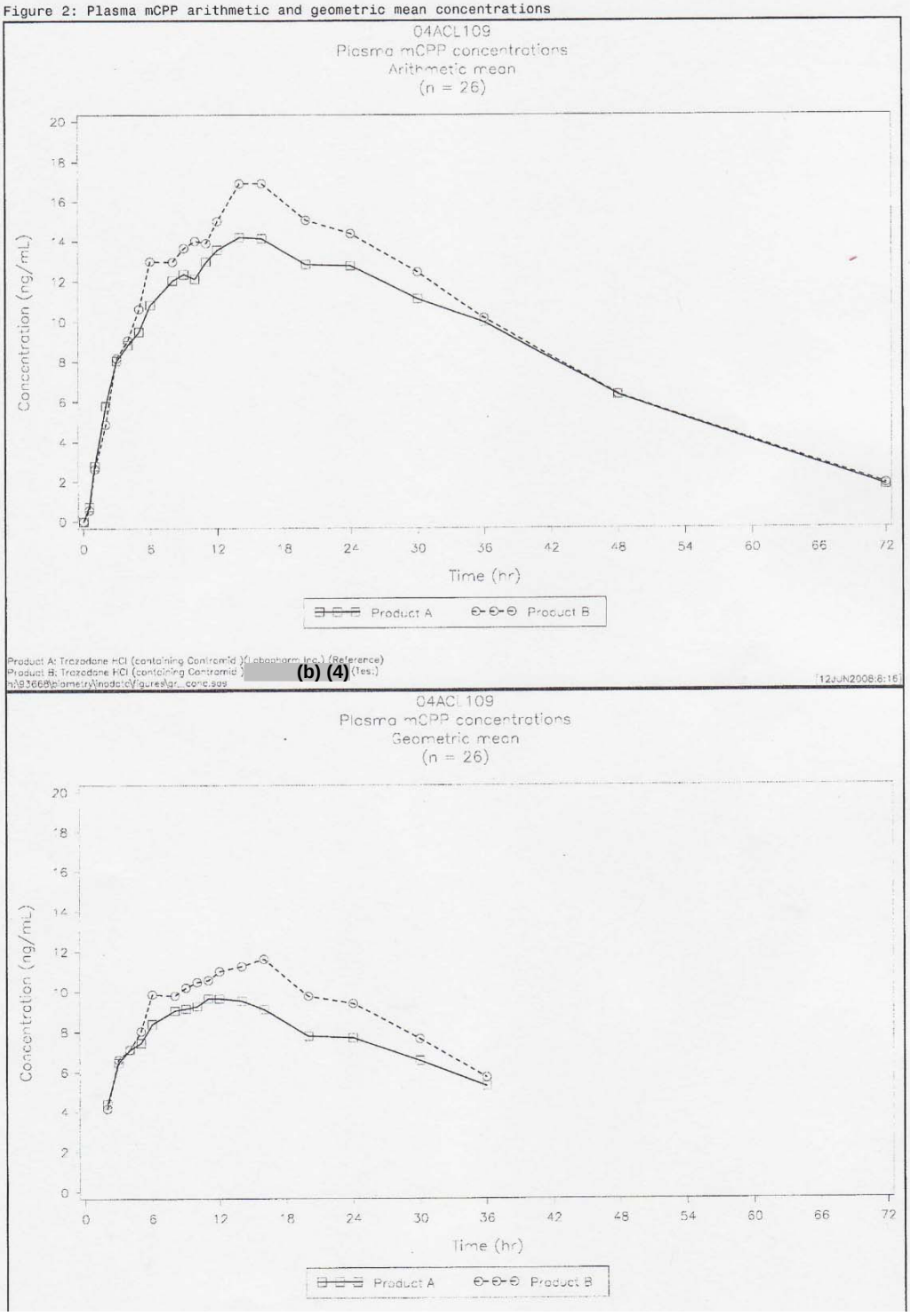
Statistical Analysis of Trazdone Pharmacokinetic Parameters at Steady State (Excluding Subjects 12 and 13)

Parameter	Point Estimate	90% CI
Cmax	1.10	101 - 120
AUC(0-24)	1.12	102 - 122

Across studies comparison of Cmax indicated that Cmax after administration of batches made at labopharm for this study was lower than that seen in other studies using batches made at Labopharm. The Cmax obtained using batches from (b) (4) *was similar to that seen in other studies using batches made at Labopharm (See table in Appendix). The sponsor intends to manufacture commercial batches only from the* (b) (4) *site. From a Clinical Pharmacology perspective, the difference in Cmax when Trazodone Contramid is manufactured at the* (b) (4) *(commercial site) compared to that Labopharm (Clinical Trial Material site) would not be clinically relevant.*

Appendix.

Figure 2: Plasma mCPP arithmetic and geometric mean concentrations



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34: Plasma trazodone pharmacokinetic variables (summary results)

Product=Reference

Subject/ Statistic	Cmax (ng/mL)	AUC(0-t) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	AUC(0-24) (hr*ng/mL)	Tmax (hr)	$t_{\frac{1}{2}}$.z (hr)	Lambda_z (1/hr)
N	26.000	26.000	26.000	26.000	26.000	26.000	26.000
Mean	990.773	27539.114	29195.951	15822.458	8.271	13.088	0.057
SD	283.889	8076.391	8011.063	4218.647	5.281	3.680	0.015
Median	884.450	24863.405	25634.025	15330.800	8.500	12.311	0.056
Minimum	611.300	13303.090	15162.601	9863.950	1.000	8.132	0.033
Maximum	1579.000	47292.867	48157.250	24018.535	24.000	20.833	0.085
GeomMean	953.929	26429.702	28170.544	15291.722	6.382	12.628	0.055
GeomSD	270.502	7942.816	7846.790	4150.245	6.318	3.470	0.015

ce: Trazodone HCl (containing Contramid)(Labopharm Inc.)
razodone HCl (containing Contramid) (b) (4)
t not included in statistical analyses

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ng 34: Plasma trazodone pharmacokinetic variables (summary results)

---------- Product=Test ----------

Subject/ Statistic	Cmax (ng/mL)	AUC(0-t) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	AUC(0-24) (hr*ng/mL)	Tmax (hr)	$t_{½}$.z (hr)	Lambda_z (1/hr)
N	26.000	26.000	26.000	26.000	26.000	26.000	26.000
Mean	1241.427	30593.345	32237.777	18067.828	9.038	12.857	0.059
SD	492.612	9506.993	9229.816	5091.840	4.984	4.547	0.017
Median	1179.000	29117.482	30220.168	17542.563	9.500	11.680	0.060
Minimum	668.600	16512.000	18267.961	10703.525	2.000	7.036	0.026
Maximum	2766.000	50773.470	51999.777	28391.550	24.000	26.656	0.099
GeomMean	1161.134	29214.414	31009.961	17378.696	7.670	12.227	0.057
GeomSD	438.965	9294.639	8993.780	5088.285	5.223	3.913	0.018

ence: Trazodone HCl (containing Contramid)(Labopharm Inc.)
Trazodone HCl (containing Contramid) (b) (4)
ect not included in statistical analyses

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g 36: Plasma mCPP pharmacokinetic variables (summary results)

Product=Reference

Subject/ Statistic	Cmax (ng/mL)	AUC(0-t) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	AUC(0-24) (hr*ng/mL)	Tmax (hr)	t½.z (hr)	Lambda_z (1/hr)
N	26.000	26.000	26.000	26.000	26.000	26.000	26.000
Mean	16.857	608.214	678.136	279.435	13.464	15.336	0.049
SD	16.962	743.597	817.113	284.147	8.311	4.090	0.016
Median	10.455	259.956	310.021	161.733	11.500	15.248	0.046
Minimum	3.690	93.748	126.730	65.518	3.000	7.781	0.032
Maximum	70.800	2954.891	3401.071	1183.874	36.000	21.979	0.089
GeomMean	11.763	358.888	416.051	196.238	11.375	14.762	0.047
GeomSD	11.554	453.582	487.002	186.726	7.439	4.387	0.014

nce: Trazodone HCl (containing Contramid)(Labopharm Inc.)

