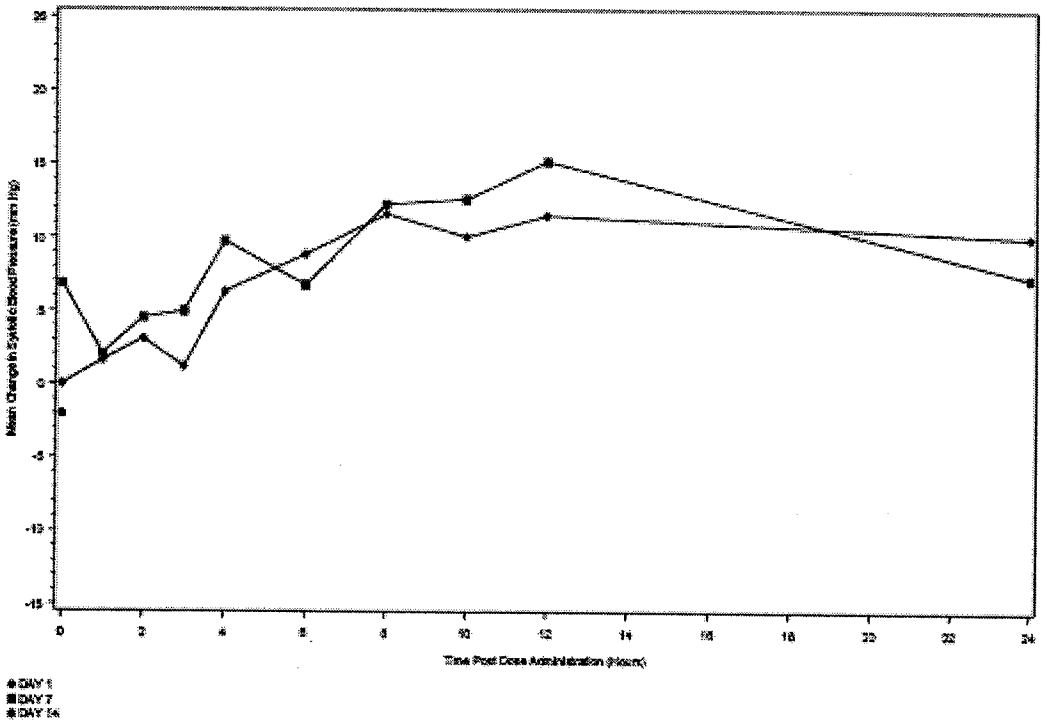
Change from Baseline in Systolic Blood Pressure
In Healthy Subjects Receiving Multiple Doses of DVS-233 SR
Protocol 0600D3-171-US

TREATMENT: DESVENLAFAXINE SR 600 MG



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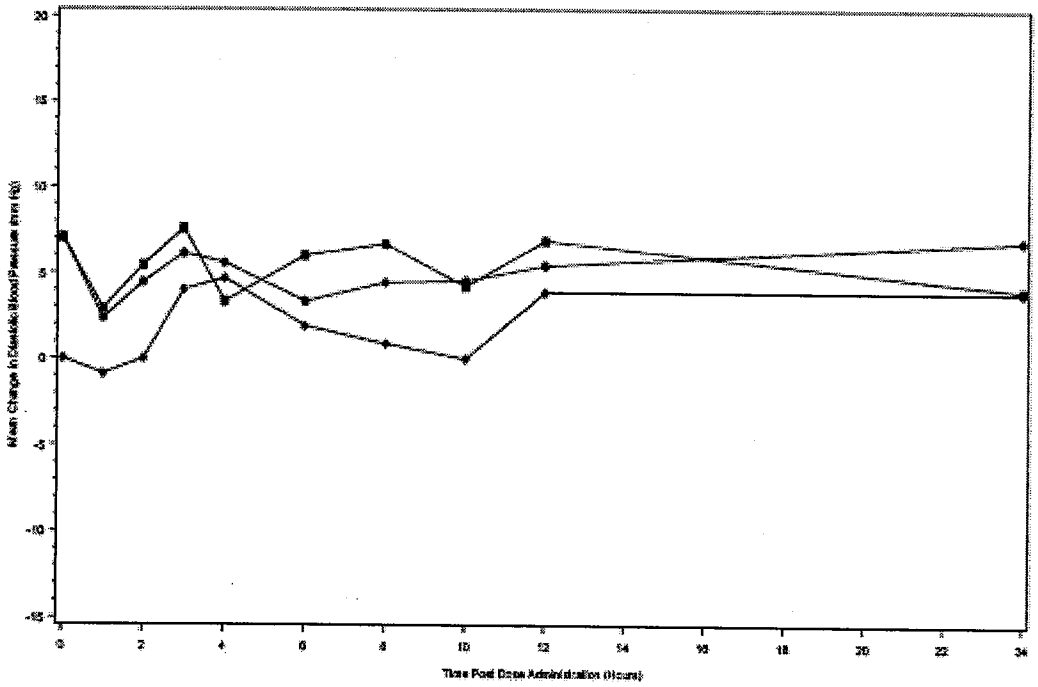
Change from Baseline in Diastolic Blood Pressure
in Healthy Subjects Receiving Multiple Doses of DVS-233 SR
Protocol DE0D3-171-US

TREATMENT: DESVENLAFAXINE SR 300 MG



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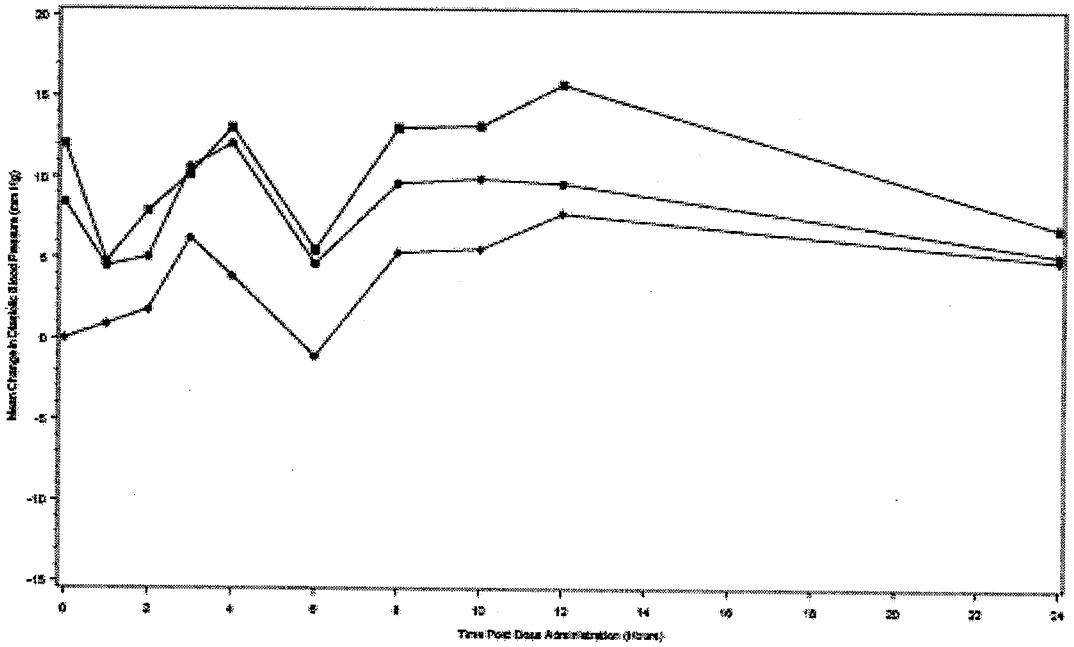
Change from Baseline in Diastolic Blood Pressure
In Healthy Subjects Receiving Multiple Doses of DVS-233 SR
Protocol 0600D3-171-US

TREATMENT: DESVENLAFAXINE SR 450 MG



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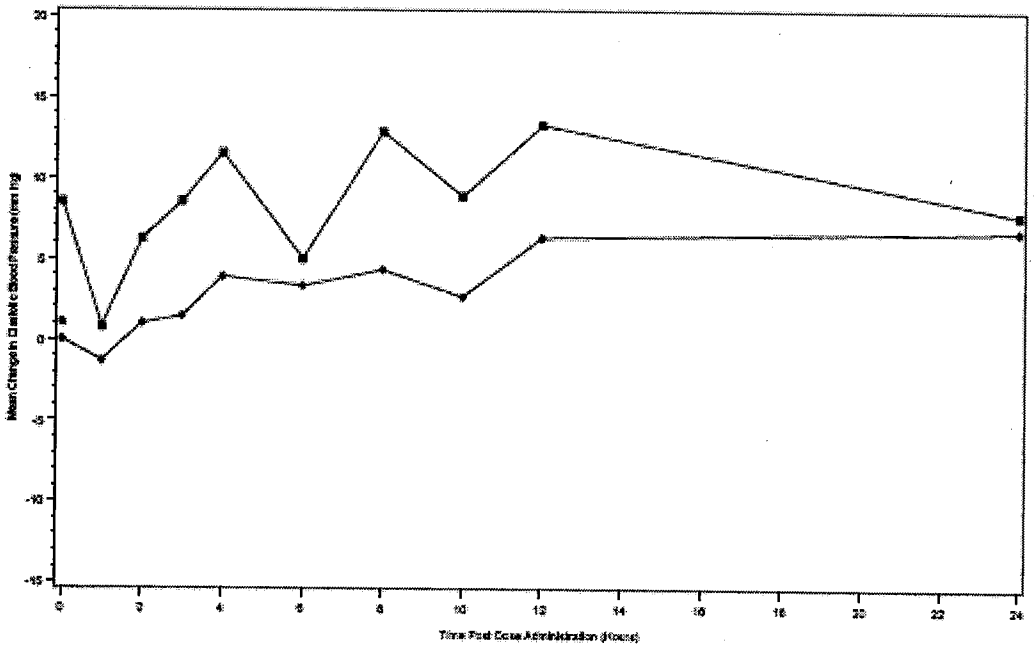
Change from Baseline in Diastolic Blood Pressure
In Healthy Subjects Receiving Multiple Doses of DVS-233 SR
Protocol 0500D3-171-US

TREATMENT: DESVENLAFAXINE SR 600 MG



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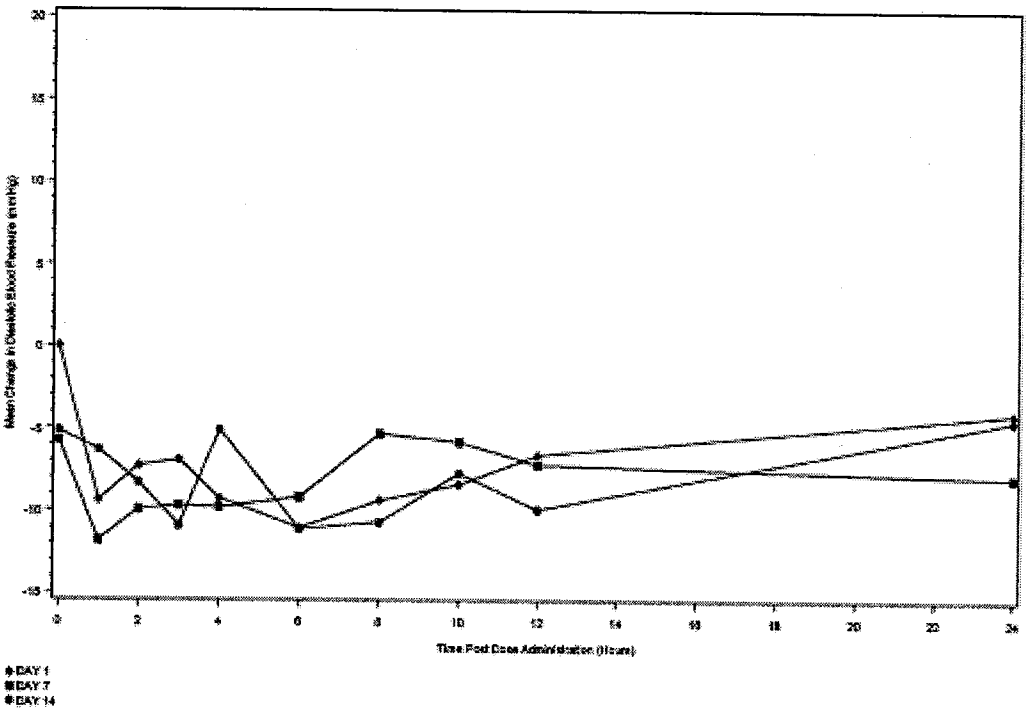
Change from Baseline in Diastolic Blood Pressure
in Healthy Subjects Receiving Multiple Doses of DVS-233 SR
Protocol D6000D3-171-US

TREATMENT: PLACEBO



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Study Title: An Open-Label, Randomized, Single-Dose, Dose-Proportionality Study Of Desvenlafaxine SR In Healthy Subjects (Protocol 0600d3-172-US; CSR-49864).

Objective: The primary objective of this study was to assess dose proportionality of single oral doses of desvenlafaxine succinate monohydrate (DVS-233) sustained-release (SR) in healthy subjects. The secondary objective was to evaluate the safety and tolerability of DVS-233 SR following single-dose oral administrations.

Study Design: This was a randomized, single-dose, open-label, inpatient, 3-treatment, crossover, dose proportionality study in healthy subjects. Subjects were randomly assigned to receive 1 of 6 treatment sequences according to the randomization schedule provided by the sponsor. The following doses of DVS-233 SR were studied: 100 mg, 300 mg, and 600 mg. Test article was administered as 1 x 100-mg tablet, 3 x 100-mg tablets, or 6 x 100-mg tablets. On study day 1 of each period (actual days 1, 5, and 9), each subject received a single dose of DVS-233 SR at 0800 hours after a medium-fat breakfast. There was a 4-day washout interval between doses in subsequent study periods. Blood samples (10 mL each) were collected at designated times to measure concentrations of desvenlafaxine. The total amount of blood collected from each subject was approximately 480 mL.

Analytical Method: Plasma samples were assayed for desvenlafaxine concentrations by using a validated high performance liquid chromatography method with fluorescence detection. Based on a 1.0-mL plasma sample, the method has a minimum quantifiable concentration of 5 ng/mL. The performance of the desvenlafaxine assays in this study is summarized in the following tables.

Table 6.5.2-1: Assay Range and Sensitivity for Plasma Samples

Standard Curve	Compound/Matrix Desvenlafaxine/Plasma
Linear range (ng/mL)	5.0 - 500
Sensitivity (ng/mL)	5.0

Source: Reference 11

Table 6.5.2-2: Analytical Summary of Desvenlafaxine Assays

	High QC (300.0 ng/mL)			Medium QC (60.0 ng/mL)			Low QC (15.0 ng/mL)		
Analyte	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Desvenlafaxine	300.05	7.12	+0.02	59.23	5.23	-1.28	15.04	4.93	+0.30

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

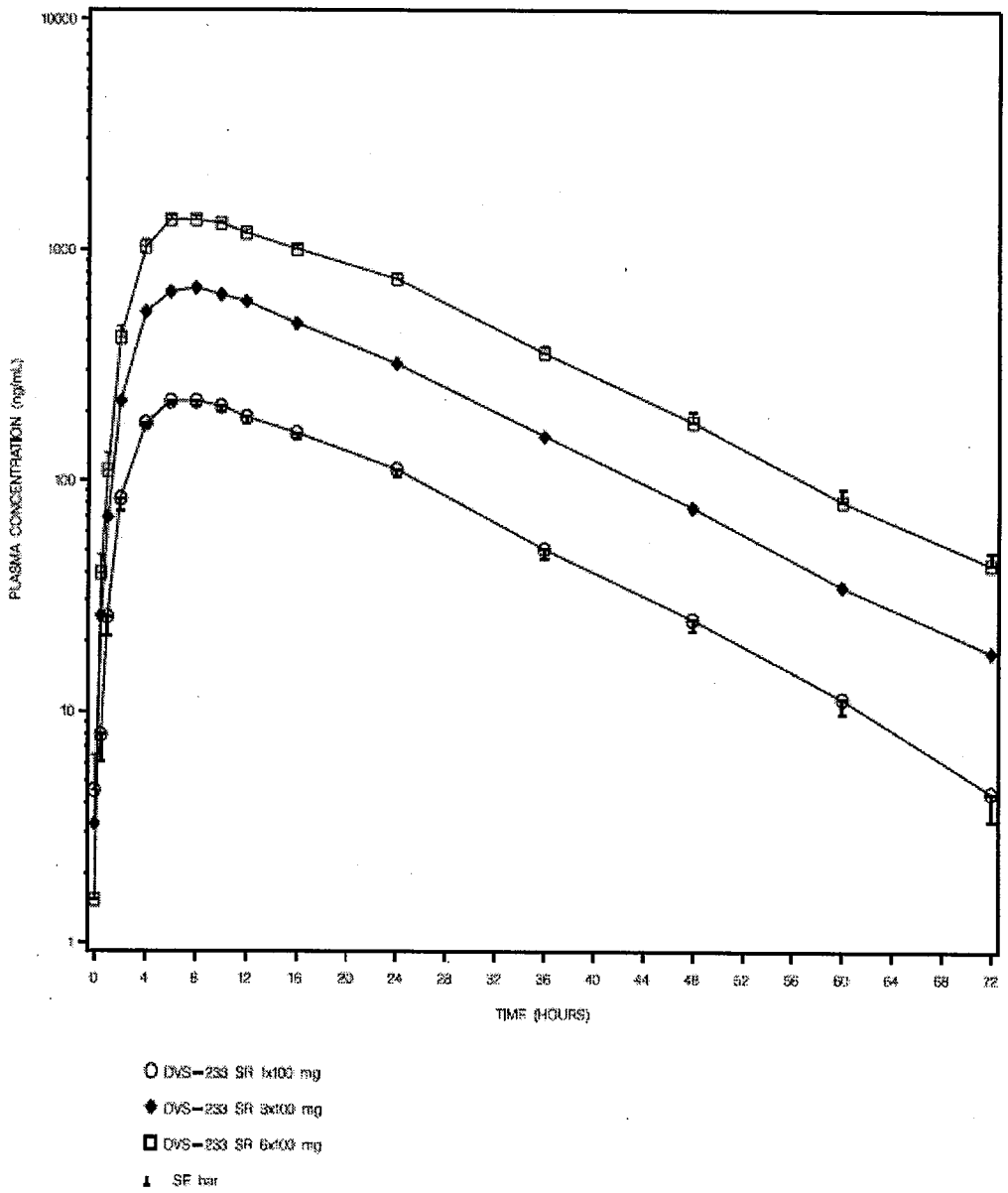
Data Analysis: The desvenlafaxine plasma concentration data for each subject were analyzed by using empirical, model-independent pharmacokinetic methods. Statistical comparisons of mean plasma concentrations at each sample collection time and mean pharmacokinetic parameters were made by using an analysis of variance (ANOVA) for a 3-period crossover study with the following statistical model.

Additionally, an exponential regression (eg, $AUC = \alpha \bullet Dose^{\beta}$) was used to evaluate the dose-proportionality relationship. The exponential equation was made linear with a log transformation (eg, $\log[AUC] = \log[\alpha] + \beta \bullet \log[Dose]$), and subject and period were included in the regression model to account for the crossover nature of the study design. In this model, linearity is evaluated with the statistical hypothesis $\beta = 1$. If $\beta = 1$, then AUC increases linearly with dose. If $\beta > 1$, then AUC increases in a greater than linearly proportional manner, and if $\beta < 1$, then AUC increases in a less than linearly proportional manner.

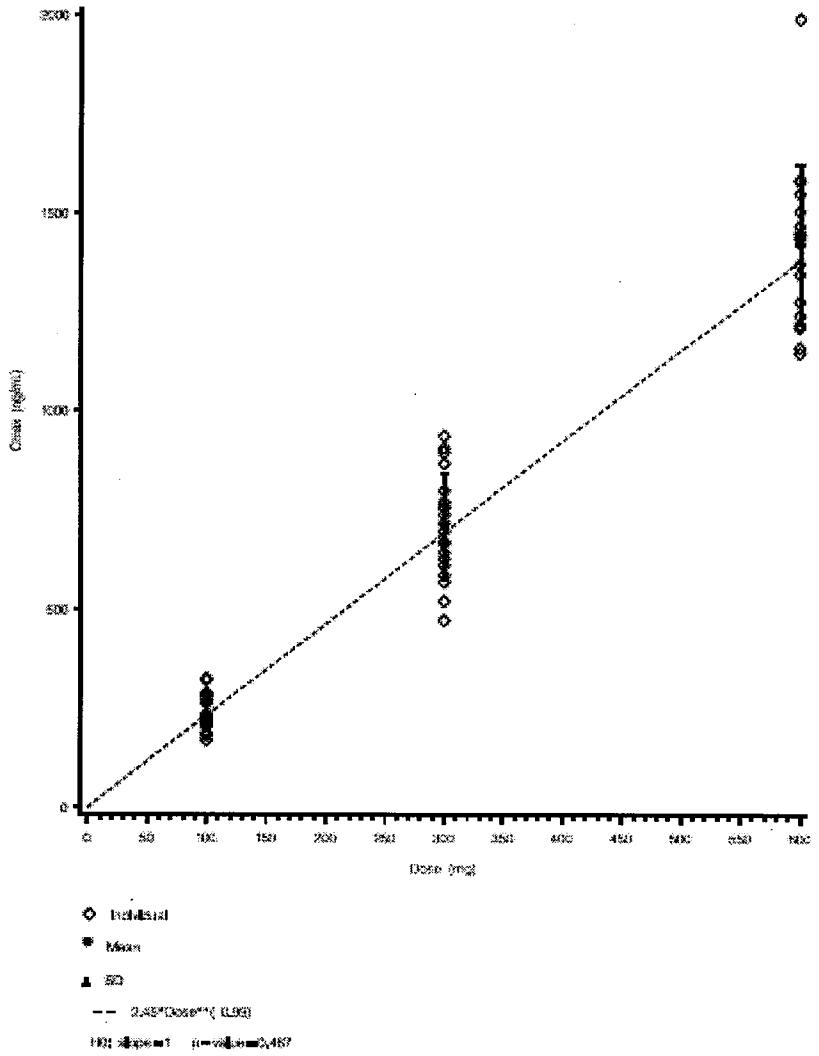
Results: A total of 24 subjects were enrolled in this study and received at least 1 dose of DVS-233 SR. Five subjects (20.8%) withdrew from the study after period 1: 2 because of AEs and 3 for other reasons. Nineteen (19) subjects completed all 3 dose levels of the clinical study. Twenty-two (22) subjects were included in the safety analysis at the 100-mg dose, 20 subjects at the 300-mg dose, and 20 subjects at the 600-mg dose.

The following figure presents the mean desvenlafaxine plasma concentrations after administration of 100-, 300-, 600-mg doses. Additionally, the desvenlafaxine C_{max} and AUC versus dose along with fitted exponential regressions are presented in the following figures. A summary of the pharmacokinetic parameter values and the statistical comparisons among the 3 dose levels are presented in the following tables.

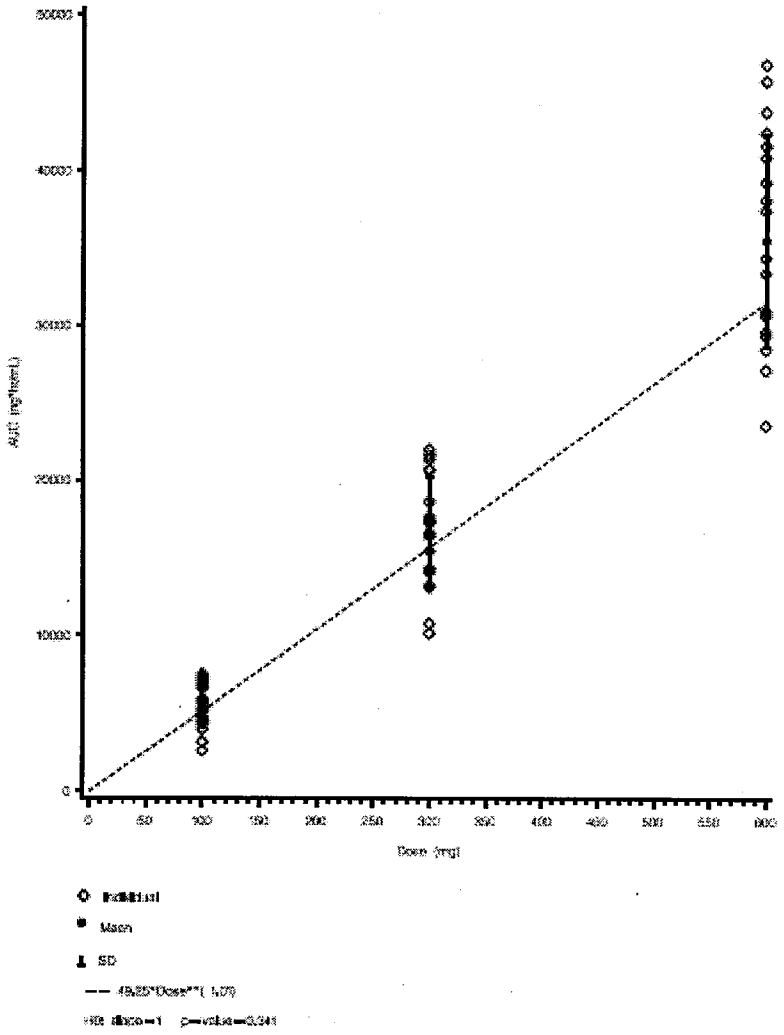
Mean Desvenlafaxine Plasma Concentrations in Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR



Desvenlafaxine Cmax Values in Healthy Subjects After Receiving a Single Dose of DVS-233 SR



Desvenlafaxine AUC Values in Healthy Subjects After Receiving a Single Dose of DVS-233-SR



Desvenlafaxine Pharmacokinetic Parameters

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (ng·h/mL)	Cl/F (L/h/kg)
100 mg[a]	238 ± 44.5	7.52 ± 1.99	11.2 ± 1.5	5560 ± 1378	0.246 ± 0.082
	234	7.28	11.1	5376	0.236
300 mg	712 ± 129.1	7.20 ± 1.77	11.0 ± 1.6	16594 ± 3553	0.238 ± 0.049
	701	7.01	10.9	16215	0.233
600 mg	1422 ± 200.5	8.32 ± 1.92	11.2 ± 1.8	35517 ± 6865	0.223 ± 0.045
	1409	8.11	11.0	34880	0.218
3-Period Crossover Analysis of Variance of Log-Transformed Data[b]					
Sequence	<0.001	0.735	0.008	<0.001	<0.001
Subject (sequence)	<0.001	0.367	<0.001	<0.001	<0.001
Treatment	0.759	0.226	0.670	0.121	0.121
Period	0.960	0.894	0.767	0.564	0.564

a: Mean±SD and geometric mean.

b: Before statistical comparisons were made, dose-dependent values (C_{max} and AUC) were normalized to the lowest dose.

Abbreviations: SD=standard deviation; C_{max}=peak concentration; t_{max}=time peak concentration occurs; $t_{½}$=terminal-phase elimination half-life; AUC=area under the concentration curve; Cl/F=apparent oral dose clearance.

