Table 49: Summary of Accuracy (% Bias) and Precision (%CV) of the QC Samples in the Plasma Assays

			Low QCs			Middle QCs			High QCs		
Study No.	Analyte	Linear Range (ng/mL)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)
167	Ven	5.0-500	15.0	+2.46	4.70	60.0	-0.71	6.26	300	-0.34	3.68
	ODV	5.0-500	15.0	+1.45	4.62	60.0	-1.61	5.87	300	-1.51	4.37
	NDV	5.0-500	15.0	+2.57	5.68	60.0	+0.54	6.25	300	+0.73	4.14
	NODV	5.0-500	15.0	+3.10	9.31	60.0	+0.64	7.27	300	+0.40	7.06
168	ODV	5.0-500	15.0	-3.65	4.49	60.0	-5.11	5.36	300	-2.07	7.25
170	ODV	5.0-500	15.0	-5.13	7.94	60.0	-5.82	7.29	300	-3.03	6.63
	Ven	5.0-500	15.0	-3.10	6.91	60.0	-3.93	7.55	300	-2.89	5.90
171	ODV	5.0-500	15.0	-5.74	6.37	60.0	-7.25	6.24	300	-8.12	5.90
172	ODV	5.0-500	15.0	+0.30	4.93	60.0	-1.28	5.23	300	+0.02	7.12
173	ODV	5.0-500	15.0	-0.01	7.25	60.0	+0.71	5.23	300	-2.78	5.90
	Ven	5.0-500	15.0	-0.59	4.81	60.0	+0.79	4.56	300	+2.84	3.93
174	ODV	5.0-500	15.0	+2.95	9.92	60.0	-7.02	6.01	300	+2.65	4.88
	ODV- S:R Ratio (20:80) S	5.0-700	15.0	+8.85	4.70	125	+10.2	2.16	400	+12.8	1.19
	ODV- S:R Ratio (20:80) R	5.0-700	15.0	-2.21	1.31	125	-2.55	0.612	400	-3.19	0.346
	ODV S:R ratio (80:20) S	5.0-700	15.0	+0.595	2.70	150	+0.283	1.37	400	-0.614	1.31
	ODV S:R ratio (80:20) R	5.0-700	15.0	-2.38	11.1	150	-1.13	5.55	400	+2.46	5.07
175	ODV	5.0-500	15.0	-0.77	5.67	60.0	-0.05	3.94	300	-1.05	4.07
177	ODV	5.0-500	15.0	+5.18	8.45	60.0	+0.39	5.08	300	-0.93	4.57

Abbreviations: Conc = concentration; CV = coefficient of variation; NDV = N-desmethylvenlafaxine; NODV = N, O-didesmethylvenlafaxine; ODV = O-desmethylvenlafaxine; ODV-R = O-desmethyvenlafaxine (R)-enantiomer; ODV-S = O-desmethylvenlafaxine (S)-enantiomer; QC = quality control; Ven = venlafaxine

Table 50: Summary of Accuracy (% Bias) and Precision (% CV) of the QC Samples in the Plasma Assays

			Low QCs			Middle QCs			High QCs		
Study No.	Analyte	Linear Range (ng/mL)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)
179	ODV-R	2.5-350	3.0	+7.0	4.8	80	+2.2	3.0	320	-0.9	3.3
	ODV-S	2.5-350	3.0	+4.4	12.8	80	+0.3	4.5	320	+0.9	12.0
180	ODV-R	2.5-350	3.0	-1.2	7.3	80	-2.1	5.3	320	-5.4	5.5
	ODV-S	2.5-350	3.0	-2.6	5.6	80	-4.1	5.3	320	-5.9	4.2
181	ODV-R	2.5-350	3.0	-6.7	6.5	100	-9.0	2.4	320	-10.3	2.9
	ODV-S	2.5-350	3.0	-6.9	7.5	100	-6.6	4.3	320	-9.3	2.4
183	ODV	2.0-500	5.0	-10.3	7.23	45	-10.6	6.04	375	-11.1	3.2
	Desipramine	0.25-100	0.5	-1.32	9.56	8	-3.01	5.78	80	-1.19	3.32
	2-OH Desipramine	0.25-100	0.5	-4.40	12.4	8	-0.881	9.21	80	-0.202	4.13
186	ODV	5.0-500	15.0	-0.21	5.54	60.0	-1.86	5.90	300	-0.90	7.26
190	ODV	5.0-500	15.0	-1.87	5.54	60.0	-4.45	4.54	300	-1.25	8.85
193	ODV	2.0-500	5.0	-4.09	7.72	45.0	-6.88	5.68	375	-6.43	6.46
	Moxifloxacin	40.0-6000	100	+3.53	13.80	750	-4.35	9.63	4500	+2.67	8.11
194	ODV-R	2.5-350	3	+0.6	5.3	80	-2.0	1.5	320	-4.5	1.4
	ODV-S	2.5-350	3	-2.4	2.8	80	-0.5	1.3	320	-6.2	1.1
	Ketoconazole	20-10,000	60	-16.3		5000	+1.60		7000	-3.57	

Abbreviations: Conc=concentration; CV=coefficient of variation; NDV=N-desmethylvenlafaxine; NODV=N,O-didesmethylvenlafaxine; ODV=O-desmethylvenlafaxine; ODV-R=O-desmethylvenlafaxine (R)-enantiomer; ODV-S=O-desmethylvenlafaxine (S)-enantiomer; QC=quality control; Ven=venlafaxine.

Table 51: Summary of Accuracy (% Bias) and Precision (%CV) of the QC Samples in the Plasma Assays

			Low QCs			Middle QCs			High QCs		
Study No.	Analyte	Linear Range (ng/mL)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Target Conc (ng/mL)	Accuracy (% Bias)	Precision (% CV)
195	ODV	2.0-500	5.0	-6.59	10.7	45.0	-7.0	3.87	375	-8.45	4.50
	Midazolam	0.1-100	0.3	-1.3	8.8	15.0	-0.7	5.3	70	-0.3	5.6
	1´-hydroxy-midazolam	0.1-100	0.3	-1.3	8.9	15.0	-0.7	4.4	70	-0.1	6.2
196	ODV	2.0-500	5.0	-9.4	5.8	45	-12.1	5.5	375	-12.0	3.7

Abbreviations: Conc=concentration; CV=coefficient of variation; NDV=N-desmethylvenlafaxine; NODV=N,O-didesmethylvenlafaxine; ODV=O-desmethylvenlafaxine; ODV-R=O-desmethylvenlafaxine (R)-enantiomer; ODV-S=O-desmethylvenlafaxine (S)-enantiomer; QC=quality control; Ven=venlafaxine.

Table 52: Summary of Accuracy (% Bias) and Precision (% CV) of the QC Samples in the Urine Assays

Study No.	Analyte	Linear Range (µg/mL)	Low QCs Target Conc (µg/mL)	Low QCs Accuracy (% Bias)	Low QCs Precision (% CV)	Middle QCs Target Conc (µg/mL)	Middle QCs Accuracy (% Bias)	Middle QCs Precision (% CV)	High QCs Target Conc (µg/mL)	High QCs Accuracy (% Bias)	High QCs Precision (% CV)
167	Unconj Ven	0.10-10.0	0.250	-2.08	9.64	1.50	+6.45	4.17	8.00	-0.09	5.11
	Unconj ODV	0.10-10.0	0.250	-1.36	9.41	1.50	+4.62	5.97	8.00	+0.91	4.74
	Unconj NDV	0.10-10.0	0.250	+0.24	7.22	1.50	+0.89	3.77	8.00	-1.33	3.56
	Unconj NODV	0.10-10.0	0.250	+1.20	8.58	1.50	+3.43	6.51	8.00	+1.41	5.73
	Total Ven	0.10-10.0	0.250	-4.64	13.59	1.50	+4.56	6.03	8.00	+0.84	5.23
	Total ODV	0.10-10.0	0.250	+1.72	9.04	1.50	+3.51	4.87	8.00	+0.84	4.78
	Total NDV	0.10-10.0	0.250	+0.48	10.55	1.50	-0.11	4.92	8.00	-0.9	3.68
	Total NODV	0.10-10.0	0.250	+0.96	8.36	1.50	+3.09	6.33	8.00	+1.70	6.28
174	Unconj ODV	0.10-10.0	0.250	+2.24	6.92	1.50	+1.95	4.92	8.00	+0.43	3.80
	Unconj NODV	0.10-10.0	0.250	+5.12	4.95	1.50	+3.55	3.17	8.00	+3.35	5.21
	Total ODV	0.10-10.0	0.250	+1.20	4.19	1.50	+0.08	2.54	8.00	-0.93	2.60
	Total NODV	0.10-10.0	0.250	+1.20	8.70	1.50	-0.42	2.68	8.00	+3.26	5.31
175	Unconj ODV	0.10-10.0	0.250	-12.60	23.3	1.50	+1.57	7.81	8.00	+0.13	3.31
179	Unconj ODV-R	0.025-25.0	0.072	-0.8	6.5	6.0	+0.9	6.2	24.0	-5.0	6.3
	Unconj ODV-S	0.025-25.0	0.072	-3.4	6.2	6.0	-4.8	4.9	24.0	-1.4	6.0
	Total ODV-R	0.025-25.0	0.072	+0.5	6.0	6.0	-2.5	6.3	24.0	-6.0	3.5
	Total ODV-S	0.025-25.0	0.072	-3.8	5.8	6.0	-5.3	4.6	24.0	-3.8	6.2
	Unconj NODV	0.04-20.0	0.12	-1.42	13.6	1.20	+6.51	6.59	15.2	+0.65	5.4
	Total NODV	0.04-20.0	0.12	-1.92	16.6	1.20	+1.5	6.84	15.2	-1.29	6.15
180	Unconj ODV-R	0.025-25.0	0.072	+0.6	7.0	6.0	-2.0	4.4	24.0	-3.2	6.4
	Unconj ODV-S	0.025-25.0	0.072	-0.2	8.0	6.0	-1.0	6.3	24.0	-4.5	5.4
	Total ODV-R	0.025-25.0	0.072	+2.9	4.5	6.0	+1.1	3.8	24.0	-2.3	6.4
	Total ODV-S	0.025-25.0	0.072	+0.6	10.3	6.0	-1.6	6.6	24.0	-2.1	3.8
	Unconj NODV	0.04-20.0	0.12	-4.17	12.2	1.20	+8.53	7.77	15.2	+3.21	3.29
	Total NODV	0.04-20.0	0.12	+3.08	7.52	1.20	-0.45	3.18	15.2	-3.87	2.53

Table 53: Summary of Accuracy (% Bias) and Precision (%CV) of the QC Samples in the Urine Assays

Study No.	Analyte	Linear Range (µg/mL)	Low QCs Target Conc (µg/mL)	Low QCs Accuracy (% Bias)	Low QCs Precision (% CV)	Middle QCs Target Conc (µg/mL)	Middle QCs Accuracy (% Bias)	Middle QCs Precision (% CV)	High QCs Target Conc (µg/mL)	High QCs Accuracy (% Bias)	High QCs Precision (% CV)
183[a]	Desipramine	10-2500 ng/mL	25 ng/mL	+6.18	5.51	150 ng/mL	-6.67	8.25	2000 ng/mL	+2.19	5.88
	2-OH Desipramine	100-25,000 ng/mL	250 ng/mL	+1.76	9.68	1500 ng/mL	-10.9	10.0	20,000 ng/mL	+0.518	9.83
194	Unconj ODV-R	0.025-25.0	0.072	+13.0	2.4	6.0	+9.6	3.2	24.0	+3.2	7.4
	Unconj ODV-S	0.025-25.0	0.072	+6.0	4.6	6.0	+7.2	7.6	24.0	+2.1	3.6
	Total ODV-R	0.025-25.0	0.072	+11.9	2.6	6.0	+11.6	1.6	24.0	+1.9	2.7
	Total ODV-S	0.025-25.0	0.072	+8.3	3.0	6.0	+5.7	3.0	24.0	+4.5	2.0
	Unconj NODV	0.04-20.0	0.120	+0.83	3.06	1.20	+8.0	3.81	15.2	-1.72	2.89
	Total NODV	0.04-20.0	0.120	+2.75	10.38	1.20	+2.28	5.02	15.2	-1.53	5.09

Abbreviations: Conc=concentration; CV=coefficient of variation; NDV=N-desmethylvenlafaxine; NODV=N,O-didesmethylvenlafaxine; ODV=O-desmethylvenlafaxine; ODV-R=O-desmethylvenlafaxine (R)-enantiomer; ODV-S=O-desmethylvenlafaxine (S)-enantiomer; QC=quality control; Unconj=unconjugated; Ven=venlafaxine.

a. The linear range and target concentrations are in units of ng/mL for study 183

2.6.2. Were the correct moieties identified and properly measured?

The active moiety, desvenlafaxine, was identified and measured in human plasma, urine and dialysate samples from clinical pharmacology studies conducted with desvenlafaxine succinate.

Several analytical methods were developed for the quantitation of desvenlafaxine in human plasma, urine, and dialysate. Analytical methods were validated for the determination of desvenlafaxine enantiomers in human plasma and urine. The long-term stability of desvenlafaxine and desvenlafaxine enantiomers in plasma and urine samples was also evaluated. In addition, analytical methods were also validated in support of the
analysis of moxifloxacin, desipramine (and its metabolite), midazolam (and its metabolites), and ketoconazole in support of clinical studies with desvenlafaxine and these therapeutic agents.

2.6.3. What bioanalytical methods were used to assess concentrations?

The following tables summarize the validation parameters for the bioanalytical methods used for the quantitation of desvenlafaxine in human plasma, urine and dialysate. Summary of the analytical methods used for the analysis of moxifloxacin, desipramine
(and its metabolite), midazolam (and its metabolites), and ketoconazole in support of clinical studies with desvenlafaxine and these therapeutic agents are also provided in the following tables.

Table 54: Validation Parameters for the Analytical Methods Used for the Quantification of Desvenlafaxine and NODV (N, O-Didesmethylvenlafaxine) in Human Plasma Samples

Parameter	Desvenlafaxine	NODV
Method	LC/Flourescence; LC/MS/MS	LC/Flourescence; LC/MS/MS
Freeze-thaw	3 cycles; 5-cycles	3 cycles; NA
Benchtop Stability at RT	24 hours	24 hours
Long term at -20°C	1 year	NA
Recovery		
Low	86.9%; 94.4%	85.4%; NA
Med	83.8%; 94.0%	84.2%; NA
High	83.4%; 94.5%	83.4%; NA

NA: not applicable (not evaluated for this metabolite)

Table 55: Validation Parameters for the Analytical Methods Used for the Quantification of Desvenlafaxine and NODV (N,O-Didesmethylvenlafaxine) in Human Urine Samples

Parameter	Desvenlafaxine	NODV
Method	LC/UV; LC/MS/MS	LC/UV; LC/MS/MS
Freeze-thaw	6 cycles	6 cycles
Benchtop Stability at RT	24 hours	24 hours
Long term at -20°C	3 months	NA
Recovery	Unconjugated	Unconjugated
Low	60.3%; 92.6%	53.7%; 87.6%
Med	66.9%; 103%	47.4%; 90.4%
High	67.6%; 98.7%	48.3%; 89.0%
Recovery	Total	Total
Low	72.3%; 99.7%	45.6%; 93.3%
Med	79.4%; 94.6%	48.7%; 97.2%
High	74.0%; 90.0%	47.1%; 89.4%

NA: not applicable (not evaluated for this metabolite)

Table 56: Validation Parameters for the Analytical Methods Used for the Quantification of Desvenlafaxine and NODV (N, O-Didesmethylvenlafaxine) in Human Dialysate Samples

Parameter	Desvenlafaxine	NODV
Method	LC/MS/MS	LC/MS/MS
Freeze-thaw	6 cycles	NA
Benchtop Stability at RT	24 hours	NA
Long term at -20°C	25 days	NA
Recovery		
Low	NA	NA
Med	NA	NA
High	NA	NA

NA: not applicable (not evaluated for this metabolite)

Table 57: Validation Parameters for the Analytical Methods Used for the Quantification of Desvenlafaxine Enantiomers in Human Plasma

Parameter	Desvenlafaxine	NODV
Method	LC/MS/MS	LC/MS/MS
Freeze-thaw	3 cycles	3 cycles
Benchtop Stability at RT	24 hours	24 hours
Long term at -20°C	2 years	2 years
Recovery		
Low	94.0%, 90.2%	90.6%; 89.8%
Med	80.4%; 92.1%	78.6%; 91.7%
High	87.2%; 91.1%	88.4%; 92.3%

Table 58: Validation Parameters for the Analytical Methods Used for the Quantification of Desvenlafaxine Enantiomers in Human Urine

Parameter	Desvenlafaxine	NODV
Method	LC/MS/MS	LC/MS/MS
Freeze-thaw	3 cycles	3 cycles
Benchtop Stability at RT	24 hours	24 hours
Long term at -20°C	At least 13 days	At least 13 days
Recovery		
Low	NA	NA
Med	NA	NA
High	NA	NA

Table 59: Summary of Analytical Methods

Analytical Method	Species/Matrix	Sample Volume	LLOQ	Linear Range
		Desvenlafaxine		
HPLC with fluorescence	Human plasma	1 mL	5 ng/mL	5-500 ng/mL (all analytes)
LC/MS/MS	Human plasma	0.2 mL	2 ng/mL	2-500 ng/mL
HPLC with UV	Human urine	0.1 mL	0.1 µg/mL	0.1-10 µg/mL (all analytes-free)
HPLC with UV	Human urine	0.1 mL	0.1 µg/mL	0.1-10 µg/mL (all analytes-total)
LC/MS/MS	Human urine	0.02 mL	0.1 µg/mL (ODV-free) 0.04 µg/mL (NODV-free)	0.1-50 µg/mL (ODV-free) 0.04-20 µg/mL (NODV-free)
LC/MS/MS	Human urine	0.05 mL	0.1 µg/mL (ODV-total) 0.04 µg/mL (NODV-total)	0.1-50 µg/mL (ODV-total) 0.04-20 µg/mL (NODV-total)
LC/MS/MS	Human dialysate	0.1 mL	1 ng/mL	1-100 ng/mL

Table 60: Summary of Analytical Methods

Analytical Method	Species/Matrix	Sample Volume	LLOQ	Linear Range
		Moxifloxacin		
LC/MS/MS	Human plasma	0.1 mL	40 ng/mL	40-6000 ng/mL
		Desipramine/2-hydroxydesipramine		
LC/MS/MS	Human plasma	0.1 mL	0.25 ng/mL	0.25-100 ng/mL
LC/MS/MS	Human urine	0.05 mL	10 ng/mL (desipramine)	10-2500 ng/mL (desipramine)
			100 ng/mL (2-hydroxy-desipramine)	100-25,000 ng/mL (2-hydroxydesipramine)
		Midazolam/1´-hydroxymidazolam/4-hydroxymidazolam		
LC/MS/MS	Human plasma	0.2 mL	0.1 ng/mL	0.1-100 ng/mL
		Ketoconazole		
LC/MS/MS	Human plasma	0.1 mL	20 ng/mL	20-10,000 ng/mL

3 Detailed Labeling Recommendations

Detailed OCP Labeling Recommendations are included in the Annotated Label attached under Appendices.

