

REPORT 8-IV-1 DESCRIPTIVE STATISTICS AND ANALYSIS WITHIN TREATMENT GROUPS FOR VITAL SIGNS AND PHYSICAL CHARACTERISTICS

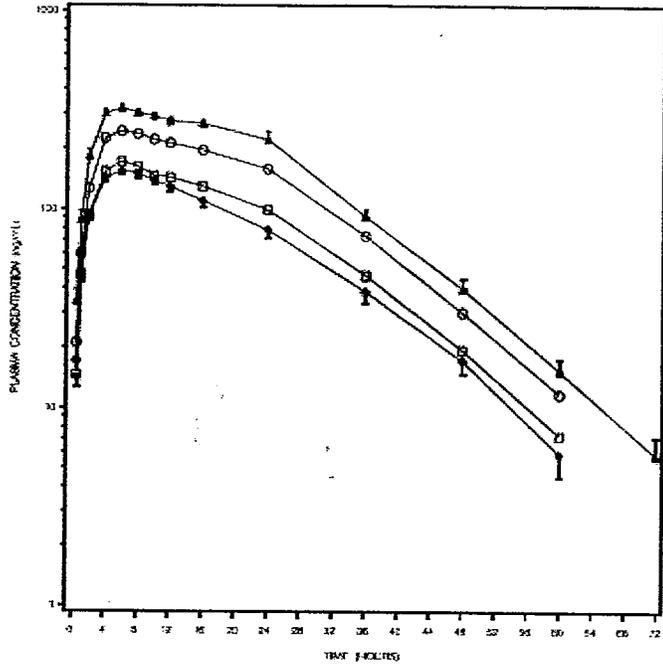
TEST: DIASTOLIC BP (Saphire) (mm Hg) / WITHIN TREATMENT GROUPS

TREATMENT PK IDENTIFIER	N	CHANGE				ADJUSTED	
		MAX	MEAN	STDEV	STERR	MEAN	STERR
DESVENLAFAXINE 1X100 mg							
Day 1, hr -0.5	20	0.00	0.00	0.00	0.00	0.00	
Day 1, hr 2	20	14.00	-2.40*	6.75	1.51	-2.72*	1.33
Day 1, hr 4	20	8.00	-0.30	3.89	0.82	0.42	0.87
Day 1, hr 8	20	6.00	-2.80	4.40	0.98	-1.17	1.11
Day 1, hr 12	20	5.00	-1.70	4.37	0.98	-1.07	1.35
Day 1, hr 24	20	10.00	-0.40	5.90	1.32	0.25	1.27
Day 1, hr 48	20	10.00	-1.20	5.76	1.26	-0.19	1.16
Day 1, hr 72	20	10.00	-2.70*	5.70	1.24	-1.82	1.20
DESVENLAFAXINE 1X200 mg							
Day 1, hr -0.5	20	0.00	0.00	0.00	0.00	0.00	
Day 1, hr 2	20	10.00	-2.90	6.91	1.55	-2.34	1.33
Day 1, hr 4	20	8.00	-1.80	4.81	1.03	-0.43	0.85
Day 1, hr 8	20	5.00	-3.80*	6.77	1.51	-3.15**	1.11
Day 1, hr 12	20	3.00	-2.80*	5.60	1.12	-2.31	1.25
Day 1, hr 24	20	14.00	1.60	5.60	1.25	2.11	1.22
Day 1, hr 48	20	12.00	-0.20	6.49	1.45	0.43	1.17
Day 1, hr 72	20	16.00	-1.60	7.09	1.59	-0.32	1.20
DESVENLAFAXINE 2X50 mg							
Day 1, hr -0.5	20	0.00	0.00	0.00	0.00	0.00	
Day 1, hr 2	20	6.00	-0.50	5.15	1.15	-1.15	1.21
Day 1, hr 4	20	8.00	-1.30	4.55	1.02	-1.92*	0.87
Day 1, hr 8	20	14.00	0.90	6.80	1.48	0.15	1.11
Day 1, hr 12	20	12.00	-0.50	6.13	1.82	-1.09	1.25
Day 1, hr 24	20	14.00	0.80	6.36	1.42	-0.62	1.22
Day 1, hr 48	20	10.00	0.50	5.58	1.25	-0.26	1.16
Day 1, hr 72	20	14.00	-1.50	7.29	1.62	-2.34	1.20
DESVENLAFAXINE 2X75 mg							
Day 1, hr -0.5	20	0.00	0.00	0.00	0.00	0.00	
Day 1, hr 2	20	10.00	-1.20	6.97	1.56	-1.87	1.33
Day 1, hr 4	20	12.00	1.10	6.44	1.44	0.50	0.87
Day 1, hr 8	20	10.00	1.00	6.14	1.37	0.21	1.11
Day 1, hr 12	20	18.00	1.80	7.83	1.75	0.45	1.25
Day 1, hr 24	20	12.00	1.20	6.40	1.43	0.65	1.22
Day 1, hr 48	20	12.00	-0.10	7.52	1.57	-0.78	1.17
Day 1, hr 72	20	16.00	-0.60	7.27	1.55	-1.34	1.20

NOTE: ALL STATISTICS ARE EVALUATED USING DATA WITH NON-MISSING BASELINE VALUES. N: THE NUMBER OF MATCHED NON-MISSING PAIRS. STATISTICAL SIGNIFICANCE AT THE .05, .01, .001 LEVELS IS DENOTED BY *, **, *** RESPECTIVELY.

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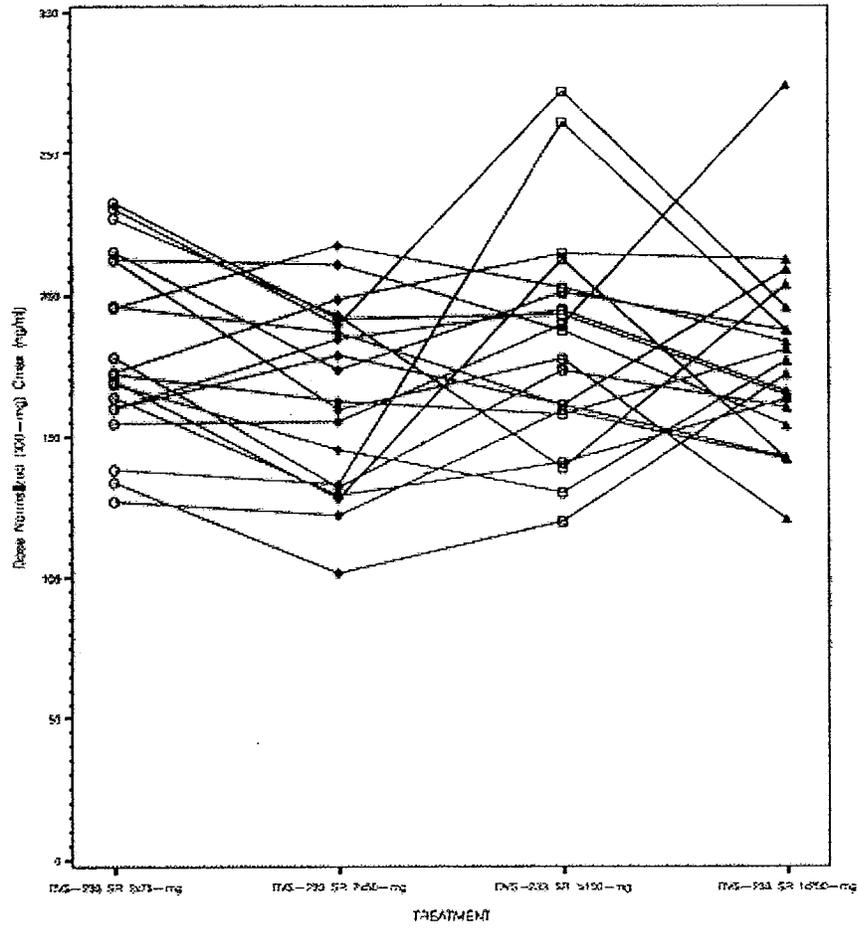
SF 8-1. MEAN DESVENLAFAXINE PLASMA CONCENTRATIONS IN HEALTHY SUBJECTS RECEIVING A SINGLE ORAL DOSE OF DVS-233 SR



- Desvenlafaxine SR 250mg tablet
- Desvenlafaxine SR 250mg tablet
- Desvenlafaxine SR 1000mg tablet
- ▲ Desvenlafaxine SR 1000mg tablet
- ▲ SR bar

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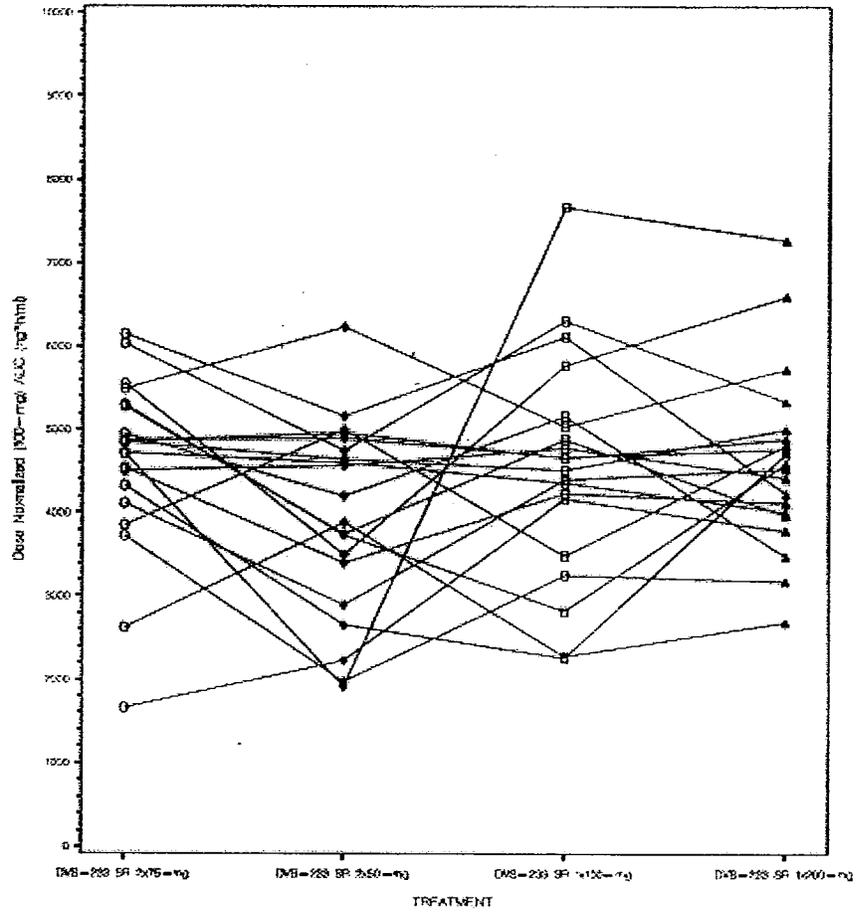
SF 8-2. DESVENLAFAXINE C_{max} IN HEALTHY SUBJECTS RECEIVING A SINGLE ORAL DOSE OF DVS-233 SR



Note to plotting: C_{max} for all treatments has been dose normalized to 100-mg.

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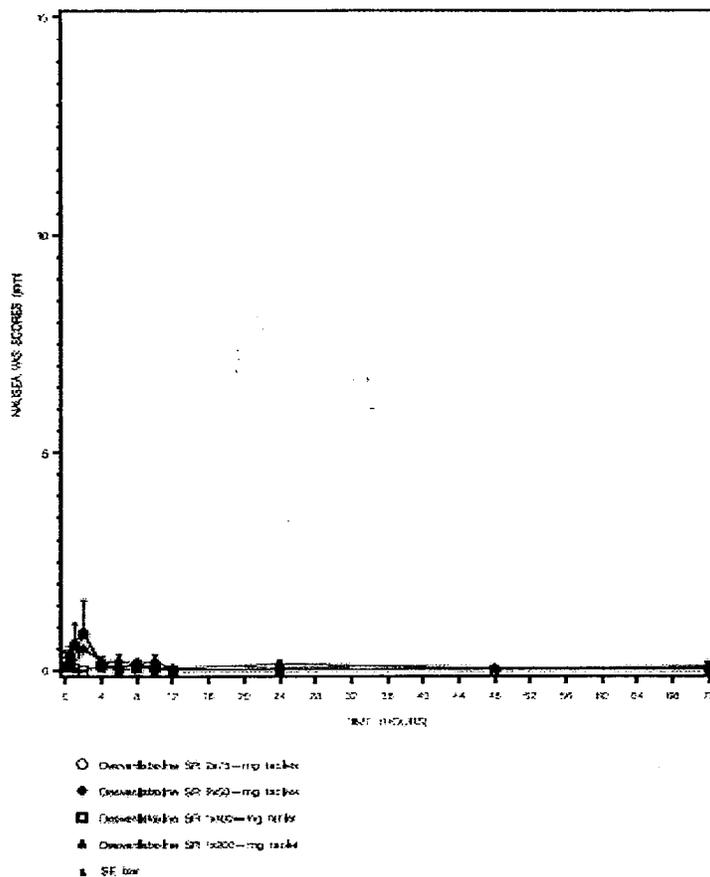
SF 8-3. DESVENLAFAXINE AUC IN HEALTHY SUBJECTS RECEIVING A SINGLE ORAL DOSE OF DVS-233 SR



Plot is 250% AUC for all treatments has been done (average is 100-mg).

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SF 8-4. MEAN NAUSEA VAS SCORES IN HEALTHY SUBJECTS RECEIVING A SINGLE ORAL DOSE OF DVS-233 SR



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Study Title: An Open-Label, 2-Period, Randomized, Crossover Study Of The Pharmacokinetic Profile, Safety, And Tolerability Of 2 Dosage Strengths (50 mg and 100 mg) Of DVS-233 SR In Healthy Adults (Protocol 0600d3-190-Us, Csr-50362).

Objectives: The primary objective of this study was to evaluate the pharmacokinetic profile of 2 dose strengths, 50 and 100 mg, of DVS-233 SR. The secondary objective was to evaluate the safety and tolerability of these 2 dose strengths when administered to healthy subjects.

Study Design: This was a single-dose, open-label, randomized, 2-period, crossover study. Healthy men aged 18 to 45 years with a body mass index of 18 to 30 kg/m² and body weight \geq 50 kg were eligible. Twenty four (24) male subjects (mean \pm SD age and weight 36.8 \pm 5.0 years and 79.7 \pm 10.7 kg, respectively) were enrolled and completed the study. 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 2 study periods and received only 1 dose of DVS-233 SR (2x50 or 1x100 mg) in each study period. The 2 study periods were separated by a 1-day washout interval. The batch number for the 50 mg SR formulation was 2002B0105. The batch number for the 100 mg SR formulation was 2002B0109.

Analytical Method: Plasma samples were assayed for desvenlafaxine concentrations by using a validated high performance liquid chromatography (HPLC) 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 during the analysis of the plasma samples from this study is summarized in the following tables.

Table 6.5.2-1: Assay Range and Sensitivity For Pharmacokinetic Samples

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

Table 6.5.2-2: Analytical Summary of Desvenlafaxine Plasma Assays

Analyte	--High QC (300.0 ng/mL)--			--Middle QC (60.0 ng/mL)--			--Low QC (15.0 ng/mL)--		
	Conc	CV%	Bias%	Conc	CV%	Bias%	Conc	CV%	Bias%
Desvenlafaxine	296.26	8.85	-1.25	57.33	4.54	-4.45	14.72	5.54	-1.87

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

Data Analysis: The plasma concentrations of desvenlafaxine were analyzed by using model-independent pharmacokinetic methods. Pharmacodynamic assessments were made by using a 100-mm visual analog scale (VAS) for nausea. The pharmacokinetic and pharmacodynamic parameters of desvenlafaxine were compared by using an analysis of variance for a 2-period crossover study design. Additionally, the geometric mean relative bioavailability and 90% confidence limits of peak concentration, the area under the concentration-time curve (AUC), and AUCT were calculated to compare the 2 DVS-233 SR formulations.

The extent of nausea experienced by each subject was evaluated using a 100-mm Visual Analogue Scale (VAS) at specified times during the study. Subjects were instructed to make a mark along a 100-mm line to indicate the severity of nausea. A mark on the far left indicated "no nausea at all," and a mark on the far right indicated "the maximum nausea ever experienced." The VAS score was the distance (in millimeters) between the left end of the 100-mm line and the subject's mark. In addition to the raw scores, the maximum VAS score (E_{max}), the time of maximum VAS score (tE_{max}), and the area under the VAS response curve (AURC) were calculated from the observed data. The AURC was calculated over the entire 72-hour observation period using the linear-trapezoidal rule.

Results

Pharmacokinetic Summary: Mean desvenlafaxine plasma concentration time profile after receiving each of the 2 treatments of DVS-233 SR are presented in the Attachment. Summary statistics and statistical comparisons between the treatments are presented in Attachments. Summary statistics and statistical comparisons, respectively, between the treatments, including the geometric mean relative bioavailability and 90% confidence limits are presented in the Attachments. The mean \pm SD and geometric mean of estimates of the desvenlafaxine pharmacokinetic parameter values for the 2 treatments, as well as the statistical comparisons between the treatments are provided in the following table.

Desvenlafaxine Pharmacokinetic Parameters

Treatment	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} (h)	AUC _T (ng*h/mL)	AUC (ng*h/mL)
DVS-233 SR 1x100 mg	178±37 ^a	6.0±2.0	11.0±1.6	4357±1474	4498±1503
	174	5.7	10.9	4038	4182
DVS-233 SR 2x50 mg	173±33	6.8±2.4	12.3±2.4	4479±1300	4649±1356
	170	6.4	12.1	4253	4418
<i>2-Period Crossover Analysis of Variance of Log-Transformed Data</i>					
Sequence	0.856	0.286	0.186	0.081	0.072
Subject (sequence)	0.073	0.141	0.004	0.002	0.001
Period	0.567	0.081	0.294	0.995	0.966
Treatment	0.670	0.208	0.007	0.501	0.457
<i>Least Squares Geometric Mean Ratio^b (Relative Bioavailability) and 90% Confidence Limits</i>					
DVS-233 SR 2x50 mg	97.8%	--	--	105.3%	105.6%
	89.6-106.7%			92.5-120.0%	93.3-119.7%

a: Mean ± SD and geometric mean.

Note: values of zero were excluded from calculations of the geometric means.

b: DVS-233 SR 1x100-mg treatment is the reference treatment.

The mean C_{max} values for the 1x100-mg and 2x50-mg treatments in the current study were similar (178 ± 37 ng/mL and 173 ± 33 ng/mL, respectively). The T_{max} and elimination half-life values were similar for both treatments. The AUC for the 2x50-mg treatment (4649 ng*h/mL) was higher (3%) than for the 1x100-mg treatment (4498 ng*h/mL). The intersubject variability for all pharmacokinetic parameters was very similar for both treatments. In comparing the 2x50-mg treatment with the reference (1x100-mg) treatment, the 2x50-mg treatment met the bioequivalence criteria for C_{max}, AUC, and AUC_T, with all 90% confidence intervals falling entirely within the regulatory limits of 80% to 125%.

The mean VAS nausea ratings versus time profile for both treatments are presented in the figures in the attachments. Summary mean ± SD VAS pharmacodynamic parameters for the 2 treatments is presented in the following table.

VAS Nausea Parameters

Treatment	E_{max} (mm)	t_{2max} (h)	AURC (mm*h)	$E_{max} \geq 10$ mm n/N (%)
DVS-233 SR 1x100 mg	5.8±10.7 (0-34) ^a	4.4±3.5 (0-12)	26.2±75.1 (0-358)	6/24 (25%)
DVS-233 SR 2x50 mg	10.7±20.4 (0-79)	2.5±1.4 (0-6)	64.4±145.4 (0-576)	7/24 (29%)
<i>2-Period Crossover Analysis of Variance</i>				
Sequence	0.430	0.299	0.880	--
Subject (sequence)	0.019	0.147	0.047	--
Period	0.571	0.780	0.431	--
Treatment	0.189	0.093	0.177	--

a: Mean ± SD and (range).

The 1x100-mg and 2x50-mg treatments had approximately the same percentage of subjects with E_{max} values greater than 10 mm (25% and 29%, respectively).

Safety Summary: The sponsor reported that all TEAEs were mild in severity. The most frequently reported TEAE was nausea, which occurred in 13 subjects. No deaths or serious adverse events occurred and no subject withdrew from the study because of an adverse event. The sponsor reported that there were no clinically important changes in laboratory test, vital sign, physical examination, or ECG results. Both dose strengths (50 and 100 mg) were generally safe and well tolerated.

Conclusion: In summary, both the C_{max} and AUC of the 50-mg formulation met the bioequivalence criteria compared with the 100-mg formulation. The sponsor reported that no significant differences were observed between the 2 treatments in terms of the nausea scores or pharmacodynamic parameters. No deaths or serious adverse events occurred and no subject withdrew from the study because of an adverse event.

Reviewer's comments: *The reviewer agrees with the sponsor's conclusions. The 50 mg SR tablet was bioequivalent to the 100 mg SR tablet.*

Attachments

Supportive Table ST 6-1. Demographic Listing
 In Healthy Subjects Receiving a Single Dose of 100 mg of DVS-233 SR
 Protocol 06003-190-US

13:43 Monday, September 28, 2002

SUBJECT	SEX	RACE	AGE	WEIGHT (kg)	HEIGHT (cm)	BMI (m ²)	RANDOM NUMBER	TREATMENT Period1 / Period2
1	Male	White	37	93.4	182.0	28.2	1	DVS-233 SR 1x100/2x50
2	Male	Black	33	76.1	177.9	24.0	2	DVS-233 SR 2x50/1x100
3	Male	Black	36	56.3	166.1	20.5	3	DVS-233 SR 1x100/2x50
4	Male	Black	34	108.7	199.0	27.4	4	DVS-233 SR 2x50/1x100
5	Male	White	33	69.4	167.0	24.9	5	DVS-233 SR 2x50/1x100
6	Male	Black	35	69.3	177.8	22.0	6	DVS-233 SR 1x100/2x50
7	Male	Black	27	71.8	171.7	24.4	7	DVS-233 SR 1x100/2x50
8	Male	Black	39	85.9	190.6	23.6	8	DVS-233 SR 2x50/1x100
9	Male	Black	39	91.5	179.3	28.5	9	DVS-233 SR 2x50/1x100
10	Male	Black	23	81.2	176.6	26.0	10	DVS-233 SR 1x100/2x50
11	Male	Black	37	92.1	186.7	23.6	11	DVS-233 SR 2x50/1x100
12	Male	Other	39	80.5	172.1	27.2	12	DVS-233 SR 1x100/2x50
13	Male	Black	44	82.0	179.0	25.6	13	DVS-233 SR 1x100/2x50
14	Male	Black	35	83.7	180.6	25.7	14	DVS-233 SR 2x50/1x100
15	Male	White	44	78.0	180.0	24.1	15	DVS-233 SR 2x50/1x100
16	Male	Black	32	67.7	170.5	23.3	16	DVS-233 SR 1x100/2x50
17	Male	Black	35	79.4	181.9	23.7	17	DVS-233 SR 2x50/1x100
18	Male	Black	41	88.7	179.8	27.4	18	DVS-233 SR 1x100/2x50
19	Male	Black	41	79.2	173.3	26.4	19	DVS-233 SR 1x100/2x50
20	Male	Black	41	72.4	176.5	23.2	20	DVS-233 SR 2x50/1x100
21	Male	White	25	78.1	171.6	26.5	21	DVS-233 SR 2x50/1x100
22	Male	Black	41	79.5	171.6	27.0	22	DVS-233 SR 1x100/2x50
23	Male	Black	40	68.0	169.7	23.6	23	DVS-233 SR 2x50/1x100
24	Male	White	41	91.4	179.4	28.4	24	DVS-233 SR 1x100/2x50
		MEAN	37	79.7	177.5	25.2		
		STD	5	10.7	7.5	2.1		
		VCV	14	13.4	4.2	8.5		
		N	24	24	24	24		

Supportive Table ST 3-4. Pharmacokinetic Parameters of Desvenlafaxine
 In Healthy Subjects Receiving a Single Dose of 100 mg of DVS-233 SR
 Protocol 060003-190-US

13:43 Monday, September 29,

SUBJECT	C _{MAX} (ng/mL)	T _{MAX} (h)	LAMBDA (1/h)	T 1/2 (h)	AUC _t (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	V _Z /F (L/kg)
DVS-233 SR 1x100 mg								
1	196	8.0	0.069	10.0	4892	5030	0.213	3.087
2	216	6.0	0.057	12.2	6055	6224	0.211	3.709
3	104	2.0	0.080	8.7	1266	1353	1.309	15.33
4	186	6.0	0.054	12.8	5102	5257	0.175	3.231
5	184	4.0	0.077	9.0	3223	3340	0.431	5.525
5	187	6.0	0.060	11.5	6083	6230	0.231	3.820
7	214	6.0	0.051	13.5	5921	6135	0.227	4.424
8	133	8.0	0.065	10.7	3991	4085	0.285	4.400
9	213	6.0	0.056	12.2	5230	5481	0.199	3.531
10	169	6.0	0.049	14.1	5390	5595	0.220	4.479
11	230	6.0	0.055	12.6	6424	6544	0.183	3.233
12	183	8.0	0.065	10.7	5447	5559	0.223	3.452
13	158	4.0	0.058	12.0	4267	4390	0.279	4.851
14	172	6.0	0.080	8.7	2863	2958	0.404	5.052
15	151	6.0	0.058	11.9	4967	5117	0.251	4.312
16	189	12.0	0.061	11.2	5008	5092	0.290	4.727
17	118	4.0	0.079	8.8	1759	1886	0.676	8.559
18	209	6.0	0.061	11.4	4773	4876	0.231	3.811
19	158	6.0	0.068	10.2	3898	4010	0.315	4.649
20	151	4.0	0.057	12.2	1969	1990	0.694	12.19
21	155	4.0	0.070	10.0	2354	2442	0.524	7.530
22	219	6.0	0.073	9.5	4681	4930	0.255	3.493
23	248	8.0	0.068	10.2	5533	5681	0.259	3.796
24	124	6.0	0.073	9.5	1545	1615	0.293	4.095

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Supportive Table ST 8-4. Pharmacokinetic Parameters of Desvenlafaxine
 In Healthy Subjects Receiving a Single Dose of 100 mg of BVS-233 SR
 Protocol 060003-190-US

13:43 Monday, September 29, 2003

SUBJECT	C _{MAX} (ng/mL)	T _{MAX} (h)	LAMBDA (1/h)	T 1/2 (h)	AUC _t (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	V _z /F (L/kg)	C _{MAX} RATIO (%)	AUC RATIO (%)
BVS-233 SR 2x50 mg										
1	169	10.0	0.057	12.3	4687	4806	0.223	3.924	86.3	95.5
2	182	8.0	0.054	12.7	5613	6012	0.219	4.014	84.3	96.6
3	200	6.0	0.070	9.9	4141	4223	0.419	6.007	132.7	312.0
4	174	6.0	0.054	13.0	4893	5036	0.183	3.425	93.5	95.8
5	169	10.0	0.072	9.7	4853	4981	0.289	4.044	91.9	149.2
6	206	4.0	0.040	17.2	6246	6708	0.215	5.323	110.2	107.7
7	174	6.0	0.044	15.8	6155	6569	0.212	4.826	81.3	107.1
8	153	4.0	0.050	14.0	3372	3555	0.327	6.609	134.7	87.0
9	162	8.0	0.052	13.2	5198	5392	0.203	3.865	76.1	98.4
10	230	8.0	0.061	11.3	5577	5794	0.213	3.468	136.1	103.6
11	195	10.0	0.052	13.4	5707	5905	0.206	3.996	84.7	88.9
12	190	6.0	0.061	11.3	4659	4789	0.259	4.235	104.0	86.1
13	117	2.0	0.041	16.9	2250	2404	0.507	12.40	74.1	55.0
14	128	6.0	0.098	7.1	1998	2105	0.667	5.787	74.5	71.2
15	141	10.0	0.067	10.3	4413	4496	0.285	4.255	93.5	87.8
16	177	6.0	0.055	12.6	5038	5176	0.285	5.205	93.6	101.6
17	203	6.0	0.048	14.3	4458	4582	0.279	5.740	171.0	243.0
18	154	6.0	0.054	12.7	4628	4811	0.234	4.300	74.0	98.7
19	163	8.0	0.052	13.2	4391	4527	0.279	5.319	102.9	112.9
20	123	6.0	0.056	12.3	1962	2091	0.661	11.76	81.2	105.1
21	156	6.0	0.070	9.9	2284	2372	0.540	7.588	100.5	97.1
22	193	4.0	0.069	10.0	4590	4711	0.267	3.865	88.4	95.6
23	257	12.0	0.061	11.4	6282	6496	0.226	3.709	103.5	114.3
24	138	6.0	0.067	10.3	2920	4044	0.271	4.037	110.8	110.0

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Supportive Table ST 8-6. Statistical Comparisons of Desvenlafaxine PK Parameters
 In Healthy Subjects Receiving a Single Dose of 100 mg of DVS-233 SR
 Protocol B600D3-190-US

13:42 Monday, September 29, 2003

Factor	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	T 1/2 (h)	AUC ₀₋₂₄ (ng*h/mL)	AUC (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
seq	0.868	0.286	0.188	0.186	0.091	0.072	0.168	0.413
sub(seq)	0.073	0.141	0.004	0.004	0.002	0.001	<0.001	<0.001
period	0.567	0.091	0.194	0.184	0.098	0.056	0.066	0.436
trt	0.670	0.208	0.002	0.007	0.501	0.457	0.457	0.505
Statistical Power	95.3				68.5	72.9		
Ratio of Least Square Geometric Means (%) †	97.8				105.3	105.6		
90% Confidence Interval Around the Ratio †	88.6-106.7				92.5-120.0	93.3-119.7		

† The reference treatment is DVS-233 SR 1x100-mg tablets, and the test treatment is DVS-233 SR 2x50-mg tablets.