A 1 x 100-mg single dose of DVS-233 SR produced a mean C_{max} of 238 ± 44.5 ng/mL and a mean AUC of 5560 ± 1378 ng•h/mL. In a 300-mg single dose of DVS-233 SR produced a mean C_{max} of 712 ± 129.1 ng/mL and a mean AUC of 16594 ± 3553 ng•h/mL, and a 600-mg single dose of DVS-233 SR produced a mean C_{max} and AUC of 1422 ± 200.5 ng/mL and 35517 ± 6855 ng•h/mL, respectively. There was a 3-fold increase in both C_{max} and AUC from the 100-mg dose to the 300-mg dose, and there was approximately a 6-fold increase in both C_{max} and AUC from the 100-mg dose to the 600-mg dose. The relationships AUC versus dose and C_{max} versus dose, using the power model, are presented in the following table.

Power Model for Desvenlafaxine Pharmacokinetic Parameters

Parameter	Model	95% CI for the exponent	p-Value (exponent = 1)
C_{max}	$C_{max} = 2.45 \cdot (Dose)^{1.09}$	0.95, 1.02	0.467
AUC	$AUC = 49.25 \cdot (Dose)^{1.02}$	0.99, 1.04	0.341

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

Desvenlafaxine C_{max} and AUC increased in a linearly dose-proportional manner ($p < 0.467$ and $p < 0.341$, respectively) over the dose range studied. Doubling the DVS-233 SR dose increased the desvenlafaxine C_{max} by 1.99-fold and increased the desvenlafaxine AUC by 2.01-fold. The mean desvenlafaxine T_{max} (≈ 8 h), T ½ (≈ 11 h), and Cl/F (≈ 0.235 L/h/kg) were similar across the 3 treatments.

Safety Summary: TEAEs were more frequently reported at DVS-233 SR doses of 600 mg than at the lower doses. The incidence of TEAEs was 65.0% in the 600-mg group, 40.0% in the 300-mg group and 18.2% in the 100-mg group. The most frequently reported TEAEs (>30%) across all treatment groups were nausea (12/24, 50%) and dizziness (11/24, 45.8%). These occurred more frequently in the 300- and 600-mg DVS-233 SR groups when compared to the 100-mg group.

Conclusion: The pharmacokinetic profile and dose proportionality of DVS-233 SR were examined after single dose administration at 3 doses: 100, 300 and 600 mg. The desvenlafaxine C_{max} and AUC both increased in a linearly dose-proportional manner over the entire dose range (100, 300, and 600 mg). The linear dose proportionality was also supported by the lack of statistically significant differences among doses in total Cl/F. The most frequently reported TEAEs (>30%) across all treatment groups were nausea and dizziness. One (1) subject experienced symptomatic hypotension; no other vital sign changes were considered clinically important.

Reviewer comments: *The reviewer agrees with the sponsor's conclusions.*

ST 8-4. Pharmacokinetic Parameters of Desvenlafaxine in Healthy Subjects Receiving a Single Dose of DVS-233 SR

Supportive Table ST 8-4. Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol D6000D3-172-US

09:44 Monday, August 4, 2003

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCL (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
DVS-233 SR 1x100 mg								
1	265	6.0	0.069	10.0	4410.4	4812.3	0.332	4.793
2	287	10.0	0.060	11.6	5619.3	5726.5	0.219	3.671
3	221	8.0	0.057	12.1	4513.3	4982.6	0.241	4.215
4	220	8.0	0.055	12.6	6721.8	6938.2	0.165	3.007
5	232	6.0	0.051	13.6	6419.9	6656.1	0.153	2.989
6	.	.	.	.	.	.	.	.
7	220	8.0	0.074	9.4	4617.1	4628.7	0.237	3.207
8	171	6.0	0.073	9.5	3974.6	4049.2	0.299	4.322
9	323	10.0	0.067	10.4	7145.8	7233.9	0.219	3.286
10	183	6.0	0.057	12.1	2441.3	2649.4	0.523	9.122
11	209	6.0	0.076	9.1	3079.5	3195.9	0.336	4.415
12	326	10.0	0.056	12.4	6784.6	6904.2	0.195	3.491
13	211	6.0	0.057	12.2	5579.0	5728.5	0.242	4.282
14	210	8.0	0.068	10.2	5545.4	5843.8	0.253	3.716
15	207	8.0	0.063	11.0	5043.0	5134.5	0.200	3.185
16	274	6.0	0.059	11.7	7186.4	7349.9	0.146	2.467
17	226	6.0	0.055	12.6	5201.1	5330.2	0.241	4.379
18	.	.	.	.	.	.	.	.
19	290	6.0	0.058	12.0	7126.6	7516.1	0.216	3.726
20	209	12.0	0.049	14.2	6777.4	7086.8	0.180	3.581
21	188	4.0	0.071	9.7	4281.2	4307.1	0.280	3.914
22	.	.	.	.	.	.	.	.
23	237	6.0	0.066	10.5	5017.4	5161.4	0.252	3.821
24	283	10.0	0.076	9.1	5813.2	5917.6	0.247	3.237
Mean	238	7.5	0.063	11.2	5395.2	5560.1	0.246	3.940

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Supportive Table ST 8-4. Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol 060003-172-US

09:44 Monday, August 4, 2003

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCL (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)	CMAX RATIO (%)	AUC RATIO (%)
DVS-233 SR 3x100 mg										
1	938	8.0	0.078	8.9	16295.4	16387.2	0.274	3.530	118.0	121.1
2	760	6.0	0.055	12.7	13875.9	14091.6	0.266	4.882	88.2	82.0
3	719	6.0	0.063	11.0	14146.6	14311.9	0.233	3.701	108.6	103.7
4	897	8.0	0.058	12.0	21510.7	21957.6	0.157	2.700	135.9	165.5
5	588	8.0	0.055	12.5	16914.9	17487.4	0.175	3.153	84.3	87.2
6	474	6.0	0.072	9.6	10095.5	10194.9	0.331	4.573	.	.
7	672	6.0	0.072	9.6	15333.4	15464.8	0.222	3.068	101.7	105.8
8	.	.	.	.	.	.	.	.	.	.
9	907	8.0	0.067	10.3	21373.5	21642.0	0.219	3.268	93.5	99.7
10	.	.	.	.	.	.	.	.	.	.
11	823	6.0	0.077	9.0	18726.6	18801.3	0.208	3.862	83.5	112.7
12	740	6.0	0.060	11.5	20192.7	20713.9	0.195	3.222	75.5	100.0
13	658	6.0	0.061	11.3	17295.4	17619.9	0.236	3.863	105.4	102.5
14	868	4.0	0.073	9.5	16441.7	16579.1	0.268	3.653	137.9	94.6
15	613	8.0	0.070	10.0	12056.5	12185.5	0.234	3.368	98.9	85.6
16	800	6.0	0.049	14.2	19864.6	20633.0	0.156	3.202	97.3	93.6
17	698	8.0	0.057	12.1	16844.8	17218.4	0.224	3.917	102.0	107.7
18	.	.	.	.	.	.	.	.	.	.
19	757	8.0	0.058	11.9	18168.6	18608.6	0.262	4.504	87.0	82.5
20	645	8.0	0.050	13.8	20529.8	21355.3	0.179	3.567	102.9	100.4
21	571	6.0	0.067	10.3	12994.9	13254.0	0.281	4.185	101.5	99.7
22	.	.	.	.	.	.	.	.	.	.
23	629	12.0	0.068	10.3	12979.8	13124.6	0.307	4.306	88.6	84.8
24	772	10.0	0.072	9.7	17269.8	17431.2	0.252	3.512	90.9	98.2
Mean	712	7.2	0.064	11.0	16286.1	16594.1	0.238	3.706	100.1	98.3

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Supportive Table ST 8-4. Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol 0600D3-172-US

09:44 Monday, August 4, 2003

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUC% (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)	CMAX RATIO (%)	AUC RATIO (%)
DVS-233 SR 6x100 mg										
1	1583	8.0	0.073	9.5	38541.3	38778.7	0.292	3.989	89.6	113.7
2	1507	8.0	0.074	9.4	34079.6	34417.6	0.318	2.953	87.4	100.2
3	1811	8.0	0.069	10.0	38336.2	38689.6	0.217	3.138	91.5	111.1
4	1469	12.0	0.053	13.0	45267.5	46829.1	0.147	2.758	111.2	112.5
5	1552	10.0	0.049	14.2	36544.7	38146.4	0.160	3.276	111.4	95.5
6	.	.	.	.	.	.	.	.	.	.
7	1276	8.0	0.083	8.4	27031.5	27158.7	0.253	3.059	96.5	93.7
8	.	.	.	.	.	.	.	.	.	.
9	1992	8.0	0.062	11.1	43244.3	43820.0	0.217	3.478	102.6	101.0
10	.	.	.	.	.	.	.	.	.	.
11	1160	10.0	0.074	9.4	23376.4	23572.3	0.273	3.765	92.6	102.9
12	1584	6.0	0.051	13.6	41037.4	42451.8	0.190	3.723	80.9	102.5
13	1451	6.0	0.055	12.5	36529.8	37477.7	0.222	4.021	114.5	109.0
14	1242	6.0	0.070	10.0	29062.8	29375.8	0.302	4.346	98.6	83.8
15	1219	10.0	0.069	10.1	29238.0	29632.2	0.308	3.035	98.3	96.2
16	1586	6.0	0.058	12.0	44561.9	45766.0	0.143	2.435	96.5	103.8
17	1246	12.0	0.062	11.2	32830.4	33434.3	0.230	3.714	98.5	104.5
18	.	.	.	.	.	.	.	.	.	.
19	1447	10.0	0.054	12.8	39631.8	40914.0	0.238	4.480	83.2	90.7
20	1147	6.0	0.049	14.2	39746.1	41636.5	0.184	3.751	91.6	97.9
21	1438	6.0	0.067	10.4	38545.5	38972.6	0.238	3.561	127.7	117.4
22	.	.	.	.	.	.	.	.	.	.
23	1372	6.0	0.071	9.7	28208.9	28453.8	0.274	3.845	96.6	91.9
24	1438	6.0	0.063	10.9	38685.3	39293.5	0.223	3.526	84.7	110.7
Mean	1422	8.3	0.063	11.2	34759.0	35516.9	0.223	3.511	98.1	103.1

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ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters in Healthy Subjects Receiving a Single Dose of DVS-233 SR

Supportive Table ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 09:44 Monday, August 4, 2003
In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol D6100D3-172-US

	CMAX (ng/mL)					TMAX (h)					LAMBDA (1/h)				
Treatment	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean
DVS-233 SR 1x100 mg	21	238	44.5	18.7	234	21	7.52	1.99	26.5	7.28	21	0.063	0.008	13.4	0.062
DVS-233 SR 3x100 mg	20	712	129.1	18.1	701	20	7.20	1.77	24.5	7.01	20	0.064	0.009	13.5	0.064
DVS-233 SR 6x100 mg	19	1422	200.5	14.1	1409	19	8.32	1.92	23.0	8.11	19	0.063	0.010	15.4	0.063

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ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters in Healthy Subjects Receiving a Single Dose of DVS-233 SR

Supportive Table ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 09:44 Monday, August 4, 2003
In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol 0600D3-172-US

	CMAX (ng/mL)					TMAX (h)					LAMBDA (1/h)				
Treatment	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean
DVS-233 SR 1x100 mg	21	238	44.5	18.7	234	21	7.52	1.99	26.5	7.28	21	0.063	0.008	13.4	0.062
DVS-233 SR 3x100 mg	20	712	129.1	18.1	701	20	7.20	1.77	24.5	7.01	20	0.064	0.009	13.5	0.064
DVS-233 SR 6x100 mg	19	1422	300.5	14.1	1409	19	8.32	1.92	23.0	8.11	19	0.063	0.010	15.4	0.063

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Supportive Table ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol D6000D3-172-US

09:44 Monday, August 4, 2003

	T 1/2 (h)					AUCt (ng*h/mL)					AUC (ng*h/mL)			
Treatment	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV
DVS-233 SR 1x100 mg	21	11.2	1.5	13.3	11.1	21	5395.2	1345.5	24.9	5210.9	21	5560.1	1377.0	24.8
DVS-233 SR 3x100 mg	20	11.0	1.6	14.1	10.9	20	16286.1	3379.0	20.7	15935.5	20	16594.1	3553.0	21.4
DVS-233 SR 6x100 mg	19	11.2	1.8	15.8	11.0	19	34759.0	6420.7	18.5	34190.6	19	35516.9	6865.2	19.3

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Supportive Table ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 09:44 Monday, August 4, 2003
In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol D6000D3-172-US

	AUC (ng*h/m	CL/F (L/h/kg)					Vz/F (L/kg)					CMAX RATIO (%)			
Treatment	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV
DVS-233 SR 1x100 mg	5376.2	21	0.246	0.082	33.1	0.236	21	3.940	1.316	33.4	3.798	.	.	.	.
DVS-233 SR 3x100 mg	16214.6	20	0.238	0.049	20.4	0.233	20	3.706	0.570	15.4	3.665	19	100.1	16.4	16.4
DVS-233 SR 6x100 mg	34879.9	19	0.223	0.045	20.4	0.218	19	3.511	0.524	14.9	3.473	19	98.1	11.7	11.9

Supportive Table ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 09:44 Monday, August 4, 2003
In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol D6000D3-172-US

	CMAX R (%)	AUC RATIO (%)				
Treatment	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean
DVS-233 SR 1x100 mg	.	.	.	.	.	.
DVS-233 SR 3x100 mg	98.9	19	98.3	10.6	10.8	97.8
DVS-233 SR 6x100 mg	97.5	19	103.1	10.1	9.8	102.6

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ST 8-6. Statistical Comparisons of Desvenlafaxine PK Parameters in Healthy Subjects Receiving a Single Dose of DVS-233 SR

Supportive Table ST 8-6. Statistical Comparisons of Desvenlafaxine PK Parameters 09:44 Monday, August 4, 2003
In Healthy Subjects Receiving a Single Dose of DVS-233 SR
Protocol 0600D3-172-US

P-Values from Analysis of Variance for a Three-Period Cross-Over Design

Factor	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCt (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
Sequence	<0.001	0.735	0.008	0.008	<0.001	<0.001	<0.001	<0.001
Sub(Seq)	<0.001	0.367	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Treatment	0.759	0.226	0.670	0.670	0.118	0.121	0.121	0.355
Period	0.960	0.894	0.767	0.767	0.582	0.564	0.564	0.485

Note: Before statistical comparisons were made, dose-dependent values(Cmax, AUCt, and AUC) were normalized to the lowest dose.

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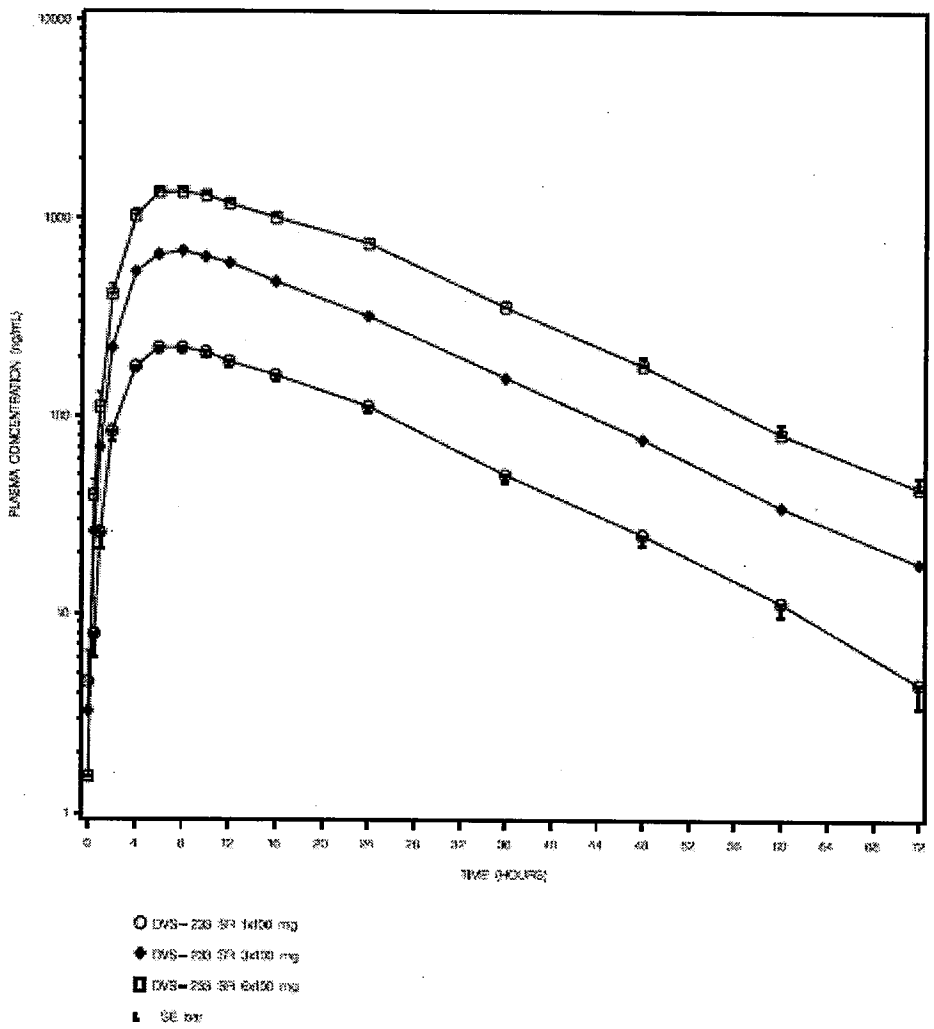
SF 8-1. Mean Desvenlafaxine Plasma Concentrations in Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR



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Title (3151A1-174-US): A study of the absolute bioavailability of an oral formulation of Desvenlafaxine in healthy subjects

Objectives: To assess the absolute bioavailability and pharmacokinetic profile of DVS in healthy subjects

Study Design: This single-dose, open-label, randomized, 2-period crossover study conducted with healthy subjects. Subjects (18 to 45 years) were randomly assigned to receive 1 of the 2 formulations of DVS in the first period and the other formulation in the second period. A single dose of test article was administered (by oral or intravenous [IV] routes) after an overnight fast of approximately 10 hours on study day 1 of each period. The 2 study periods were separated by at least 96 hours. Each subject participated in the study for 29 days. Participation included a screening evaluation within 3 weeks before study day 1 and a 9-day (8-night) inpatient stay beginning on day -1. Subjects were discharged from the unit approximately 72 hours after the final evaluation at the end of study period 2.

Subjects received test article on the morning of study day 1 (for periods 1 and 2) after a minimum 10-hour fast. At approximately 0800 hours, each subject received test article (one 100-mg DVS SR oral tablet or a 50 mg/ 60 minutes [min] DVS IV infusion) according to the randomization schedule. The oral tablet was administered with 240 mL of room-temperature water. Subjects received test article in an upright position, and remained in a semi recumbent position for 2 hours after receiving test article. Vital signs, ECGs, laboratory evaluations, pharmacokinetic blood sample collection, and urine collection were completed at designated times during the study. Adverse events were monitored continuously throughout the study.

For the oral formulation, blood samples were collected before and at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after test article administration. For the IV formulation, blood samples were collected before the infusion start (time 0) and at 0.5 (mid-infusion), 1 (end of the infusion), 1.25, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after test article administration. Urine was collected during the following time intervals: before, and at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after test article administration. Urine samples were collected and processed as described in the protocol, when appropriate for the parent compound and/or metabolite(s). Unscheduled samples for pharmacokinetic analysis were collected if a serious adverse event (SAE) occurred. The dosage strength and batch numbers used in the study are 1) DVS 50 mg (2.5 mL in 5 mL vial, 20 mg/mL), batch number 2003B0158 (Formulation 0931905J), 2) DVS 100 mg SR, batch number 2002B0109 (Formulation 0931731A).

Analytical Method: Plasma was assayed for determination of the enantiomeric ratio (S) - to (R) - of desvenlafaxine by using a validated liquid chromatography mass spectroscopy method with mass spectroscopy detection (LC/MS/MS). The linear range of the assay was 5 to 700 ng/mL and the sensitivity limit was 5 ng/mL. In addition, plasma was

assayed for racemic (R+S) desvenlafaxine by using a validated high performance liquid chromatography (HPLC) method with fluorescence detection. The minimum quantifiable concentration for desvenlafaxine was 5 ng/mL in plasma and 0.10 mg/mL in urine. The linear range was 5 to 500 ng/mL. Urine samples were assayed for unconjugated and total (unconjugated plus conjugated) desvenlafaxine and N, O-didesmethylvenlafaxine (NODV) by using HPLC with fluorescence detection. Based on a 0.1-mL urine sample, the method has a minimum quantifiable concentration of 0.1 μg/mL for both analytes.

Data analysis: Concentrations of (R)- and (S)-enantiomers of desvenlafaxine were determined as the product of each enantiomer fraction of racemic mixture and the concentration of racemic desvenlafaxine. The (R)-, (S)-, and racemic desvenlafaxine plasma concentration data for each subject were analyzed using empirical, model-independent methods.

Intravenous clearance (Cl) was calculated as IV dose divided by the AUC after IV administration. The apparent volume of distribution after IV administration based on the terminal phase (V_z) was calculated as CL/λ_z. Apparent oral-dose clearance (Cl/F) was calculated as oral dose divided by AUC after oral administration, with F being the relative bioavailability. The apparent volume of distribution after oral administration based on the terminal phase (V_z/F) was calculated as $[Cl/F]/\lambda_z$. The absolute bioavailability of (R)-, (S)-, and racemic desvenlafaxine was calculated as the dose-normalized ratio of oral to IV AUC.

Conjugated desvenlafaxine and NODV refers to glucuronidated metabolites of desvenlafaxine and NODV, respectively. Unconjugated desvenlafaxine and NODV refers to free desvenlafaxine and NODV, respectively. Urine amounts of total (conjugated and unconjugated) and unconjugated desvenlafaxine and total and unconjugated NODV were reported for each collection interval. In addition, the amounts of each analyte for each urine collection interval were summed to provide cumulative amounts excreted during the hour 0 to 72 urine collection period. Total urinary recovery values for the 72-hour period for each analyte were divided by the dosage amount of DVS SR to calculate the percentage of dose recovered in urine. The total urinary recovery of desvenlafaxine and metabolites (desvenlafaxine glucuronide, NODV, and NODV glucuronide) was calculated as the sum of total desvenlafaxine and total NODV. The total urinary recovery of desvenlafaxine and metabolites was divided by the dose of desvenlafaxine in order to provide the percentage of the dose of administered desvenlafaxine eliminated in urine. Renal clearance of desvenlafaxine (CL_R) was calculated as the total amount of unconjugated desvenlafaxine excreted in urine divided by the plasma AUC of desvenlafaxine. The percentage of IV clearance accounted for by renal elimination of unconjugated desvenlafaxine was calculated as CL_R divided by Cl.

Results: Mean plasma concentrations of racemic desvenlafaxine for IV and oral administration are displayed in the attachments. Mean plasma concentrations for (R)- and (S)-enantiomers of desvenlafaxine after IV and oral DVS administration are presented in the attachments. Descriptive statistics for the sum of urinary recovery from total desvenlafaxine and total NODV as a percentage of the administered dose of DVS SR are

provided in the attachments. The following table provides descriptive statistics for racemic desvenlafaxine (R+S) pharmacokinetic parameters after oral DVS SR and IV DVS administration.

Descriptive Statistics for Pharmacokinetic Parameters for Racemic Mixture (R+S) Desvenlafaxine

Treatment		Cmax (ng/mL)	Tmax (h)	T ½ (h)	AUC (ng*h/mL)	F (%)
DVS IV (50 mg/60 min)	Mean ± SD (%CV)	232 ± 53 (23%)	1	9.8 ± 2.1 (21%)	2442 ± 585 (24%)	N/A
DVS SR, oral 100 mg	Mean ± SD (%CV)	160 ± 42 (27%)	6.4 ± 2.1 (33%)	10.4 ± 2.0 (19%)	3993 ± 1271 (32%)	80.5 ± 16 (20%)

Descriptive statistics for pharmacokinetic parameters for each enantiomer of desvenlafaxine after oral and IV administration of DVS are provided in the following table.

Descriptive Statistics for Pharmacokinetic Parameters for Desvenlafaxine Enantiomers

	Treatment		Cmax (ng/mL)	Tmax (h)	T ½ (h)	AUC (ng*h/mL)
R-Enantiomer	DVS IV (50 mg/60 min)	Mean ± SD (%CV)	111 ± 26 (23%)	1	9.9 ± 3.1 (31%)	1173 ± 291 (25%)
	DVS SR, oral 100 mg	Mean ± SD (%CV)	77 ± 20 (26%)	7 ± 2.6	10.3 ± 1.9 (19%)	1915 ± 615 (32%)
S-Enantiomer	DVS IV (50 mg/60 min)	Mean ± SD (%CV)	120 ± 28 (23%)	1	9.5 ± 2.0 (21%)	1262 ± 299 (24%)
	DVS SR, oral 100 mg	Mean ± SD (%CV)	83 ± 22 (27%)	6.6 ± 2.1	10.2 ± 2.0 (20%)	2057 ± 643 (31%)

Descriptive statistics for urinary recovery of total desvenlafaxine and unconjugated desvenlafaxine and CL_R for intravenously administered desvenlafaxine are provided in the following table.

Descriptive Statistics for Urinary Excretion Data for Total and Unconjugated Desvenlafaxine

	Treatment		Urinary Recovery (%) 0-72h	Renal Clearance (L/h)	Renal Clearance (mL/min)	% of IV Plasma Clearance
Total desvenlafaxine	DVS IV (50 mg/60 min)	Mean ± SD (%CV)	72.3 ± 14.5 (20%)	N/A	N/A	N/A
	DVS SR, oral 100 mg	Mean ± SD (%CV)	65.5 ± 10.8 (17%)	N/A	N/A	N/A
Unconjugated desvenlafaxine	DVS IV (50 mg/60 min)	Mean ± SD (%CV)	51.5 ± 11.4 (22%)	12.1 ± 5.8 (47%)	202 ± 96 (47%)	54.3 ± 12 (22%)
	DVS SR, oral 100 mg	Mean ± SD (%CV)	46.4 ± 9.9 (21%)	13.3 ± 4.9 (37%)	222 ± 82 (37%)	N/A

Desvenlafaxine plasma concentrations peaked at the end of the 1-hour DVS IV infusion and the rate of decline was relatively constant from about 4 hours after IV administration Desvenlafaxine plasma concentrations peaked about 6 hours after oral DVS SR administration, and the rate of decline describing the terminal half-life was visible from about 36 hours after oral administration. C_{max} was approximately 45% higher after IV than after oral administration of DVS. Similar values were observed for desvenlafaxine terminal half-life after both oral and IV administration. Based on a dose-normalized comparison of AUC values for IV and oral data, the mean absolute bioavailability of DVS was 80.5%.

Urinary excretion of conjugated and unconjugated desvenlafaxine and NODV accounted for the majority of the administered dose of DVS after both IV (76%) and oral administration (69%). The major portion of desvenlafaxine elimination for both IV and oral administration was as urinary excretion of both conjugated (19% to 22%) and unconjugated desvenlafaxine (46% to 52%).

The most frequently reported TEAEs (>10%) were nausea, dizziness, and somnolence, each reported by 3 of 14 subjects (21.4%). Diarrhea and dry mouth were each reported by 2 subjects (14.3%). Nausea and dizziness were more frequently reported after DVS IV than DVS SR oral administration (21.4% of subjects after IV vs 7.1% of subjects after oral administration). Diarrhea and somnolence were more frequently reported after oral

than IV administration (14.2% of subjects after oral vs 7.1% of subjects after IV administration).

