CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-992

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-992
Generic Name:	Desvenlafaxine succinate (DVS)
Trade Name:	Pristiq™
Strength and Dosage Form:	50 mg, 100 mg, 200 mg Extended Release Tablets
Indication:	Treatment of Major Depressive Disorder
Sponsor:	Wyeth
Submission Type:	Response to Approvable letter
Submission Date:	6/27/07, 8/29/07
OCP Division:	DCP 1 (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. Recommendations

Based on the review of the data in the Clinical Pharmacology and Biopharmaceutics sections in the original application for major depressive disorder (MDD) and in the response to the approval letter for MDD issued 1/22/07, the Office of Clinical Pharmacology (OCP) accepts the response to the OCP recommendation in the approval letter. OCP supports a recommendation for approval of Desvenlafaxine Succinate (Pristiq™) 50 mg, 100 mg and 200 mg strengths provided an acceptable language for label is agreed upon by the sponsor and the Agency.

1.2. Phase IV Commitments

There are no Phase IV commitments from OCP

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

1.3.1. Background

The submission provides a complete response to the approvable letter to the application to use Pristiq for the treatment of Major Depressive Disorder (NDA 21-992) issued on January 22, 2007. The application also provides updates to the biopharmaceutics, clinical pharmacology, clinical efficacy, and clinical safety information. The submission contains the results of two 8-week, placebo-controlled, efficacy studies (studies 332 and 333) that were conducted with 50 and 100 mg Pristiq, as well as a relapse prevention studies (study 333). Included in the submission also are 3 new drug interaction studies (studies 198, 401 and 900) that compared the effect of 100 mg Pristiq on desipramine metabolism (CYP2D6 mediated). Included in the submission also is study 901 designed to determine if there were relative differences in pharmacokinetics between CYP2D6 genotype subjects [extensive metabolizers (EMs) vs poor metabolizers (PMs)] after a single-dose administration of Pristiq or Effexor. Pharmacogenomic consult was requested for the evaluation of the phenotype of the patients involved in the study.

In the approvable letter, OCP requested the sponsor agree to the following dissolution method and specification for all strengths of Pristiq.

Method:

Apparatus: USP Apparatus 1 (baskets)
Speed: 100 rpm
Medium: 900 mL 0.9% NaCl in water
Temperature: 37°C ± 0.5°C

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Specification:

Time Criteria
2 hours
4 hours
8 hours
12 hours
24 hours NLT

The sponsor agreed to the final dissolution method and specifications as presented above. Therefore, there will be no further discussion of this issue in the review. The sponsor is revising the dosing regimen for MDD and introducing a 50 mg strength commercially. This dosage form has been used in the new efficacy studies and linked via IVIVC to the 100 mg and 200 mg dosage strengths of Pristiq. The review will focus on the evaluation of the new studies submitted in the submission.

1.3.2. Co-administration of Desvenlafaxine with Desipramine:

After daily doses of 100 mg DVS SR and a single dose administration of desipramine 50 mg, desipramine Cmax and AUC showed increases of 25% and 17%, respectively. The 90% confidence interval (CI) for Cmax was outside the 80% to 125% range but AUC was contained within CI limits. The Cmax and AUC of 2-hydroxydesipramine increased by 10% and 14%, respectively, in the desipramine with DVS SR treatment. The 90% confidence intervals (CI) for desipramine AUC, 2-hydroxydesipramine AUC, and Cmax were all contained within the 80% to 125% 90% CI. The study indicated that the exposure to the metabolite of desipramine, 2-hydroxydesipramine, was similar after coadministration of desipramine with desvenlafaxine SR 100 mg once daily. The changes in desipramine Cmax was outside 90% CI limits of 80% to 125%. The clinical significance of these changes in desipramine Cmax is not clear. Therefore, caution should be used when these drugs are co-administered together.

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Statistical Evaluation of Pharmacokinetic Parameters for Desipramine After Administration of Desipramine 50 mg Without and With Co-administration of DVS SR to Healthy Subjects

Parameter[a]	n	Ratio of Mean[b]	90% CI
C_{max} (ng/mL)	31	125	119-132
AUC (ng*hr/mL)	31	117	110-125

AUC=area under the concentration-versus-time curve; CI=confidence interval; C_{max}=peak concentration.

a. Reference is desipramine-alone treatments.
b. Ratio of geometric least square means.

Statistical Analysis of Pharmacokinetic Parameters for 2-Hydroxydesipramine After Administration of Desipramine 50 mg Without and With Coadministration of DVS SR to Healthy Subjects

Parameter[a]	n	Ratio of Mean[b]	90% CI
C_{max} (ng/mL)	32	110	104–116
AUC (ng*h/mL)	32	114	110–119

AUC=total area under the concentration-versus-time curve; CI=confidence interval; C_{max}=peak concentration.

a. Reference is desipramine alone treatments.
b. Ratio of geometric least square means.

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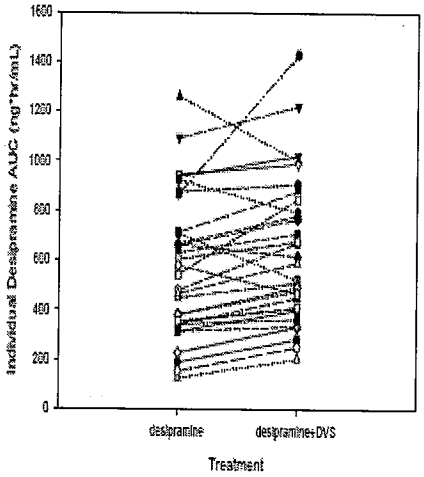
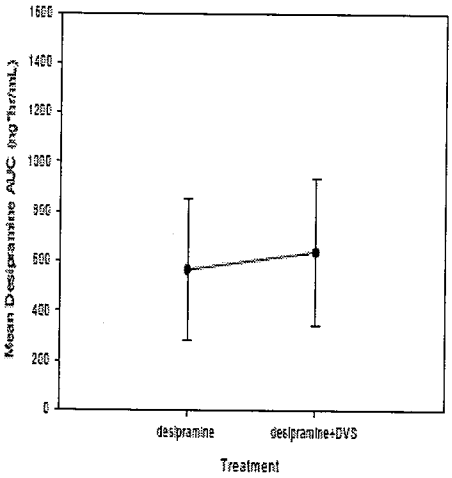
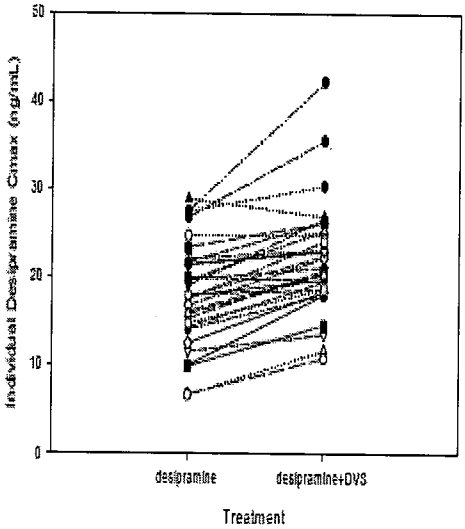
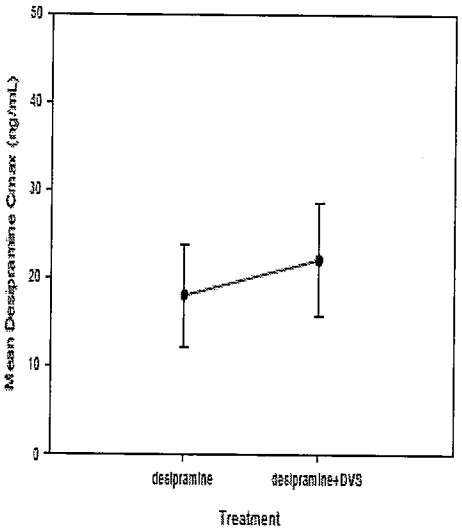
Desipramine Individual AUC and Mean AUC After Administration of Desipramine 50 mg Without and With Co-administration of DVS SR





Desipramine Individual Cmax and Mean Cmax After Administration of Desipramine 50 mg Without and With Co-administration





1.3.3. Comparison of the effect on Desipramine exposure when it is co-administered with Desvenlafaxine or Duloxetine.

The results of statistical analyses in another study using duloxetine (a known inhibitor of CYP 2D6; 30 mg twice daily) as a positive control co-administered with desipramine (50 mg single dose), indicated increases for desipramine Cmax and AUC that were significantly greater after duloxetine than after DVS SR (100 mg daily) administration with desipramine.

Statistical Analysis of Pharmacokinetic Parameters for Desipramine After administration of Desipramine Alone, Co-administration With DVS SR And Co-administration With Duloxetine to Healthy Subjects

Treatment[a]	Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Desipramine + DVS SR	Ratio of mean[b]	122%	119%
	90% CI	107%-138%	108%-130%
Desipramine + duloxetine	Ratio of mean[b]	222%	163%
	90% CI	195%-251%	149%-179%

Abbreviations: AUC=area under the concentration-versus-time curve; CI=confidence interval; Cmax=peak concentration.

a. Reference is treatment with desipramine alone.

b. Ratio of geometric least square means.

1.3.4. Comparison of the effect on Desipramine exposure when it is co-administered with Desvenlafaxine or Paroxetine.

In another study where desvenlafaxine (100 mg daily) was compared to paroxetine (a known inhibitor of CYP 2D6; 20 mg daily) when they were co-administered with desipramine (50 mg single dose), the results of statistical analyses indicated increases for desipramine Cmax and AUC that were significantly greater after paroxetine than after DVS SR administration with desipramine.

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Summary Statistical Results of Pharmacokinetic Parameters for Desipramine After Desipramine Administered Alone, Coadministered With DVS SR, and Coadministered With Paroxetine to Healthy Subjects

Treatment[a]	Variable	AUC (ng*hr/mL)	C_{max} (ng/mL)
Desipramine + DVS SR	Ratio of mean[b]	136%	130%
	90% CI	114%-163%	118%-145%
Desipramine + paroxetine	Ratio of mean[b]	519%	190%
	90% CI	433%-621%	171-210%

Abbreviations: AUC=area under the plasma-versus-time curve; CI=confidence interval; C_{max}=peak concentration.

a. Reference is desipramine alone treatments.

b. Ratio of geometric least square means.

1.3.5. Determining if the relative difference in pharmacokinetics between extensive metabolizers (EMs) and poor metabolizers (PMs) was the same between desvenlafaxine and venlafaxine extended release when a single dose of each was administered.

In a study to determine if there are differences in the pharmacokinetics after administration of venlafaxine and desvenlafaxine to Extensive Metabolizers (EMs) and Poor Metabolizer (PMs), significant differences (P<0.001) were observed between EM and PM subjects in the pharmacokinetics (PK) of both venlafaxine and desvenlafaxine after administration of venlafaxine. Desvenlafaxine PK were not significantly different between EM and PM subjects after administration of desvenlafaxine. The results indicate that the CYP2D6 phenotype does not significantly alter the PK of desvenlafaxine after administration of desvenlafaxine. CYP 2D6 isozyme is involved in the metabolism of venlafaxine to desvenlafaxine. But CYP 2D6 is not involved in the metabolism of desvenlafaxine to its inactive metabolites.

a) After administration of venlafaxine ER (75 mg) to EM and PM subjects, the mean Cmax for desvenlafaxine was approximately 346% higher for EM subjects compared with PM subjects. The mean AUC was approximately 265% higher for EM subject compared with PM subjects. Significant differences (p<0.001) in the Cmax and the AUC were observed between EM and PM subjects.

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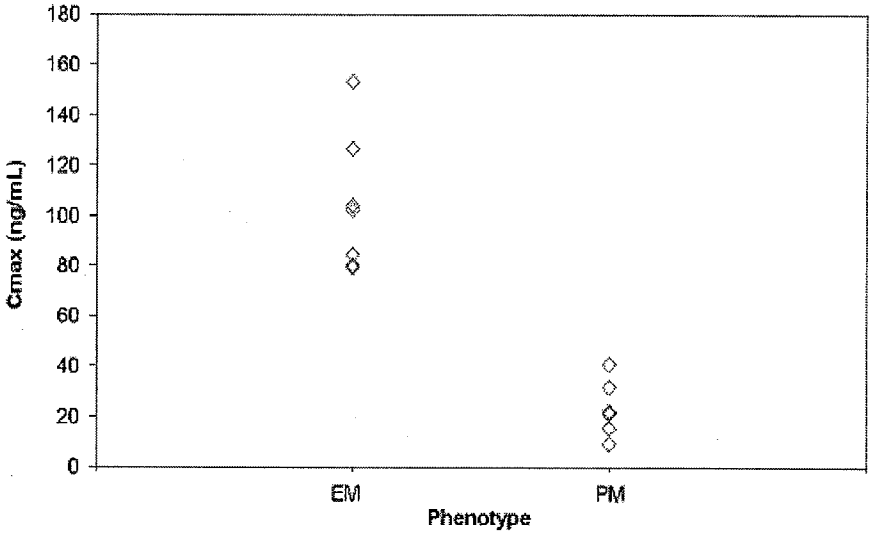
Individual Desvenlafaxine Cmax by Phenotype After Administration of Venlafaxine 75 mg



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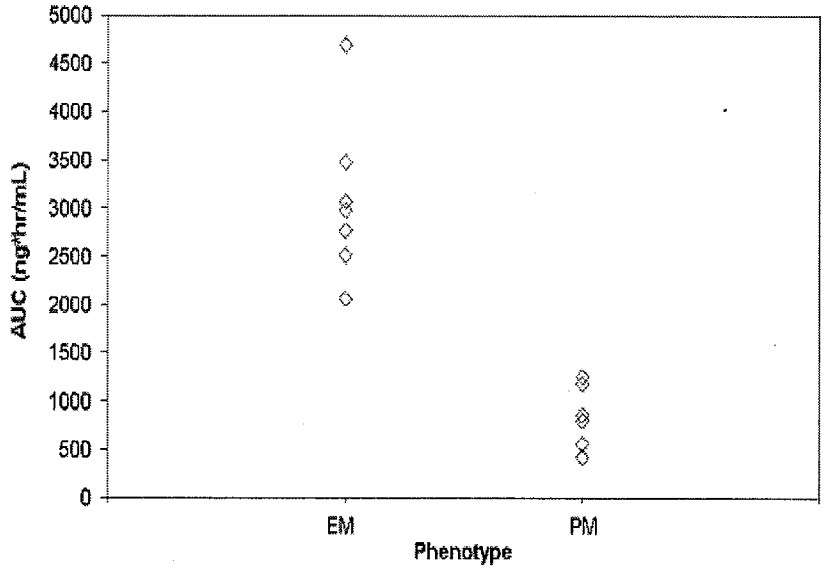
Individual Desvenlafaxine AUC by Phenotype After Administration of Venlafaxine 75 mg



Least Squares Geometric Mean and 90% Confidence Limits for Desvenlafaxine by CYP2D6 Phenotype After Administration of Venlafaxine ER (75 mg) to Healthy Subjects

Phenotype	Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Extensive metabolizer	Least squares geometric mean	3012.9	102.4
	90% Confidence limits	2344.8-3871.4	76.13-137.8
Poor metabolizer	Least squares geometric mean	771.8	20.5
	90% Confidence limits	585.4-1017.7	14.8-28.5

Abbreviations: AUC=area under the concentration-versus-time curve; C_{max}=peak concentration.

b) After administration of DVS SR (100 mg) to EM and PM subjects, the mean Cmax for desvenlafaxine was approximately 16% higher for PM subjects compared with EM subjects. The mean AUC values were about 13% lower for PM subjects compared with EM subjects. No significant differences were observed for either Cmax or AUC between EM and PM subjects.

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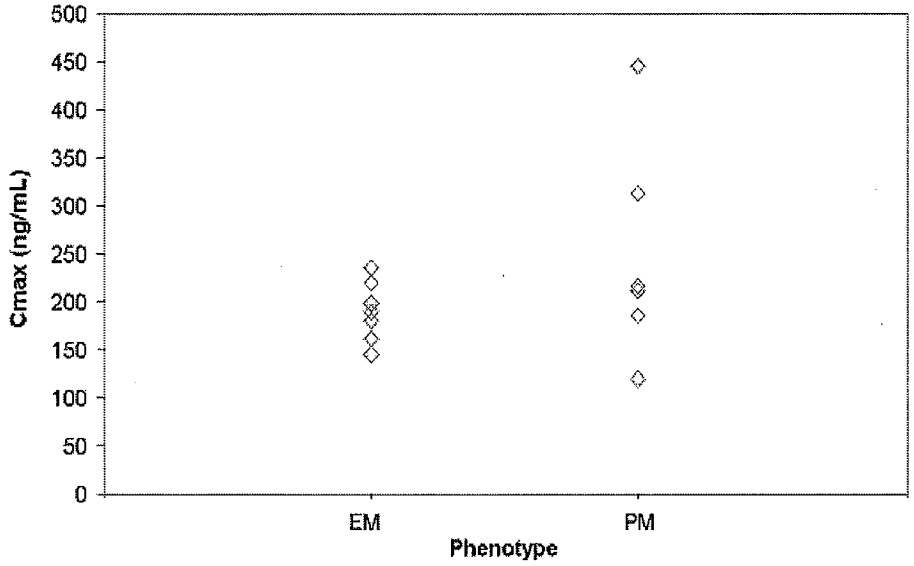
Individual Desvenlafaxine Cmax by Phenotype After Administration of DVS SR 100 mg



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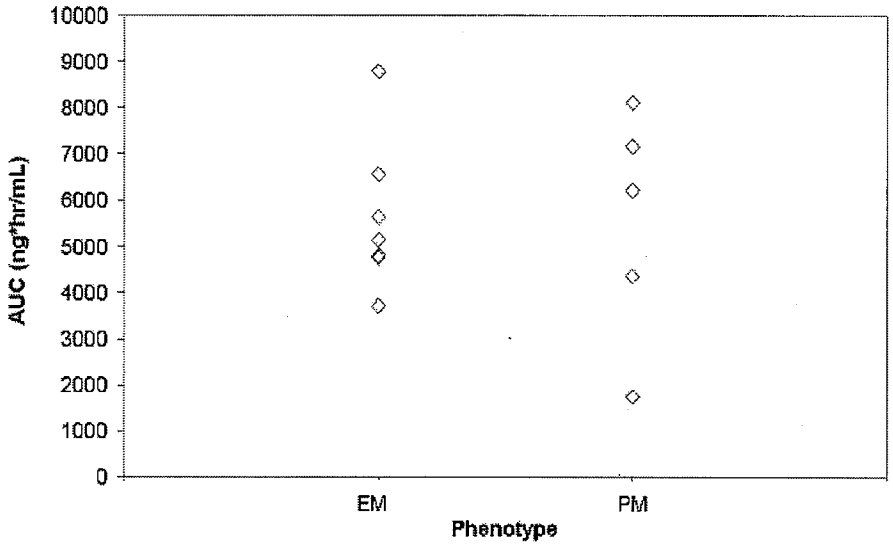
Individual Desvenlafaxine AUC by Phenotype After Administration of DVS SR 100 mg



Least Squares Geometric Mean and 90% Confidence Limits for Desvenlafaxine by CYP2D6 Phenotype After Administration of DVS SR (100 mg) to Healthy Subjects by Phenotype

Phenotype	Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Extensive metabolizers	Least squares geometric mean	5529.88	189.14
	90% Confidence limits	4063.32-7525.74	148.73-240.55
Poor metabolizers	Least squares geometric mean	4899.28	224.18
	90% Confidence limits	3487.68-6882.19	171.97-292.24

Abbreviations: AUC=area under the concentration-versus-time curve; C_{max}=peak concentration.

In contrast to statistically significant differences in the pharmacokinetics of venlafaxine and desvenlafaxine after administration of venlafaxine in extensive and poor metabolizers of CYP2D6, the CYP2D6 phenotype does not significantly alter the pharmacokinetics of desvenlafaxine after administration of DVS SR.

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1.3.6. Clinical Trial vs Commercial Formulations:

In the original application for major depressive disorder (MDD), the bioequivalence of 75 mg, 100 mg, and 200 mg clinical trial formulations of DVS SR was demonstrated. A definitive bioequivalence study using the clinical trial, to-be-marketed, and fast-release formulations of 200 mg tablets demonstrated bioequivalence of the clinical trial and to-be-marketed formulations. An in vitro/in vivo correlation was demonstrated and this was used to support the use of the proposed to be marketed product strengths of 50 and the approved commercial formulations of 100, and 200 mg. Th be marketed formulation have also been used in pivotal clinical trials for MDD (Studies 332 and 333).

The 50, 100 and 200 mg strengths are proposed for commercialization for the MDD indication, and the strengths are proposed for the vasomotor symptoms (VMS) indication. The following is a summary of the linkage of the DVS formulations that have been used in the MDD and VMS programs.