21 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-2

4.2 Clinical Pharmacology and Biopharmaceutics Individual Reports

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On Original

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On Original

4.2 Individual Study Report

Pharmacometrics Review
Office of Clinical Pharmacology

NDA:	21-992
Compound:	Desvenlafaxine (DVS)
Submission Dates:	December 25, 2005
Applicant:	Wyeth
Type of submission:	New Drug Application, NME
Pharmacometrics Reviewer:	Yaning Wang, Ph.D.

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Executive Summary

Sequential population pharmacokinetic (PK) analyses were performed for desvenlafaxine (DVS) (NDA 21-992). The applicant first developed a population pharmacokinetic model with pooled data obtained from five Phase I Studies: 0600D3-170-FR, 0600D3-171-US, 0600D3-172-US, 0600D3-175-US, 3151A1-180-US. Then the model was updated with data from major depressive disorder (MDD) patients in the Phase 3 study 3151A-306-US with sparse pharmacokinetic sampling. The resulted model was further evaluated and refined with data from a phase 2 study 0600D3-223- FR/PL/US/ZA. The final model was evaluated and further refined with data from sparse blood samples collected in elderly MDD patients (age >= 65 yr) from study 3151A1-307-US. Then based on the HAM-D17 total score results from the fixed dose study: 3151A-306-US, the applicant developed the population pharmacokinetic/pharmacodynamic relationship between desvenlafaxine exposure and efficacy.

The objective of this analysis was to evaluate the validity of the results and conclusions related to the following topics:

- To characterize the pharmacokinetics and pharmacokinetic variability of desvenlafaxine in healthy subjects and investigate the effects of demographic characteristics on pharmacokinetics of desvenlafaxine;
- To apply a population pharmacokinetic model to MDD patients data and to identify and characterize MDD patient factors which influence the pharmacokinetics of desvenlafaxine;
- To explore the relationship between desvenlafaxine exposure and effect on HAM-D17 total score.

Recommendations:
Dose for patients with severe and end-stage renal disease should be reduced to half of the standard dose for patients with normal renal function.

In the labeling for Race effect under Clinical Pharmacology, Pharmacokinetics, Special population, it should be changed to "Population PK analysis showed that race (White N=, Black N=, Hispanic N=, Other N= had no apparent impact on the pharmacokinetics of desvenlafaxine".

Dose-dependent sustained hypertension should be added to the label as a warning.

The results of the analysis showed:

- The identified effect of renal function on drug clearance is consistent with the findings from renal impairment study. Given the significant change in AUC of desvenlafaxine for patients with severe and end-stage renal disease suggested by both population pharmacokinetic analysis and the renal impairment study, dose for these patients should be reduced to half of the standard dose for patients with normal renal function.

- The lack of race effect on desvenlafaxine pharmacokinetics was supported by the power evaluation. The detailed proportions of the relevant races, however, need to be specified in the label to clarify that some minor races were combined into one category and not enough information was available for those individual races to be evaluated separately.

- Since sustained hypertension was dose related for venlafaxine, the parent compound of desvenlafaxine, the same concern exists for desvenlafaxine. With the same definition of sustained hypertension as in venlafaxine's product label, desvenlafaxine was also found to cause sustained hypertension in a dose dependent manner even though the applicant observed a lack of dose-hypertension relationship based on other definition for hypertension.

Introduction

This NDA (21-992) submission is seeking approval for the treatment of major depressive disorder (MDD).

Desvenlafaxine (O-desmethylvenlafaxine, ODV) is a selective serotonin and norepinephrine reuptake inhibitor (sSNRI). The efficacy of desvenlafaxine succinate in the treatment of major depressive disorder is thought to be related to the potentiation of these neurotransmitters in the central nervous system. Desvenlafaxine is being developed as an oral sustained-release (SR) formulation of the succinate salt (DVS SR). Desvenlafaxine is the active metabolite of venlafaxine, which is approved for the treatment of major depressive disorder, generalized anxiety disorder, and social anxiety disorder.

After oral administration, the pharmacokinetics of desvenlafaxine is linear and dose-proportional in a dose range of 100 to 600 mg/day. Peak plasma concentrations (C_{max}) are observed between 6-10 hours after oral administration. The absolute bioavailability of desvenlafaxine is estimated to

be 80%. The plasma protein binding of desvenlafaxine is estimated to be 30% and is independent of drug concentration. Approximately 50% of desvenlafaxine is excreted unchanged in urine. Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms, including UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17) and to a minor extent through oxidative metabolism. Approximately 25% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The mean terminal half-life is approximately 9-12 hours.

The applicant initially developed a population pharmacokinetic model with pooled data obtained from five Phase I Studies: 0600D3-170-FR, 0600D3-171-US, 0600D3-172-US, 0600D3-175-US, 3151A1-180-US. Then the model was updated with data from major depressive disorder (MDD) patients in the Phase 3 study 3151A-306-US with sparse pharmacokinetic sampling. The resulted model was further evaluated and refined with data from a phase 2 study 0600D3-223-FR/PL/US/ZA. The final model was evaluated and further refined with data from sparse blood samples collected in elderly MDD patients (age >= 65 yr) from study 3151A1-307-US.

The applicant also explored the relationship between desvenlafaxine exposure and effect on HAM-D17 total score based on the sparse pharmacokinetic samples and the efficacy results from the fixed dose study: 3151A-306-US.

The reviewer further explored the relationship between desvenlafaxine exposure and blood pressure side effect based on 3 fixed dose studies (223, 306 and 308).

Objective of the analysis

- To characterize the pharmacokinetics and pharmacokinetic variability of desvenlafaxine in healthy subjects and investigate the effects of demographic characteristics on pharmacokinetics of desvenlafaxine;

- To apply a population pharmacokinetic model to MDD patients data and to identify and characterize MDD patient factors which influence the pharmacokinetics of desvenlafaxine.

- To explore the relationship between desvenlafaxine exposure and effect on HAM-D17 total score

Methods

Assumptions

- All the individual pharmacokinetic parameters follow log-normal distribution
- The errors in the residual error model follow normal distribution with mean 0 and are independent
- The concentration measurements at different time points are independent
- The measurements of time and covariates are error-free

Study Design/Data

To develop the population PK model, the application used data from five Phase I pharmacokinetic data sets (0600D3-170-FR, 0600D3-171-US, 0600D3-172-US, 0600D3-175-US, 3151A1-180-US), one Phase 2 study (0600D3-223- FR/PL/US/ZA), one Phase 3 study (3151A-306-US) and one long-term open-label safety study for the analyses. Efficacy data (HAM-D17 total score) from the phase 3 study was also used to explore the exposure-response relationship. Summaries of the protocol designs are presented in the following sections.

Phase I Studies

The database available from the five Phase 1 studies for the population pharmacokinetic analysis of desvenlafaxine in healthy subjects consisted of a total of 3470 plasma samples collected from 182 healthy subjects.

Study 170 was an open-label, single rising-dose study of 150, 225, 300, 450, 600, 750 and 900 mg DVS SR tablet in 47 healthy male subjects. Pharmacokinetic blood samples were collected just prior to the morning dose after a breakfast with medium-fat diet and at 1, 2, 3, 4, 6, 7, 8, 10, 12, 16, 20, 24, 28, 36, 48, and 72 hours after the morning dose.

Study 171 was an open-label, multiple rising-dose study of 300, 450, 600 mg DVS SR tablet once daily for 14 days in 27 healthy male subjects. Pharmacokinetic blood samples were collected just prior to the morning dose after a medium-fat breakfast and at 1, 2, 3, 4, 6, 7, 8, 10, 12, 16, 20, and 24 hours after the morning dose on Day 1 and at 1, 2, 3, 4, 6, 7, 8, 10, 12, 16, 20, 24, 28, 36, 48, 60, and 72 hours on Day 14. Additional samples were collected just prior to the morning dose on Day 3, 4, 5, 7, 10, and 13.

Study 172 was an open-label, dose proportionality three-period crossover single dose study of 100, 300, and 600 mg DVS SR tablet in 24 healthy subjects (23 male and one female) with four days washout between periods. Pharmacokinetic blood samples were collected just prior to the morning dose after a medium-fat breakfast and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, and 72 hours after the morning dose in each period.

Study 175 was an open-label, single dose study of 200 or 300 mg DVS SR tablet in 48 healthy male and female subjects. There were 18 young subjects with age from 23 to 44 year old, and 17 subjects with age equal or greater than 75 years old. Pharmacokinetic blood samples were collected just prior to the morning dose after a medium-fat breakfast and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, and 72 hours after the morning dose.

Study 180 was an open-label, single dose study of 100 mg DVS SR tablet after overnight fasting for at least 10 hours in 35 subjects with mild, moderate, severe, and end-stage renal disease (ESRD) and in 8 healthy subjects. Pharmacokinetic blood samples were collected just prior to the dose and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, and 72 hours after the dose. Additional blood samples were obtained from subjects with renal impairment at 96, 120, and 144 hours after dose administration.

Phase II Study

The data available for population pharmacokinetic analysis was from the Phase 2 study 223 consisting of a total of 206 plasma samples collected from 119 MDD patients.

The Phase 2 study 223 was conducted as a double-blind, 8-week efficacy study in which patients with MDD were randomized to receive daily doses of either DVS SR 200 mg, or 400 mg or placebo. After completing 8 weeks of treatment (or at the time of discontinuation), patients who received DVS SR 400 mg were assigned to reduce the dose to 200 mg for a 3-day taper and further reduce the dose to 100 mg for a 4-day taper.
Patients who received DVS SR 200 mg were assigned to reduce the dose to 100 mg for a 3-day taper and reduce the dose to 0 mg for a 4-day taper. All other patients received a placebo taper. Approximately 200 patients were to be enrolled in the double-blind portion of the study and randomized to one of the three treatments. Blood samples (10 mL) for the desvenlafaxine assays were collected on study days 14 and 56 (or on the day of early withdrawal). If a subject withdrew before day 56, a blood sample was collected on the last day the subject took a full dose (i.e., before taper), or as soon as possible thereafter, but within 3 days of the last full dose. The protocol did not specify the time of sample collection relative to the time of last dose, and the investigator collected the sample at the time of each patient's routine office visit. The date and time of sample collection, date and time of last dose administration were recorded on the case report form. Information about the date and time of the closest meal to dose administration, and the fat content of the meal were not recorded in this study.

Phase III Study

The database available from the Phase 3 study 306 for the population pharmacokinetic analysis of desvenlafaxine in MDD patients consisted of a total of 506 plasma samples collected from 293 patients.

Study 306 was conducted as a double-blind, 8-week efficacy study in which patients with MDD were randomized to receive daily doses of either DVS SR 100, 200, or 400 mg or placebo. After completing 8 weeks of treatment (or at the time of discontinuation), patients who received DVS SR 400 mg were assigned to reduce the dose to 200 mg for a one-week taper and further reduce the dose to 100 mg for the second one-week taper. Patients who received DVS SR 200 mg were assigned to reduce the dose to 100 mg for a one-week taper and reduce the dose to 0 mg for the second one week taper. All other patients received a placebo taper. Approximately 480 patients were to be enrolled in the double-blind portion of the study and randomized to one of the four treatments. Blood samples (10 mL) for the desvenlafaxine assays were collected on study days 14 and 56 (or on the day of early withdrawal). If a subject withdrew before day 56, a blood sample was collected on the last day the subject took a full dose (i.e., before taper), or as soon as possible thereafter, but within 3 days of the last full dose. The protocol did not specify the time of sample collection relative to the time of last dose, and the investigator collected the sample at the time of each patient's routine office visit. The date and time of sample collection, date and time of last dose administration, date and time of the closest meal to dose administration, and the fat content of the meal were recorded on the case report form.

Long Term Safety Study

The data available for population pharmacokinetic analysis was from an ongoing Phase 3 study 307. This data consisted of a total of 58 plasma samples collected from 40 elderly MDD patients.

Study 307 was conducted as an open-label, flexible dose, outpatient, multicenter Phase 3 study in elderly MDD patients (age>= 65 yr). Patient received DVS SR 100 mg daily from day 1 to day 7. On day 8, the dose was increased to 200 mg. Patients who were not able to tolerate the 200 mg dose can be readjusted to 100 mg original dosage. After day 8, the dose was increased to 200 mg to increase efficacy or it was reduced back to 100 mg to improve the tolerance any time during the study. Patients were treated for 6-month followed by 1-week tapering. Approximately 75

patients were to be enrolled in the study. Blood samples (10 mL) for the desvenlafaxine assays were collected on study days 30, 90 and 180 (or on the day of early withdrawal). The protocol did not specify the time of sample collection relative to the time of last dose, and the investigator collected the sample at the time of each patient's routine office visit. The date and time of sample collection, date and time of last dose administration, date and time of the closest meal to dose administration, and the fat content of the meal were recorded on the case report form.

External Validation Database

Data from study 223 and study 307 were first used to evaluate the population model, and then combined with the model-training dataset to refine the final model parameters.

Modeling

The applicant first developed the population pharmacokinetic models to describe the time-course of DVS SR in plasma. The structural (compartmental, including covariates) and statistical (variability) population pharmacokinetic models for plasma DVS SR pharmacokinetics were first established in healthy subjects based on data from 5 Phase 1 studies. The model was updated with data from major depressive disorder (MDD) patients in the Phase 3 study 3151A-306-US with sparse pharmacokinetic sampling. The resulted model was further evaluated and refined with data from a phase 2 study 0600D3-223- FR/PL/US/ZA. The final model was evaluated and further refined with data from sparse blood samples collected in elderly MDD patients (age >= 65 yr) from study 3151A1-307-US. Based on the established model, individual plasma exposure of desvenlafaxine (AUCss) was estimated for the subjects with efficacy data to assess pharmacokinetic/pharmacodynamic relationship for efficacy.

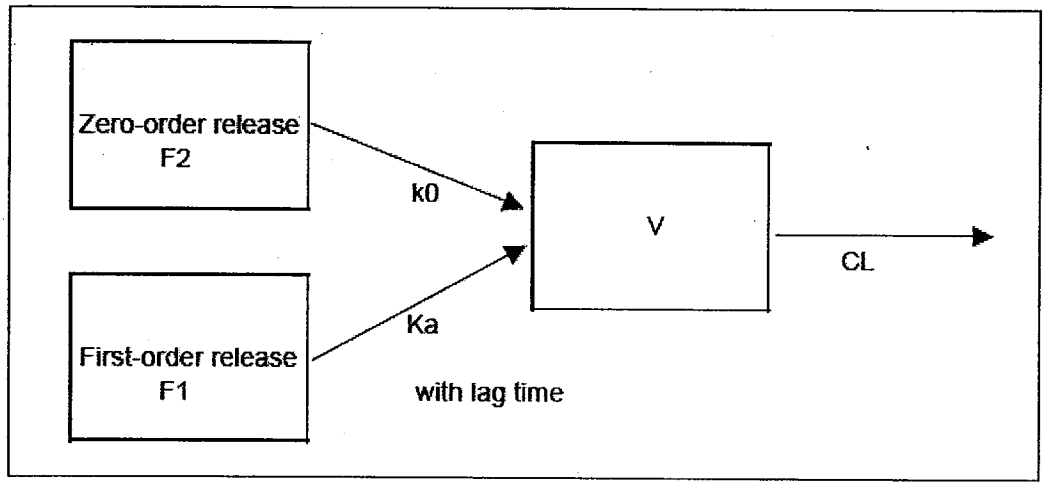
1. Software

The applicant developed the population pharmacokinetic model by applying a non-linear mixed-effects modeling approach with First Order Conditional Estimation with Interaction (FOCEI) maximum likelihood estimation in the NONMEM® program (double precision, Version 5.1.1). Visual Fortran 6.0 was the compiler used for this analysis. Data set preparation, exploration and visualization were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA) and S-PLUS 2000 release 2 for Windows (Insightful, Seattle, WA, USA). All work was conducted under Windows XP. The reviewer evaluated the results by applying the same version of NONMEM and Compaq Visual Fortran (Version 6.6A) compiler via WINGS for NONMEM (Version 409d) under the Windows XP professional operating system.

2. Structural Model

The structural base pharmacokinetic model of desvenlafaxine was developed based on intensive PK sampling from healthy subjects in five Phase 1 studies. The model, which best describes the in-vivo absorption rate of desvenlafaxine SR is presented in Figure 1.

Figure 1. Pharmacokinetic Model for Sustained-Release DVS Dosage Form



ADVAN2 from the NONMEM library of built-in models was used in the analysis. The model was an open one-compartment linear disposition model with a fraction of the dose (F1) released by a first-order process and the remaining fraction of the dose (F2 = 1 - F1) released by a zero-order process in parallel and a lag time for both processes. The model was parameterized in terms of apparent clearance (CL/F), apparent volume of distribution (V/F), the first-order rate absorption constant (ka), the fraction of dose released by the first-order process (F1), the duration of zero-order absorption (d2) and absorption lag time (tlag). The tlag is the same for both input processes. The RATE variable was set to –2 to allow estimation of the duration of zero-order input, d2 in the population PK analysis. In order to limit the F1 estimate between 0 and 1.0, the applicant applied a logit transformation to F1.

The structural base models with various kinds of input function were evaluated for the desvenlafaxine sustained-release dosage form (first-order, or zero-order, or a combination of first-order and zero-order, or a combination of one fast and one slow first-order, with or without a lag-time). The final model was selected based on likelihood objective function (OF) and model-fit diagnostic plots. The first-order method (FO) was used in all analysis at this stage since the first-order conditional method (FOCE) was tried and it failed to converge probably due to complexity of the model.

3. Random Variance Models

The applicant utilized an exponential error model to describe the inter-individual variability in all pharmacokinetic parameters, e.g., for CL/F:

$CL/F_j = CL/F_{0j} \exp(\eta_{j\,CL/F})$,

where $\exp(\eta_{j\,CL/F})$ denoted the difference (proportional) between the true individual parameter (CL/F_j) and the typical value (CL/F_{0j}) predicted for an individual with covariates equal to those of patient j. In the base model without covariates, CL/F_{0j} is the same for all individuals, and it was denoted by CL/F_0. Inter-individual variability was modeled the same way for the other parameters. The individual random effects, η's (e.g., $\eta_{j\,CL}$), are random variables following normal distribution with a mean of zero and variances of ω^2 (e.g., $\omega^2_{CL/F}$).