Mean supine systolic blood pressure (SBP) increased significantly between 4 and 60 hours after oral DVS SR and 1 to 72 hours after DVS IV administration. The maximum mean increase was 8.7 mm Hg (day 1, hour 36) and 12.4 mm Hg (day 1, hour 12) after oral and IV administration, respectively. Isolated significant increases occurred in supine DBP 0.5 to 8 hours after DVS IV administration. The maximum mean increase was 6.5.mm Hg. Mean pulse rate increased significantly for some time points between 4 and 72 hours after oral administration of DVS SR, achieving a maximum mean increase of 9.5 bpm (day 1, hour 60). No significant changes in QRS or QTc interval occurred after oral and IV administration of DVS.

Summary: Absolute oral bioavailability of about 80% was achieved for DVS SR. Urinary excretion of conjugated and unconjugated desvenlafaxine and NODV accounted for the majority of the administered dose of DVS after both IV (76%) and oral (69%) administration.

The most frequently reported TEAEs (>10%) were nausea, dizziness, and Somnolence (21.4%). Diarrhea and dry mouth were each reported by 14.3% of patients. Nausea and dizziness were more frequently reported after DVS IV than DVS SR oral administration (21.4% of subjects after IV vs 7.1% of subjects after oral administration). Diarrhea and somnolence were more frequently reported after oral than IV administration (14.2% of subjects after oral vs 7.1% of subjects after IV administration). The sponsor reported that no serious adverse events or deaths occurred during this study. The sponsor reported that DVS was generally safe and well tolerated when administered as 100 mg orally or 50 mg/60 minutes intravenously.

Reviewer's comments: The reviewer agrees with the sponsor's assessment of absolute bioavailability.

ST 8-2: PHARMACOKINETIC PARAMETERS AND DESCRIPTIVE STATISTICS FOR RACEMIC AND (R)- AND (S)-ENANTIOMERS OF DESVENLAFAXINE

Racemic PK Parameters After IV DVS Administration

Subject Number	Cmax (ng/mL)	Tmax (hr)	Lambda Z (1/hr)	$t_{1/2}$ (hr)	AUC_t (hr*ng/mL)	AUC (hr*ng/mL)	Cl (L/hr)	Cl (L/h/kg)	Vz (L)	Vz (L/kg)	Vss (L)	Vss (L/kg)	AUC %Extrap	MRTIV (hr)
1	194.195	1.0	0.078	8.84	1564	1670	29.6	0.336	380.0	4.284	372.0	4.19	6.78	12.48
2	170.203	1.0	0.095	7.29	1634	1697	29.5	0.354	310.1	3.723	303.5	3.64	3.74	10.30
3	332.046	1.0	0.094	7.34	2154	2217	22.6	0.344	238.9	3.636	207.6	3.16	2.88	9.20
4	252.755	1.0	0.056	12.33	2109	2358	21.2	0.223	377.2	3.962	308.6	3.24	10.54	14.55
5	199.844	1.0	0.076	9.10	2282	2444	20.5	0.253	268.6	3.320	266.5	3.29	6.64	13.03
6	205.809	1.0	0.059	11.75	2922	3027	16.5	0.188	280.1	3.197	296.9	3.39	3.48	17.98
7	221.108	1.0	0.073	9.54	2808	2917	17.1	0.237	236.0	3.264	237.0	3.28	3.75	13.83
8	226.717	1.0	0.065	10.66	2698	2727	18.3	0.227	281.9	3.502	265.5	3.30	4.37	14.48
9	248.127	1.1	0.059	11.90	2664	2759	18.1	0.258	311.2	4.439	277.1	3.95	3.41	15.29
10	256.933	1.0	0.050	13.88	3151	3261	15.3	0.197	307.1	3.952	237.3	3.05	3.36	15.47
11	305.360	1.0	0.077	8.99	2877	2954	16.9	0.245	219.5	3.181	204.3	2.96	2.59	12.07
12	295.105	1.0	0.066	8.10	2572	2687	18.6	0.216	217.5	2.529	217.3	2.53	4.27	11.67
13	169.003	1.0	0.094	7.37	1108	1233	40.5	0.420	431.2	4.468	400.2	4.15	10.16	9.87
14	163.389	1.0	0.065	10.68	2132	2234	22.4	0.249	345.0	3.833	340.6	3.78	4.56	15.22
N	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Mean	231.614	1.007	0.073	9.84	2327.5	2442.3	22.0	0.268	300.3	3.684	281.0	3.42	5.04	13.25
SD	52.957	0.033	0.015	2.076	587.42	584.56	6.95	0.068	64.86	0.546	60.26	0.471	2.564	2.478
Min	163.39	0.95	0.05	7.29	1109	1233	15.3	0.186	217.5	2.529	204.3	2.53	2.59	9.20
Max	332.05	1.12	0.10	13.88	3151	3261	40.5	0.420	431.2	4.468	400.2	4.19	10.54	17.98
CV%	22.9	3.3	20.6	21.1	25.2	23.9	31.6	25.5	21.6	14.9	21.4	13.8	50.9	18.7
Geometric Mean	226.150	1.007	0.072	9.64	2246.1	2366.0	21.1	0.260	294.0	3.624	275.2	3.39	4.56	13.02

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Supportive Table ST 8-2 (continued) Pharmacokinetic Parameters and Descriptive Statistics for Racemic and (R)- and (S)-Enantiomers of Desvenlafaxine

Racemic PK Parameters After Oral DVS SR Administration

Subject Number	Cmax (ng/mL)	Tmax (hr)	Lambda z (1/hr)	$t_{1/2}$ (hr)	AUC_T (hr*ng/mL)	AUC (hr*ng/mL)	Cl/F (L/hr)	Cl/F (L/h/kg)	Vz/F (L)	Vz/F (L/kg)	AUC %Extrap	MRT_{Oral} (hr)	MRT_{IV} (hr)	AUC_{oral}/AUC_{IV}	$t_{1/2,oral}/t_{1/2,IV}$	F (%)	F* (%)
1	121.659	6.0	0.068	10.18	2526	2690	37.2	0.419	546.1	6.157	6.10	19.77	7.29	1.60	1.15	80.15%	80.15%
2	136.250	6.0	0.087	7.99	3023	3166	31.6	0.379	364.1	4.371	4.52	19.94	9.64	1.87	1.10	93.28%	93.28%
3	174.097	12.0	0.094	7.35	3405	3475	28.8	0.435	305.1	4.644	1.92	15.45	6.25	1.57	1.00	78.37%	78.37%
4	167.306	6.0	0.060	11.45	3544	3789	26.4	0.277	437.3	4.593	6.46	19.41	4.86	1.61	0.93	80.34%	80.34%
5	199.071	5.0	0.070	9.97	3885	4055	24.7	0.305	354.8	4.286	4.20	24.81	11.78	1.66	1.10	82.96%	82.96%
6	144.386	4.0	0.063	11.01	4734	4825	20.7	0.236	329.2	3.758	1.88	23.28	5.30	1.59	0.94	79.70%	79.70%
7	243.309	8.0	0.062	11.21	5547	5632	17.8	0.246	287.2	3.972	1.51	19.73	5.90	1.93	1.18	96.54%	96.54%
8	135.373	8.0	0.063	10.99	4330	4495	22.2	0.278	352.9	4.384	2.56	24.80	10.32	1.65	1.09	82.42%	--
9	184.780	6.0	0.049	14.27	5602	5844	17.1	0.244	352.2	5.024	4.14	25.26	9.97	2.12	1.20	105.91%	--
10	181.229	6.0	0.054	12.72	4296	4498	22.7	0.292	417.5	5.373	2.32	21.72	6.25	1.35	0.92	67.43%	67.42%
11	210.250	4.0	0.070	9.87	5215	5341	18.7	0.271	266.6	3.864	2.35	24.81	12.24	1.81	1.10	90.40%	90.40%
12	197.130	6.0	0.064	10.87	3263	3357	29.5	0.347	467.0	5.490	2.69	18.53	6.86	1.25	1.34	62.47%	62.47%
13	89.436	4.0	0.101	6.87	900	1023	97.7	1.012	965.2	10.033	12.03	11.89	2.02	0.89	0.98	41.48%	41.48%
14	106.466	6.0	0.061	11.34	3730	3915	26.2	0.291	425.4	4.760	2.29	24.75	9.53	1.71	1.06	55.45%	55.45%
N	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	12
Mean	159.589	6.429	0.069	10.498	3861.3	3993.4	30.1	0.360	419.5	5.054	3.93	20.98	7.73	1.610	1.065	80.49%	78.22%
SD	42.240	2.102	0.015	2.002	1266.87	1270.58	20.27	0.195	174.99	1.577	2.809	3.965	2.919	0.315	0.123	15.74%	15.11%
Min	89.44	4.00	0.05	6.87	900	1023	17.1	0.236	266.6	3.758	1.51	11.89	2.02	0.890	0.917	41.48%	41.48%
Max	243.31	12.00	0.10	14.27	5602	5844	97.7	1.012	965.2	10.033	12.03	25.26	12.24	2.118	1.342	105.91%	96.54%
CV%	26.5	32.7	21.6	19.2	32.8	31.8	67.3	55.2	41.7	31.2	71.5	18.9	37.6	19.6	11.5	19.6	19.2
Geometric Mean	154.275	6.147	0.068	10.248	3579.7	3727.5	26.8	0.331	396.6	4.889	3.29	20.57	7.09	1.575	1.063	78.77%	76.56%

a: Subjects 8 and 9 were excluded from calculation because of small volume losses to intravenous dose.

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Supportive Table ST 8-2 (continued) Pharmacokinetic Parameters and Descriptive Statistics for Racemic and (R)- and (S)-Enantiomers of Desvenlafaxine

(R)-Enantiomer After IV DVS Administration

Subject Number	Cmax (ng/mL)	Tmax (hr)	Lambda Z (1/hr)	$t_{1/2}$ (hr)	AUC_T (hr*ng/mL)	AUC (hr*ng/mL)	Cl (L/hr)	Cl (L/h/kg)	Vz (L)	Vz (L/kg)	Vss (L)	Vss (L/kg)	AUC %Extrap (%)	MRT_{IV} (hr)
1	94.767	1.0	0.078	8.93	762	818	30.6	0.345	393.6	4.437	385.1	4.3	6.89	12.61
2	50.546	1.0	0.106	6.57	729	793	31.3	0.376	296.7	3.562	302.5	3.6	8.67	9.66
3	156.062	1.0	0.111	6.23	933	1017	24.6	0.374	220.9	3.362	213.4	3.2	7.72	8.68
4	118.289	1.0	0.056	12.47	963	1079	23.2	0.244	416.9	4.379	340.0	3.6	10.77	14.67
5	94.726	1.0	0.072	9.65	1080	1169	21.4	0.265	297.9	3.682	292.0	3.6	7.60	13.65
6	100.229	1.0	0.058	11.94	1433	1487	16.8	0.192	259.5	3.205	305.0	3.5	3.64	18.15
7	106.795	1.0	0.071	9.73	1333	1386	18.0	0.249	252.5	3.492	248.6	3.4	3.75	13.75
8	110.242	1.0	0.066	10.47	1251	1307	19.1	0.237	289.1	3.591	275.3	3.4	4.26	14.39
9	120.342	1.1	0.039	17.68	1278	1343	18.6	0.265	474.7	6.772	307.2	4.4	4.86	16.50
10	125.352	1.0	0.061	11.43	1509	1590	15.7	0.202	259.3	3.337	233.1	3.0	5.10	14.93
11	148.405	1.0	0.076	9.17	1400	1441	17.3	0.251	229.4	3.325	213.6	3.1	2.83	12.31
12	144.897	1.0	0.111	6.26	1237	1277	19.6	0.225	176.7	2.055	219.3	2.6	3.20	11.21
13	50.952	1.0	0.095	7.25	520	577	43.4	0.450	455.5	4.720	421.6	4.4	9.79	9.73
14	78.427	1.0	0.061	11.31	1079	1138	22.0	0.244	358.2	3.981	348.4	3.9	5.22	15.86
N	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Mean	111.454	1.007	0.076	9.93	1108.0	1173.4	23.0	0.280	315.1	3.557	293.2	3.572	6.02	13.29
SD	25.508	0.033	0.022	3.066	294.73	291.44	7.55	0.076	91.13	1.059	64.36	0.536	2.552	2.764
Min	78.43	0.98	0.04	6.23	520	577	15.7	0.192	176.7	2.055	213.4	2.550	2.83	8.68
Max	156.06	1.12	0.11	17.68	1509	1590	43.4	0.450	474.7	6.772	421.6	4.382	10.77	18.15
CV%	22.9	3.3	29.2	30.9	26.6	24.8	32.9	27.0	28.9	27.4	22.1	15.0	42.4	20.8
Geometric Mean	108.799	1.007	0.073	9.53	1068.4	1134.1	22.0	0.272	303.0	3.736	286.7	3.534	5.53	13.01

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Supportive Table ST 8-2 (continued) Pharmacokinetic Parameters and Descriptive Statistics for Racemic and (R)- and (S)-Enantiomers of Desvenlafaxine

(S)-Enantiomer After IV DVS Administration

Subject Number	Cmax (ng/mL)	Tmax (hr)	Lambda 2 (1/hr)	$t_{1/2}$ (hr)	AUC_T (hr*ng/mL)	AUC (hr*ng/mL)	Cl (L/hr)	Cl (L/h/kg)	Vz (L)	Vz (L/kg)	Vss (L)	Vss (L/kg)	AUC %Extrap (%)	MRT_{IV} (hr)
1	99.425	1.0	0.079	8.75	802	859	23.1	0.328	367.3	4.141	389.7	4.1	6.62	12.36
2	89.357	1.0	0.107	6.49	786	868	29.1	0.349	272.9	3.276	275.4	3.3	8.33	9.45
3	175.984	1.0	0.109	6.38	1080	1175	21.3	0.324	198.7	2.979	189.8	2.9	8.09	8.93
4	134.466	1.0	0.057	12.21	1146	1279	19.5	0.205	344.4	3.618	282.6	3.0	10.36	14.46
5	105.118	1.0	0.050	8.63	1202	1277	19.6	0.242	243.8	3.014	244.9	3.0	5.93	12.51
6	105.580	1.0	0.060	11.57	1498	1539	16.2	0.185	271.2	3.096	289.2	3.3	3.33	17.81
7	114.318	1.0	0.072	9.60	1474	1533	16.3	0.225	225.8	3.123	227.1	3.1	3.80	13.92
8	118.475	1.0	0.065	10.74	1357	1420	17.6	0.219	272.8	3.389	256.0	3.2	4.44	14.54
9	127.785	1.1	0.058	12.00	1387	1437	17.4	0.243	301.1	4.295	269.0	3.8	3.52	15.46
10	131.550	1.0	0.061	11.41	1553	1634	15.3	0.197	252.0	3.243	223.0	2.9	4.95	14.57
11	156.955	1.0	0.074	9.42	1477	1515	16.5	0.239	224.2	3.249	197.0	2.9	2.52	11.93
12	150.208	1.0	0.085	8.13	1335	1397	17.9	0.208	209.9	2.441	209.8	2.4	4.45	11.72
13	58.051	1.0	0.100	6.91	588	652	38.4	0.398	352.3	3.962	372.5	3.9	9.80	9.74
14	84.962	1.0	0.068	10.21	1053	1097	22.8	0.253	335.7	3.730	333.3	3.7	3.98	14.62
N	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Mean	120.159	1.007	0.077	9.46	1194.5	1262.3	21.2	0.259	278.5	3.397	266.4	3.246	5.72	13.00
SD	27.582	0.032	0.018	2.006	301.23	298.62	6.63	0.065	59.54	0.504	57.75	0.466	2.526	2.525
Min	84.96	0.98	0.06	6.38	588	652	15.3	0.185	195.7	2.441	189.8	2.440	2.52	8.93
Max	175.98	1.12	0.11	12.21	1553	1634	38.4	0.398	352.3	4.295	372.5	4.055	10.36	17.81
CV%	23.0	3.3	23.2	21.2	25.2	23.7	31.2	25.1	21.4	14.8	21.7	14.4	44.2	19.4
Geometric Mean	117.329	1.007	0.075	9.25	1153.1	1223.5	20.4	0.252	272.8	3.362	260.8	3.215	5.24	12.77

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Supportive Table ST 8-2 (continued) Pharmacokinetic Parameters and Descriptive Statistics for Racemic and (R)- and (S)-Enantiomers of Desvenlafaxine

(R)-Enantiomer After Oral DVS Administration

Subject Number	Cmax (ng/mL)	Tmax (hr)	Lambda 2 (1/hr)	$t_{1/2}$ (hr)	AUC_T (hr*ng/mL)	AUC (hr*ng/mL)	Cl/F (L/hr)	Cl/F (L/h/kg)	Vz/F (L)	Vz/F (L/kg)	AUC %Extrap (%)	MRT_{OBAL} (hr)	MRT_{IV} (hr)	AUC_{Oral}/ AUC_{IV}	$t_{1/2}$, Oral/ $t_{1/2}$, IV
1	58.515	6.0	0.067	10.42	1223	1306	38.3	0.432	575.2	6.495	6.41	20.06	7.45	1.60	1.17
2	65.536	6.0	0.084	8.21	1461	1536	32.6	0.391	385.5	4.631	4.89	20.28	10.62	1.92	1.28
3	80.259	12.0	0.103	6.70	1490	1555	32.2	0.490	311.0	4.734	4.18	14.80	6.12	1.53	1.08
4	78.701	6.0	0.061	11.46	1627	1742	28.7	0.301	474.5	4.584	6.59	19.41	4.74	1.61	0.92
5	66.059	8.0	0.062	11.05	1806	1899	26.3	0.325	419.6	5.187	4.91	25.16	11.51	1.62	1.16
6	71.038	4.0	0.062	11.20	2362	2409	20.8	0.237	335.3	3.628	1.96	23.59	5.44	1.62	0.94
7	115.085	8.0	0.068	10.26	2496	2561	19.5	0.270	259.1	3.595	2.53	19.79	6.01	1.85	1.06
8	67.664	8.0	0.062	10.95	2158	2215	22.6	0.281	357.5	4.441	2.58	24.96	10.57	1.69	1.08
9	90.936	12.0	0.049	14.02	2717	2828	17.7	0.252	357.7	5.103	3.93	24.97	8.47	2.11	0.79
10	88.440	6.0	0.059	11.82	2070	2153	23.2	0.299	396.1	5.098	3.83	21.45	6.62	1.35	1.03
11	100.710	4.0	0.069	10.04	2520	2583	19.4	0.281	255.4	4.064	2.44	24.34	12.03	1.79	1.09
12	95.608	6.0	0.065	10.25	1523	1602	31.2	0.363	461.5	5.366	4.96	18.19	6.95	1.25	1.64
13	41.767	4.0	0.102	6.78	425	461	104.0	1.078	1017.8	10.547	11.71	11.78	2.05	0.83	0.93
14	53.310	8.0	0.065	10.61	1902	1944	25.7	0.286	393.7	4.374	2.19	24.99	9.13	1.71	0.94
N	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Mean	76.658	7.000	0.070	10.273	1841.4	1915.4	31.6	0.375	432.5	5.203	4.51	20.98	7.70	1.607	1.074
SD	20.027	2.572	0.016	1.944	613.35	615.03	21.69	0.214	186.02	1.631	2.558	4.108	2.850	0.310	0.201
Min	41.77	4.00	0.05	6.70	425	461	17.7	0.237	280.4	3.628	1.96	11.78	2.05	0.834	0.793
Max	115.09	12.00	0.10	14.02	2717	2828	104.0	1.078	1017.8	10.547	11.71	25.16	12.03	2.106	1.637
CV%	26.1	36.7	22.4	18.9	33.3	32.1	68.7	56.7	43.0	32.3	56.8	19.6	37.0	19.3	18.7
Geometric Mean	74.175	6.594	0.069	10.085	1703.6	1784.6	28.0	0.346	407.6	5.025	3.98	20.55	7.09	1.574	1.058

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Supportive Table ST 8-2 (continued) Pharmacokinetic Parameters and Descriptive Statistics for Racemic and (R)- and (S)-Enantiomers of Desvenlafaxine

(S)-Enantiomer Desvenlafaxine After Oral DVS Administration

Subject Number	Cmax (ng/mL)	Tmax (hr)	Lambda Z (1/hr)	$t_{1/2}$ (hr)	AUC_T (hr*ng/mL)	AUC (hr*ng/mL)	Cl/F (L/hr)	Cl/F (L/h/kg)	Vz/F (L)	Vz/F (L/kg)	AUC %Extrap (%)	MRT_{ORAL} (hr)	MRT_{CL} (hr)	AUC_{oral}/ AUC_{IV}	$t_{1/2}$, Oral/ $t_{1/2}$, IV
1	62.141	6.0	0.070	9.97	1308	1384	26.1	0.407	519.6	5.858	5.81	19.49	7.13	1.61	1.14
2	70.714	6.0	0.089	7.78	1562	1631	20.7	0.369	344.2	4.133	4.19	19.62	10.18	1.90	1.20
3	93.838	12.0	0.097	7.12	1794	1887	26.5	0.403	272.3	4.145	4.95	15.34	6.41	1.61	1.12
4	90.666	8.0	0.062	11.16	1917	2043	24.5	0.257	394.2	4.141	6.17	19.30	4.84	1.60	0.91
5	72.012	8.0	0.075	9.22	2077	2157	23.2	0.287	308.3	3.811	3.69	24.58	12.07	1.69	1.07
6	73.348	4.0	0.062	11.04	2372	2416	20.7	0.236	329.6	3.762	1.83	22.99	5.18	1.57	0.95
7	128.224	8.0	0.064	10.84	2781	2864	17.5	0.242	273.0	3.776	2.87	20.25	6.33	1.87	1.13
8	70.709	8.0	0.063	11.01	2222	2279	21.9	0.272	348.4	4.328	2.54	24.65	10.11	1.60	1.03
9	94.238	6.0	0.048	14.50	2886	3017	16.6	0.237	346.6	4.944	4.35	25.54	10.03	2.10	1.21
10	92.789	6.0	0.059	11.82	2136	2218	22.5	0.290	384.4	4.947	3.68	21.17	6.60	1.36	1.04
11	109.540	4.0	0.071	9.71	2695	2757	18.1	0.262	254.1	3.683	2.28	24.28	12.35	1.82	1.03
12	101.522	6.0	0.066	10.56	1645	1737	28.8	0.335	435.7	5.101	5.27	18.28	6.56	1.24	1.30
13	47.669	4.0	0.100	6.94	476	542	92.2	0.955	923.2	9.567	12.32	12.00	2.26	0.53	1.00
14	53.372	6.0	0.062	11.14	1323	1570	26.7	0.297	429.5	4.776	2.20	24.35	9.73	1.70	1.09
N	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Mean	83.092	6.571	0.071	10.202	1975.2	2057.3	29.0	0.346	397.6	4.784	4.44	20.85	7.85	1.607	1.087
SD	22.321	2.138	0.015	2.000	637.52	642.88	18.97	0.155	167.87	1.515	2.657	3.927	2.944	0.311	0.104
Min	47.67	4.00	0.05	6.94	476	542	16.6	0.236	254.1	3.683	1.83	12.00	2.26	0.831	0.919
Max	128.22	12.00	0.10	14.50	2886	3017	92.2	0.955	923.2	9.567	12.32	25.54	12.35	2.100	1.299
CV%	26.9	32.5	21.2	19.6	32.2	31.2	65.4	53.3	42.2	31.7	59.9	18.8	37.5	19.3	9.6
Geometric Mean	80.264	6.275	0.069	10.013	1839.1	1925.3	26.0	0.320	375.2	4.624	3.90	20.45	7.23	1.574	1.082

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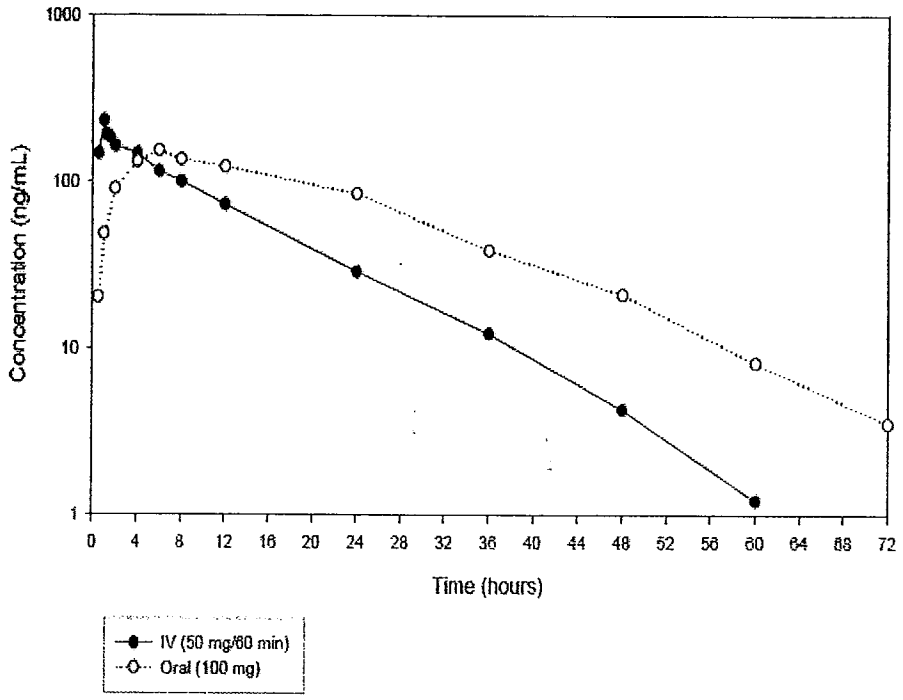
SF 8-1: MEAN RACEMIC MIXTURE (R+S) DESVENLAFAXINE CONCENTRATION PROFILE



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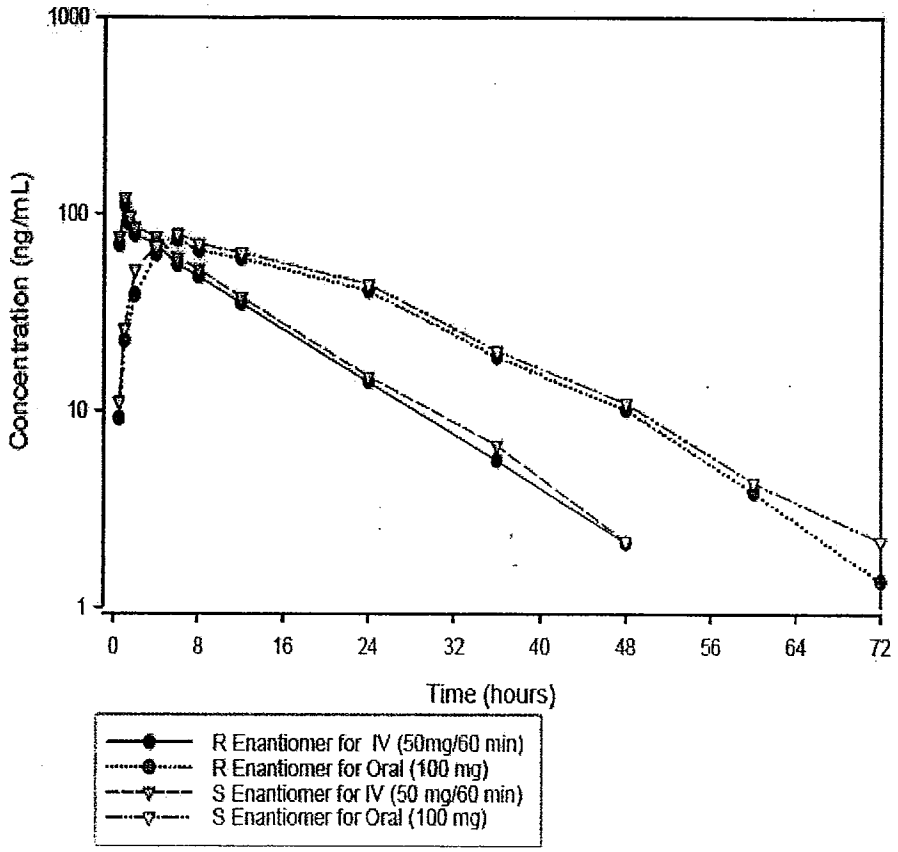

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Title (Protocol 0600D3-175-US): The Effects of Age and Gender on the Pharmacokinetics, Safety, and Tolerability of Desvenlafaxine SR Administered Orally to Healthy Subjects.