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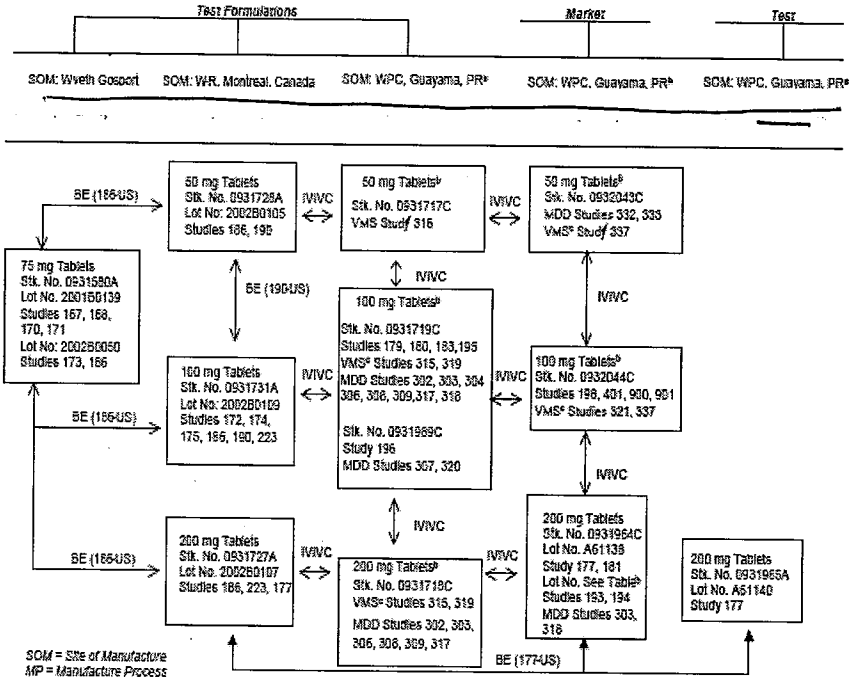
Summary of Linkages Between DVS Formulations

DVS Linkage Summary



a. WPC, Guayama, PR was formerly referred to as AWPI, Guayama, PR.
b. Lot numbers provided in Table 3.1-1, Table 3-1-2, or both.
c. Studies for the treatment of vasomotor symptoms (VMS) associated with menopause.

2. Detailed Labeling Recommendations

Detailed OCP Labeling Recommendations are included in the proposed label attached under Appendices

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_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

3.2. Individual Study Reports

3.2.1. Title (Protocol No.: 3151A1-198-US): An Open-Label, 2-Period Sequential Drug Interaction Study To Evaluate The Effect Of A 100-Mg Dose Of DVS SR On The Pharmacokinetics Of Desipramine (A CYP2D6 Substrate) When Coadministered In Healthy Subjects

Objectives: The primary objective was to evaluate the effect of multiple doses of 100 mg DVS SR on the pharmacokinetics of desipramine (a CYP2D6 substrate) when coadministered to healthy subjects. The secondary objective was to assess the safety and tolerability of DVS SR and desipramine when coadministered to healthy subjects. In addition, the steady-state pharmacokinetics of a 100-mg dose of DVS SR were evaluated.

Study Design: This was an open-label, 2-period, sequential, inpatient study conducted in men or nonpregnant, nonlactating women, 18 to 45 years of age, inclusive, on study day 1. The study consisted of 2 study periods: in period 1, the administration of desipramine alone, and in period 2, coadministration of DVS SR and desipramine. In period 1, all subjects received a single oral dose of 50 mg desipramine. Period 2 started 6 days later when subjects received single oral daily doses of 100 mg DVS SR for the next 5 days. On the next day, all subjects received a single oral dose of 100 mg DVS SR and concomitantly received a single oral dose of 50 mg desipramine. For the next 4 days, subjects continued to receive single oral daily doses of 100 mg DVS SR. All doses were administered with 240 mL of water.

Predose desvenlafaxine pharmacokinetic blood sample was obtained not more than 2 hours before test article administration, but as close to administration as possible. In the evening prior to dose administration, an overnight fast was imposed so that no food was taken within at least 10 hours before test article administration. Vital signs, pharmacokinetic blood samples for desvenlafaxine, and urine samples for conjugated and unconjugated desvenlafaxine and conjugated and unconjugated NODV analysis were obtained. Water was permitted in the 2 hours before and after test article administration.
Standard medium-fat meals, served according to the clinic's schedule, could be started 4 hours after test dose administration.

The formulation, strength, batch numbers, and manufacturer locations of the study drugs are summarized in the following table.

Study Drug Information

Study Drug	Dosage (mg)	Batch Number	Formulation Number	Manufacturer Location
Desvenlafaxine SR	100	A97186	0932044C	WPC
Desipramine	50	NA	NA	Sandoz

NA=not applicable; WPC=Wyeth Puerto Rico.

Test article administration was administered as shown in the following table.

Test Article Administration

	Dose Regimen
Period 1	
Day 1	Single oral 50-mg desipramine tablet (fasting). PK to follow up through 120 hours.
Days 2 to 6	No test article administration.
Period 2	
Days 1 to 5	Single oral daily 100-mg DVS SR tablets (on day 5 PK to follow up to 24 hours).
Day 6	Single oral 100-mg DVS SR tablet coadministered with a single oral 50-mg desipramine tablet (fasting) (PK to follow up through 120 hours).
Days 7 to 10	Single oral daily 100-mg DVS SR tablets.

PK=pharmacokinetics.

Cytochrome P450 (CYP)2D6 genotyping assay will be performed in order to characterize alleles *1, *2, *2XN, *3 to *8, *10, *17, *29 and *40. CYP2D6 genotyping will be used evaluate the potential impact of genetic polymorphism for any outliers (characterized by poor metabolizer [PM], extensive metabolizer [EM], and ultrarapid metabolizer [UM] status), with respect to pharmacokinetics of desipramine, when given simultaneously with DVS SR

Analytical Method: Blood samples (5 mL) were collected for determination of desipramine and 2-hydroxydesipramine concentrations in period 1 on day 1 and in period 2 on day 6 before (within 2 hours before test article administration) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after test article administration. Blood samples were also collected for the determination of desvenlafaxine plasma concentrations in period 2 on day 5 at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after test article administration. In addition, a blood sample was collected in period 2 on day 4 to confirm steady-state desvenlafaxine plasma concentration. Urine samples were collected for determination of desipramine and 2-hydroxydesipramine concentrations in period 1 on day 1 through day 6, and also in period 2 on day 6 through day 11 at the following time intervals: predose (-2 to 0 h) and at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 hours after test article administration. In addition urine samples were collected for determination of desvenlafaxine concentration in period 2 on day 5 at the following time intervals: predose (-2 to 0 hours) and at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after test article administration.

Desipramine and 2-hydroxydesipramine concentrations in plasma and in urine, and desvenlafaxine concentrations in plasma were measured using a validated liquid chromatography/tandem mass spectrometry method (LC/MS/MS). The inter-assay coefficients of variation of the desipramine quality controls for the analytical runs ranged from 4.69% to 16.5%, with percent differences from theoretical ranging from 2.71% to 9.70%. The inter-assay coefficients of variation of the 2-hydroxydesipramine quality controls for the analytical runs ranged from 3.75% to 5.13%, with percent differences from theoretical ranging from -4.99% to 5.18%.

A validated LC/MS/MS method was also used for the determination of desvenlafaxine and NODV in human urine. Calibration curve standards and quality control (QC) samples met the acceptance criteria for all the runs used for the final data. All accepted runs had "r^2" values of 0.997677 or better for the calibration standard curves. For calibration standards, the inter-day

precision (CV) was 4.4% or better and the accuracy ranged from 97.2 to 102%. For the QC samples, the inter-day precision (CV) was 3.3% or better and the accuracy ranged from 107 to 109%. For calibration standards of urine samples, the inter-day precision (CV) for O-desmethylvenlafaxine was 6.1% or better and the accuracy ranged from 94.0 to 106%. All the O-desmethylvenlafaxine standards were within the acceptance criteria. The accuracy for N, O-didesmethylvenlafaxine calibration standards ranged from 93.0 to 105%. All the N, O-didesmethylvenlafaxine standards were within the acceptance criteria. For the QC samples for O-desmethylvenlafaxine in urine, the inter-day precision (CV) was 5.7% or better and the accuracy ranged from 96.1 to 109%.

The performance of the desipramine and 2-hydroxydesipramine assays during analysis of the plasma samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Desipramine and 2-Hydroxydesipramine in Plasma Samples

Standard Curve	Compound/Matrix Desipramine/Plasma	Compound/Matrix 2-Hydroxydesipramine/Plasma
Linear range (ng/mL)	0.25-100	0.25-100
Sensitivity (ng/mL)	0.25	0.25

Analytical Summary of Desipramine and 2-Hydroxydesipramine Assays in Plasma Samples

	Low CS (0.600 ng/mL)			Medium CS (5.25 ng/mL)			High CS (75.0 ng/mL)		
Analyte	Conc	CV%	Bias %	Conc	CV%	Bias %	Conc	CV%	Bias %
Desipramine	0.621	8.40	3.43	5.41	14.7	2.97	74.7	3.70	-0.422
2-Hydroxydesipramine	0.587	7.59	-2.20	5.41	16.6	3.10	75.7	3.21	0.941

Conc=concentration; CS=calibration standards; CV=coefficient of variation.

The performance of the desipramine and 2-hydroxydesipramine assays during analysis of the urine samples from this study are summarized in the following table.

Assay Range and Sensitivity for Desipramine and 2-Hydroxydesipramine in Urine Samples

Standard Curve	Compound/Matrix Desipramine/Urine	Compound/Matrix 2-Hydroxydesipramine/Urine
Linear range (ng/mL)	10-2500	100-25000
Sensitivity (ng/mL)	10	100

Analytical Summary of Desipramine Assays in Urine Samples

	Low CS (25.0 ng/mL)			Medium CS (150 ng/mL)			High CS (1950 ng/mL)		
Analyte	Conc	CV%	Bias %	Conc	CV%	Bias %	Conc	CV%	Bias %
Desipramine	26.2	4.69	4.76	154	5.18	2.71	2070	5.16	6.00

Conc=concentration; CS=calibration standards; CV=coefficient of variation.

The performance of the desvenlafaxine assay during analysis of plasma samples from this study is summarized in the following table.

Assay Range and Sensitivity for Desvenlafaxine in Plasma Samples

Standard Curve	Compound/Matrix Desvenlafaxine/Plasma
Linear range (ng/mL)	2.0-500
Sensitivity (ng/mL)	2.0

Analytical Summary of Desvenlafaxine Assays in Plasma Samples

	High QC (375.0 ng/mL)			Medium QC (45.0 ng/mL)			Low QC (5.0 ng/mL)		
Analyte	Conc	CV%	Bias %	Conc	CV%	Bias %	Conc	CV%	Bias %
Desven	399.7	1.8	7	48.87	2.6	9	5.406	3.3	8

Conc=concentration; CV=coefficient of variation; Desven=desvenlafaxine; QC=quality control.

The performance of desvenlafaxine and NODV assays during analysis of the urine samples are summarized in the following table.

Assay Range and Sensitivity for Desvenlafaxine and NODV in Urine Samples

Compound/Matrix	Standard Curve Linear range (ug/mL)	Sensitivity (ug/mL)
Total desvenlafaxine	0.10-50.00	0.10
Total NODV	0.04-20.00	0.04
Unconjugated desvenlafaxine	0.10-50.00	0.10
Unconjugated NODV	0.04-20.00	0.04

NODV=N,O-didesmethylvenlafaxine.

Analytical Summary of Desvenlafaxine Assays of Urine Samples

	High QC (38.00 ug/mL)			Medium QC (3.00 ug/mL)			Low QC (0.30 ug/mL)		
Analyte	Conc	CV%	Bias %	Conc	CV%	Bias %	Conc	CV%	Bias %
Total desven	36.50	5.3	-3.9	3.155	5.7	5	0.327	5.1	9
Unconjugated. desven	37.45	2.4	-1.4	3.181	6.0	6	0.315	6.8	5

Conc=concentration; CV=coefficient of variation; Desven=desvenlafaxine; QC= quality control.

Analytical Summary of NODV Assays of Urine Samples

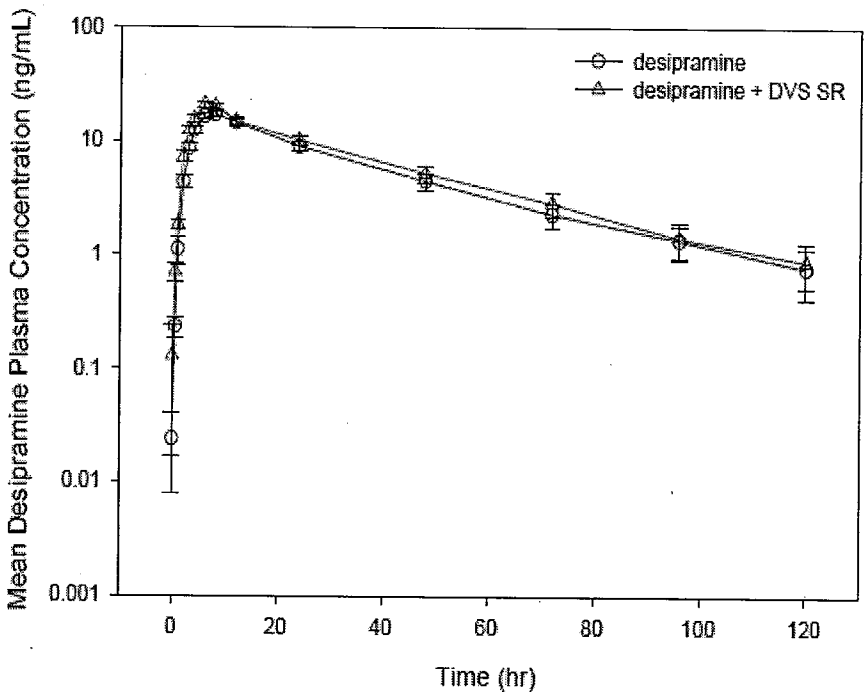
	High QC (15.20 ug/mL)			Medium QC (1.20 ug/mL)			Low QC (0.12 ug/mL)		
Analyte	Conc	CV%	Bias %	Conc	CV%	Bias %	Conc	CV%	Bias %
Total NODV	14.73	4.3	-3.1	1.292	2.4	8	0.129	2.8	7
Unconjugated NODV	15.35	2.1	1	1.29	4.9	8	0.126	6.5	5

Conc=concentration; CV=coefficient of variation; NODV=N,O-didesmethylvenlafaxine; QC= quality control.

Data Analysis: The plasma concentration data and PK parameters of desipramine and 2-hydroxy desipramine (100 mg) will be compared between the monotherapy, (ie, desipramine administered alone), and the combination therapy by using a 1-factor analysis of variance with subject as a repeated random effect. Geometric mean ratios for desipramine (combination therapy) vs. desipramine (monotherapy) with 90% confidence limits will be the primary method to estimate the magnitude of the effect of DVS SR on the PK profile of desipramine (using desipramine monotherapy as the reference treatment and 80%–125% as the no effect boundary. PK parameters for desvenlafaxine in plasma and desvenlafaxine and NODV in urine will be assessed descriptively. CYP2D6 genotype (PM, IM, EM, UM) will be assessed descriptively. A noncompartmental PK method was used to analyze the plasma and urinary excretion data of desipramine, 2-hydroxy desipramine and desvenlafaxine.

Results: The mean desipramine plasma concentrations with and without concomitant administration of DVS SR is depicted in the following figure.

Desipramine Mean Plasma Concentration-Versus-time Profile After Administration of Desipramine 50 mg without and with co-administration of DVS SR



The following figures contain the individual and mean comparisons of Cmax and AUC after administration of desipramine without and with co-administration of DVS SR.

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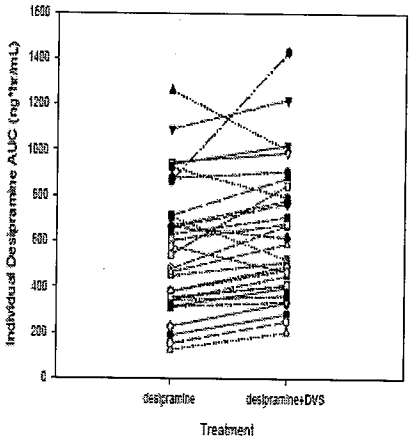
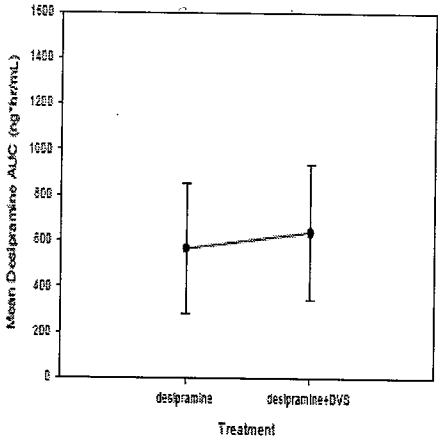
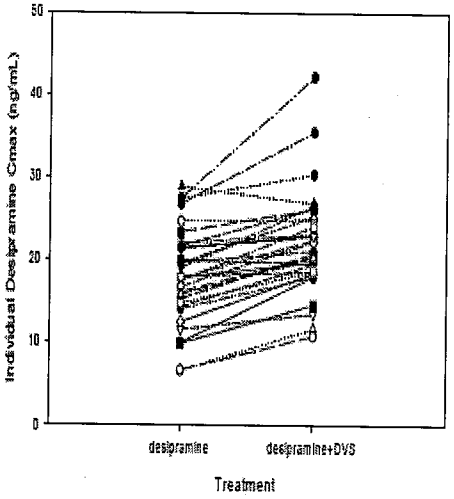
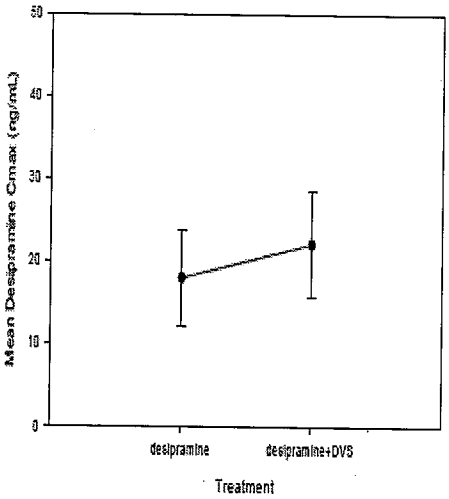
Desipramine Individual AUC and Mean AUC After Administration of Desipramine 50 mg Without and With Co-administration of DVS SR





Desipramine Individual Cmax and Mean Cmax After Administration of Desipramine 50 mg Without and With Co-administration





Summary pharmacokinetic parameters of desipramine for both treatments are contained in the following table. The results of statistical analysis for desipramine with and without coadministration of DVS SR are provided in the following table.

Summary of Pharmacokinetic Parameters for Desipramine After Administration of Desipramine 50 mg Without and With Co-administration of DVS SR to Healthy Subjects

Treatment	Variables	C_{max} (ng/mL)	t_{max}[a] (h)	AUC (ng*h/mL)	$t_{1/2}$ (h)	Cl/F (L/h/kg)	Ae (%)	CL_R (L/h/kg)
Desipramine 50 mg	n[b]	31	31	31	31	31	31	31
	Mean±SD	18.05±5.86	8.0	566±287	21.22±6.37	1.50±1.07	1.46±0.73	0.017±0.005
	%CV	32.5		50.8	30.0	71.5	50.0	27.4
	Geo mean	16.99		491	20.37	1.25	1.25	0.016
	Min-max	6.67–28.90	4.0–12.0	127–1261	11.21–42.96	0.53–4.92	0.22-2.52	0.010–0.028
Desipramine 50 mg+DVS SR	n[b]	31	31	31	31	31	31	31
	Mean±SD	22.12±6.38	6.0	638±297	21.47±6.16	1.21±0.64	1.74±0.85	0.017±0.005
	%CV	28.8		46.6	28.7	53.0	48.8	29.7
	Geo mean	21.28		573	20.69	1.07	1.52	0.017
	Min-max	10.80–42.2	4.0–8.0	203–1429	12.67–41.28	0.45–3.08	0.54-3.53	0.007-0.031

Ae=amount extracted; AUC=area under the concentration-versus-time curve; Cl/F=apparent oral-dose clearance; CL_R=renal clearance; C_{max}=peak concentration; CV=coefficient of variation; Geo mean=geometric mean; Max=maximum; Min=minimum; SD=standard deviation; $t_{1/2}$=apparent terminal- half-life; tmax=time to peak concentration.

a. Median value and range are listed for t_{max}.