Trazodone HCl (containing Contramid) (b) (4)

ct not included in statistical analyses

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ıg 36: Plasma mCPP pharmacokinetic variables (summary results)

Product=Test

Subject/ Statistic	Cmax (ng/mL)	AUC(0-t) (hr*ng/mL)	AUC(0-inf) (hr*ng/mL)	AUC(0-24) (hr*ng/mL)	Tmax (hr)	$t_{\frac{1}{2}}$.z (hr)	Lambda_z (1/hr)
N	26.000	26.000	26.000	26.000	26.000	26.000	26.000
Mean	19.264	666.474	743.752	315.649	14.269	15.565	0.049
SD	19.941	775.970	870.221	306.644	6.570	5.236	0.016
Median	11.450	315.445	339.916	179.494	14.000	14.707	0.047
Minimum	3.850	111.685	155.956	75.115	5.000	8.699	0.023
Maximum	84.700	2827.328	3473.509	1141.015	30.000	29.800	0.080
GeomMean	13.300	403.475	464.153	223.728	12.801	14.782	0.047
GeomSD	13.152	496.485	529.862	210.745	6.729	4.945	0.016

ence: Trazodone HCl (containing Contramid)(Labopharm Inc.)
Trazodone HCl (containing Contramid) (b) (4)
ect not included in statistical analyses

Across Study Comparison of Pharmacokinetic Parameters for Pivotal Studies

Study No.	Treatment	Cmax (ng/mL)	AUC (ng*h/mL)
104 (Food)	Fed	2113	31259
	Fasting	1137	26471
105 (DP, 300 mg)	Fasting	1179	16388
107 (Chrono)	A (10am 4h after LM)	1050	29698
	B (10pm 4h after LM)	1544	31094
10 (SD BE)	IR	2948	35259
	Contramid OAD	1231	29672
108 (SS BE)	IR	3023	32159
	Contramid OAD	1709	27568
109 (Site Chage)	(b) (4) (Comm)	1167	31136
	Labopharm (CTM)	960	29672

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/s/

Kofi Kumi
5/22/2009 02:58:55 PM
BIOPHARMACEUTICS

Raman Baweja
5/22/2009 03:45:01 PM
BIOPHARMACEUTICS

Mehul Mehta
5/22/2009 04:07:16 PM
BIOPHARMACEUTICS

ONDQA (Biopharmaceutics) Review

NDA:	22-411
Submission Date:	09/18/08
Product:	OLEPTRO™ (Trazodone Contramid®)
Dosage Form:	Extended-Release Once a Day (OAD) Oral Caplets (150, 300 mg)
Type of Submission:	Original NDA
Sponsor:	Labopharm Inc.
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: The original New Drug Application (NDA 22-441) is for extended-release (ER) once a day (OAD) oral tablets (150 and 300 mg) of trazodone hydrochloride indicated for the treatment of major depressive disorder. If approved, Trazodone Contramid® OAD Caplets will be the first extended-release formulation of trazodone hydrochloride in the US. Desyrel® , the first immediate-release (IR) formulation, was introduced by Mead Johnson Pharmaceuticals in the US in December 1981. The product was subsequently discontinued in September 2006; however, generic products are still available on the US market. Currently, oral dosage forms of trazodone hydrochloride available in the US consist of IR tablets (50, 100, 150 and 300 mg).

The purpose of this review is to recommend dissolution specifications for the proposed product exhibiting appropriate controlled release over the 24 hr period with an *in vitro* dissolution profile closely matching *in vivo* profile.

According to the sponsor, the development of bio-relevant and biopharmaceutically appropriate dissolution test conditions for Trazodone Contramid® Once-a-Day tablets was subject to the following constraints:

- They should be bio-relevant and so include an initial low pH incubation step to mimic the gastric milieu. Media with a pH of 1.2 was chosen to meet this criterion.

- They should be bio-relevant and so include a neutral pH incubation step to mimic upper GI conditions.

- They should allow sink conditions to be met. Since trazodone displays pH dependent solubility, test media were limited to pH 7.5

- They should provide a method with appropriate discriminatory power.

Recommendation: The following recommendation for dissolution specification should be conveyed to the sponsor:

Reviewer's Comments:

- *Use of 50 – 75 rpm in USP Type II apparatus is recommended. The sponsor is required to provide data using the appropriate condition at different speeds (rpms) to justify 150 rpm proposed for the proposed dissolution methodology.*

- *The alcohol interaction study using the USP Apparatus III is not adequate. The study needs to be repeated using appropriate dissolution conditions in the proposed USP Apparatus II.*

- *In the event that the product is approved, the following dissolution specification with the proposed method should be adopted as an* ***interim*** *basis for one year; during this one year period, the sponsor is required to revise the dissolution method addressing the Agency's above mentioned comments and submit that to the Agency for review.*

Strength	**Dissolution Limits at each timepoint (%)**			
	1 hr	**6 hrs**	**12 hrs**	**20 hrs**
150 mg				
300 mg				

(b) (4)

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. . _____

Description and Composition of the Drug Product

Trazodone Contramid® OAD Caplets are an extended release dosage form, consisting of a (b) (4) Contramid®:Trazodone. Contramid® OAD Caplets is intended to be commercialized in two different strengths: 150 mg and 300 mg.

- Trazodone Contramid® OAD 150 mg Caplets are scored on both sides and coated with a non-functional yellowish-beige coating. The bisectable coated caplets are printed with a logo on one side.

- Trazodone Contramid® OAD 300 mg Caplets are scored on both sides and coated with a non-functional beige-orange coating. The bisectable coated caplets are printed with a logo on one side.

The following Tables provide the composition of the 150 mg and 300 mg Trazodone Contramid® OAD Caplets respectively.

Composition of 150 mg Caplets

Component and Quality Standard	Function	Composition (mg)	% Composition
(b) (4)			
Active substance			
Trazodone hydrochloride, USP	Active substance	150.00	(b) (4)
Excipients			
Contramid®[1] (b) (4)	(b) (4)	(b) (4)	
Hypromellose (b) (4) (b) (4) USP			
Colloidal Silicon Dioxide, NF			
Sodium Stearyl Fumarate, NF			
(b) (4)			
(b) (4) Yellow (b) (4)			
			(b) (4)
(b) (4)			
(b) (4) Black Ink (b) (4)	(b) (4)		-
Caplet Total		(b) (4)	*100.00%*

[1] Contramid® is a (b) (4) modified starch (NF).
(b) (4)

Composition of 150 mg Caplets

Component and Quality Standard	Function	Composition (mg)	% Composition
(b) (4)			
Active substance			
Trazodone hydrochloride, USP	Active substance	300.00	(b) (4)
Excipients			
Contramid®[1] (b) (4)	(b) (4)	(b) (4)	
Hypromellose (b) (4) (b) (4) USP			
Colloidal Silicon Dioxide, NF			
Sodium Stearyl Fumarate, NF			
(b) (4) (b) (4)			
(b) (4)			
(b) (4) Black Ink (b) (4)			
Caplet Total		(b) (4)	*100.00%*

[1] Contramid® is a (b) (4) modified starch (NF). (b) (4)

Development of Dissolution Method:

Type III USP dissolution apparatus was used for initial development since this tool provided a convenient method to achieve the multi-media test conditions envisioned above. A number of test conditions were evaluated and three (including the conditions prescribed by (b) (4) using Type I apparatus) are shown in Figure 3.