Objectives: The primary objective was to evaluate the pharmacokinetic profile of DVS SR in healthy men and women of different ages. The secondary objective was to assess the safety and tolerability of a single oral dose of DVS SR in healthy men and women of different ages.

Study Design: Healthy men and women, aged 18 to 45 years inclusive (young), 65 to 75 years inclusive (young-elderly), and >75 years (elderly) on study day 1. Body mass index in the range of 18 to 30 kg/m2 and body weight ≥50 kg participated in the study. The estimated creatinine clearance had to be within the age-appropriate normal range. The young-elderly and elderly could enroll with a chronic illness, provided it was well controlled and did not interfere with the primary objective of the study. For subjects in the young adult age group, concomitant treatments were not permitted throughout the study. Tobacco use or the consumption of any caffeine-containing products (eg, coffee, tea, chocolate, or cola), grapefruit, grapefruit-containing products, or alcoholic beverages was prohibited from at least 48 hours before study day 1 until the end of the inpatient confinement period. No strenuous exercise was permitted throughout the study period. The study enrolled 48 subjects (24 women and 24 men) and 48 completed the study. There were 16 subjects in the young adult group (18 to 45 years, inclusive), 15 subjects in the young-elderly group (65 to 75 years, inclusive) and 17 subjects in the elderly group (older than 75 years). DVS SR was administered orally as a single dose approximately 30 minutes after consuming a medium-fat breakfast. For the first 10 subjects, the single dose was 300 mg (3 x 100-mg tablets). Subsequently, the dose was changed to 200 mg (2 x 100-mg tablets), which was given to the remaining subjects. The batch number was 2002B0109.

Blood samples (10 mL each) were collected to measure concentrations of desvenlafaxine on study day 1 before dose administration (predose, within 2 hours before dose administration) and 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after test article administration. The predose samples were collected within 2 hours before dose administration. The total amount of blood collected from each subject was less than 250 mL. Urine samples were obtained to measure desvenlafaxine concentrations predose from hour -12 to hour 0 (before test article administration) and on day 1 from 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after administration of DVS SR. Urine samples were collected and processed (as described in the protocol). The date, actual collection time (24-hour clock), creatinine, pH, and sample volumes were collected.

Analytical Method: Plasma and urine were assayed for desvenlafaxine concentrations by using a validated high performance liquid chromatography method with fluorescence detection. The minimum quantifiable concentration for desvenlafaxine was 5 ng/mL in plasma and 0.10 mg/mL in urine. The performance of the desvenlafaxine assays during the analysis of the plasma and urine samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Pharmacokinetic Samples

	Compound/Matrix	
Standard Curve	Desvenlafaxine/Plasma (ng/mL)	Desvenlafaxine/Urine (µg/mL)
Linear range	5.0-500	0.10-10.0
Sensitivity	5.0	0.10

Analytical Summary of Desvenlafaxine Plasma Assays

	High QC (300.0 ng/mL)			Medium QC (60.0 ng/mL)			Low QC (15.0 ng/mL)		
Analyte	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Desvenlafaxine	296.8	4.07	-1.05	59.97	3.94	-0.05	14.88	5.67	-0.77

Abbreviations: QC = quality control.

Data Analysis: The desvenlafaxine plasma concentration data for each subject were analyzed by using empirical, model-independent methods.

Results: A summary of the demographic characteristics of the subjects who participated in the study are provided in the following table.

Demographic and Baseline

	DVS SR Dose (mg)									
Characteristic	200 18-45 yr Men (n=5)	200 18-45 yr Women (n=8)	200 65-75 yr Men (n=4)	200 65-75 yr Women (n=6)	200 >75 yr Men (n=7)	200 >75 yr Women (n=8)	300 18-45 yr Men (n=3)	300 65-75 yr Men (n=3)	300 65-75 yr Women (n=2)	300 >75 y Men (n=2)
Age (years)										
Mean	29.6	38.0	68.8	68.8	76.9	77.9	37.7	71.7	73.0	82.0
SD	7.1	5.1	3.6	2.7	1.2	2.4	5.5	1.2	0.0	1.4
Min, max	23.0,39.0	29.0,44.0	66.0,74.0	66.0,72.0	76.0,79.0	75.0,81.0	32.0,43.0	71.0,73.0	73.0,73.0	81.0,83.0
Median	27.0	38.0	67.5	68.5	76.0	78.0	38.0	71.0	73.0	82.0
Ethnic origin n (%)										
Black	3 (60)	1 (13)								
Other	1 (20)	1 (13)	1 (25)	5 (83)		1 (13)				
White	1 (20)	6 (75)	3 (75)	1 (17)	7 (100)	7 (88)	3 (100)	3 (100)	2 (100)	2 (100)
Height (cm)										
Mean	178.5	157.3	165.6	158.8	170.3	157.0	183.8	177.8	159.0	167.7
SD	5.7	7.5	3.8	7.5	5.0	6.4	9.4	12.0	1.2	2.8
Min, max	170.0,183.5	140.0,165.0	160.0,168.0	147.0,168.0	165.0,180.1	145.0,165.0	172.9,189.4	169.1,191.5	158.1,159.8	165.7,169.7
Median	181.8	160.0	167.3	159.0	168.0	158.0	189.0	172.7	159.0	167.7
Weight (kg)										
Mean	86.8	62.9	69.9	67.3	77.6	63.0	85.5	89.7	57.2	77.4
SD	11.1	10.3	5.7	9.2	13.2	7.3	9.8	17.6	6.5	14.9
Min, max	73.8,100.2	45.4,76.4	62.8,75.9	56.4,78.2	58.6,91.8	49.1,71.4	74.8,94.1	74.2,108.8	52.6,61.8	66.8,87.9
Median	90.9	62.4	70.5	66.9	83.6	65.0	87.5	86.1	57.2	77.4

Abbreviations: cm = centimeter; DVS SR = desvenlafaxine sustained-release; kg = kilogram; max = maximum; mg = milligram; min = minimum; n = number; SD = standard deviation.

The following table summarizes the mean ± SD and geometric mean of the dose-normalized desvenlafaxine pharmacokinetic parameter values and the statistical comparisons among the treatments.

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Desvenlafaxine Pharmacokinetic Parameters

Age/Sex Group	n	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (ng•h/mL)	Cl/F (L/h/kg)	Cl_r (mL/min)
Young Men	8	411 ± 93[a]	7.3 ± 2.1	11.8 ± 4.5	9702 ± 4134	0.28 ± 0.11	121 ± 35
		402	7.0	11.1	8713	0.26	117
Young Women	8	562 ± 133	5.8 ± 0.7	9.2 ± 0.9	10237 ± 2249	0.32 ± 0.05	113 ± 44
		549	5.7	9.1	9913	0.32	100
Young-Elderly Men	7	450 ± 61	9.7 ± 2.9	11.1 ± 1.7	12037 ± 3284	0.23 ± 0.05	105 ± 26
		446	9.3	11.0	11425	0.22	102
Young-Elderly Women	8	566 ± 140	6.3 ± 1.7	11.1 ± 3.4	14126 ± 5342	0.24 ± 0.06	102 ± 29
		551	6.0	10.7	13065	0.23	98
Elderly Men	9	582 ± 135	8.7 ± 2.6	11.7 ± 1.9	14941 ± 4660	0.19 ± 0.04	91 ± 44
		569	8.3	11.6	13994	0.18	82
Elderly Women	8	688 ± 132	8.5 ± 3.2	10.6 ± 1.3	15851 ± 4669	0.22 ± 0.07	83± 21
		678	7.9	10.6	14899	0.21	81
2-Factor Analysis of Variance of Log-Transformed Data							
Age		0.001	0.060	0.433	0.001	<0.001	0.119
Sex		<0.001	0.011	0.091	0.288	0.096	0.555
Age/Sex		0.633	0.200	0.543	0.934	0.713	0.870

a: Mean ± SD and geometric mean. C_{max} and AUC were normalized to a common 200-mg dose.

Comparing within each age group, women have an 18% to 36% higher C_{max} and a slightly shorter t_{max} than men. However, women have only a 6% to 17% higher total exposure (AUC) than men. The women in each group on average weighed less than men in that age group. Desvenlafaxine Cl/F was approximately 22% and 28% lower in the young-elderly and elderly subjects than in the young adult subjects. Consequently, desvenlafaxine C_{max} and AUC both increased with increasing age. Desvenlafaxine C_{max} differed by only 5% between the young and the young-elderly subjects, but desvenlafaxine C_{max} was approximately 25% higher in the elderly subjects than in the 2 younger age groups. On the other hand, AUC increased by approximately 32% from the young to the young-elderly, and by an additional 18% from the young-elderly to the elderly. Approximately 32% to 40% of the administered dose of desvenlafaxine was recovered in urine as unchanged drug in the 6 age/sex groups, and the urinary recovery was not significantly different among the groups.

The following table summarizes the nausea VAS pharmacodynamic parameters (mean ± SD) for the 6 age/sex groups.

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Nausea VAS Parameters

Dosage	n	E_{max} (mm)	t_{Emax} (h)	AURC (mm*h)	VAS ≥10 mm (% of subjects)
DVS SR 300 mg 18-45 yr Men	3	23±21[a]	4.0±0.0	141±185	66.7%
DVS SR 300 mg 65-75 yr Men	3	13±11	14.0±14.1	70±61	66.7%
DVS SR 300 mg 65-75 yr Women	2	43±28	6.0±0.0	505±572	100.0%
DVS SR 300 mg > 75 yr Men	2	0±0	NA	0±0	0.0%
DVS SR 200 mg 18-45 yr Men	5	3±4	7.0±7.1	17±35	20.0%
DVS SR 200 mg 18-45 yr Women	8	13±14	3.6±2.9	63±76	50.0%
DVS SR 200 mg 65-75 yr Men	4	4±8	2.0±NA	18±35	25.0%
DVS SR 200 mg 65-75 yr Women	6	5±8	7.3±4.2	12±16	16.7%
DVS SR 200 mg >75 yr Men	7	2±1	6.6±9.1	10±7	0.0%
DVS SR 200 mg >75 yr Women	8	13±14	7.2±7.7	68±71	50.0%
p-Values from ANOVA					
Age		0.758	0.582	0.947	
Sex		0.007	0.691	0.029	
Dose		0.002	0.783	0.004	
Age*Sex		0.729	0.870	0.799	

a: Mean ± SD
Abbreviations: DVS SR = desvenlafaxine sustained release; NA = not applicable.

Eleven (11) of the 48 subjects in the study exhibited a VAS E_{max} ≥20 mm, and the overall mean E_{max} was 10 mm (range 0 to 62 mm). The 10 subjects (8 men and 2 women) who received a single dose of DVS SR 300 mg had significantly higher (p=0.002) mean VAS E_{max} than the 40 subjects who received DVS SR 200 mg (15.4 vs 4.7 mm). Although there were fewer women who received the higher dose, the mean VAS E_{max} was significantly higher (p=0.007) in women than in men (13.4 vs 6.3 mm). There was no significant relationship between VAS E_{max} and age (mean values 11.5, 11.3, and 7.0 mm for young, young-elderly, and elderly subjects, respectively).

Summary: After oral, postprandial administration of DVS SR 200 or 300 mg to young, young-elderly and elderly men and women, desvenlafaxine was slowly absorbed with mean t_{max} ranging from 6 to 10 hours after administration. In the 6 age/sex groups, 32% to 40% of the administered dose was recovered unchanged in the urine.

Reviewer comments: The reviewer agrees with the sponsor's conclusions.

Attachments

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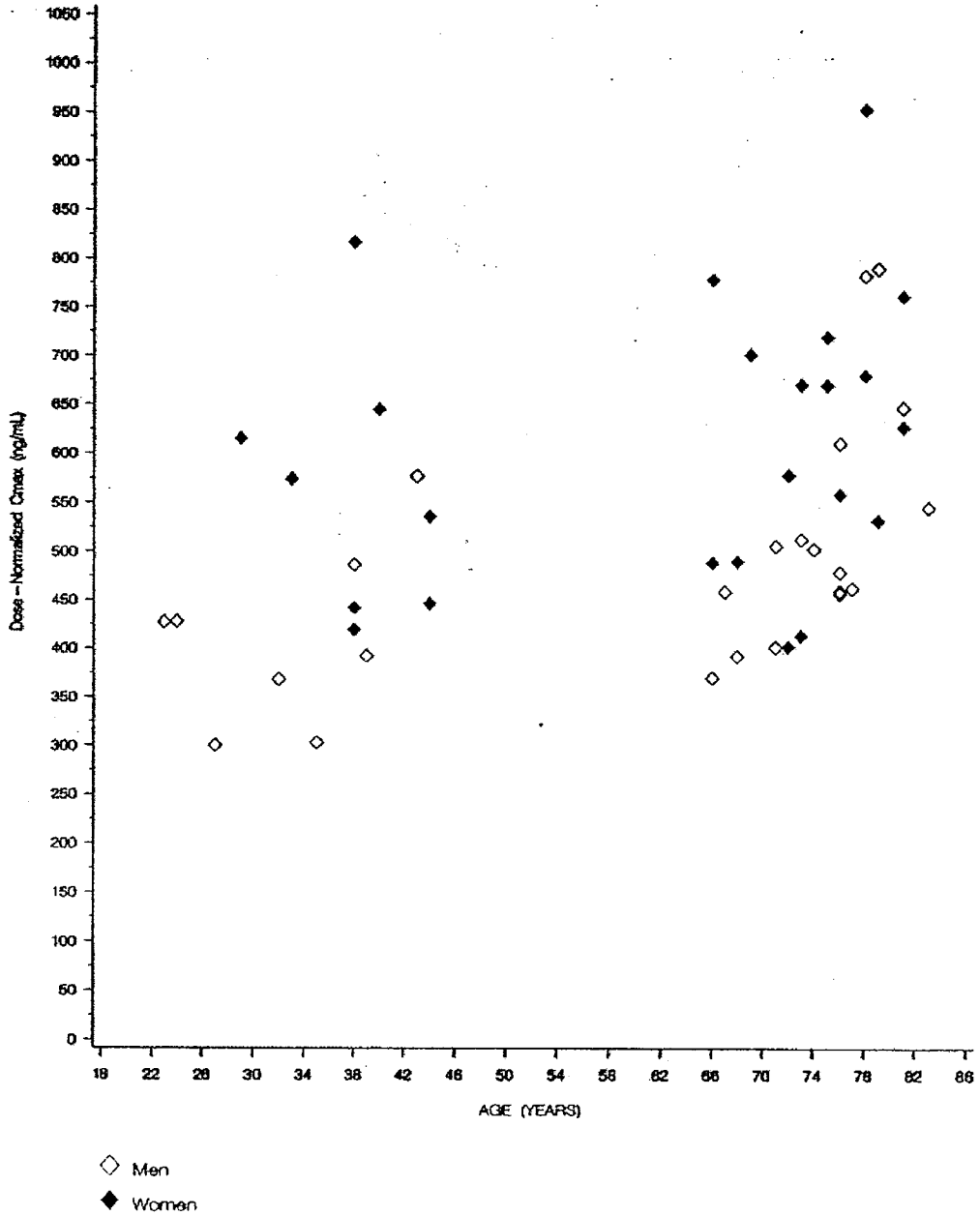
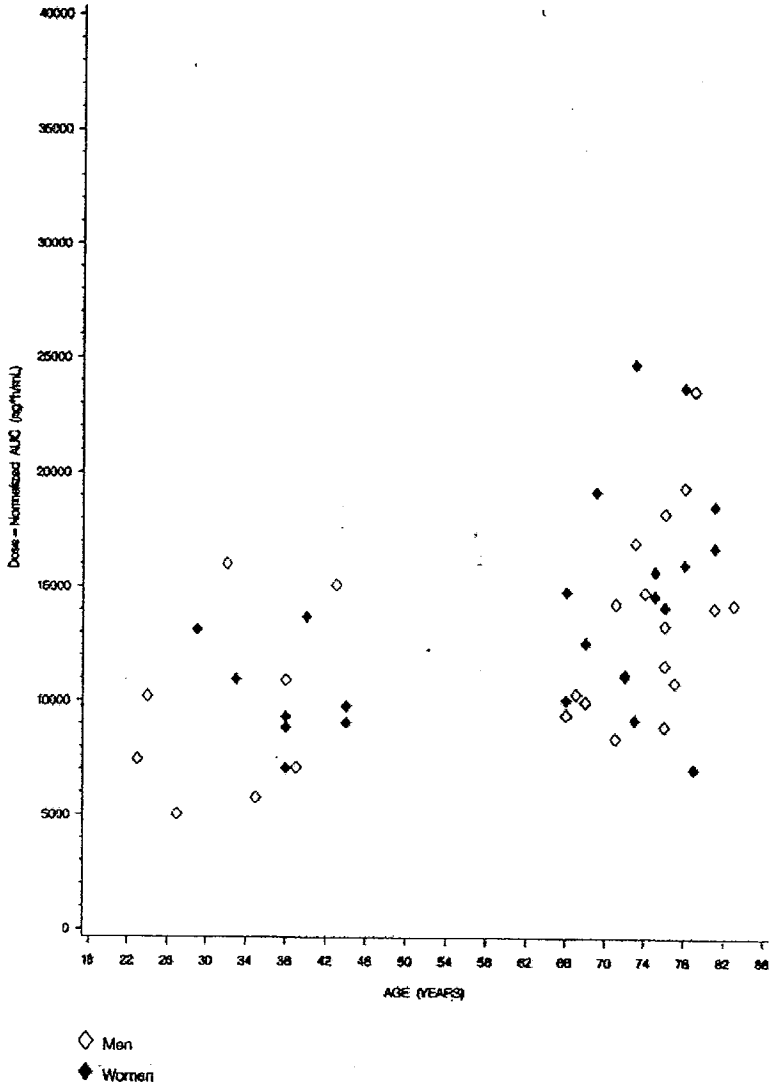
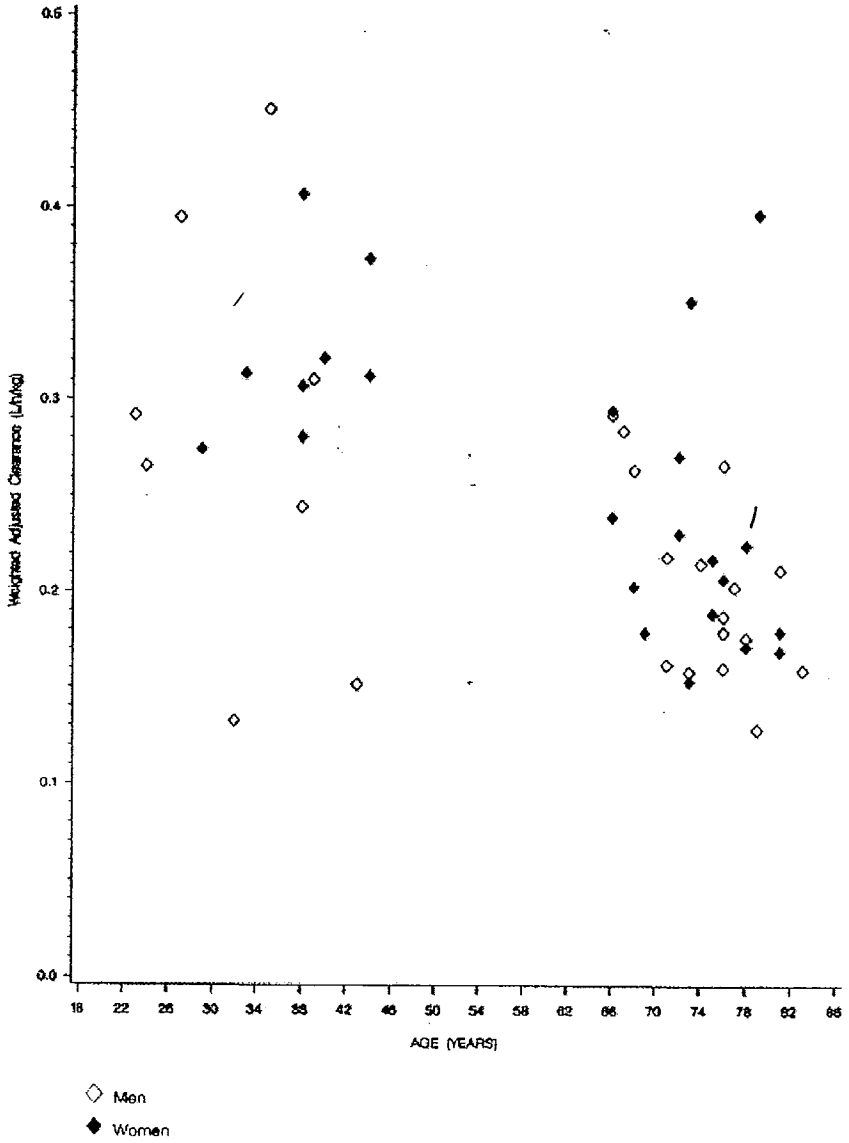
SF 8-2. Age vs Dose-Normalized C_{max} in Healthy Subjects Receiving a Single Dose of DVS SR



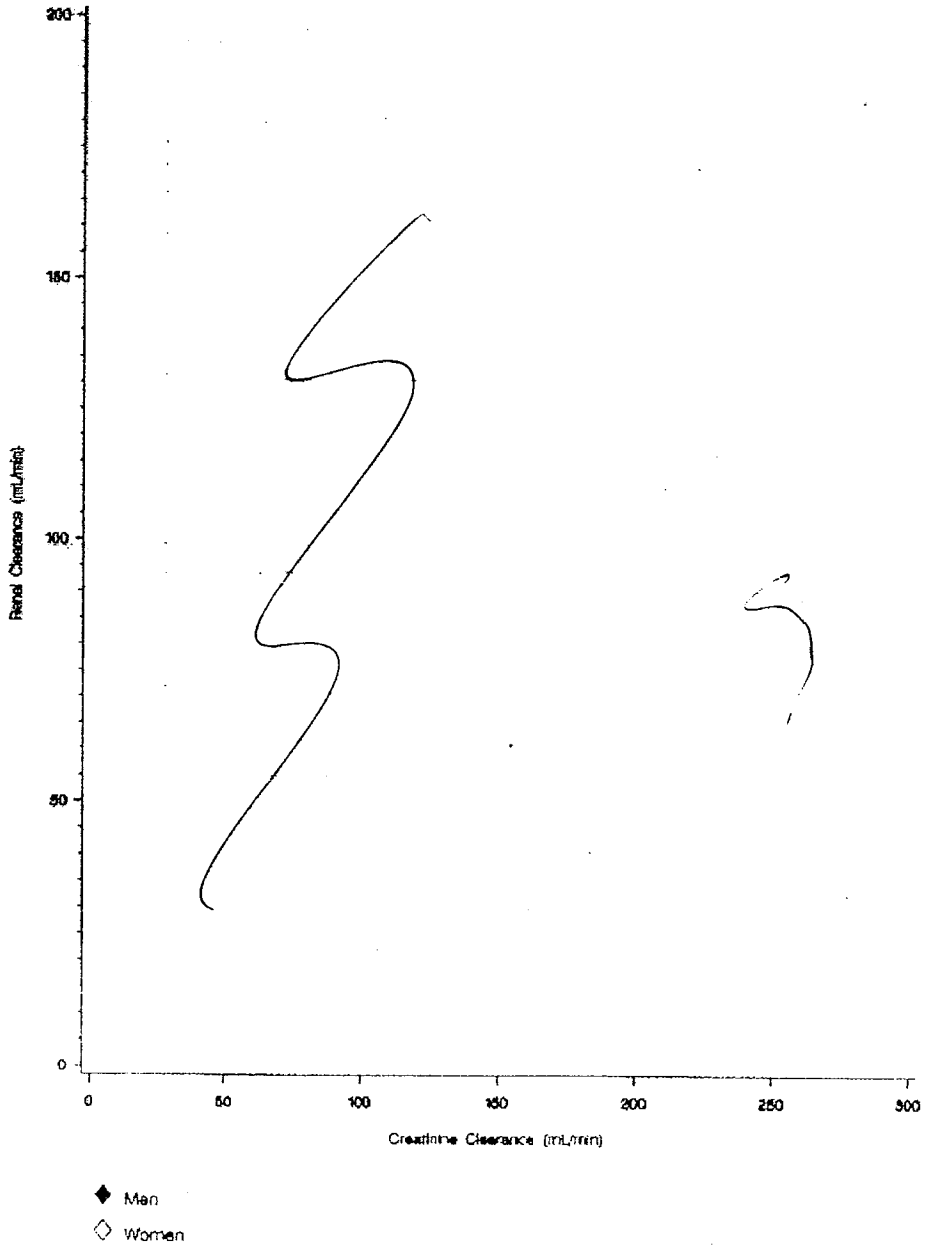
SF 8-3. Age vs Dose-Normalized AUC in Healthy Subjects Receiving a Single Dose of DVS SR



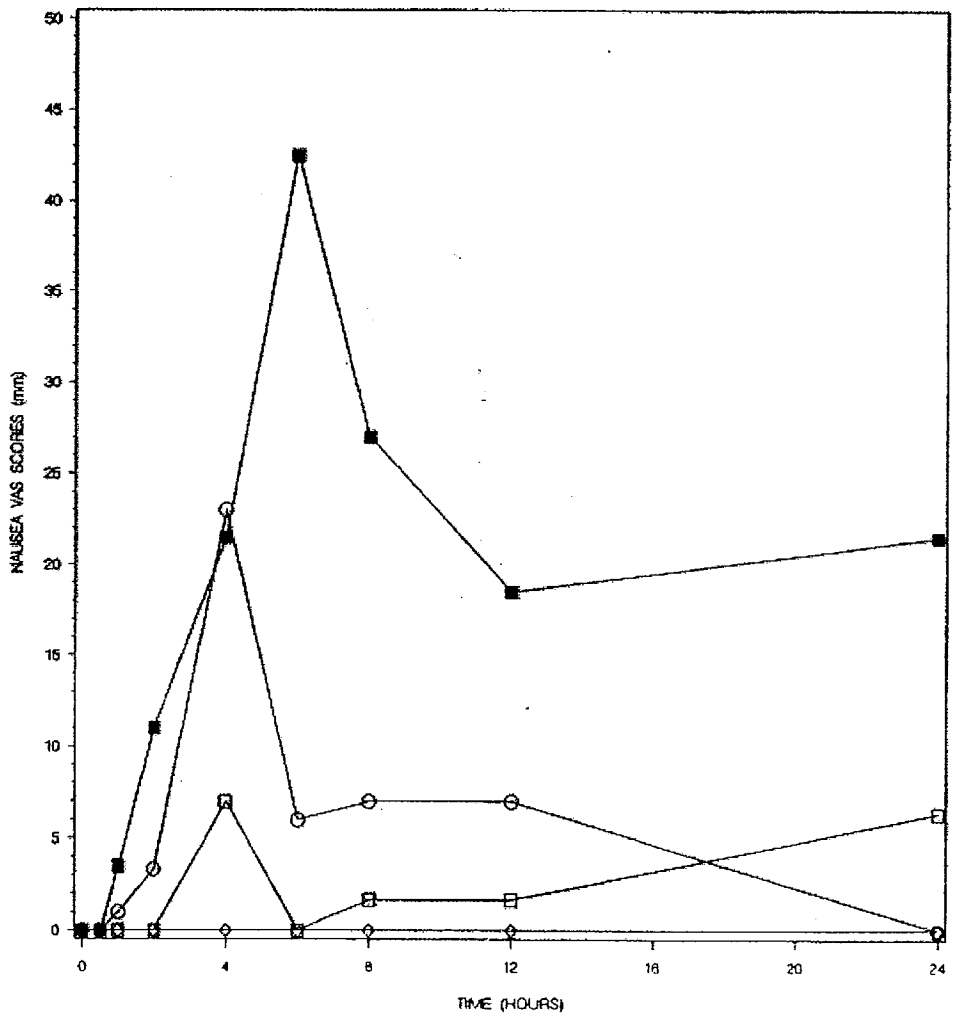
SF 8-4. Age vs Weight-Adjusted Clearance in Healthy Subjects Receiving a Single Dose of DVS SR