Statistical Evaluation of Pharmacokinetic Parameters for Desipramine After Administration of Desipramine 50 mg Without and With Co-administration of DVS SR to Healthy Subjects

Parameter[a]	n	Ratio of Mean[b]	90% CI
C_{max} (ng/mL)	31	125	119-132
AUC (ng*hr/mL)	31	117	110-125

AUC=area under the concentration-versus-time curve; CI=confidence interval; C_{max}=peak concentration.

a. Reference is desipramine-alone treatments.
b. Ratio of geometric least square means.

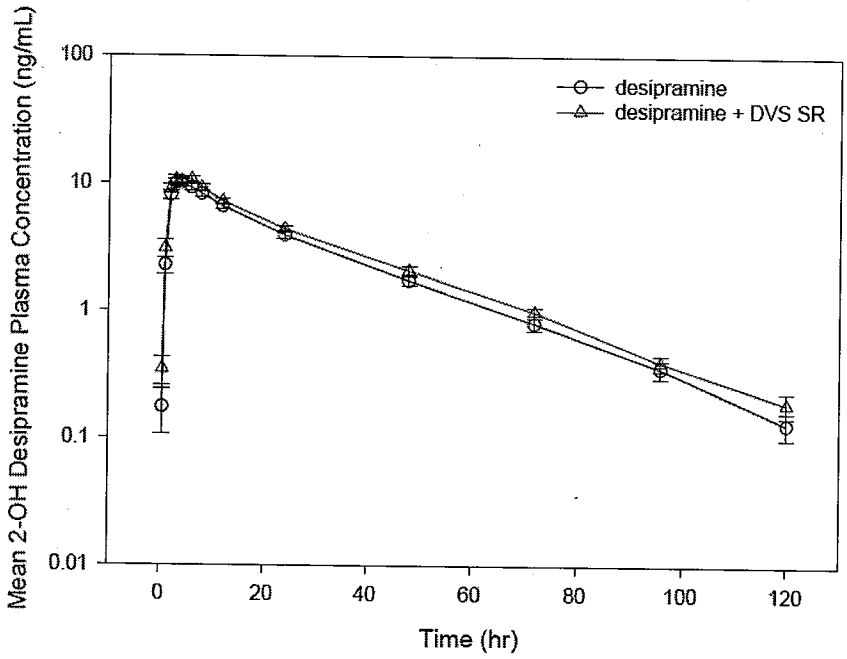
Mean Cmax after concomitant administration of desipramine and DVS SR was approximately 25% higher than Cmax when desipramine was administered alone. The 90% confidence interval

(CI) was outside the 80% to 125% confidence limits. The AUC after concomitant administration of desipramine and DVS SR was approximately 17% higher than the AUC when desipramine was administered alone. The 90% CI was within the interval of 80% to 125%. Mean apparent oral dose clearance (Cl/F) decreased approximately 14% with concomitant administration of desipramine and DVS SR, whereas mean renal clearance (CLR) values were similar for the 2 treatments.

2-Hydroxydesipramine

The following figure contains the mean plasma concentration time profile for 2-Hydroxydesipramine after administration

2-Hydroxydesipramine Mean Plasma Concentration-Versus-Time Profile After Administration of Desipramine 50 mg Without and With Coadministration of DVS SR



A summary of the pharmacokinetic parameters for 2-hydroxydesipramine are provided in the following tables.

Summary of Pharmacokinetic Parameters for 2-Hydroxydesipramine after Administration of Desipramine 50 mg Without and With Coadministration of DVS SR to Healthy Subjects

Treatment	Variables	C_{max} (ng/mL)	t_{max}[a] (h)	AUC (ng*h/mL)	$t_{1/2}$ (h)	AUC Ratio[b]	Ae (%)	CL_R (L/h/kg)
Desipramine 50 mg	n[c]	32	32	32	32	31	32	32
	Mean±SD	11.22±3.29	3.5	283±73	20.71±6.39	0.63±0.30	40.49±8.49	0.95±0.25
	%CV	29.3		25.8	30.9	47.0	21.0	26.4
	Geo. mean	10.74		273	19.64	0.57	39.47	0.92
	Min-max	4.63-19.80	2.0-8.0	110-418	7.10-36.24	0.21-1.43	19.65-55.74	0.49-1.42
Desipramine 50 mg+DVS SR	n[c]	32	32	32	32	31	32	32
	Mean±SD	12.39±3.97	4.0	320±76	21.86±6.50	0.60±0.25	38.80±6.48	0.81±0.21
	%CV	32.1		23.8	29.7	41.0	16.7	26.5
	Geo. mean	11.77		312	21.00	0.55	38.24	0.78
	Min-max	5.25-23.20	2.0-8.0	174-478	11.05-40.92	0.22-1.24	24.19-51.38	0.39-1.18

Ae=amount extracted; AUC=area under the concentration-versus-time curve; CL_R=renal clearance; C_{max}=peak concentration; CV=coefficient of variation; Geo mean=geometric mean; Max=maximum; Min=minimum; SD=standard deviation; $t_{1/2}$=apparent terminal half-life; t_{max}=time to peak concentration.

a. Median value and range are listed for tmax.
b. AUC Ratio=$AUC_{2\text{-hydroxydesipramine}}/AUC_{desipramine}$.

Statistical Analysis of Pharmacokinetic Parameters for 2-Hydroxydesipramine After Administration of Desipramine 50 mg Without and With Coadministration of DVS SR to Healthy Subjects

Parameter[a]	n	Ratio of Mean[b]	90% CI
C_{max} (ng/mL)	32	110	104–116
AUC (ng*h/mL)	32	114	110–119

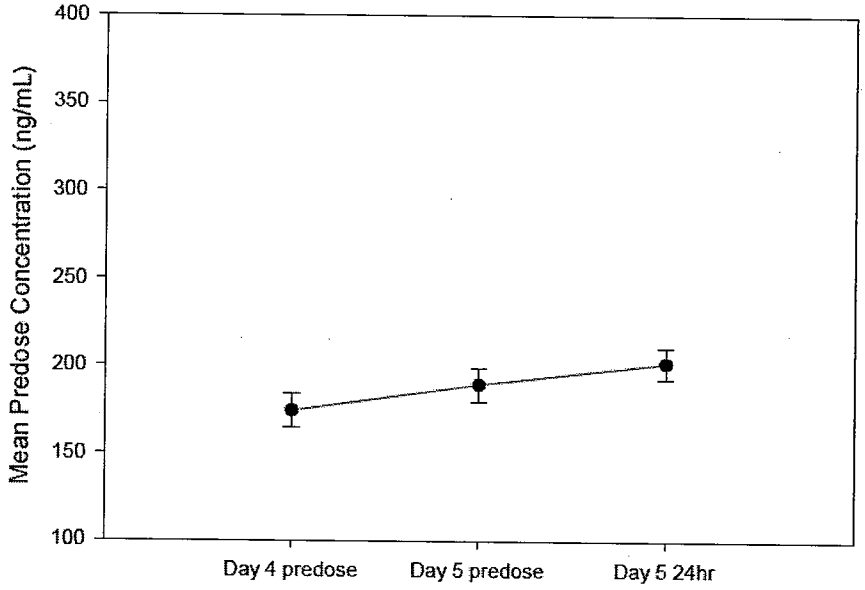
AUC=total area under the concentration-versus-time curve; CI=confidence interval; C_{max}=peak concentration.

a. Reference is desipramine alone treatments.
b. Ratio of geometric least square means.

The 2-hydroxydesipramine Cmax after concomitant administration of desipramine and DVS SR was about 10% higher than Cmax when desipramine was administered without DVS SR. Coadministration of DVS SR increased the mean 2-hydroxydesipramine AUC by 14%. The 90% CI was contained within the 80% to 125% regulatory limit. The CLR of 2-hydroxydesipramine decreased approximately 15% during concomitant administration of desipramine and DVS SR.

Desvenlafaxine: The following figures represent the mean desvenlafaxine plasma concentration-time profile in period 2 on day 5 and the mean desvenlafaxine pre-dose plasma concentration on days 4 and 5 and at 24 hours on day 5

Desvenlafaxine Mean Plasma Predose Concentration in Period 2 on Day 4 and Day 5



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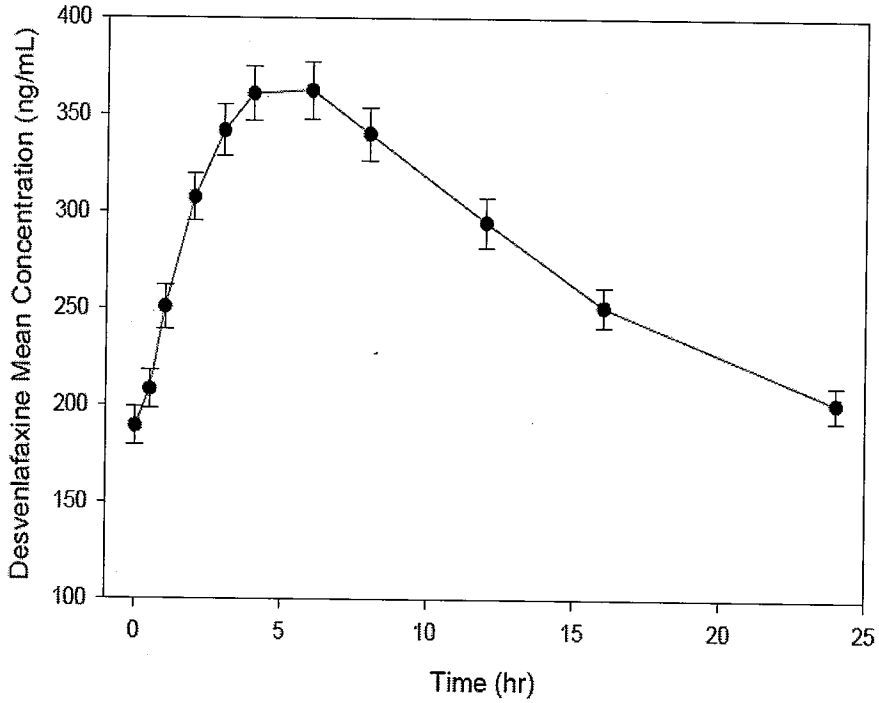
Desvenlafaxine Mean Plasma Concentration-Versus Time Profile After Multiple Dose Administration of 100 mg Once Daily



The following tables contain the plasma and urine pharmacokinetic parameters after multiple dose administration of desvenlafaxine.

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Desvenlafaxine Multiple-Dose Plasma Pharmacokinetic Parameters

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng*h/mL)	Cl/F (L/h)	Cl/F (L/h/kg)
n	34	34	34	34	34
Mean±SD	376.1±85.9	4.0	6747±1526	15.45±2.97	0.19±0.04
%CV	22.8		22.6	19.2	20.3
Geo mean	367.5		6602	15.15	0.19
Min-max	249.0-675.7	3.0-12.0	4726-12227	8.18-21.16	0.09-0.28

AUC_{0-24}=area under the concentration-versus-time curve from time 0 to 24 hours; Cl/F=apparent oral-dose clearance (dose/AUC); C_{max}=peak concentration; CV=coefficient of variation; Geo mean=geometric mean; Max=maximum; Min=minimum; SD=standard deviation; t_{max}=time to peak concentration.

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Desvenlafaxine Multiple-Dose Urine Pharmacokinetic Parameters

		Urinary Recovery (%) 0-24 hours	Renal Clearance (L/h)	Renal Clearance (L/h/kg)	Renal Clearance (mL/min)	% of Plasma Clearance (%)
Total desvenlafaxine	n	34				
	Mean±SD	52.3±7.5				
	%CV	14.4	-	-	-	-
	Geo mean	51.8				
	Min-Max	39.1–71.8				
Unconjugated desvenlafaxine	n	34	34	34	34	34
	Mean±SD	33.9±8.6	5.16 ± 1.50	0.063 ± 0.017	86.0 ± 24.9	33.9 ± 8.6
	%CV	25.4	29.0	27.6	29.0	25.4
	Geo mean	32.7	4.95	0.061	82.5	32.7
	Min-Max	15.4–48.9	2.29–8.98	0.030–0.107	38.2–149.7	15.4–48.9
Total NODV	n	34				
	Mean±SD	3.2±0.9				
	%CV	27.2	-	-	-	-
	Geo mean	3.1				
	Min-Max	1.5–5.3				
Unconjugated NODV	n	34				
	Mean±SD	1.6±0.7				
	%CV	41.6	-	-	-	-
	Geo mean	1.5				
	Min-Max	0.6–3.5				
Total desvenlafaxine + Total NODV	n	34				
	Mean±SD	55.4±7.9				
	%CV	14.2	-	-	-	-
	Geo mean	54.9				
	Min-Max	41.8–75.9				

CV=coefficient of variation; Geo mean=geometric mean; Max=maximum; Min=minimum; NODV=N,O-didesmethylvenlafaxine; SD=standard deviation.

The mean concentrations (±standard deviation [SD]) of desvenlafaxine before dose administration on days 4 and 5 and at 24 hours after dose administration on day 5 were 174.1 ng/mL (±56.8), 189.4 ng/mL (±56.9) and 201.7 ng/mL (±52.6), respectively. These data indicate that desvenlafaxine plasma concentrations were approximately at steady state on day 5 in period 2. Urinary recovery of unconjugated desvenlafaxine was 33.9% and the CL_R of unconjugated desvenlafaxine was approximately 34% of plasma clearance of desvenlafaxine.

Pharmacogenomics: The results of the pharmacogenomic analysis are provided in the following table

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CYP2D6 Genotype, Predicted CYP2D6 Phenotype, Sex and Age Listings

Subject	Sex	Age	Race	BMI (kg/m^2)	Ht (cm)	Wt (kg)	CYP2D6_ Genotype	CYP2D6_ Phenotype
1	Male	34	White	28.5	182	94.3		EM
2	Male	30	Black or African American	29.5	177	92.3		EM
3	Male	25	White	24.7	173	74		EM
4	Female	29	Black or African American	24.2	170	69.9		EM
5	Male	31	Black or African American	25.2	166	69.4		EM
6	Male	34	White	29.3	173	87.8		EM
7	Female	28	Black or African American	23	180	74.6		EM
8	Male	32	Black or African American	27.4	165	74.5		EM
9	Female	44	Black or African American	25.3	188	89.5		EM
10	Male	29	Black or African American	26.6	171	77.8		EM
11	Male	33	Black or African American	22.9	168	64.7		EM
12	Male	24	Black or African American	24.3	170	70.1		EM
13	Male	34	Other	28	187	98		EM
14	Male	38	Black or African American	28	185	95.8		EM
15	Male	25	Black or African American	31.4	188	111		EM
16	Male	37	White	24.2	169	69.1		EM
17	Female	36	Black or African American	29.8	173	89.3		EM
18	Male	43	Black or African American	30	175	91.8		IM
19	Male	24	White	22.9	187	80.1		EM
20	Male	43	White	29.9	174	90.6		EM
21	Male	37	Black or African American	26	182	86.2		EM
22	Male	38	White	28.5	177	89.2		EM
23	Male	39	Asian	24.4	177	76.4		EM

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CYP2D6 Genotype, Predicted CYP2D6 Phenotype, Sex and Age Listings contd.

Subject	Sex	Age	Race	BMI (kg/m²)	Ht (cm)	Wt (kg)	CYP2D6_ Genotype	CYP2D6_ Phenotype
24	Male	19	White	22.1	179	70.9		EM
25	Male	44	Black or African American	23	179	73.7		UM
26	Male	32	Black or African American	27.5	191	100.2		EM
27	Male	33	Other	28	188	98.9		EM
28	Male	20	White	23.5	171	68.8		EM
29	Male	42	Black or African American	21.9	173	65.4		EM
30	Male	42	Black or African American	25.6	174	77.4		EM
31	Male	33	Black or African American	24.1	177	75.6		PM
32	Male	28	Black or African American	24.7	177	77.4		EM
33	Male	29	Black or African American	25.9	178	82.1		EM
34	Male	18	Black or African American	27.9	175	85.5		IM
35	Female	43	Black or African American	28.3	178	89.6		EM
36	Male	26	Black or African American	27.2	192	100.1		EM
37	Male	36	Black or African American	22.7	179	72.8		EM
38	Female	34	Black or African American	27.5	161	71.2		EM

BMI=body mass index; EM: extensive metabolizer; ht=height; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultra-rapid metabolizer; wt=weight.

Subject 31 was classified as a PM for the CYP2D6 phenotype and had the slowest observed Cl/F of desipramine of which is approximately one tenth of the mean value for Cl/F of 1.50 L/h/kg (desipramine without DVS SR). Concentrations for subject 31 at 120 hours were still high (for desipramine without DVS SR and for coadministration treatment). For the subject 31, sampling for 120 hours was insufficient to characterize the terminal elimination. Subject 25 was classified as a UM for the CYP2D6 phenotype and had the fastest observed Cl/F of desipramine, of , which is approximately 10-fold greater than the mean value for Cl/F of 1.50 L/h/kg (desipramine without DVS SR) observed in EM subjects. For the UM (subject 25), desipramine plasma concentrations remained low without a visible elimination profile during the 120-hour sampling period. For both the PM and UM subjects, the percentage of extrapolated AUC was more than 20% and therefore statistics for AUC, apparent terminal half life (T ½), apparent volume of distribution (V/F), clearance, and confidence interval calculations excluded values from these subjects.

Safety Summary: The sponsor reported that the incidence of any TEAEs was higher when subjects were receiving daily DVS SR (62.9%) than when they received a single dose of desipramine alone (21.1%) or the DVS SR + desipramine combination (20.6%). TEAEs in the DVS SR treatment group that occurred at a frequency 10% included headache, anorexia, nausea, dizziness, and insomnia. No TEAEs reported after desipramine alone or desipramine + DVS SR occurred at a frequency 10%. All TEAEs were rated as mild or moderate in severity. Most TEAEs were reported as drug related.

Summary and Conclusions: Desvenlafaxine elimination occurs primarily through glucuronidation and renal excretion of desvenlafaxine and the glucuronide conjugate of desvenlafaxine. CYP3A4 metabolism of desvenlafaxine to NODV is a minor elimination pathway (<5%). In vitro studies

indicate that desvenlafaxine is a weak inhibitor of CYP2D6 activity but has no inhibitory effects on other CYPs and does not induce CYP3A4 expression.

Desipramine is primarily eliminated through CYP2D6-mediated metabolism to 2-hydroxydesipramine and is commonly used as a probe substrate for testing CYP2D6 activity. In the presence of CYP2D6 inhibitors, concentrations of desipramine are expected to increase, whereas those of the primary metabolite, 2-hydroxydesipramine, would decrease.

After daily doses of 100 mg DVS SR, desipramine exposure, as measured by Cmax and AUC, showed increases of 25% and 17%, respectively. The confidence interval was outside the 80% to 125% range for desipramine Cmax but within the CI for AUC. The Cmax and AUC of 2-hydroxydesipramine increased by 10% and 14%, respectively, in the desipramine with DVS SR treatment. The 90% confidence intervals for desipramine AUC, 2-hydroxydesipramine AUC, and Cmax were all inside the 80% to 125% interval,
The ratio of AUC for 2-hydroxydesipramine to desipramine changed from 0.63 to 0.60.

Conclusion: The sponsor reports that the results of the current study indicate that coadministration of the CYP2D6 substrate desipramine with 100-mg daily doses of DVS SR results in approximately similar exposures to desipramine and 2-hydroxydesipramine.

Reviewer's comments: The study indicated that the exposure to the metabolite of desipramine, 2-hydroxydesipramine, was similar after coadministration of desipramine with desvenlafaxine SR 100 mg once daily. However, there were significant changes in desipramine Cmax. The Cmax was outside the 80% to 125% 90% CI limits.

3.2.2. Title (Protocol 3151A1-401-US): A Randomized, Open-Label, Crossover, Drug Interaction Study To Evaluate The Effects Of DVS SR And Duloxetine On The Pharmacokinetics Of Desipramine In Healthy Subjects.

Objectives: The objective was to evaluate the effects of multiple doses of DVS SR and duloxetine on the pharmacokinetics of a single dose of desipramine in healthy subjects.

Study Design: This was a single-center, randomized, open-label, 4-period crossover, inpatient study to evaluate the effects of multiple doses of DVS SR and duloxetine on the PK of a single dose of desipramine in healthy subjects. Subjects were randomly assigned at a ratio of 1:1 to receive either the sequence A or sequence B treatment regimen (See below). Subjects were admitted to the clinic for inpatient confinement for up to 30 days and were required to follow a medium-fat diet. Test article was administered at predetermined time points for up to 30 days.