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Supportive Table ST 8-8. Descriptive Statistics of Nausea VAS Raw Scores and Pharmacodynamic Parameters
 In Healthy Subjects Receiving a Single Dose of 100 mg of DVS-233 SR
 Protocol 060003-190-US 13:43 Monday, September 29, 2003

Treatment	(Unit = mm)																			
	TIME AFTER ADMINISTRATION (HOURS)																			
	***** 0 *****				***** 0.5 *****				***** 1 *****				***** 2 *****				***** 4 *****			
N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	
DVS-233 SR 1x100-mg	24	0.0	0.0	.	24	0.0	0.0	.	24	1.7	6.0	362	24	2.6	7.1	271	24	2.8	6.9	242
DVS-233 SR 2x50-mg	24	0.0	0.0	.	24	0.0	0.0	.	24	0.1	0.4	359	24	10.0	20.2	202	24	6.4	19.9	235

Supportive Table ST 8-8. Descriptive Statistics of Nausea VAS Raw Scores and Pharmacodynamic Parameters
 In Healthy Subjects Receiving a Single Dose of 100 mg of DVS-233 SR
 Protocol 060003-190-US 13:43 Monday, September 29, 2003

Treatment	(Unit = mm)																			
	TIME AFTER ADMINISTRATION (HOURS)																			
	***** 6 *****				***** 8 *****				***** 10 *****				***** 12 *****				***** 24 *****			
N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	
DVS-233 SR 1x100-mg	24	0.2	0.8	400	24	1.4	6.7	480	24	0.0	0.0	.	24	1.4	6.9	490	24	0.1	0.6	490
DVS-233 SR 2x50-mg	24	5.1	14.5	285	24	3.7	10.5	284	24	3.1	7.8	252	24	1.3	4.3	342	24	0.0	0.0	.

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Supportive Table ST 8-8. Descriptive Statistics of Nausea VAS Raw Scores and Pharmacodynamic Parameters
 In Healthy Subjects Receiving a Single Dose of 100 mg of EVS-233 ER 13:43 Monday, September 29, 2003
 Protocol 060003-190-US

(Unit = mm)

Treatment	TIME AFTER ADMINISTRATION (HOURS)				***** 48 *****				***** 72 *****				***** ERAX *****				***** tERAX *****				***** AURC *****			
	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV	N	Mean	S.D.	%CV
DVS-233 ER 1x100-mg	24	0.0	0.0	.	24	0.0	0.0	.	24	9.8	10.7	108	8	4.4	3.5	79	24	26.2	15.1	587				
DVS-233 ER 2x50-mg	24	0.0	0.0	.	24	0.0	0.0	.	24	10.7	20.4	192	10	2.5	1.4	57	24	64.4	145.4	226				

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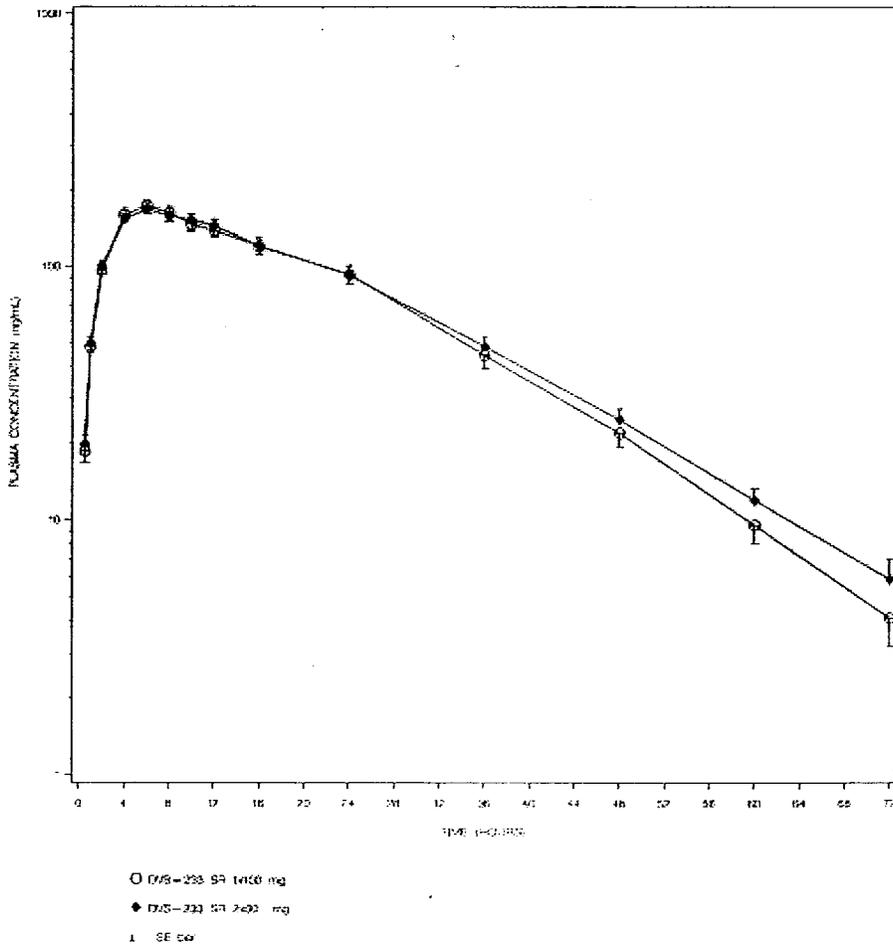
Supportive Table ST 9-9. Statistical Comparisons of Hauska VAS Raw Scores and Pharmacodynamic Parameters
 In Healthy Subjects Receiving a Single Dose of 100 mg of EVE-223 SR
 Protocol 060003-190-HS
 13:43 Monday, September 29, 2003

Factor	F-Values from Analysis of Variance for a Two-Period Cross-Over Design														
	0	0.5	1	2	4	6	8	10	12	24	48	72	Emax	tEmax	AURC
seq	.	.	0.335	0.242	0.266	0.574	0.675	0.839	0.279	0.328	.	.	0.430	0.299	0.680
sub(seq)	.	.	0.486	0.080	0.025	0.516	0.892	0.900	0.903	0.500	.	.	0.019	0.147	0.047
period	.	.	0.247	0.618	0.760	0.616	0.104	0.839	0.174	0.328	.	.	0.571	0.780	0.431
trt	.	.	0.222	0.059	0.111	0.121	0.291	0.070	0.984	0.328	.	.	0.189	0.093	0.177

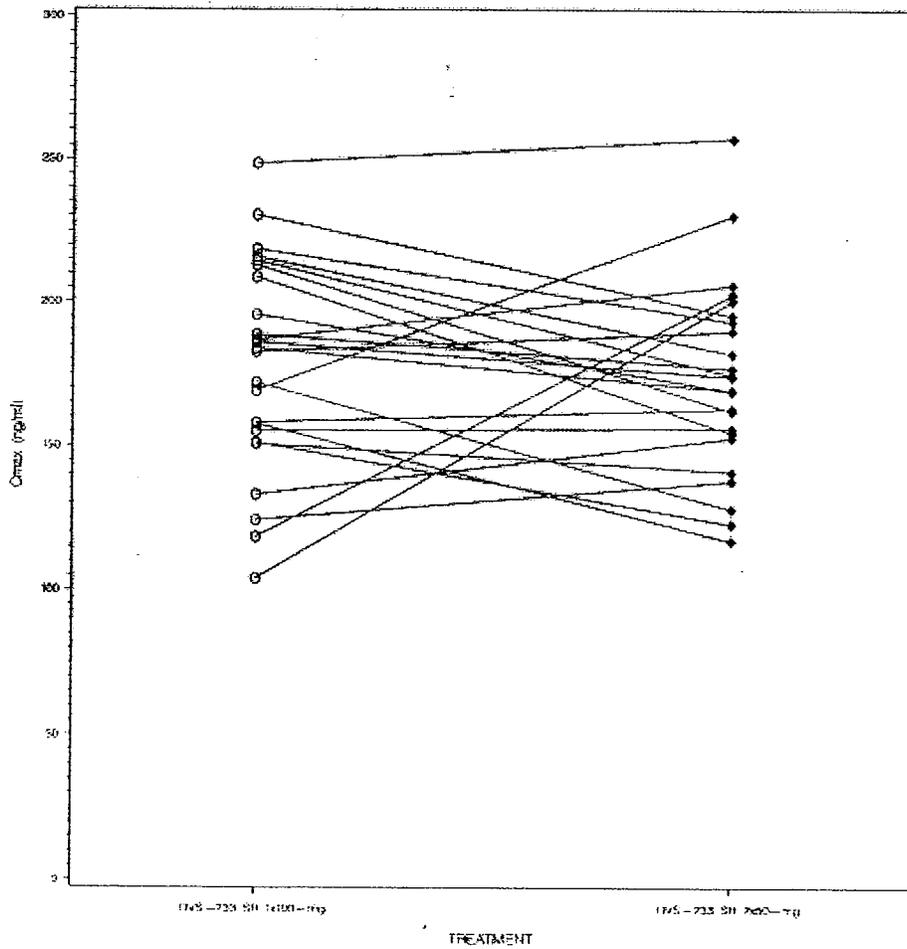
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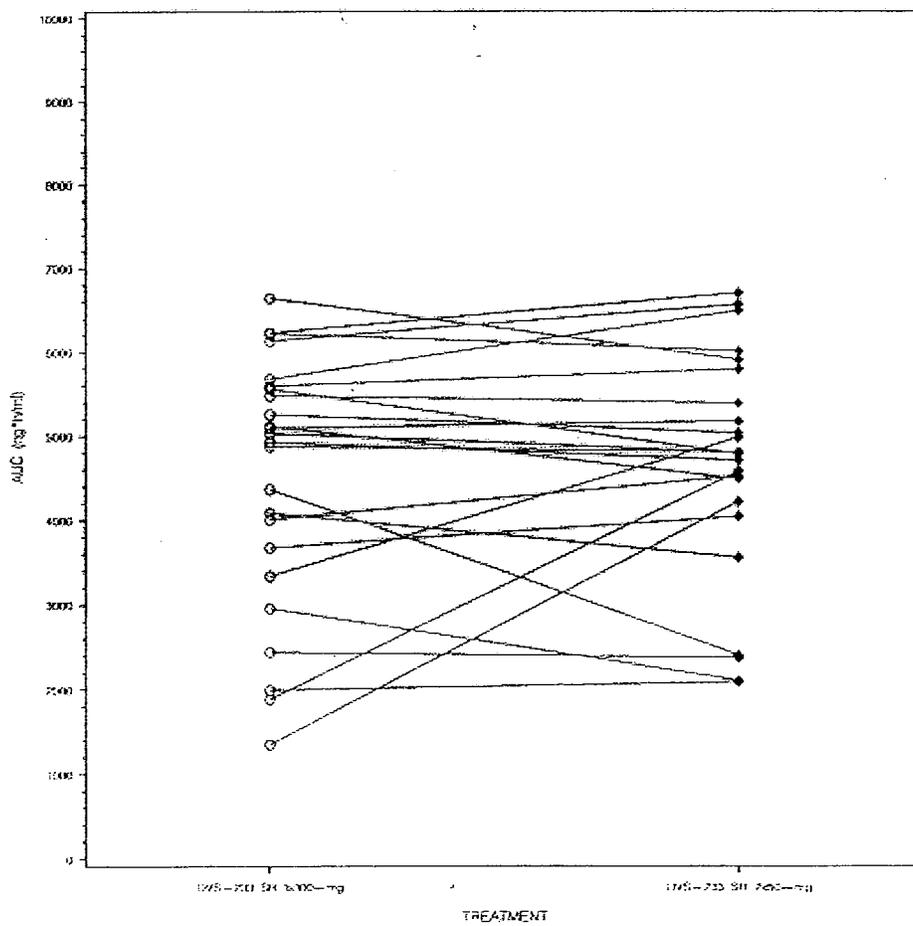
Supportive Figure SF 8-1: Mean Desvenlafaxine Plasma Concentrations In Subjects Receiving a Single Oral Dose of DVS 233 SR.



Supportive Figure SF 8-2: Comparing Desvenlafaxine C_{max} In Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR



Supportive Figure SF 8-3: Comparing Desvenlafaxine AUC in Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR



Study Title (Protocol 3151A1-194-EU, CSR-58755): An Open-Label, Nonrandomized, 2-Period, Sequential Study To Evaluate The Effect Of Multiple Doses Of Ketoconazole (A Cytochrome P450 3A4 Inhibitor) On The Pharmacokinetics Of A Single Dose Of DVS-233 SR Administered Orally To Healthy Subjects

Objectives: The primary objective of this study was to evaluate the potential inhibitory effect of ketoconazole (a CYP3A4 inhibitor) on the metabolism of DVS-233 SR in healthy young subjects. The secondary objective of this study was to assess the safety and tolerability of DVS-233 SR when co-administered with ketoconazole.

Study Design: This was an open-label, nonrandomized, 2-period, sequential, inpatient study performed in 15 healthy subjects between the ages of 18 to 45 years (mean \pm SD 32.9 ± 6.6 years; mean weight 75.01 ± 10.20 kg). On study day 1 of period 1, each subject received 400 mg (2 tablets each containing 200 mg) DVS SR approximately 10 minutes after a low-fat breakfast. Study period 2 included study days 5 through 12. After a washout period of 4 days subjects were administered 200 mg ketoconazole every 12 hours under fed conditions for 8 consecutive days (study days 5 to 12). On study day 9, the morning dose of 200 mg ketoconazole was coadministered with 400 mg of DVS SR approximately 10 minutes after a low-fat breakfast. In all instances, the test articles were administered with 240 mL of room-temperature water. A baseline ketoconazole blood sample was collected before ketoconazole administration on study day 5. All subjects were permitted to drink water except for 2 hours before until 2 hours after dose administration. Trough PK sample collections were performed in the morning of study days 7 and 8 before the ketoconazole administration. AE and concomitant-medication monitoring were continuous. A baseline PK blood sample (5 mL) was collected before DVS SR administration and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hours after test article administration on study days 1 and 9. Plasma was assayed for (R)- and (S)-enantiomers of desvenlafaxine. Racemic (R+S) desvenlafaxine concentrations and the R/S ratio were calculated. A baseline ketoconazole PK blood sample was collected on study day 5 before ketoconazole administration. Trough PK samples (5 mL) were collected before the morning test article administration on study days 7, 8, and 9. Urine PK samples were collected at the following time intervals: before and from 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 60, 60 to 72, and 72 to 96 hours after test article administration on study days 1 and 9. On study day 13, or at the time of early termination, a final clinical evaluation was performed. The formulation, strength and batch number(s) of the study drug are summarized in the following table.

Study Drug Information

Study Drug (xx mg)	Dosage (mg)	Batch Number	Formulation Number
DVS SR	200	A64103	0931964C
Ketoconazole	200	04IV012	NA

Abbreviations: NA=not applicable.

Analytical Method: The plasma samples were analyzed for (R)- and (S)-enantiomers of desvenlafaxine using a validated liquid chromatography mass spectroscopy method with mass spectroscopy detection (LC/MS/MS). Urine was assayed for the (R)- and (S)-enantiomers of desvenlafaxine (unconjugated) and (R)- and (S)-enantiomers of total (unconjugated plus conjugated) desvenlafaxine, as well as unconjugated and total NODV, using a validated LC/MS/MS method.

Plasma samples were assayed for ketoconazole concentrations by using a validated high performance liquid chromatography (HPLC) method with mass spectroscopy detection (LC/MS/MS). The minimum quantifiable concentration for ketoconazole was 20 ng/mL in plasma.

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

Assay Range and Sensitivity for Plasma Samples of Ketoconazole

Standard Curve	Compound/Matrix Ketoconazole
Linear range (ng/mL)	20-10,000
Sensitivity (ng/mL)	20

Analytical Summary of Plasma Ketoconazole Assays

QC Concentration (ng/mL)	Conc	Bias %
60.0	50.2	-16.3
5000	5080	1.60
7000	6750	-3.57

Abbreviations: Conc=concentration; QC=quality control.

The plasma samples were analyzed for (R)- and (S)-enantiomers of desvenlafaxine by a validated liquid chromatography mass spectroscopy method with mass spectroscopy detection (LC/MS/MS). The performance of the desvenlafaxine ®- and (S)-enantiomer assays during the analysis of the plasma samples from this study are provided in the following tables.

Assay Range and Sensitivity for Plasma Samples R- or S- Desvenlafaxine

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

Analytical Summary of Plasma Desvenlafaxine Enantiomer Assays

QC Concentration (ng/mL)	S-Desvenlafaxine			R-Desvenlafaxine		
	Conc.	CV%	Bias %	Conc	CV%	Bias %
3	2.93	2.8	-2.4	3.02	5.3	0.6
12	11.5	1.7	-4.3	11.7	4.2	-2.7
25	23.9	1.8	-4.3	24.6	2.2	-1.5
80	76.0	1.3	-5.0	78.4	1.5	-2.0
100	94.4	1.5	-5.6	95.9	1.2	-4.1
320	300	1.1	-6.2	306	1.4	-4.5

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

Urine was assayed for the (R)- and (S)-enantiomers of desvenlafaxine (unconjugated) and (R)-and (S)-enantiomers of total (unconjugated plus conjugated) desvenlafaxine, as well as unconjugated and total NODV, using a validated LC/MS/MS method. 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 for R- or S- Desvenlafaxine

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

Analytical Summary of Urine Desvenlafaxine Enantiomer Assays

QC Concentration (µg/mL)	S-Desvenlafaxine			R-Desvenlafaxine		
	Conc	CV%	Bias %	Conc	CV%	Bias %
0.072	0.076	4.6	6.0	0.081	2.4	13.0
0.288	0.315	2.9	9.4	0.305	2.8	5.9
3	3.15	3.1	5.1	3.30	3.1	10.0
6	6.43	7.6	7.2	6.58	3.2	9.6
12	12.5	2.5	4.2	12.3	2.8	2.6
24	24.5	3.6	2.1	24.8	7.4	3.2

Abbreviations: Conc=concentration; CV=coefficient of variation; 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 NODV

Standard Curve	Compound	
	Unconjugated NODV	Total NODV
Linear range ($\mu\text{g/mL}$)	0.04-20.0	0.04-20.0
Sensitivity ($\mu\text{g/mL}$)	0.040	0.040

Abbreviation: NODV=N,O-didesmethylvenlafaxine.

Analytical Summary of Urine NODV Assays

QC Concentration ($\mu\text{g/mL}$)	Unconjugated NODV			Total NODV		
	Conc	CV%	Accuracy %	Conc	CV%	Accuracy %
0.120	0.12110	3.06	100.83	0.1233	10.38	102.75
1.20	1.2960	3.81	108.00	1.2273	5.02	102.28
15.2	14.9389	2.89	98.28	14.9670	5.09	98.47

Abbreviations: Conc=concentration; CV=coefficient of variation; NODV=N,O-didesmethylvenlafaxine; 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 desvenlafaxine. A model-independent method of analysis was used to analyze the plasma concentrations of the (R)-, (S)-, and racemic (R+S)-enantiomers of desvenlafaxine.

Results: The mean plasma concentrations for (R)-, (S)- and (R+S)-enantiomers of desvenlafaxine for individual subjects are presented in the Attachments. Summary pharmacokinetic parameters of (R)-, (S)-, and (R+S)-enantiomers of desvenlafaxine after oral administration of DVS SR alone or with multiple doses of Ketoconazole are provided in the following tables. The means and 90% confidence intervals for C_{max} , AUC_{T} , and AUC are also provided.

Summary of Pharmacokinetic Parameters for (R) Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg to 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/h/kg)	V _Z /F (L/kg)	CL _R (L/h/kg)
DVS (N=14)	Mean±SD	388±78.3	6.87±2.70	10677±2182	10764±2190	10.30±1.15	0.261±0.051	3.84±0.63	0.128±0.038
	%CV	20.2%	39.2%	20.4%	20.3%	11.2%	19.4%	16.4%	29.7%
	Geo. mean	381	6.40	10478	10565	10.24	0.256	3.79	0.122
	Min-Max	278-550	4.00-12.00	7918-15541	7989-15639	8.28-11.89	0.176-0.350	2.78-5.04	0.054-0.180
DVS+Keto (N=13)	Mean±SD	423±82.7	9.22±5.72	15153±3127	15393±3259	13.83±1.65	0.185±0.037	3.65±0.68	0.098±0.019
	%CV	19.5%	62.0%	20.6%	21.2%	11.9%	20.1%	18.6%	19.2%
	Geo. mean	416	7.93	14889	15113	13.73	0.181	3.59	0.096
	Min-Max	301-552	4.00-23.92	11478-23577	11621-24202	11.06-16.59	0.114-0.241	2.41-5.27	0.064-0.133

Abbreviations: AUC=area under the concentration-versus-time curve; AUC_T=AUC from time of drug administration; C_{max}=peak concentration; Cl/F=apparent oral-dose clearance; CL_R=renal clearance; Geo=geometric; KETO=ketoconazole; max=maximum; min=minimum; SD=standard deviation; t_{1/2}=apparent terminal half-life; T_{max}=time to peak concentration; V_Z/F=apparent volume of distribution.

Summary of Pharmacokinetic Parameters for (S) Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg to 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/h/kg)	V _Z /F (L/kg)	CL _R (L/h/kg)
DVS (N=14)	Mean±SD	434±88.4	7.16±3.22	11092±2164	11192±2165	9.75±0.87	0.250±0.042	3.49±0.55	0.105±0.032
	%CV	20.4%	45%	19.5%	19.3%	8.9%	16.8%	15.8%	30.6%
	Geo. Mean	425	6.62	10897	10998	9.71	0.246	3.45	0.100
	Min-Max	284-574	4.00-16.03	7388-15939	7496-16013	8.45-11.37	0.172-0.318	2.64-4.55	0.043-0.151
DVS+KETO (N=13)	Mean±SD	465±105	7.70±4.15	15664±3169	15850±3243	13.22±1.30	0.178±0.030	3.38±0.55	0.086±0.017
	%CV	22.5%	53.9%	20.2%	20.5%	9.9%	16.8%	16.1%	19.1%
	Geo. Mean	454	6.86	15401	15579	13.16	0.176	3.34	0.085
	Min-Max	330-640	4.00-16.00	12008-24052	12160-24487	10.82-15.79	0.112-0.224	2.23-4.56	0.059-0.116

Abbreviations: AUC=area under the concentration-versus-time curve; AUC_T=AUC from time of drug administration; C_{max}=peak concentration; Cl/F=apparent oral-dose clearance; CL_R=renal clearance; Geo=geometric; KETO=ketoconazole; max=maximum; min=minimum; SD=standard deviation; t_{1/2}=apparent terminal half-life; T_{max}=time to peak concentration; V_Z/F=apparent volume of distribution.