SF 8-5. Renal Clearance vs Creatinine Clearance in Healthy Subjects Receiving DVS SR



SF 8-7. Mean Nausea VAS Scores in Healthy Subjects Receiving a Single 300-MG Dose of DVS 233 SR



○ DVS - 233 SR 18 - 45 yr Men

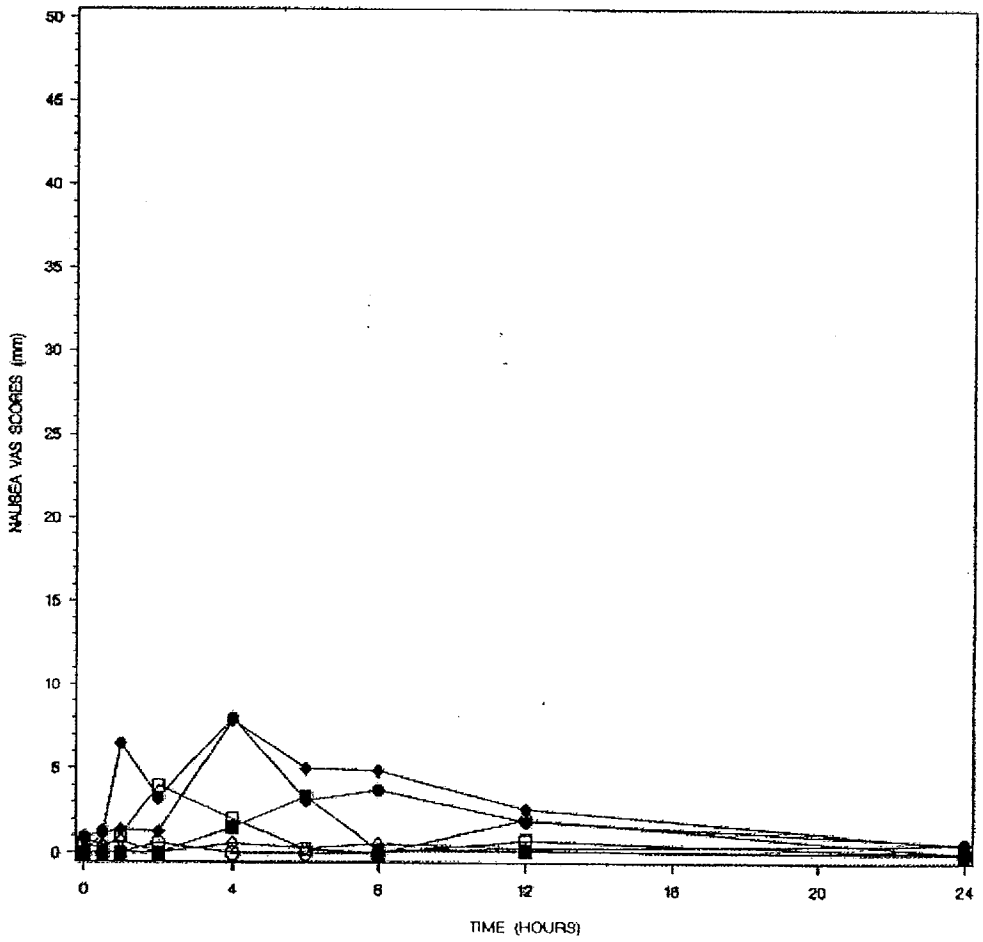
□ DVS - 233 SR 65 - 75 yr Men

■ DVS - 233 SR 65 - 75 yr Women

◇ DVS - 233 SR > 75 yr Men

⊥ SE bar

SF 8-8. Mean Nausea VAS Scores in Healthy Subjects Receiving a Single 200-MG Dose of DVS 233 SR



○ DVS – 233 SR 18 – 45 yr Men

● DVS – 233 SR 18 – 45 yr Women

□ DVS – 233 SR 65 – 75 yr Men

■ DVS – 233 SR 65 – 75 yr Women

◇ DVS – 233 SR > 75 yr Men

◆ DVS – 233 SR > 75 yr Women

SE bar

ST 8-5. Pharmacokinetic Parameters of Desvenlafaxine In Healthy Subjects Receiving DVS SR

Supportive Table ST 8-5: Pharmacokinetic Parameters of Desvenlafaxine 09:00 Friday, Ap
In Healthy Subjects Receiving DVS SR
Protocol 0600D3-175-US

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCt (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
DVS SR 300mg 18-45 yr Men								
9	866.0	12	0.058	12.0	22122	22621	0.15	2.62
10	730.1	6	0.087	7.9	16314	16404	0.24	2.80
11	553.2	8	0.036	19.2	21488	24037	0.13	3.67
DVS SR 300mg 65-75 yr Men								
3	770.3	6	0.060	11.5	24715	25504	0.16	2.62
6	603.5	12	0.074	9.3	12524	12617	0.22	2.94
8	759.4	12	0.055	12.7	20903	21478	0.16	2.97
DVS SR 300mg 65-75 yr Women								
1	1006.7	6	0.039	17.8	34115	37135	0.15	3.95
2	621.3	6	0.052	13.4	13423	13812	0.35	6.82
DVS SR 300mg >75 yr Men								
4	571.7	12	0.065	10.7	20897	21214	0.21	3.25
5	519.0	6	0.053	13.0	20792	21416	0.16	3.00

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Supportive Table ST 8-5: Pharmacokinetic Parameters of Desvenlafaxine 09:00 I
In Healthy Subjects Receiving DVS SR
Protocol 0600D3-175-US

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCt (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
DVS SR 200mg 18-45 yr Men								
12	392.9	6	0.076	9.1	6991	7088	0.31	4.08
13	300.7	6	0.088	7.9	4940	5055	0.39	4.49
14	427.1	6	0.038	18.1	7302	7446	0.29	7.62
15	303.2	6	0.076	9.1	5694	5773	0.45	5.92
16	428.3	3	0.064	10.9	10067	10214	0.27	4.18
DVS SR 200mg 18-45 yr Women								
50	536.0	6	0.095	7.3	8917	9060	0.37	3.92
51	645.2	6	0.076	9.1	13601	13703	0.32	4.21
52	442.3	6	0.072	9.7	6972	7070	0.41	5.69
53	446.8	6	0.072	9.6	9678	9766	0.31	4.33
54	419.7	6	0.078	8.9	8734	8856	0.31	3.95
55	817.3	4	0.075	9.2	9228	9323	0.28	3.74
56	574.3	6	0.076	9.1	10885	10970	0.31	4.12
57	615.5	6	0.067	10.3	12989	13149	0.27	4.08
DVS SR 200mg 65-75 yr Men								
17	303.4	12	0.056	12.5	14355	14504	0.22	3.88
47	392.9	6	0.054	12.8	9696	9990	0.26	4.89
48	459.6	3	0.066	10.4	10192	10324	0.28	4.28
49	370.7	12	0.080	8.7	9343	9406	0.29	3.68

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Supportive Table ST 8-5: Pharmacokinetic Parameters of Desvenlafaxine 09:00
In Healthy Subjects Receiving DVS SR
Protocol 0600D3-175-US

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCt (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
DVS SR 200mg 65-75 yr Women								
44	402.9	4	0.072	9.5	11078	11218	0.23	3.15
45	578.4	4	0.072	9.6	10947	11123	0.27	3.77
46	490.8	8	0.067	10.3	12423	12584	0.20	3.02
64	702.2	8	0.057	12.2	18769	19218	0.18	3.14
65	779.2	8	0.080	8.7	14730	14812	0.24	3.01
66	489.2	6	0.096	7.2	10015	10084	0.29	3.06
DVS SR 200mg >75 yr Men								
18	479.6	8	0.064	10.8	11449	11610	0.19	2.93
43	460.4	8	0.079	8.8	8811	8933	0.27	3.38
59	783.5	12	0.057	12.2	18987	19404	0.18	3.10
60	791.1	12	0.044	15.6	22388	23615	0.13	2.90
61	463.3	6	0.066	10.5	10694	10855	0.20	3.08
62	457.7	6	0.062	11.2	13107	13356	0.18	2.89
63	611.0	8	0.055	12.6	17739	18276	0.16	2.91
DVS SR 200mg >75 yr Women								
41	762.1	12	0.067	10.3	16577	16789	0.18	2.67
42	559.3	6	0.054	12.9	13744	14165	0.21	3.84
58	532.6	4	0.073	9.5	6954	7055	0.40	5.42
67	670.9	6	0.068	10.2	15517	15723	0.19	2.78
68	680.6	8	0.064	10.8	15915	16041	0.22	3.51
69	720.2	12	0.078	8.8	14577	14665	0.22	2.78
70	627.6	12	0.066	10.5	18336	18608	0.17	2.57
71	954.0	8	0.058	11.9	23221	23759	0.17	2.95

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Supportive Table ST 8-6: Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters In Healthy Subjects Receiving DVS SR
Protocol 0600D3-175-US

09:00 Friday,

TREATMENT	CMAX (ng/mL) N	Mean	S.D.	%CV	Geo. Mean	TMAX (h) N	Mean	S.D.	%CV	Geo. Mean
DVS SR 300mg 18-45 yr Men	3	716.4	156.8	21.9	704.6	3	8.7	3.1	35.3	8.3
DVS SR 300mg 65-75 yr Men	3	711.1	93.3	13.1	706.7	3	10.0	3.5	34.6	9.5
DVS SR 300mg 65-75 yr Women	2	814.0	272.5	33.5	790.8	2	6.0	0.0	0.0	6.0
DVS SR 300mg >75 yr Men	2	895.4	108.0	12.1	892.1	2	9.0	4.2	47.1	8.5
DVS SR 200mg 18-45 yr Men	5	370.4	64.1	17.3	365.8	5	6.4	0.9	14.0	6.4
DVS SR 200mg 18-45 yr Women	5	562.1	132.9	23.6	549.3	5	5.8	0.7	12.3	5.7
DVS SR 200mg 65-75 yr Men	4	431.6	61.0	14.1	428.4	4	9.5	3.0	31.6	9.1
DVS SR 200mg 65-75 yr Women	6	573.8	142.8	24.9	559.3	6	6.3	2.0	31.0	6.1
DVS SR 200mg >75 yr Men	7	578.1	152.7	26.4	562.1	7	8.6	2.5	29.2	8.3
DVS SR 200mg >75 yr Women	8	688.4	132.0	19.2	678.1	8	8.5	3.2	37.2	7.9

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Supportive Table ST 8-6: Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 09:00 Friday, April 30, 2004
In Healthy Subjects Receiving DVS SR
Protocol 0600D3-175-US

	LAMBDA (1/h)					T 1/2 (h)				
TREATMENT	N	Mean	S.D.	%CV	Geo. Mean	N	Mean	S.D.	%CV	Geo. Mean
DVS SR 300mg 18-45 yr Men	3	0.060	0.03	42.7	0.057	3	13.0	5.7	43.8	12.2
DVS SR 300mg 65-75 yr Men	3	0.063	0.01	16.0	0.063	3	11.2	1.7	15.2	11.1
DVS SR 300mg 65-75 yr Women	2	0.045	0.01	19.9	0.045	2	15.6	3.1	19.9	15.5
DVS SR 300mg >75 yr Men	2	0.059	0.01	13.7	0.059	2	11.9	1.6	13.7	11.8
DVS SR 200mg 18-45 yr Men	5	0.068	0.02	27.7	0.066	5	11.0	4.1	37.3	10.5
DVS SR 200mg 18-45 yr Women	3	0.076	0.01	10.9	0.076	3	9.2	0.9	9.6	9.1
DVS SR 200mg 65-75 yr Men	4	0.064	0.01	18.5	0.063	4	11.1	1.9	17.3	11.0
DVS SR 200mg 65-75 yr Women	6	0.074	0.01	17.8	0.073	6	9.6	1.7	17.2	9.5
DVS SR 200mg >75 yr Men	7	0.061	0.01	17.5	0.060	7	11.7	2.1	18.3	11.5
DVS SR 200mg >75 yr Women	8	0.066	0.01	11.5	0.066	8	10.8	1.3	12.1	10.6

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Supportive Table ST 8-6: Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters In Healthy Subjects Receiving DVS SR
Protocol 0600D3-175-US

09:00 Friday, April 30, 2004

TREATMENT	AUCt (ng*h/mL) N	Mean	S.D.	%CV	Geo. Mean	AUC (ng*h/mL) N	Mean	S.D.	%CV	Geo. Mean
DVS SR 300mg 18-45 yr Men	3	19974.4	3185.8	15.9	19793.5	3	21020.3	4060.3	19.3	20738.3
DVS SR 300mg 65-75 yr Men	3	19380.7	6236.4	32.2	18633.9	3	19866.3	6593.4	33.2	19048.0
DVS SR 300mg 65-75 yr Women	2	23769.1	14631.5	61.6	21399.3	2	25473.2	16491.7	64.7	22647.2
DVS SR 300mg >75 yr Men	2	20844.5	74.7	0.4	20844.4	2	21314.5	142.9	0.7	21314.3
DVS SR 200mg 18-45 yr Men	5	6998.6	1965.0	28.1	6791.9	5	7115.0	1984.9	27.9	6907.3
DVS SR 200mg 18-45 yr Women	8	10125.5	2242.6	22.1	9913.0	8	10236.9	2249.0	22.0	10025.7
DVS SR 200mg 65-75 yr Men	4	10896.7	2331.8	21.4	10729.8	4	11131.2	2478.0	22.3	10947.3
DVS SR 200mg 65-75 yr Women	6	12993.5	3269.0	25.2	12687.4	6	13173.4	3380.5	25.7	12852.7
DVS SR 200mg >75 yr Men	7	14739.2	5009.2	34.0	14022.6	7	15149.5	5359.5	35.4	14360.0
DVS SR 200mg >75 yr Women	8	15605.1	4564.9	29.3	14899.3	8	15851.0	4669.4	29.5	15129.2

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Supportive Table ST 8-8: Statistical Comparisons of Desvenlafaxine PK Parameters 09:00 Friday, Apr
In Healthy Subjects Receiving DVS SR
Protocol 0600D2-175-US

**********P-values from Log-Transformed Analysis of Variance**********

Factor	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCt (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
Age	0.001	0.060	0.433	0.433	0.001	0.001	<0.001	0.004
Sex	<0.001	0.011	0.091	0.091	0.242	0.288	0.096	0.690
Age*Sex	0.633	0.200	0.543	0.543	0.937	0.934	0.713	0.961

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Study Title: The Pharmacokinetic Profile, Safety, And Tolerability Of Three Different 200-Mg Tablet Formulations Of DVS-233 SR, In Healthy Adults From Two Different Manufacturing Sites (Protocol 3151A1-177-US, CSR 54268)

Objectives: The primary objective of this study was to evaluate the bioequivalence, using the pharmacokinetic profile, of 3 different 200-mg formulations of desvenlafaxine succinate (DVS) sustained release (SR) tablets from 2 different manufacturing sites (Montreal, Canada and Guayama, Puerto Rico), and to provide additional data to support the in vivo/in vitro correlation model for DVS SR tablets. The secondary objective was to evaluate the safety and tolerability of 200-mg tablets of DVS SR from 2 different manufacturing sites, when the tablets were administered to healthy subjects.

Study Design: This study was a single-dose, open-label, randomized, 3-period crossover study. Thirty (26 completed analyzed for PK) healthy men and women, ages 18 to 45 and >45 to 65 years, inclusive, with no clinically important findings on medical history, physical examination, clinical laboratory test results, vital signs, and 12-lead electrocardiogram (ECG) were enrolled. A single oral dose of test article was administered to healthy subjects after an overnight fast of at least 10 hours on study day 1 of each study period. Each subject participated in 3 study periods and received only 1 dose of DVS SR in each study period. The doses were separated by a washout interval of 4 days.

DVS SR 200-mg tablets manufactured in Guayama, Puerto Rico (PR formulation); batch number A61138. Also, a second formulation of 200 mg DVS SR (manufactured in Puerto Rico) having a dissolution rate approximately 10% higher than the other 200-mg tablets (PR fast-release formulation); batch number A61140. Both formulations were administered orally. The reference formulation was DVS SR 200-mg tablets that were manufactured in Montreal, Canada (CAN formulation); batch number 2002B0107. This reference formulation was used in the phase 2 study.

Venous blood samples (5 mL) were collected to measure concentrations of desvenlafaxine on study day 1 before and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours after test article administration in study periods 1, 2, and 3. The predose samples could have been collected within 2 hours before dose administration at the same time as the blood sample for laboratory evaluations.

Analytical Method: The plasma samples were analyzed for desvenlafaxine by a validated high-performance liquid chromatography method with ultraviolet detection. The lower limit of quantitation was 5 ng/mL. The validated method had been approved by WR.
The performance of the desvenlafaxine assays during the analysis of the plasma samples from this study is summarized in the tables below

Table 6.5.2-1: Assay Range and Sensitivity for Plasma Samples

Standard Curve	Compound/Matrix Desvenlafaxine/Plasma
Linear range (ng/mL)	5.0-500
Sensitivity (ng/mL)	5.0

Table 6.5.2-2: Analytical Summary of Desvenlafaxine Assays

	High QC[a] (300.0 ng/mL)			Medium QC (60.0 ng/mL)			Low QC (15.0 ng/mL)		
Analyte	Conc.	CV%	Bias %	Conc.	CV%	Bias %	Conc.	CV%	Bias %
Desvenlafaxine	297.2	4.57	-0.93	60.23	5.08	0.39	15.78	8.45	5.18

a: QC=Quality Control.

Data Analysis: The plasma concentrations of desvenlafaxine were analyzed using model-independent pharmacokinetic methods. The desvenlafaxine plasma concentrations at each sampling time and the desvenlafaxine pharmacokinetic parameters were compared among the 3 treatments (CAN, PR, and PR fast-release) by using an analysis of variance (ANOVA) for a 3-period crossover design. Assessments of the magnitude of differences between the 2 formulations manufactured in Guayama, Puerto Rico (PR and PR fast-release formulations) and the reference formulation manufactured in Montreal, Canada (CAN formulation) were made using the 90% confidence limits from the two 1-sided bioequivalence test procedure applied to log-transformed data. The formulations manufactured in Puerto Rico were produced using [redacted] the Montreal, Canada formulation was manufactured using [redacted]

Results: Mean plasma concentrations of desvenlafaxine for the 3 formulations are provided in the Attachments. C_{max} and AUC values for all 3 formulations for each subject are presented in the Attachments.

Summary of the mean (± SD) and geometric mean of estimates of the desvenlafaxine PK parameter values for the 3 formulations as well as the statistical comparisons among the formulations are provided in the following tables.

Desvenlafaxine Pharmacokinetic Parameters

DVS SR 200-mg Formulation	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng*h/mL)	AUC (ng*h/mL)
CAN	324±99[a]	7.1±3.6	10.9±2.1	8332±2873	8540±2989
	310	6.4	10.8	7675	7862
PR	330±75	8.8±5.4	10.7±2.7	8780±2448	8984±2536
	322	7.8	10.4	8398	8588
PR fast-release	390±97	6.4±2.5	10.7±1.9	8706±2474	8870±2547
	377	6.0	10.5	8270	8425
3-Period Crossover Analysis of Variance of Log-Transformed Data					
Sequence	0.669	0.168	0.849	0.717	0.705
Period	0.206	0.280	0.222	0.023	0.024
Treatment	<0.001	0.060	0.903	0.375	0.397
Least Squares Geometric Mean Ratio[b] (Relative Bioavailability) and 90% Confidence Limits					
PR	101%	--	--	106%	106%
	94-108%			94-119%	94-119%
PR fast-release	123%	--	--	107%	106%
	115-132%			96-118%	96-117%

Abbreviations: CAN = Montreal, Canada formulation (reference); PR = Puerto Rico formulation; PR fast-release = Puerto Rico fast-dissolving formulation.

a: Mean ± standard deviation and geometric mean.
Note: values of zero were excluded from calculations of the geometric means.

b: DVS SR 200 mg manufactured in Montreal, Canada is the reference formulation.

Similar plasma concentration profiles were observed for the PR formulation and the CAN formulation with respect to t_{max}, C_{max} and AUC. In comparison, the PR fast-release formulation had C_{max} values occurring approximately 1 to 2 hours before the PR and CAN formulations. C_{max} was approximately 18% to 20% higher for the PR fast-release formulation compared with the PR and CAN formulations. AUC values for the PR fast-release formulation were similar to the other 2 formulations. Mean half-life values of approximately 11 hours were similar for all 3 formulations.

Regulatory bioequivalence criteria require that 90% confidence intervals for test formulations fall within 80% to 125%. An examination of confidence intervals for AUC showed that both of the formulations manufactured in Puerto Rico (PR and PR fast-release) met the regulatory criteria when compared with the CAN formulation (reference formulation). In contrast, for C_{max} values, only the PR formulation met the regulatory criteria when compared to the CAN formulation. The PR fast-release formulation did not meet the regulatory criteria with respect to Cmax when compared to the CAN formulation.

Safety Summary: The sponsor reported that TEAEs were reported by 29 of 30 subjects (96.7%). The most frequently reported TEAEs (≥30%) were nausea (53.3% of subjects), diarrhea (43.3%), headache (36.7%), vomiting (33.3%), and somnolence (30%). Women experienced more nausea, diarrhea, and vomiting than men. Nine (9) of 12 women (75%) experienced vomiting compared with 1 of 18 men (5.5%). TEAEs that were reported less frequently (≥15% but <30%) included dizziness (26.7%), asthenia (23.3%), and vasodilatation (16.7%). After the administration of the PR fast-release formulation, nausea was reported in 44.8% of subjects compared with the PR (40.7%) and the CAN (34.5%) formulations. The incidence of diarrhea after receiving the PR fast-release formulation was 31% compared with the PR (22.2%) and CAN (27.6%) formulations. The incidence of headache after the PR fast-release formulation was 20.7% compared with CAN (17.2%) and PR (11.1%) formulations. The incidence of vomiting after the PR fast-release and CAN formulations was 17.2% for each compared with the PR formulation (3.7%). Somnolence was reported by 20.7% of subjects after the PR fast-release administration, 18.5% of subjects after the PR formulation, and 17.2% of subjects after the CAN formulation. No deaths occurred during the study. One (1) death was reported to the investigator by the medical examiner more than 3 weeks after the subject had been discharged from the clinical pharmacology unit upon study completion. The investigator and the WR medical monitor determined that this event was not related to test article.

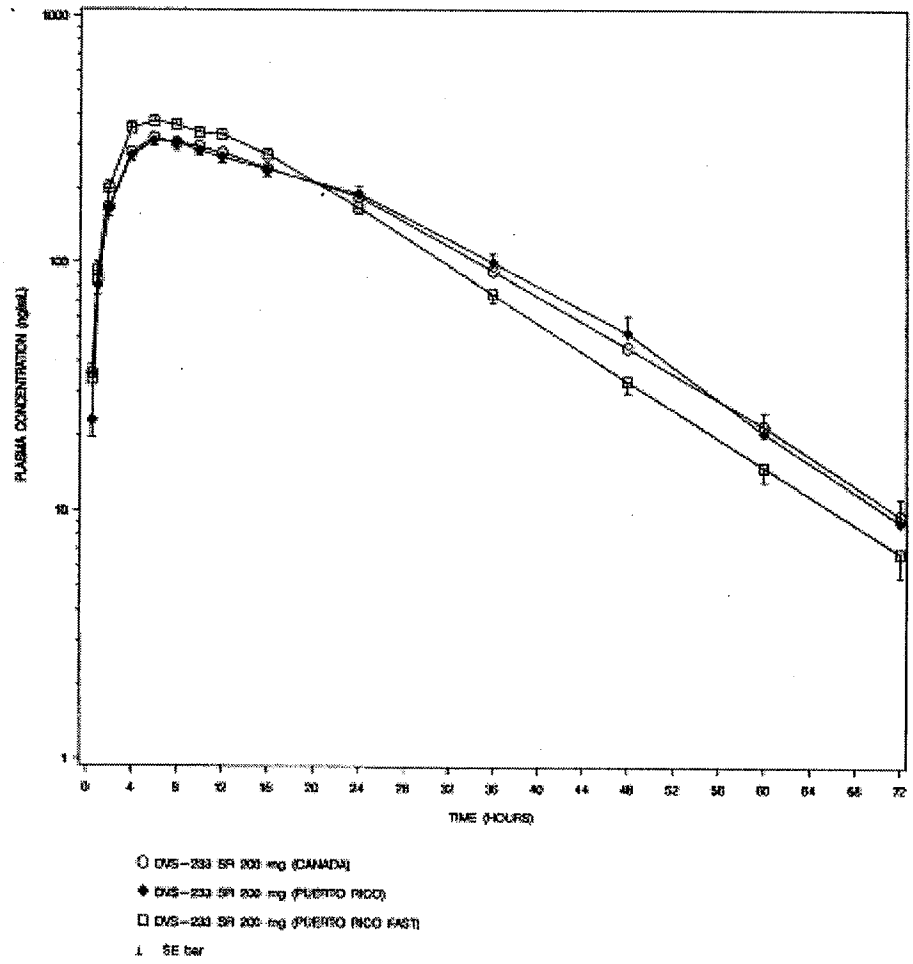
Four (4) of 30 subjects (13.3%) had one or more ECG results of potential clinical importance. Subject 17701-103, a 59-year-old woman, had prolonged QTc intervals (487 ms at screening), approximately 96 hours after the first DVS SR dose (PR fast-release; 474 ms) and 72 hours after the third DVS SR dose (PR; 485 ms). The QTc interval 2 hours before the first DVS SR dose (PR fast-release) was 446 ms. The remaining QTc intervals after DVS dose administration were in a range of 407 to 441 ms. Subject 17701-124, a 51-year-old man, had 2 isolated QTc interval prolongations approximately 96 hours after receiving DVS SR (CAN; 460 ms) and 72 hours after DVS SR (PR fast-release; 451 ms). The remaining QTc intervals after DVS SR administration were in a range of 374 to 422 ms. Subject 17701-108, a 47-year-old man, had an incomplete right bundle branch block prestudy that continued throughout the study. His QRS interval at baseline was 114 ms. Potentially clinically important prolonged QRS intervals (in the range of 120 to 123 ms) occurred 8 and 72 hours after DVS SR administration of the PR fast-release and CAN formulations. Subject 17701-107, a 62-year-old woman, had a single occurrence of supraventricular premature beats approximately 96 hours after receiving DVS SR (PR fast-release). The investigator determined that this was not clinically significant.