In period 1, a single 50-mg dose of desipramine was administered followed by 120 hours of pharmacokinetic (PK) sample collection. In period 2, DVS SR or duloxetine was administered alone on predetermined study days followed by co-administration with desipramine on subsequent study days. Blood samples for PK analysis were collected for up to 120 hours. Period 3 was the washout phase. In period 4, DVS SR or duloxetine was administered alone on predetermined study days followed by co-administration with

desipramine on other study days. The dose of duloxetine (30 mg BID) was the therapeutic dose of this medication. Duloxetine was included in this study as a positive control, because it is a known moderate CYP2D6 inhibitor. Blood samples for PK analysis were collected for up to 120 hours. Blood sample collection for the CYP2D6 genotype was required to ensure the validity of changes in desipramine PK observed in this study. The blood sample collection for the CYP2D6 genotype occurred at the time of admission to the clinic on day -1. The flowing is a flow chart for PK blood sampling.

Pharmacokinetic Flowchart

Study Interval	Predose	Postdose												
Study Day	Days 1, 11, 25	Days 1 Through 6, 11 Through 16, and 25 Through 30												
Time Relative to Dose	Hour 0	Hour 0.5	Hour 1	Hour 2	Hour 3	Hour 4	Hour 6	Hour 8	Hour 12	Hour 24	Hour 48	H 72	H 96	H 120
PK blood sample[a] collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PK=pharmacokinetic.

a. Dietary requirements included a medium-fat diet. Drinking water was allowed 2 hours before and 2 hours after dose administration. Timing of meals was according to the clinic schedule before drug administration. Overnight fasting (at least 10 hours before dose administration) was required at screening and on day 1, day 11, and day 25. No breakfast was served on days 1, 11, and 25. Drug administration had to be within 5 minutes after the subject finished breakfast for the remainder of the study.

Subjects fasted overnight for at least 10 hours before the required blood sample collection and administration of desipramine. Desipramine was administered with 240 mL of room temperature water. On study day 12, 13, 14, 26, 27-29 test article was administered with 240 mL of room-temperature water within 5 minutes after the subject finished breakfast. Additional drinking water was allowed up to 2 hours before and 2 hours after dose administration.

On day 1, subjects must have fasted overnight for at least 10 hours before the required blood sample collection and desipramine administration. Desipramine was administered with 240 mL of room temperature water. Subjects did not receive breakfast on this study day. Food was allowed 4 hours after test article administration. On days 6 through 10, test article was administered with 240 mL of room-temperature water within 5 minutes after the subject finished breakfast. Additional drinking water was allowed up to 2 hours before and 2 hours after dose administration. On days 11-14, 20- 24 subjects fasted overnight for at least 10 hours before the required blood sample collection and administration of desipramine and test article (duloxetine or DVS SR). Desipramine and test article were given with 240 mL of room-temperature water. Additional drinking water was allowed 2 hours before and 2 hours after dose administration. Subjects did not

receive breakfast on this study day. Food was allowed 4 hours after test article administration. On day 25, subjects fasted overnight for at least 10 hours before the required blood sample collection and administration of desipramine and test article (duloxetine or DVS SR). Desipramine and test article were given with 240 mL of room-temperature water. Additional drinking water was allowed 2 hours before and 2 hours after dose administration. Subjects did not receive breakfast on this study day. Food was allowed 4 hours after test article administration. On days 26 through 29, test article was administered with 240 mL of room-temperature water within 5 minutes after the subject finished breakfast. Test articles for the study included desipramine 50-mg tablets, DVS SR 100-mg tablets, and duloxetine 30-mg capsules. The strengths, batch numbers, and formulation numbers of the study drugs and the test article are summarized in the following table.

Study Drug Information

Study Drug (mg)	Dosage (mg)	Batch Number	Formulation Number
Desipramine	50	149898	9206895
DVS SR	100	A97186	0932044C
Duloxetine	30	A168220	9206983

Study Drug Treatment

	DVS SR	Duloxetine	Desipramine
Dose	100 mg	30 mg BID	50 mg
Dosage forma	Tablet	Capsule	Tablet
Duration and schedule	Subjects were given 1 tablet on days 6 to 14 and 20 to 28.	Subjects were given 1 tablet twice daily on days 6 to 14 and 20 to 28.	Subjects were given 1 tablet on days 1, 11, and 25.

Abbreviation: BID=twice daily.

a. All treatments given orally.

The test articles were given by the clinic as follows:

Sequence Group A
Day 1: Single dose of desipramine 50 mg
Days 6 to 10: Daily dose of DVS SR 100 mg
Day 11: Desipramine 50 mg coadministered with DVS SR 100 mg
Days 12 to14: Daily dose of DVS SR 100 mg
Days 20 to 24: Duloxetine 30 mg BID
Day 25: Desipramine 50 mg coadministered with duloxetine 30 mg BID
Days 26 to 28: Duloxetine 30 mg BID

Sequence Group B
Day 1: Single dose of desipramine 50 mg
Days 6 to 10: Duloxetine 30 mg BID
Day 11: Desipramine 50 mg coadministered with duloxetine 30 mg BID
Days 12 to 14: Duloxetine 30 mg BID
Days 20 to 24: Daily dose of DVS SR 100 mg
Day 25: Desipramine 50 mg coadministered with DVS SR 100 mg
Days 26 to 28: Daily dose of DVS SR 100 mg

Blood samples were collected for determination of desipramine and 2-hydroxydesipramine concentrations on study days 1 to 6, study days 11 to 16, and study days 25 to 30 within 2 hours before and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after test article administration. Twice during each period, 2 (days 11 and 12) and 4 (days 25 and 26), blood samples were collected to measure steady-state trough DVS SR and duloxetine plasma concentrations within 30 minutes before desipramine administration.

Pharmacogenomic Measurements

CYP2D6 genotyping was used to evaluate the potential impact of genetic polymorphisms for any outliers with respect to the PK of desipramine when given simultaneously with DVS SR. The following CYP2D6 alleles were investigated to characterize the metabolizer status (ultrarapid metabolizer [UM], extensive metabolizer [EM], intermediate metabolizer [IM], or poor metabolizer [PM]) of each subject: *1, *2, *2xN (gene duplication), *3 to *10, *17, *29, and *41. Note that CYP2D6*1 is defined in this study as the absence of CYP2D6*2, *3, *4, *5, *6, *7,*8, *9, *10, *17, *29, *41, and *2xN polymorphisms and does not, therefore, necessarily imply wild-type status. Individuals assigned *1 alleles for CYP2D6 in this study may possess other nucleotide polymorphisms in CYP2D6 that were not evaluated in this study. The *2xN allele is specifically defined as a duplication of the *2 allele, and in the current study, duplication is assumed to represent 1 extra copy of CYP2D6. Two patients with UM or IM type were excluded in the sensitivity analysis to compare the treatment difference. All phenotype

predictions in this study are based on the assumption that 2 heterozygous positions that are characteristic for the alleles investigated are located on different chromosomes.

Analytical Method

Desipramine and 2-hydroxydesipramine concentrations in sodium heparin-treated plasma and desvenlafaxine and duloxetine concentrations in plasma were measured using validated liquid chromatography/tandem mass spectrometry (LC/MS/MS). The performance of the desipramine and 2-hydroxydesipramine assays during analysis of the plasma samples from this study are summarized in the following table.

Assay Range and Sensitivity for Desipramine and 2-Hydroxydesipramine in Plasma Samples

Standard Curve	Compound/Matrix Desipramine/Plasma	Compound/Matrix 2-Hydroxydesipramine/Plasma
Linear range (ng/mL)	0.25-100	0.25-100
Sensitivity (ng/mL)	0.25	0.25

Analytical Summary of Desipramine and 2-Hydroxydesipramine Assays in Plasma Sample

	Low CS (0.600 ng/mL)			Medium CS (5.25 ng/mL)			High CS (75.0 ng/mL)		
Analyte	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Desipramine	0.568	8.24	-5.34	5.09	2.61	-2.98	73.3	3.67	-2.30
2-Hydroxydesipramine	0.607	9.22	1.15	5.13	2.82	-2.29	72.4	3.17	-3.47

Abbreviations: Conc=concentration; CS=calibration standards; CV%=coefficient of variation.

The performance of the desvenlafaxine assay during analysis of plasma samples from this study is summarized in the following tables

Assay Range and Sensitivity for Desvenlafaxine in Plasma Samples

Standard Curve	Desvenlafaxine/Plasma
Linear range (ng/mL)	2.0-500
Sensitivity (ng/mL)	2.0

Analytical Summary of Desvenlafaxine Assays in Plasma Samples

Analyte	High QC (375.0 ng/mL)			Medium QC (45.0 ng/mL)			Low QC (5.0 ng/mL)		
	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Desvenlafaxine	379.5	NA	1	46.96	NA	4	5.142	NA	3

Abbreviations: Conc=concentration; CV%=coefficient of variation; QC=quality control.
NA: The precision (CV%) could not be calculated because n was less than 3.

The performance of the duloxetine assay during analysis of plasma samples from this study is summarized in the following tables.

Standard Curve	Compound/Matrix Duloxetine/Plasma
Linear range (ng/mL)	0.2-50.0
Sensitivity (ng/mL)	0.2

Analytical Summary of Duloxetine Assays in Plasma Samples

Analyte	High QC[a] (37.50 ng/mL)			Medium QC (5.000 ng/mL)			Low QC (0.6000 ng/mL)		
	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Duloxetine	37.45	2.7	-0.1	4.929	4.9	-1.4	0.6443	5.8	7.0

Abbreviations: Conc=concentration; CV%=coefficient of variation; QC=quality control.

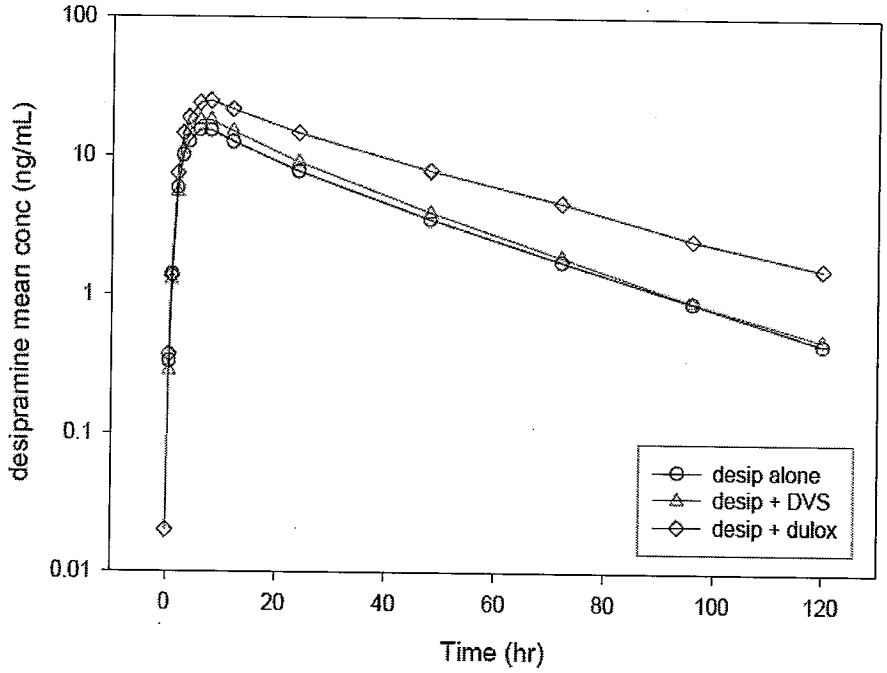
Data Analysis

A noncompartmental PK method was used to analyze the plasma concentrations of desipramine and 2-hydroxydesipramine. To assess the effect of each combination therapy on the AUC and Cmax of desipramine, the 90% confidence interval on the ratio of each combination therapy to the AUC and Cmax of desipramine alone was calculated. The comparison of AUC and Cmax between combination therapies was calculated with a 2-period crossover analysis of variance (ANOVA) on the logarithms of the AUC and Cmax. Pharmacokinetic variations based on CYP2D6 genotypic activity (PM: lack of active enzyme gene alleles; EM: normal complement of 2 fully active enzyme gene alleles; IM: homozygous for 2 reduced-activity enzyme gene alleles or heterozygous for an inactive allele; UM: more than 2 copies of active enzyme gene alleles) were assessed using a sensitivity analysis that excluded subjects who were not predicted to have an EM phenotype. See Pharmacogenomic evaluation.

Results

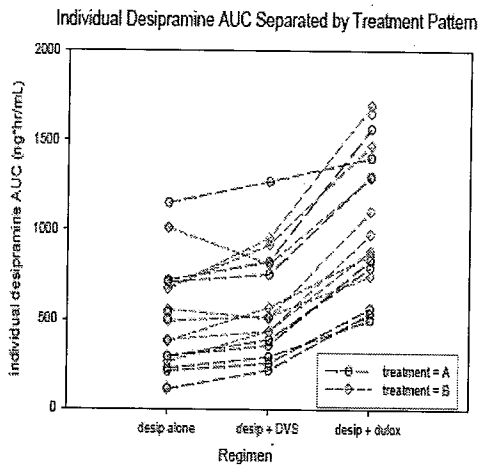
The following figure displays mean desipramine plasma concentrations after administration of desipramine, coadministration of desipramine and DVS SR, and coadministration of desipramine and duloxetine.

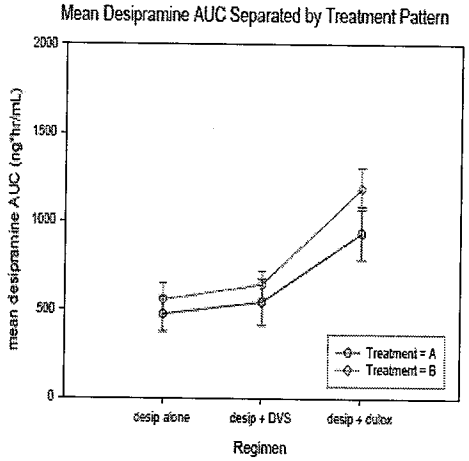
Desipramine Mean Plasma Concentration-Verusus-Time Profile After Desipramine Administration Alone, Coadministration with DVS SR and Coadministration with Duloxetine



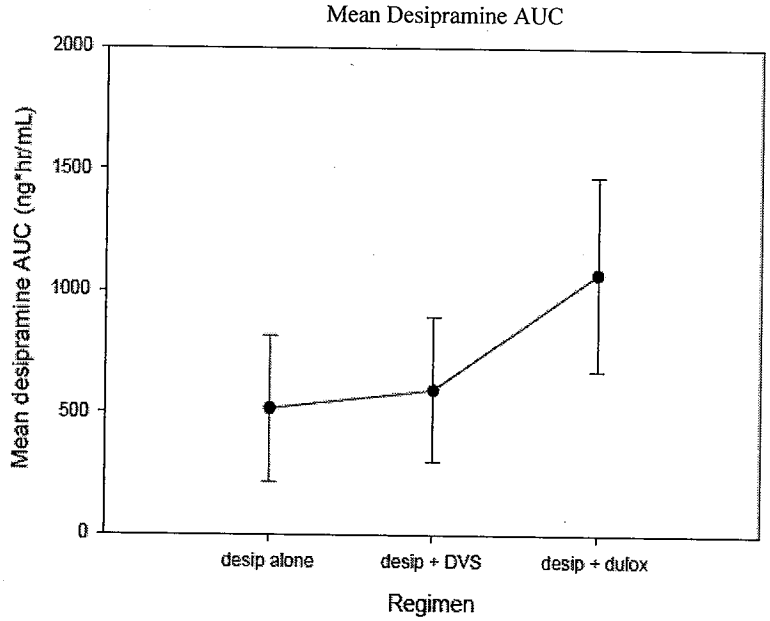
The following figures present individual and mean values of desipramine AUC and Cmax, respectively.

Desipramine Individual AUC and Mean AUC After Administration of Desipramine Without and With Coadministration of DVS SR or Duoloxetine





Treatment Pattern A = Desipramine alone / Desipramine +DVS / Desipramine +Duloxetine;
Treatment Pattern B = Desipramine alone / Desipramine + Duloxetine / Desipramine +DVS.



The following tables provide summary of pharmacokinetic parameters of desipramine for the 3

treatments periods and the results of the statistical analysis on desipramine for the 3 treatment periods.

Summary of Pharmacokinetic Parameters (Plasma) for Desipramine After Treatment With Desipramine Alone, Co-administration With DVS SR, and Coadministration With Duloxetine to Healthy Subjects

Treatment	Variables	C_{max} (ng/mL)	t_{max}[a] (h)	AUC (ng*h/mL)	AUC_Extrapolated (%)	$t_{½}$ (h)	CI/F (L/h/kg)	V_z/F (L/kg)
Desipramine 50 mg	n	20	20	20	20	20	20	20
	Mean±SD	16.09±6.22	8.0	516±301	4.18±2.71	20.0±7.1	1.83±1.47	43.61±22.57
	CV%	38.6		58.3		35.6	80.3	51.7
	Geo. mean	14.70		428		18.9	1.45	39.57
	Min–max	4.98–26.30	4.0–16.0	111–1151		10.8–33.6	0.57–6.01	27.05–103.57
Desipramine 50 mg + DVS SR 100 mg once daily	n	16	16	16	16	16	16	16
	Mean±SD	18.60±5.53	8.0	594±298	4.23±2.20	22.2±6.4	1.33±0.71	37.47±12.28
	CV%	29.7		50.1		28.6	53.8	32.8
	Geo. mean	17.75		528		21.3	1.17	35.82
	Min–max	9.58–28.80	6.0–16.0	217–1271		10.5–34.2	0.52–3.05	21.77–64.35
Desipramine 50 mg + Duloxetine 30 mg twice daily	n	17	17	17	17	17	17	17
	Mean±SD	25.76±7.90	8.0	1069±399	6.98±4.85	29.4±7.0	0.67±0.29	26.39±7.21
	CV%	30.7		37.3		23.7	43.2	27.3
	Geo. mean	24.70		995		28.6	0.62	25.60
	Min–max	13.10–48.30	6.0–16.0	449–1695		20.1–41.5	0.33–1.30	18.82–43.68

Abbreviations: AUC=area under the plasma concentration-versus-time curve; Cmax=peak concentration; CI/F=apparent oral-dose clearance; CV%=coefficient of variation; t½=apparent terminal half life; tmax=time to peak concentration; Min=minimum; max=maximum; SD=standard deviation; Vz/F=apparent volume of distribution.

a. Median value and range.

Statistical Analysis of Pharmacokinetic Parameters for Desipramine After administration of Desipramine Alone, Co-administration With DVS SR And Co-administration With Duloxetine to Healthy Subjects

Treatment[a]	Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Desipramine + DVS SR	Ratio of mean[b]	122%	119%
	90% CI	107%-138%	108%-130%
Desipramine + duloxetine	Ratio of mean[b]	222%	163%
	90% CI	195%-251%	149%-179%

Abbreviations: AUC=area under the concentration-versus-time curve; CI=confidence interval; Cmax=peak concentration.

a. Reference is treatment with desipramine alone.

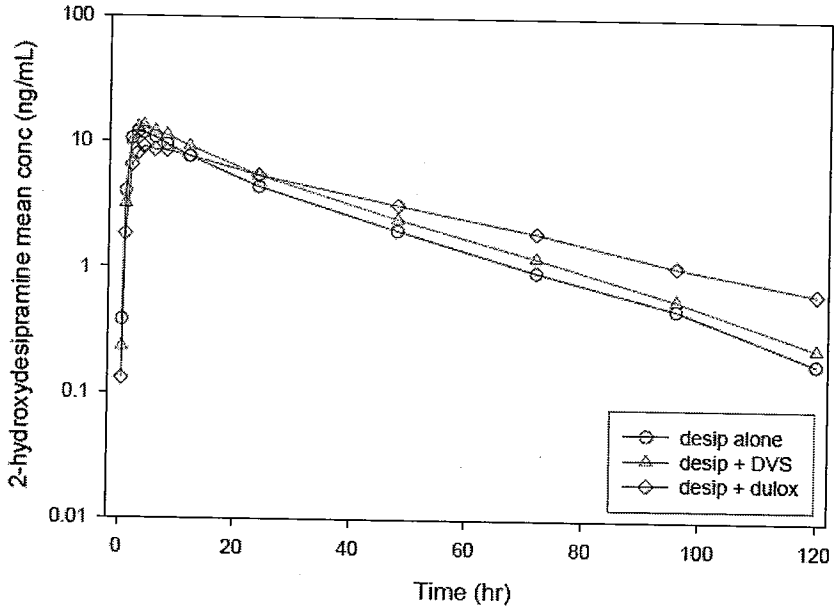
b. Ratio of geometric least square means.

Coadministration of DVS SR increased the mean desipramine AUC by approximately 22% and Cmax by 19%. Mean Cl/F decreased approximately 27% with concomitant administration of desipramine and DVS SR and decreased approximately 63% with concomitant administration of desipramine and duloxetine. The results of the statistical analyses for the desipramine Cmax indicated that the increase in the Cmax for desipramine was significantly greater after duloxetine administration than after DVS SR administration ($p<0.001$). Similar results were seen for the AUC ($p<0.001$).