Summary of Pharmacokinetic Parameters for (R+S) Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg to 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/h/kg)	V _Z /F (L/kg)	CL _R (L/h/kg)
DVS (N=14)	Mean±SD	819±161	7.30±3.31	21784±4310	21942±4321	9.79±0.98	0.255±0.045	3.59±0.63	0.117±0.035
	%CV	19.7%	45.3%	19.8%	19.7%	10.0%	17.8%	17.6%	30.0%
	Geo. mean	804	6.73	21398	21557	9.75	0.251	3.54	0.111
	Min-Max	562-1105	4.00-16.03	15568-31485	15607-31654	8.14-11.36	0.174-0.333	2.71-4.78	0.049-0.165
DVS+KETO (N=13)	Mean±SD	884±185	8.15±4.27	30820±6260	31245±6463	13.49±1.47	0.181±0.033	3.50±0.60	0.092±0.017
	%CV	21.0%	52.4%	20.3%	20.7%	10.9%	18.3%	17.1%	19.0%
	Geo. mean	865	8.65	30301	30702	13.42	0.178	3.45	0.090
	Min - Max	631 - 1192	4.00 - 16.00	23914 - 47640	24079 - 48697	10.94 - 16.2	0.113 - 0.229	2.32 - 4.85	0.061 - 0.124

Abbreviations: AUC=area under the concentration-versus-time curve; AUC_T=AUC from time of drug administration; C_{max}=peak concentration; Cl/F=apparent oral-dose clearance; CL_R=renal clearance; Geo=geometric; KETO=ketoconazole; max=maximum; min=minimum; SD=standard deviation; t_{1/2}=apparent terminal half-life; T_{max}=time to peak concentration; V_Z/F=apparent volume of distribution.

Statistical analysis of Pharmacokinetic Parameters for (R+S) Enantiomers of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg Alone and with Ketoconazole to Healthy Subjects

Parameter	p-Value	Variables	+ Ketoconazole
C _{max} (ng/mL)	0.112	Ratio of Means ^a 90% CI ^b	108 100-117
AUC _T (ng•h/mL)	<0.001	Ratio of Means ^a 90% CI ^b	142 137-148
AUC (ng•h/mL)	<0.001	Ratio of Means ^a 90% CI ^b	143 138-149

Abbreviations: AUC=area under the drug concentration-versus-time curve; AUC_T=AUC from the time of drug administration; C_{max}=peak concentration;

a. Ratio of geometric least square means with DVS SR alone as reference.

b. 90% confidence interval

AUC_T and AUC of (R+S)-enantiomers of desvenlafaxine were significantly higher in subjects receiving DVS SR with multiple doses of ketoconazole than in subjects receiving DVS SR alone. Trends for C_{max}, Cl/F, t_{1/2}, and T_{max} for subjects receiving DVS SR with multiple doses of ketoconazole. After administration of a single oral dose of DVS SR with multiple oral doses of ketoconazole, an approximate 8% increase in mean C_{max} and a 43% increase in mean AUC of (R+S)- enantiomers of desvenlafaxine were observed relative to subjects receiving DVS SR alone.

Consistent with the change in AUC, the mean Cl/F was 29% lower for the treatment group receiving DVS SR with multiple doses of ketoconazole. The mean V_Z/F was similar in both groups however the mean t_{1/2} was approximately 38% longer in the group receiving DVS SR with multiple doses of ketoconazole than in subjects receiving DVS SR alone. The 90% confidence intervals for the ratios of the mean AUC_T and AUC in both treatment groups were outside the acceptable limits of 80% to 125%. The mean T_{max}

of (R+S)-enantiomers of desvenlafaxine was approximately 12% longer in subjects receiving DVS SR with multiple doses of ketoconazole than in those receiving DVS SR alone. Similar trends were observed for the pharmacokinetic parameters of (R)- and (S)-enantiomers of desvenlafaxine.

The following table provides summary of urinary excretion of unconjugated and total (R) and (S) enantiomers of desvenlafaxine and unconjugated and total NODV. The CL_R of (R+S)-enantiomers of desvenlafaxine accounted for approximately 46% of the Cl/F in healthy subjects.

Summary of Urinary Excretion of Unconjugated and Total (R)- and (S)-Enantiomers of Desvenlafaxine and Unconjugated and Total NODV After Single Oral Administration of DVS SR 400 mg to 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
DVS (N=14)	Mean±SD	24.7±6.8	21.1±5.9	1.02±0.59	32.1±7.4	31.0±7.3	3.83±1.43	63.41±19.63
	%CV	27%	28%	58%	23%	24%	37%	31%
DVS+KETO (N=13)	Mean±SD	26.4±4.1	24.1±3.6	0.62±0.29	34.7±4.3	33.4±4.7	2.63±0.84	70.80±9.32
	%CV	16%	15%	47%	12%	14%	32%	13%

Abbreviation: DVS=desvenlafaxine succinate; DVS SR=desvenlafaxine succinate sustained-release formulation; KETO=ketoconazole; NODV=N,O didesmethylvenlafaxine; SD=standard deviation

a. % Dose refers to the 400 mg of DVS SR, which is a combination of both R- and S-enantiomers.

The mean urinary recovery of unconjugated (R)- and (S)-enantiomers of desvenlafaxine in subjects receiving DVS SR alone was 24.7% and 21.1% of the 400-mg DVS SR dose, respectively. In these subjects, the mean total (unconjugated + conjugated) (R)- and (S)-enantiomers of desvenlafaxine recovery were 32.1% and 31.0% of the 400-mg dose of DVS SR, respectively.

There was a trend for urinary recoveries of unconjugated and total (unconjugated + conjugated) (R)- and (S)-enantiomers of desvenlafaxine to increase when DVS SR was administered with multiple doses of ketoconazole. There was a decrease in urinary recoveries of mean conjugated and total (unconjugated + conjugated) NODV in subjects receiving DVS SR with ketoconazole. The average combined urinary excretion of total R-, total S-desvenlafaxine and total NODV was 63.4% of the 400-mg DVS SR dose in the DVS SR treatment group and was 70.8% in the DVS SR/ketoconazole group.

The observed changes in the oral pharmacokinetics of desvenlafaxine indicate an increase in the oral bioavailability of desvenlafaxine during concomitant administration of DVS SR and ketoconazole. Increases in oral bioavailability typically result from either an increase in absorption of drug and/or decreased clearance. It is expected that the CYP3A4 mediated metabolism of desvenlafaxine to NODV would be inhibited in the presence of concentrations of ketoconazole. The decrease in the amount of drug excreted as

conjugated and unconjugated NODV (mean values decreasing from 3.83% to 2.63% of the oral-dose of desvenlafaxine) is consistent with decreases in the metabolism of desvenlafaxine to NODV.

Safety Summary: The sponsor reported that across all treatment periods the most frequent TEAE (ie those reported by > 25% of the subjects) occurred in the following body system categories: 15 (100%) subjects had nervous system TEAEs, 13 (86.7%) subjects had digestive-system TEAEs, 9 (60%) subjects had body-as a whole TEAEs, 9 (60%) subjects had special-senses TEAEs, 5 (33.3%) subjects reported respiratory TEAEs and 4 (26.7%) subjects reported cardiovascular TEAEs. In the category "body as a whole" the sponsor stated that headache was the most frequently reported event. Headache was reported by 6 (40%) subjects overall.

In conclusion, the sponsor indicated that increase in concentrations of desvenlafaxine occurred after concomitant administration of DVS SR with the CYP3A4 inhibitor ketoconazole. DVS SR 400 mg was safe and well tolerated when administered alone or in conjunction with ketoconazole 200 mg q12h.

Reviewer's comments: The reviewer agrees with the sponsor's conclusion that co-administration of DVS with ketoconazole significantly increased the exposure (AUC) to desvenlafaxine. This is consistent with the observation a minor pathway for the metabolism of desvenlafaxine is the CYP 3A4 pathway.

Attachment

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ST 8-14: Individual and Mean Pharmacokinetic Parameters of (R)-Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg Alone to Healthy Subjects

Subject	T _{max} (hr)	C _{max} (ng/mL)	AUC _T (ng.hr/mL)	AUC ₉₆ (ng.hr/mL)	AUC (ng.hr/mL)	t _{1/2} (hr)	Cl/F (L/hr/kg)	V _Z /F (L/kg)	CL _R (L/hr/kg)
1	6.00	297	8335	8436	8460	10.11	0.327	4.76	0.145
2	4.00	278	8127	8127	8171	11.81	0.255	4.34	0.123
3	10.00	550	12918	12918	12968	11.89	0.236	4.05	0.116
4	6.00	468	9184	9219	9225	8.28	0.309	3.69	0.174
6	6.00	410	11479	11600	11626	9.45	0.204	2.78	0.138
7	4.02	302	9665	9665	9717	11.12	0.253	4.06	0.146
8	12.00	475	15541	15541	15639	11.72	0.176	2.97	0.054
9	10.00	359	7918	7976	7989	9.98	0.350	5.04	0.093
10	6.00	415	11564	11651	11668	9.10	0.319	4.18	0.180
11	4.00	331	11089	11089	11126	10.23	0.243	3.58	0.180
12	4.00	366	8710	8781	8794	9.01	0.281	3.65	0.117
13	6.00	375	10714	10844	10878	10.41	0.218	3.28	0.071
14	8.00	350	12735	12735	12820	11.46	0.219	3.63	0.115
15	10.13	453	11494	11596	11620	9.65	0.265	3.69	0.148
N	14	14	14	14	14	14	14	14	14
Mean	6.87	388	10677	10727	10764	10.30	0.261	3.84	0.128
SD	2.70	78.3	2182	2171	2190	1.15	0.051	0.63	0.038
Min	4.00	278	7918	7976	7989	8.28	0.176	2.78	0.054
Median	6.00	371	10902	10966	11002	10.17	0.254	3.69	0.130
Max	12.00	550	15541	15541	15639	11.89	0.350	5.04	0.180
CV %	39.2	20.2	20.4	20.2	20.3	11.2	19.4	16.4	29.7
Geo Mean	6.40	381	10478	10530	10565	10.24	0.256	3.79	0.122

ST 8-15: Individual and Mean Pharmacokinetic Parameters of (R)-Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg With Multiple Oral Doses of Ketoconazole 200 mg Every 12 Hours to Healthy Subjects

Subject	T _{max} (hr)	C _{max} (ng/mL)	AUC _T (ng.hr/mL)	AUC ₉₆ (ng.hr/mL)	AUC (ng.hr/mL)	t _{1/2} (hr)	Cl/F (L/hr/kg)	V _Z /F (L/kg)	CL _R (L/hr/kg)
1	4.00	317	11654	11654	11738	11.06	0.235	3.75	0.106
2	4.00	325	12979	12979	13204	13.56	0.158	3.08	0.064
3	8.00	531	15405	15405	15655	15.20	0.196	4.29	0.113
4	8.00	452	14162	14162	14229	11.25	0.201	3.25	0.096
7	16.00	400	15388	15388	15786	16.59	0.156	3.73	0.103
8	23.92	493	23577	23577	24202	14.67	0.114	2.41	0.082
9	10.00	463	11478	11478	11621	15.18	0.241	5.27	0.116
10	6.00	552	16313	16313	16436	12.53	0.226	4.09	0.133
11	6.08	430	15896	15896	16186	14.38	0.167	3.46	0.096
12	4.00	301	12361	12361	12477	12.39	0.198	3.54	0.102
13	6.00	344	14911	14911	15154	14.39	0.157	3.25	0.073
14	11.92	410	17382	17382	17758	15.15	0.158	3.46	0.083
15	11.92	484	15480	15480	15665	13.39	0.197	3.80	0.102
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N	13	13	13	13	13	13	13	13	13
Mean	9.22	423	15153	15153	15393	13.83	0.185	3.65	0.098
SD	5.72	82.7	3127	3127	3259	1.65	0.037	0.68	0.019
Min	4.00	301	11478	11478	11621	11.06	0.114	2.41	0.064
Median	8.00	430	15388	15388	15655	14.38	0.196	3.54	0.102
Max	23.92	552	23577	23577	24202	16.59	0.241	5.27	0.133
CV %	62.0	19.5	20.6	20.6	21.2	11.9	20.1	18.6	19.2
Geo Mean	7.93	416	14889	14889	15113	13.73	0.181	3.59	0.096

ST 8-16: Individual and Mean Pharmacokinetic Parameters of (S)-Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg Alone to Healthy Subjects

Subject	T _{max} (hr)	C _{max} (ng/mL)	AUC _T (ng.hr/mL)	AUC ₉₆ (ng.hr/mL)	AUC (ng.hr/mL)	t _{1/2} (hr)	Cl/F (L/hr/kg)	V _Z /F (L/kg)	CL _R (L/hr/kg)
1	6.00	317	8933	9030	9050	9.12	0.305	4.02	0.123
2	4.00	284	7388	7473	7496	10.53	0.278	4.22	0.103
3	8.00	574	12497	12593	12616	9.92	0.243	3.47	0.090
4	6.00	550	10320	10364	10371	8.45	0.275	3.35	0.147
6	6.00	442	11578	11679	11700	9.05	0.203	2.64	0.115
7	4.02	321	9690	9690	9733	10.80	0.253	3.94	0.120
8	16.03	517	15939	15939	16013	11.37	0.172	2.82	0.043
9	10.00	426	8713	8774	8788	9.91	0.318	4.55	0.077
10	6.00	475	12411	12497	12515	9.00	0.297	3.86	0.151
11	6.00	388	11622	11757	11784	9.10	0.229	3.01	0.145
12	4.00	439	9774	9854	9869	8.96	0.250	3.23	0.095
13	6.00	440	11154	11273	11303	10.08	0.210	3.05	0.058
14	8.00	388	12779	12779	12843	10.75	0.219	3.40	0.093
15	10.13	515	12487	12581	12601	9.39	0.245	3.31	0.117
N	14	14	14	14	14	14	14	14	14
Mean	7.16	434	11092	11163	11192	9.75	0.250	3.49	0.105
SD	3.22	88.4	2164	2153	2165	0.87	0.042	0.55	0.032
Min	4.00	284	7388	7473	7496	8.45	0.172	2.64	0.043
Median	6.00	440	11366	11476	11502	9.65	0.247	3.38	0.109
Max	16.03	574	15939	15939	16013	11.37	0.318	4.55	0.151
CV %	45.0	20.4	19.5	19.3	19.3	8.9	16.8	15.8	30.6
Geo Mean	6.62	425	10897	10971	10998	9.71	0.246	3.45	0.100

ST 8-17: Individual and Mean Pharmacokinetic Parameters of (S)-Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg With Multiple Oral Doses of Ketoconazole 200 mg Every 12 Hours to Healthy Subjects

Subject	T _{max} (hr)	C _{max} (ng/mL)	AUC _T (ng.hr/mL)	AUC ₉₆ (ng.hr/mL)	AUC (ng.hr/mL)	t _{1/2} (hr)	Cl/F (L/hr/kg)	V _z /F (L/kg)	CL _R (L/hr/kg)
1	4.00	334	12260	12260	12340	10.82	0.224	3.50	0.096
2	4.00	332	12008	12008	12160	13.33	0.171	3.29	0.059
3	6.00	589	15643	15643	15810	13.95	0.194	3.90	0.099
4	8.00	515	15706	15706	15784	11.39	0.181	2.97	0.086
7	16.00	388	15031	15031	15350	15.79	0.160	3.65	0.096
8	16.00	548	24052	24052	24487	13.77	0.112	2.23	0.069
9	10.00	516	12666	12666	12804	14.47	0.218	4.56	0.102
10	6.00	640	17928	17928	18056	12.39	0.206	3.68	0.116
11	6.08	514	16135	16135	16336	13.28	0.165	3.17	0.081
12	4.00	330	13274	13274	13393	12.35	0.184	3.28	0.092
13	4.00	368	15133	15133	15343	13.82	0.155	3.08	0.066
14	8.00	451	17751	17751	17994	13.72	0.156	3.10	0.070
15	8.05	517	16047	16047	16199	12.73	0.190	3.49	0.091
N	13	13	13	13	13	13	13	13	13
Mean	7.70	465	15664	15664	15850	13.22	0.178	3.38	0.086
SD	4.15	105	3169	3169	3243	1.30	0.030	0.55	0.017
Min	4.00	330	12008	12008	12160	10.82	0.112	2.23	0.059
Median	6.08	514	15643	15643	15784	13.33	0.181	3.29	0.091
Max	16.00	640	24052	24052	24487	15.79	0.224	4.56	0.116
CV %	53.9	22.5	20.2	20.2	20.5	9.9	16.8	16.1	19.1
Geo Mean	6.86	454	15401	15401	15579	13.16	0.176	3.34	0.085

ST 8-18: Individual and Mean Pharmacokinetic Parameters of (R+S)-Enantiomers of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg Alone to Healthy Subjects

Subject	T _{max} (hr)	C _{max} (ng/mL)	AUC _T (ng.hr/mL)	AUC ₀₋₆ (ng.hr/mL)	AUC (ng.hr/mL)	t _{1/2} (hr)	Cl/F (L/hr/kg)	V _Z /F (L/kg)	CL _R (L/hr/kg)
1	6.00	614	17268	17475	17521	10.07	0.315	4.58	0.133
2	4.00	562	15568	15568	15607	10.36	0.267	3.99	0.114
3	10.00	1105	25478	25478	25519	9.74	0.240	3.37	0.103
4	6.00	1018	19504	19584	19597	8.37	0.291	3.52	0.160
6	6.00	852	23058	23279	23326	9.25	0.203	2.71	0.126
7	4.02	623	19355	19355	19450	10.97	0.253	4.00	0.133
8	16.03	974	31485	31485	31654	11.36	0.174	2.85	0.049
9	10.00	785	16631	16750	16777	9.94	0.333	4.78	0.085
10	6.00	890	23975	24149	24183	9.05	0.307	4.01	0.165
11	6.00	715	22796	22796	22826	8.14	0.237	2.78	0.162
12	4.00	805	18484	18635	18664	8.98	0.265	3.43	0.105
13	6.00	815	21870	22119	22183	10.24	0.214	3.16	0.064
14	8.00	738	25514	25514	25664	11.12	0.219	3.52	0.104
15	10.13	968	23982	24178	24222	9.52	0.254	3.49	0.132
N	14	14	14	14	14	14	14	14	14
Mean	7.30	819	21784	21883	21942	9.79	0.255	3.59	0.117
SD	3.31	161	4310	4292	4321	0.98	0.045	0.63	0.035
Min	4.00	562	15568	15568	15607	8.14	0.174	2.71	0.049
Median	6.00	810	22333	22457	22504	9.84	0.254	3.51	0.120
Max	16.03	1105	31485	31485	31654	11.36	0.333	4.78	0.165
CV %	45.3	19.7	19.8	19.6	19.7	10.0	17.8	17.6	30.0
Geo Mean	6.73	804	21398	21502	21557	9.75	0.251	3.54	0.111

ST 8-19: Individual and Mean Pharmacokinetic Parameters of (R+S)-Enantiomers of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg With Multiple Oral Doses of Ketoconazole 200 mg Every 12 Hours to Healthy Subjects

Subject	T _{max} (hr)	C _{max} (ng/mL)	AUC _T (ng.hr/mL)	AUC ₉₆ (ng.hr/mL)	AUC (ng.hr/mL)	t _{1/2} (hr)	Cl/F (L/hr/kg)	V _Z /F (L/kg)	CL _R (L/hr/kg)
1	4.00	651	23914	23914	24079	10.94	0.229	3.62	0.101
2	4.00	657	24989	24989	25354	13.05	0.164	3.09	0.061
3	8.00	1115	31048	31048	31464	14.60	0.195	4.10	0.106
4	8.00	967	29868	29868	30013	11.33	0.190	3.11	0.090
7	16.00	788	30420	30420	31135	16.20	0.158	3.69	0.099
8	16.00	1032	47640	47640	48697	14.26	0.113	2.32	0.076
9	10.00	979	24145	24145	24423	14.67	0.229	4.85	0.109
10	6.00	1192	34243	34243	34494	12.46	0.216	3.87	0.124
11	6.08	944	32036	32036	32526	13.86	0.166	3.32	0.088
12	4.00	631	25635	25635	25871	12.37	0.191	3.41	0.097
13	4.00	702	30045	30045	30497	14.11	0.156	3.17	0.070
14	8.00	850	35148	35148	35765	14.49	0.157	3.29	0.077
15	11.92	981	31528	31528	31865	13.07	0.193	3.65	0.096
N	13	13	13	13	13	13	13	13	13
Mean	8.15	884	30820	30820	31245	13.49	0.181	3.50	0.092
SD	4.27	185	6260	6260	6463	1.47	0.033	0.60	0.017
Min	4.00	631	23914	23914	24079	10.94	0.113	2.32	0.061
Median	8.00	944	30420	30420	31135	13.86	0.190	3.41	0.096
Max	16.00	1192	47640	47640	48697	16.20	0.229	4.85	0.124
CV %	52.4	21.0	20.3	20.3	20.7	10.9	18.3	17.1	19.0
Geo Mean	7.22	865	30301	30301	30702	13.42	0.178	3.45	0.090

SF 8-7: Individual and Mean Trough Plasma Concentrations of Ketoconazole After Multiple Oral Administrations of Ketoconazole 200 mg Every 12 Hours Alone (Days 7 and 8) or With Single Oral Administration of DVS SR 400 mg (Day 9) to Healthy Subjects

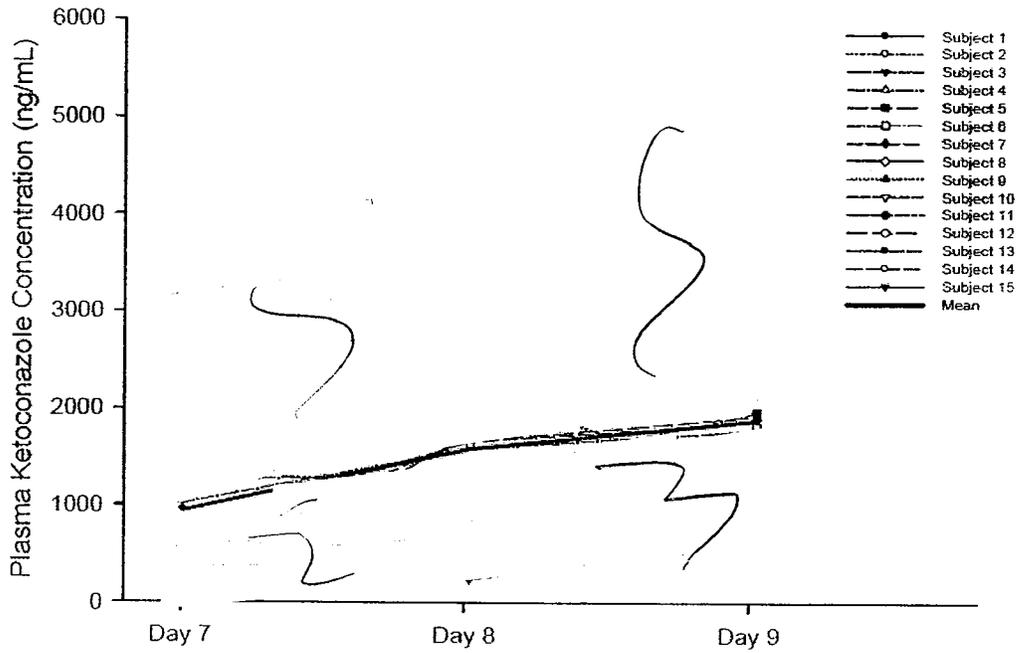


Figure 8.1-1: Mean Plasma Concentration-Time Profiles of (R)-Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg With and Without Multiple Oral Doses of Ketoconazole 200 mg Every 12 Hours to Healthy Subjects

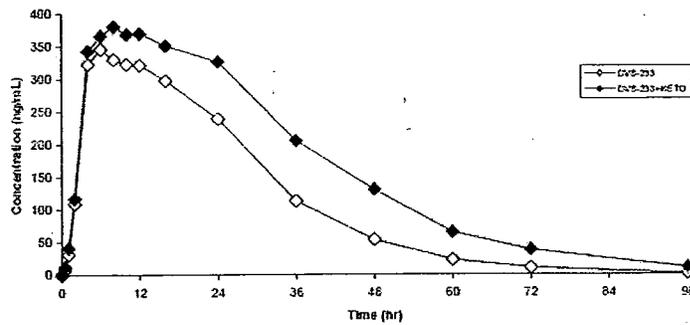
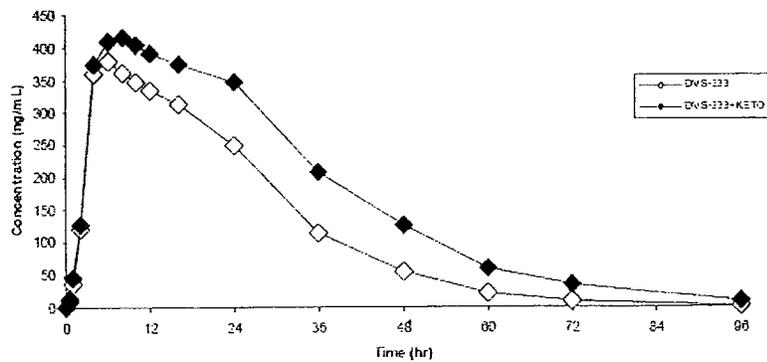
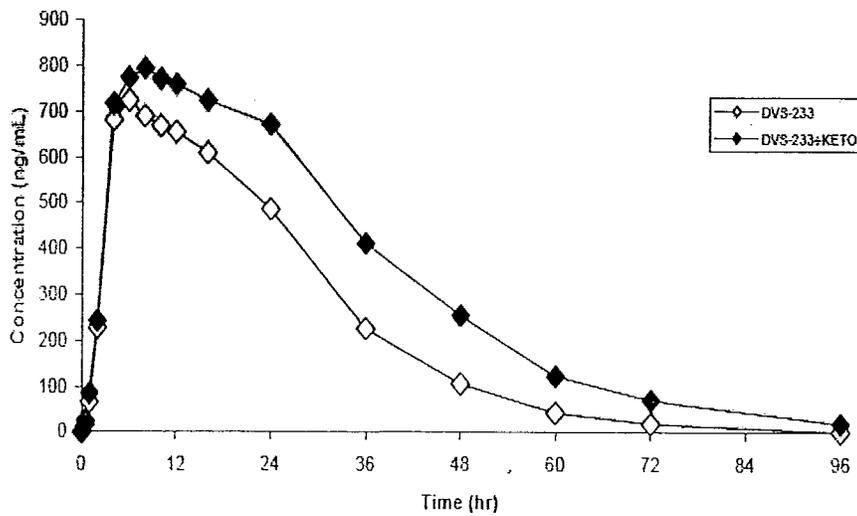


Figure 8.1-2: Mean Plasma Concentration-Time Profiles of (S)-Enantiomer of Desvenlafaxine After Single Oral Administration of DVS SR 400 mg With and Without Multiple Oral Doses of Ketoconazole 200 mg Every 12 Hours to Healthy Subjects

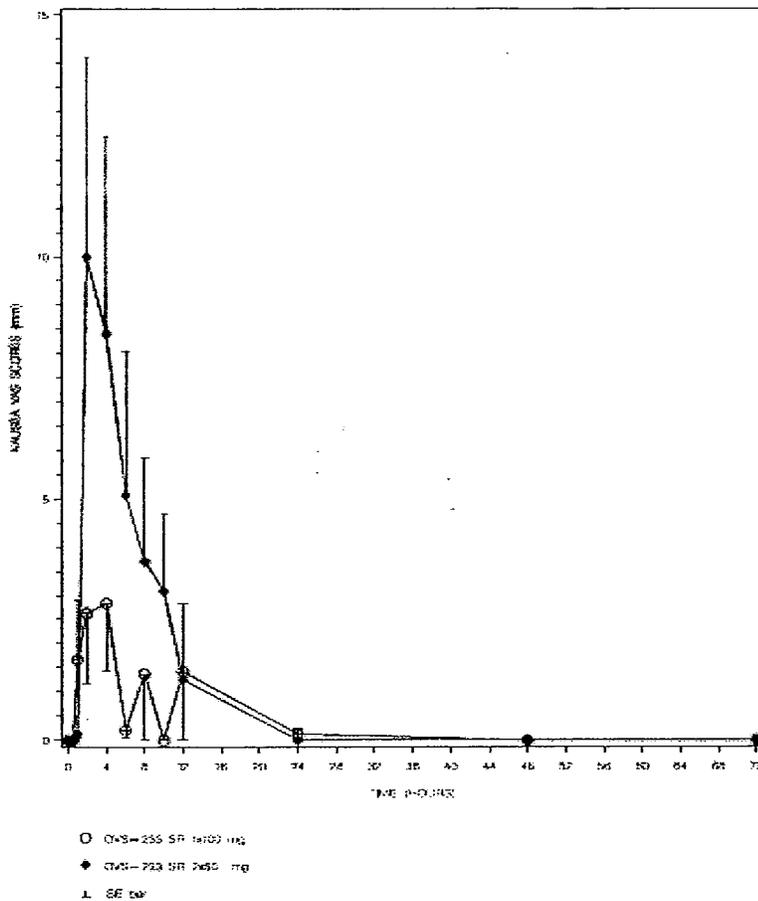


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Figure 8.1-3: Mean Plasma Concentration-Time Profiles of (R+S)-Enantiomers of Desvenlafaxine Following Single Oral Administration of DVS SR 400 mg With and Without Multiple Oral Doses of Ketoconazole 200 mg Every 12 Hours to Healthy Subjects



Supportive Figure SF 3-4: Mean Nausea VAS Scores in Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR



Study Title (Protocol No. 3151A1-195-US, CSR 58756): An Open-Label, 2-Period, Sequential Drug Interaction Study To Evaluate The Effect Of Multiple Doses Of DVS 233 SR On The Pharmacokinetics Of Midazolam (A Cyp3A4 Substrate) When Co-administered In Healthy Subjects.