In the event that diagnostic procedures suggest the presence of inter-occasion variability in individual parameter estimates, an additional level of random effects was added to the inter-individual error model as

$CL/F_{jk} = CL/F_{0j} \exp(\eta_{j\ CL/F} + \kappa_{jk\ CL/F})$,

In this equation, CL/F_{jk} is the individual value for the pharmacokinetic parameter in the *jth* individual on the *kth* occasion, $\eta_{j\ CL/F}$ is an independent random variable with mean zero and variance $\omega^2_{CL/F}$, and κ_{jk} is an independent random variable with mean zero and variance $\pi^2_{CL/F}$ on the *kth* occasion. With this error model, $\omega_{CL/F}$ represents the approximate time averaged inter-individual coefficient of variation for the parameter value CL/F, and $\pi_{CL/F}$ represents the approximate coefficient of variation in CL/F between occasions for the typical individual.

Inclusion of the between occasion variability was mainly driven by study 171 and study 172 to improve model-fit diagnostic plots and resulted in a significant decrease in the OF. Further more, using one proportional error parameter for data from study 170 and study 171 and another proportional error parameter for data from study 172, study 175 and study 180 resulted in an improvement of the goodness of fit and a significant decrease in the OF (94 point drop).

The applicant modeled the residual variability with a combined additive and constant coefficient of variation (CCV) model:

$Y_{ij} = F_{ij} + F_{ij} \exp(\varepsilon_{ij1}) + \varepsilon_{ij2}$.

Y_{ij} and F_{ij} were the i_{th} measured and model predicted plasma concentrations for the j_{th} patient, respectively. ε_{ij1} and ε_{ij2} are random error terms with means of zero and variances σ_1^2 and σ_2^2. The independency between ε_{ij} and $\varepsilon_{i'j'}$ where $i \neq i'$ or $j \neq j'$ was assumed.

4. Covariate Model

The applicant explored for influential prognostic factors from demographic data and lab covariates:

- Gender (SEX, males: 0, females:1)
- Race/Ethnicity (RACE, Caucasian = 0, Arabic=1, African American = 2, Hispanic = 3, Asian = 4, Others = 5)
- Age (AGE), years
- Body weight (WT), kg
- Creatinine clearance (CRCL, mL/min), estimated from serum creatinine measurement (SCR, mg/dL) by the Cockcroft-Gault method: CRCL= WT*(140-AGE)/(72*SCR) for males and CRCL=0.85*WT*(140-AGE)/(72*SCR) for females
- Alanine aminotransferase (ALT), U/L
- Aspartate aminotransferase (AST), U/L
- Total bilirubine (TBIL), mg/dL
- Alkaline phosphatase (ALKP), U/L

- DOSE, mg
- AMPM (1 for morning dosing, 2 for afternoon dosing)
- FAST (0 for fasting, 1 for low fat meal, 2 for medium fat meal, 3 for high fat meal, 4 for unknown meal)
- Multiple dose (MD =1) vs. single dose (MD = 0)

The applicant explored the continuous covariates with the following three typical functional forms, including linear, power and allometric scale functions shown in the following equations:

Linear: $\widetilde{X}_j = \theta_X^{int} + \theta_X^{cov} \cdot (COV_j)$

Allometric scale: $\widetilde{X}_j = \theta_X^{int} \cdot \left(\frac{WT_j}{Median}\right)^{\theta_X^{cov}}$

where:

$\widetilde{X}_j$ = The estimated typical parameter value in the jth patient;

COV_j = The measured value of a particular covariate, cov, in the jth patient;

θ_X^{int} = The population mean parameter estimate for patients with the mean value of cov; and

θ_X^{COV} = linear - the population mean estimate describing the change in the parameter value per unit change in cov;
allometric scale - the population mean estimate describing the change in the log parameter estimate per unit change in the log of cov;

Dichotomous and categorical variables were evaluated as a proportional model as shown in the following equation:

$\widetilde{X}_j = \theta_X (1 + \theta_X^{cov} \cdot COV_j)$

where:

$\widetilde{X}_j$ = The estimated typical parameter value in the jth patient;

COV_j = The value of the variable (either 0 or 1) defined for a specific dichotomous covariate in the jth patient;

θ_X = The estimated population mean parameter value; and

θ_X^{COV} = The mean proportional or additive increase or decrease in θ_X for patients with cov_j=1

After graphical exploratory analysis of the correlation between random effects (ETA) of individual subjects and their continuous and discrete variables, the effect of each potential explanatory variable was evaluated individually on the base model. During the model-building process, the following decision criteria were considered to evaluate goodness-of-fit

1. When one parameter was added to the base model, the change in OF was compared to a chi-squared random variable with 1 degree of freedom (χ12) to assess the degree of improvement in the model's ability to describe the data. In the case of model building, the effect of the

explanatory variable (e.g. age) significantly improved the model if the OF was reduced by more than 3.84 ($p<0.05$).
2. Minimization of the standard errors with respect to the parameter estimates.
3. Random scatter around the line of identity in plots of weighted residual-versus predicted concentrations.
4. Minimization of inter-individual variances and an improvement in their precision.
5. Reduction in the magnitude of residual variability.

All of the explanatory variables that meet the statistical criteria in the model building step (forward selection) were included into one large population model, which was referred to as the full model. If the effects of two explanatory variables were highly correlated, it was not possible to include both parameters into the full model. In this case, the variable with the highest significance (i.e. the largest decrease in OF from the base model) was used.

Starting with the full model, the contribution of each explanatory variable was assessed by removing it from the model and evaluating the increase in OF (backward elimination). When one parameter was removed from the population model, the change in OF was compared to a chi-squared random variable with 1 degree of freedom ($\chi 12$) to assess the impact on the model's ability to describe the data. In the case of model reduction, the effect of the explanatory variable (e.g., age) did significantly contribute to the full model if the OF was reduced by more than 7.88 ($p<0.005$) when the variable was removed from the model. A more conservative criterion was used for model reduction ($p<0.005$) than for model building ($p<0.05$) to reduce the likelihood of accepting a statistical artifact. After the impact of all variables in the full model were evaluated, the explanatory variable with the smallest non-significant effect on the OF was removed from the model. This process was repeated until all remaining explanatory values significantly contribute to the model's ability to describe the data [i.e. increase in OF > 7.88 ($p<0.005$)] when the variable was removed.

5. Final Model Evaluation

The applicant evaluated the stability by the bootstrap technique, which involved resampling from the original data and each individual subject as a sampling unit. A minimum of 1000 replicates of the data was generated by bootstrap for the NONMEM analysis to obtain the mean and %CV of the fixed-effect and random-effect parameters.

In addition, the external model validation method was used to evaluate the performance of the final model based on some sparse blood samples collected in a Phase 2 study, 0600D3-223-US, and in some elderly MDD patients (age>=65 yr) from the study 3151A1-307-US. All THETA, and OMEGA initial values were fixed to the final parameter estimates to obtain the population and individual model-predicted concentrations and empirical Bayesian estimates of individual PK parameters using the POSTHOC option. The following diagnostic plots were prepared to evaluate the predictive performance of the model:
1. Population weighted residuals (WRES) and Individual weighted residual (IRES) computed by NONMEM versus population predicted concentrations;
2. Plot of WRES and IRES versus time post the latest intake;
3. Histogram and kernel probability density plots of WRES and IRES;
4. Plots of WRES versus covariates;
5. Plots of parameter random effects (ETA) versus covariates;

After evaluation of the final model, data from the two external datasets were combined with the data used in the previous population pharmacokinetic analysis to improve the parameter estimates of the final model.

6. Pharmacokinetic/Pharmacodynamic Correlation for Efficacy

The applicant utilized the final pharmacokinetic model to explore the relationship between desvenlafaxine plasma exposure and efficacy (change from baseline on the HAM-D_{17} total score) based on study 306.

A concentration effect analysis was performed, relating the final on-therapy HAM-D_{17} change from baseline to the DVS blood concentrations. A linear regression model was used with center and baseline also included as explanatory variables. A logistic regression model was also fit to the response on the HAM-D17, with the baseline score and the DVS concentrations as covariate and center as a factor. Another analysis was performed using the AUC as an explanatory variable for the final on-therapy HAM-D_{17} change from baseline.

7. Pharmacokinetic/Pharmacodynamic Correlation for Safety

The applicant observed no clear dose relationship for blood pressure change even though blood pressure was significantly increased from baseline for all dose groups compared to placebo group. The reviewer explored the dose-sustained hypertension relationship based on the 3 fixed dose studies, 223, 306 and 308. A sustained hypertension was defined as supine diastolic blood pressure (SDBP) >/= 90 mm Hg and >/= 10 mm Hg above baseline for 3 consecutive on-therapy visits, a definition used for venlafaxine in its product label. The reviewer also explored the relationship between individual predicted AUC and sustained hypertension based on study 306.

Results

Data Integrity

The data set for population analysis included incorrect dosing records for occasions 2 and 3 in studies 171 and 172 (Table 1). Specifically, the applicant reset the system to zero by using EVID=4 at occasions 2 and 3. The previous dosing records were repeated at later occasions. Since the applicant utilized between-occasion variability (BOV) on PK parameters, this means that there are 3 sets of PK parameters for the first dose and 2 sets of PK parameters for the second dose in study 172. In study 171, the applicant utilized a fixed multiple dose effect (MD=1 or OCC=2) on CL and V, which means that there are two sets of population mean PK parameters for the first dose.

Table 1. **Sample Dataset Including Dosing Error**

#PROT	SITE	SUB	DATE	TIME	AMT	CMT	EVID	OCC	MDV
172	1	71	10/18/2002	8:29	100000	1	1	1	1
172	1	71	10/18/2002	8:29	100000	2	1	1	1
...	...	...	...	...	...	...	...	...	...

172	1	71	10/18/2002	8:29	100000	1	4	2	1
172	1	71	10/18/2002	8:29	100000	2	1	2	1
172	1	71	10/22/2002	8:00	300000	1	1	2	1
172	1	71	10/22/2002	8:00	300000	2	1	2	1
...	...	...	...	...	...	...	...	...	...
172	1	71	10/18/2002	8:29	100000	1	4	3	1
172	1	71	10/18/2002	8:29	100000	2	1	3	1
172	1	71	10/22/2002	8:00	300000	1	1	3	1
172	1	71	10/22/2002	8:00	300000	2	1	3	1
172	1	71	10/26/2002	8:00	600000	1	1	3	1
172	1	71	10/26/2002	8:00	600000	2	1	3	1

The reviewer evaluated the impact of these wrong dosing records on model development and parameter estimation and found that only minor differences were observed on parameter estimates and sometimes the status of minimization was different. The value for objective function is always higher for the raw dataset than that with corrected dosing records. Overall, the impact of these errors on the final conclusion of population PK analysis was evaluated by the reviewer to be minimal.

Model and Model Selection

Model description

A coding error was found in every step of model development, CL = TVCL**EXP(ET1). The correct equation should be CL = TVCL*EXP(ET1). The impact of this error on model development and parameter estimates was evaluated by the reviewer. The overall model development was not significantly impacted while the between-subject variability (BSV) and between-occasion variability (BOV) for CL were significantly underestimated.

The one-compartmental model with two parallel input functions (a first-order input and a zero-order input with a lag-time) was found to be the best model to describe the in vivo drug release for the desvenlafaxine SR dosage form based on the population pharmacokinetic analysis of data collected from healthy subjects in five Phase 1 studies. Creatinine clearance (CRCL) and body weight were shown to be the major factors affecting desvenlafaxine CL/F in the population PK analysis. To avoid confounding covariate effects in model building, the effects of creatinine clearance and body weight on CL/F were added to the base model as follow:

$CL/F = [CLr/F \times (CRCL/110) + CLm/F] \times (Weight/70)^{\theta 1}$

where the total body clearance, CL/F was defined as the sum of renal clearance (CLr/F) and non-renal clearance (CLm/F). In addition, body weight was shown to be the primary factor affecting desvenlafaxine V/F and was added to the base model as follow:

$V/F = Vd/F \times (Weight/70)^{\theta 2}$

In order to avoid over-parameterization of the model, the applicant fixed Ka, d2, EE1 and tlag parameters and their BSV and BOV to prior estimates of the parameters from population pharmacokinetic analysis of the data from the Phase 1 studies. These parameters described the absorption of the drug from the SR dosage form. The sparse PK samples collected from MDD patients were not adequate to estimate these parameters. The reviewer evaluated the case where all the parameters were fitted simultaneously and found the results are similar to the applicant's original results.

In the final model, the effects of creatinine clearance, body weight, age group, dose, alkaline phosphatase level, multiple dose and gender were significant factors on CL/F of desvenlafaxine. Body weight, gender and food were significant factors on V/F.

Parameter estimation results

The parameter estimates, their estimation precision, inter-individual variability and residual error were tabulated in Table 2. The correct BSV and BOV for CLr/F should be 30% and 9.7% after the coding error is corrected (CL = TVCL*EXP(ET1)). All other parameters only changed in a minor manner as a result of this correction (not listed).

Table 2. **Population Pharmacokinetics Parameters of Desvenlafaxine in MDD Patients Obtained from the Final Model**

Parameters	Mean [a]	BSV (%)[b]	BOV (%)[c]
CLr/F (L/hr) [d, e]	8.12 (17)	12 (11)	3.2 fixed
CLm/F (L/hr) [d, e]	11.4 (13)	-	-
V/F (L) [d, e]	323 (6)	22 (17)	9.5 fixed
Ka (hr-1)	0.514 fixed	61.1 fixed	The same as BSV
D2 (hr)	24.2 fixed	23.9 fixed	0. fixed
EE1 f	1.61 fixed	111 fixed	0. fixed
Tlag (hr)	0.289 fixed	14 fixed	The same as BSV
Effect of WT on CL/F	0.24 (59)	-	-
Effect of WT on V/F	0.77 (21)	-	-
Effect of Age Group on CL/F	0.14 (52)	-	-
Effect of Gender on CL/F	-0.26 (15)	-	-
Effect of Gender on V/F	-0.091 (50)	-	-
Effect of Dose on CL/F	-0.039 (26)	-	-
Effect of MD on CL/F	-0.18 (15)	-	-
Effect of Food on V/F	-0.093 (54)	-	-
Effect of ALKP on CL/F	-0.20 (60)	-	-

Proportional residual error 9.3 %, additive residual error 2.7 for Study 170 and 171
Proportional residual error 13.3 %, additive residual error 2.7 for Study 172, 175 and 180
Proportional residual error 29 % for Study 306
[a] Parameter precision is expressed as coefficient of variation (% CV)
[b] BSV = between subject variability calculated as $(\text{variance})^{1/2}*100$ and its precision as % CV for all PK parameters except EE1 which is calculated as $(\text{variance})^{1/2}$
[c] BOV = between occasion variability calculated the same way as BSV
[d] $CL/F = CLr/F *(CRCL/110) + CLm/F *(ALKP/74)^{-0.2}$
CL/F and V/F of the population mean values were normalized to 70 kg body weight.
[e] Correlation between CL/F and V/F is 0.43, calculated as covariance12 ÷ $(\text{variance1}*\text{variance2})^{1/2}*100$, where variance1 and variance2 are variances of random effects for the two parameters and covariance12 is their covariance
[f] F1 = exp(EE1)/(1+exp(EE1)) = 83 %, F2 = 1 – F1 = 17 %

The updated parameters after two external datasets were combined with the model development dataset are comparable to the original parameters (Table 3)

Table 3. **Comparison of Mean (%CV) Population Pharmacokinetics Parameters of Desvenlafaxine in the MDD Patients**

Parameters	Study 307, 223 and 306[a]	Study 223 and 306[b]	Study 306[e]	Bootstrap[c]
CLr/F (L/hr) d	8.0 (18)	7.9 (18)	8.1 (17)	8.04 (14)
CLm/F (L/hr) d	11.5 (13)	11.5 (13)	11.4(13)	11.4 (10)
V/F (L) d	323 (6)	322 (6)	323 (6)	322 (4)
BSV of CL/F	11 % (11)	11 % (11)	12 % (11)	12 % (4)
BSV of V/F	22 % (19)	22 % (18)	22 % (17)	21 % (6)
Effect of WT on CL/F	0.26 (52)	0.27 (50)	0.24 (59)	0.25 (41)
Effect of WT on V/F	0.78 (21)	0.78 (21)	0.77 (21)	0.76 (15)
Effect of Age Group on CL/F	0.15 (46)	0.15 (49)	0.14 (52)	0.15 (42)
Effect of Gender on CL/F	-0.25 (14)	-0.26 (14)	-0.26 (15)	-0.26 (13)
Effect of Gender on V/F	-0.08 (58)	-0.08 (57)	-0.091 (50)	-0.11 (34)
Effect of Dose on CL/F	-0.036 (29)	-0.036 (30)	-0.039 (26)	-0.040 (20)
Effect of MD on CL/F	-0.18 (15)	-0.18 (15)	-0.18 (15)	-0.18 (12)
Effect of Food on V/F	-0.091 (55)	-0.086 (58)	-0.093 (54)	-0.093 (40)
Effect of ALKP on CL/F	-0.19 (65)	-0.20 (61)	-0.20 (60)	-0.18 (55)

[a] Mean (%CV) of population PK parameter estimates after including studies 223 and 307
[b] Mean (%CV) of population PK parameter estimates after including study 223
[c] Mean (%CV) of 1000 repli cates by bootstrap method
[d] $CL/F = CL_r/F*(CRCL/110) + CL_m/F*(ALKP/74)^{-0.2}$
CL/F and V/F of the population mean values were normalized to 70 kg body weight.
[e] Mean (%CV) of population PK parameter estimates from raw final model

Goodness of fit

The diagnostic plots shown in Figures 1-2 demonstrated the goodness of fit of the final population pharmacokinetic model for data from study 306 (Figure 2) and phase 1 studies (Figure 3).