2-Hydroxydesipramine

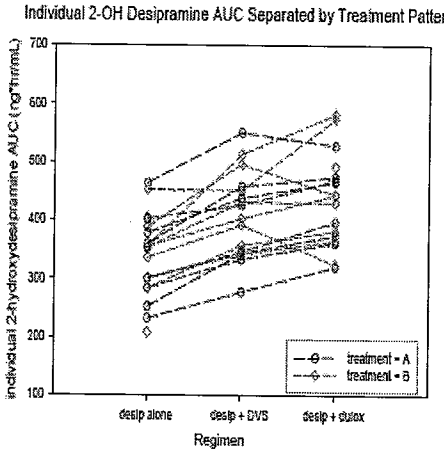
The following figure displays mean 2-hydroxydesipramine plasma concentrations after treatments of desipramine alone, coadministration of desipramine and DVS SR, and coadministration of desipramine and duloxetine.

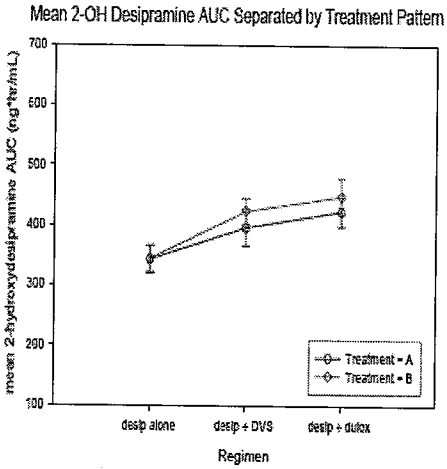
2-Hydroxydesipramine Plasma Concentration- Versus-Time Profile After Administration of Desipramine Alone, Coadministration With DVS SR, and Coadministration With Duloxetine



The following figures present individual and mean values of 2-hydroxydesipramine AUC and Cmax, respectively.

2-Hydroxydesipramine Individual AUC and Mean AUC After Administration of Desipramine Without and With Coadministration of DVS SR or Duloxetine





Treatment Pattern A = Desipramine alone / Desipramine +DVS / Desipramine +Duloxetine;
Treatment Pattern B = Desipramine alone / Desipramine + Duloxetine / Desipramine +DVS.

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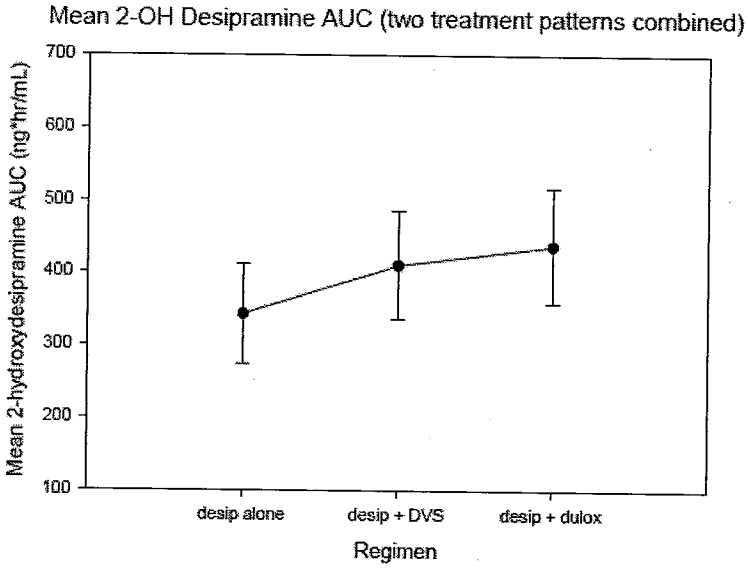
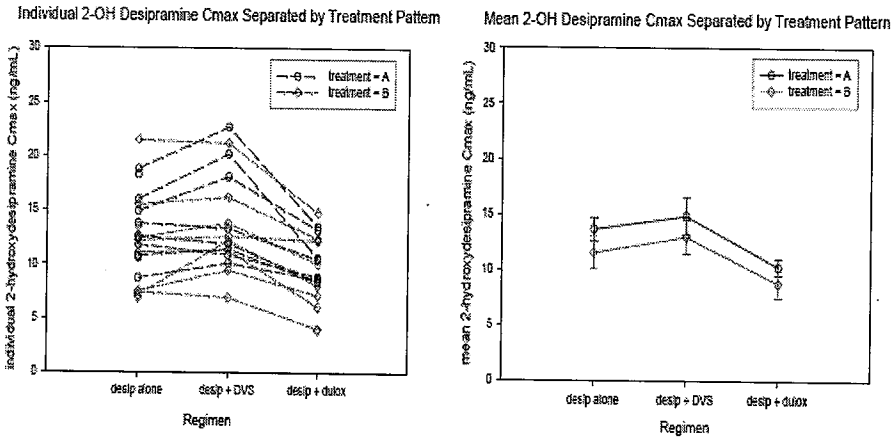
2-Hydroxydesipramine Mean AUC After Administration Of Desipramine Without and With Coadministration of DVS SR or Duloxetine (From Both Treatment Patterns Combined)

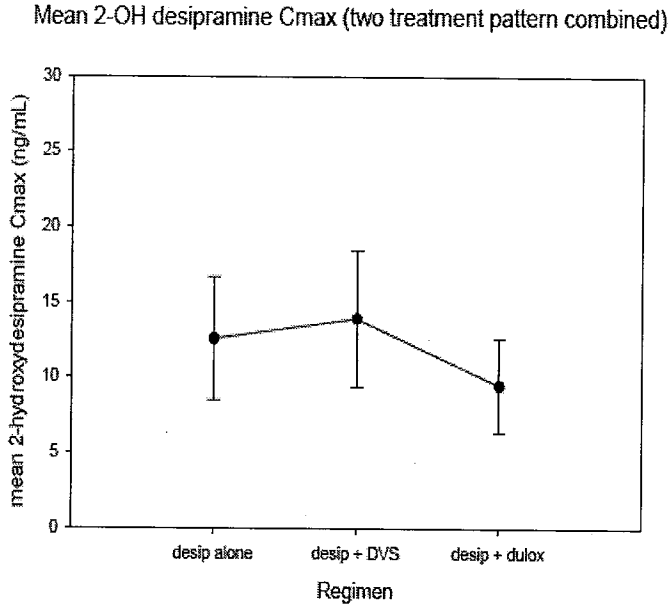


2-Hydroxydesipramine Individual Cmax and Mean Cmax After Administration of Desipramine Without and With Coadministration of DVS SR or Duloxetine



Treatment Pattern A = Desipramine alone / Desipramine +DVS / Desipramine +Duloxetine;
Treatment Pattern B = Desipramine alone / Desipramine + Duloxetine / Desipramine +DVS.

2-Hydroxydesipramine Mean Cmax After Administration of Desipramine Without and With Coadministration of DVS SR or Duloxetine From Both Treatment Patterns Combined



The following tables provide summary PK parameters of 2-hydroxydesipramine for the 3 treatments and the results of statistical analysis for 2-hydroxydesipramine for the 3 treatments.

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Summary of Pharmacokinetic Parameters (Plasma) for 2-Hydroxydesipramine After Treatment With Desipramine Alone, Coadministration With DVS SR and Coadministration With Duloxetine to Healthy Subjects

Treatment	Variables	C_{max} (ng/mL)	t_{max}[a] (h)	AUC (ng*h/mL)	AUC_Extrapolated (%)	$t_{½}$ (h)	AUC Ratio[b]
Desipramine 50 mg	n	20	20	20	20	20	20
	Mean±SD	12.57±4.09	3.0	343±69	4.84±2.76	21.5±7.7	0.89±0.49
	%CV	32.5		20.2		35.6	55.0
	Geo. mean	11.94		336		20.4	0.79
	Min–max	6.89–21.50	2.0–16.0	208–464		11.9–37.0	0.35–2.28
Desipramine 50 mg + DVS SR 100 mg once daily	n	16	16	16	16	16	16
	Mean±SD	13.89±4.52	7.0	410±75	3.81±2.41	22.2±6.3	0.83±0.34
	%CV	32.6		18.2		28.5	40.6
	Geo. mean	13.24		403		21.5	0.76
	Min–max	6.93–22.70	2.0–16.0	277–550		15.4–37.5	0.43–1.57
Desipramine 50 mg + Duloxetine 30 mg twice daily	n	17	17	17	17	17	20
	Mean±SD	9.47±3.15	11.9	437±79	9.69±9.41	33.9±12.9	0.46±0.16
	%CV	33.3		18.2		38.2	34.9
	Geo. mean	8.90		430		32.1	0.43
	Min–max	3.97–14.80	2.0–16.0	320–582		21.6–74.9	0.22–0.72

Abbreviations: AUC=area under the plasma concentration-versus-time curve; C_{max}=peak concentration; CV%=coefficient of variation; $t_{½}$=apparent terminal half-life; t_{max}=time to peak concentration; Min=minimum; max=maximum; SD=standard deviation.

a. Median value and range.

b. AUC ratio=$AUC_{2\text{-hydroxydesipramine}}/AUC_{desipramine}$.

Results of Statistical Analysis of Pharmacokinetic Parameters for 2-Hydroxydesipramine After Administration of Desipramine Alone, Coadministration With DVS SR, and Coadministration With Duloxetine to Healthy Subjects

Treatment[a]	Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Desipramine + DVS SR	Ratio of mean[b]	119%	109%
	90% CI	114%-125%	100%-119%
Desipramine + duloxetine	Ratio of mean[b]	126%	76%
	90% CI	120%-132%	71%-83%

Abbreviations: AUC=area under the concentration-versus-time curve; CI=confidence interval; C_{max}=peak concentration.

a. Reference is treatment with desipramine alone.

b. Ratio of geometric least square means.

The mean Cmax for 2-hydroxydesipramine was approximately 9% higher with concomitant administration of DVS SR than the Cmax when desipramine was administered alone. The mean Cmax after coadministration of duloxetine was approximately 24% lower than the Cmax when desipramine was administered alone. The mean AUC for 2-hydroxydesipramine was about 19% higher with concomitant administration of DVS SR than the AUC when desipramine was administered alone. The mean after coadministration of duloxetine was approximately 26% higher than AUC when desipramine was administered alone.

The mean predose concentrations (±SD) of desvenlafaxine on days 11 and 12 were 166.96 (±49.62) and 201.36 (±65.69) ng/mL, respectively. The mean predose concentrations (±SD) of desvenlafaxine on days 25 and 26 were 200.50 (±55.24) and 207.04 (±50.46) ng/mL, respectively. The mean predose concentrations (±SD) of duloxetine on days 11 and 12 were 35.85 (±17.30) and 38.34 (±18.64) ng/mL, respectively. The mean predose concentrations (±SD) of duloxetine on days 25 and 26 were 32.36 (±9.50) and 34.57 (±10.80) ng/mL, respectively.

Pharmacogenomic Summary: The sponsor reported that 18 subjects (90%) were predicted to have an EM phenotype. One subject (5%) was predicted to have an IM phenotype, and 1 subject (5%) was predicted to have a UM phenotype. No subjects were predicted to have a PM phenotype.

Safety Summary: Headache was the most frequently reported AE overall and was reported by somewhat more subjects in the DVS SR/duloxetine sequence group. Diarrhea was the next most frequently reported AE and was more prevalent in the duloxetine/DVS SR sequence. Nausea and tachycardia were reported in 3 subjects overall. Tachycardia occurred in 2 (20%) subjects in the DVS SR/duloxetine sequence group and 1 (10%) in the duloxetine/DVS SR sequence group. There was 1 SAE reported in the study, a seizure followed by hypotension.

Conclusions: The sponsor concluded that the results of this study indicate that coadministration of the CYP2D6 substrate desipramine with 100-mg daily doses of DVS SR resulted in approximately similar exposure to desipramine and 2-hydroxydesipramine. This contrasts with the greater exposure to desipramine after coadministration with duloxetine.

Reviewer comments: Co-administration of DVS with desipramine resulted in significant increases in desipramine concentrations(about 20%). The increases were less than that seen when desipramine were co-administered with duloxetine, a CYP 2D6 inhibitor (about 2-fold). Desvenlafaxine has an inhibitory potential on CYP2D6 isozyme. Dosage adjustment is not recommended; however, caution should be used when Desvenlafaxine is co-administered with desipramine.

3.2.3. Title (3151A1-900-US): A Randomized, Open-Label, Crossover, Drug Interaction Study To Evaluate The Effects Of DVS SR And Paroxetine On The Pharmacokinetics Of Desipramine In Healthy Subjects

Objective: To evaluate the effects of multiple doses of DVS SR and paroxetine on the pharmacokinetics (PK) of a single dose of desipramine in healthy subjects.

Study Design: This was a single-center, randomized, open-label, 4-period crossover, inpatient study. Twenty subjects were enrolled in this study at 1 investigational site. The mean ±SD age and weight were 35 ± 7.7 years and 79.9 ± 9.8 kg, respectively. Subjects

were randomly assigned at a ratio of 1:1 to receive either the sequence A or sequence B treatment regimen. Subjects were admitted to the clinic for inpatient confinement for up to 29 days and were required to follow a medium-fat diet. Subjects were administered test article at predetermined time points for up to 29 days.

In period 1, a single 50-mg dose of desipramine was administered followed by 120 hours of PK sample collection. In period 2, DVS SR or paroxetine was administered alone on predetermined study days followed by coadministration with desipramine on subsequent study days. Blood samples for PK analysis were collected for up to 120 hours. Period 3 was the washout phase. In period 4, DVS SR or paroxetine was administered alone on predetermined study days followed by coadministration with desipramine on other study days. Blood samples for PK analysis were collected for up to 120 hours.

Blood sampling for the cytochrome P450 (CYP2D6) genotype was required to ensure the validity of changes in desipramine PK observed in this study. The blood sample collection for the CYP2D6 genotype occurred at the time of admission to the clinic on day-1. However, completion of the genotype assay was not required before initiation of other study procedures. Subjects must have had consented to blood sample collection for the CYP2D6 genotyping to participate in the study. The following table contains blood sampling times for pharmacokinetic analysis.

Pharmacokinetic Flowchart

Study Interval	Predose	Post Dose												
Study Day	Days 1, 11, 25	Days 1 Through 5, 11 Through 15, and 25 Through 29												
Time Relative to Dose	Hr 0	Hr 0.5	Hr 1	Hr 2	Hr 3	Hr 4	Hr 6	Hr 8	Hr 12	Hr 24	Hr 48	Hr 72	Hr 96	Hr 120
PK blood sample[a] collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Dietary requirement of a medium-fat diet. Drinking water was allowed 2 hours before and 2 hours after dose administration. Timing of meals was according to the clinic schedule before drug administration. Overnight fasting (at least 10 hours before dosing) occurred at screening and on days 1, 11, and 25. No breakfast was eaten on days 1, 11 and 25. Drug administration must have been within 5 minutes after the subject finished breakfast for the remainder of the study.

On study days 1, 11, 25, 27 and 28, subjects fasted overnight for at least 10 hours before the required blood sample collection and administration of desipramine. On study days 6 through 10, 12, 13, 14, 20 through 24, 26 test article was administered with 240 mL room-temperature water within 5 minutes after the subject finished breakfast.
Test articles for the study-included desipramine, 50-mg tablets; DVS SR, 100-mg tablets; and paroxetine, 20-mg tablets. The formulation, strength and batch numbers of the study are summarized in the following table.

Study Drug Information

Study Drug (mg)	Dosage (mg)	Batch Number	Formulation Number
Desipramine	50	149898	9206995
DVS SR	100	A97186	0932044C
Paroxetine	20	764Z77	9206994

The following table provides a summary of study treatment dose and regimen.

Study Treatment Dose and Regimen

	Test Article	Test Article	Test Article (Test Substrate)
Name	Desvenlafaxine SR	Paroxetine	Desipramine
Dose	100 mg	20 mg	50 mg
Dosage form	Tablet	Tablet	Tablet
Route of administration	Orally	Orally	Orally
Duration and schedule	Subjects were given 1 tablet on days 6 to 14 and 20 to 28.	Subjects were given 1 tablet on days 6 to 14 and 20 to 28.	Subjects were given 1 tablet on days 1, 11, and 25.

A summary of when the test article were given by the clinic is provided below:

Sequence Group A
Day 1: Single dose of desipramine 50 mg
Days 6 to 10: Daily dose of DVS SR 100 mg
Day 11: Desipramine 50 mg coadministered with DVS SR 100 mg
Days 12 to14: Daily dose of DVS SR 100 mg
Days 20 to 24: Daily dose of paroxetine 20 mg
Day 25: Desipramine 50 mg coadministered with paroxetine 20 mg
Days 26 to 28: Daily dose of paroxetine 20 mg

Sequence Group B
Day 1: Single dose of desipramine 50 mg
Days 6 to 10: Daily dose of paroxetine 20 mg
Day 11: Desipramine 50 mg coadministered with paroxetine 20 mg
Days 12 to 14: Daily dose of paroxetine 20 mg
Days 20 to 24: Daily dose of DVS SR 100 mg
Day 25: Desipramine 50 mg coadministered with DVS SR 100 mg

Days 26 to 28: Daily dose of DVS SR 100 mg

Blood samples were collected for determination of desipramine and 2-hydroxy desipramine concentrations on study days 1 to 5, on study days 11 to 15, and study days 25 to 29 before (within 2 hours before predose) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after test article administration.

Twice each in periods 2 (days 11 and 12) and 4 (days 25 and 26), within 30 minutes before desipramine administration, blood samples were collected to measure steady state trough desvenlafaxine and paroxetine plasma concentrations.

Analytical Method: Desipramine and 2-hydroxydesipramine concentrations in sodium heparin-treated plasma, Desvenlafaxine and paroxetine concentrations in plasma were measured using validated liquid chromatography/tandem-mass spectroscopy (LC/MS/MS). The range of quantitation in plasma was from 0.250-100 ng/mL.

Data Analysis: The PK of orally administered desipramine were determined when the drug was administered alone and in combination with DVS SR and paroxetine. The performance of the desipramine and 2-hydroxydesipramine assays during analysis of the plasma samples from this study are summarized in the following tables.

Assay Range and Sensitivity for Desipramine and 2-Hydroxydescipramine in Plasma Samples

Standard Curve	Compound/Matrix Desipramine/Plasma	Compound/Matrix 2-Hydroxydesipramine/Plasma
Linear range (ng/mL)	0.25-100	0.25-100
Sensitivity (ng/mL)	0.25	0.25

Analytical Summary of Desipramine and 2-Hydroxydesipramine Assays in Plasma Samples

	Low CS (0.600 ng/mL)			Medium CS (5.25 ng/mL)			High CS (75.0 ng/mL)		
Analyte	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Desipramine	0.600	6.76	0.016	5.19	3.14	-1.14	75.0	2.02	-0.058
2-Hydroxydesipramine	0.602	14.5	0.300	5.16	3.38	-1.64	74.9	4.49	-0.103

Abbreviations: Conc=concentration; CS calibration standards; CV%=coefficient of variation.

The performance of the desvenlafaxine assay during analysis of plasma samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Desvenlafaxine in Plasma Samples

Standard Curve	Desvenlafaxine/Plasma
Linear range (ng/mL)	2.0-500
Sensitivity (ng/mL)	2.0

Analytical Summary of Desvenlafaxine Assays in Plasma Samples

	High QC (375.0 ng/mL)			Medium QC (45.0 ng/mL)			Low QC (5.0 ng/mL)		
Analyte	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Desvenlafaxine	326.1	4.2	-13.0	40.98	5.4	-8.9	4.777	7.2	-4.5

Abbreviations: Conc=concentration; CV%=coefficient of variation; QC= quality control.

The performance of the paroxetine assay during analysis of plasma samples from this study is summarized in the following table.

Assay Range and Sensitivity for Paroxetine in Plasma Samples

Standard Curve	Compound/Matrix Paroxetine/Plasma
Linear range (ng/mL)	0.2-50.0
Sensitivity (ng/mL)	0.2

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Analytical Summary of Paroxetine Assays in Plasma Samples

	High QC (40.00 ng/mL)			Medium QC (4.000 ng/mL)			Low QC (0.5000 ng/mL)		
Analyte	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Paroxetine	38.34	4.1	-4.1	3.988	5.4	-0.3	0.5075	4.4	2.0

Abbreviations: Conc=concentration; CV%=coefficient of variation; QC= quality control.