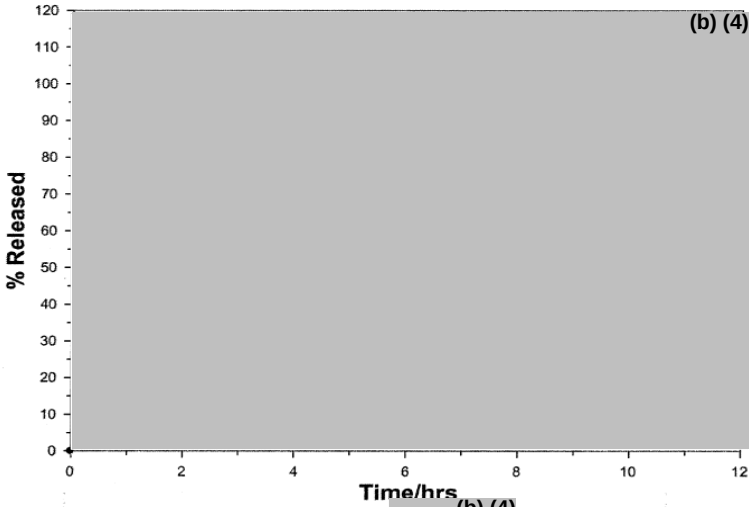


Figure 3: Dissolution profiles generated by (b) (4) tablets (n=6) under various *in vitro* test conditions. Low pH incubations were performed for 1hr; pH 6.0 incubation was performed for 11hr (12hr for (b) (4) conditions); pH 6.8 incubation was performed for 4hr; pH 7.5 incubation was performed for 7hr. All experiments were performed at 37°C with agitation rates of 15 dpm.

From these experiments it appears that using conditions of 1 hr in pH 1.2 and 11 hr in pH 6.0 is the best *in-vitro* dissolution conditions. Here both low pH (to mimic gastric conditions) and neutral pH (to mimic duodenal conditions) are utilized but trazodone is kept below its pKa of approximately 6.7; sink conditions are therefore assured. These conditions were then extrapolated, extending the pH 6.0 incubation to 23hr, and used for development of a 24hr controlled release formulation. Development was performed by iterative testing of a series of prototypes of various composition with the intention of identifying that which displayed an *in vitro* release rate as close as possible to the *in vitro* 24hr target (Figure 4).

The target *in vitro* profile used for development of a 24 hr formulation is shown in Figure 4 while the *in vivo* profile generated by Loo-Riegelman convolution of this profile is shown in Figure 5. It is evident that the model predicts a formulation with an *in vitro* trazodone release rate (under the conditions described in Table 1) matching the profile shown in Figure 4 will generate a plasma profile of the shape shown in Figure 5.

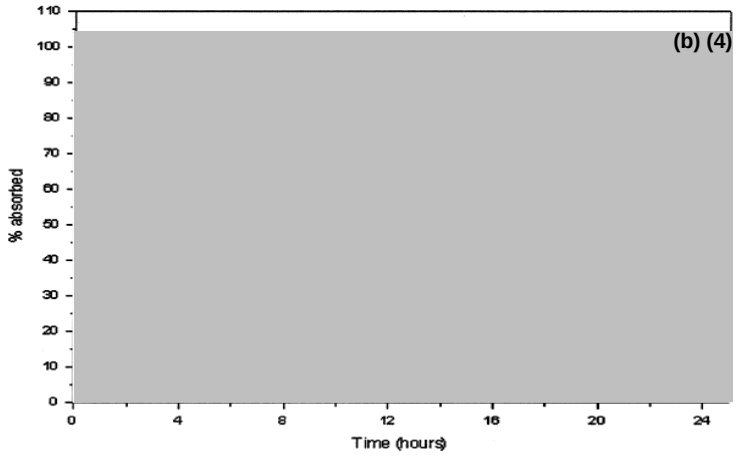


Figure 4: *In vitro* target dissolution (absorption) profile for iterative formulation development.

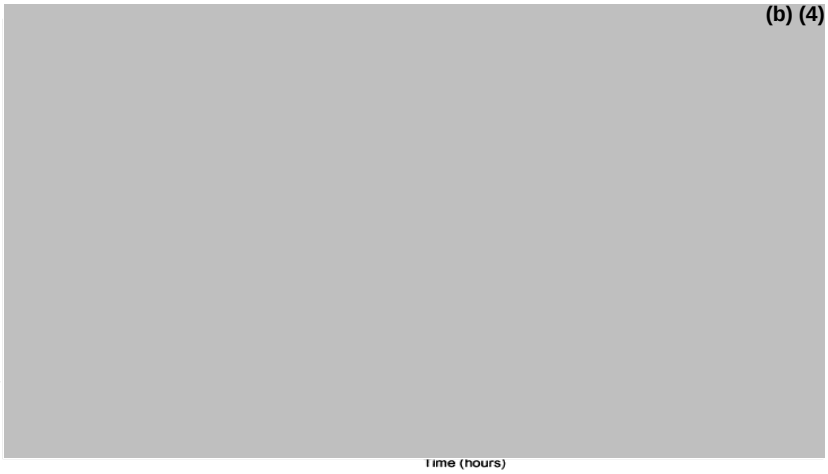


Figure 5: Plasma profile generated by Loo-Riegelman convolution the profile given in Figure 4. Performance of an IR product is also shown. (b) (4)

(b) (4)

Table 1: Best fit *in vitro* dissolution conditions extrapolated to 24hr

Apparatus	Stage 1	Stage 2	Temperature	Agitation
USP Type III apparatus	250 mL pH 1.2 : 1hr	250 mL sodium phosphate buffer 50 mM pH 6.0 : 23hr	37 °C	15 dips/min

Labopharm proceeded to manufacture and dissolution test an iterative series of formulation prototypes until a match with the target profile was reached. This was performed first for the 300 mg prototype and Figure 6 shows the dissolution performance of the selected formulation under conditions described in Table 1.