Figure 2. Desvenlafaxine Data from Study 306 Goodness of Fit Plots

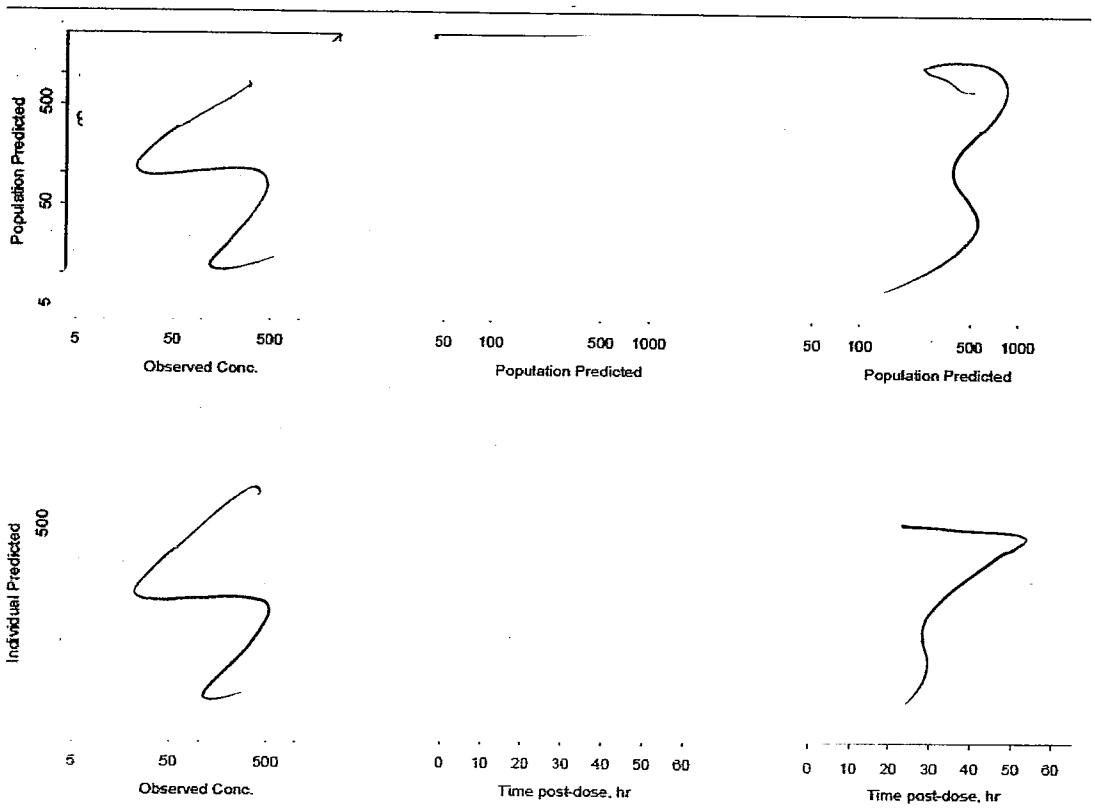


Figure 3. Desvenlafaxine Data from Phase 1 Studies Goodness of Fit Plots

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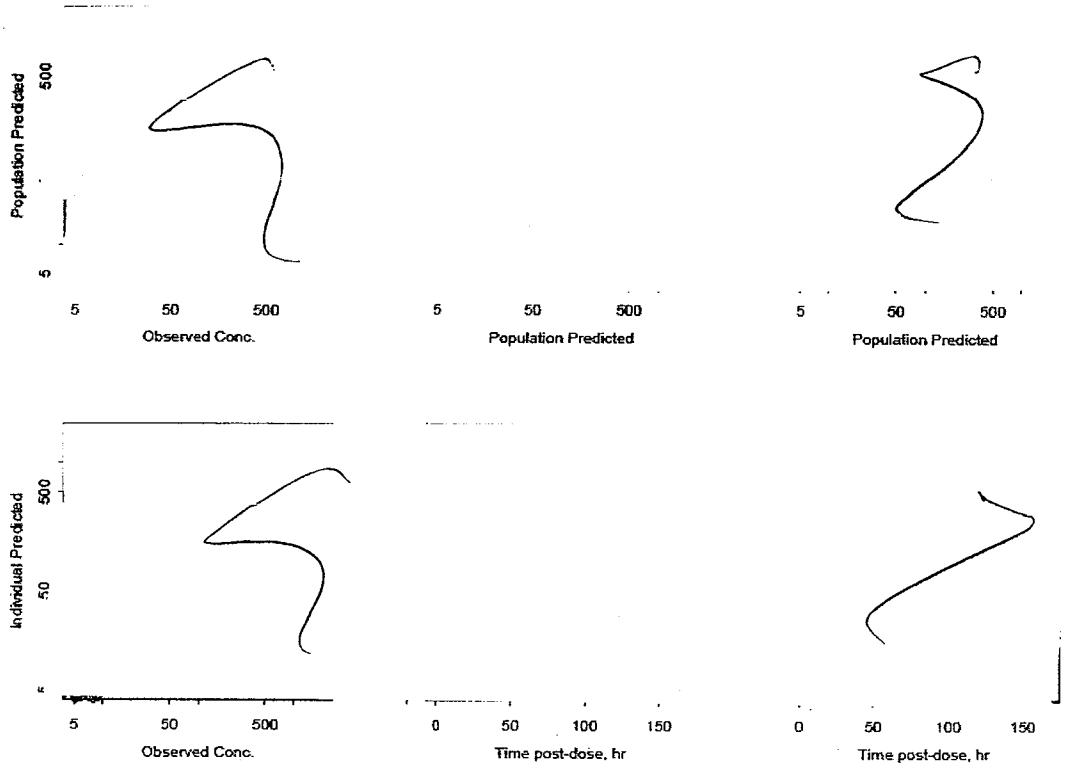


Covariate Selection

Several covariates were identified during the model building evaluation. Renal function, body weight, age, gender, dose, food and liver function were found to affect the CL/F and/or V/F to various degrees.

Since lack of race effect from this analysis is proposed to be included in the product label, power evaluation was conducted to confirm this result is not due to the lack of power. The race distribution in the model development dataset is listed in Table 4. The following assumptions were made for the power evaluation:

1. 30% difference in CL between any two races will be considered significant
2. Bonferroni method is used to adjust type I error for multiple comparisons
3. 32% between subject variability for CL based on individual post-hoc CL estimate
4. ANOVA test for race effect at alpha level of 0.05
5. Shrinkage due to empirical Bayesian estimation of individual CL is ignorable given the standard deviation of individual post-hoc ETA_CL is 0.32 and the square root of the BSV variance estimate for CL is 0.41 (0.32/0.41=0.79).

The result of the power evaluation showed that given the distribution of the various races in the dataset, the power to detect a significant race effect (30%) on CL is more than 95%. Therefore, the lack of race effect is not due to a lack of power to detect such an effect.

Table 4. **Race Distribution in Model Development Dataset**

Race/Ethnicity	Phase 3 Study 306 (N=293)	Phase 1 Studies (N=182)	Overall (N=475)
Caucasian	226	104	330
Black	25	60	85
Hispanic	32	0	32
Others	10	18	28

Model Evaluation

The applicant conducted internal (1000 bootstrap) and external model evaluation to evaluate the stability and predictive performance of the final population pharmacokinetic model. The results of these evaluations supported the final model. The details of the results were referenced to the applicant's original population PK report (rpt-58974.pdf, rpt-58975.pdf and rpt-58976.pdf) to avoid duplication of too many plots.

Pharmacokinetic/Pharmacodynamic Correlation for Efficacy

For PK/PD efficacy model, the applicant only submitted a brief summary without detailed report and results. The applicant reported that both linear model and logistic regression suggested that with higher concentrations of DVS, a greater drop in HAM-D17 scores or higher odds of HAM-D17 response could be expected. The applicant mentioned that the results should be interpreted with caution since the concentration data only explained a small amount of the variability in the data (adjusted R^2=6%) and the odds ratio for desvenlafaxine concentration was 1.001 (CI, 1.001, 1.002). Similar results were obtained when AUC was used as the exposure variable (adjusted R^2=2.57%). The reviewer conducted independent analysis and confirmed the applicant's overall results.

Pharmacokinetic/Pharmacodynamic Correlation for Safety

Even though sustained hypertension is related to dose for venlafaxine, the parent compound of desvenlafaxine, the applicant observed the lack of a clear dose-hypertention relationship for desvenlafaxine. Therefore, the reviewer conducted independent analysis to explore the relationship between desvenlafaxine and sustained hypertension defined as supine diastolic blood pressure (SDBP) >/= 90 mm Hg and >/= 10 mm Hg above baseline for 3 consecutive on-therapy visits. a definition used for venlafaxine in its product label. A clear dose dependent relationship was demonstrated by both the frequency summary (0) and the results from a logistic modeling (0).

Figure 4. Dose Dependent Sustained Hypertension

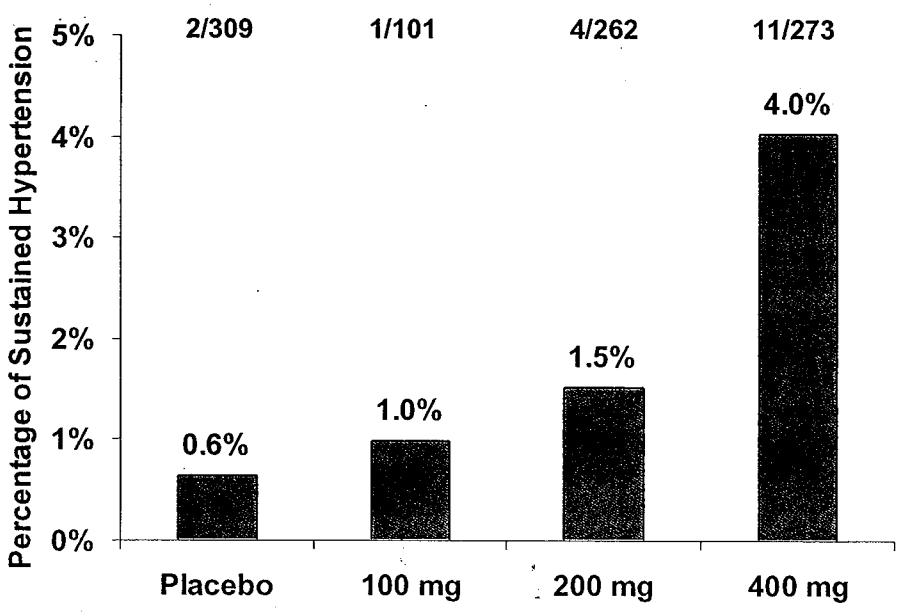


Table 5. **Logistic Modeling Results for Sustained Hypertension**

Parameter	N	Estimate	SE	Odds Ratio (95% CI)	p-value
Dose	945	0.00474	0.0017	1.005 (1.001, 1.008)	0.0046
Hosmer-Lemeshow Goodness-of-fit Test=0.01 with 2 Degree of Freedom (p-value=0.995)				Area Under the ROC Curve=0.693	

Discussion and Conclusion

The population pharmacokinetics of desvenlafaxine was described reasonably well by the model developed by the applicant.

Dosing errors were found in the data sets used for analysis. Even though the impact of these errors may not be significant, maximum efforts should be applied to ensure the quality of the data sets.

A coding error related to the between-subject variability for CL led to significant underestimates of between-subject and between-occasion variability for CL even though the overall model development and other parameter estimates were not affected dramatically.

The identified effects of renal and hepatic functions on drug clearance are consistent with the findings from renal and hepatic impairment studies. Given the significant change in AUC of desvenlafaxine for patients with severe and end-stage renal disease suggested by both population pharmacokinetic analysis and the renal impairment studies, dose for these patients should be reduced to half of the standard dose for patients with normal renal function.

The lack of race effect on desvenlafaxine pharmacokinetics was supported by the power evaluation. The detailed proportions of the relevant races, however, need to be specified in the label to clarify that some minor races were combined into one category and not enough information was available for those individual races to be evaluated separately.

The applicant developed a pharmacokinetic/pharmacodynamic relationship between desvenlafaxine plasma exposure and change from baseline on the HAM-D17 total score. The small proportion of variability in HAM-D17 total score explained by the desvenlafaxine exposure suggested that the other unidentified factors also contribute to the variability in HAM-D17 total score and the studied exposure range may be located around the plateau region on the exposure-response curve.

Since sustained hypertention was dose related for venlafaxine, the parent compound of desvenlafaxine. With the same definition of sustained hypertension as in venlafaxine's product label, desvenlafaxine was also found to cause sustained hypertension in a dose dependent manner even though the applicant observed a lack of dose-hypertension relationship based on other definition for hypertension.

Recommendations

Dose for patients with severe and end-stage renal disease should be reduced to half of the standard dose for patients with normal renal function.

Population PK analysis showed that race (White N=330, Black N=85, Hispanic N=32, Other N=28) had no apparent impact on the pharmacokinetics of desvenlafaxine.

Dose-dependent sustained hypertension should be added to the label as a warning.

General Comments to be Sent to Applicant

- More efforts should be put to ensure the quality of data sets for analysis
- More efforts should be put to QC the accuracy of codes for population pharmacokinetics to avoid overhaul of the whole model development.
- The unusually low between-subject variability (11%) for CL/F should have raised enough concern to look for errors in coding or datasets.

_____Date: _____
Yaning Wang, Ph.D.
Pharmacometrics Reviewer

o

Office of Clinical Pharmacology

Concurrence: Joga Gobburu, Ph.D. (TL) _____Date: _____

4 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 3

STUDY REPORT: CSR-58754 **ITEM-VOLUME-PAGE:** 1 TO 309

TITLE: A SINGLE-DOSE, DOUBLE-BLIND, CROSSOVER, PLACEBOAND MOXIFLOXACIN-CONTROLLED STUDY OF THE EFFECTS OF DVS-233 SR ON CARDIAC REPOLARIZTION IN HEALTHY ADULT FEMALE SUBJECTS

INVESTIGATOR:

STUDY CENTER:

STUDY PERIOD:
17 January 2005 to 28 February 2005

OBJECTIVES:

- The primary objective of this study was to assess the effect of desvenlafaxine succinate monohydrate (DVS) sustained-release (SR) formulation on the QT interval corrected for heart rate (QTc). The secondary objective was to characterize the pharmacokinetic and pharmacodynamic (PK/PD) relationships.

DESIGN:
This was a randomized, single-dose, double-blind, placebo- and moxifloxacin-controlled, 4-period crossover study. Each period had a 1-day placebo run-in period. There was a 5-day washout period between doses.

POPULATION:
Seventy-one (71) healthy women, ranging in age from 18 to 54 years (mean, 41.1 years) and in weight from 60 to 80 kg (mean 68.8 kg) were enrolled in this study. The demographics are listed in Table 1.

Table 1: Demographics

Characteristic	Treatment Sequence: D200/D600/ Mox/Pbo (n=18)	D600/Pbo/ D200/Mox (n=18)	Mox/D200/ Pbo/D600 (n=17)	Pbo/Mox/ D600/D200 (n=18)	Total (n=71)
Age (year)					
n	18	18	17	18	71
Mean	43.17	37.94	42.12	41.39	41.14
Standard deviation	10.99	8.91	10.16	8.91	9.77
Minimum	18.00	21.00	21.00	24.00	18.00
Maximum	54.00	53.00	54.00	53.00	54.00
Median	47.50	40.00	44.00	42.00	42.00
Sex					
Female	18 (100)	18 (100)	17 (100)	18 (100)	71 (100)
Race					
Asian	0	0	1 (5.9)	0	1 (1.4)
Black or African American	2 (11.1)	2 (11.1)	2 (11.8)	3 (16.7)	9 (12.7)
Other	0	1 (5.6)	0	0	1 (1.4)
Other: Native Hawaiian/ Alaska Native	0	1 (5.6)	0	0	1 (1.4)
Other: Mestisa	0	0	1 (5.9)	0	1 (1.4)
Other: Mulata	0	1 (5.6)	0	0	1 (1.4)
White	16 (88.9)	13 (72.2)	13 (76.5)	15 (83.3)	57 (80.3)
Ethnic origin					
Hispanic or Latino	18 (100)	17 (94.4)	17 (100)	16 (88.9)	68 (95.8)
Non-Hispanic and Non-Latino	0	1 (5.6)	0	2 (11.1)	3 (4.2)
Baseline height (cm)					
n	18	18	17	18	71
Mean	161.11	160.11	158.35	160.64	160.08
Standard deviation	6.99	5.79	5.04	6.73	6.15
Minimum	147.00	146.00	152.00	150.00	146.00
Maximum	175.00	167.00	168.00	170.00	175.00
Median	159.00	161.50	157.00	160.50	159.00
Baseline weight (kg)					
n	18	18	17	18	71
Mean	70.67	69.20	67.01	68.19	68.79
Standard deviation	8.42	6.64	5.28	7.48	7.05
Minimum	60.00	60.00	60.00	60.00	60.00
Maximum	88.00	80.00	75.00	84.00	88.00
Median	69.80	69.50	67.00	66.85	68.00
BMI (kg/m**2)					
n	18	18	17	18	71
Mean	27.21	27.00	26.80	26.40	26.85
Standard deviation	2.54	2.23	2.67	1.99	2.34
Minimum	22.73	22.41	22.59	22.98	22.41
Maximum	30.59	30.02	30.02	29.76	30.59
Median	26.87	27.81	27.25	26.41	27.24

Abbreviations: BMI = body mass index; D200 = DVS SR 200 mg; D600 = DVS SR 600 mg; Mox = moxifloxacin; Pbo = Placebo.

DURATION:
Two months.

PROCEDURE:
This was a randomized, single-dose, double-blind, placebo- and moxifloxacin-controlled, 4-period crossover study. Each period had a 1-day placebo run-in period. There was a 5-day washout period between doses.

All measurements of ECG intervals were performed blinded on digital, standard 12-lead ECG by a qualified vendor. With the exception of the screening visit and day -2 visits, ECGs were collected in triplicate at each nominal time point, 1 to 2 minutes apart. The triplicate tracings were

averaged at each nominal time point for each subject. Statistical analyses were conducted on the averages of the triplicate.

For each subject, treatment period, and ECG sampling time, the sample collected on day -1 and day 1 hour 0 before test article administration (predose sample) was subtracted from the measurement collected on study day 1, 2 3, 4, and 5 at the same nominal clock time after test article administration (postdose sample). The computation of time-matched baseline-adjusted measurements is listed in table 2.

Three (3) different heart rate correction formulas were applied to the data: the QT interval corrected by Fridericia's formula (QTcF) and population-specific correction formula (QTcN) as primary corrections, and QT interval corrected by Bazett's formula (QTcB) as a secondary correction.

Table 2: Computation of Time-Matched Baseline-Adjusted Measurements for Each Subject and Treatment Period

	Predose Sample		Postdose Sample		
Study Hour [a]	Study Day/ Clock Time	Sample	Study Day/ Clock time	Sample	Time-Matched Baseline-Adjusted Sample
0.5	-1/0830	Predose1	1/0830	Postdose1	Postdose1 -Predose1
1	-1/0900	Predose 2	1/0900	Postdose2	Postdose2 -Predose2
2	-1/1000	Predose 3	1/1000	Postdose3	Postdose3 -Predose3
4	-1/1200	Predose 4	1/1200	Postdose4	Postdose4 -Predose4
6	-1/1400	Predose 5	1/1400	Postdose5	Postdose5 -Predose5
8	-1/1600	Predose 6	1/1600	Postdose6	Postdose6 -Predose6
10	-1/1800	Predose 7	1/1800	Postdose7	Postdose7 -Predose7
12	-1/2000	Predose 8	1/2000	Postdose8	Postdose8 -Predose8
16	-1/2400	Predose 9	1/2400	Postdose9	Postdose9 -Predose9
24	1/0800[a]	Predose 10	2/0800	Postdose10	Postdose10 -Predose10
48	1/0800[a]	Predose 10	3/0800	Postdose11	Postdose11 -Predose10
72	1/0800[a]	Predose 10	4/0800	Postdose12	Postdose12 -Predose10
96	1/0800[a]	Predose 10	5/0800	Postdose13	Postdose13 -Predose10

a: The study hour 0 sample collected on study day 1 at 0800 was taken before test article administration and was treated as the predose sample for the sample collected at study hours 24, 48, 72, and 96.