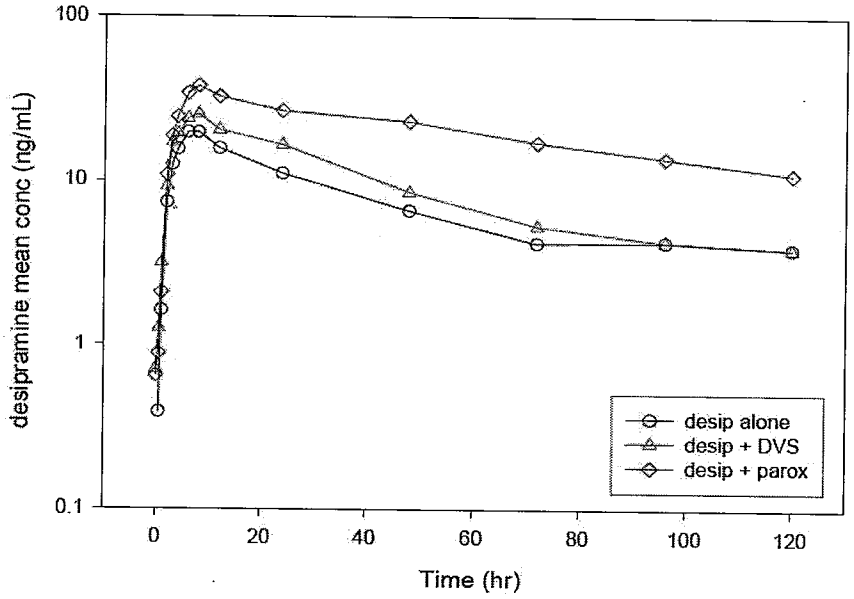
Data Analysis: A noncompartmental PK method was used to analyze the plasma concentrations of desipramine and 2-hydroxydesipramine.

To assess the effect of each treatment on the AUC and Cmax, the 90% confidence interval on the ratio of each combination therapy to the AUC and Cmax of desipramine alone was calculated. The comparison of AUC and Cmax between treatments was performed with a 2-period crossover analysis of variance (ANOVA) on the logarithms ratios of AUC and Cmax on the combination therapy to the desipramine alone.

Pharmacogenetic Measurements: For CYP2D6 genotyping, a 5-mL whole blood sample was collected and stored, refrigerated, in an upright position at 4 °C until shipped. CYP2D6 genotyping was used to evaluate the potential impact of genetic polymorphisms for any outliers with respect to the PK of desipramine when given simultaneously with DVS SR. The following CYP2D6 alleles were investigated to characterize the metabolizer status (UM=ultrarapid metabolizer, EM=extensive metabolizer, IM=intermediate metabolizer, and PM=poor metabolizer) of each subject: *1, *2, *2xN (gene duplication), *3 to *8, *10, *17, *29, *40, and *41. Note that CYP2D6*1 is defined in this study as the absence of CYP2D6*2, *3, *4, *5, *6, *7, *8, *9 *10, *17, *29, *41, and *2xN polymorphisms and does not, therefore, necessarily imply wild-type status. Individuals assigned *1 alleles for CYP2D6 in this study may possess other nucleotide polymorphisms in CYP2D6 that were not evaluated in this study. The *2xN allele is specifically defined as a duplication of the *2 allele, and in the current study, duplication is assumed to represent 1 extra copy of CYP2D6.

Pharmacokinetic Results: The following figure displays mean plasma concentration-time profile after administration of desipramine, coadministered with DVS SR and coadministered with paroxetine.

Desipramine Mean Plasma Concentration Versus Time Profile After Desipramine Administered Alone, Coadministered with DVS SR, and Coadministered with Paroxetine



Summary pharmacokinetic parameters of desipramine for the 3 treatment pattern are provided in the following table.

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Summary of Pharmacokinetic Parameters (Plasma) for Desipramine After Desipramine Administered Alone, Coadministered with DVS SR, and Coadministered With Paroxetine to Healthy Subjects

Treatment	Variables	C_{max} (ng/mL)	t_{max}[a] (hr)	AUC (ng*hr/mL)	AUC-Extrapolated (%)	$t_{1/2}$ (hr)	Cl/F (L/hr/kg)	V/F (L/kg)
Desipramine 50 mg	n	20	20	20	20	20	20	20
	Mean±SD	21.43±9.68	7.0	966±1089	8.09±10.33	26.72±20.54	1.50±1.32	36.24±18.85
	CV%	45.2		113		76.9	87.7	52.0
	Geometric mean	19.35		609		21.91	1.04	32.89
	Min - Max	7.36-44.60	3.0-12.0	120-4432		11.41-83.83	0.15-5.26	19.58-86.61
Desipramine 50 mg + DVS SR 100 mg	n	20	20	20	20	20	20	20
	Mean±SD	27.27±10.56	8.0	1217±1230	6.58±7.76	26.60±14.20	1.02±0.75	28.27±11.99
	CV%	38.7		101		53.4	74.2	42.4
	Geometric mean	25.25		831		23.68	0.76	25.96
	Min-Max	10.40-48.40	3.0-24.2	224-4389		11.10-62.31	0.15-3.01	11.11-59.23
Desipramine 50 mg + paroxetine 20 mg	n	20	20	20	20	20	20	20
	Mean±SD	38.15±10.03	8.0	3631±1671	28.65±13.28	66.83±25.24	0.25±0.24	18.47±5.62
	CV%	26.3		46.0		37.8	96.5	30.4
	Geometric mean	36.73		3160		61.51	0.20	17.80
	Min-Max	18.90-55.70	6.0-12.0	661-7124		21.22-115.24	0.09-1.02	13.17-33.32

Abbreviations: AUC=area under the plasma concentration-versus-time curve; C_{max}=peak concentration; Cl/F=dose clearance; CV%=coefficient of variation; $t_{1/2}$=terminal half life; t_{max}=time to peak concentration; Min=minimum; Max=maximum; SD=standard deviation.

a. Median value and range

The following figures present individual and mean values of desipramine AUC and Cmax, respectively.

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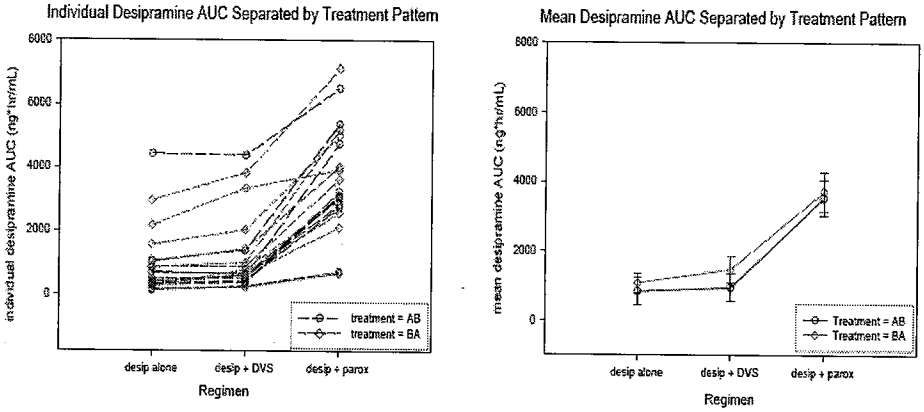
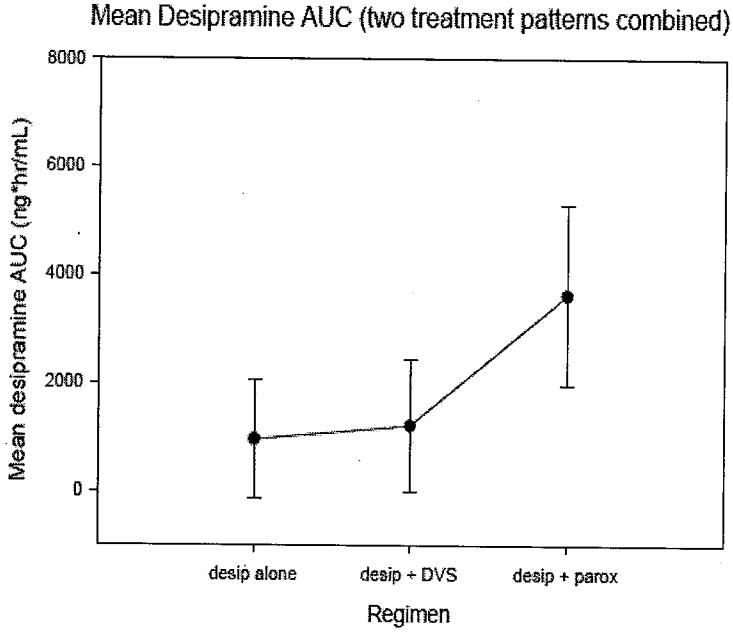
Desipramine Individual and Mean AUC After Administration of Desipramine Without and With Coadministration of DVS SR or Paroxetine

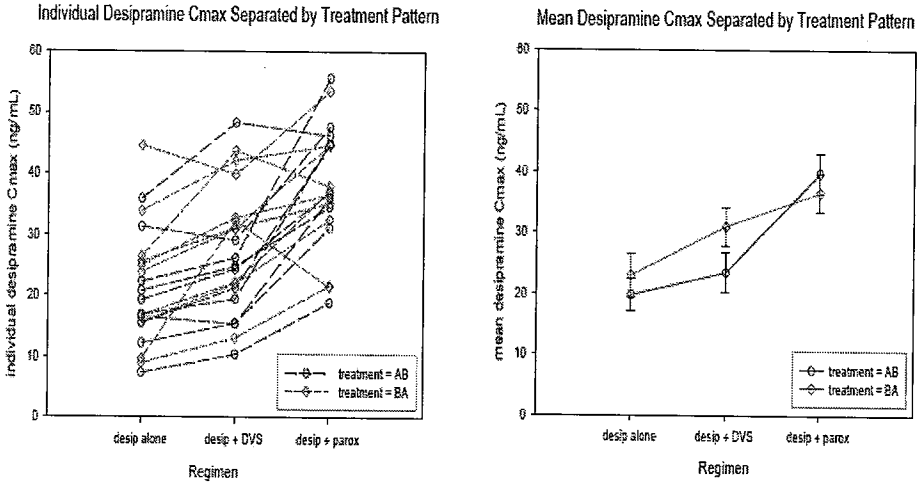


Treatment Pattern AB = Desipramine alone / Desipramine +DVS / Desipramine +Paroxetine;
Treatment Pattern BA = Desipramine alone / Desipramine + Paroxetine / Desipramine +DVS.

Desipramine Mean AUC After Administration of Desipramine Without and With Coadministration of DVS SR or Paroxetine From Both Treatment Patterns Combined



Desipramine Individual Cmax and Mean Cmax After Administration of Desipramine Without and With Coadministration of DVS SR or Paroxetine



Treatment Pattern AB = Desipramine alone / Desipramine +DVS / Desipramine +Paroxetine;
Treatment Pattern BA = Desipramine alone / Desipramine + Paroxetine / Desipramine +DVS.

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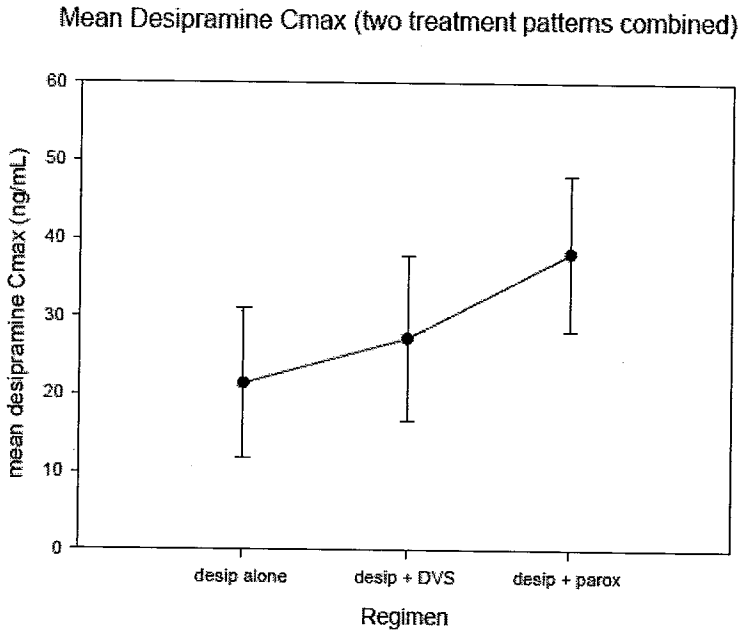
Desipramine Mean Cmax After Administration of Desipramine Without and With Coadministration of DVS SR or Paroxetine From Both Treatments Patterns Combined



The statistical results for desipramine for the 3 treatment patterns are provided in the following table.

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Summary Statistical Results of Pharmacokinetic Parameters for Desipramine After Desipramine Administered Alone, Coadministered With DVS SR, and Coadministered With Paroxetine With Paroxetine to Healthy Subjects

Treatment[a]	Variable	AUC (ng*hr/mL)	C_{max} (ng/mL)
Desipramine + DVS SR	Ratio of mean[b]	136%	130%
	90% CI	114%-163%	118%-145%
Desipramine + paroxetine	Ratio of mean[b]	519%	190%
	90% CI	433%-621%	171-210%

Abbreviations: AUC=area under the plasma-versus-time curve; CI=confidence interval; C_{max}=peak concentration.

a. Reference is desipramine alone treatments.

b. Ratio of geometric least square means.

After concomitant administration of desipramine and DVS SR, the mean Cmax for desipramine was approximately 30% higher than Cmax when desipramine was administered alone. Mean Cmax after concomitant administration of desipramine and paroxetine was approximately 90% higher than Cmax when desipramine was administered alone. Median tmax values were approximately similar for the 2 concomitant treatments (8.0 hours). This was slightly higher than the median tmax after administration of desipramine alone (7.0 hours). Coadministration of DVS SR increased the desipramine mean AUC by approximately 36%. Coadministration of paroxetine increased the mean AUC by 419%.

2-Hydroxydesipramine: The individual and mean values of desipramine AUC and Cmax are presented in the following figures.

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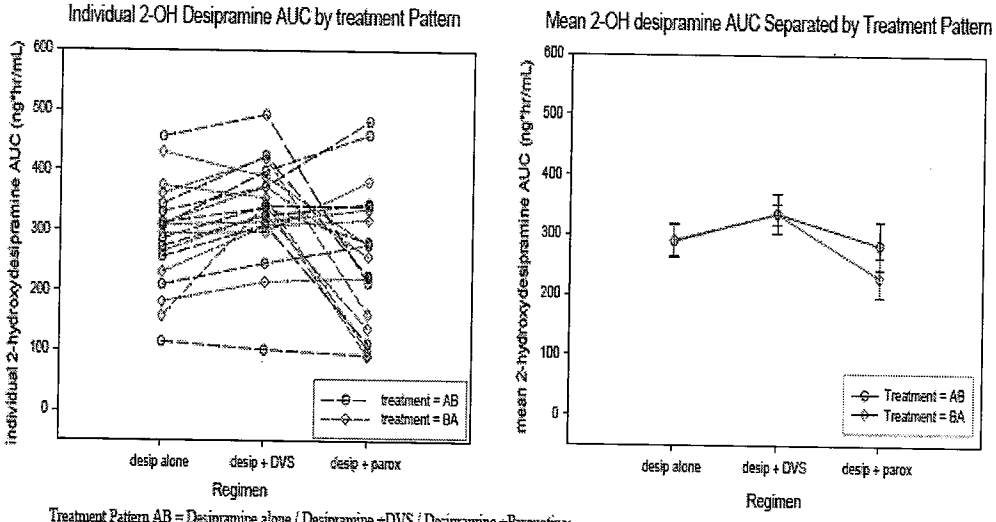
2-Hydroxydesipramine Individual AUC and Mean AUC Administration of Desipramine Without and With Coadministration of DVS SR or Paroxetine



Treatment Pattern AB = Desipramine alone / Desipramine +DVS / Desipramine +Paroxetine;
Treatment Pattern BA = Desipramine alone / Desipramine + Paroxetine / Desipramine +DVS.

2-Hydroxydesipramine Mean AUC After Administration of Desipramine Without and With Coadministration of DVS SR or Paroxetine

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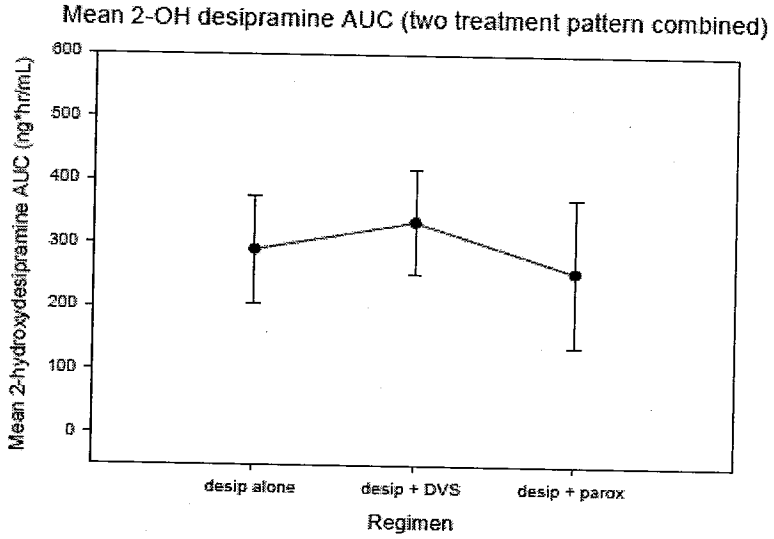
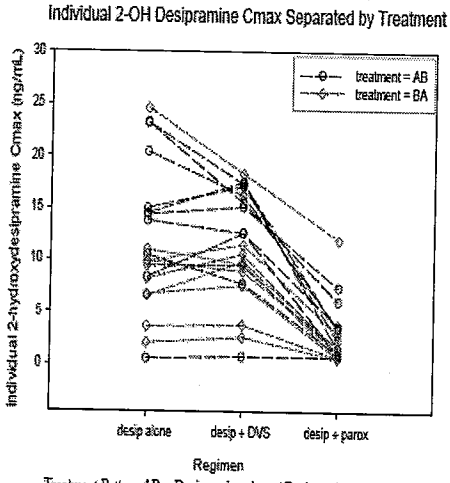
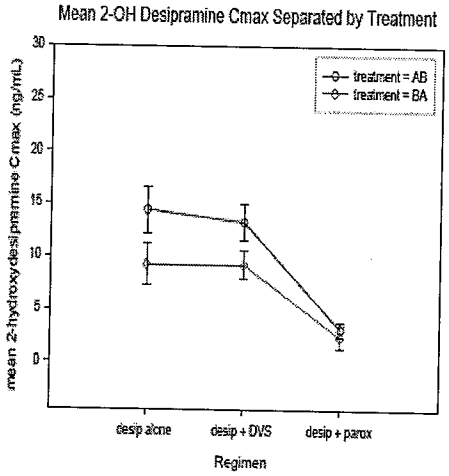


2-Hydroxydesipramine Individual Cmax and Mean Cmax After Administration of Desipramine Without and With Coadministration of DVS SR or Paroxetine





Treatment Pattern AB = Desipramine alone / Desipramine +DVS / Desipramine +Paroxetine;
Treatment Pattern BA = Desipramine alone / Desipramine + Paroxetine / Desipramine +DVS.

The following tables provide summary pharmacokinetic parameters and the results of statistical analysis for 2-hydroxydesipramine for the 3 treatment patterns.