Conclusion: The PR fast-release formulation met the bioequivalence criteria for AUC but, as expected, did not meet the bioequivalence criteria for C_{max} when compared to the CAN formulation. Both C_{max} and AUC values for the PR formulation met bioequivalence criteria compared with the CAN formulation. The most frequently reported TEAEs (≥ 30%) were nausea (53.3% of subjects), diarrhea (43.3%), headache (36.7%), vomiting

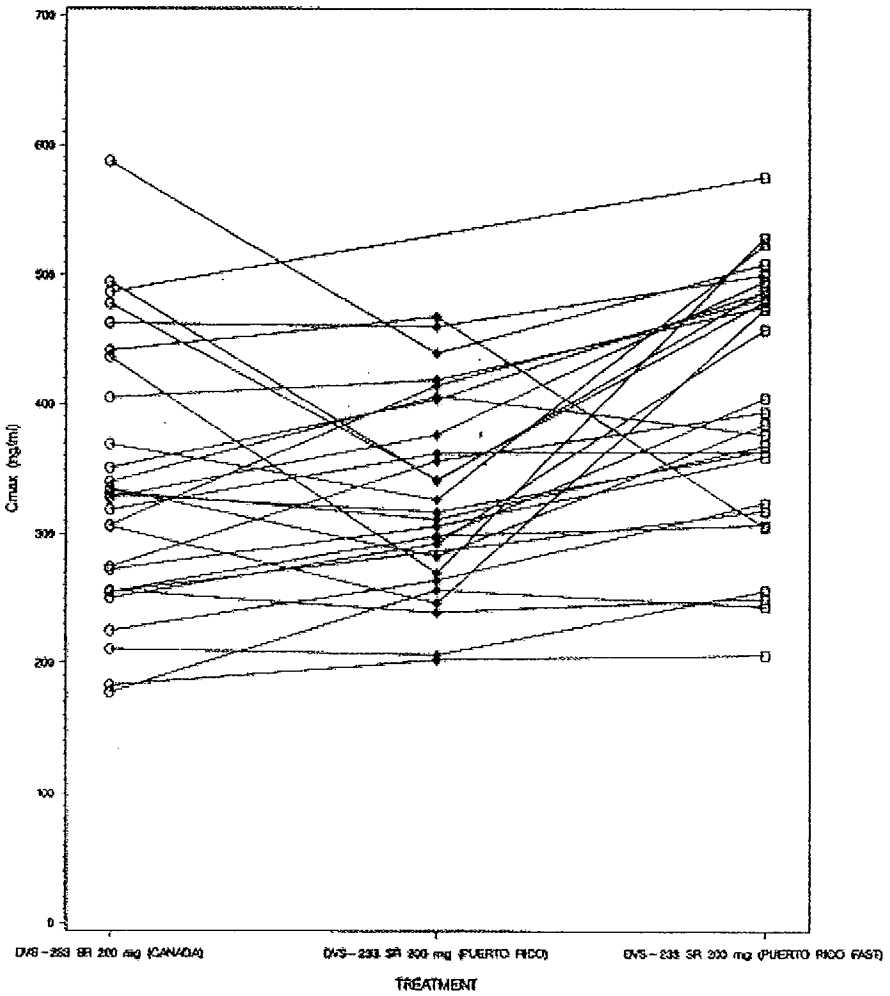
(33.3%), and somnolence (30%). Among the most frequently reported individual TEAEs, there was a general tendency for more frequent occurrence after administration of the PR fast-release formulation than after PR and CAN formulations. Nausea, vomiting, somnolence, and headache were more frequently reported after administration of the PR fast-release formulation than after the PR and CAN formulations. There were no withdrawals from this study because of adverse events.

Reviewer's comments: *The reviewer agrees with the sponsor's conclusions. Except for the PR-Fast Release formulations, the products were bioequivalent.*

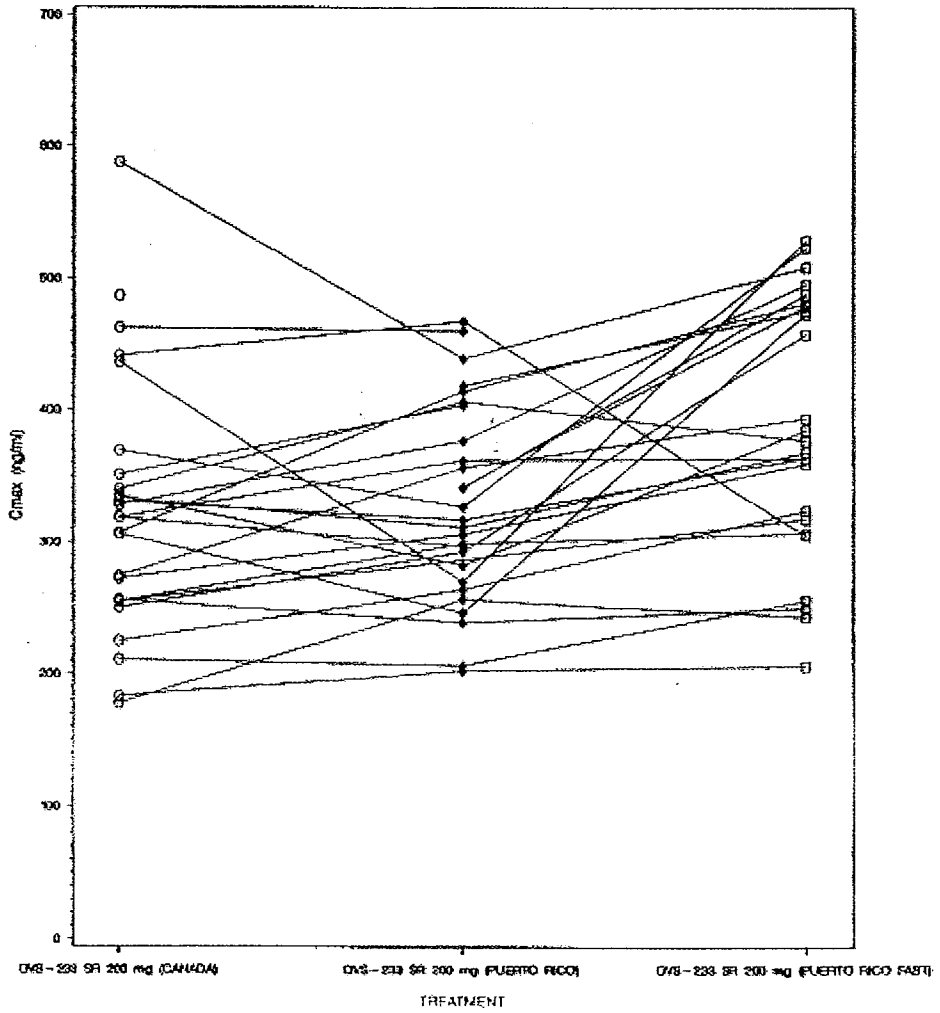
SF 8-1. Mean Desvenlafaxine Plasma Concentrations in Healthy Subjects Receiving a Single Oral Dose of DVS



SF 8-2. Desvenlafaxine Cmax in Healthy Subjects Receiving a Single Oral Dose of DVS
(All Subjects)

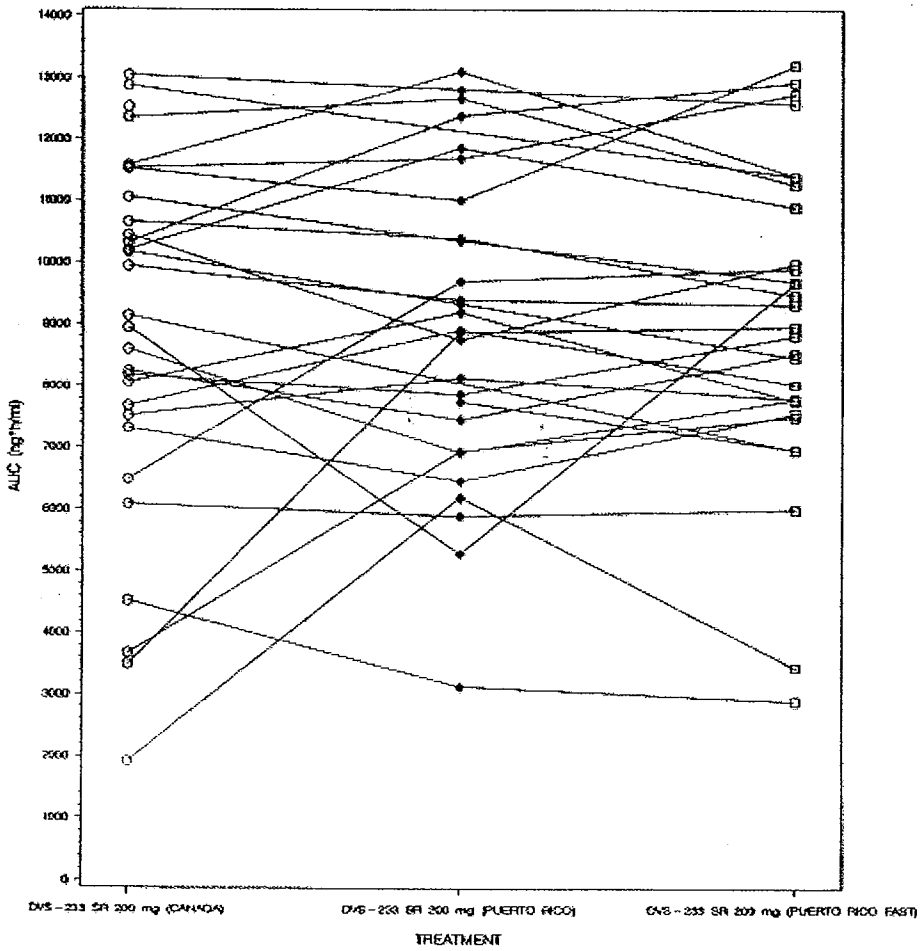


SF 8-3. Desvenlafaxine C_{max} in Healthy Subjects Receiving a Single Oral Dose of DVS (Excluding Subjects Who Vomited)

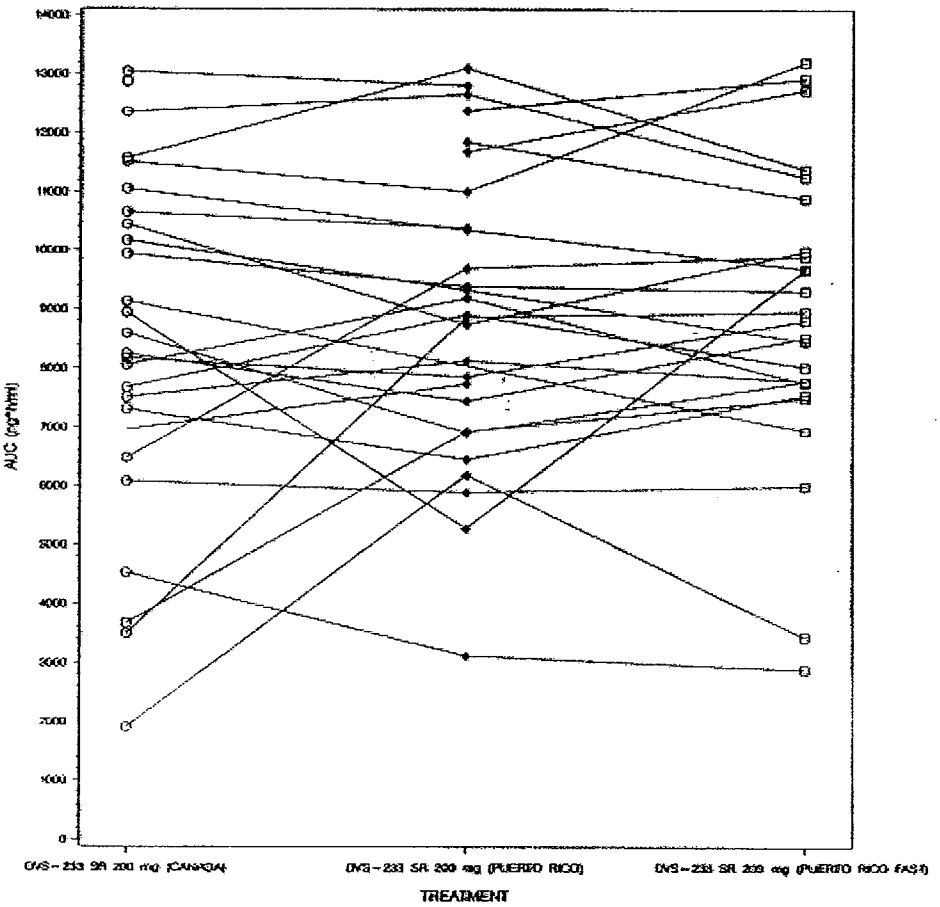


Note: Subjects were excluded due to vomiting adverse event

SF 8-4. Desvenlafaxine AUC in Healthy Subjects Receiving a Single Oral Dose of DVS
(All Subjects)



SF 8-5. Desvenlafaxine AUC in Healthy Subjects Receiving a Single Oral Dose of DVS
(Excluding Subjects Who Vomited)



Note: Subjects were excluded due to vomiting adverse event.

ST 8-4. Pharmacokinetic Profiles of Desvenlafaxine by Subject

Supportive Table ST 8-4. Pharmacokinetic Parameters of Desvenlafaxine 15:05 Tuesda
In Healthy Subjects Receiving a Single Dose of 200 mg of DVS-233
Protocol 3151A1-177-US

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCt (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
DVS-233 SR 200 mg (CANADA)								
101	251	4.0	0.086	8.1	3434.8	3494.3	0.744	8.677
102	330	6.0	0.072	9.7	6385.4	6490.2	0.379	5.284
103	369	6.0	0.055	12.7	11993.2	12358.3	0.254	4.662
104	257	4.0	0.057	12.1	7142.8	7312.1	0.337	5.905
105*	478	8.0	0.061	11.3	10141.4	10322.7	0.276	4.503
106	333	6.0	0.071	9.8	8091.0	8176.7	0.283	3.991
107	436	6.0	0.063	11.0	8831.0	8943.7	0.274	4.373
108	441	6.0	0.073	9.5	7927.4	8062.1	0.326	4.456
109*	465	6.0	0.080	8.7	11359.8	11530.6	0.321	4.032
110*	495	10.0	0.066	10.5	10105.3	10203.5	0.244	3.698
111	255	10.0	0.058	11.9	8876.2	9141.4	0.218	3.741
112	-	-	-	-	-	-	-	-
113	274	12.0	0.061	11.4	10174.0	10446.2	0.201	3.299
114	225	6.0	0.056	12.4	3574.7	3674.5	0.699	12.51
115	255	6.0	0.071	9.8	7582.9	7678.4	0.389	5.480
116	462	6.0	0.039	17.7	12127.9	13048.8	0.205	5.216
117	351	10.0	0.072	9.6	10526.8	10656.9	0.276	3.807
118	588	6.0	0.077	9.0	10984.6	11055.4	0.355	4.601
119	183	4.0	0.074	9.4	4426.5	4525.8	0.517	7.011
120	272	6.0	0.057	12.1	9597.8	9938.9	0.250	4.352
121	487	4.0	0.064	10.8	12675.0	12877.6	0.281	4.374
122	335	16.0	0.053	13.0	11122.4	11515.3	0.187	3.504
123*	463	12.0	0.063	11.0	12307.9	12530.9	0.264	4.206
124	178	2.0	0.083	8.3	1815.5	1918.2	1.361	16.38
125	328	6.0	0.070	9.9	7446.8	7520.7	0.304	4.353
126	340	12.0	0.058	12.0	8439.4	8593.8	0.344	5.956
127	307	16.0	0.049	14.0	11051.4	11571.4	0.231	4.281
128	319	4.0	0.074	9.4	8163.7	8245.7	0.304	4.129
129	211	6.0	0.076	9.1	6019.3	6081.0	0.348	4.568
130	386	8.0	0.065	10.7	9964.0	10167.3	0.285	4.397

* SUBJECT EXCLUDED FROM SUMMARY STATISTICS AND STATISTICAL COMPARISONS DUE TO VOMITING ADVERSE EVENT.

Supportive Table 97 8-4. Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving a Single Dose of 200 mg of DVS-233
Protocol 3151A1-177-US

15:05 Tuesday, March 15, 2005

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCt (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)	CMAX RATIO (%)	AUC RATIO (%)
DVS-233 SR 200 mg [PUERTO RICO]										
101	293	6.0	0.087	8.0	8751.9	8874.6	0.293	3.368	116.8	254.0
102	317	6.0	0.073	9.5	9576.1	9707.6	0.253	3.470	95.9	149.6
103	327	16.0	0.046	14.9	12081.0	12669.9	0.248	5.341	88.6	102.5
104	239	6.0	0.060	11.6	6288.0	6465.9	0.381	6.375	93.1	88.4
105	342	24.0	0.061	11.4	12072.2	12388.0	0.230	3.784	-	-
106	312	6.0	0.068	10.2	7765.9	7868.4	0.294	4.331	93.5	96.2
107	270	8.0	0.055	12.6	5198.8	5287.3	0.464	8.462	61.9	59.1
108	467	6.0	0.071	9.7	9134.9	9197.4	0.285	4.009	105.9	114.1
109	419	6.0	0.082	8.5	11607.7	11694.6	0.317	3.881	-	-
110	341	8.0	0.065	10.6	11615.7	11864.5	0.210	3.206	-	-
111	-	-	-	-	-	-	-	-	-	-
112	297	16.0	0.085	8.1	7655.5	7745.8	0.355	4.152	-	-
113	356	6.0	0.073	9.5	8662.6	8756.1	0.246	3.299	129.9	81.8
114	264	6.0	0.060	11.6	5801.0	5938.3	0.370	6.192	117.5	188.8
115	299	6.0	0.065	10.6	8772.1	8915.7	0.335	5.142	117.0	116.2
116	460	8.0	0.067	10.4	12617.2	12816.5	0.208	3.122	99.5	98.2
117	404	6.0	0.078	8.9	10297.7	10400.4	0.282	3.625	115.0	97.6
118	439	8.0	0.078	8.9	10268.0	10354.2	0.379	4.862	74.7	93.7
119	203	6.0	0.072	9.6	3021.1	3130.5	0.748	10.35	110.6	69.2
120	356	6.0	0.072	9.6	9295.5	9397.3	0.354	3.647	112.5	94.6
121	-	-	-	-	-	-	-	-	-	-
122	283	8.0	0.032	22.0	9688.1	11014.8	0.195	6.179	84.3	95.7
123	-	-	-	-	-	-	-	-	-	-
124	257	4.0	0.082	8.4	6074.0	6197.0	0.421	5.124	144.7	323.1
125	377	6.0	0.069	10.1	8048.5	8138.8	0.281	4.095	114.8	108.2
126	406	8.0	0.060	11.6	6812.9	6924.2	0.427	7.139	119.4	80.6
127	415	16.0	0.057	12.1	12712.0	13111.2	0.186	3.268	135.1	113.2
128	382	6.0	0.073	9.4	7306.4	7459.8	0.336	4.580	113.6	90.5
129	307	6.0	0.072	9.6	5804.9	5900.3	0.359	4.984	98.0	96.9
130	247	24.0	0.065	10.7	9162.1	9337.7	0.310	4.765	80.6	91.8

* SUBJECT EXCLUDED FROM SUMMARY STATISTICS AND STATISTICAL COMPARISONS DUE TO VOMITING ADVERSE EVENT.

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Supportive Table 57 8-4. Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving a Single Dose of 200 mg of DVS-233
Protocol 3151A1-177-US

15:05 Tuesday, March 15, 2005

SUBJECT	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUCt (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)	CMAX RATIO (%)	AUC RATIO (%)
DVS-233 SR 200 mg (PUERTO RICO FASTI)										
101	458	12.0	0.085	8.2	8840.2	8979.1	0.290	3.421	182.7	257.0
102	364	6.0	0.071	9.7	9817.0	9917.6	0.248	3.480	110.3	152.8
103	524	6.0	0.062	11.1	11113.9	11271.6	0.279	4.478	141.9	91.2
104	251	4.0	0.058	12.0	7404.1	7568.1	0.325	5.649	97.6	103.5
105	480	4.0	0.059	11.7	12670.6	12939.5	0.220	3.734	-	-
106	369	12.0	0.065	10.6	8706.6	8826.5	0.262	4.011	110.6	107.9
107	529	6.0	0.061	11.3	9558.4	9686.1	0.253	4.139	121.4	108.3
108	306	6.0	0.069	10.1	7688.4	7774.2	0.338	4.906	69.3	96.4
109	476	10.0	0.079	8.8	12650.6	12744.8	0.291	3.699	-	-
110	489	6.0	0.063	10.9	10771.8	10904.9	0.228	3.601	-	-
111	318	10.0	0.054	12.9	5776.9	5961.7	0.287	5.345	124.8	76.2
112*	405	6.0	0.096	7.2	5863.0	5972.6	0.394	4.090	-	-
113	394	4.0	0.065	10.6	9854.0	10002.9	0.210	3.219	143.6	95.8
114	325	4.0	0.065	10.7	7408.6	7509.8	0.342	5.270	144.3	204.4
115	307	8.0	0.069	10.0	7947.8	8041.6	0.371	5.383	120.4	104.7
116*	501	6.0	0.068	10.1	12442.7	12586.1	0.212	3.101	108.3	96.5
117*	487	4.0	0.081	8.6	9336.1	9481.0	0.310	3.838	138.9	89.0
118	509	6.0	0.081	8.5	9596.6	9702.9	0.309	3.025	86.6	87.8
119	207	4.0	0.072	9.7	2812.9	2960.9	0.807	11.29	112.7	64.1
120	369	10.0	0.061	11.4	9152.7	9326.4	0.256	4.187	132.1	93.8
121*	575	4.0	0.068	10.3	11285.7	11402.5	0.317	4.653	118.3	88.5
122	385	6.0	0.039	17.8	12265.0	13219.7	0.163	4.164	114.9	114.8
123	-	-	-	-	-	-	-	-	-	-
124	244	4.0	0.076	9.1	3339.5	3447.8	0.757	9.964	137.3	179.7
125	496	6.0	0.074	9.3	7679.3	7798.9	0.493	3.953	151.2	103.7
126	377	4.0	0.063	10.9	7704.2	7793.8	0.379	5.980	110.9	90.7
127	482	6.0	0.057	12.2	11159.3	11409.0	0.214	3.772	157.0	98.5
128	364	6.0	0.065	10.6	8411.6	8532.9	0.294	4.499	114.2	103.5
129	257	6.0	0.071	9.8	5883.5	6011.3	0.352	4.955	121.7	98.8
130	474	4.0	0.079	8.8	8372.7	8476.2	0.341	4.333	154.8	83.4

* [illegible]

ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters

Supportive Table ST 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 15:05 Tuesday, March 15, 2005
In Healthy Subjects Receiving a Single Dose of 200 mg of DVS-233
Protocol 3151A1-177-US

Treatment	CMAX (ng/mL) N	Mean	S.D.	%CV	Geo. Mean	TMAX (h) N	Mean	S.D.	%CV	Geo. Mean
DVS-233 SR 200 mg (CANADA)	25	324	98.7	30	310	25	7.12	3.61	51	6.38
DVS-233 SR 200 mg (PUERTO RICO)	27	330	74.6	23	322	27	8.81	5.41	61	7.74
DVS-233 SR 200 mg (PUERTO RICO FAST)	25	390	97.1	25	379	25	6.40	2.52	39	5.94

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Supportive Table 37 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 15:05 Tuesday, March 15, 2005
in Healthy Subjects Receiving a Single Dose of 200 mg of DVS-233
Protocol 3151A1-177-US

Treatment	LAMBDA (1/h) N	Mean	S.D.	%CV	Geo. Mean	T 1/2 (h) N	Mean	S.D.	%CV	Geo. Mean
DVS-233 SR 200 mg (CANADA)	25*	0.065	0.011	17	0.064	25	10.9	2.1	19	10.8
DVS-233 SR 200 mg (PUERTO RICO)	27	0.068	0.012	18	0.066	27	10.7	2.7	25	10.4
DVS-233 SR 200 mg (PUERTO RICO FAST)	25	0.066	0.010	15	0.066	25	10.7	1.9	18	10.5

NOTE: SUBJECTS WHO VOMITED WERE EXCLUDED FROM SUMMARY STATISTICS.

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Supportive Table 97 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 15:05 Tuesday, March 15, 2005
In Healthy Subjects Receiving a Single Dose of 200 mg of DVS-233
Protocol 3151A1-177-US

Treatment	AUCt (ng*h/mL) N	Mean	S.D.	%CV	Geo. Mean	AUC (ng*h/mL) N	Mean	S.D.	%CV	Geo. Mean
DVS-233 SR 200 mg (CANADA)	25	8331.9	2872.6	34	7675.4	25	8540.3	2989.1	35	7862.0
DVS-233 SR 200 mg (PUERTO RICO)	27	8779.7	2447.7	28	8398.2	27	8983.7	2536.4	28	8587.7
DVS-233 SR 200 mg (PUERTO RICO FAST)	25	8706.3	2474.4	28	8269.6	25	8869.9	2546.3	29	8424.9

NOTE: SUBJECTS 2010 WERE EXCLUDED FROM SUMMARY STATISTICS.

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Supportive Table 97 8-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 15:05 Tuesday, March 15, 2005
In Healthy Subjects Receiving a Single Dose of 200 mg of DVS-233
Protocol 3151A1-177-US

Treatment	CL/F (L/h/kg) N	Mean	S.D.	%CV	Geo. Mean	Vz/F (L/kg) N	Mean	S.D.	%CV	Geo. Mean
DVS-233 SR 200 mg (CANADA)	25	0.373	0.248	66	0.330	25	5.572	2.962	53	5.118
DVS-233 SR 200 mg (PUERTO RICO)	27	0.321	0.113	35	0.306	27	4.843	1.717	35	4.608
DVS-233 SR 200 mg (PUERTO RICO FAST)	25	0.329	0.149	45	0.307	25	4.906	1.885	38	4.666

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Supportive Table 27 B-5. Descriptive Statistics of Desvenlafaxine Pharmacokinetic Parameters 15:35 Tuesday, March 15, 2005
In Healthy Subjects Receiving a Single Dose of 200 mg of DVS-233
Protocol 3151A1-177-US

Treatment	CMAX RATIO (%) N	Mean	S.D.	%CV	Geo. Mean	AUC RATIO (%) N	Mean	S.D.	%CV	Geo. Mean
DVS-233 SR 200 mg (CANADA)	.	.	.	.	.	.	.	.	.	.
DVS-233 SR 200 mg (PUERTO RICO)	23	105.3	19.8	19	103.4	23	117.6	60.7	52	108.0
DVS-233 SR 200 mg (PUERTO RICO FAST)	22	125.5	25.4	20	122.9	22	114.4	45.3	40	102.2

NOTE: SUBJECTS WHO VOMITED WERE EXCLUDED FROM SUMMARY STATISTICS.