Blood samples (5 mL) were collected to measure concentrations of desvenlafaxine and moxifloxacin. Blood samples were collected on study day 1 before (predose), and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours after test article administration in study periods 1, 2, 3, and 4. The predose samples could be collected within 2 hours before dose administration at the same time as the blood sample for laboratory evaluations.

LOT:

TEST FORMULATION

DVS SR 200-mg tablets administered as single oral doses of 200 mg or 600 mg (batch number A83596). Matched placebo for DVS SR (batch number 2003B0035).

REFERENCE FORMULATION

Moxifloxacin (400 mg tablets) administered orally (batch number 2004B0210) and matched placebo for moxifloxacin (batch number 2004B0209).

STATISTICS:

PHARMACODYNAMIC ANAYLSIS:

The main focus of the analysis was the comparison of QTc for the 200- and 600-mg doses of DVS SR to placebo. The primary statistical objective was to estimate the effect on QTc at the

postdose 8 hour time point. For each dose of DVS SR, a 90% confidence interval (CI) for the baseline-adjusted difference in QTc at the postdose 8 hour time point between the active treatment and placebo was computed. The change from baseline QTc averaged over postdose hours 6, 8, and 10 sampling times (AvgQTc) was statistically analyzed as a secondary endpoint. An analysis was also conducted on the change from baseline QTc at the most commonly occurring observed value (ie, mode) of tmax if it was not 8 hours. The tracings' change from baseline in QTcB was also analyzed. Moxifloxacin was statistically compared with placebo at postdose hour 1, the reported tmax, and the most commonly occurring observed value of tmax for assay sensitivity.

PHARMACOKINETIC ANAYLSIS:
The plasma concentrations of desvenlafaxine and moxifloxacin were analyzed using model-independent pharmacokinetic methods. Single-dose pharmacokinetics were derived from the plasma concentration versus time data.

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) ANAYLSIS:
The PK/PD relationship for desvenlafaxine and moxifloxacin in relation to QT interval was examined graphically using plots showing the time course of desvenlafaxine and QTc and moxifloxacin and QTc based on a population-specific correction formula (QTcN). Hysteresis plots showing concentrations of desvenlafaxine and moxifloxacin versus QT values were also examined. The relationship between desvenlafaxine concentrations and QTcN were modeled using a nonlinear mixed-effect model. An Emax model was used to describe both desvenlafaxine and moxiflo xacin plasma concentrations in relation to QTc data.

RESULTS:

Pharmacodynamic:
The applicant applied the method recommended by ICH E14 with primary focus on only one time point, the postdose 8 hour time point. The 90% CIs at 8 hours postdose for DVS SR 200 mg compared with placebo of QTcF and QTcN were (-0.88, 3.88) and (0.87, 5.50) ms, respectively, and for DVS SR 600 mg, the 90% CIs were (-4.90, 0.04) and (-1.42, 3.38) ms, respectively. All CIs at other time points were exclusive of and less than10 ms (Table 3).

Moxifloxacin was used as a positive control to establish assay sensitivity. Moxifloxacin produced a statistically significant increase over placebo in QTcF and QTcN at the population tmax (postdose hour 1) and the tmax of this study, postdose hour 4. The 90% CI at postdose hour 1 for QTcF and QTcN were (2.77, 7.49) ms and (2.88, 7.47) ms, respectively. At postdose hour 4, the 90% CIs were (8.44, 13.16) ms and (8.62, 13.22) ms, respectively. The CIs for both corrections were inclusive of and exceeded 10 ms at hour 4 after moxifloxacin administration.

No subject had a single observed QTc >500 ms for any of the corrections.

Table 3: Mean and 90% CI Estimates of Change from Baseline in QTcF

Comparison with Placebo	Estimate	Lower	Upper
0.5 hours for 200mg	2.1822	-0.1966	4.561
0.5 hours for 600mg	0.7797	-1.6874	3.2468
1 hours for 200mg	1.5263	-0.8628	3.9155
1 hours for 600mg	1.8004	-0.6667	4.2675
1.5 hours for 200mg	1.5691	-0.8098	3.9479
1.5 hours for 600mg	0.9817	-1.4858	3.4491
2 hours for 200mg	1.1774	-1.2012	3.5561
2 hours for 600mg	1.0958	-1.3713	3.563
4 hours for 200mg	-0.4385	-2.8173	1.9402
4 hours for 600mg	-3.699	-6.1661	-1.2319
6 hours for 200mg	-2.6419	-5.0216	-0.2621
6 hours for 600mg	-5.9685	-8.4357	-3.5013
8 hours for 200mg	***1.5026***	***-0.8768***	***3.8819***
8 hours for 600mg	***-2.4291***	***-4.8975***	***0.03932***
10 hours for 200mg	3.7641	1.3849	6.1432
10 hours for 600mg	1.4051	-1.0624	3.8725
12 hours for 200mg	2.0047	-0.374	4.3834
12 hours for 600mg	-1.5523	-4.0199	0.9154
16 hours for 200mg	-0.8812	-3.2606	1.4982
16 hours for 600mg	-5.1237	-7.591	-2.6564
24 hours for 200mg	0.6972	-1.6823	3.0768
24 hours for 600mg	-1.6996	-4.1684	0.7692
48 hours for 200mg	-1.0961	-3.4756	1.2835
48 hours for 600mg	-2.0819	-4.5507	0.3869
72 hours for 200mg	1.8603	-0.5193	4.2398
72 hours for 600mg	1.2451	-1.2478	3.738
96 hours for 200mg	-1.2087	-3.5883	1.1708
96 hours for 600mg	-3.7314	-6.2113	-1.2514

Pharmacokinetic:

Desvenlafaxine (Table 4): Cmax and AUC values increased approximately 3-fold when results for the 600-mg dose were compared with the 200-mg dose of DVS SR. Cl/F and Vz/F were approximately similar for the 200- and 600-mg doses of DVS SR. The greatest number of tmax values occurred at hour 6 for both the 200- and 600-mg doses of DVS SR. This was closely followed by the hour 8 sampling time.

Moxifloxacin (Table 5): The majority of tmax values (approximately 69%) occurred at hour 4 for the 400-mg dose of moxifloxacin. The average t1/2 was approximately 14 hours. Plasma concentrations of moxifloxacin were quantifiable out to 72 hours in many subjects. A few subjects had quantifiable plasma concentrations of moxifloxacin out to 96 hours.

Table 4: Pharmacokinetic Parameters of Desvenlafaxine after Single Oral Doses in Healthy Female Volunteers

Treatment Dose		Cmax (ng/mL)	tmax (h)	t1/2 (h)	AUCT (ng*h/mL)	AUC (ng*h/mL)	Cl/F (L/h/kg)	Vz/F (L/kg)
DVS SR 200 mg	Mean± SD	470 ± 87	7 ± 3	9.2 ± 1.5	10731 ± 3017	10566 ± 2396	0.293 ± 0.084	3.80 ± 0.81
	%CV	19%	36%	17%	28%	23%	29%	21%
	N	63	62	61	62	61	61	61
	Geom. Mean	462	7	9.1	10343	10268	0.284	3.72
	Min – Max	279 – 802	2 – 16	5.6 – 13.3	3506 – 25104	3533 – 15872	0.18 – 0.7	2.68 – 6.43
DVS SR 600 mg	Mean± SD	1466± 318	8 ± 3	9.2 ± 1.5	31414 ± 7120	31522 ± 7148	0.334 ± 0.385	4.28 ± 4.62
	%CV	22%	34%	16.0%	23%	23%	115%	108%
	N	55	54	54	54	54	54	54
	Geom. Mean	1419	8	9.0	30041	30151	0.289	3.77
	Min – Max	290 – 2027	2 – 16	6.2 – 13.4	3192 – 44892	3253 – 45536	0.18 – 3.07	2.65 – 37.28

Table 5: Pharmacokinetic Parameters of Mosifloxacin after Single Oral Doses in Healthy Female Volunteers

Treatment		Cmax (ng/mL)	tmax (h)	t1/2 (h)	AUCT (ng*h/mL)	AUC (ng*h/mL)	Cl/F (L/h/kg)	Vz/F (L/kg)
Moxifloxacin 400 mg	Mean± SD	2967 ± 508	4 ± 1	14.2 ± 3.8	40874 ± 7536	42335 ± 7387	0.144 ± 0.025	2.86 ± 0.72
	%CV	17%	30%	27 %	18%	17%	18%	25%
	N	65	65	65	65	65	65	65
	Geom. Mean	2925	4	13.7	40173	41690	0.141	2.78
	Min – Max	1923 – 4373	1 – 6	8.6 – 23.4	25033 – 66018	26234 – 67588	0.09 – 0.20	1.83 – 5.74

Pharmacokinetic/Pharmacodynamic:
The applicant examined the PK/PD relationship for desvenlafaxine and moxifloxacin in relation to QT using plots showing the QTc based on a population-specific correction formula (QTcN) versus plasma concentrations of desvenlafaxine and moxifloxacin (Figure 1 and Figure 2).

Figure 1. Population-Based QTc Shown as Change From Baseline Versus Plasma Concentrations of Desvenlafaxine

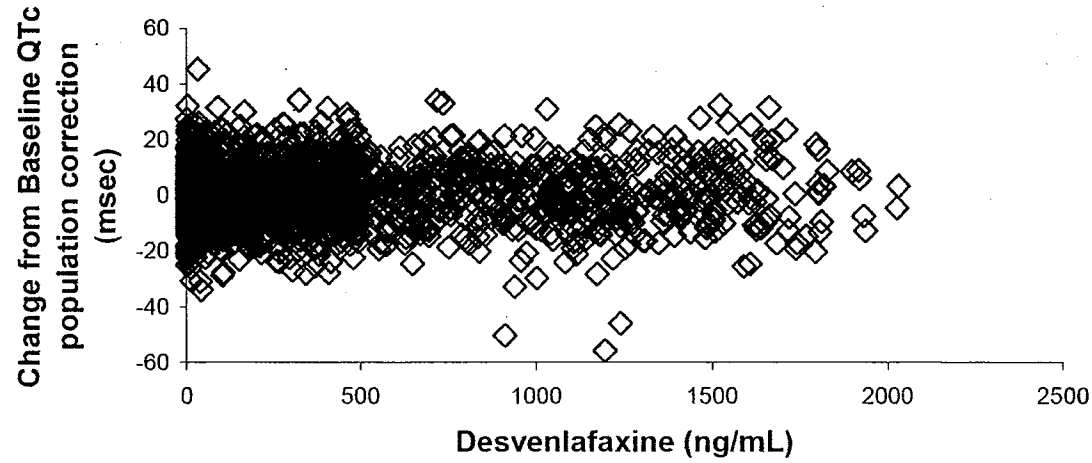
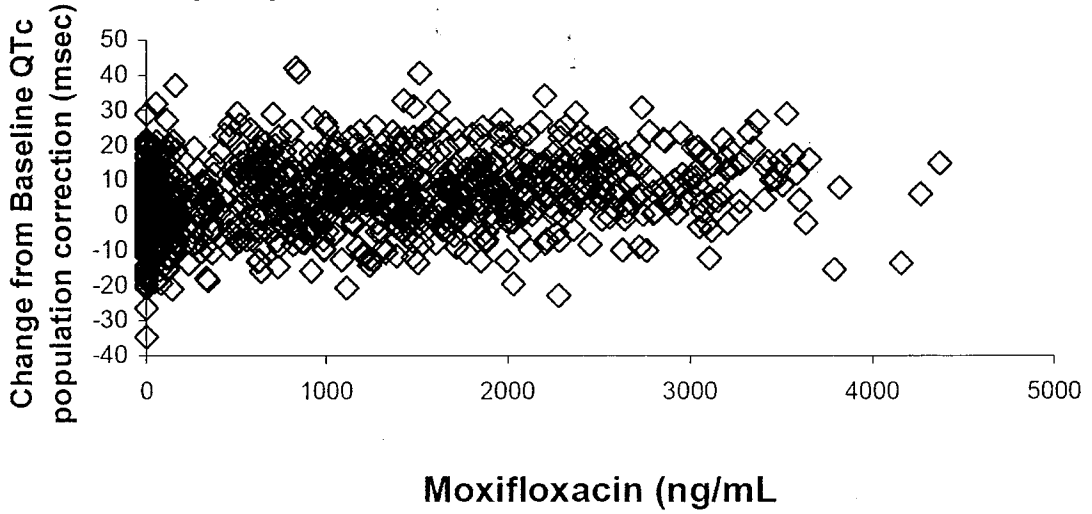


Figure 2. Population-Based QTc Shown as Change From Baseline Versus Plasma Concentrations of Moxifloxacin



The applicant also examined the relationship between concentrations of desvenlafaxine and moxifloxacin and QT (described by QTc using the population correction) using both Emax and linear models (Tables 6-9):
E_{max} model: $QTc = E_0 + (E_{max} * C) / (C + EC_{50})$ Equation (1)
Linear model: $QTc = E_0 + Slope*C$ Equation (2)

For desvenlafaxine, both the E_{max} and linear models had poor predicative value because of high variability in the parameters' estimate, indicating that the data gave no clear evidence of any relationship between desvenlafaxine concentrations and QTc.

Both the E_{max} and the linear models provided a good fit to the data for moxifloxacin and indicated a positive increase in QTc for the observed concentrations of moxifloxacin. The E_{max} model estimated a population mean maximum increase in QTc for moxifloxacin of 9.7 ms. Using the linear model, the observed C_{max} of 2967 ng/mL would predict an 8.3 ms increase in QTc.

The results from PK/PD analysis supported the pharmacodynamic analysis results based on ICH E14 method.

Table 6: Parameter Estimates for an Emax Model Describing the Effect of Desvenlafaxine Concentrations on Population-Predicted QTc Values

Parameter (-2* Log-likelihood = 10982)	E0 (ms)	Emax (ms)	EC50 (ng/mL)
Population Mean ± SE	406 ± 1.33	1.74 ± 4.09	1,690 ± 7,990
Population Variability as %CV	2.5% ± 0.94%	566% ± 874%	668% ± 1113%

Table 7: Parameter Estimates for a Linear Model Describing the Effect of Desvenlafaxine Concentrations on Population-Predicted QTc Values

Parameter (-2* Log-likelihood = 10985)	E0 (ms)	Slope (ms/[ng/mL])
Population Mean ± SE	406 ± 1.25	0.00052 ± 0.00063
Population Variability as %CV	2.49% ± 0.9%	764% ± 1237%

Table 8: Parameter Estimates for an Emax Model Describing the Effect of Moxifloxacin Concentrations on Population-Predicted QTc Values

Parameter[a] (-2* Log-likelihood = 5380)	E0 (ms)	Emax (ms)	EC50 (ng/mL)
Population Mean ± SE	406 ± 1.31	9.70 ± 1.14	507 ± 191
Population Variability as %CV	2.39% ± 0.9%	42.7% ± 30%	NCa

a: Parameter not estimated.

Table 9: Parameter Estimates for a Linear Model Describing the Effect of Moxifloxacin Concentrations on Population-Predicted QTc Values

Parameter (-2* Log-likelihood = 5416)	E0 (ms)	Slope (ms/[ng/mL])
Population Mean ± SE	408 ± 1.22	0.00279 ± 0.000315
Population Variability as %CV	2.39% ± 0.9%	55.4% ± 38%

REVIEWER'S CONCLUSIONS AND COMMENTS:

The reviewer agrees with the applicant's conclusions. The lack of QT prolonging effect due to desvenlafaxine is supported by both the max-mean approach and PK/PD analysis. The 90% CIs at 8 hours postdose for desvenlafaxine 200 mg compared with placebo of QTcF and QTcN were (-0.88, 3.88) and (0.87, 5.50) ms, respectively, and for desvenlafaxine 600 mg, the 90% CIs were (-4.90, 0.04) and (-1.42, 3.38) ms, respectively. All CIs at other time points were exclusive of and less than 10 ms. High variability in the parameters' estimate for both the E_{max} and linear models indicated that the data gave no clear evidence of any relationship between desvenlafaxine concentrations and QTc. The sensitivity of the study to detect significant QTc prolonging effect was confirmed by the positive finding for moxifloxacin. Given the proposed dose of 100 mg for desvenlafaxine, the studied dose range is sufficient to cover potential exposure encountered in clinical practice.

Study Title: An Open-Label, Randomized, Three-Period Crossover Study Of The Relative Bioavailability And Tolerability Of Two Single Doses Of Two Formulations Of Desvenlafaxine In Healthy Adults (Protocol 0600D3-167-FR, CSR-45089).

Objective: The primary objective of this study was to evaluate the relative bioavailability of 2 formulations of desvenlafaxine (O-desmethylvenlafaxine, ODV), compared with the same doses of the marketed extended-release (ER) formulation of venlafaxine. The secondary objective was to assess the safety and tolerability of single oral doses of 75 mg and 150 mg of 2 formulations of desvenlafaxine succinate (DVS-233).

Study Design: This was an open-label, randomized, single-dose, inpatient study conducted with 2 cohorts at a single investigational site. Thirty-five healthy men and women from 18 to 45 years of age inclusive participated in the study. In cohort 1, the 75-mg dose of DVS-233 immediate-release (IR) and DVS-233 sustained-release (SR) were tested in a 3-period crossover design with the 75-mg venlafaxine ER formulation. The second cohort received both DVS-233 formulations and venlafaxine ER at a dose of 150-mg (2 x 75 mg), also in a randomized, 3-period crossover design. Each subject participated in the study for approximately 29 days. There was at least 5-day washout interval between doses. The test formulations were DVS-233 (75 mg), 2 formulations, immediate release (IR) and sustained release (SR) that were administered orally; batch numbers were 2001B0149 and 2001B0139 for the IR and SR, respectively. The reference formulation was Venlafaxine ER (75 mg); batch number was 2001B0306.

At predetermined times venous blood samples (10 mL) were obtained in tubes containing sodium heparin or lithium heparin for determination of venlafaxine and desvenlafaxine plasma concentrations and of the conjugated and unconjugated metabolites of desvenlafaxine. Urine samples were collected at predose and postdose times, as indicated in the subject flow chart.