Objective: 1) The primary objective was to evaluate the effect of DVS SR on the pharmacokinetics (PK) of midazolam (used as a CYP3A4 substrate) when DVS SR and midazolam were coadministered to healthy subjects. 2) The secondary objective was to assess the safety and tolerability of DVS SR and midazolam when coadministered to healthy subjects.

Study Design: This open-label, 2-period, sequential inpatient study was conducted at a single investigational site. The study consisted of 2 treatment periods: administration of midazolam alone for 1 day (period 1) and coadministration of DVS SR and midazolam after titration of DVS SR to steady state (period 2). DVS steady state was achieved after the administration of single daily doses of DVS SR over a period of up to 7 days. Healthy men and women aged 18 to 45 years were eligible for enrollment if all other qualifying criteria were met. DVS SR 100-mg tablets (Batch A43077) was given orally and titrated from 100 mg once daily on day 1 of period 2 up to 400 mg once daily by day 8 of period 2. Midazolam liquid was given orally in a single dose of 4 mg (2 mg/mL); midazolam is a marketed product. The medications were administered after an overnight fast of 10 hours. The administration of test article is provided in the following table. Blood samples (5 mL) were collected for determination of midazolam and 1'-hydroxymidazolam concentrations within 2 hours before test article administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hour after test article administration in period 1, day 1, and in period 2, day 8. Blood samples (5 mL) were collected before test article administration on study days 6, 7, and 8 in period 2 to confirm steady state for DVS SR plasma concentrations.

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Administration of Test Articles

Period	Dose	Dose Regimen
Day(s)		
Period 1		
Day 1	4 mg midazolam	2 mL midazolam liquid (2 mg/mL) administered (fasting) followed by PK assessment for 24 hours
Day 2	NA	NA
Period 2		
Day 1	100 mg DVS SR	1 x 100-mg DVS SR tablet (nonfasting)
Days 2-3	200 mg DVS SR	2 x 100-mg DVS SR tablet (nonfasting)
Days 4-7	400 mg DVS SR	4 x 100-mg DVS SR tablet (nonfasting)
Day 8	400 mg DVS SR and 4 mg midazolam	4 x 100-mg DVS SR tablet and 2 mL midazolam liquid (2 mg/mL) coadministered (fasting) followed by PK assessment for 24 hours
Days 9-10	200 mg DVS SR	2 x 100-mg DVS SR tablet (nonfasting)
Day 11	100 mg DVS SR	1 x 100-mg DVS SR tablet (nonfasting)
Day 12	NA	NA

Abbreviations: NA = not applicable; PK = pharmacokinetics.

Analytical Method: Desvenlafaxine was measured using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method with mass spectroscopy detection. The performance of desvenlafaxine assay during the analysis of the plasma samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Plasma Samples

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

Analytical Summary of Desvenlafaxine Assay

	High CS	Medium CS	Low CS
Nominal Conc	375.0 ng/mL	45.0 ng/mL	5.0 ng/mL
Mean	343.3	41.8	4.67
% CV	4.5	3.9	10.7
% Bias	8.4	7.0	6.6

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

The bioanalytical method for measuring midazolam and 1'-hydroxymidazolam in sodium heparin-treated plasma employed a single, validated LC/MS/MS procedure.

Assay Range and Sensitivity for Plasma Samples

Standard Curve	Compound/Matrix
	Midazolam and 1'-Hydroxymidazolam
Linear range (ng/mL)	0.1-100
Sensitivity (ng/mL)	0.1

Analytical Summary of Midazolam Assay

Nominal Conc	High CS 100 ng/mL	Medium CS 40 ng/mL	Low CS 0.1 ng/mL
Mean	98.9	39.4	0.0986
% CV	5.2	4.2	3.4
% Dev	-1.2	-1.5	-1.4

Abbreviations: Conc = concentration; CS = calibration standard; CV = coefficient of variation; Dev = deviation.

Data Analysis: A model-independent method of analysis was used to analyze the plasma concentrations of the midazolam and 1'-hydroxymidazolam.

Results: Twenty-four subjects completed the study and contributed data to the PK analysis. The subjects ranged in age from 23 years to 45 years (mean, 34.9 years). The following tables provide PK parameters and statistical results for midazolam PK parameters when given alone or with DVS SR.

After administration of a single oral 4-mg dose of midazolam with a 400-mg dose of DVS SR, an approximately 16% decrease in mean C_{max} and a 31% decrease in mean AUC of midazolam were observed when compared with the midazolam-alone treatment. The mean $T_{1/2}$ of midazolam was 12% shorter after midazolam was coadministered with DVS SR. The mean T_{max} value was also 18% shorter after midazolam was coadministered with DVS SR compared with the midazolam-alone treatment. The 90% confidence intervals for C_{max} and AUC were outside the generally acceptable limits of 80% to 125%.

Summary of Pharmacokinetic Parameters for Midazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects

Treatment	Variables	C _{max} (ng/mL)	t _{max} (h)	AUC _T (ng•h/mL)	AUC (ng•h/mL)	t _{1/2} (h)	Cl/F (L/h/kg)	V _Z /F (L/kg)
Midazolam Alone (n = 24)	Mean±SD	20.1±9.02	0.55±0.25	44.52±19.78	45.72±20.31	4.29±1.63	1.31±0.54	7.54±3.54
	%CV	45%	46%	44%	44%	38%	41%	47%
	Geo mean	18.3	0.50	40.78	41.90	3.96	1.21	6.89
	Min - max	7.37-48.4	0.25-1.00	20.50-103.8	21.12-106.6	1.48-7.31	0.49-2.30	3.92-16.7
Midazolam + DVS SR (N=24)	Mean±SD	16.5±6.24	0.45±0.16	30.62±12.81	31.41±13.03	3.79±1.75	1.89±0.76	9.36±4.85
	%CV	38%	35%	42%	41%	46%	40%	52%
	Geo Mean	15.4	0.43	28.17	28.95	3.39	1.75	8.53
	Min - max	6.32-29.2	0.25-1.00	14.20-58.72	14.94-59.76	1.54-6.82	0.73-3.31	4.55-28.4

Abbreviations: Geo = geometric; max = maximum; min = minimum.

Statistical Analysis of Pharmacokinetic Parameters for Midazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects

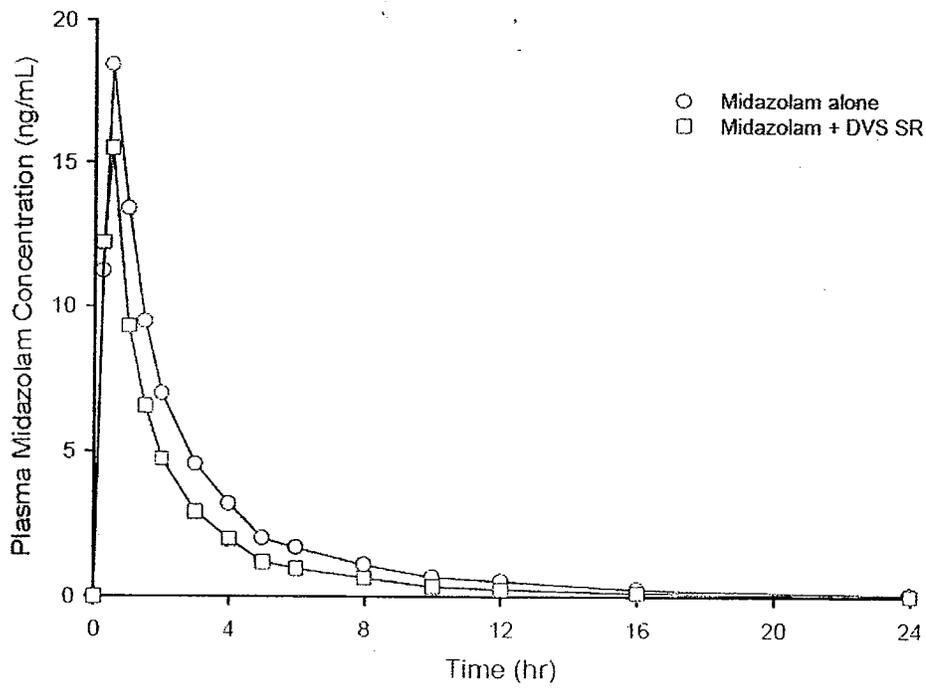
Parameter	Ratio of Means ^A
	90% CI
C _{max} (ng/mL)	83.86 72.27-97.32
AUC _T (ng•h/mL)	69.08 61.30-77.86
AUC (ng•h/mL)	69.08 61.34-77.79

Abbreviations: CI = confidence interval; C_{max} = peak concentration; AUC_T = area under the concentration-versus-time curve to the last observable concentration at time T; AUC = total area under the concentration-versus-time curve.

a. Ratio of geometric least square means with midazolam alone as reference.

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Mean Plasma Concentrations of Midazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects



The following table provides summary pharmacokinetic parameters of 1'-hydroxymidazolam in healthy subjects when midazolam was given alone or with DVS SR. The mean plasma concentrations of 1'-hydroxymidazolam when midazolam was given alone or with DVS SR are displayed in the following figure

Summary pharmacokinetic parameters of 1'-hydroxymidazolam in healthy subjects when midazolam was given alone or with DVS SR are provided in the following tables. The mean plasma concentrations of 1'-hydroxymidazolam when midazolam was given alone or with DVS SR are displayed in the following figure.

Treatment	Variables	C _{max} (ng/mL)	t _{max} (h)	AUC _T (ng·h/mL)	AUC (ng·h/mL)	t _{1/2} (h)
Midazolam Alone (N=24)	Mean±SD	9.73±4.32	0.58±0.23	18.94±6.39	19.99±6.42 ^a	4.72±2.15 ^a
	%CV	44%	39%	34%	32%	45%
	Geo Mean	8.86	0.55	17.90	19.02	4.27
	Min-Max	4.24-19.50	0.25-1.00	9.55-32.05	10.28-33.77	1.57-9.05
Midazolam + DVS SR (N=24)	Mean±SD	9.27±3.29	0.49±0.14	16.33±4.83	17.44±5.56 ^b	5.51±4.30 ^b
	%CV	35%	28%	30%	32%	78%
	Geo Mean	8.72	0.48	15.69	16.59	4.39
	Min-Max	4.65-16.7	0.25-1.00	9.54-27.69	10.01-26.23	1.88-15.43

a: N=22; b: N=15.

Abbreviations: AUC = total area under the concentration-versus-time curve; AUC_T = area under the concentration-versus-time curve to the last observable concentration at time T; CV = coefficient of variation; Geo = geometric; max = maximum; min = minimum.

Statistical Analysis of Pharmacokinetic Parameters for 1'-Hydroxymidazolam Following Single Oral Administration of DVS SR 400 mg to Healthy Subjects

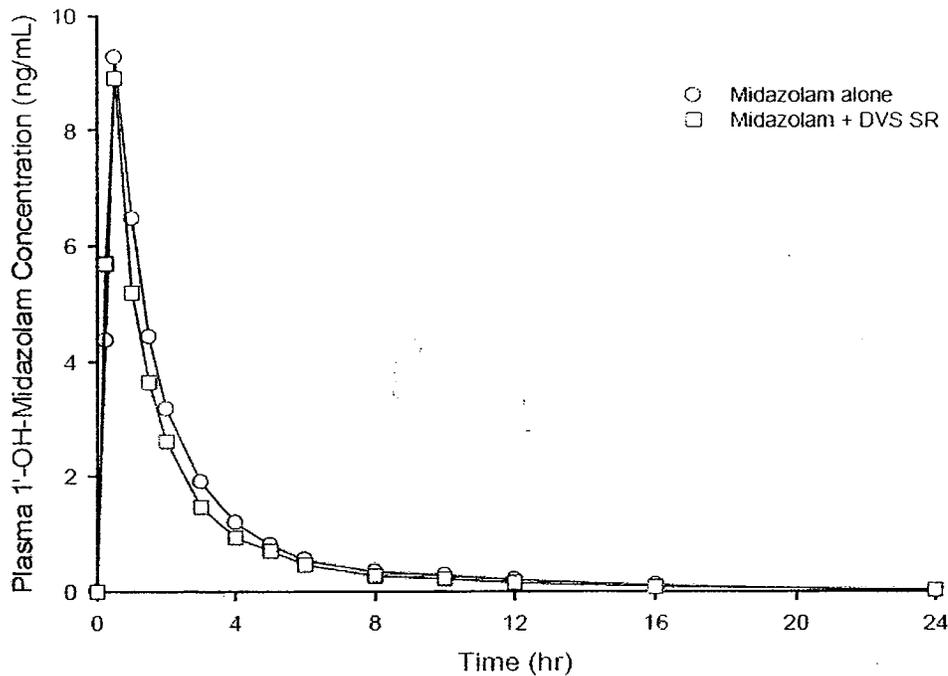
Parameter	Ratio of Means ^a 90% CI
C_{max} (ng/mL)	98.38 85.36-113.40
AUC_T (ng•h/mL)	87.66 81.29-94.53
AUC (ng•h/mL)	92.23 86.72-98.08

Abbreviations: AUC = total area under the concentration-versus-time curve; AUC_T = area under the concentration-versus-time curve to the last observable concentration at time T; CI = confidence interval.

a: Ratio of geometric least square means with midazolam alone as reference.

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Mean Plasma Concentrations of 1'-Hydroxymidazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects



After coadministration of a single oral 4-mg dose of midazolam with a 400-mg dose of DVS SR, an approximately 13% decrease in mean AUC of 1'-hydroxymidazolam was observed when compared with administration of midazolam alone. The mean C_{max} values of 1'-hydroxymidazolam were similar between the treatments with midazolam alone and midazolam coadministered with DVS SR. An approximately 17% longer mean $T_{1/2}$ value and a 16% shorter T_{max} value for 1'-hydroxymidazolam were observed after treatment with midazolam coadministered with DVS SR as compared with the midazolam-alone treatment. The 90% CIs for AUC and C_{max} were within the 80% to 125% range.

The following table provides summary plasma concentrations of desvenlafaxine after administration of multiple oral doses of DVS SR to healthy subjects. The predose mean plasma concentrations of desvenlafaxine were similar on days 7 and 8 suggesting that steady state of desvenlafaxine was achieved before concomitant administration of midazolam and DVS SR..

Summary of Predose Plasma Concentrations of Desvenlafaxine After Multiple Oral Administrations of DVS SR 400 mg Alone to Healthy Subjects

Day	Variables	Desvenlafaxine (ng/mL)
6	Mean ± SD	492.91 ± 131.83
	%CV	27%
7	Mean ± SD	525.67 ± 104.28
	%CV	20%
8	Mean ± SD	527.48 ± 124.87
	%CV	24%

Abbreviation: CV = coefficient of variation.

Safety Summary: The most frequent TEAEs occurred during period 2, study days 1 through 7, ie, the DVS SR titration period. Headache, constipation, and asthenia were each reported by 3 of 25 (12.0%) subjects. Diarrhea, dry mouth, nausea, dizziness, somnolence, and trismus each occurred in 2 of 25 (8.0%) subjects. All TEAEs were mild to moderate in severity except 1 occurrence of severe constipation. Subject 195-001-000016 had severe constipation, which was considered drug related by the investigator, during the DVS SR titration period. The constipation resolved after 45 hours without treatment. No subjects were discontinued for safety-related reasons, and no serious adverse events occurred. The sponsor reported that there were no clinically significant findings involving vital signs, clinical laboratory tests, or ECG data.

Summary: Desvenlafaxine elimination occurs primarily through glucuronidation and renal excretion of desvenlafaxine and the glucuronide conjugate of desvenlafaxine. CYP3A4 metabolism of desvenlafaxine to NODV is a minor elimination pathway (<5%). In vitro studies indicate that desvenlafaxine is a weak inhibitor of CYP2D6 activity but has no inhibitory effects on other cytochrome P450s (CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4) and does not induce CYP3A4 expression. The objective of this study was to determine the likelihood of interactions with CYP3A4 substrates using the pharmacokinetics of midazolam to assess and quantify any effect of desvenlafaxine on CYP3A4 metabolism in humans. The sponsor concluded that the results of the study indicate that a decrease in relative bioavailability of midazolam occurred after concomitant administration with DVS SR. And that there was no indication of inhibition of the metabolism of midazolam to 1'-hydroxymidazolam in the presence of desvenlafaxine.

Reviewer Comments: Decrease in midazolam AUC (about 31% decrease) and C_{max} (about 16% decrease) were observed when midazolam was co-administered with DVS. There was about 8 - 13% decrease in AUC in the primary metabolite (1'-hydroxymidazolam) but C_{max} was similar when midazolam was co-administered with

C_{max}. The exact mechanism of these changes in AUC and C_{max} observed is not clear from this study. DVS has not been reported to be an inducer of CYP3A4.

Study Title (Protocol No. 3151A1-195-US, CSR 58756): An Open-Label, 2-Period, Sequential Drug Interaction Study To Evaluate The Effect Of Multiple Doses Of DVS 233 SR On The Pharmacokinetics Of Midazolam (A Cyp3A4 Substrate) When Co-administered In Healthy Subjects

Objective: 1) The primary objective was to evaluate the effect of DVS SR on the pharmacokinetics (PK) of midazolam (used as a CYP3A4 substrate) when DVS SR and midazolam were coadministered to healthy subjects. 2) The secondary objective was to assess the safety and tolerability of DVS SR and midazolam when coadministered to healthy subjects.

Study Design: This open-label, 2-period, sequential inpatient study was conducted at a single investigational site. The study consisted of 2 treatment periods: administration of midazolam alone for 1 day (period 1) and coadministration of DVS SR and midazolam after titration of DVS SR to steady state (period 2). DVS steady state was achieved after the administration of single daily doses of DVS SR over a period of up to 7 days. Healthy men and women aged 18 to 45 years were eligible for enrollment if all other qualifying criteria were met. DVS SR 100-mg tablets (Batch A43077) was given orally and titrated from 100 mg once daily on day 1 of period 2 up to 400 mg once daily by day 8 of period 2. Midazolam liquid was given orally in a single dose of 4 mg (2 mg/mL); midazolam is a marketed product. The medications were administered after an overnight fast of 10 hours. The administration of test article is provided in the following table. Blood samples (5 mL) were collected for determination of midazolam and 1'-hydroxymidazolam concentrations within 2 hours before test article administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hour after test article administration in period 1, day 1, and in period 2, day 8. Blood samples (5 mL) were collected before test article administration on study days 6, 7, and 8 in period 2 to confirm steady state for DVS SR plasma concentrations.

Administration of Test Articles

Period	Dose	Dose Regimen
Day(s)		
Period 1		
Day 1	4 mg midazolam	2 mL midazolam liquid (2 mg/mL) administered (fasting) followed by PK assessment for 24 hours
Day 2	NA	NA
Period 2		
Day 1	100 mg DVS SR	1 x 100-mg DVS SR tablet (nonfasting)
Days 2-3	200 mg DVS SR	2 x 100-mg DVS SR tablet (nonfasting)
Days 4-7	400 mg DVS SR	4 x 100-mg DVS SR tablet (nonfasting)
Day 8	400 mg DVS SR and 4 mg midazolam	4 x 100-mg DVS SR tablet and 2 mL midazolam liquid (2 mg/mL) coadministered (fasting) followed by PK assessment for 24 hours
Days 9-10	200 mg DVS SR	2 x 100-mg DVS SR tablet (nonfasting)
Day 11	100 mg DVS SR	1 x 100-mg DVS SR tablet (nonfasting)
Day 12	NA	NA

Abbreviations: NA = not applicable; PK = pharmacokinetics.

Analytical Method: Desvenlafaxine was measured using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method with mass spectroscopy detection. The performance of desvenlafaxine assay during the analysis of the plasma samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Plasma Samples

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

Analytical Summary of Desvenlafaxine Assay

	High CS	Medium CS	Low CS
Nominal Conc	375.0 ng/mL	45.0 ng/mL	5.0 ng/mL
Mean	343.3	41.8	4.67
% CV	4.5	3.9	10.7
% Bias	8.4	7.0	6.6

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

The bioanalytical method for measuring midazolam and 1'-hydroxymidazolam in sodium heparin-treated plasma employed a single, validated LC/MS/MS procedure.

Assay Range and Sensitivity for Plasma Samples

Standard Curve	Compound/Matrix
	Midazolam and 1'-Hydroxymidazolam
Linear range (ng/mL)	0.1-100
Sensitivity (ng/mL)	0.1

Analytical Summary of Midazolam Assay

	High CS	Medium CS	Low CS
Nominal Conc	100 ng/mL	40 ng/mL	0.1 ng/mL
Mean	98.9	39.4	0.0986
% CV	5.2	4.2	3.4
% Dev	-1.2	-1.5	-1.4

Abbreviations: Conc = concentration; CS = calibration standard; CV = coefficient of variation; Dev = deviation.

Data Analysis: A model-independent method of analysis was used to analyze the plasma concentrations of the midazolam and 1'-hydroxymidazolam.

Results: Twenty-four subjects completed the study and contributed data to the PK analysis. The subjects ranged in age from 23 years to 45 years (mean, 34.9 years). The following tables provide PK parameters and statistical results for midazolam PK parameters when given alone or with DVS SR.

After administration of a single oral 4-mg dose of midazolam with a 400-mg dose of DVS SR, an approximately 16% decrease in mean C_{max} and a 31% decrease in mean AUC of midazolam were observed when compared with the midazolam-alone treatment. The mean $T_{1/2}$ of midazolam was 12% shorter after midazolam was coadministered with DVS SR. The mean T_{max} value was also 18% shorter after midazolam was coadministered with DVS SR compared with the midazolam-alone treatment. The 90% confidence intervals for C_{max} and AUC were outside the generally acceptable limits of 80% to 125%.

Summary of Pharmacokinetic Parameters for Midazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects

Treatment	Variables	C_{max} (ng/mL)	t_{max} (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)	$t_{1/2}$ (h)	Cl/F (L/h/kg)	V_z/F (L/kg)
Midazolam Alone (n = 24)	Mean±SD	20.1±9.02	0.55±0.25	44.52±19.78	45.72±20.31	4.29±1.63	1.31±0.54	7.54±3.54
	%CV	45%	46%	44%	44%	38%	41%	47%
	Geo mean	18.3	0.50	40.78	41.90	3.96	1.21	6.89
	Min - max	7.37-48.4	0.25-1.00	20.50-103.8	21.12-106.6	1.48-7.31	0.49-2.30	3.92-16.7
Midazolam + DVS SR (N=24)	Mean±SD	16.5±6.24	0.45±0.16	30.62±12.81	31.41±13.03	3.79±1.75	1.89±0.76	9.36±4.85
	%CV	38%	35%	42%	41%	46%	40%	52%
	Geo Mean	15.4	0.43	28.17	28.95	3.39	1.75	8.53
	Min - max	6.32-29.2	0.25-1.00	14.20-58.72	14.94-59.76	1.54-6.82	0.73-3.31	4.55-28.4

Abbreviations: Geo = geometric; max = maximum; min = minimum.