Study Title (Protocol 3151A1-179-EU, CSR 58916): An Open Label, Single 100-mg Dose, Parallel-Group Study Of The Pharmacokinetics And Safety Of DVS-233 SR In Subjects With Chronic Hepatic Impairment And In Matched Healthy Adults

Objectives: The primary objective was to assess the pharmacokinetics (PK) of desvenlafaxine succinate (DVS) sustained-release (SR) in subjects with chronic hepatic impairment and in matched healthy adults. The secondary objective was to assess the safety and tolerability of DVS SR in subjects with chronic hepatic impairment and in matched healthy adults.

Study Design: This was an open-label, single-dose, parallel-group, inpatient, nonrandomized study conducted in subjects with chronic hepatic impairment and in healthy adults matched by age, sex, weight, and, if possible, smoking habit.
Each subject received the test article with 240 mL of room temperature water. The test article was administered as 1 x 100-mg tablet of DVS SR (orally) after an overnight fast of at least 8 hours. AE monitoring was continuous. Vital signs, electrocardiograms (ECGs), and pharmacokinetic (PK) sample collection were completed at designated times during the study. The blood sample for PK analysis was collected at the following time points: 0 (within 2 hours before test article administration), 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hours after dose administration. Urine PK samples were collected in separate containers during the following time periods: predose, 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, 36 to 48 hours, 48 to 72 hours, and 72 to 96 hours. The dose strength, batch number and formulation of the test article administered were DVS SR 100 mg tablets, A43076 and 0931719C , respectively.

Hepatically-impaired subjects may have continued to take any medication necessary for the management of their hepatic disease or concurrent illness. The same dosage schedule was to have been stable for 7 days before test article administration and maintained throughout the study.

Analytical Method: The plasma samples were analyzed for (R)- and (S)-enantiomers of DVS by a validated liquid chromatography mass spectroscopy method with mass spectroscopy detection. The performance of the (R)- and (S)-enantiomer assays during the analysis of the plasma samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Plasma Samples

	Compound/Matrix
Standard Curve	(R)- or (S)-Desvenlafaxine
Linear range (ng/mL)	2.5-350
Sensitivity (ng/mL)	2.5

Analytical Summary of Plasma Desvenlafaxine Enantiomer Assays

QC[a] Concentration (ng/mL)	(S)-Desvenlafaxine			(R)-Desvenlafaxine		
	Conc.	CV%	Bias %	Conc.	CV%	Bias %
3	3.13	12.8	4.4	3.21	4.8	7.0
12	12.43	4.1	3.6	12.14	3.9	1.2
25	25.45	5.4	1.8	25.88	5.2	3.5
80	80.21	4.5	0.3	81.76	3.0	2.2
100	101.81	7.6	1.8	100.68	4.3	0.7
320	323.03	12.0	0.9	317.26	3.3	-0.9

a. QC=Quality Control

Urine was assayed for the (R)- and (S)- enantiomers of DVS (unconjugated) and (R)- and (S)-enantiomers of total DVS (unconjugated plus conjugated), as well as, unconjugated and total NODV, using a validated liquid chromatography mass spectroscopy method with mass spectroscopy detection. The performance of the (R)- and (S)- enantiomer assays during the analysis of the urine samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Urine Samples

	Compound
Standard Curve	R- or S-Desvenlafaxine
Linear range (µg/mL)	0.025-25
Sensitivity (µg/mL)	0.025

Analytical Summary of Urine Desvenlafaxine Enantiomer Assays

QC[a] Concentration (µg/mL)	Unconjugated (S)-Desvenlafaxine			Unconjugated (R)-Desvenlafaxine		
	Conc.	CV%	Bias %	Conc.	CV%	Bias %
0.072	0.070	6.2	-3.4	0.071	6.5	-0.8
0.288	0.281	4.4	-2.3	0.275	5.2	-4.5
3	2.898	6.1	-3.4	2.969	5.9	-1.0
6	5.712	4.9	-4.8	6.056	6.2	0.9
12	11.447	6.2	-4.6	11.489	6.6	-4.3
24	23.671	6.0	-1.4	22.791	6.3	-5.0
200 (1 in 10 dilution)	182.640	3.5	-8.7	184.263	2.4	-7.9
	Total (S)-Desvenlafaxine			Total (R)-Desvenlafaxine		
(µg/mL)	Conc.	CV%	Bias %	Conc.	CV%	Bias %
0.072	0.069	5.8	-3.8	0.072	6.0	0.5
0.288	0.285	4.3	-1.1	0.274	5.3	-4.9
3	2.895	3.7	-3.5	3.033	5.7	1.1
6	5.680	4.6	-5.3	5.851	6.3	-2.5
12	11.781	4.8	-1.8	11.459	3.4	-4.5
24	23.077	6.2	-3.8	22.566	3.5	-6.0
200 (1 in 10 dilution)	200.966	1.5	0.5	201.019	0.8	0.5

a. QC = quality control

The performance of the unconjugated and total NODV assays during the analysis of the urine samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Urine Samples

Standard Curve	Compound Unconjugated NODV	Total NODV
Linear range (μg/mL)	0.04-20.0	0.04-20.0
Sensitivity (μg/mL)	0.040	0.040

Analytical Summary of Urine NODV Assays

QC[a] Concentration (μg/mL)	Unconjugated NODV			Total NODV		
	Conc.	CV%	Bias %	Conc.	CV%	Bias %
0.120	0.1183	13.6	-1.42	0.1177	16.6	-1.92
1.20	1.2781	6.59	6.51	1.2178	6.84	1.50
15.2	15.2983	5.40	0.65	15.0033	6.15	-1.29

a. QC=Quality Control

Data Analysis: The concentration of the racemic mixture ([R+S]-enantiomers) was calculated as the sum of concentrations of (R)- and (S)- enantiomers of DVS. A model-independent method of analysis was used to analyze the plasma concentrations of the (R)-, (S)-, and racemic (R+S)-enantiomers of DVS.

To assess which demographic characteristic or biochemical index of liver function most significantly correlates with any observed change in drug disposition among the groups, an exploratory stepwise linear regression was performed on DVS SR AUC and Cl/F. The variables considered in the stepwise procedure were weight, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, serum albumin, serum creatinine, glomerular filtration rate (GFR, estimated by creatinine clearance [Clcr]), prothrombin time (PT), and activated partial prothrombin time (aPTT). The significance criteria for entering and remaining in the stepwise linear regression model were both set at the nominal value of $\alpha = 0.15$.

Results: The following table summarizes the demographic and baseline characteristics for all subjects enrolled in the study.

Demographic and Baseline Characteristics for All Subjects

Characteristic	Chronic Hepatic-Impaired Subjects			Healthy Subjects	Total
	Child-Pugh A n = 8	Child-Pugh B n = 8	Child-Pugh C n = 8	n = 12	n = 36
Age (y)					
Mean ± SD	53.13 ± 4.42	52.50 ± 10.18	49.88 ± 6.33	50.58 ± 6.96	51.42 ± 7.04
Range	46.0 to 58.0	31.0 to 65.0	41.0 to 59.0	36.0 to 62.0	31.0 to 65.0
Median	55.00	53.50	50.00	52.50	53.00
Sex, n (%)					
Women	4 (50.0)	3 (37.5)	1 (12.5)	4 (33.3)	12 (33.3)
Men	4 (50.0)	5 (62.5)	7 (87.5)	8 (66.7)	24 (66.7)
Ethnic origin, n (%)					
White	8 (100)	8 (100)	8 (100)	12 (100)	36 (100)
Weight (kg), n					
Mean ± SD	76.65 ± 12.62	76.38 ± 17.38	91.11 ± 20.62	79.13 ± 18.19	80.63 ± 17.75
Range	66.0 to 103.5	56.0 to 113.0	50.2 to 120.0	52.5 to 105.0	50.2 to 120.0
Median	73.75	73.50	95.00	79.50	79.00
Height (cm)					
Mean ± SD	162.69 ± 7.79	167.25 ± 11.87	171.13 ± 5.06	171.21 ± 7.87	168.42 ± 8.78
Range	152.0 to 172.0	150.0 to 180.0	165.0 to 179.0	158.0 to 185.0	150.0 to 185.0
Median	163.50	167.50	170.50	171.00	170.00
BMI (kg/m²)					
Mean ± SD	28.96 ± 4.12	27.11 ± 3.94	31.03 ± 6.85	26.73 ± 4.64	28.26 ± 5.06
Range	22.8 to 35.8	21.3 to 34.9	18.4 to 42.0	21.0 to 34.9	18.4 to 42.0
Median	29.30	26.25	31.75	26.65	27.55

Abbreviations: BMI= body mass index; SD = standard deviation.
Source: Clinical Programming SAS Reports/3151A1 DVS/179/DEMO4

Summary pharmacokinetic parameters of (R)-, (S)-, and (R+S)-enantiomers of DVS in subjects with hepatic impairment and healthy subjects are in the following tables. Urinary excretion data for (R)- and (S)-enantiomers of DVS are provided in the following tables. Statistical results for (R+S)-enantiomers of DVS PK parameters in subjects with hepatic impairment and healthy subjects are provided in the following tables. The mean concentration time profile for each treatment for the (R)-, (S)-, and (R+S)-enantiomers of DVS, respectively are presented in the ATTACHMENTS.

Summary of Pharmacokinetic Parameters for (R) enantiomer of Desvenlafaxine Following Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects

Subject Group	Variables	C_{max} (ng/mL)	T_{max} (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
Healthy	Mean ± SD	91.04 ± 26.21	8.00 ± 3.91	2516 ± 813	2591 ± 839	10.11 ± 1.81	0.267 ± 0.052	3.83 ± 0.67	0.133 ± 0.030
(n = 12)	%CV	29%	49%	32%	32%	18%	20%	17%	23%
	Geo. Mean	87.43	7.06	2393	2466	9.98	0.263	3.78	0.130
	Min – Max	52.16 – 131.77	2.00 – 16.00	1335 – 3747	1410 – 3903	8.15 – 14.14	0.185 – 0.344	2.96 – 4.99	0.088 – 0.181
Child-Pugh A	Mean ± SD	110.95 ± 26.88	7.50 ± 3.66	2574 ± 1022	2640 ± 1049	9.62 ± 1.82	0.277 ± 0.072	3.82 ± 1.24	0.112 ± 0.041
(n = 8)	%CV	24%	49%	40%	40%	19%	26%	32%	37%
	Geo. Mean	107.94	6.93	2412	2476	9.48	0.268	3.67	0.105
	Min – Max	76.43 – 141.37	4.00 – 16.00	1392 – 4617	1463 – 4772	7.42 – 12.54	0.156 – 0.390	2.38 – 6.46	0.064 – 0.185
Child-Pugh B	Mean ± SD	103.39 ± 31.06	9.75 ± 4.46	3453 ± 1596	3601 ± 1738	13.51 ± 6.52	0.237 ± 0.129	4.04 ± 1.57	0.124 ± 0.052
(n = 8)	%CV	30%	46%	46%	48%	48%	54%	39%	42%
	Geo. Mean	99.18	8.85	3084	3193	12.57	0.211	3.83	0.115
	Min – Max	61.21 – 146.70	4.00 – 16.00	1560 – 5409	1600 – 6141	8.65 – 29.05	0.099 – 0.464	2.88 – 7.37	0.069 – 0.230
Child-Pugh C	Mean ±S D	105.29 ± 24.68	8.75 ± 3.20	3592 ± 1650	3689 ± 1688	13.92 ± 2.21	0.207 ± 0.141	3.93 ± 2.34	0.081 ± 0.030
(n = 8)	%CV	23%	37%	46%	46%	16%	68%	60%	37%
	Geo. Mean	102.01	8.17	3183	3278	13.78	0.173	3.43	0.076
	Min – Max	52.70 – 129.90	4.00 – 12.00	954 – 6214	1009 – 6366	11.16 – 17.82	0.076 – 0.475	1.60 – 7.64	0.043 – 0.132

Abbreviations: CV = confidence interval; SD = standard deviation.

Summary of Pharmacokinetic Parameters for (S) enantiomer of Desvenlafaxine Following Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects

Subject Group	Variables	C_{max} (ng/mL)	T_{max} (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
Healthy (n = 12)	Mean ± SD	92.27 ± 24.75	8.33 ± 3.89	2486 ± 691	2552 ± 700	9.83 ± 1.68	0.267 ± 0.046	3.78 ± 0.92	0.114 ± 0.027
	%CV	27%	47%	28%	27%	17%	17%	24%	23%
	Geo. Mean	89.14	7.37	2395	2462	9.71	0.263	3.68	0.111
	Min – Max	54.25 – 130.58	2.00 – 16.00	1374 – 3623	1444 – 3709	7.51 – 13.04	0.204 – 0.350	2.91 – 5.69	0.073 – 0.157
Child-Pugh A (n = 8)	Mean ± SD	115.50 ± 27.22	7.50 ± 3.66	2659 ± 1066	2725 ± 1094	9.53 ± 1.78	0.268 ± 0.069	3.66 ± 1.16	0.097 ± 0.034
	%CV	24%	49%	40%	40%	19%	26%	32%	35%
	Geo. Mean	112.59	6.93	2494	2558	9.39	0.260	3.52	0.092
	Min – Max	80.98 – 149.55	4.00 – 16.00	1481 – 4889	1557 – 5045	7.41 – 12.37	0.148 – 0.384	2.34 – 6.11	0.055 – 0.156
Child-Pugh B (n = 8)	Mean ± SD	106.63 ± 31.70	9.50 ± 4.38	3510 ± 1615	3653 ± 1750	13.44 ± 6.40	0.232 ± 0.123	4.00 ± 1.73	0.110 ± 0.046
	%CV	30%	46%	46%	48%	48%	53%	43%	41%
	Geo. Mean	102.44	8.65	3144	3253	12.53	0.207	3.75	0.104
	Min – Max	64.01 – 149.41	4.00 – 16.00	1602 – 5486	1656 – 6215	8.86 – 28.79	0.098 – 0.450	2.80 – 7.78	0.064 – 0.205
Child-Pugh C (n = 8)	Mean ± SD	110.70 ± 25.80	8.75 ± 3.20	3654 ± 1519	3750 ± 1534	13.93 ± 1.63	0.194 ± 0.124	3.77 ± 2.13	0.073 ± 0.028
	%CV	23%	37%	42%	41%	12%	64%	57%	38%
	Geo. Mean	107.42	8.17	3296	3397	13.84	0.167	3.33	0.068
	Min – Max	57.06 – 144.16	4.00 – 12.00	1025 – 6059	1089 – 6178	11.51 – 16.72	0.079 – 0.440	1.56 – 7.30	0.039 – 0.120

Abbreviations: CV = confidence interval; SD = standard deviation.

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Summary of Pharmacokinetic Parameters for (R+S) enantiomer of Desvenlafaxine Following Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects

Subject Group	Variables	C_{max} (ng/mL)	T_{max} (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
Healthy (n = 12)	Mean ± SD	183.26 ± 50.69	8.17 ± 3.95	5003 ± 1496	5143 ± 1529	9.99 ± 1.63	0.267 ± 0.048	3.81 ± 0.77	0.124 ± 0.028
	%CV	28%	48%	30%	30%	16%	18%	20%	23%
	Geo. Mean	176.61	7.19	4792	4931	9.87	0.263	3.74	0.120
	Min – Max	106.41 – 262.35	2.00– 16.00	2709 – 7268	2854 – 7473	7.84 – 13.64	0.197 – 0.340	2.94 – 5.11	0.081 – 0.169
Child-Pugh A (n = 8)	Mean ± SD	226.45 ± 54.04	7.50 ± 3.66	5233 ± 2086	5365 ± 2141	9.58 ± 1.80	0.273 ± 0.070	3.74 ± 1.20	0.104 ± 0.038
	%CV	24%	49%	40%	40%	19%	26%	32%	36%
	Geo. Mean	220.55	6.93	4906	5035	9.43	0.264	3.59	0.098
	Min – Max	157.41 – 290.92	4.00 – 16.00	2873 – 9507	3020 – 9818	7.41 – 12.45	0.152 – 0.387	2.37 – 6.28	0.059 – 0.171
Child-Pugh B (n = 8)	Mean ± SD	210.00 ± 62.73	9.75 ± 4.46	6963 ± 3208	7254 ± 3484	13.44 ± 6.44	0.235 ± 0.126	4.00 ± 1.60	0.117 ± 0.049
	%CV	30%	46%	46%	48%	48%	54%	40%	42%
	Geo. Mean	201.61	8.85	6229	6447	12.52	0.209	3.78	0.109
	Min – Max	125.08 – 296.11	4.00 – 16.00	3163 – 10895	3261 – 12353	8.76 – 28.87	0.098 – 0.457	2.84 – 7.44	0.067 – 0.217
Child-Pugh C (n = 8)	Mean ± SD	215.98 ± 50.29	8.75 ± 3.20	7246 ± 3161	7439 ± 3212	13.96 ± 1.86	0.200 ± 0.132	3.85 ± 2.23	0.077 ± 0.029
	%CV	23%	37%	44%	43%	13%	66%	58%	38%
	Geo. Mean	209.46	8.17	6482	6679	13.85	0.169	3.39	0.072
	Min – Max	109.76 – 274.06	4.00 – 12.00	1979 –12274	2098 – 12544	11.34 – 17.32	0.077 – 0.457	1.58 – 7.47	0.041 – 0.125

Abbreviations: CV = confidence interval; SD = standard deviation.

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Summary of Urinary Excretion of Unconjugated and Total (R) and (S) enantiomers of Desvenlafaxine and Unconjugated and Total N, O-Didesmethylvenlafaxine After Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects

Subject Group	Variables	Unconjugated (% Dose[a])			Total Unconjugated and Conjugated (% Dose[a])			
		(R)-enantiomer	(S)-enantiomer	NODV	(R)-enantiomer	(S)-enantiomer	NODV	Sum of Total (R)-, (S)-desvenlafaxine and NODV
Healthy (n = 12)	Mean ± SD	24.9 ± 5.23	21.2 ± 4.33	1.60 ± 0.51	30.9 ± 4.40	28.8 ± 3.73	3.66 ± 0.46	63.4 ± 7.8
	%CV	21%	20%	32%	14%	13%	13%	12%
Child-Pugh A (n = 8)	Mean ± SD	22.1 ± 11.9	19.7 ± 9.77	0.77 ± 0.48	31.5 ± 16.0	30.4 ± 15.6	2.20 ± 0.65	64.1 ± 31.9
	%CV	54%	50%	62%	51%	51%	30%	50 %
Child-Pugh B (n = 8)	Mean ± SD	28.0 ± 7.94	25.6 ± 7.39	0.78 ± 0.36	34.7 ± 12.7	33.3 ± 12.9	1.60 ± 0.81	69.7 ± 31.9
	%CV	28%	29%	46%	37%	39%	51%	38 %
Child-Pugh C (n = 8)	Mean ± SD	23.8 ± 9.87	22.3 ± 10.0	1.10 ± 1.05	27.3 ± 10.5	26.2 ± 10.80	1.85 ± 1.47	55.4 ± 22.4
	%CV	41%	45%	95%	38%	41%	79%	41 %

Abbreviations: CV = confidence interval; NODV = N, O-didesmethylvenlafaxine, SD = standard deviation.
a. % Dose refers to the 100 mg of DVS SR, which is a combination of both (R)- and (S)-enantiomers.

Statistical Analysis of Pharmacokinetic Parameters for (R+S) enantiomers of Desvenlafaxine After Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects

Parameter	p-Value	Variables	Child-Pugh A	Child-Pugh B	Child-Pugh C
C_{max}	0.345	Ratio of Means[a]	125	114	119
(ng/mL)		90% CI[b]	100–156	91.6–142	95.2–148
AUC_T	0.341	Ratio of Means[a]	102	130	135
(ng•h/mL)		90% CI[b]	72.9–144	92.5–183	96.3–-190
AUC	0.325	Ratio of Means[a]	102	131	135
(ng•h/mL)		90% CI[b]	72.8–143	93.2–184	96.5–190
Cl/F	0.084	Ratio of Means[a]	100	79.6	64.5
(L/hr)		90% CI[b]	73.6–137	58.3–109	47.3–88.0

a. Ratio of geometric least square means with healthy subjects as reference.

b. 90% confidence interval.

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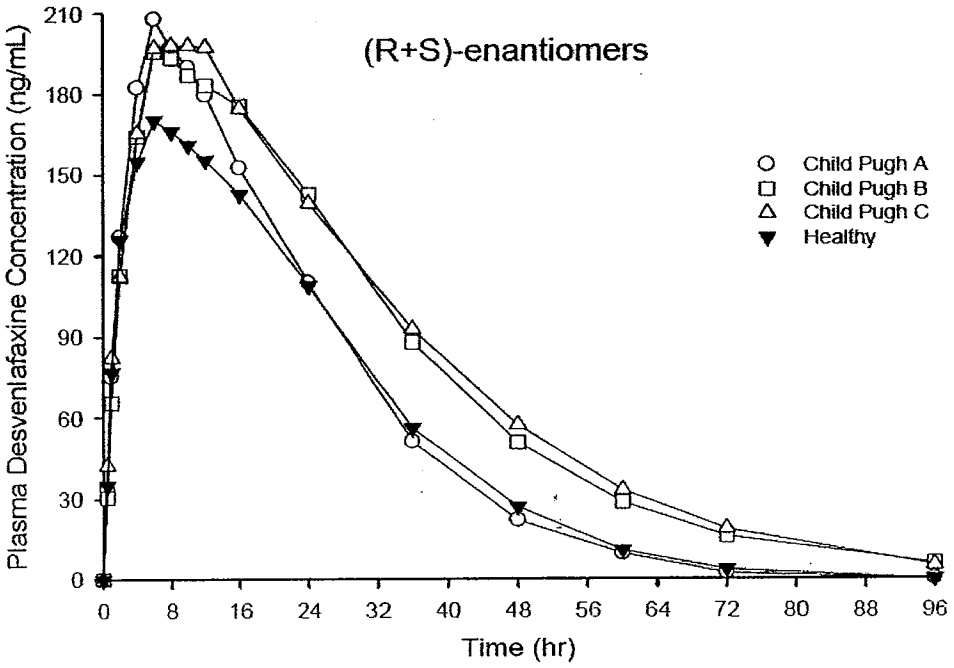
Mean Plasma Concentrations of (R+S)-enantiomers of Desvenlafaxine After Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects



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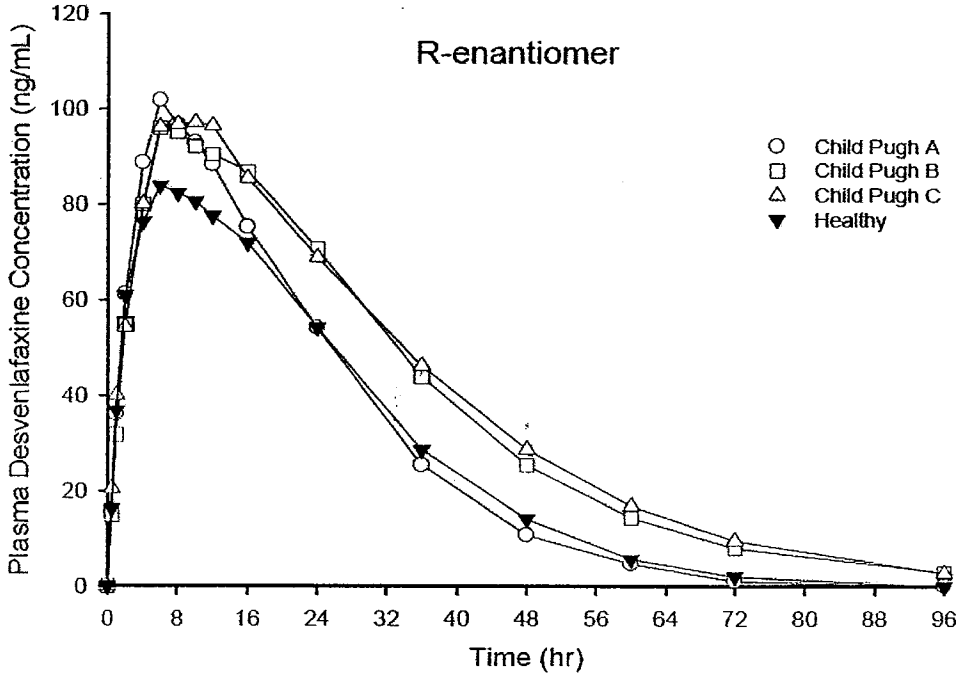
Mean Plasma Concentrations of (R)-enantiomers of Desvenlafaxine After Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects



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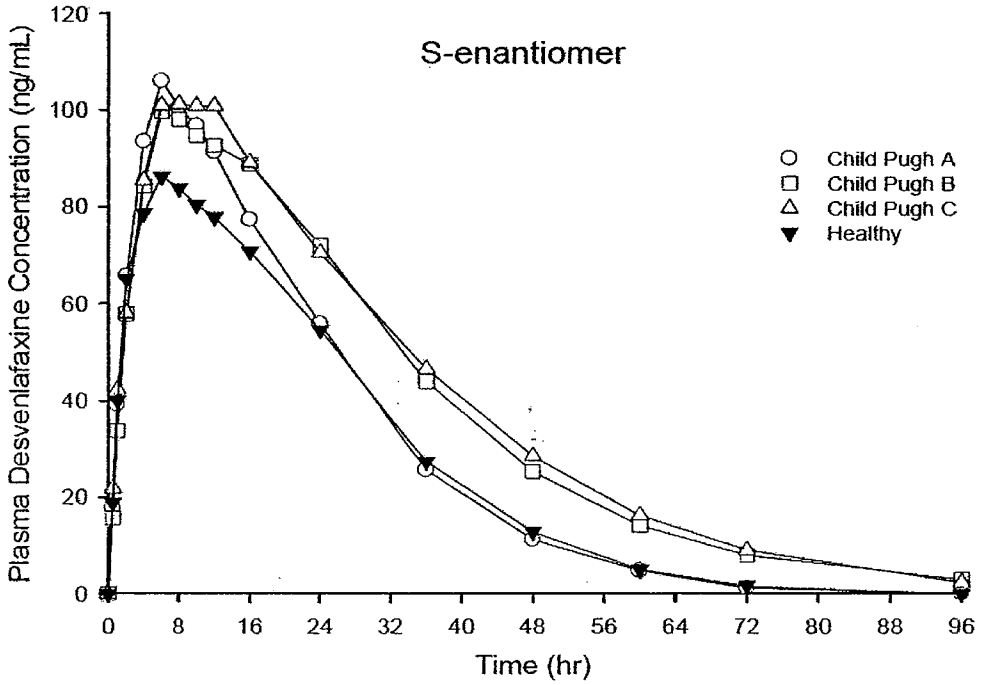
Mean Plasma Concentrations of (S)-enantiomers of Desvenlafaxine After Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects



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After administration of a single oral DVS SR 100-mg dose, approximately equal concentrations of the (R)- and (S)-enantiomers of desvenlafaxine were obtained from all plasma samples assayed for this study. The current study was powered to detect statistically significant differences in primary pharmacokinetic parameters of 50% or greater. Using these criteria, there were no statistically significant differences ($p<0.05$) in C_{max}, AUC_T, AUC or Cl/F of (R+S)-enantiomers of desvenlafaxine between the subjects with Child-Pugh A, B, and C hepatic impairment and healthy subjects. Despite the lack of statistically significant differences, there were trends as described below for exposure, as measured by AUC and C_{max}, to increase with increasing severity of hepatic impairment for subjects with moderate and severe hepatic impairment (Child-Pugh B and C). The 90% confidence intervals were not contained within 80% to 125% . There appeared to be no difference in T_{max} between the subjects with hepatic impairment and healthy subjects. The mean C_{max} of R-, S-, and (R+S)-enantiomers of desvenlafaxine was similar in subjects with Child-Pugh A, B, or C but was up to 25% higher than the mean C_{max} in healthy subjects. A 31% and 35% higher mean AUC of (R+S)-enantiomers was observed in subjects with Child-Pugh B and C hepatic impairment as compared to healthy subjects. The mean $t_{1/2}$ was similar between healthy subjects and those with Child-Pugh A hepatic impairment and longer in subjects with Child-Pugh B and C hepatic impairment.