Analytical Method: Plasma samples were assayed for venlafaxine, desvenlafaxine, NDV, and NODV by using a validated high performance liquid chromatography method with fluorescence. Based on a 1.0-mL plasma sample, the method has a minimum quantifiable concentration of 5.0 ng/mL for all 4 analytes. Urine samples were assayed for unconjugated and total (unconjugated plus conjugated) venlafaxine, desvenlafaxine, NDV, and NODV by using a high performance liquid chromatography method with fluorescence detection. Based on a 0.1-mL urine sample, the method has a minimum quantifiable concentration of 0.1 µg/mL for all 4 analytes. The performance of the venlafaxine, desvenlafaxine, NDV, and NODV assays during the analysis of the plasma samples, urine samples are summarized in the following tables.

Table 6.5.2A. Assay Range and Sensitivity for Plasma Samples

	Compound/Matrix			
Standard Curve	Venlafaxine/Plasma	ODV/Plasma	NDV/Plasma	NODV/Plasma
Linear range (ng/mL)	5.0-500	5.0-500	5.0-500	5.0-500
Sensitivity (ng/mL)	5.0	5.0	5.0	5.0

Abbreviation: ODV = O-desmethylvenlafaxine or desvenlafaxine, NDV = N-desmethyl-venlafaxine, NODV = N,O-didesmethylvenlafaxine

Table 6.5.2B. Summary of Assay Validation and in-Process Performance for Plasma Samples

Assay	Compound/Matrix: Venlafaxine/Plasma		ODV/Plasma		NDV/Plasma		NODV/Plasma	
Standards/QCs	Interday	Intraday	Interday	Intraday	Interday	Intraday	Interday	Intraday
Validation standards/QCs[a]								
Accuracy (%)	-3.5, 3.2	-2.0, 5.3	-1.7, 3.0	-2.0, 5.3	-2.0, 2.2	-2.8, 4.0	-6.6, 4.0	-3.0, 3.5
Precision (%)	0.4, 4.8	0.6, 3.3	0.0, 4.7	0.6, 3.3	0.5, 5.7	0.5, 4.0	0.9, 8.6	0.7, 7.4
In-process standards[a]								
Accuracy (%)	-3.2, 5.5	--	-2.6, +3.2	--	-3.2, 4.5	--	-2.7, 2.3	--
Precision (%)	2.4, 7.6	--	2.9, 7.1	--	2.9, 7.5	--	3.6, 9.4	--
In-process QCs[a]								
Accuracy (%)	-0.7, 5.8	--	-1.6, 6.9	--	0.5, 4.8	--	0.4, 8.7	--
Precision (%)	3.7, 6.3	--	4.4, 5.9	--	4.1, 6.2	--	7.1, 9.3	--

a: Values are ranges of accuracy and precision.
Abbreviations: ODV = O-desmethylvenlafaxine; NDV = N-desmethylvenlafaxine; NODV = N,O-didesmethylvenlafaxine; QC = quality control.

Table 6.5.2C. Assay Range and Sensitivity for Urine Samples

Standard Curve	Compound/Matrix: Venlafaxine/Urine (µg/mL)	ODV/Urine (µg/mL)	NDV/Urine (µg/mL)	NODV/Urine (µg/mL)
Linear range	0.10 – 10.0	0.10 – 10.0	0.10 – 10.0	0.10 – 10.0
Sensitivity	0.10	0.10	0.10	0.10

Abbreviations: ODV = O-desmethylvenlafaxine; NDV = N-desmethylvenlafaxine; NODV = N,O-didesmethylvenlafaxine.

Table 6.5.2D. Summary of Assay Validation and in-Process Performance for Urine Samples

Assay	Compound/Matrix: Venlafaxine/Urine		ODV/Urine		NDV/Urine		NODV/Urine	
Standards/QCs	Interday	Intraday	Interday	Intraday	Interday	Intraday	Interday	Intraday
Validation standards/QCs[a]								
Accuracy (%)	-4.8, 4.0	1.1, 5.2	-2.8, 3.2	-1.9, 2.0	-4.4, 6.0	-4.1, 0.4	-4.4, 10.0	-6.1, -1.2
Precision (%)	1.7, 5.8	7.4, 8.8	1.7, 4.0	1.6, 2.4	1.7, 3.8	1.6, 2.2	1.7, 3.6	4.8, 6.0
In-process standards[a]								
Accuracy (%)	-8.2, 5.3	–	-5.9, 3.5	–	-1.7, 2.4	–	-2.4, 1.7	–
Precision (%)	1.6, 9.0	–	1.8, 8.8	–	2.0, 7.9	–	2.3, 6.7	–
In-process QCs[a]								
Accuracy (%)	-2.1, 6.4	–	-1.4, 4.6	–	-1.3, 1.8	–	-5.7, 3.4	–
Precision (%)	1.9, 9.6	–	4.7, 9.4	–	0.9, 7.2	–	3.5, 8.6	–

a: Values are ranges of accuracy and precision.
Abbreviations: ODV = O-desmethylvenlafaxine; NDV = N-desmethylvenlafaxine; NODV = N,O-didesmethylvenlafaxine; QC = quality control.

Data Analysis: The venlafaxine, desvenlafaxine (ODV), NDV, and NODV plasma concentration data for each subject were analyzed by using empirical, model-independent methods.

The extent of nausea experienced by each subject was evaluated by using the visual analog scale (VAS) scores for nausea 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 for nausea is the distance (in mm) 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}) for nausea, the time of maximum VAS score (t_{Emax}) for nausea, and the area under the VAS response curve (AURC) for nausea were calculated from the observed data. The AURC was calculated over the entire 72-hour observation period by using the linear-trapezoidal rule.

Results: The following tables summarize the pharmacokinetic parameters of venlafaxine ER and desvenlafaxine at the 75- and 150-mg dose levels.

Venlafaxine ER Pharmacokinetic Parameters

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	Cl/F (L/h/kg)
75-mg venlafaxine ER					
Mean±SD[a]	40±16	5.9±0.5	9.5±2.4	628±265	2.2±1.7
%CV	39.9%	8.0%	25.6%	42.2%	80.8%
Min – Max	11 – 77	4 – 6	4.8 – 13.8	139 – 1292	0.7 – 8.9
150-mg venlafaxine ER					
Mean±SD	81±41	5.9±1.8	11.9±4.8	1609±1895	2.2±1.3
%CV	50.7%	30.6%	40.8%	117.8%	56.0%
Min – Max	29 - 178	4 - 12	5.9 – 23.5	336 – 8654	0.3 – 5.4

Abbreviation: SD = standard deviation; C_{max} = peak concentration; t_{max} = time peak plasma concentration occurs; $t_{1/2}$ = terminal-phase elimination half-life; AUC = area under the plasma concentration-time curve; and Cl/F = apparent oral dose clearance.

Desvenlafaxine Pharmacokinetic Parameters

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	Cl/F (L/h/kg)
75-mg Venlafaxine ER					
Mean±SD	88±25	9.3±2.9	13.2±4.0	2430±647	0.5±0.1
%CV	28.9%	31.2%	30.4%	26.6%	23.0%
Min – Max	37 – 142	6 – 16	7.6 – 24.8	1582 – 3835	0.3 – 0.6
75-mg DVS-233 IR					
Mean±SD	281±57	3.1±1.3	9.4±1.4	3491±814	0.3±0.1
%CV	20.1%	43.0%	14.7%	23.3%	28.0%
Min – Max	173 - 399	0.5 - 6	6.8 – 11.5	1667 – 5086	0.2 – 0.6
75-mg DVS-233 SR					
Mean±SD	135±54	7.3±5.5	9.3±1.9	3185±944	0.4±0.2
%CV	39.9%	75.4%	20.5%	29.6%	42.9%
Min – Max	65 - 279	2 - 28	6.1 – 13.7	1100 – 4767	0.2 – 0.9
150-mg Venlafaxine ER					
Mean±SD	159±50	8.6±3.4	13.1±4.0	4404±1070	0.5±0.2
%CV	31.6%	40.1%	30.2%	24.3%	31.2%
Min – Max	32 – 258	4 – 16	9.8 – 26.0	2011 – 6164	0.3 – 1.1
150-mg DVS-233 IR					
Mean±SD	532±116	3.3±1.0	8.3±1.0	6251±1567	0.4±0.1
%CV	21.9%	29.9%	12.8%	25.1%	26.8%
Min – Max	370 - 781	2 - 4	6.5 – 9.9	4091 – 9993	0.2 – 0.6
150-mg DVS-233 SR					
Mean±SD	284±83	5.6±1.1	9.1±2.1	6100±1863	0.4±0.2
%CV	29.2%	18.7%	23.3%	30.5%	41.5%
Min – Max	173 - 413	4 - 8	6.3 – 15.4	2416 – 10094	0.2 – 0.9

Abbreviation: SD = standard deviation; C_{max} = peak concentration; t_{max} = time peak plasma concentration occurs; $t_{1/2}$ = terminal-phase elimination half-life; AUC = area under the plasma concentration-time curve; and Cl/F = apparent oral dose clearance.

After administration of the DVS-233 IR and SR formulations desvenlafaxine C_{max} and AUC both were higher values than that following administration of venlafaxine ER. For DVS-233 IR, the drug was absorbed rapidly with high and early peak concentrations in all subjects. However, for the DVS-233 SR formulation, the drug was absorbed more slowly than DVS-233 IR with Tmax occurring later (7.3 ± 5.5 versus. 3.1 ± 1.3 hours at 75 mg and 5.6 ± 1.1 versus 3.3 ± 1.0 hours at 150-mg) and C_{max} being lower (135 ± 54 versus 281 ± 57 ng/mL at 75 mg and 284 ± 83 versus 532 ± 116 ng/mL at 150 mg). The total venlafaxine plus desvenlafaxine C_{max} (~129 ng/mL at 75 mg and ~240 ng/mL at 150 mg) and AUC (~3079 at 75 mg and ~6013 ng•h/mL at 150 mg) for venlafaxine ER are similar to the desvenlafaxine C_{max} and AUC for desvenlafaxine SR (C_{max} ~135 and 284 ng/mL, AUC ~3185 and 6100 ng•h/mL, at 75 and 150 mg, respectively).

Summary of the pharmacokinetic parameters of NDV after administration of 75 mg and 150 mg of venlafaxine ER are provided in the following tables. All subjects for the 2 formulations of DVS-233 had NDV concentrations below the quantifiable limit.

N-Desmethylvenlafaxine Pharmacokinetic Parameters

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	Cl/F (L/h/kg)
75-mg Venlafaxine ER					
Mean±SD	2.7±4.0	7.4±2.2	42.3±35.9	94±228	2.6±1.7
%CV	145.8%	30.0%	85%	242.1%	68.0%
Min – Max	0.0 – 14.0	6 – 12	13.5 – 82.5	0 – 800	1.4 – 4.6
150-mg Venlafaxine ER					
Mean±SD	6.9±7.3	8.9±9.6	19.6±19.4	205±326	14.0±15.7
%CV	106.0%	107.8%	99.4%	158.7%	111.7%
Min – Max	0.0 – 27.9	4 – 36	2.8 – 64.1	0 – 1107	1.8 – 52.1

Abbreviation: SD = standard deviation; C_{max} = peak concentration; t_{max} = time peak plasma concentration occurs; $t_{1/2}$ = terminal-phase elimination half-life; AUC = area under the plasma concentration-time curve; and Cl/F = apparent oral dose clearance.

Summary pharmacokinetic parameters of NODV after administration of 75 mg and 150 mg of venlafaxine ER, DVS-233 IR, and DVS-233 SR is provided in the following table. At 75 mg, only the venlafaxine ER formulations had NODV concentrations above the quantifiable lower limit.

N,O- Didesmethylvenlafaxine Pharmacokinetic Parameters

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	Cl/F (L/h/kg)
75-mg Venlafaxine ER					
Mean±SD	10.3±5.6	11.0±5.1	40.2±42.5	535±420	2.1±0.9
%CV	54.0%	46.0%	105.9%	78.5%	43.9%
Min – Max	0.0 – 22.3	6 – 24	11.2 – 178.5	0 – 1708	0.7 – 3.7
150-mg Venlafaxine ER					
Mean±SD	22.0±11.9	10.8±4.5	16.8±6.1	762±485	3.17±1.44
%CV	54.4%	41.9%	36.3%	63.6%	45.4%
Min – Max	0 – 42.5	4 - 20	8 – 26	0 – 1771	1.3 – 6.1
150-mg DVS-233 IR					
Mean±SD	5.2±4.4	6.2±1.1	21.6±12.4	157±196	8.4±5.1
%CV	84.6%	17.4%	57.5%	124.9%	60.9%
Min – Max	0.0 – 11.8	4 - 8	11.5 – 51.0	0 – 571	3.6 – 19.0
150-mg DVS-233 SR					
Mean±SD	3.5±3.5	17.8±5.3	37.7±20.8	170±267	6.5±4.7
%CV	100.1%	30.0%	55.1%	157.1%	71.4%
Min – Max	0.0 – 8.8	12 - 24	11.6 – 58.9	0 – 690	3.0 – 14.3

Abbreviation: SD = standard deviation; C_{max} = peak concentration; t_{max} = time peak plasma concentration occurs; $t_{1/2}$ = terminal-phase elimination half-life; AUC = area under the plasma concentration-time curve; and Cl/F = apparent oral dose clearance.

At the 150-mg dose, there is a significant difference in the treatments for C_{max}, t_{max}, AUC_T, AUC, and Cl/F. Venlafaxine ER C_{max} is 4- to 6-fold higher than the C_{max} of DVS-233 IR and DVS-233 SR. The NODV metabolite peaks first in DVS-233 IR ($t_{max} \approx 6.2$) then in venlafaxine ER ($t_{max} \approx 10.8$) and lastly in DVS-233 SR ($t_{max} \approx 17.8$). The NODV AUC for DVS-233 SR is only about 22% of the NODV AUC of venlafaxine ER.

Summary urinary recovery of unconjugated and total venlafaxine are provided in the following table.

Urinary Recovery of Venlafaxime

Treatment	n	Unconjugated A_e (%-Dose ± SD)	Total A_e (%-Dose ± SD)
75-mg Venlafaxine ER	18	4.3 ± 2.3	4.3 ± 2.3
150-mg Venlafaxine ER	18	5.9 ± 8.2	5.6 ± 7.6

Abbreviation: A_e = amount excreted in urine; SD = standard deviation

Summary urinary recovery of unconjugated and total desvenlafaxine are provided in the following table.

Urinary Recovery Desvenlafaxine

Treatment	n	Unconjugated A_e (%-Dose ± SD)	Total A_e (%-Dose ± SD)
75 mg			
Venlafaxine ER	18	26.0 ± 6.1	37.0 ± 6.2
DVS-233 IR	18	38.8 ± 10.6	59.7 ± 10.0
DVS-233 SR	18	35.7 ± 12.0	52.0 ± 14.2
150 mg			
Venlafaxine ER	17	24.6 ± 6.2	36.7 ± 9.5
DVS-233 IR	17	36.1 ± 7.1	52.6 ± 14.7
DVS-233 SR	17	35.3 ± 9.4	50.1 ± 17.9

Abbreviation: A_e = amount excreted in urine; SD = standard deviation.

The mean desvenlafaxine urinary recovery was higher for DVS-233 IR than for DVS-233 SR. The following table summarizes the urinary recovery of unconjugated and total NDV. The urinary excretion of unconjugated and total NDV was very similar to each other.

Urinary Recovery of N-Desmethylvenlafaxine (NODV)

Treatment	n	Unconjugated A_e (%-Dose ± SD)	Total A_e (%-Dose ± SD)
75 mg			
Venlafaxine ER	18	0.4 ± 1.0	0.5 ± 1.0
150 mg			
Venlafaxine ER	17	0.6 ± 0.9	0.6 ± 0.8

Abbreviations: A_e = amount excreted in urine; SD = standard deviation.

The following table summarizes the urinary recovery of unconjugated and total NODV.

Urinary Recovery of N, O-Didesmethylvenlafaxine

Treatment	n	Unconjugated A_e (%-Dose ± SD)	Total A_e (%-Dose ± SD)
75-mg			
Venlafaxine ER	18	4.7 ± 2.6	6.9 ± 3.0
DVS-233 IR	18	1.1 ± 0.5	2.9 ± 1.0
DVS-233 SR	18	1.0 ± 0.5	2.7 ± 1.3
150-mg			
Venlafaxine ER	17	6.3 ± 3.5	7.3 ± 4.1
DVS-233 IR	17	1.5 ± 0.7	3.2 ± 1.4
DVS-233 SR	16	1.5 ± 0.8	3.0 ± 1.4

Abbreviation: A_e = amount excreted in urine; SD = standard deviation.

After desvenlafaxine administration, approximately 1% of the dose is recovered as unconjugated NODV, and approximately 3% is recovered as total NODV. The lower recovery of NODV following desvenlafaxine administration may indicate that NODV is primarily formed by O-demethylation of NDV.

The following table provides the overall mean urinary recovery of unconjugated and total for all 4 analytes.

Overall Urinary Recovery: Percent of Administered Dose

Dose	Venlafaxine ER		DVS-233 IR		DVS-233 SR		Venlafaxine IR[a]	
Analyte	Unconj. A_e	Total A_e	Unconj. A_e	Total A_e	Unconj. A_e	Total A_e	Unconj. A_e	Total A_e
75-mg								
Venlafaxine	4.3	4.3	--	--	--	--	4.7	4.7
ODV	26.0	37.0	38.8	59.7	35.7	52.0	29.4	55.8
NDV	0.4	0.5	--	--	--	--	1.0	1.0
NODV	4.7	6.9	1.1	2.9	1.0	2.7	9.8	16.0
Total analytes	35.4	48.7	39.9	62.6	36.7	54.7	44.9	77.5
150-mg								
Venlafaxine	5.9	5.6	--	--	--	--	--	--
ODV	24.6	36.7	36.1	52.6	35.3	50.1	--	--
NDV	0.6	0.6	--	--	--	--	--	--
NODV	6.3	7.3	1.5	3.2	1.5	3.0	--	--
Total analytes	37.4	50.2	37.6	55.8	36.8	53.1	--	--

a: Data from Study (0600A-109-US).[3]
Abbreviation: A_e = amount excreted in urine, ODV = desvenlafaxine, O-desmethylvenlafaxine; NDV = N-desmethylvenlafaxine; NODV = N,O-didesmethylvenlafaxine; Unconj. = unconjugated.