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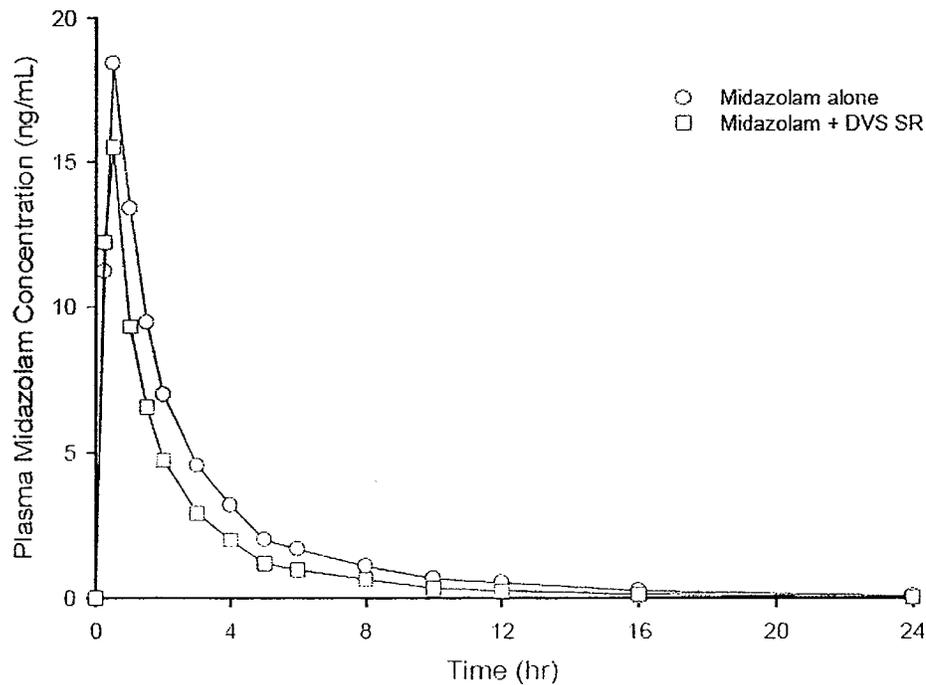
Statistical Analysis of Pharmacokinetic Parameters for Midazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects

Parameter	Ratio of Means ^A
	90% CI
C_{max} (ng/mL)	83.86 72.27-97.32
AUC_T (ng·h/mL)	69.08 61.30-77.86
AUC (ng·h/mL)	69.08 61.34-77.79

Abbreviations: CI = confidence interval; C_{max} = peak concentration; AUC_T = area under the concentration-versus-time curve to the last observable concentration at time T; AUC = total area under the concentration-versus-time curve.

a. Ratio of geometric least square means with midazolam alone as reference.

Mean Plasma Concentrations of Midazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects



The following table provides summary pharmacokinetic parameters of 1'-hydroxymidazolam in healthy subjects when midazolam was given alone or with DVS SR. The mean plasma concentrations of 1'-hydroxymidazolam when midazolam was given alone or with DVS SR are displayed in the following figure

Summary pharmacokinetic parameters of 1'-hydroxymidazolam in healthy subjects when midazolam was given alone or with DVS SR are provided in the following tables. The mean plasma concentrations of 1'-hydroxymidazolam when midazolam was given alone or with DVS SR are displayed in the following figure.

Treatment	Variables	C _{max} (ng/mL)	t _{max} (h)	AUC _T (ng•h/mL)	AUC (ng•h/mL)	t _{1/2} (h)
Midazolam Alone (N=24)	Mean±SD	9.73±4.32	0.58±0.23	18.94±6.39	19.99±6.42 ^a	4.72±2.15 ^a
	%CV	44%	39%	34%	32%	45%
	Geo Mean	8.86	0.55	17.90	19.02	4.27
	Min-Max	4.24-19.50	0.25-1.00	9.55-32.05	10.28-33.77	1.57-9.05
Midazolam + DVS SR (N=24)	Mean±SD	9.27±3.29	0.49±0.14	16.33±4.83	17.44±5.56 ^b	5.51±4.30 ^b
	%CV	35%	28%	30%	32%	78%
	Geo Mean	8.72	0.48	15.69	16.59	4.39
	Min-Max	4.65-16.7	0.25-1.00	9.54-27.69	10.01-26.23	1.88-15.43

a: N=22; b: N=15.

Abbreviations: AUC = total area under the concentration-versus-time curve; AUC_T = area under the concentration-versus-time curve to the last observable concentration at time T; CV = coefficient of variation; Geo = geometric; max = maximum; min = minimum.

Statistical Analysis of Pharmacokinetic Parameters for 1'-Hydroxymidazolam Following Single Oral Administration of DVS SR 400 mg to Healthy Subjects

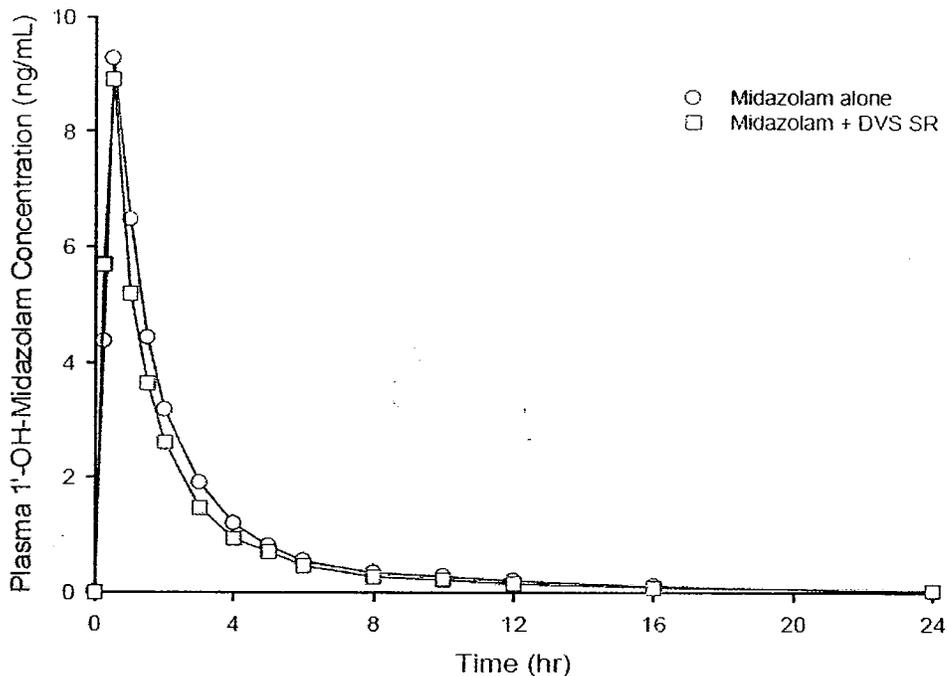
Parameter	Ratio of Means ^a 90% CI
C _{max} (ng/mL)	98.38 85.36-113.40
AUC _T (ng•h/mL)	87.66 81.29-94.53
AUC (ng•h/mL)	92.23 86.72-98.08

Abbreviations: AUC = total area under the concentration-versus-time curve; AUC_T = area under the concentration-versus-time curve to the last observable concentration at time T; CI = confidence interval.

a: Ratio of geometric least square means with midazolam alone as reference.

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Mean Plasma Concentrations of 1'-Hydroxymidazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects



After coadministration of a single oral 4-mg dose of midazolam with a 400-mg dose of DVS SR, an approximately 13% decrease in mean AUC of 1'-hydroxymidazolam was observed when compared with administration of midazolam alone. The mean C_{max} values of 1'-hydroxymidazolam were similar between the treatments with midazolam alone and midazolam coadministered with DVS SR. An approximately 17% longer mean $T_{1/2}$ value and a 16% shorter T_{max} value for 1'-hydroxymidazolam were observed after treatment with midazolam coadministered with DVS SR as compared with the midazolam-alone treatment. The 90% CIs for AUC and C_{max} were within the 80% to 125% range.

The following table provides summary plasma concentrations of desvenlafaxine after administration of multiple oral doses of DVS SR to healthy subjects. The predose mean plasma concentrations of desvenlafaxine were similar on days 7 and 8 suggesting that steady state of desvenlafaxine was achieved before concomitant administration of midazolam and DVS SR.

Summary of Predose Plasma Concentrations of Desvenlafaxine After Multiple Oral Administrations of DVS SR 400 mg Alone to Healthy Subjects

Day	Variables	Desvenlafaxine (ng/mL)
6	Mean ± SD	492.91 ± 131.83
	%CV	27%
7	Mean ± SD	525.67 ± 104.28
	%CV	20%
8	Mean ± SD	527.48 ± 124.87
	%CV	24%

Abbreviation: CV = coefficient of variation.

Safety Summary: The most frequent TEAEs occurred during period 2, study days 1 through 7, ie, the DVS SR titration period. Headache, constipation, and asthenia were each reported by 3 of 25 (12.0%) subjects. Diarrhea, dry mouth, nausea, dizziness, somnolence, and trismus each occurred in 2 of 25 (8.0%) subjects. All TEAEs were mild to moderate in severity except 1 occurrence of severe constipation. Subject 195-001-000016 had severe constipation, which was considered drug related by the investigator, during the DVS SR titration period. The constipation resolved after 45 hours without treatment. No subjects were discontinued for safety-related reasons, and no serious adverse events occurred. The sponsor reported that there were no clinically significant findings involving vital signs, clinical laboratory tests, or ECG data.

Summary: Desvenlafaxine elimination occurs primarily through glucuronidation and renal excretion of desvenlafaxine and the glucuronide conjugate of desvenlafaxine. CYP3A4 metabolism of desvenlafaxine to NODV is a minor elimination pathway (<5%). In vitro studies indicate that desvenlafaxine is a weak inhibitor of CYP2D6 activity but has no inhibitory effects on other cytochrome P450s (CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4) and does not induce CYP3A4 expression. The objective of this study was to determine the likelihood of interactions with CYP3A4 substrates using the pharmacokinetics of midazolam to assess and quantify any effect of desvenlafaxine on CYP3A4 metabolism in humans. The sponsor concluded that the results of the study indicate that a decrease in relative bioavailability of midazolam occurred after concomitant administration with DVS SR. And that there was no indication of inhibition of the metabolism of midazolam to 1'-hydroxymidazolam in the presence of desvenlafaxine.

Reviewer Comments: Decrease in midazolam AUC (about 31% decrease) and C_{max} (about 16% decrease) were observed when midazolam was co-administered with DVS. There was about 8 - 13% decrease in AUC in the primary metabolite (1'-

hydroxymidazolam) but C_{max} was similar when midazolam was co-administered with C_{max}. The exact mechanism of these changes in AUC and C_{max} observed is not clear from this study. DVS has not been reported to be an inducer of CYP3A4.

Title (3151A1-196-EU): Final Report: A Study Of The Potential Pharmacodynamic Interaction Between DVS SR And Ethanol In Healthy Subjects

Objectives: The primary objective was to assess the potential pharmacodynamic (PD) interaction on coadministration of DVS SR and ethanol in healthy subjects. The secondary objective was to assess the safety and tolerability of DVS SR when coadministered with ethanol.

Study Design: This study included 2 sequential, nonrandomized treatment periods. Men or nonlactating and nonpregnant women aged 18 to 45 years, inclusive, on study day were enrolled. Subjects received DVS SR placebo in period 1 and DVS SR in period 2. Before the start of period 2, DVS SR was titrated up from a 100-mg daily dose to 400 mg at steady state. DVS SR and DVS SR placebo in both treatment periods were administered under single-blind conditions. In periods 1 and 2, subjects were randomly assigned to receive both ethanol 0.5 g/kg and an ethanol placebo, on consecutive days, under double-blind conditions. This design generates a 4-way crossover in which each subject receives all 4 possible treatment combinations:

Period 1:

DVS SR placebo + 0.5 g/kg ethanol

DVS SR placebo + ethanol placebo

Period 2:

DVS SR 400 mg steady state + 0.5 g/kg ethanol

DVS SR 400 mg steady state + ethanol placebo

On study day 14, or at the time of early withdrawal, a final clinical evaluation was performed. This included a physical examination, supine and orthostatic vital sign measurements (blood pressure and pulse rate), laboratory evaluations, a 12-lead ECG, and a serum pregnancy test (for WOCBP only). The formulation, strength, and batch number(s) of the study drug are summarized in the following tables.

Study Drug Formulation

Study Drug	Dosage (mg)	Batch Number	Formulation Number	Manufacturing Location
DVS SR placebo	tablet	2003B0249	0931803C	Montreal
DVS SR	100-mg tablet	A66484	0931989C	Montreal

The ethanol placebo was prepared with 2.5 g ethanol (vodka 40%) poured on top of (floated on) 300 mL of orange juice. The sponsor stated the amount was intended to disguise the fact that the subject was administered the placebo by producing the smell and the taste of alcohol.

In period 1, under single-blind conditions, subjects were given DVS SR placebo on study days 1 and 2. Six (6) hours after each DVS SR placebo administration, subjects received either ethanol or ethanol placebo under double-blind conditions according to a randomization schedule. On study day 3, under single-blind conditions, all subjects were given DVS SR. Daily doses of DVS SR were titrated from 100 mg, on study day 3, to 400 mg, at steady state on day 8. Steady state was maintained for the next 2 days (study days 9 and 10). Six (6) hours after DVS SR administration on study days 9 and 10, subjects received either ethanol or ethanol placebo under double-blind conditions according to a randomization schedule. DVS SR placebo (period 1) or DVS SR (titration phase and period 2) was administered with 240 mL of room-temperature water, approximately 10 minutes after a low-fat breakfast.

Ethanol or ethanol placebo administration occurred approximately 6 hours after DVS SR or DVS SR placebo administration. The dose of ethanol (vodka 40%) administered was adjusted for each subject's body weight (0.5 g/kg). Ethanol placebo consisted of 2.5 g of ethanol floated on 300 mL of orange juice. Both ethanol and ethanol placebo were consumed within a 15-minute period. The lag time between DVS SR and ethanol administrations allowed their respective maxima to be reached simultaneously (DVS SR time at which peak concentration occurs [T_{max}] = approximately 7 hours; ethanol T_{max} = approximately 1 hour). A tapering period of DVS SR began on day 11 and continued until day 13. The final study evaluation visit was performed on study day 14. The treatment schedule is as follows

Period 1:

Day 1: DVS SR placebo (1 tablet)

Day 1, +6 hours: Ethanol placebo or ethanol (0.5 g/kg)

Day 2: DVS SR placebo (1 tablet)

Day 2, +6 hours: Ethanol placebo or ethanol (0.5 g/kg)

Titration Phase:

Day 3: 100 mg of DVS SR (1 × 100-mg tablet)

Day 4: 200 mg of DVS SR (2 × 100-mg tablet)

Day 5: 200 mg of DVS SR (2 × 100-mg tablet)

Day 6: 400 mg of DVS SR (4 × 100-mg tablet)

Day 7: 400 mg of DVS SR (4 × 100-mg tablet)

Day 8: 400 mg of DVS SR (4 × 100-mg tablet)

Period 2:

Day 9: 400 mg of DVS SR (4 × 100-mg tablet)

Day 9, +6 hours: Ethanol placebo or ethanol (0.5 g/kg)

Day 10: 400 mg of DVS SR (4 × 100-mg tablet)

Day 10, +6 hours: Ethanol placebo or ethanol (0.5 g/kg)

Tapering Phase:

Day 11: 200 mg of DVS SR (2 × 100-mg tablet)

Day 12: 200 mg of DVS SR (2 × 100-mg tablet)

Day 13: 100 mg of DVS SR (1 × 100-mg tablet)

A PK blood sample (5 mL blood) for desvenlafaxine analysis was collected before test article administration on study day 3, and desvenlafaxine trough samples (5 mL) were collected before test article administration on study days 7, 8, 9, and 10 to confirm steady-state conditions. Blood alcohol concentration (BAC) was estimated from breath alcohol concentration. BAC was measured on study day -1 at the start of the

inpatient phase and before the cognitive drug research (CDR) assessment training session. Baseline measurements were taken before ethanol or ethanol placebo administration on study days 1, 2, 9, and 10. BAC was measured before and after the CDR battery performed 1 and 3 hours after ethanol or ethanol placebo administration on study days 1, 2, 9, and 10.

Analytical Method: Desvenlafaxine plasma samples were assayed by using a validated liquid chromatography/mass spectroscopy method with mass spectroscopy detection (LC/MS/MS). The minimum quantifiable concentration for desvenlafaxine was 2 ng/mL in plasma. The performance of the desvenlafaxine assays in this study is summarized in the following tables.

Assay Range and Sensitivity

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

Analytical Summary of Desvenlafaxine Assay

Analyte	High QC (375.0 ng/mL)			Medium QC (45.0 ng/mL)			Low QC (5.0 ng/mL)		
	Conc	CV%	Bias %	Conc	CV%	Bias %	Conc	CV%	Bias %
Desvenlafaxine	330.1	3.7	-12.0	39.55	5.5	-12.1	4.53	5.8	-9.4

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

BACs were estimated from breath alcohol concentrations in expelled air, using an electronic measuring instrument. This machine converts the measured breath alcohol concentration into an equivalent BAC in g/L, which was recorded on the CRF.

Data Analysis: Pharmacodynamics was assessed by using the CDR computerized system for cognitive performance. The CDR battery included assessments of vigilance and psychomotor performance (simple reaction time, choice reaction time, digit vigilance, and visual tracking), memory (immediate and delayed word recall and numeric working memory), and subjective assessments of alertness, calmness, and contentment (Bond-Lader visual analog scales). The CDR battery took approximately 15 minutes to complete. Four (4) training sessions were held on study day -1 to familiarize the subjects with the performance tests and to minimize learning effects. The CDR battery baselines were assessed before any test article administration on study day 1. Additional pretreatment observations were performed just before ethanol or ethanol placebo administration (ie, approximately 6 hours after DVS SR or DVS SR placebo administration) on study days 1, 2, 9, and 10. The CDR battery was performed 1 and 3 hours after ethanol or ethanol placebo administration (ie, 7 and 9 hours after DVS SR or DVS SR placebo administration) on study days 1, 2, 9, and 10. Pharmacodynamic (PD) data were evaluated by using a repeated-measures analysis of variance (ANOVA) for postethanol observations. The preethanol observations were analyzed separately using ANOVA at each time point to assess any treatment differences. The main focus of the analysis was the potentiation of ethanol effects when given with DVS SR on the response time of the digit vigilance task at 1 hour after ethanol administration (approximate simultaneous maxima of DVS SR and ethanol). Linear contrasts were constructed to test the main ethanol effect, the main DVS SR effect, and the DVS SR × ethanol interaction effect (ie, potentiation) for all PD test

scores. Pairwise comparisons of the 4 treatments were performed to clarify any statistically significant interaction effects. The mean values of BAC measurements before and after CDR battery tests were used for descriptive statistics. Using predetermined criteria, individual data for vital signs, ECGs, and laboratory tests were evaluated for potential clinical importance (PCI). Safety results (vital signs, ECGs, and routine laboratory tests), as well as the PD test scores, were analyzed using summary statistics (eg, mean \pm standard deviation [SD]) for each of the 4 treatments.

The simple linear contrasts, shown below, were used to analyze the PD results in addition to a more complex linear contrasts specified below.

Simple Contrasts

- The main ethanol effect ([PBO+ETH] versus [PBO+PBO])
- The main DVS SR effect ([DVS+PBO] versus [(PBO+PBO)])
- DVS SR \times ethanol interaction effect (potentiation = [DVS+ETH] versus [PBO+ETH])

Complex Contrasts

- The main ethanol effect (ie, [DVS+ETH] + [PBO+ETH] versus [DVS+PBO] + [PBO+PBO])
- The main DVS SR effect (ie, [DVS+ETH] + [DVS+PBO] versus [PBO+PBO] + [PBO+ETH])
- DVS SR \times ethanol interaction effect (ie, potentiation = [DVS+ETH] + [PBO+PBO] versus [DVS+PBO] + [PBO+ETH])

where ETH = ethanol and PBO = placebo.

Safety assessment methods: Safety was evaluated from reported AEs, scheduled physical examinations, vital signs, 12-lead ECGs, and clinical laboratory test results.

Results: A total of 22 subjects were enrolled in the study. Nineteen (19) subjects completed the study and 3 subjects discontinued because of AEs. The demographics and baseline characteristics of the subjects are provided in the Attachment. The main goal of this study was to examine the potential PD interaction between desvenlafaxine and ethanol; therefore, plasma concentrations of desvenlafaxine were examined solely for the purpose of confirming exposure to desvenlafaxine and that plasma concentrations of desvenlafaxine had attained steady state.

A summary of the desvenlafaxine concentration values on days 3, 7, 8, 9, and 10 is presented in the following table. Day 3 plasma samples were undetectable for all subjects because only DVS SR placebo had been administered at this time. Desvenlafaxine concentrations obtained on study days 8 and 9 were similar, indicating that concentrations of desvenlafaxine had reached steady-state conditions by day 8.

Desvenlafaxine Concentrations					
	Day 3	Day 7	Day 8	Day 9	Day 10
Mean ± SD (ng/mL)	0.00 ± 0.00	456.9 ± 128.8	489.6 ± 127.0	485.6 ± 144.9	530.0 ± 149.4
%CV	0	28.2	25.9	29.8	28.2
Geo mean	-	442.16	475.1	465.9	511.7
Min - Max	0.00-0.00	299.7-776.2	308.4-781.0	306.9-741.1	343.4-902.4

Abbreviations: SD = standard deviation; CV = coefficient of variation; Geo = geometric. Max = maximum; Min = minimum.

The BAC values on study day -1 and before the CDR training session were zero for all subjects, indicating that the subjects were alcohol-free at this time. Baseline BAC measurements taken before ethanol or ethanol placebo administration on study days 1, 2, 9, and 10 were undetectable, as were the results after the ethanol placebo. A summary of BAC values is presented in the following table.

Mean Blood Alcohol Concentrations for Ethanol Treatment Periods

Treatment Period	Mean ± SD BAC ^a (g/L) at Time (Hour) After Ethanol Administration					
	1 Hour	1.25 Hours	1 Hour Average	3 Hours	3.25 Hours	3 Hours Average
DVS SR placebo + ethanol	0.38 ± 0.11	0.36 ± 0.09	0.37 ± 0.10	0.19 ± 0.08	0.15 ± 0.08	0.17 ± 0.08
DVS SR + ethanol	0.43 ± 0.13	0.41 ± 0.11	0.42 ± 0.12	0.21 ± 0.08	0.16 ± 0.08	0.18 ± 0.08

Abbreviations: BAC = blood alcohol concentration; DVS SR = desvenlafaxine, sustained-release.

a. Blood alcohol concentration was derived from breath alcohol concentration in expelled air.

The following table summarizes the statistically significant results for CDR task performance analyses after ethanol (ie, 1 and 3 hours after ethanol administration; 7 and 9 hours after DVS administration).

Summary of the Statistically Significant Results for CDR Task Performance Analyses After Ethanol Administration (1 and 3 Hours After Ethanol)

Analysis	Ethanol		DVS		Potentiation (Interaction)	
	Complex	Simple	Complex	Simple	Complex	Simple
Digit vigilance—speed	↓ 1 h	↓ 1 h	↓ 3 h	↓ 3 h	NS	NS
Digit vigilance—targets detected	↓ 3 h	↓ 3 h	↓ 1 h	NS	NS	↓ 1 h
Power of attention	NS	NS	↓ 1 h	NS	NS	NS
Continuity of attention	↓ 1 h	↓ 1 h	↓ 1 h	NS	NS	NS
Simple reaction time	↓ 3 h	NS	↓ 3 h	NS	NS	NS
Choice reaction time	NS	NS	NS	NS	NS	NS
Numeric working memory—SI	↓ 1 h	↓ 1 h	↓ 1 h	NS	NS	NS
Numeric working memory—speed	↓ 3 h	NS	↓ 3 h	NS	NS	↓ 3 h
Immediate recall	↓ 3 h	NS	NS	NS	NS	NS
Delayed recall	NS	NS	NS	NS	NS	NS
Tracking	↓ 1 h	↓ 1 h	↑ 3 h	↑ 3 h	NS	NS
Alertness	↓ 1 h	↓ 1 h	↑ 3 h	↑ 3 h	NS	NS
Contentment	NS	NS	NS	NS	NS	NS
Calmness	NS	NS	NS	NS	NS	NS

Abbreviations: ↓ = impairment; ↑ = improvement; CDR = cognitive drug research; DVS = desvenlafaxine, sustained-release; h = hour(s); NS = not statistically significant ($p > 0.05$); SI = sensitivity index.

↓ 1 h: impairment (increase of reaction time) of statistical significance ($p \leq 0.05$) detected 1 hour after ethanol administration (7 hours after DVS administration).

↓ 3 h: impairment (increase of reaction time) of statistical significance ($p \leq 0.05$) detected 3 hours after ethanol administration (9 hours after DVS administration).

↑ 3 h: improvement (shortening of reaction time) of statistical significance ($p \leq 0.05$) detected 3 hours after ethanol administration (9 hours after DVS administration).

Ethanol alone produced statistically significant impairments of performance in the following PD tests: digit vigilance speed, power of attention, simple reaction time, choice reaction time, immediate word recall, delayed word recall, and alertness in the subjective evaluation, indicating that ethanol was impairing attention and secondary memory.

No statistically significant decrement of the ethanol impairment in the presence of DVS 400 mg at steady state was detected for the digit vigilance speed test. This test was selected as the primary parameter to detect ethanol impairment and potentiation of impairment, because the sponsor stated it has been reported to be a sensitive and robust marker for monitoring ethanol effects.

Digit vigilance targets detected, showed a statistically significant impairment at peak ethanol and DVS concentrations (1 hour). The difference between the combined placebo conditions and the condition in which ethanol and active DVS were administered was 1.87%; this difference can be equated to an impairment in performance of 1 fewer target detected out of a total of 45 targets,

with 1 target being equivalent to 2.2%. This exceedingly small change does not support a clinically relevant potentiation of ethanol effects by DVS for this test. Percentage of correct targets detected in the digit vigilance test is an indication of sustained attention. Other tests, which measure sustained attention, eg, accuracy measures for the choice reaction time and the tracking test, as well as the composite score for continuity of attention, did not confirm this result. At 3 hours only, statistically significant potentiations of ethanol effects were reported for numeric working memory sensitivity index (SI) and self-rated alertness.