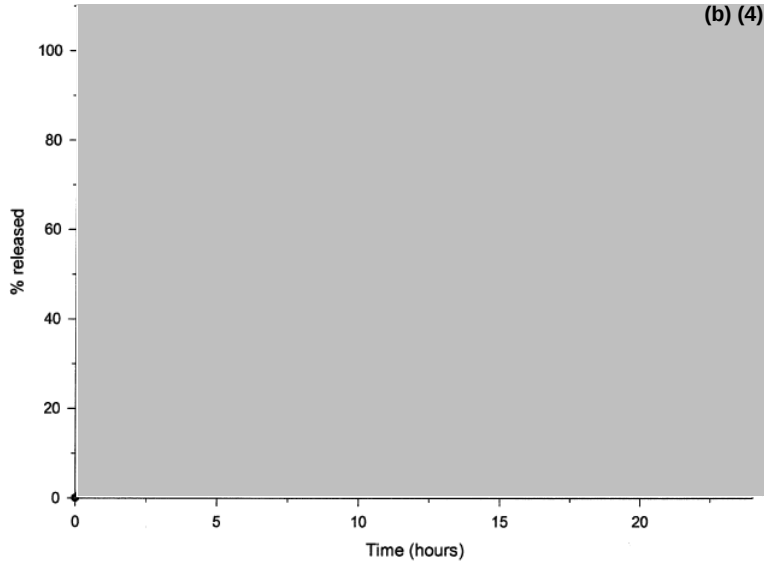


Figure 6: Dissolution profiles of three process reproducibility batches of the Once-a-Day prototype chosen for clinical evaluation; as may be seen performance closed matches the target matrix profile. Conditions as in Table 1.

***In vivo* Assessments.**

A GMP Clinical batch of the chosen prototype was produced and used to assess the pharmacokinetic performance of the formulation in humans. The study (04ACL101) was a randomized crossover design and compared the relative bioavailability of the once-a-day prototype formulation with a marketed immediate release reference product administered every eight hours (Desyrel; Mead-Johnson – 100 mg immediate release tablets). Mean plasma trazodone concentration profiles for the Contramid® once-a-day formulation are given in Figure 7 where they are compared to those obtained with Desyrel.

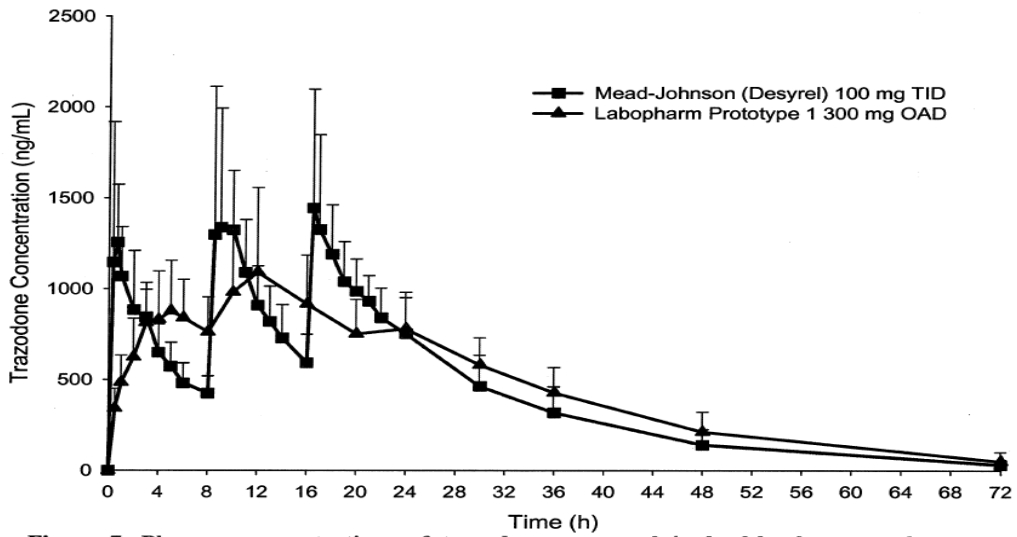


Figure 7. Plasma concentrations of trazodone measured in healthy human volunteers after administration of the once a day (▲) or Desyrel immediate release (■) formulations. Desyrel was administered at 0, 8 and 16hr. Trazodone levels were measured using a HPLC method validated for human samples.

The prototype appears to have exhibited appropriate controlled release over the 24hr period with a profile closely matching that in Figure 4. Thus, time to plateau, C_{max} and T_{max} values were approximately 4hrs, 1000 ng/mL and 12 hrs respectively. Most importantly, the once-a-day formulation was shown to be equivalent to the reference in terms of exposure or area under the curve.

Discriminatory Ability of the Dissolution Method.

The discriminatory ability of the method was demonstrated by its ability to show performance differences between early development formulations of differing composition as described below. These formulations were not chosen for clinical testing since they did not meet target profile dissolution performance.

Effect of Contramid® concentration:

Figure 8 shows results from studies performed prior to selection of the prototype for clinical evaluation, and demonstrates the effect of diluting Contramid®, the key controlled release excipient in the tablet. As may be seen, as the Contramid®

concentration drops, less controlled release is achieved. The method is able to discriminate between these formulations easily.

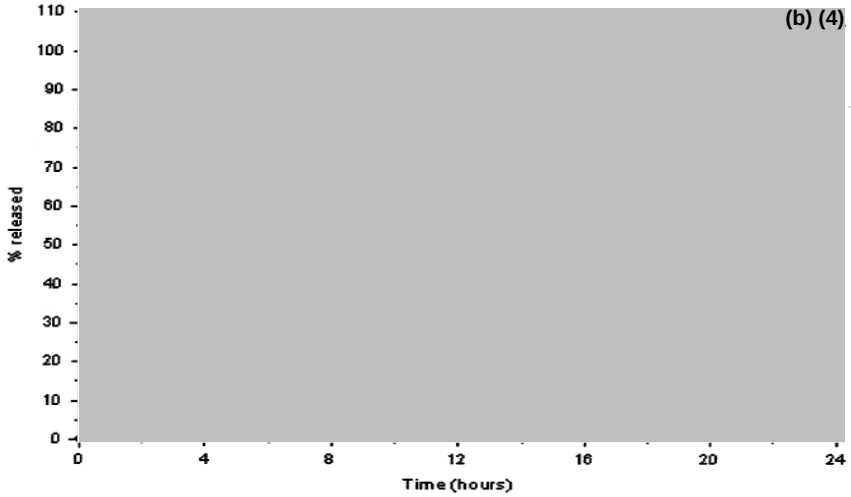


Figure 8: Effect of reducing Contramid® concentration on *in vitro* trazodone release rates. The (b) (4)

Effect of (b) (4) *on release kinetics:*

Labopharm also investigated the effect of (b) (4) as a potential solubility aid for trazodone at pH above its pKa. As may be seen in Figure 9, the dissolution system was able to discriminate between formulations containing between (b) (4) in a concentration dependent manner. (b) (4) was not selected as an excipient for tablets undergoing clinical evaluation.

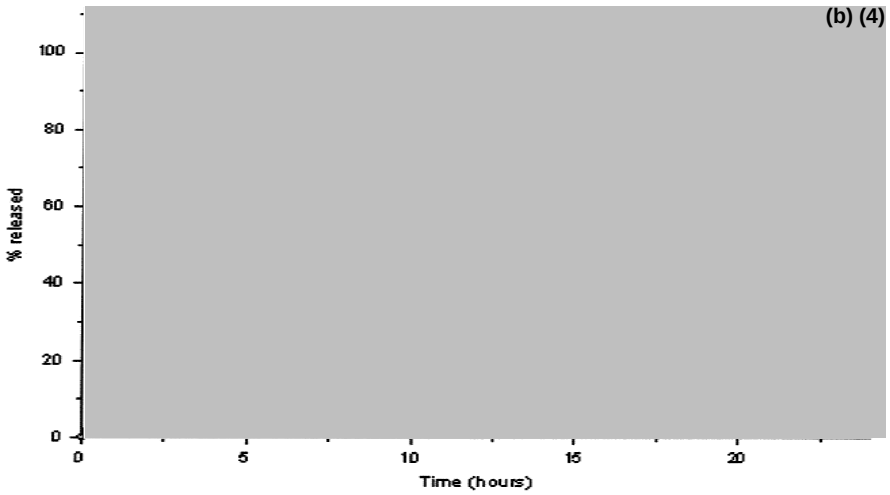


Figure 9: Effect of (b) (4) **concentration on tablet release rates.** (b) (4) (b) (4)

According to the sponsor, these data demonstrate that the dissolution method can appropriately discriminate between batches of different composition used as surrogates for inappropriately manufactured product batches.