Generally the renal clearance (CL_R) of (R+S)-enantiomers of desvenlafaxine decreased in subjects with hepatic impairment as compared to healthy subjects. The largest decrease of 38% in CL_R occurred for subjects in the Child-Pugh C group. There was no trend for urinary recoveries of unconjugated and total (unconjugated + conjugated) (R)- and (S)-enantiomers of desvenlafaxine to increase or decrease as hepatic impairment increased. The mean conjugated and total (unconjugated + conjugated) NODV urinary recovery was only 1.60% and 3.66% of the DVS SR dose, respectively, in healthy subjects. There was a decrease in urinary recoveries of total (unconjugated + conjugated) NODV in subjects with the hepatic impairment. There was no clear trend for the combined amount of desvenlafaxine and NODV excreted in urine to increase or decrease as the degree of hepatic impairment increased.

Plots of special laboratory parameters versus AUC and Cl/F of (R+S)-enantiomers of desvenlafaxine are shown in the Attachments. Exploratory stepwise linear regression was performed on (R+S)-enantiomers of desvenlafaxine AUC and Cl/F. The significance criteria for entering and remaining in the stepwise linear regression model was set at the nominal value of $\alpha = 0.15$. The following table provides parameter estimates based on the multiple stepwise linear regression.

Significant Parameters (α= 0.15) in Predicting AUC and Cl/F Using Multiple Linear Stepwise Regression

Model Number	Dependant Variable	Intercept	Weight (kg)	Alkaline Phosphatase (U/L)	PT (sec)	Serum Creatinine (µmol/L)	CL_{CR} (mL/min)	Model R^2
1	AUC (ng.h/mL)	2838	-	-	596	-	48.4	0.368
2	AUC (ng.h/mL)	236	-	0.279	-	-0.870	-1.11	0.579
3	Cl/F (mL/h)	4.26	-0.330	-	-1.69	0.311	0.382	0.434
4	Cl/F (mL/h/kg)	0.306	-	-0.0005	-	-	-	0.0935

Abbreviations: AUC = total area under the concentration-time curve; Cl/F = apparent oral dose clearance; CL_{CR} = creatinine clearance PT = prothrombin time.

- = term was not significant in the model. Values reported are the estimated effects of the terms.

Safety: The most common TEAEs were nausea, reported by 5 (14%) subjects (2 [16.7%] healthy subjects and 3 [12.5%] hepatically-impaired subjects), and vomiting, reported by 3 (8.3%) subjects (1 [8.3%] healthy subject and 2 [8.3%] hepatically-impaired subjects).

Conclusion: The sponsor reported that the administration of a single oral dose of 100 mg DVS was safe and well tolerated in both healthy and hepatically-impaired subjects.

Reviewer's comments: The most increase in exposure (30 to 35% in AUC) was seen in patients with hepatic impairment of Child-Pugh B and C category. The increase in exposure was less than 50% and the study was designed a priori to detect a 50% difference in exposure. In accordance with the recommendations of the FDA Guidance on Studies in Hepatic Impairment Patients, no dosage adjustment is recommended for all categories of patients with hepatic impairment. However, is suggested that care should be taken when treating patients with hepatic impairment of the Child Pugh B and C category. And the doses for patients in Child Pugh B or C category should not be escalated to 200 mg.

ST 8-21. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF R-ENANTIOMER OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH A)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{48} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
1	6	76.43	2058	2076	2094	8.34	0.295	3.55	0.139
4	6	136.26	2738	2758	2781	8.91	0.272	3.50	0.116
7	4	83.22	1595	1613	1644	11.48	0.390	6.46	0.065
10	6	141.37	2316	2341	2382	10.92	0.288	4.53	0.064
44	8	109.71	2657	2683	2715	9.30	0.278	3.73	0.135
46	8	123.73	3219	3243	3266	8.06	0.205	2.38	0.185
48	6	82.44	1392	1432	1463	7.42	0.333	3.57	0.093
53	16	134.44	4617	4720	4772	12.54	0.156	2.83	0.098
N	8	8	8	8	8	8	8	8	8
Mean	7.50	110.95	2574	2608	2640	9.62	0.277	3.82	0.112
SD	3.66	26.88	1022	1043	1049	1.82	0.072	1.24	0.041
Min	4.00	76.43	1392	1432	1463	7.42	0.156	2.38	0.064
Median	6.00	116.72	2487	2512	2548	9.11	0.283	3.56	0.107
Max	16.00	141.37	4617	4720	4772	12.54	0.390	6.46	0.185
CV%	49	24	40	40	40	19	26	32	37
Geo Mean	6.93	107.94	2412	2444	2476	9.48	0.268	3.67	0.105

ST 8-22. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF R-ENANTIOMER OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH B)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{48hr} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
2	6	74.48	1566	1582	1600	8.90	0.411	5.28	0.230
5	16	126.61	4268	4351	4387	11.86	0.181	3.10	0.089
8	8	102.05	3361	3424	3454	12.22	0.179	3.15	0.095
9	8	136.96	4463	4463	4510	12.80	0.161	2.97	0.099
41	12	61.21	1893	1914	1937	8.65	0.231	2.88	0.168
42	4	79.31	1560	1578	1607	11.02	0.464	7.37	0.109
49	16	99.78	5409	5409	6141	29.05	0.099	4.14	0.069
50	8	146.70	5106	5106	5173	13.62	0.174	3.42	0.131
N	8	8	8	8	8	8	8	8	8
Mean	9.75	103.39	3453	3479	3601	13.51	0.237	4.04	0.124
SD	4.46	31.06	1596	1593	1738	6.52	0.129	1.57	0.052
Min	4.00	61.21	1560	1578	1600	8.65	0.099	2.88	0.069
Median	8.00	100.92	3815	3888	3920	12.04	0.180	3.29	0.104
Max	16.00	146.70	5409	5409	6141	29.05	0.464	7.37	0.230
CV%	46	30	46	46	48	48	54	39	42
Geo Mean	8.85	99.18	3084	3111	3193	12.57	0.211	3.83	0.115

ST 8-23. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF R-ENANTIOMER OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH C)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	$AUC_{0\infty}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
3	12	98.18	2997	3044	3067	12.37	0.166	2.97	0.132
6	12	99.31	2777	2822	2841	11.90	0.196	3.36	0.114
43	4	52.70	954	974	1009	11.16	0.475	7.64	0.089
45	6	129.90	2586	2634	2668	14.21	0.373	7.64	0.080
47	8	106.90	4526	4526	4589	13.46	0.146	2.84	0.073
57	12	120.95	5113	5113	5312	17.82	0.108	2.77	0.059
59	10	128.94	6214	6214	6366	14.54	0.076	1.60	0.043
60	6	105.40	3565	3565	3661	15.93	0.114	2.63	0.057
N	8	8	8	8	8	8	8	8	8
Mean	8.75	105.29	3592	3612	3689	13.92	0.207	3.93	0.081
SD	3.20	24.68	1650	1635	1688	2.21	0.141	2.34	0.030
Min	4.00	52.70	954	974	1009	11.16	0.076	1.60	0.043
Median	9.00	106.15	3281	3305	3364	13.84	0.156	2.90	0.077
Max	12.00	129.90	6214	6214	6366	17.82	0.475	7.64	0.132
CV%	37	23	46	45	46	16	68	60	37
Geo Mean	8.17	102.01	3183	3211	3278	13.78	0.173	3.43	0.076

ST 8-24. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF R-ENANTIOMER OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO HEALTHY SUBJECTS

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{24hr} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
16	6	121.73	2872	2901	2938	9.64	0.213	2.96	0.128
17	16	70.96	2142	2162	2183	8.58	0.260	3.22	0.133
18	10	89.81	3270	3345	3382	12.40	0.185	3.31	0.098
19	8	91.42	3643	3727	3764	11.94	0.201	3.47	0.088
20	6	106.89	2443	2471	2508	9.58	0.332	4.59	0.138
51	6	116.10	2246	2282	2316	8.15	0.328	3.85	0.145
52	4	131.77	3747	3839	3903	14.14	0.244	4.99	0.137
54	12	77.47	1794	1823	1852	8.28	0.275	3.29	0.123
55	6	109.33	3199	3244	3250	9.41	0.249	3.38	0.181
56	2	52.16	1335	1368	1410	9.56	0.344	4.74	0.160
58	8	63.84	1828	1850	1879	9.62	0.302	4.20	0.176
61	12	61.03	1667	1685	1712	10.08	0.276	4.01	0.092
N	12	12	12	12	12	12	12	12	12
Mean	8.00	91.04	2516	2558	2591	10.11	0.267	3.83	0.133
SD	3.91	26.21	813	835	839	1.81	0.052	0.67	0.030
Min	2.00	52.16	1335	1368	1410	8.15	0.185	2.96	0.088
Median	7.00	90.62	2344	2376	2412	9.60	0.268	3.66	0.135
Max	16.00	131.77	3747	3839	3903	14.14	0.344	4.99	0.181
CV%	49	29	32	33	32	18	20	17	23
Geo Mean	7.06	87.43	2393	2431	2466	9.98	0.263	3.78	0.130

ST 8-25. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF S-ENANTIOMER OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH A)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_t (ng·hr/mL)	AUC_{∞} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
1	6	80.98	2166	2185	2205	8.49	0.280	3.43	0.123
4	6	139.77	2798	2817	2840	8.84	0.267	3.40	0.104
7	4	88.86	1628	1644	1671	11.04	0.384	6.11	0.057
10	6	149.55	2478	2506	2554	11.12	0.268	4.30	0.055
44	8	109.78	2688	2714	2745	9.26	0.275	3.68	0.115
46	8	127.14	3145	3165	3182	7.72	0.210	2.34	0.156
48	6	87.85	1481	1523	1557	7.41	0.313	3.35	0.082
53	16	140.04	4889	4994	5045	12.37	0.148	2.64	0.085
N	8	8	8	8	8	8	8	8	8
Mean	7.50	115.50	2659	2694	2725	9.53	0.268	3.66	0.097
SD	3.66	27.22	1066	1089	1094	1.78	0.069	1.16	0.034
Min	4.00	80.98	1481	1523	1557	7.41	0.148	2.34	0.055
Median	6.00	118.46	2583	2610	2649	9.05	0.272	3.42	0.095
Max	16.00	149.55	4889	4994	5045	12.37	0.384	6.11	0.156
CV%	49	24	40	40	40	19	26	32	35
Geo Mean	6.93	112.59	2494	2526	2558	9.39	0.260	3.52	0.092

ST 8-26. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF S-ENANTIOMER OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH B)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{168hr} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
2	6	77.42	1632	1649	1670	9.11	0.394	5.18	0.205
5	16	127.02	4202	4271	4294	11.11	0.185	2.96	0.080
8	8	102.70	3229	3281	3301	11.56	0.187	3.12	0.086
9	8	146.33	4785	4785	4838	12.95	0.150	2.80	0.088
41	10	64.01	1992	2016	2043	8.86	0.219	2.80	0.146
42	4	84.11	1602	1621	1656	11.98	0.450	7.78	0.098
49	16	102.04	5486	5486	6215	28.79	0.098	4.06	0.064
50	8	149.41	5151	5151	5208	13.13	0.173	3.28	0.116
N	8	8	8	8	8	8	8	8	8
Mean	9.50	106.63	3510	3532	3653	13.44	0.232	4.00	0.110
SD	4.38	31.70	1615	1609	1750	6.40	0.123	1.73	0.046
Min	4.00	64.01	1602	1621	1656	8.86	0.098	2.80	0.064
Median	8.00	102.37	3715	3776	3798	11.77	0.186	3.20	0.093
Max	16.00	149.41	5486	5486	6215	28.79	0.450	7.78	0.205
CV%	46	30	46	46	48	48	53	43	41
Geo Mean	8.65	102.44	3144	3170	3253	12.53	0.207	3.75	0.104

ST 8-27. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF S-ENANTIOMER OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH C)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{48hr} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
3	12	106.51	3385	3459	3516	14.71	0.145	3.08	0.120
6	12	106.45	2955	3006	3031	12.25	0.183	3.24	0.106
43	4	57.06	1025	1048	1089	11.51	0.440	7.30	0.082
45	6	144.16	2945	3009	3058	14.80	0.325	6.94	0.070
47	8	109.75	4669	4669	4730	13.24	0.142	2.71	0.064
57	12	120.75	4792	4792	4934	16.72	0.116	2.80	0.053
59	10	133.37	6059	6059	6178	13.76	0.079	1.56	0.039
60	6	107.52	3399	3399	3463	14.44	0.121	2.52	0.050
N	8	8	8	8	8	8	8	8	8
Mean	8.75	110.70	3654	3680	3750	13.93	0.194	3.77	0.073
SD	3.20	25.80	1519	1504	1534	1.63	0.124	2.13	0.028
Min	4.00	57.06	1025	1048	1089	11.51	0.079	1.56	0.039
Median	9.00	108.64	3392	3429	3489	14.10	0.143	2.94	0.067
Max	12.00	144.16	6059	6059	6178	16.72	0.440	7.30	0.120
CV%	37	23	42	41	41	12	64	57	38
Geo Mean	8.17	107.42	3296	3330	3397	13.84	0.167	3.33	0.068

ST 8-28. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF S-ENANTIOMER OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO HEALTHY SUBJECTS

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{96hr} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
16	6	123.15	2664	2684	2706	8.74	0.231	2.91	0.107
17	16	77.79	2349	2371	2394	8.58	0.237	2.94	0.113
18	10	80.16	2901	2949	2957	9.85	0.211	3.00	0.084
19	10	91.10	3623	3690	3709	10.66	0.204	3.14	0.073
20	8	101.22	2591	2632	2717	12.87	0.307	5.69	0.115
51	6	114.67	2119	2146	2168	7.51	0.350	3.79	0.125
52	4	130.58	3376	3442	3480	13.04	0.274	5.16	0.120
54	12	85.21	1970	2003	2038	8.47	0.250	3.06	0.105
55	6	115.78	3167	3207	3211	9.23	0.252	3.36	0.157
56	2	54.25	1374	1405	1444	9.23	0.336	4.47	0.138
58	8	69.64	1958	1982	2015	10.02	0.282	4.07	0.149
61	12	63.72	1744	1762	1787	9.79	0.264	3.73	0.079
N	12	12	12	12	12	12	12	12	12
Mean	8.33	92.27	2486	2523	2552	9.83	0.267	3.78	0.114
SD	3.89	24.75	691	704	700	1.68	0.046	0.92	0.027
Min	2.00	54.25	1374	1405	1444	7.51	0.204	2.91	0.073
Median	8.00	88.16	2470	2501	2550	9.51	0.258	3.54	0.114
Max	16.00	130.58	3623	3690	3709	13.04	0.350	5.69	0.157
CV%	47	27	28	28	27	17	17	24	23
Geo Mean	7.37	89.14	2395	2430	2462	9.71	0.263	3.68	0.111

ST 8-29. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF (R+S)-ENANTIOMERS OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH A)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{last} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
1	6	157.41	4224	4261	4299	8.42	0.287	3.49	0.131
4	6	276.03	5535	5575	5622	8.88	0.270	3.45	0.110
7	4	172.08	3224	3258	3316	11.26	0.387	6.28	0.061
10	6	290.92	4794	4847	4935	11.02	0.278	4.41	0.059
44	8	219.49	5346	5397	5460	9.28	0.277	3.71	0.125
46	8	250.87	6365	6408	6447	7.90	0.208	2.37	0.171
48	6	170.29	2873	2955	3020	7.41	0.323	3.46	0.087
53	16	274.48	9507	9714	9818	12.45	0.152	2.73	0.091
N	8	8	8	8	8	8	8	8	8
Mean	7.50	226.45	5233	5302	5365	9.58	0.273	3.74	0.104
SD	3.66	54.04	2086	2130	2141	1.80	0.070	1.20	0.038
Min	4.00	157.41	2873	2955	3020	7.41	0.152	2.37	0.059
Median	6.00	235.18	5070	5122	5198	9.08	0.277	3.47	0.101
Max	16.00	290.92	9507	9714	9818	12.45	0.387	6.28	0.171
CV%	49	24	40	40	40	19	26	32	36
Geo Mean	6.93	220.55	4906	4970	5035	9.43	0.264	3.59	0.098

ST 8-30. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF (R+S)-ENANTIOMERS OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH B)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{48hr} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
2	6	151.90	3197	3231	3270	9.00	0.402	5.23	0.217
5	16	253.63	8470	8622	8680	11.49	0.183	3.03	0.084
8	8	204.75	6590	6705	6755	11.90	0.183	3.14	0.090
9	8	283.29	9248	9248	9348	12.88	0.155	2.88	0.093
41	12	125.08	3884	3930	3980	8.76	0.225	2.84	0.157
42	4	163.42	3163	3199	3261	11.28	0.457	7.44	0.104
49	16	201.82	10895	10895	12353	28.87	0.098	4.09	0.067
50	8	296.11	10257	10257	10381	13.38	0.174	3.35	0.123
N	8	8	8	8	8	8	8	8	8
Mean	9.75	210.00	6963	7011	7254	13.44	0.235	4.00	0.117
SD	4.46	62.73	3208	3199	3484	6.44	0.126	1.60	0.049
Min	4.00	125.08	3163	3199	3261	8.76	0.098	2.84	0.067
Median	8.00	203.29	7530	7664	7718	11.70	0.183	3.24	0.098
Max	16.00	296.11	10895	10895	12353	28.87	0.457	7.44	0.217
CV%	46	30	46	46	48	48	54	40	42
Geo Mean	8.85	201.61	6229	6283	6447	12.52	0.209	3.78	0.109

ST 8-31. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF (R+S)-ENANTIOMERS OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH C)

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{48hr} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
3	12	204.69	6383	6504	6581	13.64	0.155	3.05	0.125
6	12	205.76	5732	5828	5872	12.08	0.189	3.30	0.110
43	4	109.76	1979	2022	2098	11.34	0.457	7.47	0.085
45	6	274.06	5532	5643	5726	14.54	0.347	7.28	0.075
47	8	216.65	9195	9195	9319	13.35	0.144	2.77	0.069
57	12	241.70	9905	9905	10246	17.32	0.112	2.79	0.056
59	10	262.31	12274	12274	12544	14.17	0.077	1.58	0.041
60	6	212.92	6965	6965	7124	15.24	0.117	2.58	0.053
N	8	8	8	8	8	8	8	8	8
Mean	8.75	215.98	7246	7292	7439	13.96	0.200	3.85	0.077
SD	3.20	50.29	3161	3131	3212	1.86	0.132	2.23	0.029
Min	4.00	109.76	1979	2022	2098	11.34	0.077	1.58	0.041
Median	9.00	214.79	6674	6734	6852	13.91	0.149	2.92	0.072
Max	12.00	274.06	12274	12274	12544	17.32	0.457	7.47	0.125
CV%	37	23	44	43	43	13	66	58	38
Geo Mean	8.17	209.46	6482	6545	6679	13.85	0.169	3.39	0.072

ST 8-31. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF (R+S)-ENANTIOMERS OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO SUBJECTS WITH CHRONIC HEPATIC IMPAIRMENT (CHILD PUGH C)

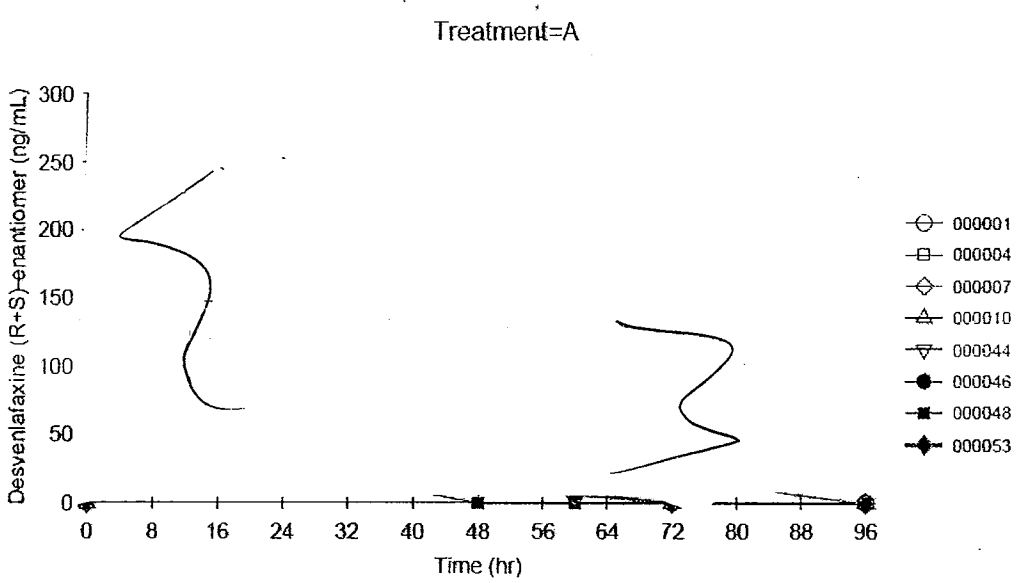
Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_t (ng·hr/mL)	AUC_{48hr} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
3	12	204.69	6383	6504	6581	13.64	0.155	3.05	0.125
6	12	205.76	5732	5828	5872	12.08	0.189	3.30	0.110
43	4	109.76	1979	2022	2098	11.34	0.457	7.47	0.085
45	6	274.06	5532	5643	5726	14.54	0.347	7.28	0.075
47	8	216.65	9195	9195	9319	13.35	0.144	2.77	0.069
57	12	241.70	9905	9905	10246	17.32	0.112	2.79	0.056
59	10	262.31	12274	12274	12544	14.17	0.077	1.58	0.041
60	6	212.92	6965	6965	7124	15.24	0.117	2.58	0.053
N	8	8	8	8	8	8	8	8	8
Mean	8.75	215.98	7246	7292	7439	13.96	0.200	3.85	0.077
SD	3.20	50.29	3161	3131	3212	1.86	0.132	2.23	0.029
Min	4.00	109.76	1979	2022	2098	11.34	0.077	1.58	0.041
Median	9.00	214.79	6674	6734	6852	13.91	0.149	2.92	0.072
Max	12.00	274.06	12274	12274	12544	17.32	0.457	7.47	0.125
CV%	37	23	44	43	43	13	66	58	38
Geo Mean	8.17	209.46	6482	6545	6679	13.85	0.169	3.39	0.072

ST 8-32. INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS OF (R+S)-ENANTIOMERS OF DESVENLAFAXINE FOLLOWING SINGLE ORAL ADMINISTRATION OF DVS SR 100 mg TO HEALTHY SUBJECTS

Subject	T_{max} (hr)	C_{max} (ng/mL)	AUC_T (ng·hr/mL)	AUC_{∞} (ng·hr/mL)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL_R (L/hr/kg)
16	6	244.88	5537	5585	5644	9.21	0.221	2.94	0.118
17	16	148.75	4491	4533	4577	8.58	0.248	3.07	0.122
18	10	169.97	6172	6294	6343	11.60	0.197	3.30	0.091
19	10	182.26	7268	7420	7473	11.22	0.203	3.28	0.081
20	6	207.76	5038	5107	5221	11.09	0.319	5.11	0.126
51	6	230.77	4365	4428	4484	7.84	0.338	3.83	0.135
52	4	262.35	7123	7281	7383	13.64	0.259	5.09	0.129
54	12	162.68	3764	3826	3890	8.38	0.262	3.17	0.114
55	6	225.11	6366	6451	6461	9.32	0.251	3.37	0.169
56	2	106.41	2709	2773	2854	9.39	0.340	4.60	0.149
58	8	133.48	3787	3832	3892	9.66	0.292	4.07	0.162
61	12	124.75	3411	3448	3498	9.93	0.270	3.86	0.085
N	12	12	12	12	12	12	12	12	12
Mean	8.17	183.26	5003	5081	5143	9.99	0.267	3.81	0.124
SD	3.95	50.69	1496	1531	1529	1.63	0.048	0.77	0.028
Min	2.00	106.41	2709	2773	2854	7.84	0.197	2.94	0.081
Median	7.00	176.12	4764	4820	4899	9.53	0.260	3.60	0.124
Max	16.00	262.35	7268	7420	7473	13.64	0.340	5.11	0.169
CV%	48	28	30	30	30	16	18	20	23
Geo Mean	7.19	176.61	4792	4866	4931	9.87	0.263	3.74	0.120

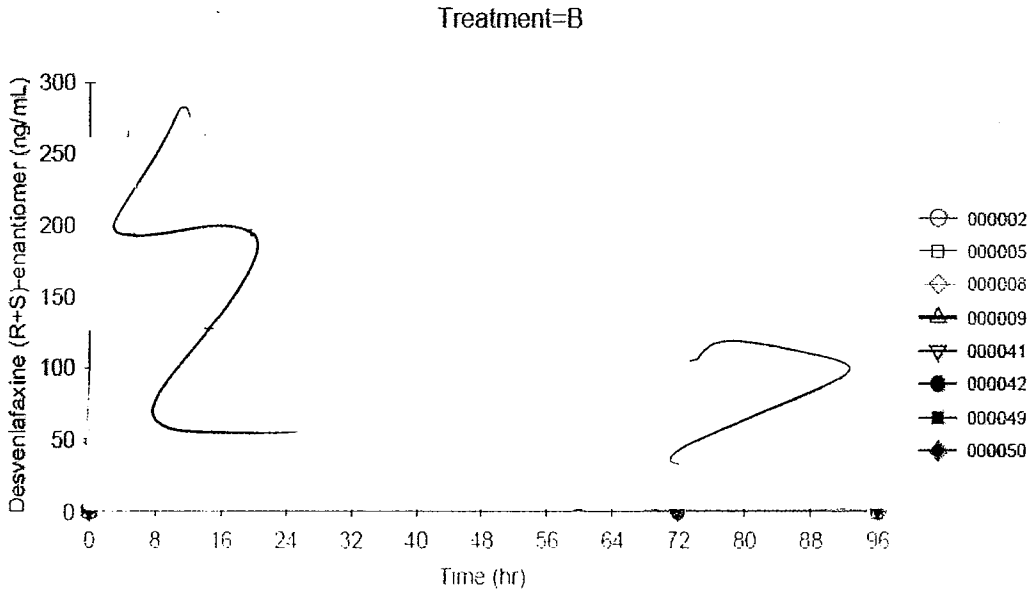
APPEARS THIS WAY
ON ORIGINAL

SF 8-9. Individual plasma concentration-time profiles of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with chronic hepatic impairment (Child Pugh A)



APPEARS THIS WAY
ON ORIGINAL

SF 8-10. Individual plasma concentration-time profiles of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with chronic hepatic impairment (Child Pugh B)



APPEARS THIS WAY
ON ORIGINAL

SF 8-11. Individual plasma concentration-time profiles of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with chronic hepatic impairment (Child Pugh C)