After single-dose administration of venlafaxine ER, the 72-hour urinary recovery of the unconjugated and conjugated forms of venlafaxine and its 3 metabolites accounted for approximately 50% of the administered venlafaxine dose. After administration of DVS-233 IR and DVS-233 SR, the urinary recovery of venlafaxine and its known metabolites accounted for 56% to 63% and 53% to 55%, respectively, of the administered dose. The urinary recovery of these compounds was slightly higher for DVS-233 IR and DVS-233 SR than for venlafaxine ER. The urinary recoveries of unconjugated and total desvenlafaxine indicated that desvenlafaxine was conjugated to a similar extent after administration of either venlafaxine or DVS-233.

Pharmacodynamic Results: The nausea ratings from the visual analog scale and the pharmacodynamic parameters derived from these data are presented in the following table. The mean VAS ratings for nausea versus time profile for all 3 treatments are presented in the Attachments.

Visual Analog Scale (VAS) for Nausea (% of Subjects) and the VAS Pharmacodynamic Parameters for Treatment Groups

Treatment	E_{max} (mm)	t_{Emax} (h)	AUC (mm•h)	VAS ≥ 10 mm (% of subjects)
75 mg				
Venlafaxine ER	15.3 ± 22.2	7.1 ± 17.4	161 ± 271	27.8%
DVS-233 IR	17.5 ± 24.7	2.5 ± 3.2	111 ± 126	44.4%
DVS-233 SR	2.4 ± 4.0	9.4 ± 21.1	28 ± 41	5.6%
150 mg				
Venlafaxine ER	9.4 ± 18.4	10.6 ± 15.9	102 ± 168	29.4%
DVS-233 IR	8.6 ± 7.7	4.0 ± 5.9	63 ± 70	52.9%
DVS-233 SR	4.2 ± 6.8	22.0 ± 26.2	38 ± 38	17.6 %

Abbreviations: E_{max} = the maximum visual analog scale (VAS) score; t_{Emax} = the maximum VAS score; AUC = total area under the concentration-time curve.

At both dose levels, administration of the desvenlafaxine SR capsule had a lower incidence of VAS of nausea ratings greater than 10 mm than either DVS-233 IR or venlafaxine ER. DVS-233 SR also appeared to reduce the maximum nausea effect with lower Emax and later TEmax compared with the other treatments.

Safety Summary: Nausea was the most common adverse event reported in all of the treatment groups. Nausea was reported by 10 (55.6%) subjects after treatment with DVS-233 IR 75 mg, 10 (58.8%) subjects after treatment with DVS-233 IR 150 mg, 2 (11.1%) subjects after treatment with DVS-233-SR 75 mg, 6 (35.3%) subjects after treatment with DVS-233 SR 150 mg, 8 (44.4%) subjects after treatment with venlafaxine ER 75 mg, and 6 (35.3%) subjects after venlafaxine ER 150 mg.

The adverse event profile for DVS-233 was reported by the sponsor to be similar to that reported for venlafaxine ER. DVS-233 SR produced fewer reports of nausea than DVS-233 IR at equivalent doses. In addition, no reports of vomiting occurred after administration of the DVS-233 SR formulation (75 and 150 mg) or venlafaxine ER at 75 mg, whereas a few events of vomiting were reported with DVS-233 IR (75 and 150 mg) and venlafaxine ER (150 mg). The sponsor reported that in general, fewer TEAEs were reported for DVS-233 SR than for the DVS-233 IR formulation or venlafaxine ER. Cardiovascular monitoring (blood pressure, heart rate, and ECG data) and laboratory test results showed no clinically relevant changes after administration of DVS-233. The sponsor reported that no serious adverse events and no clinically important medical events were recorded in this study.

Reviewer's comments: *This was a pilot study to evaluate two dosage formulations of DVS-SR. The reviewer agrees with the sponsor's summary of pharmacokinetic profile of the formulations tested.*

Attachments

SUPPORTIVE TABLE ST 8-12. STATISTICAL COMPARISONS OF O-DESMETHYLVENLAFAXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS RECEIVING A SINGLE DOSE (150-mg GROUP)

Protocol 060003-167-FR

10:40 Wednesday
July 31, 2002

TREATMENT: 150 mg

		CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	t1/2 (h)	AUCt - (ng*h/mL) -	AUC	Cl/F (L/h/kg)	Vz/F (L/kg)	CLR (L/h/kg)
Venlafaxine Extended Release	MEAN	159.3	8.6	0.056	13.10	4176	4404	0.54	10.88	0.13
	S.D.	50.3	3.4	0.012	3.95	1083	1070	0.17	8.14	0.03
	% CV	31.6	40.1	21.1	30.2	25.9	24.3	31.2	74.8	26.2
	GEOMETRIC MEAN	148.0	8.0	0.055	12.68	4015	4264	0.52	9.55	0.12
Desvenlafaxine Immediate Release	MEAN	531.7	3.3	0.085	8.26	6106	6251	0.38	4.43	0.13
	S.D.	116.3	1.0	0.011	1.06	1517	1567	0.10	0.99	0.03
	% CV	21.9	29.9	12.9	12.8	24.8	25.1	26.8	22.2	21.8
	GEOMETRIC MEAN	520.5	3.1	0.085	8.20	5934	6072	0.37	4.33	0.13
Desvenlafaxine Sustained Release	MEAN	284.2	5.6	0.079	9.12	5920	6106	0.41	5.21	0.13
	S.D.	83.0	1.1	0.016	2.12	1860	1863	0.17	1.87	0.03
	% CV	29.2	18.7	20.4	23.3	31.4	30.5	41.5	35.9	22.6
	GEOMETRIC MEAN	272.8	5.5	0.078	8.91	5625	5808	0.38	4.93	0.13

P-VALUES FROM LOG-TRANSFORMED ANALYSIS OF VARIANCE FOR A THREE-PERIOD CROSS-OVER DESIGN

SOURCE OF VARIATION									
SEQUENCE	.92	.52	.14	.14	.58	.52	.23	.73	.24
SUB(SEQUENCE)	.02	.11	.05	.05	.005	.003	.005	.02	.001
TREATMENT	.001	.001	.001	.001	.001	.001	.001	.001	.52
PERIOD	.37	.04	.91	.91	.03	.02	.02	.15	.95

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SUPPORTIVE TABLE ST 8-10. STATISTICAL COMPARISONS OF O-DESMETHYLVENLAFAXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS RECEIVING A SINGLE DOSE (75-mg GROUP)

Protocol 060003-167-FR

10:40 Wednesday
July 31, 2002

TREATMENT: 75 mg

		CMAX (ng/mL)	TMAX (h)	LAMBDA z(1/h)	t1/2 (h)	AUCt - (ng*h/mL) -	AUC	Cl/F (L/h/kg)	Vz/F (L/kg)	CLR (L/h/kg)
Venlafaxine Extended Release	MEAN	87.8	9.3	0.056	13.21	2253	2430	0.46	8.59	0.12
	S.D.	25.3	2.9	0.015	4.01	621	647	0.11	2.65	0.03
	% CV	28.9	31.2	26.1	30.4	27.6	26.6	23.0	30.8	24.9
	GEOMETRIC MEAN	84.1	8.9	0.054	12.72	2175	2351	0.45	8.24	0.11
Desvenlafaxine Immediate Release	MEAN	281.7	3.1	0.075	9.44	3378	3491	0.32	4.33	0.12
	S.D.	56.7	1.3	0.012	1.39	791	814	0.09	1.25	0.03
	% CV	20.1	43.0	16.2	14.7	23.4	23.3	28.0	28.9	21.7
	GEOMETRIC MEAN	276.0	2.8	0.074	9.34	3281	3393	0.31	4.19	0.12
Desvenlafaxine Sustained Release	MEAN	134.7	7.3	0.077	9.32	3013	3185	0.37	4.83	0.12
	S.D.	53.7	5.5	0.016	1.91	925	944	0.16	1.85	0.03
	% CV	39.9	75.4	20.2	20.5	30.7	29.6	42.9	38.3	25.5
	GEOMETRIC MEAN	125.8	6.3	0.076	9.14	2842	3016	0.35	4.61	0.12

P-VALUES FROM LOG-TRANSFORMED ANALYSIS OF VARIANCE FOR A THREE-PERIOD CROSS-OVER DESIGN

SOURCE OF VARIATION									
SEQUENCE	.37	.52	.37	.37	.06	.07	.09	.29	.04
SUB(SEQUENCE)	.001	.28	.001	.001	.002	.002	.003	.19	.001
TREATMENT	.001	.001	.001	.001	.001	.001	.001	.001	.85
PERIOD	.32	.32	.05	.05	.49	.53	.53	.83	.08

SUPPORTIVE TABLE 97 8-22. STATISTICAL COMPARISONS OF N,O-DIDESMETHYLVENLAFAXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS RECEIVING A SINGLE DOSE (150-mg GROUP)

Protocol 060003-167-FR

10:40 Wednesday
July 31, 2002

TREATMENT: 150 mg

		CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	t1/2 (h)	AUCt - (ng*h/mL) -	AUC	Cl/F (L/h/kg)	Vz/F (L/kg)	CLR (L/h/kg)
Venlafaxine Extended Release	MEAN	22.0	10.8	0.048	16.76	587	762	3.17	71.34	0.19
	S.D.	11.9	4.5	0.020	6.09	401	485	1.44	40.81	0.05
	% CV	54.4	41.9	42.2	36.3	68.3	63.6	45.4	57.2	26.1
	GEOMETRIC MEAN	23.3	9.9	0.044	15.64	580	783	2.85	64.21	0.18
Desvenlafaxine Immediate Release	MEAN	5.2	6.2	0.038	21.56	73	157	8.43	220.67	0.15
	S.D.	4.4	1.1	0.014	12.40	103	196	5.13	92.10	0.06
	% CV	84.6	17.4	35.8	57.5	140.7	124.9	60.9	41.7	36.4
	GEOMETRIC MEAN	7.8	6.1	0.036	19.48	50	100	7.33	206.11	0.14
Desvenlafaxine Sustained Release	MEAN	3.5	17.8	0.029	37.73	55	170	6.52	248.33	0.12
	S.D.	3.5	5.3	0.023	20.78	78	267	4.65	70.17	0.07
	% CV	100.1	30.0	80.0	55.1	142.1	157.1	71.4	28.3	54.0
	GEOMETRIC MEAN	6.5	17.1	0.022	31.09	71	150	5.38	241.12	0.11

P-VALUES FROM LOG-TRANSFORMED ANALYSIS OF VARIANCE FOR A THREE-PERIOD CROSS-OVER DESIGN

SOURCE OF VARIATION									
SEQUENCE	.80	.54	.53	.53	.92	.72	.68	.86	.13
SUB(SEQUENCE)	.001	.03	.76	.76	.009	.05	.19	.02	.98
TREATMENT	.001	.001	.30	.30	.001	.001	.001	.001	.49
PERIOD	.94	.31	.71	.71	.80	.83	.82	.69	.65

FIGURE SP 8-2. MEAN VENLAFAXINE PLASMA CONCENTRATIONS IN HEALTHY SUBJECTS RECEIVING A SINGLE 150-mg DOSE

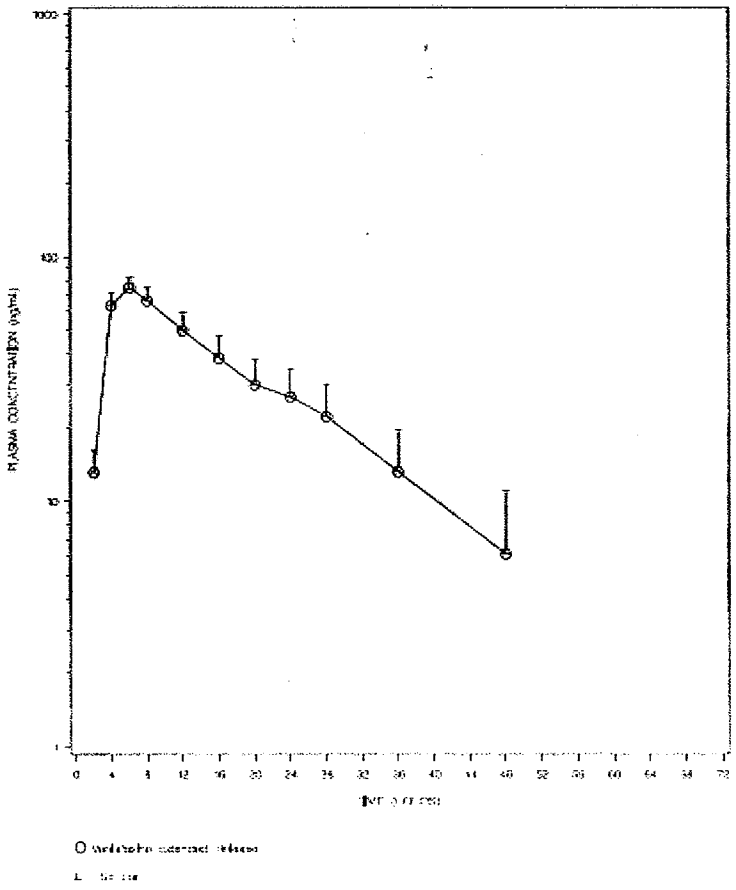

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FIGURE SF 8-2. MEAN VENLAFAXINE PLASMA CONCENTRATIONS IN HEALTHY SUBJECTS RECEIVING A SINGLE 150-mg DOSE

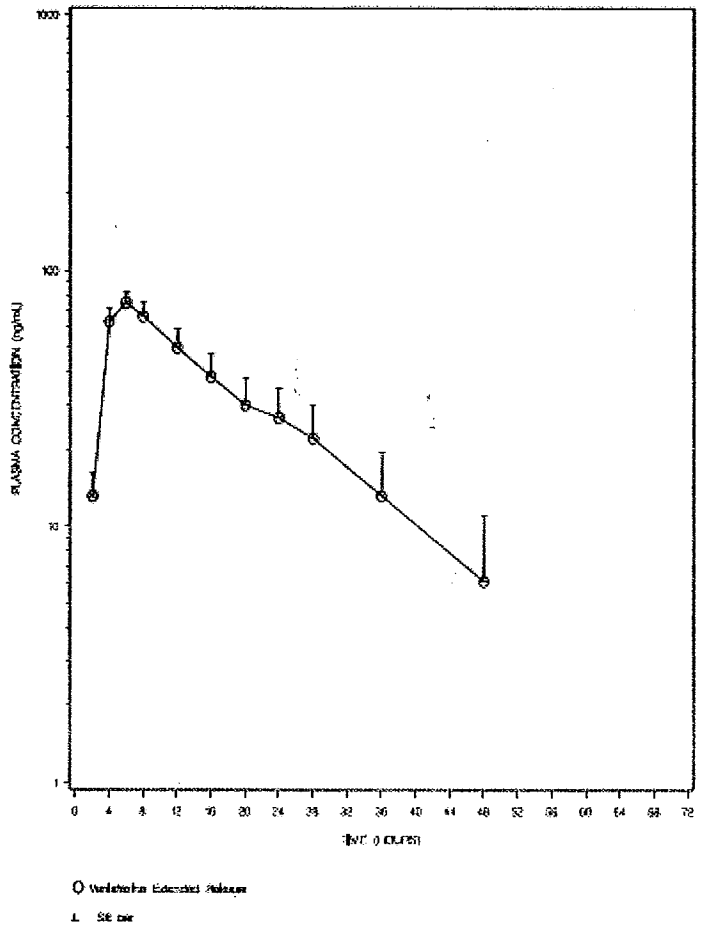

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FIGURE SF 8-3. MEAN DESVENLAFAXINE PLASMA CONCENTRATIONS IN HEALTHY SUBJECTS RECEIVING A SINGLE 75-mg DOSE

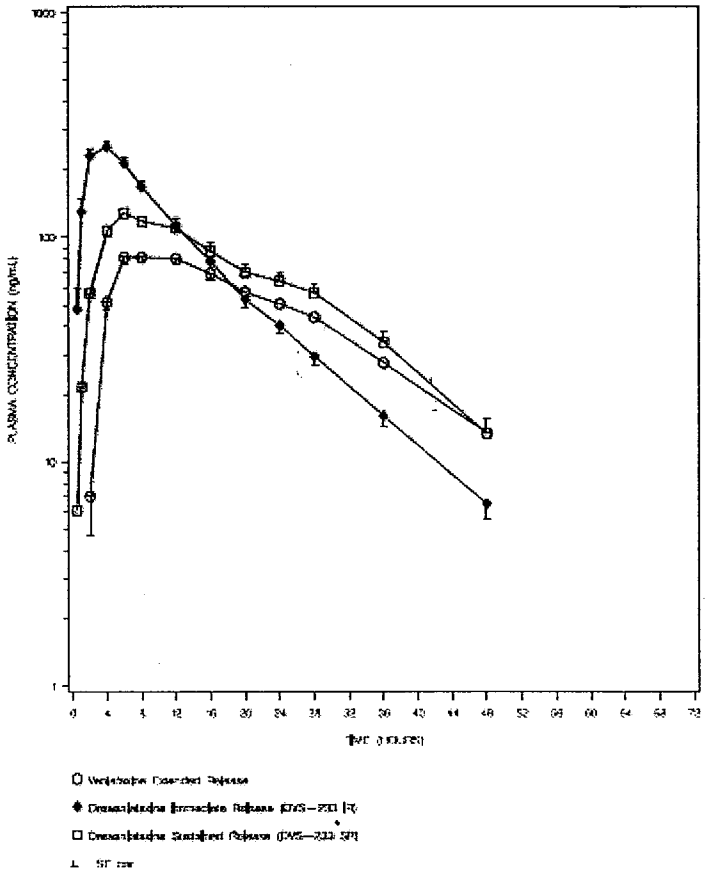

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FIGURE SF 8-4. MEAN DESVENLAFAXINE PLASMA CONCENTRATIONS IN HEALTHY SUBJECTS RECEIVING A SINGLE 150-mg DOSE

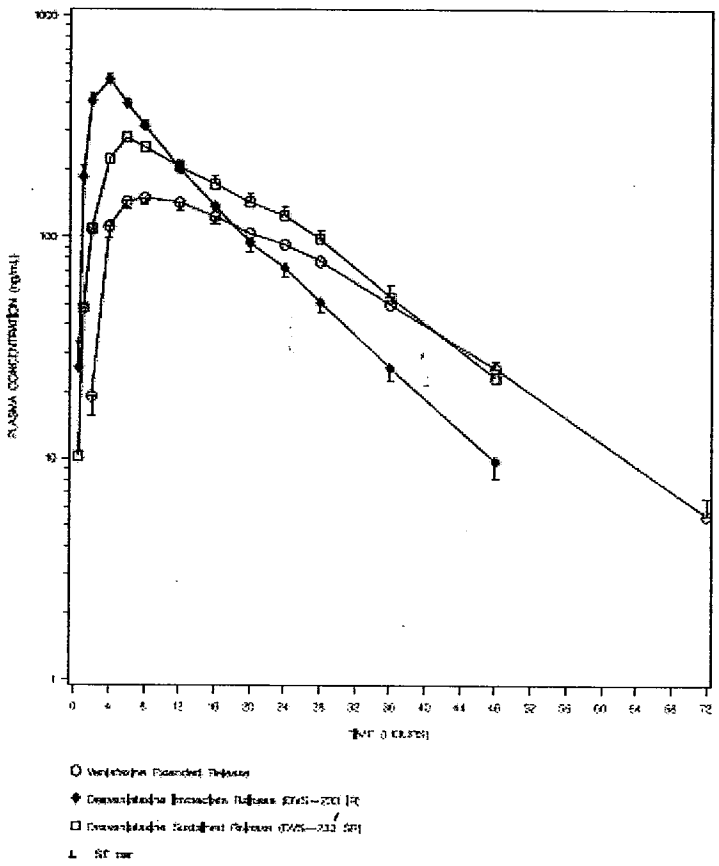

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FIGURE SF 8-5. MEAN VENLAFAXINE PLUS DESVENLAFAXINE PLASMA CONCENTRATIONS IN HEALTHY SUBJECTS RECEIVING A SINGLE 75-mg DOSE