Development of Methods for Quality Control Testing: Comparisons between Development and QC Methods

Although Type III UPS dissolution apparatus provided a convenient tool for screening and selection of early formulation prototypes it is less suited to commercial Quality Control laboratory operations. Therefore, prior to initiating pilot phannacokinetic studies, Labopharm developed an easily transferable USP Type II based method more suited to routine product testing. Development of the method was undertaken in two steps;

Identification of a USP Type II method where release rates of Trazodone Once-a-Day tablets met those achieved in Type III.

Labopharm retained the strategies used for screening early prototypes i.e. that media should be bio-relevant and allow sink conditions to be met at all times. To minimize potential differences between the methods Labopharm retained the test media and durations of incubation used for Type III testing viz. pH 1.2 for 1hr and pH 6.0 for 23hr.

However, while the higher fluid velocities achievable with Type II apparatus suggested this system could generate matching profiles without turbulence, studies were required to identify agitation (stirring) rates that generated the highest correlation in tablet performance. A series of studies were therefore performed and a stirring rate of 150 rpm was selected. The following figures 9A and 9B show dissolution profiles obtained for (b) (4) reproducibility batches of the clinical formulation using both methods.

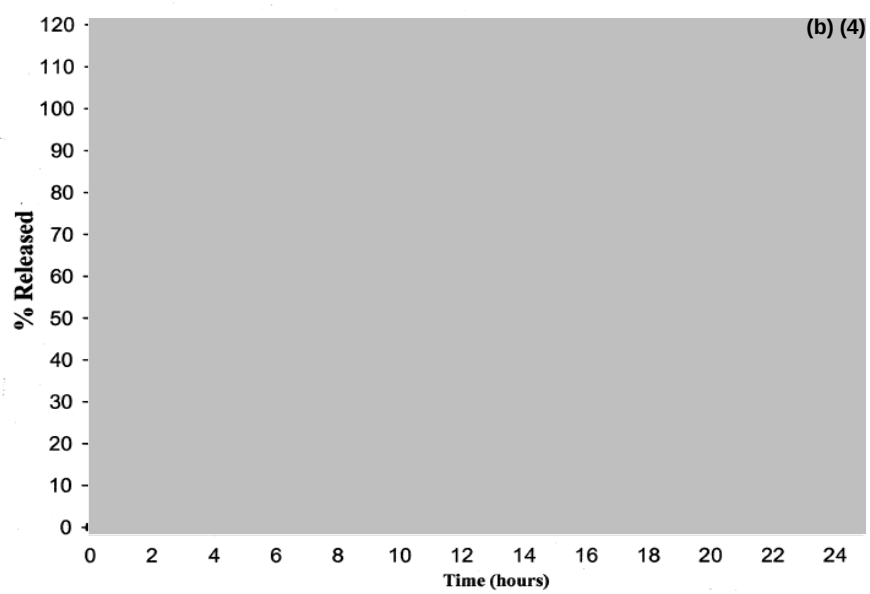


Figure 9A: Comparison of target profile and dissolution profiles of 3 reproducibility batches on USP Type III Apparatus; details given above.

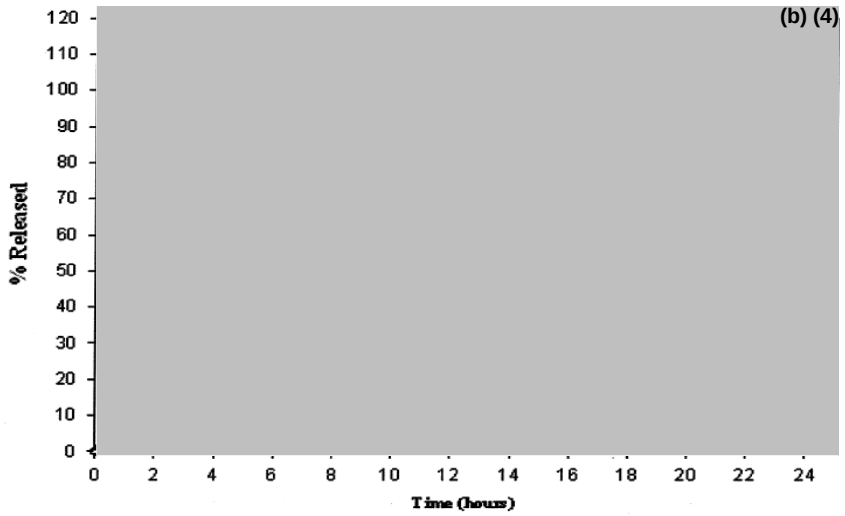


Figure 9B: Dissolution profiles of 3 reproducibility batches on USP type II apparatus; details given above.

In order to justify the USP Type II method where release rates of Trazodone Once-a-Day tablets met those achieved in Type III, the sponsor conducted point by point linear regression analysis with % release data obtained using two different dissolution apparatus. The results are described in the following Figures 10 and 11.

Figure 10. Correlation between USP Type III (pH 1.2/1hr; pH 6.0/23; 15 dpm) and Type II (pH 1.2/1hr; pH 6.0/23; 150rpm) dissolution methods by linear regression analysis. Trazodone 300 mg tablets, lot 04A05302

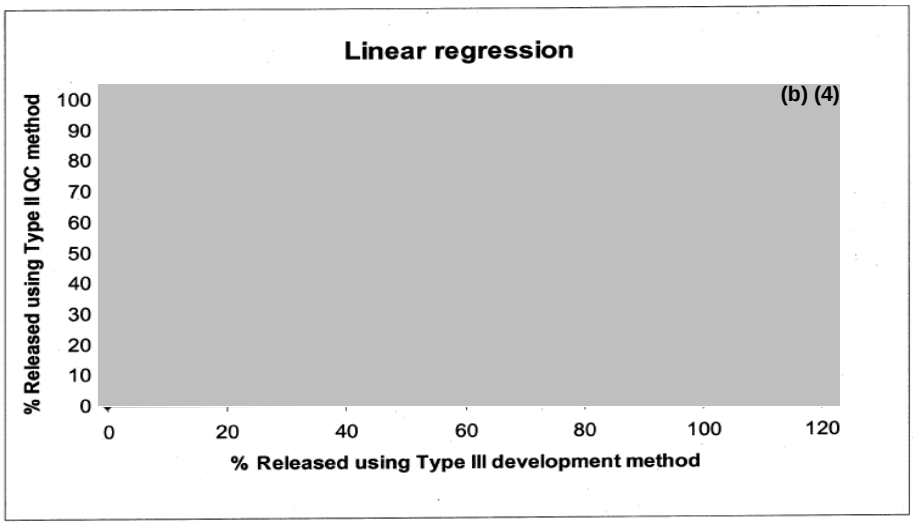


Figure 11. Correlation between USP Type III (pH 1.2/1hr; pH 6.0/23; 15 dpm) and Type II (pH 1.2/1hr; pH 6.0/23; 150rpm) dissolution methods by linear regression analysis Trazodone 150 mg tablets, lot 04A15001

As may be seen from the Figures, both the slope and correlation coefficient were close to 1 for the 300mg and the 150mg strength tablets, validating that tablets perform in the same manner irrespective of dissolution apparatus and therefore the suitability of the Type II method.