Summary of Pharmacokinetic Parameters for 2-Hydroxydesipramine After Treatment With Desipramine Alone, Coadministered With DVS SR and Coadministered With Paroxetine to Healthy Subjects

Treatment	Variables	C_{max} (ng/mL)	t_{max}[a] (hr)	AUC (ng*hr/mL)	AUC-Extrapolated (%)	$t_{1/2}$ (hr)	AUC Ratio[b]
Desipramine 50 mg	n	20	20	20	20	20	20
	Mean±SD	11.81±6.90	4.0	290±85	9.78±14.38	34.06±36.05	0.66±0.49
	CV%	58.4		29.4		105.8	75.1
	Geometric mean	9.17		277		25.38	0.45
	Min-Max	0.60-24.60	2.0-12.0	115-456		10.88-168.05	0.03-1.82
Desipramine 50 mg + DVS SR 100 mg	n	20	20	20	20	20	20
	Mean±SD	11.24±5.13	4.0	335±83	9.58±11.43	32.41±20.29	0.53±0.36
	CV%	45.6		24.8		62.6	67.1
	Geometric mean	9.35		321		27.93	0.39
	Min-Max	0.78-18.30	2.0-12.0	102-493		14.49-80.92	0.02-1.33
Desipramine 50 mg + Paroxetine 20 mg	n	20	20	20	20	20	20
	Mean±SD	2.74±2.86	24.1	256±117	40.26±16.40	98.31±38.54	0.12±0.14
	CV%	104.5		45.7		39.2	117.8
	Geometric mean	1.86		228		89.00	0.07
	Min-Max	0.66-12.00	2.0-48.1	92-483		23.91-161.68	0.01-0.58

Abbreviations: AUC=area under the plasma concentration-versus-time curve; C_{max}=peak concentration; Cl/F=dose clearance; CV%=coefficient of variation; $t_{1/2}$=terminal half life; t_{max}=time to peak concentration; Min=minimum; Max=maximum; SD=standard deviation.

a. Median value and range

b. AUC ratio=$AUC_{2\text{-hydroxydesipramine}}/AUC_{desipramine}$

Results of Statistical Tests of Pharmacokinetic Parameters for 2-Hydroxydesipramine After Administration of Desipramine Alone, Coadministered With DVS SR and Coadministered With Paroxetine to Healthy Subjects

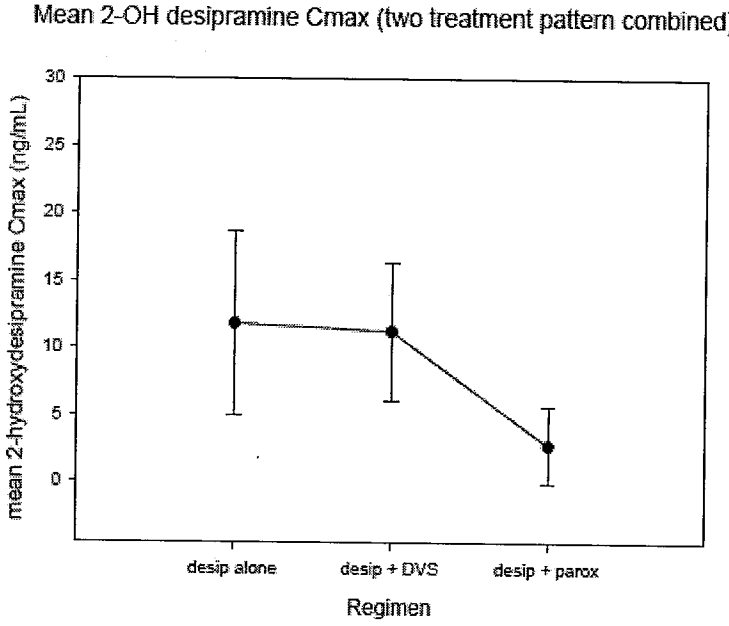
Treatment[a]	Variable	AUC (ng*hr/mL)	C_{max} (ng/mL)
Desipramine + DVS SR	Ratio of Mean[b]	116%	100%
	90% CI	100 - 134%	83 - 121%
Desipramine + Paroxetine	Ratio of Mean[b]	82%	18%
	90% CI	71 - 95%	15 - 22%

Abbreviations: AUC=area under the curve; CI=confidence interval; C_{max}=maximum concentration.

a. Reference is desipramine alone treatments

b. Ratio of geometric least square means

2-Hydroxydesipramine Mean Cmax After Administration of Desipramine Without and With Coadministration of DVS SR or Paroxetine



Mean Cmax for 2-hydroxydesipramine was approximately similar for each treatment pattern with concomitant administration of desipramine and DVS SR compared with administration of desipramine alone. In contrast, the mean Cmax after coadministration of paroxetine was approximately 82% lower than the Cmax when desipramine was administered alone. The 90% CI for Cmax after coadministration of Desipramine with DVS SR compared to Desipramine alone was contained within 80% – 125% confidence interval. Coadministration of DVS SR increased the 2-hydroxydesipramine mean AUC by 16%. Coadministration of paroxetine decreased the mean AUC by 18%.

Desvenlafaxine: The mean predose concentrations (±SD) of desvenlafaxine on days 11 and 12 were 193.40±77.20 ng/mL and 211.21±68.70 ng/mL, respectively. The mean predose concentrations (±SD) of desvenlafaxine on days 25 and 26 were 152.55±54.29 ng/mL and 144.34±65.61 ng/mL, respectively. These data are consistent with desvenlafaxine plasma concentrations reaching steady-state after 5 days of dose administration.

Paroxetine: The mean predose concentrations (±SD) of paroxetine on days 11 and 12 were 19.59±14.02 and 22.30±15.24 ng/mL, respectively. The mean predose

concentrations (±SD) of paroxetine on days 25 and 26 were 13.87±8.89 ng/mL and 14.78±10.69 ng/mL, respectively. These data are consistent with paroxetine plasma concentrations approaching steady-state after 5 days of dose administration.

Pharmacogenomic Results: Of 20 subjects genotyped, a total of 16 subjects (80%) were predicted to exhibit an EM phenotype. A total of 3 subjects (15%) were predicted to exhibit IM phenotypes, and 1 subject (0.5%) was predicted to possess a PM phenotype. No subjects were predicted to exhibit the UM phenotype. See pharmacogenomic review for evaluation of the phenotypes.

Safety Summary: Nausea was the most frequent AE, reported by 3 of subjects (30%) in the DVS SR/paroxetine group and by 2 of subjects (20%) in the paroxetine/DVS SR group. Headache was the next most frequent AE, reported by 2 subjects (20%) in each treatment group. Other AEs reported by more than 1 subject in a group included diarrhea and dizziness.

Pharmacokinetic Summary and Conclusions: In the current study, desipramine exposure, as measured by Cmax and AUC, increased by 30% and 36%, respectively, during coadministration of desipramine and DVS SR. In contrast, desipramine Cmax and AUC increased by 90% and 419%, respectively, during coadministration of desipramine and paroxetine. The Cmax of 2-hydroxydesipramine was approximately similar. The AUC of 2-hydroxydesipramine increased by 16% with coadministration of DVS SR.

The results of this study indicate that coadministration of the CYP2D6 substrate desipramine with 100-mg daily doses of DVS SR resulted in approximately similar exposure to desipramine and 2-hydroxydesipramine. This contrasts with the changes observed in desipramine PK after coadministration of the strong CYP2D6 inhibitor, paroxetine.

Reviewer's conclusion: Coadministration of desipramine with 100 mg DVS SR to healthy subjects resulted in significant changes in the exposure (as measured by Cmax and AUC) to desipramine (about 36% increase in AUC) when compared to administration of desipramine alone. However, the changes in desipramine exposure were relatively moderate when compared to the changes observed in desipramine exposure (about 419% increase in AUC) when co-administered with paroxetine. The changes in exposure to 2-hydroxydesipramine when desipramine is co-administered with DVS SR were relative minor. Dose adjustments may not be needed when desipramine and DVS SR are co-administered. However, caution is to be used when these drugs are administered together.

3.2.4. Study Title (Protocol 315A1-901-US): A Randomized, Open-Label, 2-Period, Parallel-Group, Crossover Study to Evaluate the Pharmacokinetics of Venlafaxine Extended Release and DVS SR in Healthy Subjects Who Are Extensive or Poor Cytochrome P450 2D6 Substrate Metabolizers

Objectives: To determine if the relative difference in pharmacokinetics (PK) between extensive metabolizers (EMs) and poor metabolizers (PMs) was the same between desvenlafaxine succinate sustained release (DVS SR) and venlafaxine extended release (venlafaxine ER) when a single dose of each was administered.

Study Design: This was a single-center, randomized, open-label, 2-period crossover inpatient/outpatient study to evaluate the effects of single doses of DVS SR and venlafaxine ER on the PK in healthy subjects who were EMs and PMs. Fourteen (14) subjects were enrolled. The mean ± SD age and weight were 24 ± 4.7 years and 71.5 ± 11.9 kg, respectively. Test article was administered by site personnel at predetermined time points for 16 days. Subjects were randomly assigned in a 1:1 ratio to receive either the sequence group A or sequence group B regimen. In period 1, a single 100-mg dose of DVS SR or 75 mg of venlafaxine ER was administered followed by 120 hours of PK sample collection. Test article washout occurred between study days 7 and 10. In period 2, a single 100-mg dose of DVS SR or 75 mg of venlafaxine ER was administered, followed by 120 hours of PK sample collection. Blood sample collection for the CYP2D6 genotype occurred at the screening visit. The formulation, strength and batch numbers of the study are summarized in the following table.

Study Drug Information

Study Drug	Dosage (mg)	Batch Number	Formulation Number
DVS SR	100 mg	A97186	0932044C
Venlafaxine ER	75 mg	2003B0097	0931288D

Analytical Method: Blood samples (5 mL) were collected from an indwelling catheter or by direct venipuncture for the determination of venlafaxine and desvenlafaxine concentrations on study days 1 to 6 and on study days 11 to 16 pre-dose (within 2 hours predose), and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, and 120 hours after test article administration. Both desvenlafaxine and venlafaxine were measured using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method with mass spectroscopy detection. The lower limit of quantitation for desvenlafaxine and venlafaxine was 5 ng/mL. The performance of the venlafaxine and desvenlafaxine assays during analysis of the plasma samples from this study are summarized in the following tables.

Assay Range and Sensitivity for Venlafaxine and Desvenlafaxine in Plasma Samples

Standard Curve	Compound/Matrix Venlafaxine	Compound/Matrix Desvenlafaxine
Linear range (ng/mL)	2.0–500	2.0–500
Sensitivity (ng/mL)	2.0	2.0

Analytical Summary of Venlafaxine and Desvenlafaxine Assays in Plasma Samples

	High CS (375.0 ng/mL)			Medium CS (45.00 ng/mL)			Low CS (5.000 ng/mL)		
Analyte	Conc.	CV%	Bias%	Conc.	CV%	Bias%	Conc.	CV%	Bias%
Venlafaxine	372.6	4.8	-0.6	47.98	1.5	7.0	5.158	4.5	3.0
Desvenlafaxine	349.2	5.2	-6.9	41.75	5.4	-7.2	4.611	5.7	-7.8

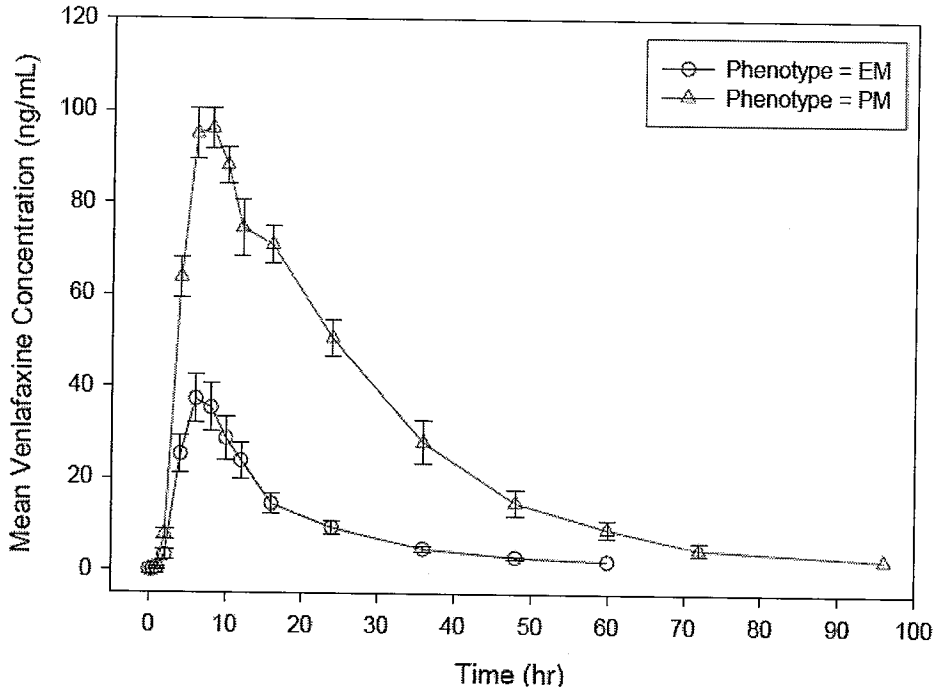
Abbreviations: Conc=concentration; CS=calibration standards; CV%=coefficient of variation.

Data Analysis: A noncompartmental PK method was used to analyze the plasma concentrations of venlafaxine and desvenlafaxine. Summary statistics (arithmetic mean, STD, range and geometric mean) were provided for treatment by phenotype (PM and EM). To assess the difference of PM and EM of each therapy (dosed DVS, DVS from VEN and dosed VEN) on the AUC and Cmax, the 90% confidence interval of each treatment to the AUC and Cmax was calculated. The comparison of AUC and Cmax between phenotype within each treatment was calculated with analysis of variance (ANOVA) on the logarithms of the AUC and Cmax. The difference between PM and EM on AUC and Cmax for each treatment group was tested by using the two-tailed Wilcoxon Exact Test.

To assess the difference between PM and EM subjects for each therapy, ratios can be calculated for AUC and Cmax using the desvenlafaxine concentration data after DVS SR administration and venlafaxine concentration data after venlafaxine ER administration collected for the same subject. The AUC ratio is calculated as the desvenlafaxine AUC after DVS SR administration divided by the AUC for venlafaxine after venlafaxine ER administration. The Cmax ratio is calculated in a similar manner. This test used the 2-tailed Wilcoxon exact test. The null hypothesis was that the ratio of venlafaxine:desvenlafaxine for AUC (or Cmax) is the same for EM and PM subjects.

Results: The following figures present mean concentration values for venlafaxine and desvenlafaxine after administration of venlafaxine ER (75 mg) to EM and PM subjects.

Venlafaxine Mean Concentration vs. Time Profiles by Phenotype After Administration of Venlafaxine 75 mg



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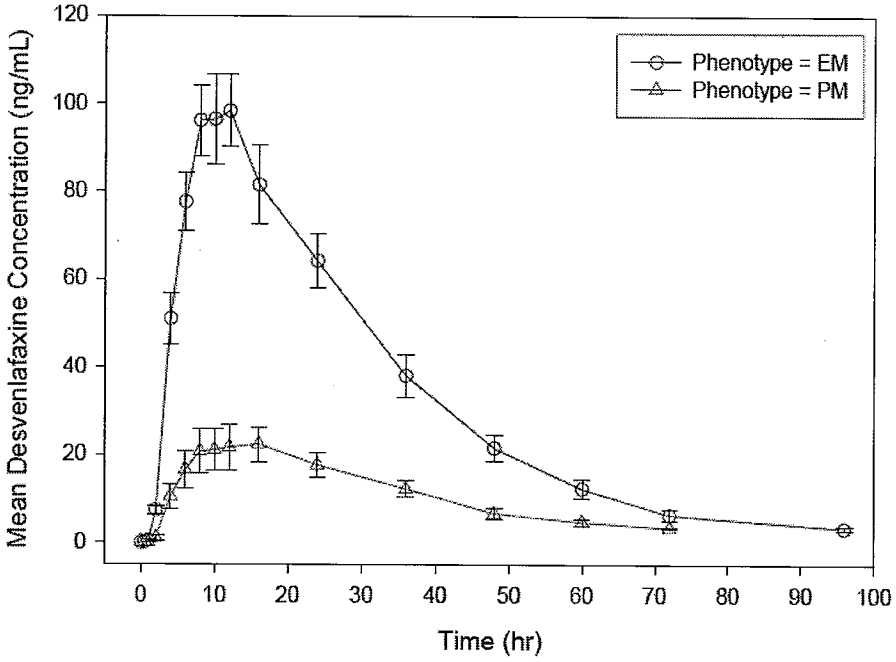
Desvenlafaxine Mean Concentraton vs. Time Profiles by Phenotype After Administration of Venlafaxine 75 mg



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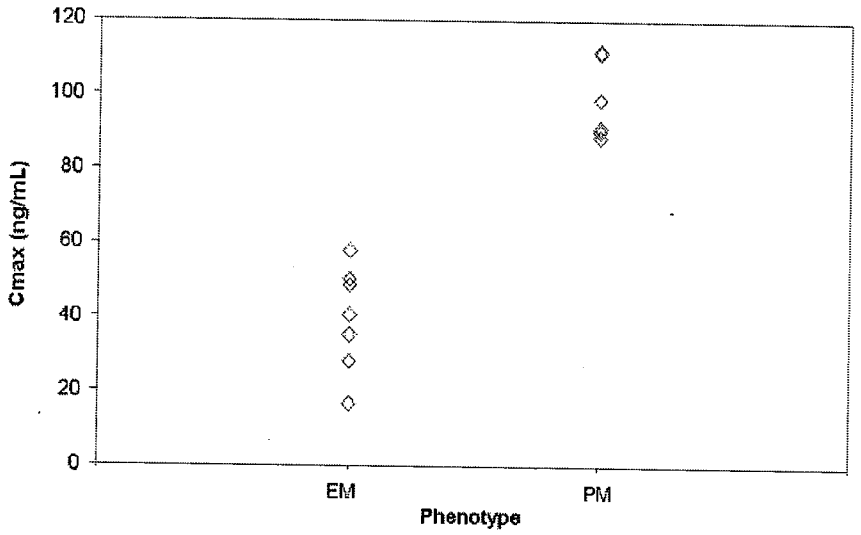
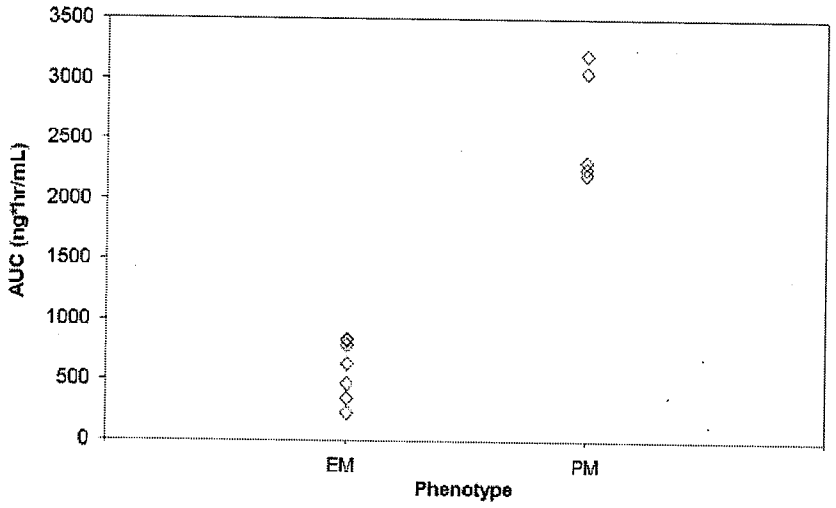
Individual Venlafaxine Cmax by Phenotype After Administration of Venlafaxine 75 mg



Individual Venlafaxine AUC by Phenotype After Administration of Venlafaxine 75 mg



The following tables provide a summary of venlafaxine PK parameters and results for the statistical analysis after administration of venlafaxine ER (75 mg) to EM and PM subjects.

Summary of Mean Venlafaxine Pharmacokinetic Parameters (Plasma) After Administration of Venlafaxine ER (75 mg) to Healthy Subjects by Phenotype

Phenotype	Variables	C_{max} (ng/mL)	t_{max}[a] (h)	AUC (ng*h/mL)	t½ (h)	Cl/F (L/h/kg)	V_z/F (L/kg)
Extensive metabolizer	n	7	7	7	7	7	7
	Mean±SD	39.6±14.1		591±246	10.9±2.4	2.3±1.3	32.6±13.7
	%CV	35.7		41.5	22.4	56.4	42.0
	Median	40.4	6.0	631	10.4	1.5	28.2
	Geo. mean	37.0		538	10.6	2.0	30.5
	Min-max	16.8–57.8	6.0–10.0	229–838	8.2–14.9	1.2–4.4	17.4–57.7
Poor metabolizer	n	6	6	6	6	6	6
	Mean±SD	98.6±10.6		2548±451	12.7±1.8	0.4±0.14	7.5±1.8
	%CV	10.7		17.7	14.1	31.8	24.1
	Median	94.8	7.0	2287	12.1	0.5	7.3
	Geo. mean	98.1		2517	12.6	0.4	7.3
	Min-max	88.7–111.8	6.0–10.0	2211–3200	10.4–15.1	0.2–0.6	5.0–10.3

Abbreviations: AUC=area under the concentration-versus-time curve; Cl/F=apparent oral-dose clearance; C_{max}=peak concentration; %CV=coefficient of variation; ER=extended release; Geo. mean=geometric mean; Min=minimum; max=maximum; SD=standard deviation; t½=apparent terminal half-life; t_{max}=time to peak concentration; V_z/F=volume of distribution.

a. Median value and range are listed for t_{max}.

ANOVA of the Geometric Mean analysis for Venlafaxine by CYP2D6 Phenotype After Administration of Venlafaxine ER (75 mg) to Healthy Subjects

Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Phenotype	<0.001	<0.001
Sequence	0.207	0.359

Abbreviations: AUC=area under the concentration-versus-time curve; C_{max}=peak concentration; ER=extended release.

p-Values of <0.05 are considered statistically significant.

Least Squares Geometric Mean and 90% Confidence Limits for Venlafaxine by CYP2D6 Phenotype After Administration of Venlafaxine ER (75 mg) to Healthy Subjects

Phenotype	Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Extensive metabolizers	Least squares Geometric mean	559.7	36.2
	90% Confidence limits	389.6-804.2	267.0-48.7
Poor metabolizers	Least squares geometric mean	2521.6	94.6
	90% Confidence limits	1772.4-3587.5	70.6-126.8

Abbreviations: AUC=area under the concentration-versus-time curve; C_{max}=peak concentration; ER=extended release.