The overall trend in the PD tests suggests that the combination of DVS + ethanol gave, in general, a poorer performance than either DVS placebo + ethanol or DVS + ethanol placebo, although this trend was not statistically significantly different from DVS placebo + ethanol.

Safety Results: One or more treatment-emergent AEs (TEAEs) were reported by 21 (96%) subjects. Four (18%) subjects reported TEAEs after receiving DVS placebo, 19 (86%) subjects reported TEAEs after receiving DVS placebo + ethanol, 5 (24%) subjects reported TEAEs after receiving DVS placebo + ethanol placebo, 19 (91%) subjects reported TEAEs during the DVS titration period (100 to 400 mg), 1 (5%) subject reported TEAEs after receiving DVS 400 mg, 12 (63%) subjects reported TEAEs after receiving DVS 400 mg + ethanol, and no subject reported TEAEs either after receiving DVS 400 mg + ethanol placebo or during the DVS tapering period (200 mg to 100 mg). The most commonly reported TEAEs were dizziness, reported by 14 (64%) subjects, constipation, reported by 9 (41%) subjects, insomnia, reported by 9 (41%) subjects, yawning, reported by 7 (32%) subjects, and nausea, reported by 6 (27%) subjects. Of the 21 (96%) subjects who reported a TEAE, 2 (9%) subjects reported events that were considered not related to the test article and 19 (86%) subjects reported events that were considered by the investigator to be related to the test article. Five (23%) subjects reported TEAEs that were mild, 13 (59%) subjects reported TEAEs that were moderate, and 3 (14%) subjects reported TEAEs that were severe.

Summary: Desvenlafaxine elimination is primarily through glucuronidation and renal excretion of desvenlafaxine and the glucuronide conjugate of desvenlafaxine. CYP3A4 metabolism of desvenlafaxine to N,O-didesmethylvenlafaxine (NODV) is a minor elimination pathway (<5%). The major enzyme responsible for ethanol metabolism is alcohol dehydrogenase; to a lesser extent, cytochrome P450 2E1 is also involved. The current study was designed to examine the possibility for desvenlafaxine to potentiate the CNS effects of ethanol.

The statistical analysis of the PD tests did not provide support for any clinically relevant potentiation of ethanol impairments by DVS 400 mg at steady state at a BAC of approximately 0.4 g/L or below. Although potentiation of ethanol cannot be completely ruled out. DVS SR was safe and well tolerated when administered alone or in conjunction with ethanol.

Reviewer's comments: There appears to be no pharmacodynamic interaction between DVS and ethanol. Ethanol appears to potentiate the effect of DVS. However, the significance of this potentiation is not clear from this study.

Attachments

Digit Vigilance----- Targets Detected: Observed Change From DVS Placebo and Ethanol Placebo for Each Treatment (Mean \pm SD)

Treatment	Observed Values		Observed Change From DVS Placebo + ETH Placebo	
	1 Hour	3 Hours	1 Hour	3 Hours
DVS placebo + ETH placebo				
N	21	21		
Mean	97.46	97.35	-	-
Standard deviation	± 4.88	± 3.34		
DVS placebo + ETH				
N	21	22	20	21
Mean	98.1	97.37	0.56	-0.11
Standard deviation	± 2.36	± 4.15	± 5.34	± 4.07
DVS 400 mg + ETH placebo				
N	19	21	19	19
Mean	96.49	96.96	-0.94	-0.12
Standard deviation	± 4.15	± 3.25	± 6.12	± 3.27
DVS 400 mg + ETH				
N	19	19	19	19
Mean	95.56	95.79	-1.87	-1.29
Standard deviation	± 7.80	± 5.83	± 5.98	± 4.40

Abbreviations: DVS = desvenlafaxine, sustained-release; ETH = ethanol; SD = standard deviation.

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Digit Vigilance----- Targets Detected: Complex and Simple Comparisons
(With p-Values)

Digit Vigilance—Targets Detected	Complex			Simple		
	Main Ethanol Effect	Main DVS Effect	Potential (Interaction) Effect	Main Ethanol Effect	Main DVS Effect	Potential (Interaction) Effect
	1 hour	0.9551	0.0215*	0.5160	0.6636	0.2319
3 hours	0.5177	0.3124	0.7638	0.7981	0.6127	0.3499

Abbreviation: DVS = desvenlafaxine, sustained-release.

P-values for the linear contrasts from the primary analysis.

*Statistical significance at the p-value level < 0.05.

Power of Attention: Observed Change From DVS Placebo and Ethanol Placebo for Each Treatment (Mean ± SD)

Treatment	Observed Values		Observed Change From DVS Placebo + ETH Placebo	
	1 Hour	3 Hours	1 Hour	3 Hours
DVS placebo + ETH placebo				
N	21	21		
Mean	1089.48	1091.17	-	-
Standard deviation	±92.77	±75.01		
DVS placebo + ETH				
N	21	22	20	21
Mean	1148.08	1120.73	74.03	35.67
Standard deviation	±76.78	±90.26	±77.21	±59.65
DVS 400 mg + ETH placebo				
N	19	19	19	19
Mean	1123.59	1127.53	24.3	27.53
Standard deviation	±85.99	±94.71	±85.85	±82.15
DVS 400 mg + ETH				
N	19	19	19	19
Mean	1183.47	1161.206	84.18	61.21
Standard deviation	±102.22	±131.14	±102.9	±109.5

Abbreviations: DVS = desvenlafaxine, sustained-release; ETH = ethanol; SD = standard deviation.

Simple Reaction Time: Observed Change From DVS Placebo and Ethanol Placebo for Each Treatment

Treatment	Observed Values		Observed Change From DVS Placebo +ETH Placebo	
	1 Hour	3 Hours	1 Hour	3 Hours
DVS placebo + ETH placebo				
N	21	21		
Mean	253.89	259.32	-	-
Standard deviation	±27.78	±23.59		
DVS placebo + ETH				
N	21	22	20	21
Mean	269.14	261.02	18.03	2.69
Standard deviation	±23.99	±27.26	±16.07	±24.45
DVS 400 mg + ETH placebo				
N	19	19	19	19
Mean	266.02	270.38	9.65	9.88
Standard deviation	±41.60	±41.45	±40.42	±42.29
DVS 400 mg + ETH				
N	19	19	19	19
Mean	285.06	277.81	28.69	17.31
Standard deviation	±54.51	±58.97	±50.54	±52.10

Abbreviations: DVS = desvenlafaxine, sustained-release; ETH = ethanol; SD = standard deviation.
 Magnitude of change calculated in terms of the mean change by each subject between treatments; therefore, data from subject 19 are excluded.

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Digit Vigilance--- Speed: Complex Change from DVS Placebo and Ethanol Placebo for Each Treatment (Mean ± SD)

Treatment	Observed Values (milliseconds)		Observed Change From DVS Placebo +ETH Placebo (milliseconds)	
	1 Hour	3 Hours	1 Hour	3 Hours
DVS placebo + ETH placebo				
N	21	21		
Mean	411.55	407.50		
SD	±32.79	±36.05		
DVS placebo + ETH				
N	21	22	20 ^a	21
Mean	433.90	424.50	28.70	20.00
SD	±40.56	±38.50	±42.36	±26.04
DVS 400 mg + ETH placebo				
N	19	19	19	19
Mean	423.82	428.43	10.83	18.02
SD	±41.55	±41.26	±32.29	±25.70
DVS 400 mg + ETH				
N	19	19	19	19
Mean	444.59	436.82	31.59	26.42
SD	±37.77	±37.22	±35.22	±34.27

Abbreviations: DVS = desvenlafaxine, sustained-release; ETH = ethanol; SD = standard deviation.

a. Magnitude of change calculated in terms of the mean change by each subject between treatments; therefore, data from subject 19 are excluded.

Digit Vigilance----- Speed:Complex and Simple Comparisons

Digit Vigilance—Speed	Complex			Simple		
	Main Ethanol Effect	Main DVS Effect	Potential (Interaction) Effect	Main Ethanol Effect	Main DVS Effect	Potential (Interaction) Effect
1 hour	<0.0001*	0.2298	0.5998	0.0005*	0.2210	0.6249
3 hours	0.0092*	0.0158*	0.2540	0.0061*	0.0125*	0.3464

Abbreviation: DVS = desvenlafaxine, sustained-release.

Linear contrasts from the primary analysis. *p < 0.05.

Digit Vigilance----- Speed: Observed Change From DVS Placebo and Ethanol Placebo for Each Treatment (Mean \pm SD)

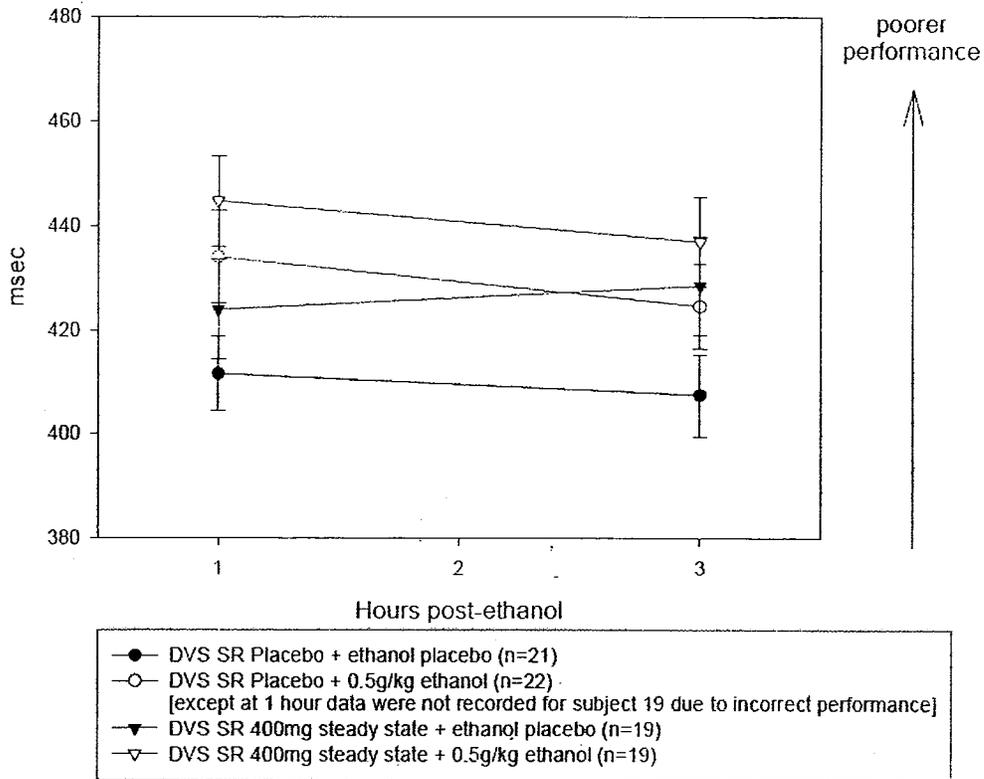
Treatment	Observed Values (milliseconds)		Observed Change From DVS Placebo +ETH Placebo (milliseconds)	
	1 Hour	3 Hours	1 Hour	3 Hours
DVS placebo + ETH placebo				
N	21	21		
Mean	411.55	407.50		
SD	± 32.79	± 36.05		
DVS placebo + ETH				
N	21	22	20 ^a	21
Mean	433.90	424.50	28.70	20.00
SD	± 40.56	± 38.50	± 42.36	± 26.04
DVS 400 mg + ETH placebo				
N	19	19	19	19
Mean	423.82	428.43	10.83	18.02
SD	± 41.55	± 41.26	± 32.29	± 25.70
DVS 400 mg + ETH				
N	19	19	19	19
Mean	444.59	436.82	31.59	26.42
SD	± 37.77	± 37.22	± 35.22	± 34.27

Abbreviations: DVS = desvenlafaxine, sustained-release; ETH = ethanol; SD = standard deviation.

a. Magnitude of change calculated in terms of the mean change by each subject between treatments; therefore, data from subject 19 are excluded.

**APPEARS THIS WAY
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Digit Vigilance--- Speed (Mean \pm SEM)



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Numeric Working Memory----- Sensitivity Index: Observed Change From DVS Placebo and Ethanol Placebo for Each Treatment (Mean \pm SD)

Treatment	Observed Values		Observed Change From DVS Placebo + ETH Placebo	
	1 Hour	3 Hours	1 Hour	3 Hours
DVS placebo + ETH placebo				
N	21	21		
Mean	0.088	0.092	-	-
Standard deviation	± 0.09	± 0.05		
DVS placebo + ETH				
N	22	21	21	21
Mean	0.87	0.91	-0.01	-0.01
Standard deviation	± 0.08	± 0.08	± 0.07	± 0.08
DVS 400 mg + ETH placebo				
N	19	19	19	19
Mean	0.91	0.92	0.2	-0.01
Standard deviation	± 0.07	± 0.05	± 0.08	± 0.04
DVS 400 mg + ETH				
N	19	19	19	19
Mean	0.9	0.85	0.01	-0.07
Standard deviation	± 0.07	± 0.14	± 0.09	± 0.15

Abbreviations: DVS = desvenlafaxine, sustained-release; ETH = ethanol; SD = standard deviation.

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Numeric Working Memory----- Sensitivity Index: Complex and Simple Comparisons (With p-values)

Numeric Working Memory—Sensitivity Index	Complex			Simple		
	Main Ethanol Effect	Main DVS Effect	Potentialion (Interaction) Effect	Main Ethanol Effect	Main DVS Effect	Potentialion (Interaction) Effect
	1 hour	0.3827	0.1597	0.8036	0.4082	0.4101
3 hours	0.0251*	0.0421*	0.0760	0.7258	0.8401	0.0075*

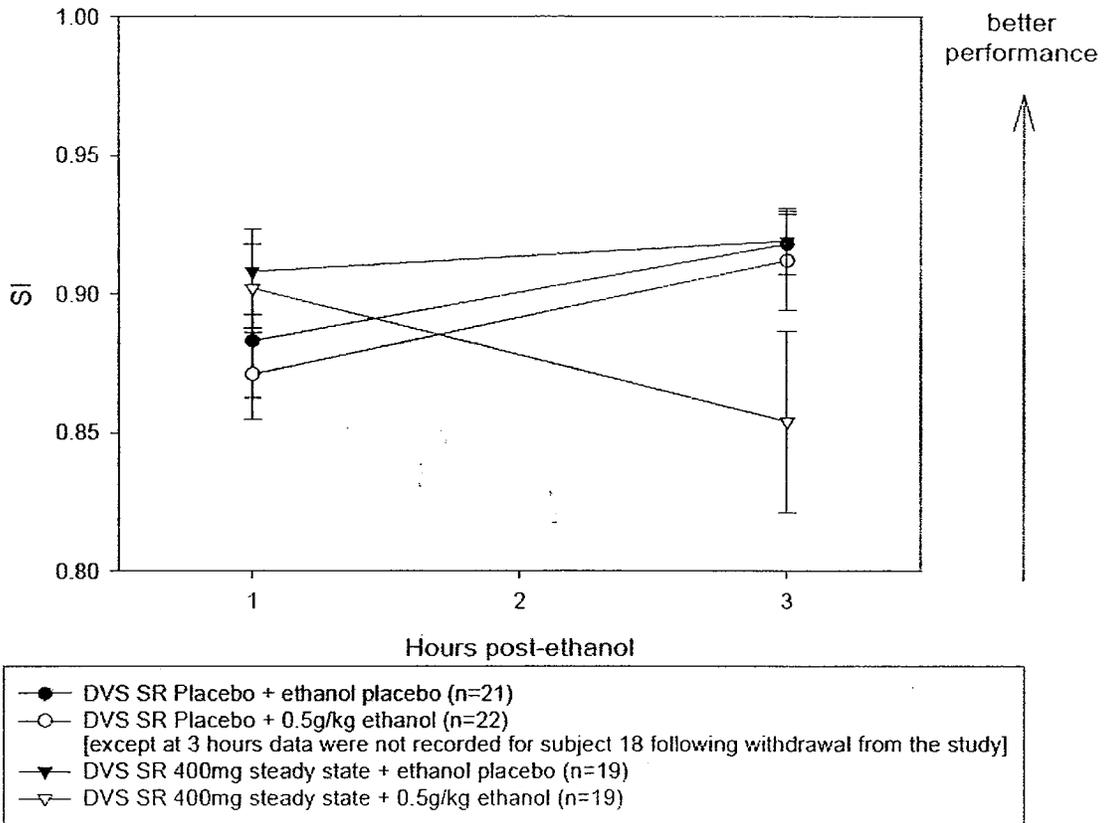
Abbreviation: DVS = desvenlafaxine, sustained-release.

P-values for the linear contrasts from the primary analysis.

*Statistical significance at the p-value level < 0.05.

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Numeric Working Memory---- Sensitivity Index (Mean \pm SEM)



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Desvenlafaxine Plasma Concentrations (ng/mL) on Days 3, 7, 8, 9 and 10

Subject	Day 3	Day 7	Day 8	Day 9	Day 10
1	BQL				
2	BQL				
3	BQL				
4	BQL				
5	BQL				
8	BQL				
9	BQL				
10	BQL				
11	BQL				
12	BQL				
13	BQL				
14	BQL				
16	BQL				
17	BQL				
19	BQL				
20	BQL				
21	BQL				
22	BQL				
23	BQL				
N	19	19	19	19	19
Mean	0.00	456.93	489.62	485.57	530.01
SD	NC	128.76	126.97	144.87	149.42
SE	NC	29.54	29.13	33.24	34.28
Min	NC	299.70	308.40	306.90	343.40
Median	NC	426.20	485.50	450.80	465.70
Max	NC	776.20	781.00	741.10	902.40
CV%	NC	28.2	25.9	29.8	28.2
Geometric Mean	NC	442.16	475.10	465.93	511.73

BQL: Below limit of quantification.
 NC: Not calculated.

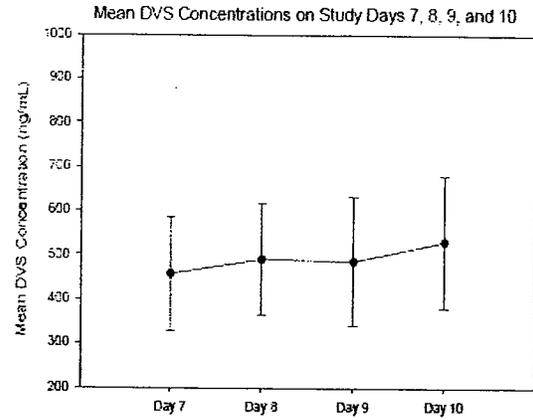
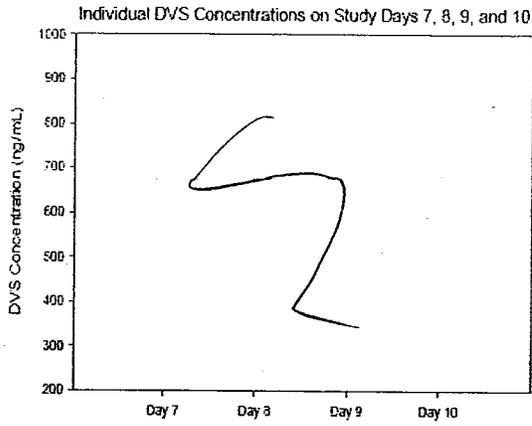
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Blood Alcohol Concentrations (g/l) in Healthy Subjects Receiving Ethanol after DVS SR or DVS SR Placebo

Subject	DVS_Placebo + Ethanol Time after Ethanol Administration						DVS + Ethanol Time after Ethanol Administration					
	1 hr	1.25 hr	1 hr Avg.	3 hr	3.25 hr	3 hr Avg.	1 hr	1.25 hr	1 hr Avg.	3 hr	3.25 hr	3 hr Avg.
1			0.29			0.16			0.23			0.15
2			0.31			0.13			0.32			0.15
3			0.53			0.20			0.32			0.10
4			0.40			0.19			0.33			0.18
5			0.65			0.27			0.62			0.28
6			0.36			0.13			0.33			0.13
9			0.41			0.24			0.57			0.21
10			0.41			0.31			0.51			0.34
11			0.39			0.22			0.38			0.23
12			0.31			0.10			0.38			0.08
13			0.33			0.16			0.47			0.24
14			0.40			0.20			0.36			0.19
16			0.32			0.15			0.46			0.26
17			0.30			0.15			0.34			0.16
19			0.33			0.05			0.38			0.00
20			0.37			0.13			0.33			0.13
21			0.20			0.00			0.57			0.23
22			0.45			0.23			0.51			0.23
23			0.37			0.24			0.63			0.26
N	19	19	19	19	19	19	19	19	19	19	19	19
Mean	0.38	0.38	0.37	0.19	0.15	0.17	0.43	0.41	0.42	0.21	0.16	0.18
SD	0.11	0.09	0.10	0.08	0.08	0.08	0.13	0.11	0.12	0.08	0.08	0.08
SE	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.03	0.02	0.02	0.02
Min	0.23	0.16	0.20	0.00	0.00	0.00	0.24	0.22	0.23	0.00	0.00	0.00
Median	0.38	0.34	0.37	0.19	0.14	0.16	0.40	0.36	0.38	0.21	0.16	0.19
Max	0.69	0.60	0.65	0.33	0.28	0.31	0.69	0.58	0.63	0.36	0.32	0.34
CV%	27.3	25.3	25.8	41.9	52.2	45.8	29.8	26.8	27.8	39.8	48.6	43.2

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Individual and Mean Desvenlafaxine Plasma Concentrations (ng/mL)



- | | | | |
|---|------------|---|------------|
| ● | Subject 1 | ● | Subject 13 |
| ○ | Subject 2 | ○ | Subject 14 |
| ▼ | Subject 3 | ● | Subject 16 |
| ▽ | Subject 4 | ○ | Subject 17 |
| ■ | Subject 5 | ▼ | Subject 19 |
| □ | Subject 8 | ▽ | Subject 20 |
| ◆ | Subject 9 | ■ | Subject 21 |
| ◇ | Subject 10 | □ | Subject 22 |
| ▲ | Subject 11 | ◆ | Subject 23 |
| △ | Subject 12 | | |

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Development of IVIVC for DVS SR

Background: The sponsor has developed a level A IVIVC for desvenlafaxine succinate monohydrate (DVS) sustained release (SR) tablets ranging in strength from 50 to 200 mg. The IVIVC was based upon a single release rate formulation with the assumption that the in vitro release was independent of all dissolution test conditions, most notably the pH of the dissolution media. However, in a discussion with the Agency in November 2003, it was noted that dissolution independent conditions were not demonstrated for the 200 mg dosage strength. The Agency recommended that the sponsor develop a 200 mg SR tablet with a faster in vitro release rate to determine its in vivo impact. Therefore, a separate IVIVC was developed for the 200 mg tablet. The sponsor states that the two level A IVIVCs encompass the range of tablet strengths proposed for the treatment of major depressive disorder and would allow the use of these SR tablets to serve as surrogates for the in vivo bioequivalence. The sponsor would like to use the IVIVC developed to assess the effects of further modifications; to justify changes in production equipment, materials, manufacturing site, etc and to set and justify appropriate dissolution specifications.

Two level A IVIVCs have been established, one each for the low and high strength SR tablets. For the low strength SR tablet (50 mg), which contains ~~_____~~ the in vitro release was independent of the dissolution conditions. Therefore, the level A IVIVC for this strength was based on a single release formulation. The high strength SR tablet (200 mg) contain ~~_____~~ and its dissolution was dependent on dissolution conditions. Therefore, Level A IVIVC for this strength was developed with two formulations exhibiting different in vitro release rates, controlled by varying the ~~_____~~ level.

DVS tablets have been manufactured in strengths of 50, 75, 100 and 200 mg. The major difference among the various strength SR tablets ~~_____~~ (Table 1).

Methods: DVS formulations tablets ~~_____~~ Hence, the sponsor developed two level A IVIVC, one each for the low and high strength SR tablets. For the low strength SR tablet (50 mg), which contains ~~_____~~, the in vitro release was independent of the dissolution conditions. Therefore, the level A IVIVC for this strength was based on a single release rate formulation. The high strength SR tablet (200 mg) contains ~~_____~~ and its dissolution was not independent of dissolution conditions. Therefore, the Level A IVIVC for the 200 mg strength was developed with two formulations exhibiting different in vitro release rates, ~~_____~~. The detailed procedure that was used in the development of the IVIVC is provided in Attachment A.

The dissolution method developed for DVS uses USP Apparatus 1 (basket) at 100 rpm in 0.9% NaCl at 37°C. Dissolution testing was done on 50, 75, 100 and 200 mg DVS tablets. Additional dissolution testing in media of varying pH was conducted on the three batches used in a bioavailability study (study 177). The alternate media included water, 0.1N HCl (pH 1.0), 0.02 M sodium acetate buffer (pH 4.5), 0.05-M potassium phosphate buffer (pH 6.8) and 0.1N HCl/pH 6.8 buffer two-stage method. The two stage dissolution method tests the tablets in 0.1N HCl media for the first 2 hours of the dissolution run, then the pH is adjusted to 6.8 with 0.2 M phosphate for the duration of the dissolution run. Each dissolution run was conducted with 12 tablets and the mean dissolution data was used in the IVIVC.

The mean plasma O-desmethylvenlafaxine (ODV) concentration-time profile data from four bioavailability studies (Studies 168-EU, 186-US, 190-US and 177-US) conducted with DVS SR tablets were utilized to develop the Level A IVIVCs. Study 168 administered 75 mg DVS-233 as an immediate release capsule (batch 2001B0149) and as an SR tablet (batch 2001B0139) following an overnight fast and following a high-fat breakfast. Study 186 administered DVS-233 as 2x50 mg SR tablets (batch 2002B0105), 2x75 mg SR tablets (batch 2002B0050), 1x100 mg SR tablet (batch 2002B0109) and 1x200 mg SR tablet (batch 2002B0107) following an overnight fast. Study 190 administered 100 mg DVS-233 as 2x50 mg SR tablets (batch 2002B0105) and 1x100 mg SR tablet (batch 2002B0109) following an overnight fast. Study 177 administered 200 mg DVS-233 as 1x200 mg SR tablets (batches 2002B0107, A61138, and A61140) following an overnight fast. The same batches of 50 and 100 mg SR tablets (2002B0105 and 2002B0109, respectively) were administered in studies 186 and 190 and the same batch of 200 mg SR tablets (2002B0107) was administered in studies 186 and 177. Two different batches (2001B0139 and 2002B0050) of 75 mg SR tablets were used in studies 168 and 186, respectively; however, their dissolution profiles were very similar ($f_2=90$).