Demonstration that the discriminatory power of the method had been retained:

The discriminatory power of the Type II method was assessed by comparing the release profiles of intact and bisected 300 mg tablets. While bisecting the tablets does not result in a change in pharmacokinetic performance (intact and bisected tablets are bioequivalent – see Labopharm Study report 04ACL105 provided in the original submission) the small increase in surface area caused by bisection was expected to result in an increase in *in vitro* release rate and this change should be evident in an appropriately discriminatory dissolution method.

When assessed using Type III apparatus under conditions given in Table 1, bisected tablets, as expected displayed a small but consistent increase in dissolution rate (Figure 12).

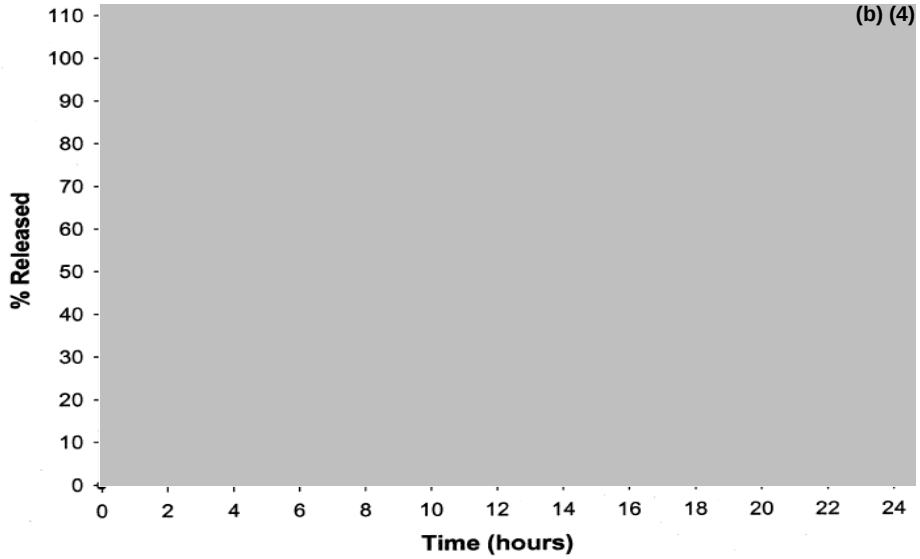


Figure 12: Dissolution profiles of intact and bisected (half tablets) 300mg Trazodone Once-a-Day tablet tested under conditions described in Table 1. (b) (4)

(b) (4)

When intact and bisected 300mg tablets were tested using USP Type II apparatus under the condition described above, the method was also able to detect the change in surface area caused by the bisection (Figure 13); 150mg tablets tested under the same conditions maintained this effect (Figure 14).

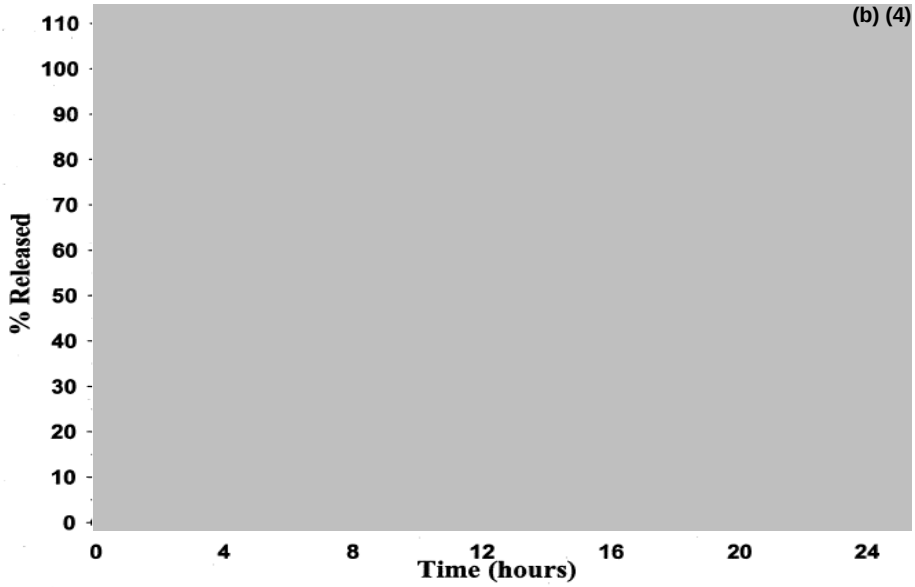


Figure 13. Type II dissolution profiles (Avg±SD) of Trazodone Once-a-Day tablets whole and bisected; lot 04A19602 (pH1.2/1hr+pH6.0/23hrs; 150 rpm). The increase in release rate caused by bisecting the tablets is evident.

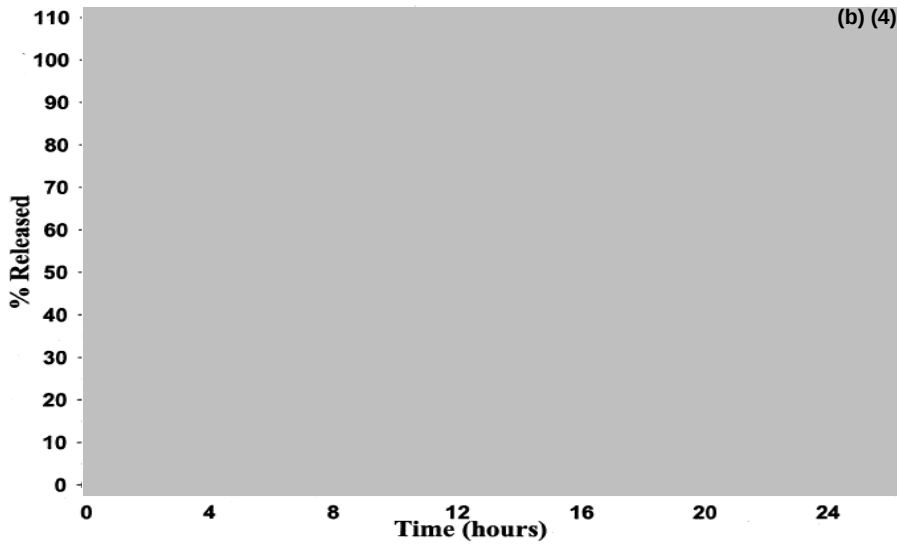


Figure 14. Comparison of type II dissolution profiles (Avg±SD) of Trazodone Once-a-Day tablets whole and bisected; lot 04A19503 (pH1.2/1hr+pH6.0/23hrs; 150 rpm). The increase in release rate caused by bisecting the tablets is evident.

These data partially supported that the Type II method and conditions retained the discriminatory power of the original test and thus that it was appropriate for Quality Control purposes.