After administration of venlafaxine ER 75 mg to EM and PM subjects, the mean Cmax for venlafaxine was approximately 161% higher for PM subjects compared with EM subjects. The mean AUC was approximately 350% higher for PM subjects compared with EM subjects. Significant differences ($p<0.001$) were observed for venlafaxine Cmax and AUC between EM and PM subjects.

Summary of Desvenlafaxine Pharmacokinetic Parameters (Plasma) After Administration of Venlafaxine ER (75 mg) to Healthy Subjects by Phenotype

Phenotype	Variables	C_{max} (ng/mL)	t_{max}[a] (h)	AUC (ng*h/mL)	$t_{½}$ (h)
Extensive metabolizer	n	7	7	7	7
	Mean±SD	104.3±27.4		3078±838	13.6±3.2
	%CV	26.3		27.2	23.7
	Median	102.3	10.0	2975	13.0
	Geo. mean	101.5		2989	13.3
	Min-max	79.3–153.2	8.0–12.0	2057–4686	9.7–18.5
Poor metabolizer	n	6	6	6	6
	Mean±SD	23.4±11.5		844±329	14.4±3.6
	%CV	49.1		39.0	25.1
	Median	21.7	16.0	826	15.8
	Geo. mean	21.0		787	14.0
	Min-max	9.03-41.1	8.0–16.0	421–1248	9.4–19.1

Abbreviations: AUC=area under the concentration-versus-time curve; C_{max}=peak concentration; %CV=coefficient of variation; ER=extended release; Geo. mean=geometric mean; Min=minimum; max=maximum; SD=standard deviation; $t_{½}$=apparent terminal half-life; t_{max}=time to peak concentration.

a: Median value and range are listed for t_{max}

Least Squares Geometric Mean and 90% Confidence Limits for Desvenlafaxine by CYP2D6 Phenotype After Administration of Venlafaxine ER (75 mg) to Healthy Subjects

Phenotype	Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Extensive metabolizer	Least squares geometric mean	3012.9	102.4
	90% Confidence limits	2344.8-3871.4	76.13-137.8
Poor metabolizer	Least squares geometric mean	771.8	20.5
	90% Confidence limits	585.4-1017.7	14.8-28.5

Abbreviations: AUC=area under the concentration-versus-time curve; C_{max}=peak concentration.

After administration of venlafaxine ER (75 mg) to EM and PM subjects, the mean Cmax for desvenlafaxine was approximately 346% higher for EM subjects compared with PM subjects. The mean AUC was approximately 265% higher for EM subject compared with PM subjects. Significant differences ($p<0.001$) in the Cmax and the AUC were observed between EM and PM subjects.

The following figures present mean concentration values for desvenlafaxine after administration of DVS SR (100 mg) to EM and PM subjects. And individual values of the desvenlafaxine Cmax and AUC after administration of DVS SR (100 mg) to EM and PM subjects, respectively.

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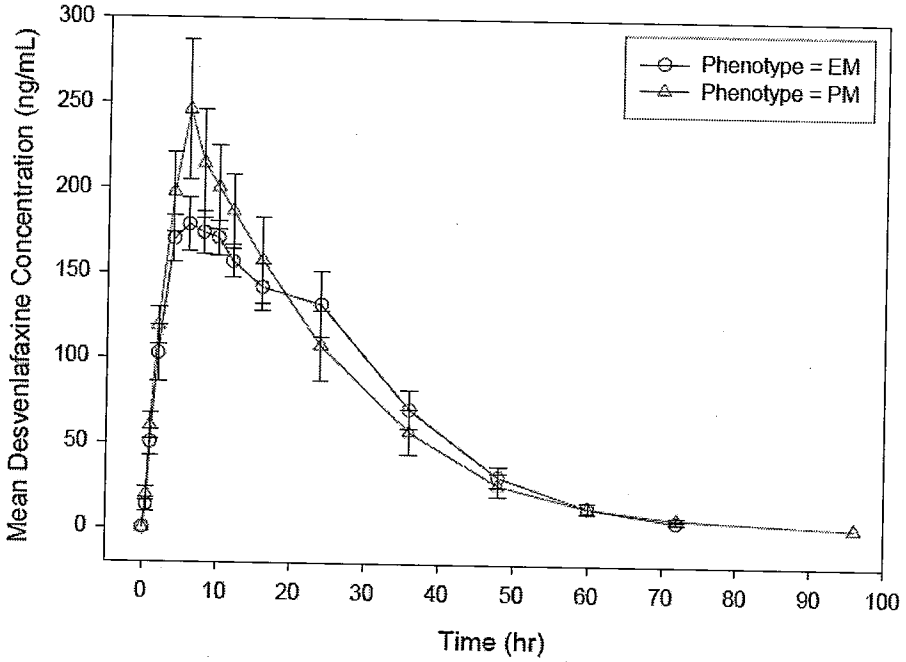
Desvenlafaxine Mean Concentration vs. Time Profiles by Phenotype After Administration of Desvenlafaxine 100 mg



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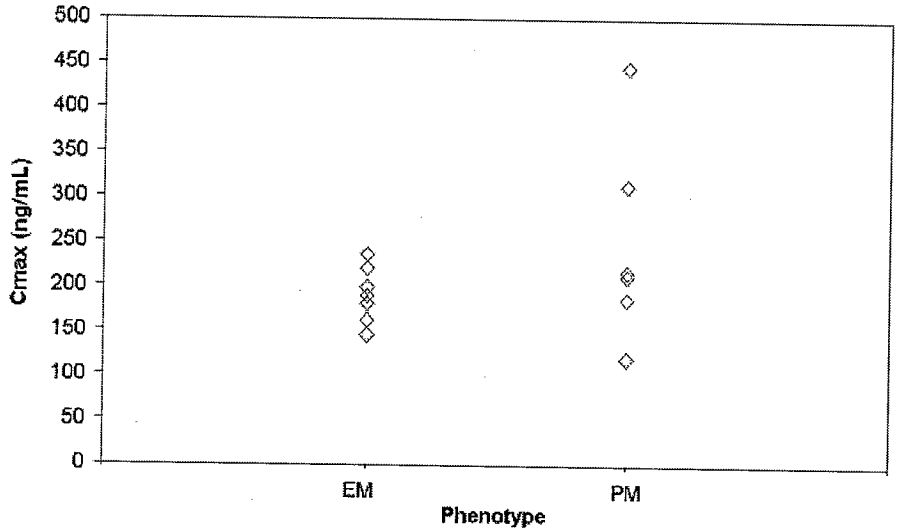
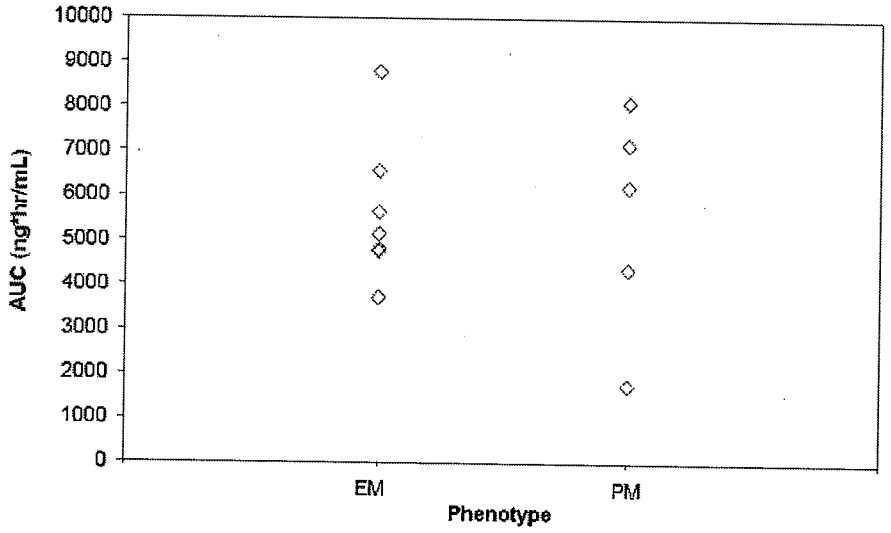
Individual Desvenlafaxine Cmax by Phenotype After Administration of DVS SR 100 mg



Individual Desvenlafaxine AUC by Phenotype After Administration of DVS SR 100 mg



The following tables provide a summary PK parameters and results of statistical analysis of desvenlafaxine after administration of DVS SR.

Summary of Desvenlafaxine Pharmacokinetic Parameters (Plasma) After Administration of DVS SR (100 mg) to Healthy Subjects by Phenotype

Phenotype	Variables	C_{max} (ng/mL)	t_{max}[a] (h)	AUC (ng*h/mL)	t½ (h)	CL/F (L/h/kg)	V_z/F (L/kg)
Extensive metabolizer	n	7	7	7	7	7	7
	Mean±SD	190.0±31.6		5630±1641	9.51±0.65	0.27±0.07	3.64±0.71
	%CV	16.6		29.1	6.8	24.2	19.6
	Median	189.4	8.0	5162	9.38	0.27	3.49
	Geo. mean	187.8		5446	9.49	0.26	3.58
	Min-max	144.9–236.0	4.0–24.0	3714–8782	8.74–10.43	0.17–0.36	2.54–4.56
Poor metabolizer	n	7	7	7	7	7	7
	Mean±SD	249.6±105.0		5992±2281	11.43±3.82	0.28±0.13	4.37±1.84
	%CV	42.1		38.1	33.5	47.4	42.1
	Median	216.8	6.0	6224	10.38	0.24	3.56
	Geo. mean	232.0		5428	10.98	0.26	4.10
	Min-max	119.2–445.9	4.0–12.0	1741–8119	8.34–19.45	0.18–0.56	3.13–7.85

Abbreviations: AUC=area under the concentration-versus-time curve; Cl/F=apparent oral-dose clearance; C_{max}=peak concentration; %CV=coefficient of variation; ER=extended release; Geo. mean=geometric mean; Min=minimum; max=maximum; SD=standard deviation; t½=apparent terminal half-life; t_{max}=time to peak concentration; V_z/F=volume of distribution.

a. Median value and range are listed for t_{max}.

Least Squares Geometric Mean and 90% Confidence Limits for Desvenlafaxine by CYP2D6 Phenotype After Administration of DVS SR (100 mg) to Healthy Subjects by Phenotype

Phenotype	Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Extensive metabolizers	Least squares geometric mean	5529.88	189.14
	90% Confidence limits	4063.32-7525.74	148.73-240.55
Poor metabolizers	Least squares geometric mean	4899.28	224.18
	90% Confidence limits	3487.68-6882.19	171.97-292.24

Abbreviations: AUC=area under the concentration-versus-time curve; C_{max}=peak concentration.

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ANOVA Results for Desvenlafaxine AUC and Cmax Geometric Means by CYP2D6 Phenotype After Administration of DVS SR (100 mg) to Healthy Subjects

Variable	AUC (ng*h/mL)	C_{max} (ng/mL)
Phenotype	0.641	0.408
Sequence	0.418	0.595

Abbreviations: AUC=area under the concentration-versus-time curve; C_{max}=peak concentration.
p-Values of <0.05 are considered statistically significant.

After administration of DVS SR (100 mg) to EM and PM subjects, the mean Cmax for desvenlafaxine was approximately 16% higher for PM subjects compared with EM subjects. The mean AUC values were about 13% lower for PM subjects compared with EM subjects. No significant differences were observed for either Cmax or AUC between EM and PM subjects.

Pharmacogenomic Results: Of 14 enrolled subjects, 7 were predicted to exhibit an EM phenotype and 7 were predicted to possess a PM phenotype. See pharmacogenomic (PG) review for comments. The sponsor results are provided in the attachments.

Safety Results: The sponsor reported that 6 out of 7 subjects experienced AEs in both EM and PM groups (86%). Nausea was the most frequent AE, experienced by 2 EMs (both taking venlafaxine ER) (29%) and by 2 PMs in both the venlafaxine ER and DVS SR groups. The next most frequent events were headache and insomnia, experienced by 3 and 2 subjects, respectively, all PMs. There was only 1 report of headache in the venlafaxine ER group and the other 2 were in the DVS SR group. Insomnia was not reported by any subjects in the venlafaxine ER group. There were no clinically important changes in laboratory assessments or vital signs.

Summary: Desvenlafaxine elimination is primarily through glucuronidation and renal excretion of desvenlafaxine and the glucuronide conjugate of desvenlafaxine. Metabolism of desvenlafaxine to NODV is a minor elimination pathway (<5%) that is predominantly mediated by CYP3A4. In vitro studies indicate that the formation of desvenlafaxine from venlafaxine is catalyzed by the CYP2D6 enzyme. The objective of this study was to confirm results of in vitro studies that predict that the CYP2D6 phenotype will not result in clinically relevant changes in the PK of desvenlafaxine after administration of DVS SR. Venlafaxine, which does require the CYP2D6 enzyme for metabolism of venlafaxine to desvenlafaxine, was used as a positive control for comparison purposes.

In the current study, after administration of venlafaxine, significant differences ($p<0.001$) were observed between EM and PM subjects in the PK of both venlafaxine and desvenlafaxine. Much higher concentrations of venlafaxine and lower concentrations of

desvenlafaxine were observed in PM subjects compared with EM subjects. Desvenlafaxine PK results were not significantly different between EM and PM subjects after administration of DVS SR. The results of this study indicate that the CYP2D6 phenotype does not significantly alter the PK of desvenlafaxine after administration of DVS SR.

Reviewer Comments: The reviewer agrees with the overall conclusions of the sponsor. Administration of DVS SR does not affect the pharmacokinetics of desvenlafaxine in PM compared to EM subjects tested. The PG reviewer generally agrees with the phenotype characterization except for one subject. See PG review for details.

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13.2 Prediction of CYP2D6 Phenotype

ALLELE	*1	*2	*3	*4	*5	*6	*7	*8	*9	*10	*17	*29	*41	*1xN	*2xN
*1	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	UM	UM
*2		EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	UM	UM
*3			PM	PM	PM	PM	PM	PM	IM	IM	IM	IM	IM	EM	EM
*4				PM	PM	PM	PM	PM	IM	IM	IM	IM	IM	EM	EM
*5					PM	PM	PM	PM	IM	IM	IM	IM	IM	EM	EM
*6						PM	PM	PM	IM	IM	IM	IM	IM	EM	EM
*7							PM	PM	IM	IM	IM	IM	IM	EM	EM
*8								PM	IM	IM	IM	IM	IM	EM	EM
*9									IM	IM	IM	IM	IM	EM	EM
*10										IM	IM	IM	IM	EM	EM
*17											IM	IM	IM	EM	EM
*29												IM	IM	EM	EM
*41													IM	EM	EM

UM=ultra-rapid metabolizer; EM=extensive metabolizer; IM= intermediate metabolizer; PM=poor metabolizer

13.10 CYP2D6 Genotypes and Predicted Phenotypes

Subject ID	CYP2D6 GENOTYPE	CYP2D6 PHENOTYPE
004		EM
005		PM
006		PM
007		PM
008		EM
015		PM
023		EM
026		PM
036		EM
038	*	EM
039		PM
041		EM
046		EM
049		PM

EM=extensive metabolizer; PM=poor metabolizer.

13.11 Nucleotide Identity at Defining Polymorphic Positions for CYP2D6 Alleles Tested

Subject	*2 -1584	*3 2549	*4 1846	*6 1707	*7 2935	*8 1758	*9 2613	*10 100	*17 1023	*29 16589	*41 2988	Gene copy number	CYP2D6 GENOTYPE	CYP2D6 PHENOTYPE

13.7 Individual Pharmacokinetic Parameters and Descriptive Statistics by Phenotype for Desvenlafaxine After Administration of Venlafaxine ER 75 mg

Phenotype	Subject	C_{max} (ng/mL)	T_{max} (h)	AUC_T (h*ng/mL)	AUC (h*ng/mL)	AUC_Extrap (%)	$t_{1/2}$ (h)
EM	4	153.20	10.0	4581.0	4685.9	2.24	16.13
	8	80.22	10.0	2013.1	2057.2	2.14	11.74
	23	102.30	12.0	2462.6	2514.6	2.07	10.59
	36	126.70	8.0	2938.3	2975.1	1.24	9.70
	38	84.34	10.0	2714.4	2767.0	1.90	15.66
	41	79.34	12.0	2961.0	3069.1	3.52	18.51
	46	104.00	8.0	3435.9	3477.6	1.20	13.04
	N	7	7	7	7	7	7
	Mean	104.30	10.0	3015.2	3078.1	2.04	13.62
	SD	27.38	1.6	820.3	837.8	0.78	3.24
	SE	10.35	0.6	310.1	316.7	0.29	1.22
	Min	79.34	8.0	2013.1	2057.2	1.20	9.70
	Median	102.30	10.0	2938.3	2975.1	2.07	13.04
	Max	153.20	12.0	4581.0	4685.9	3.52	18.51
	CV%	26.3	16.4	27.2	27.2	38.0	23.7
	Geometric Mean	101.48	9.9	2927.5	2988.7	1.93	13.30

Source: Clinical Pharmacology

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13.7 Individual Pharmacokinetic Parameters and Descriptive Statistics by Phenotype for Desvenlafaxine After Administration of Venlafaxine ER 75 mg (Cont.)

Phenotype	Subject	C_{max} (ng/mL)	T_{max} (h)	AUC_T (h*ng/mL)	AUC (h*ng/mL)	AUC_Extrap (%)	$t_{1/2}$ (h)
PM	5	31.79	12.0	1183.2	1248.1	5.21	14.03
	7	21.46	16.0	741.3	851.2	12.91	16.35
	15	9.03	16.0	358.1	420.9	14.93	16.31
	26	21.94	16.0	526.5	558.2	5.68	9.42
	39	15.30	16.0	703.0	801.3	12.27	19.10
	49	41.11	8.0	1129.4	1183.8	4.59	11.10
	N	6	6	6	6	6	6
	Mean	23.44	14.0	773.6	843.9	9.26	14.39
	SD	11.51	3.3	326.8	329.0	4.59	3.62
	SE	4.70	1.4	133.4	134.3	1.88	1.48
	Min	9.03	8.0	358.1	420.9	4.59	9.42
	Median	21.70	16.0	722.2	826.3	8.97	15.17
	Max	41.11	16.0	1183.2	1248.1	14.93	19.10
	CV%	49.1	23.9	42.3	39.0	49.6	25.1
	Geometric Mean	20.97	13.6	712.9	786.5	8.28	13.98

13.8 Individual Pharmacokinetic Parameters and Descriptive Statistics by Phenotype for Desvenlafaxine After Administration of DVS SR 100 mg

Phenotype	Subject	C_{max} (ng/mL)	T_{max} (h)	AUC_T (h*ng/mL)	AUC (h*ng/mL)	AUC_Extrap (%)	$t_{1/2}$ (h)	V/F (L)	V/F (L/kg)	CL/F (L/h)	CL/F (L/h/kg)
EM	4	236.00	24.0	8620.7	8782.1	1.84	10.26	168.6	2.54	11.39	0.171
	8	144.90	12.0	3687.2	3714.1	0.72	8.74	339.6	4.56	26.92	0.362
	23	189.40	6.0	4720.1	4759.4	0.83	8.97	272.0	3.53	21.01	0.272
	36	219.30	6.0	4758.9	4795.0	0.75	9.38	282.1	4.56	20.86	0.337
	38	161.90	4.0	5094.2	5162.1	1.32	9.07	253.5	3.49	19.37	0.267
	41	198.60	8.0	5539.9	5631.8	1.63	10.43	267.1	3.36	17.76	0.223
	46	179.70	8.0	6442.6	6567.6	1.90	9.69	212.8	3.46	15.23	0.248
	N	7	7	7	7	7	7	7	7	7	7
	Mean	189.97	9.7	5551.9	5630.3	1.28	9.51	256.5	3.64	18.93	0.269
	SD	31.57	6.8	1592.6	1641.1	0.52	0.65	54.1	0.71	4.90	0.065
	SE	11.93	2.6	602.0	620.3	0.20	0.25	20.4	0.27	1.85	0.025
	Min	144.90	4.0	3687.2	3714.1	0.72	8.74	168.6	2.54	11.39	0.171
	Median	189.40	8.0	5094.2	5162.1	1.32	9.38	267.1	3.49	19.37	0.267
	Max	236.00	24.0	8620.7	8782.1	1.90	10.43	339.6	4.56	26.92	0.362
	CV%	16.6	69.9	28.7	29.1	40.4	6.8	21.1	19.6	25.9	24.2
	Geometric Mean	187.70	8.3	5376.2	5446.2	1.19	9.49	251.3	3.58	18.36	0.262