The correlations for the 50 mg and 200 mg SR tablet were developed in a two stage procedure; deconvolution of the mean plasma ODV concentration-time profiles to generate the ODV absorption profile followed by a comparison of the percent of drug absorbed to the percent of drug dissolved (Attachment A). The in vivo absorption profiles were obtained by a numerical deconvolution procedure on the mean plasma ODV concentration-time profile data of the SR tablets. The mean plasma ODV concentration-time profile from the immediate release capsule in study 168 were used as the unit impulse function (weighting function) for the numerical deconvolution. The deconvolution algorithm treated any calculated value less than zero over the deconvolution time interval as being equal to zero. The in vitro dissolution profiles and the in vivo absorption profiles were compared point to point, with no time scaling or time shifting, out to 24 hours and equations were derived that described the relationship between absorption and dissolution for the SR tablets. A power function most appropriately described the relationships between the absorption of ODV and the dissolution of DVS

Absorption = a. Dissolution^b

The correlation for the 50 mg DVS SR tablet was developed as single release rate formulation IVIVC. The correlation for the 200 mg SR was developed using in vitro and in vivo data for the ~~50 mg SR tablet~~. The evaluation, or validation of the Level A IVIVCs consisted of both internal and external predictability measures. The detailed procedure that was used for the development of the IVIVC is provided in Attachment A.

The dissolution data for the 50 mg SR tablets were used to estimate the plasma ODV concentration-time profile in order to assess the internal predictability of the IVIVC. Since the IVIVC for the 50 mg tablet was developed with a single release rate formulation, there were no additional data for 50 mg SR tablets for external predictability measures. Therefore, external predictability was evaluated using data from the 75 and 100 mg SR tablets which were administered in the same study as the 50 mg SR tablet. The dissolution data of these two strength formulations were used to estimate the plasma ODV concentration-time profiles and AUC and

tablets with in vitro dissolution profiles at $\pm 10\%$ of the mean dissolution profiles are less than 20%.

During the review of the IVIVC, it was noted the sponsor has normalized the data used in the development of the IVIVC. The reviewers therefore requested that the sponsor recalculate the data on the development and validation of the IVIVC without normalization across studies of the plasma desvenlafaxine concentration-time data to account for subject population differences. The internal validation of the DVS SR tablet IVIVC was performed with the 200 mg fast release and 200 mg target release (to be marketed) formulations administered in study 177, and the external validation was performed with the 200 mg target release formulation administered in study 177 and the 50 mg and 100 mg target release formulations administered in study 186.

The results of this repeat analysis are presented and compared to the data calculated with normalization and provided in figures 16 and 17. The rank order and relative position among the three absorption profiles has not changed when computed without normalization. However, each profile calculated without normalization has shifted upwards by approximately 10%. The absolute %PE was higher for both internal and external validation when the validation was performed with values without normalization (Table 8 and 9). However, the predictability measures for the IVIVC model developed without normalization of plasma desvenlafaxine concentrations across studies met the criteria for a validated IVIVC. The absolute %PE were all less than 10% (Tables 8 and 9).

Summary: Plasma ODV concentration-time profile data from DVS SR tablets and their respective in vitro dissolution profiles have been used to develop two Level A IVIVCs.

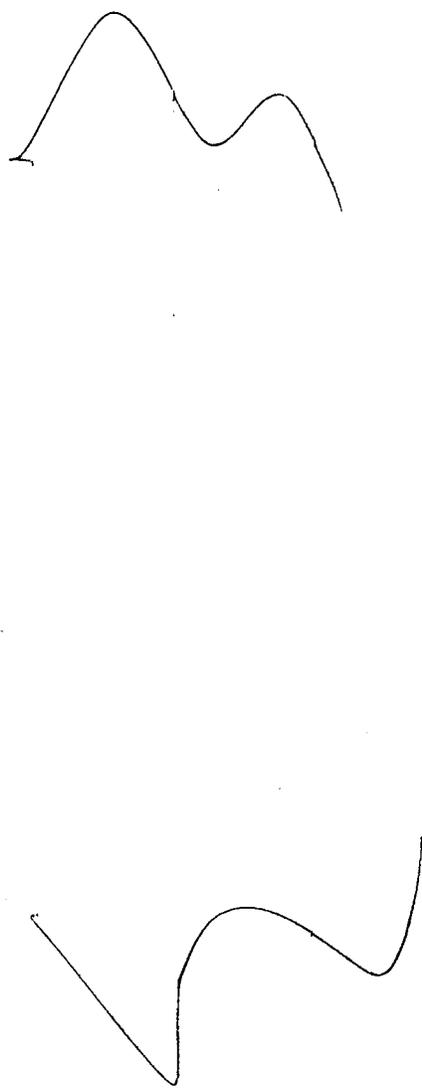
The sponsor reported that the in vitro release of the low strength (50 mg) is independent of dissolution conditions. Therefore, the correlation for the 50 mg SR tablet was developed with a single release rate formulation and the correlation for the 200 mg tablet was established with two formulations with different release rates.

The correlations developed were used to determine that dissolution could be set at about the mean dissolution profile of a DVS SR tablet, and that would predict bioequivalence with respect to C_{max} and AUC of SR tablets with the in vitro release at the limits of dissolution.

Reviewer's comments: The sponsor has developed a Level A IVIVC. The Level A IVIVCs were based on one formulation for the 50 mg and two formulations for the 200 mg tablet. The 50 mg formulation was independent of dissolution. The % prediction error (%PE) for both internal and external predictability was less than 10%, even after the validation was calculated with values without normalization to account for subject population differences. Based on the recommendations from the Agency's Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, the %PE are within the acceptable limits. Therefore, the Level A IVIVC for the 50 mg and 200 mg SR formulations are acceptable.

6.1 DVS-233 SR Tablet Composition

Ingredient	50 mg		75 mg		100 mg		200 mg	
	mg	%w/w	mg	%w/w	mg	%w/w	mg	%w/w
WAY-45233 Succinate Monohydrate	2002B0105	2001B0139	2002B0109	2002B0107	Batch A61138	Batch A61140	mg	%w/w
HPMC JSP								
HPMC USP								
Microcrystalline Cellulose NF								
Talc USP								
Magnesium Stearate EP/NF								
Totals ^a								
Manufacturing Method								
Manufacturing Site	St. Laurent	St. Laurent	St. Laurent	St. Laurent	Guayama	Guayama		



a: Total mg and % w/w are exclusive of coating components.

Table 2

6.3 Dissolution of DVS-233 SR 50 mg Tablets: Evaluation of pH			
Media	Time (hr)	Batch A35065	
		AVG (%)	Range (%)
Water			
0.1N HCl			
pH 4.5 Buffer			
pH 6.8 Buffer			
0.1N HCl/pH 6.8 Buffer 2-stage			
	f_2		
0.9% NaCl	2	26	
	4	42	
	8	63	
	12	77	
	24	97	

Dissolution conditions: USP apparatus 1 (baskets), 100 rpm, 0.9 L of media, 37°C
 Reference media: 0.9% NaCl.

Table 3

6.4 Dissolution of DVS-233 SR 200 mg Tablets: Evaluation of pH							
Media	Time (hr)	Batch A61140		Batch A61138		Batch A43079	
		AVG (%)	Range (%)	AVG (%)	Range (%)	AVG (%)	Range (%)
Water							
0.1N HCl							
pH 4.5 Buffer							
pH 6.8 Buffer							
0.1N HCl/pH 6.8 Buffer 2-stage							
0.9% NaCl	2	32		24		25	
	4	48		39		39	
	8	71		59		60	
	12	86		74		76	
	24	99		97		97	
Dissolution conditions: USP apparatus 1 (baskets), 100 rpm, 0.9L of media, 37°C Reference media: 0.9% NaCl within each batch							

Table 4

6.5 Absorption of ODV From DVS-233 SR Tablets	
50 mg SR Tablets	
Time (Hr)	Cumulative Percent ODV Absorbed
	Batch 2002B0105
0.5	12
1	21
2	35
4	46
6	53
8	58
10	62
12	65
16	69
24	77

200 mg SR Tablets			
Time (Hr)	Cumulative Percent ODV Absorbed		
	Batch A61140	Batch A61138	Batch 2002B0107
0.5	11	7	12
1	21	21	20
2	35	32	32
4	55	44	44
6	62	53	52
8	69	59	56
10	73	63	60
12	78	66	63
16	83	72	68
24	86	82	77

Table 5

6.6 Parameter Estimates and Correlation Coefficients of the Relationship Between Absorption of ODV and Dissolution of DVS-233 From DVS-233 SR Tablets			
50 mg SR Tablets			
50 mg Batch	a	b	R ²
2002B0105	3.35	0.688	0.996

200 mg SR Tablets			
Individual 200 mg Batches	a	b	R ²
A61140			
A61138			
2002B0107			
Level A IVIVC Model	2.59	0.763	0.990
Power Function Model: Absorption = a·Dissolution ^b			

Table 6

6.7 Internal and External Predictability Measures of the Level A IVIVC for DVS-233 SR mg Tablets						
50 mg SR Tablets						
Internal Predictability						
Batch	Observed AUC	Predicted AUC	Absolute % PE	Observed C _{max}	Predicted C _{max}	Absolute % PE
2x50 mg 2002B0105	4695	4876	3.86	169	156	7.25
External Predictability						
Batch	Observed AUC	Predicted AUC	Absolute % PE	Observed C _{max}	Predicted C _{max}	Absolute % PE
2x75 mg 2002B0050	6908	7156	3.59	246	241	2.32
1x100 mg 2002B0109	4542	4710	3.71	173	158	8.78

200 mg SR Tablets						
Internal Predictability						
Batch	Observed AUC	Predicted AUC	Absolute % PE	Observed C _{max}	Predicted C _{max}	Absolute % PE
A61140	8870	9080	2.37	362	344	4.95
A61138	8984	9192	2.32	314	307	2.07
Average % PE			2.34	Average % PE		3.51
External Predictability						
Batch	Observed AUC	Predicted AUC	Absolute % PE	Observed C _{max}	Predicted C _{max}	Absolute % PE
2002B0107	8540	8737	2.31	308	309	0.36

AUC units: ng·hr/mL
C_{max} units: ng/mL

Table 7

6.8 Bioavailability Assessment of Dissolution Specifications for DVS-233 SR Tablets Based on Mean Dissolution Profile			
Dissolution of 50 mg SR Tablets – Cumulative Percent Released			
Time (Hr)	Reference Profile	Lower Limit (-10%)	Upper Limit (+10%)
2	27	17	37
4	41	31	51
8	62	51	72
12	76	66	86
24	96	86	106
Bioavailability of 2x50 mg DVS-233 SR Tablet			
Parameter	Reference Tablet	Lower Limit Tablet	Upper Limit Tablet
AUC (ng-hr/mL)	4798	4462	5108
% Difference ^a	--	7.0	6.5
% Difference ^b	--		13
C_{max} (ng/mL)	157	143	173
% Difference ^a	--	9.1	10
% Difference ^b	--		18
t_{max} (hr)	6	10	6
Dissolution of 200 mg SR Tablets – Cumulative Percent Released			
Time (Hr)	Reference Profile	Lower Limit (-10%)	Upper Limit (+10%)
2	25	15	35
4	38	28	48
8	59	49	69
12	75	65	85
24	98	88	108
Bioavailability of 1x200 mg DVS-233 SR Tablet			
Parameter	Reference Tablet	Lower Limit Tablet	Upper Limit Tablet
AUC (ng-hr/mL)	9558	8802	10286
% Difference ^a	--	7.9	7.6
% Difference ^b	--		14
C_{max} (ng/mL)	308	282	340
% Difference ^a	--	8.4	10
% Difference ^b	--		17
t_{max} (hr)	8	10	8
a: Difference from reference			
b: Difference from lower limit to upper limit			

Fig 1

7.1 Dissolution Profiles of DVS-233 from DVS-233 SR 50, 75 and 100 mg Tablets by Method L22332-072: USP Apparatus 1 (Baskets), 100 rpm, 0.9 L of 0.9% NaCl, 37°C

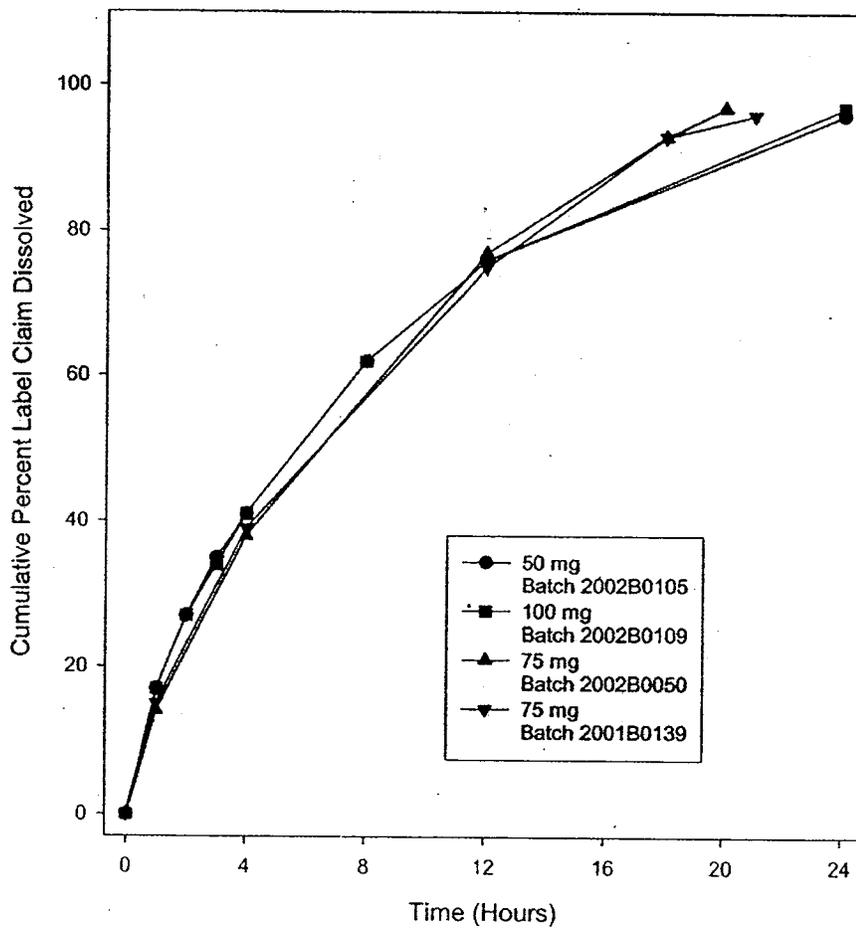


Fig 2

7.2 Dissolution Profiles of DVS-233 from DVS-233 SR 200 mg Tablets by Method L22332-072: USP Apparatus 1 (Baskets), 100 rpm, 0.9 L of 0.9% NaCl, 37°C

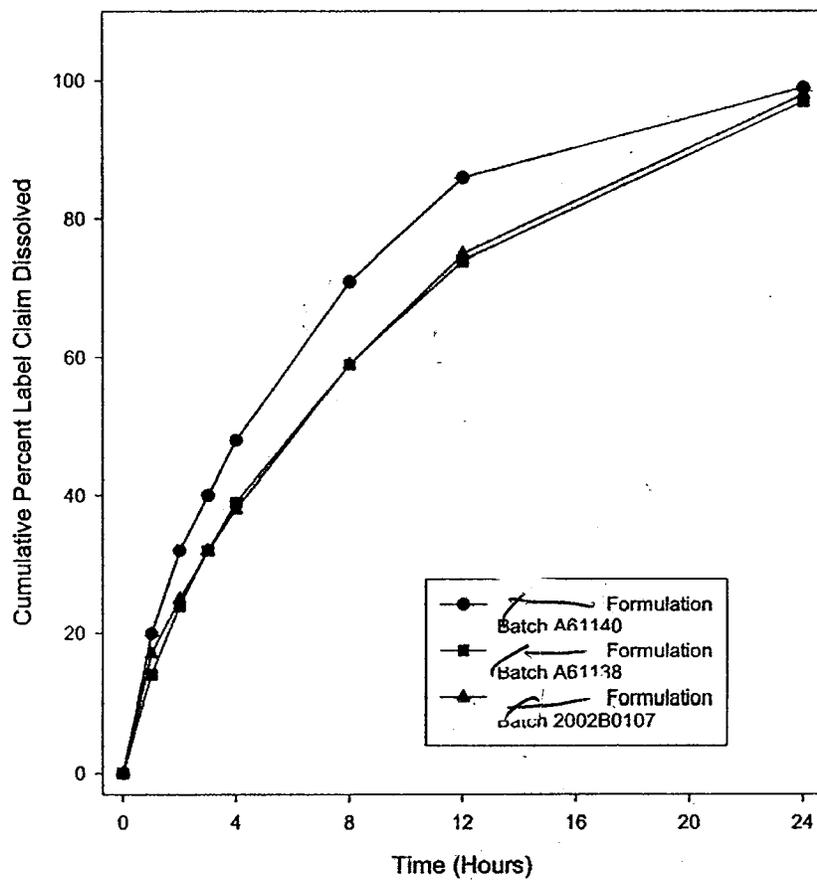


Fig 3: Dissolution Profiles of Desvenlafaxine from DVS-233 SR50 mg Tablets (Batch A35065) in Multiple Media (Dissolution Condition: USP Apparatus 1 (Baskets), 100 rpm, 0.9L of Media, 37° C)

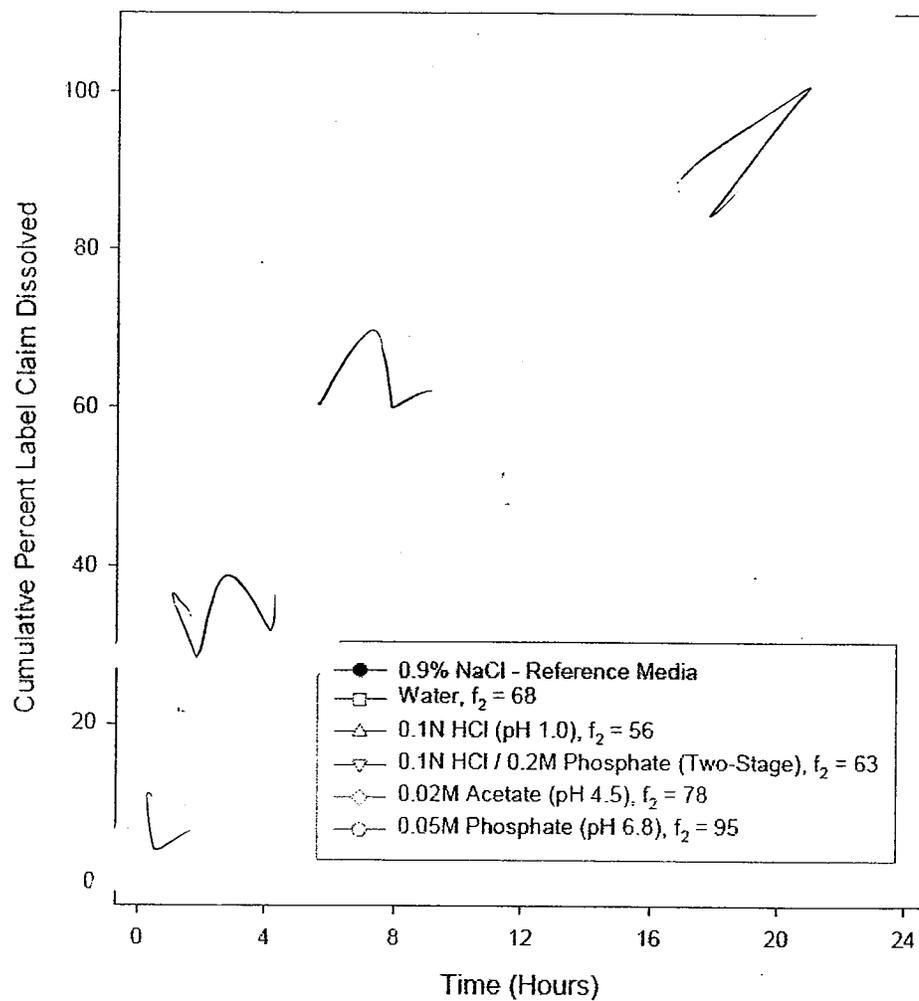


Fig 4: Dissolution Profiles of Desvenlafaxine from DVS-233 SR 200 mg Tablets (Batch A61140) in Multiple Media (Dissolution Condition: USP Apparatus 1 (Baskets), 100 rpm, 0.9L of Media, 37°C)

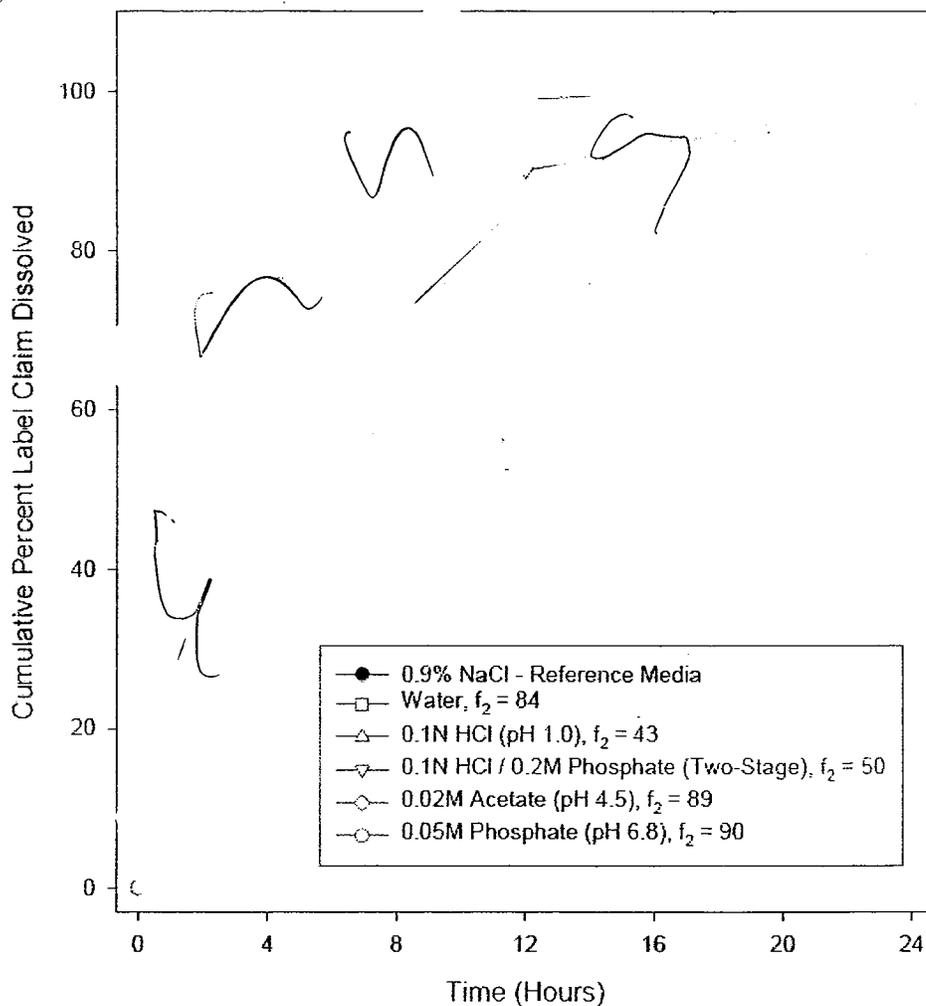


Fig.5: Dissolution Profiles of Desvenlafaxine from DVS-233 SR 200 mg Tablets (Batch A61138) in Multiple Media (Dissolution Condition: USP Apparatus 1 (Baskets). 100 rpm, 0.9L of Media, 37° C)

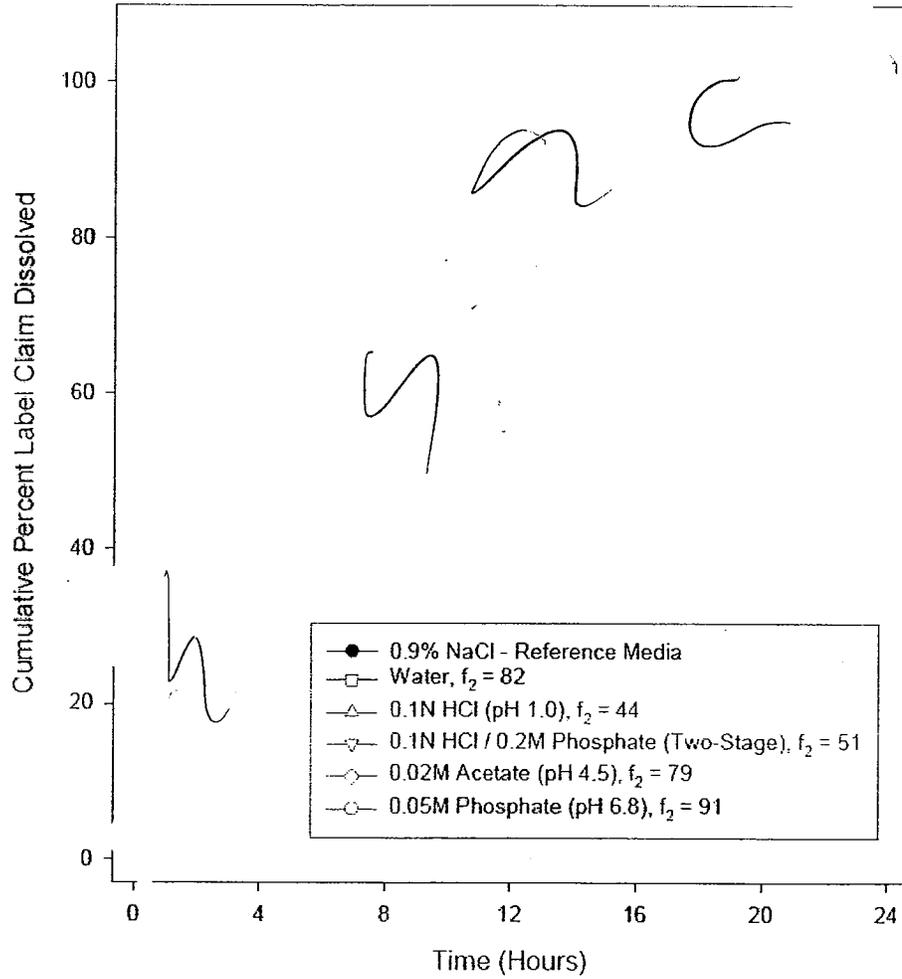


Fig 6: Dissolution Profiles of Desvenlafaxine from DVS-233 SR 200 mg Tablets (Batch A43079) in Multiple Media (Dissolution Condition: USP Apparatus 1 (Baskets), 100 rpm, 0.9L of Media, 37°C)