Effect of pH

150 mg and 300 mg strengths were subject to the conditions shown in Table 2 in order to demonstrate the sensitivity of the two formulations to changes in pH; dissolution profiles generated under the various conditions were compared using 12 analysis to results obtained under standard conditions. All studies were carried out at 37°C.

Table 2: Similarity factors for 150 mg and 300 mg Trazodone Contramid® OAD caplet dissolution performance under various environmental test conditions

Strength	Apparatus	Agitation Rate	Dissolution Medium	Duration	f_2
150 mg	USP Type II	150rpm	pH 1.2/pH 6.0	1hr/23hr	100
			pH 1.2	24hr	77.2
			pH 4.0	24hr	60.0
			pH 6.0	24hr	63.3
300 mg	USP Type II	150rpm	pH 1.2/pH 6.0	1hr/23hr	100
			pH 1.2	24hr	65.8
			pH 4.0	24hr	56.3
			pH 6.0	24hr	64.1

Despite the pH dependent solubility of trazodone (pKa approximately 6.7 in water) similarity factors in all media were above 50 demonstrating that formulation performance was independent of *in vitro* conditions.

Effect of Alcohol

These studies sought to demonstrate the potential for alcohol, at a concentration of 40% v/v, to influence the release properties of the formulations and, most importantly, whether dose dumping occurs. Figure 15 shows that for the 150 mg caplet there was no effect at all, while Figure 16 shows that for the 300 mg caplet there was a slight increase in release rate but that f2 values were well above 50.

Figure 15: Dissolution of 150mg caplets in USP Type III apparatus at 37°C and a dip rate of 15 dpm. Dissolution media were pH 1.2 + 40% v/v ethanol over 1hr and pH 6.0 + 40% ethanol over 23 hr.

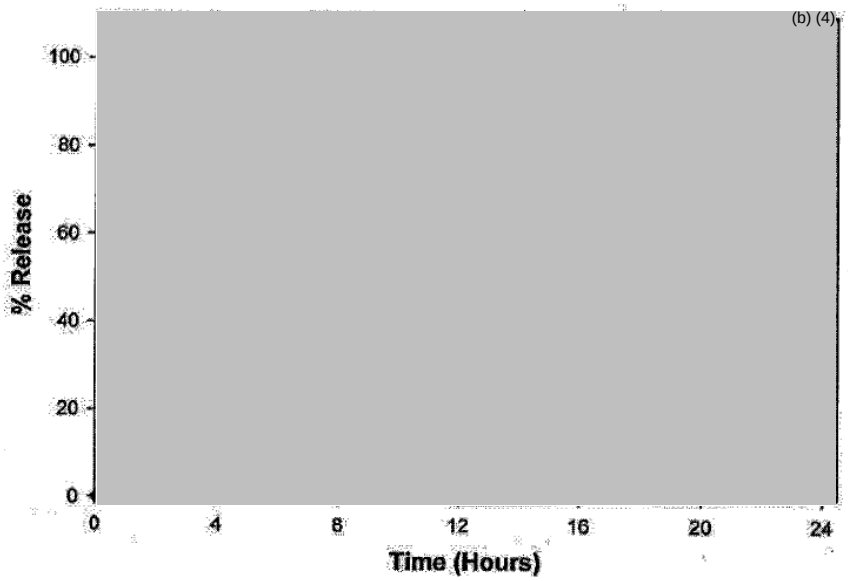
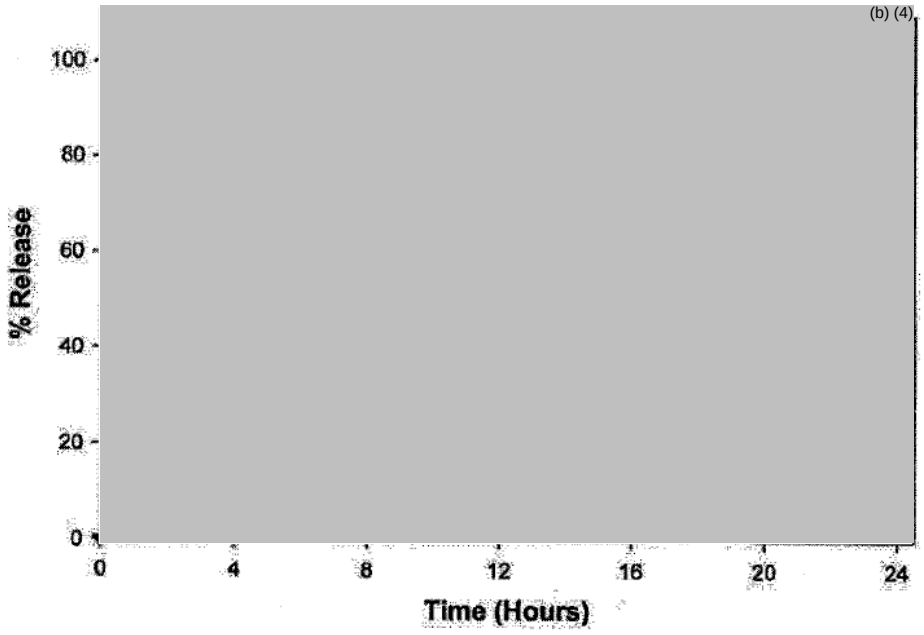


Figure 16: Dissolution of 150mg caplets in USP Type III apparatus at 37°C and a dip rate of 15 dpm. Dissolution media were pH 1.2 + 40% v/v ethanol over 1hr and pH 6.0 + 40% ethanol over 23 hr.



Conclusion

Labopharm developed a bio-relevant dissolution conditions using a 2 stage dissolution media for this drug in USP Type III apparatus where sink condition was maintained throughout the test period. Labopharm then used these dissolution conditions to generate a 24 hr controlled release formulation. Demonstration of the discriminatory ability of the method was attempted by its ability to readily separate formulations of differing composition.

Prior to conducting pilot pharmacokinetic studies, Labopharm transferred the dissolution method to Type II apparatus where highly comparable release rates for the tablets were displayed. The Type II based method was claimed to possess discriminatory power equivalent to the original Type III based system using minimal studies. The sponsor, however, claims that the dissolution condition using USP Type II apparatus is appropriate for Quality Control purposes and conducted dissolution studies, as described below to develop dissolution specification.

Analytical Procedure A034 (Quantification of Trazodone HCl during Trazodone Caplets Dissolution)

The method described herein applies for the dissolution of trazodone HCl finished products using type II apparatus with UV detection.

The method was validated over the range of 5% to 250% of the working concentration of 0.17 mg/mL of trazodone HCl (for the 150mg strength) i.e. equivalent to 2.5% to 125% of the working concentration of 0.33 mg/mL of trazodone HCI (for the 300mg strength) and 10% to 500% of the working concentration of 0.084 mg/mL of trazodone HCI (for the 150mg half-caplet). This method is found to be suitable for its intended purpose with following characteristics:

- Highly specific, free of interference from placebo and dissolution media.

- Linear in the range of 2.5% to 125% of nominal working concentration (0.33 mg/mL of trazodone HCl) for 300 mg caplets, equivalent to 5% to 250% of nominal working concentration (0.17 mg/mL of trazodone HCI) for 150 mg caplets, with a correlation coeffcient (r^2) value better than 0.999. Linearity was determined in both dissolution media (HCl/NaCI at pH 1.2 medium and phosphate buffer at pH 6.0) in the specified range and the linearity data was used to determine the values for the limit of detection (LOD) and quantitation (LOQ) of trazodone HCl.