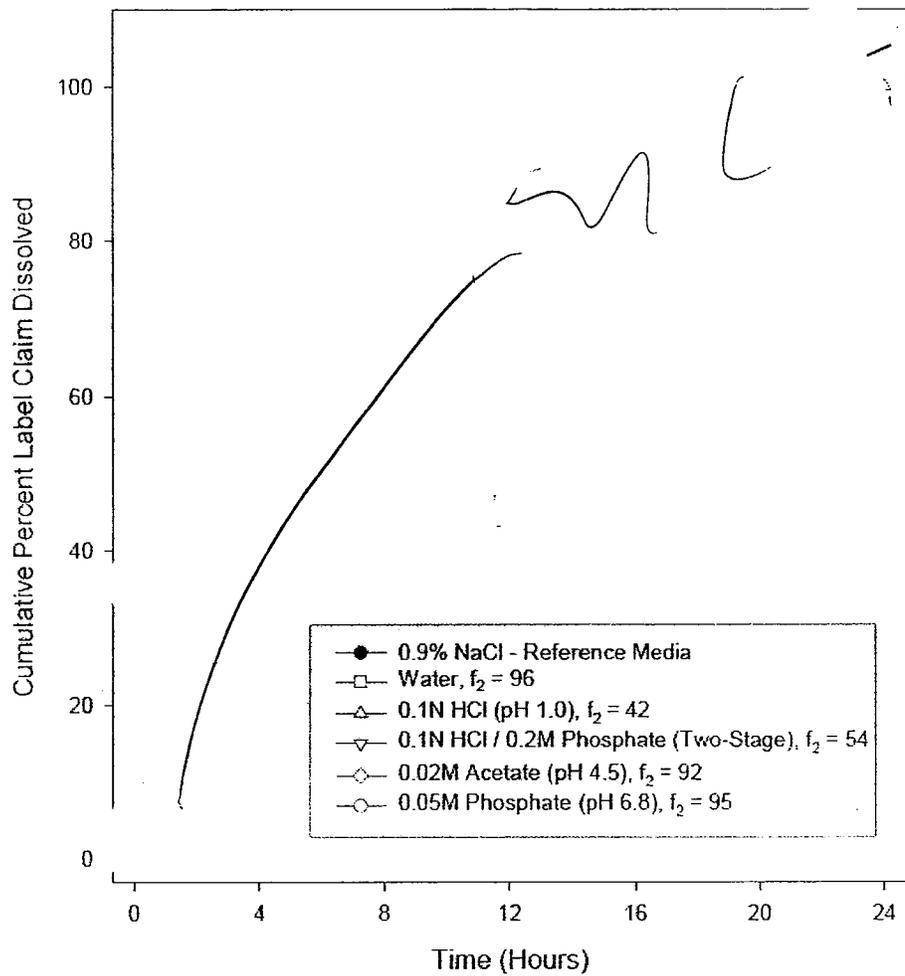


Fig. 7

7.7 Absorption Profile of ODV from DVS-233 SR 50 mg Tablets

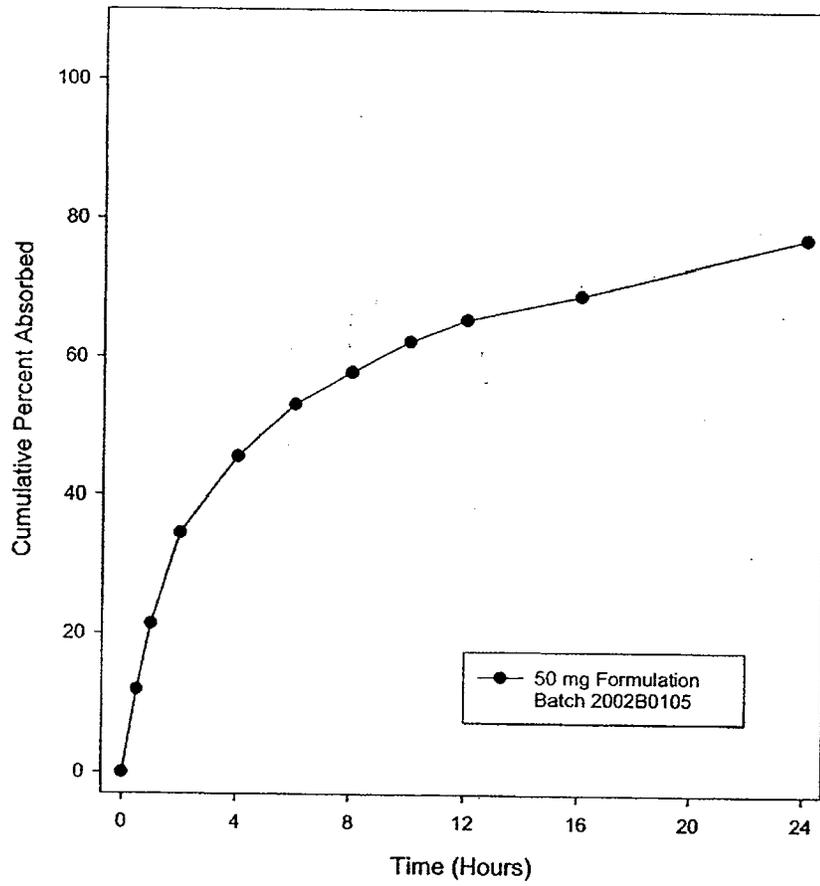


Fig. 8

7.8 Absorption Profiles of ODV from DVS-233 SR 200 mg Tablets

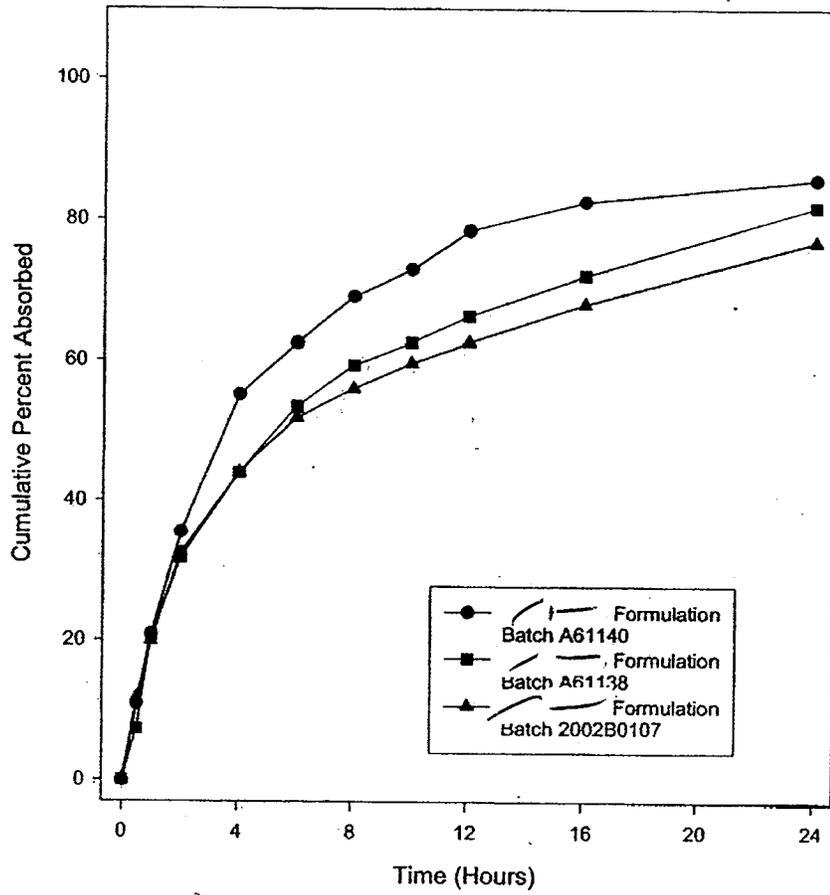


Fig. 9

7.9 Absorption of ODV Versus Dissolution of DVS-233 Relationship for DVS-233 SR 50 mg Tablets

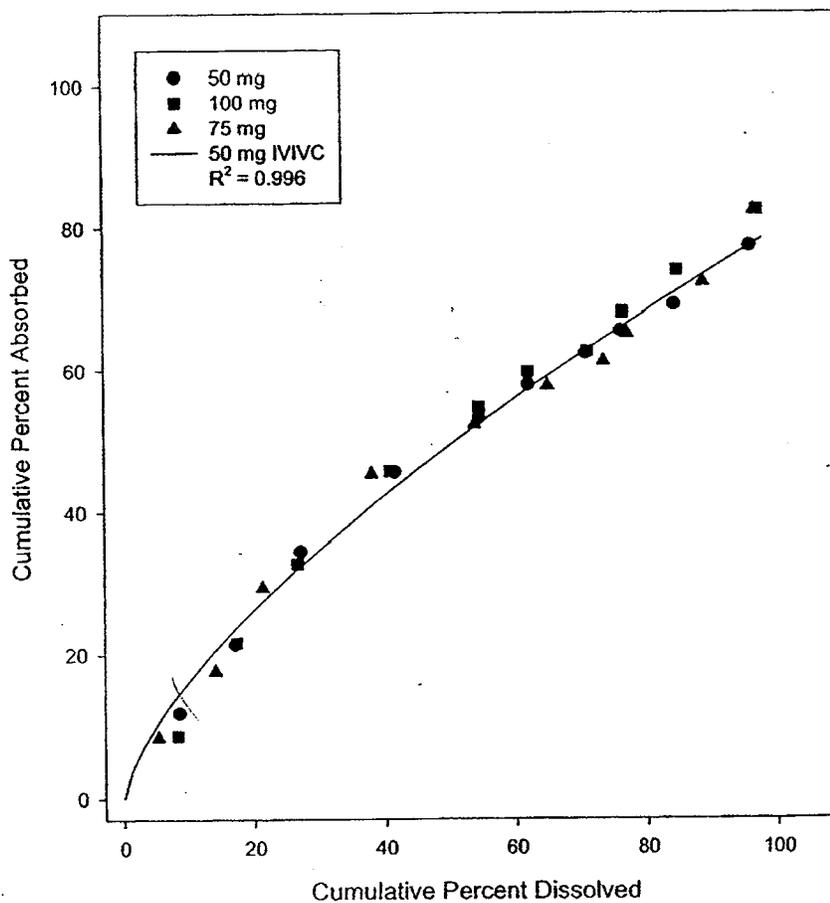


Fig. 10

7.10 Absorption of ODV Versus Dissolution of DVS-233 Relationship for DVS-233 SR 200 mg Tablets

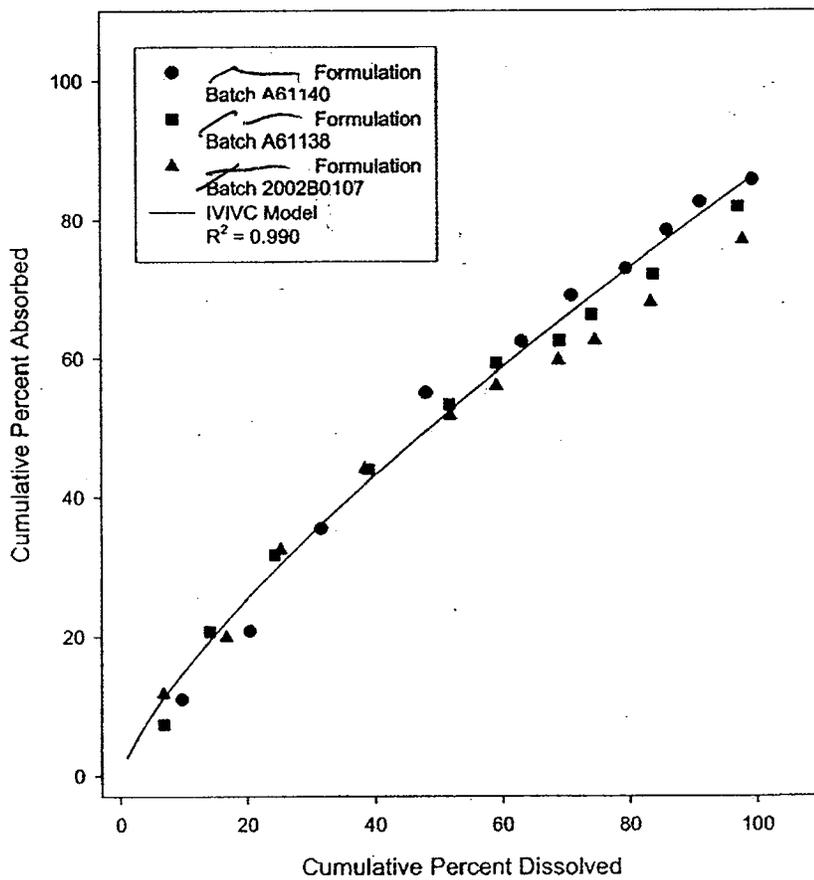


Fig. 11

7.11 Observed Mean (SD) and Level A IVIVC Predicted Mean Plasma ODV Concentration-Time Profiles from Single Dose Administration of 2x50 mg DVS-233 SR Tablets (Batch 2002B0105)

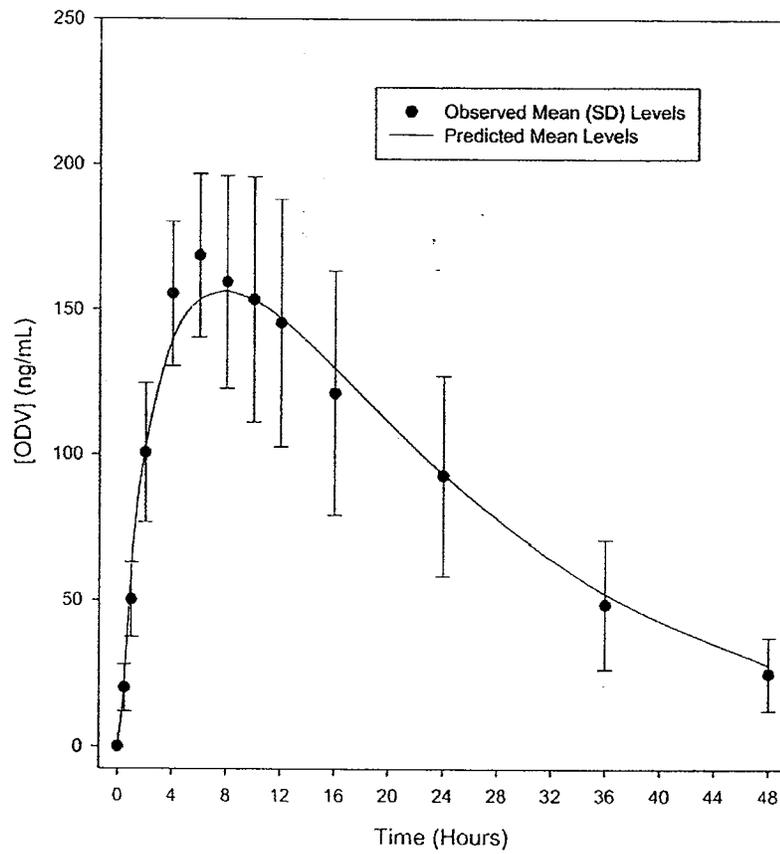


Fig. 12

7.13 Observed Mean (SD) and Level A IVIVC Predicted Mean Plasma ODV Concentration-Time Profiles from Single Dose Administration of 1x100 mg DVS-233 SR Tablets (Batch 2002B0109)

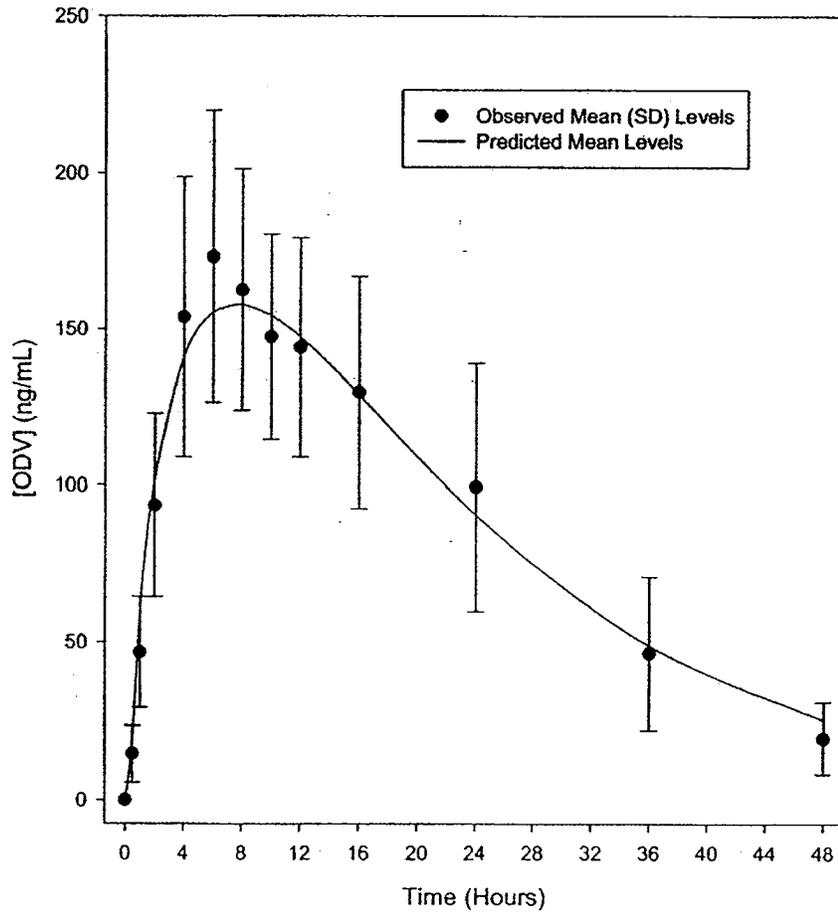


Fig. 13

7.14 Observed Mean (SD) and Level A IVIVC Predicted Mean Plasma ODV Concentration-Time Profiles from Single Dose Administration of 1x200 mg DVS-233 SR Tablets (Batch A61140)

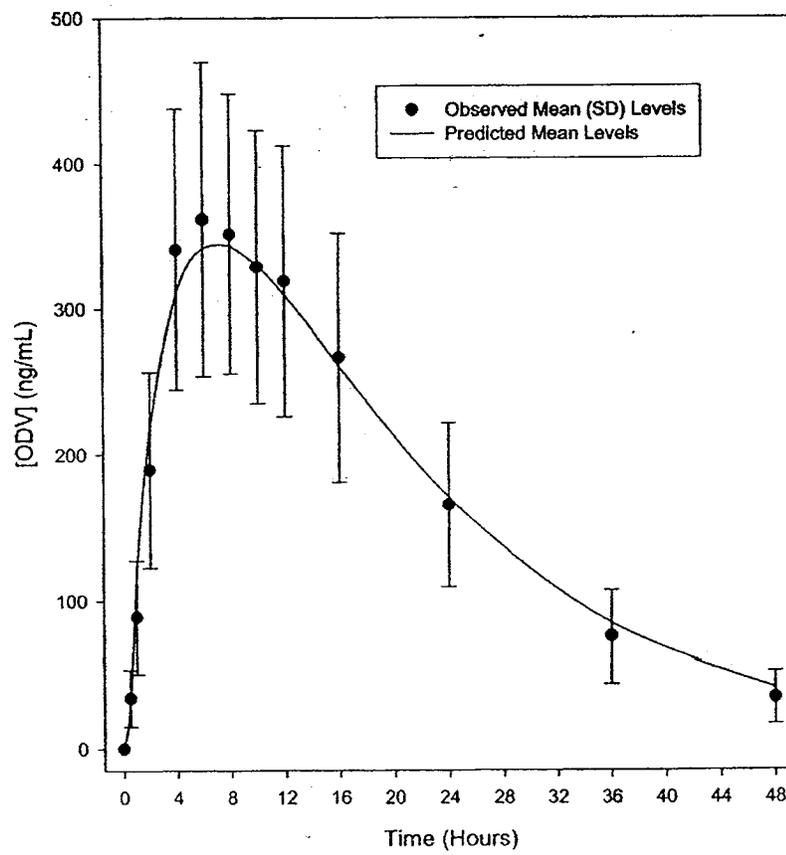


Fig. 14

7.17 Level A IVIVC Predicted Plasma ODV Concentration-Time Profiles from Single Dose Administration of 2x50 mg DVS-233 ST Tablet from Mean Dissolution and at Dissolution Limits ($\pm 10\%$)

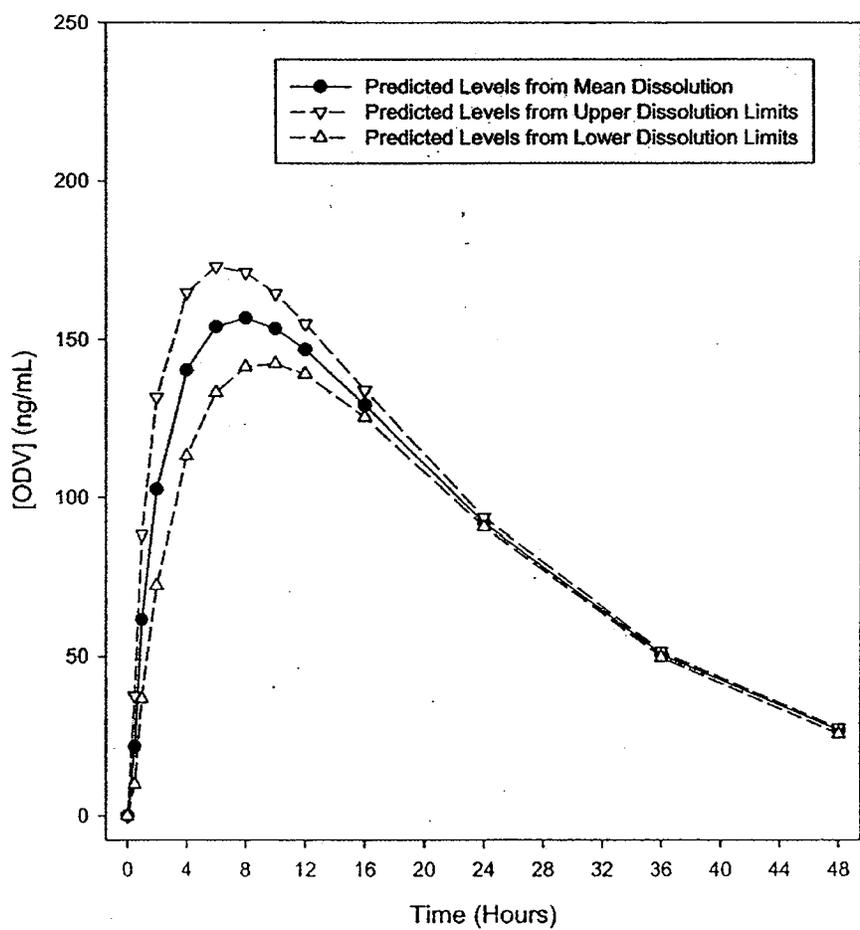


Fig. 15

7.18 Level A IVIVC Predicted Plasma ODV Concentration-Time Profiles from Single Dose Administration of 1x200 mg DVS-233 SR Tablet from Mean Dissolution and at Dissolution Limits ($\pm 10\%$)

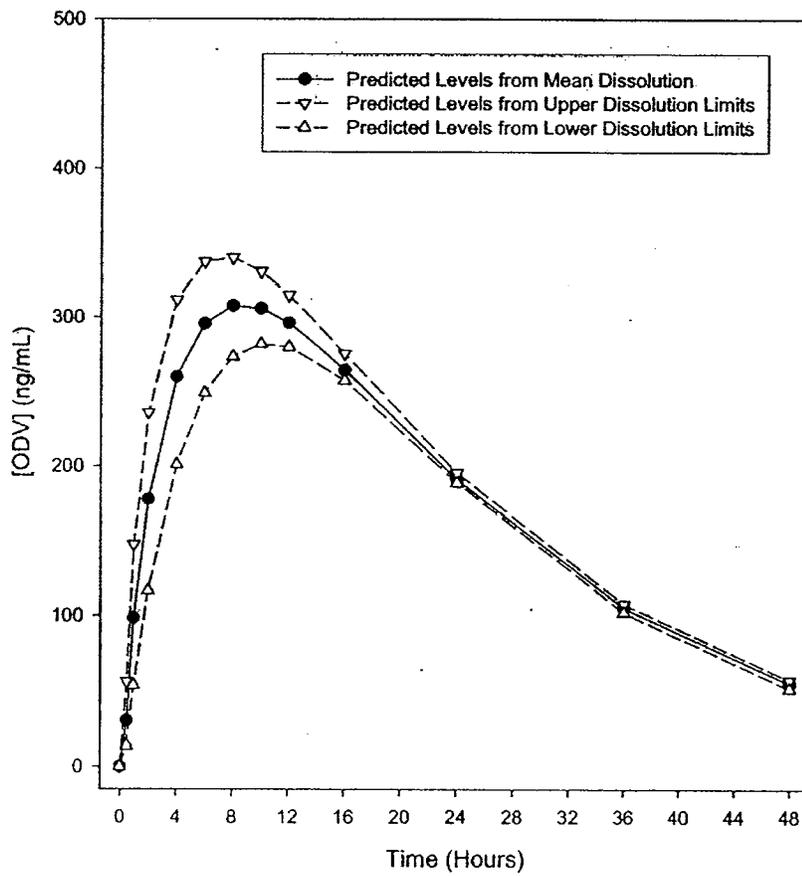


Fig. 16

Absorption Profiles of Desvenlafaxine from 200 mg Desvenlafaxine Succinate Extended Release Tablets