- Accurate and precise over the selected range with average recoveries of trazodone HCI from reconstituted samples of 98.3% with RSD 1.93% for the 5% spike level, and within 98.2% to 100.0% for the 50% and the 125% spike levels with RSD always below 1.10%.

- Solution stability was tested for the standard and sample solutions kept at room temperature and in the fridge for a period of storage of several days. Stability study shows these solutions to be stable for a period of at least 8 days when kept at room temperature.

Equipment & Parameters

- Analytical balance
- On-line Spectrophotometer UV-Visible (HP-8453)**
- Type II Dissolution apparatus (Varian VK7000 System) **
  Dissolution should be conducted as directed in current USP <711>, applying the following conditions unless otherwise specified.
  - Apparatus: USP Apparatus II
  - Speed: 150 rpm
  - Temperature: 37 ± 0.5 °C
  - Filters: 10 µm Varian full flow filters
  - Sinker Basket: Japanese sinker baskets from Vankel cat.# 12-3070
  - Medium: 1) Acid stage: 900 mL HCl/NaCl pH 1.2 solution, followed by
    2) Buffer stage: 900 mL 50 mM phosphate buffer pH 6.0.
  - Sampling time*: 15 min.; 30 min.; 45 min.; 1h; in acid stage.
    30 min.; 1h; 2h; 2.5h; 3h; 3.5h; 4h; 5h; 6h; 7h; 8h; 9h; 10 h; 11h; 12h; 14h; 15h; 16h; 18h; 19h; 21h; 23h; in "Phosphate buffer pH 6.0".

Note: **These sampling times should be considered when complete dissolution profile is requested, otherwise sampling times indicated in the specification document should be considered.*

***Note**: **Equivalent equipments may be used*

Dissolution Procedure

(b) (4)

[redacted]

SETTING OF TIME POINTS

Dissolution tests are performed over 24hr with 4 individual test points included at 1, 6, 12 and 24 hours.

1 hour timepoint: This ensures the desired effective plasma concentration is achieved within 2hr and that is there is no early dose dumping.

6 hour timepoint: This ensures that the therapeutic concentrations are maintained during the dosing interval and ensures that no mid-phase dose dumping occurs.

12 hour timepoint: This again ensures that the therapeutic concentrations are maintained during the dosing interval and that controlled release is maintained.

24 hour timepoint: this limit ensures that the therapeutic concentrations are maintained during the dosing interval and that at least (b) (4) of the drug is released.

SPECIFICATION

Based on the limited batch history available, Labopharm has set ranges of ± 10% around the average result obtained for the sampling points that are selected to cover the entire dissolution profile. See tables below for batch history and proposed specifications.

Table 3: Dissolution results for Trazodone Contramid® OAD 150 mg caplets

Batch #	Manufacturer	Dissolution results (%)			
		1 hr	6 hrs	12 hrs	24 hrs
04A19502	Labopharm	(b) (4)			
04A19503	Labopharm				
04A19504	Labopharm				
04A19506	Labopharm				
04A19507	Labopharm				
112366	(b) (4)				
112655					
112657					
112737					
112737P					
04A14912	Labopharm				
Average					
Average ± 10%					
Limits on specification					

Table 4: Dissolution results for Trazodone Contramid® OAD 300 mg caplets

Batch #	Manufacturer	Dissolution results (%)			
		1 hr	6 hrs	12 hrs	24 hrs
04A19602	Labopharm	(b) (4)			
04A19603	Labopharm				
04A19604	Labopharm				
04A19605	Labopharm				
112365	(b) (4)				
112524					
112525					
112526					
112526P					
04A17402	Labopharm				
04A08506	Labopharm				
Average					
Average ± 10%					
Limits on specification					

Figure 17: Average Dissolution Profiles of 150 mg and 300 mg caplets from batched mentioned in Tables 3 and 4 above respectively in USP Type II apparatus at 37°C at 150 rpm

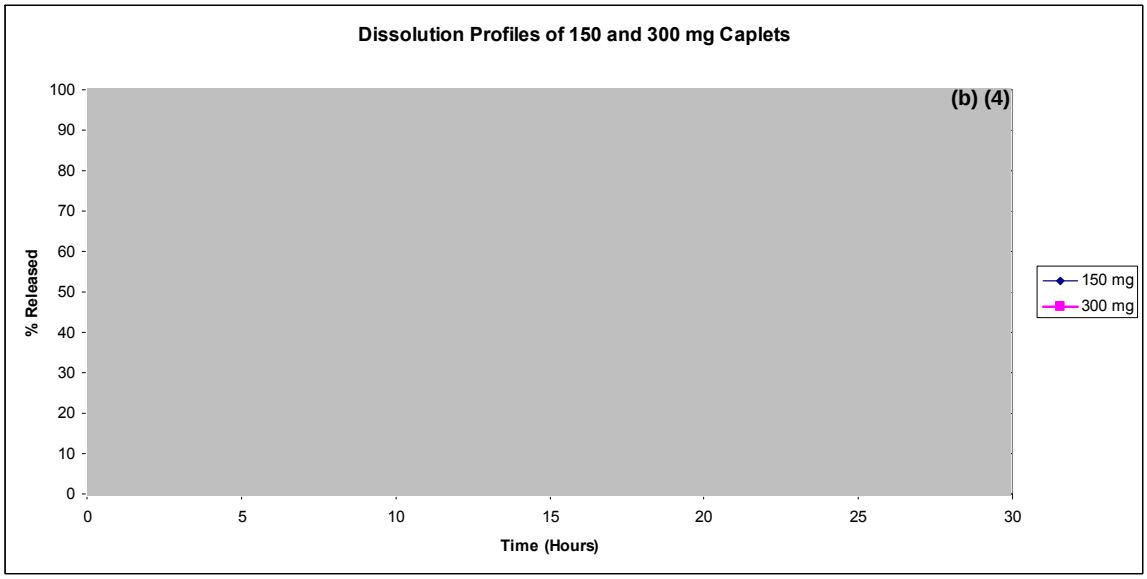


Table 5: Sponsor's Proposed Dissolution Limits for Trazodone Contramid® OAD caplets based on data presented in Tables 3 and 4 above

Strength	Dissolution Limits at each timepoint (%)			
	1 hr	*6 hrs*	*12 hrs*	*24 hrs*
150 mg	(b) (4)			
300 mg				

Reviewer's Comments:

- *Use of 50 – 75 rpm in USP Type II apparatus is recommended. The sponsor is required to provide data using the appropriate condition at different speeds (rpms) to justify 150 rpm proposed for the proposed dissolution methodology.*

- *Alcohol interaction study using the USP Apparatus III is not adequate. The study needs to be repeated using appropriate dissolution conditions in the proposed USP Apparatus II.*

- *In the event that the product is approved, the following dissolution specification with the proposed method should be adopted as an **interim** basis for one year; during this one year period, the sponsor is required to revise the dissolution method addressing the Agency's above mentioned comments and submit that to the Agency for review.*

Strength	**Dissolution Limits at each timepoint (%)**			
	1 hr	**6 hrs**	**12 hrs**	**20 hrs**
150 mg	(b) (4)			
300 mg				

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/s/

Tapash Ghosh
7/9/2009 02:25:07 PM
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