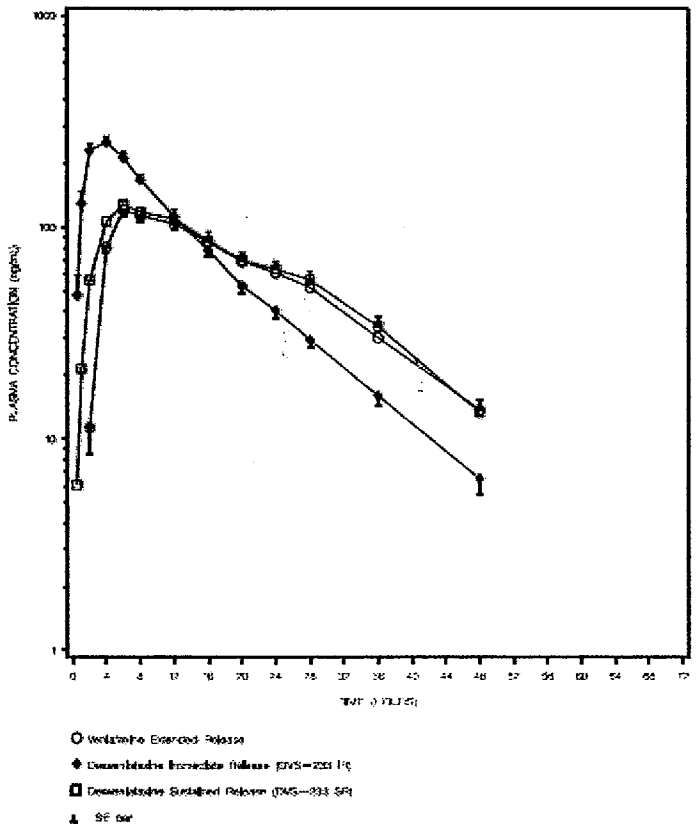

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FIGURE SF 8-6. MEAN VENLAFAXINE PLUS DESVENLAFAXINE PLASMA CONCENTRATIONS IN HEALTHY SUBJECTS RECEIVING A SINGLE 150-mg DOSE

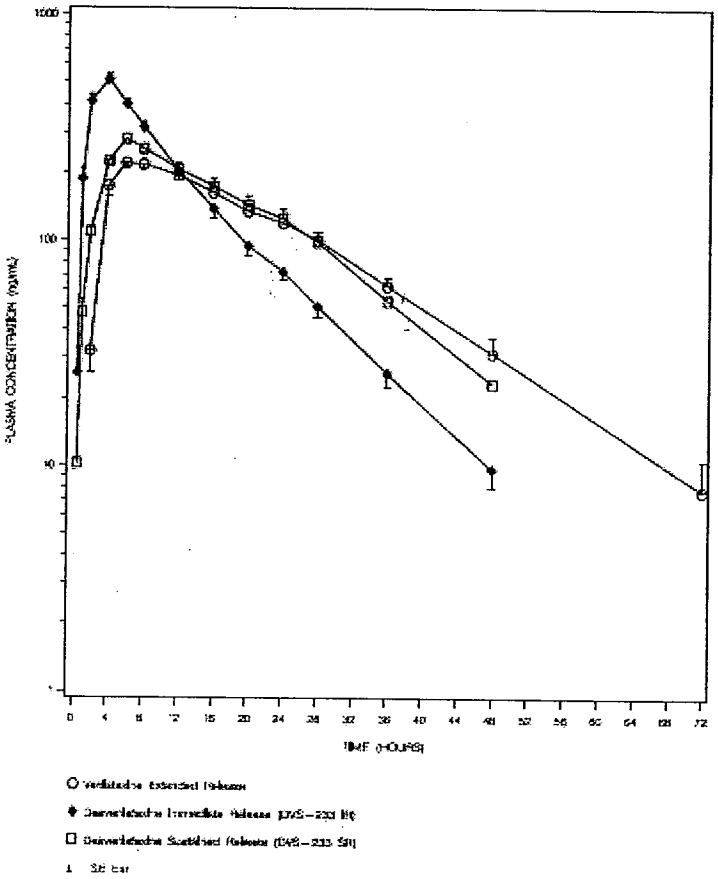

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FIGURE SF 8-7. MEAN NAUSEA VAS SCORES IN HEALTHY SUBJECTS RECEIVING A SINGLE 75-mg DOSE

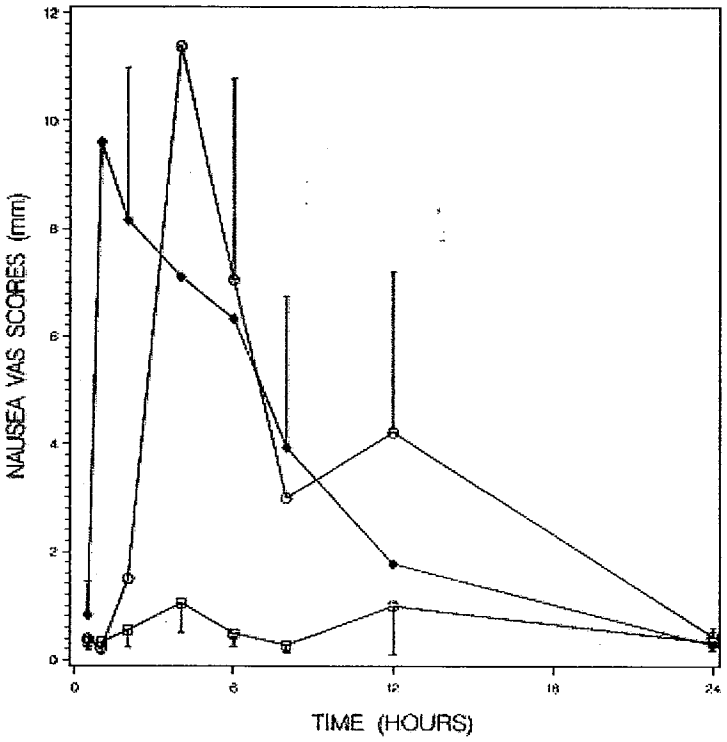

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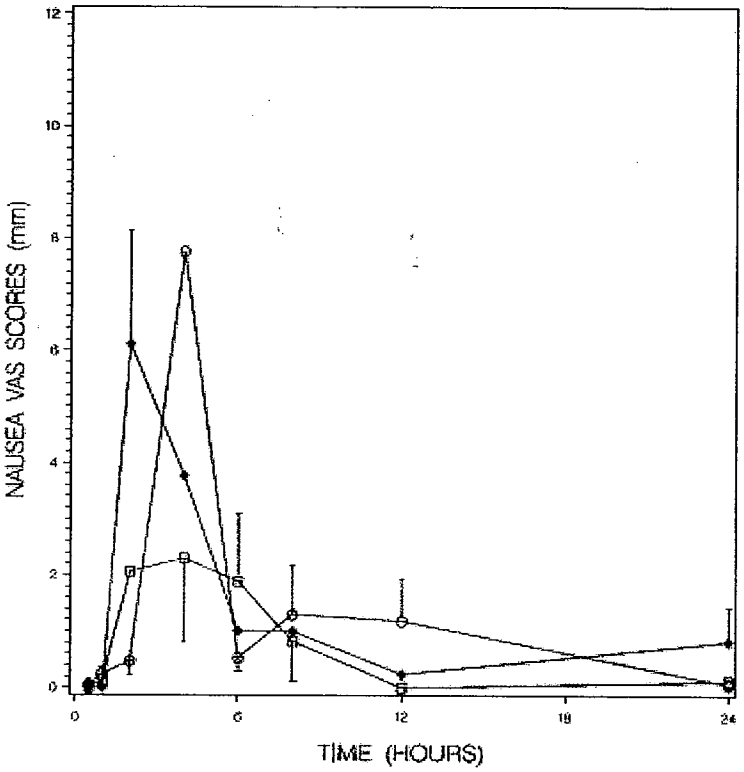
FIGURE SF 8-8. MEAN NAUSEA VAS SCORES IN HEALTHY SUBJECTS RECEIVING A SINGLE 150-mg DOSE



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Study Title: An Ascending Single-Dose Study Of The Safety, Pharmacokinetics, And Pharmacodynamics Of Desvenlafaxine SR in Healthy Subjects (Protocol 0600D3-170-FR)

Objectives: The primary objective was to assess the safety and tolerability of ascending, single, oral doses of a sustained-release (SR) formulation of desvenlafaxine succinate monohydrate (DVS-233) in healthy subjects. The secondary objectives were the assessment of the preliminary pharmacokinetics and pharmacodynamics of ascending single oral doses of DVS-233 SR, the comparison of the safety of DVS-233 SR with a fixed 150-mg dose of the extended-release (ER) formulation of venlafaxine, and the preliminary assessment of food effect at a high dose of DVS-233 SR.

Study Design: This randomized, double-blind, placebo-controlled, inpatient, sequential-group, ascending single oral dose study was conducted with healthy subjects at a single investigational site. Each subject participated in only 1 dose group and received only 1 dose of either DVS-233 SR, venlafaxine ER, or placebo. Each cohort consisted of 10 subjects (6 receiving DVS-233 SR, 2 receiving venlafaxine ER, and 2 receiving placebo). The cohorts were studied in 2 subgroups of 5 subjects each (3 receiving DVS-233 SR, 1 receiving venlafaxine ER, and 1 receiving placebo); there was a minimum 24-hour time interval between these 2 dose administrations. All doses of DVS-233 SR were administered with DVS-233 SR 75-mg tablets. The following doses were studied sequentially in ascending order: 150 mg, 225 mg, 300 mg, 450 mg, 600 mg, 750 mg, and 900 mg. Test article (DVS-233 SR, venlafaxine ER, or placebo) was administered at only 1 dose level at a time. Treatment at the next higher dose level was not begun until the safety and tolerability of the preceding dose had been confirmed. The food effect was evaluated at the maximum tolerated dose (MTD), 750 mg, in a final additional cohort of 10 subjects who received test article under fasting conditions, i.e., after an overnight fast of at least 8 hours. Each subject received a medium-fat breakfast on the morning of day 1 at approximately 0730, which was completed approximately 10 minutes before test article administration. All test articles were administered with 240 mL of room-temperature water with the subject in an upright position. The dosage strengths and batch numbers of the study medications are summarized in the following table.

Study Medication Batch Numbers

Study Medication (mg)	Batch Number	Formulation Number	Strength
DVS-233 SR 75-mg tablet	2001B0139	0931580A	——mg/tablet
Venlafaxine ER 75-mg tablet	2000B0443	0930331D	——mg/tablet
Placebo tablets			
for DVS-233 SR	2001B0236	0931645A	Absent; < 75 µg/tablet
for Venlafaxine	2001B0012	0930313D	Absent; < 37.5 µg/tablet

Abbreviations: DVS-233 SR = desvenlafaxine sustained release; ER = extended release.

Analytical Method: Plasma was assayed for venlafaxine and desvenlafaxine by using a validated high performance liquid chromatography (HPLC) method with fluorescence detection. The minimum quantifiable concentration (MQC) for both compounds was approximately 5 ng/mL. The performance of the venlafaxine and desvenlafaxine assays during the analysis of the plasma samples from this study is summarized from the following table

Assay Range and Sensitivity for Plasma Samples

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

Source: Reference 16

Table 6.5.2.1-2: Summary of Assay Performance

	--Low QC (15.0 ng/mL)---			--Middle QC (60.0 ng/mL)--			--High QC (300 ng/mL)---		
Analyte	Conc	CV%	Bias%	Conc	CV%	Bias%	Conc	CV%	Bias%
Desvenlafaxine	14.23	7.94	–5.13	56.51	7.29	–5.82	288.22	6.63	–3.03
Venlafaxine	14.53	6.91	–3.10	57.64	7.55	–3.93	291.33	5.90	–2.89

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

Data Analysis: The venlafaxine and desvenlafaxine plasma concentration data for each subject were analyzed by using empirical, model-independent pharmacokinetic methods. The profile of nausea intensity over time for each treatment was evaluated by using a Visual Analogue Scale (VAS) for nausea at specified times during the study.

The linear dose proportionalities of the C_{max} and AUC were assessed by using the following exponential regression model that measured the degree of nonlinear

proportionality:

Cmax or AUC + a * $Dose^b$

a = coefficient
b = exponent of the regression mode

If the pharmacokinetic parameters (C_{max} or AUC) exhibited linear dose proportionality for the doses, then b should be equal to unity. The parameters a and b were estimated by linear least squares regression after a log transformation as follows:

$$\text{Log}(C_{max} \text{ or AUC}) = \log(a) + b \cdot \log(\text{Dose})$$

where

Log (a) = Intercept of the regression line
b = slope of the regression line

Testing H_0: b = 1 versus H_a: b ≠ 1

Results:

The following table summarizes the mean ± SD and geometric mean of estimates of desvenlafaxine pharmacokinetic parameter values for all treatments, including the results of the statistical comparisons among the DVS-233 SR treatments.

Desvenlafaxine Pharmacokinetic Parameters

Treatment	n	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	Cl/F (L/h/kg)
Venlafaxine ER 150 mg Postprandial and Fasting	16	172 ± 41[a] 166	7.9 ± 1.0 7.9	12.4 ± 2.7 12.2	4602 ± 963 4503	0.47 ± 0.10 0.46
DVS-233 SR 150 mg Postprandial	6	216 ± 81 204	5.2 ± 2.9 4.5	9.1 ± 1.5 9.1	5004 ± 1379 4838	0.43 ± 0.15 0.41
DVS-233 SR 225 mg Postprandial	6	431 ± 105 421	7.5 ± 4.5 6.6	11.3 ± 2.4 11.1	10601 ± 3030 10202	0.31 ± 0.06 0.31
DVS-233 SR 300 mg Postprandial	6	446 ± 32 445	10.5 ± 9.9 7.1	10.4 ± 1.8 10.3	14554 ± 3151 14258	0.30 ± 0.08 0.29
DVS-233 SR 450 mg Postprandial	6	822 ± 158 808	5.0 ± 1.1 4.9	10.2 ± 0.9 10.1	18580 ± 3680 18278	0.36 ± 0.06 0.35
DVS-233 SR 600 mg Postprandial	6	1099 ± 195 1084	5.3 ± 1.5 5.2	10.2 ± 1.1 10.2	26920 ± 7932 26098	0.33 ± 0.07 0.32
DVS-233 SR 750 mg Postprandial	5[b]	1906 ± 431 1869	6.0 ± 1.6 5.8	9.9 ± 0.8 9.9	41816 ± 6347 41478	0.26 ± 0.03 0.26
DVS-233 SR 900 mg Postprandial	4[c]	1572 ± 336 1541	7.3 ± 1.0 7.2	9.6 ± 1.0 9.6	38546 ± 8646 37758	0.32 ± 0.11 0.31
DVS-233 SR 750 mg Fasting	6	1683 ± 310 1659	6.8 ± 1.0 6.8	9.5 ± 1.2 9.5	36800 ± 6214 36349	0.29 ± 0.08 0.28
1-Factor ANOVA of Log-Transformed Data (DVS-233 SR Postprandial Data Only)[d]						
Treatment		0.015	0.667	0.408	0.063	0.144

a: Mean ± standard deviation and geometric mean.
b: Excluding subject 17001-0058 who vomited and exhibited very low plasma concentrations.
c: Excluding subjects 17001-0066 and 17001-0070 who vomited and exhibited very low plasma concentrations.
d: Before statistical comparisons, C_{max} and AUC were normalized to the lowest dose.
Abbreviations: ER = extended release; DVS-233 SR = desvenlafaxine sustained release; ANOVA = analysis of variance.

Following administration of DVS-233 SR, desvenlafaxine was slowly absorbed with the mean Tmax occurring between 5 and 11 hours after dose administration and was slowly eliminated with a mean T ½ of 9 to 11 hours. With the exception of desvenlafaxine C_{max}, no statistically significant differences were found among the doses in any of the single-dose pharmacokinetic parameters. The higher than expected C_{max} and AUC values in the postprandial DVS-233 SR 750-mg treatment produced a nonlinearity (10% to 15%) in the increases in desvenlafaxine C_{max} and AUC with increasing dose.

Considering the exponential regression equation (see Data Analysis section), a 2-fold increase in dose is estimated to produce a 2.31-fold increase in desvenlafaxine C_{max} and a 2.22-fold increase in desvenlafaxine AUC. Therefore, although the slope parameter of the exponential regression was statistically significantly different from 1, the actual magnitude of nonlinearity was small, with a 2-fold increase in dose producing 10% to 15% higher values than what would be expected based upon linear dose proportionality. Administration of DVS-233 SR 750 mg with a medium-fat meal produced slightly higher desvenlafaxine C_{max} and AUC compared with fasting administration, but the meal did not alter the slow release characteristics of the DVS-233 SR formulation.

Pharmacodynamic Results: Summary of nausea VAS results are presented in the following table.

Nausea VAS Parameters

Treatment	E_{max} (mm)	t_{max} (h)	AURC (mm•h)	VAS ≥ 10 mm (% of subjects)
Placebo	0.5 ± 2.0[a]	2.0 ± 0.0	0.5 ± 2.0	0.0
Venlafaxine ER 150 mg	13.1 ± 23.5	6.2 ± 4.0	51.6 ± 110.0	25.0
DVS-233 SR 150 mg Postprandial	4.8 ± 8.9	3.0 ± 0.0	8.6 ± 17.8	16.7
DVS-233 SR 225 mg Postprandial	12.2 ± 20.0	8.0 ± 5.7	106.3 ± 241.9	33.3
DVS-233 SR 300 mg Postprandial	15.3 ± 22.9	3.0 ± 1.0	48.9 ± 80.3	33.3
DVS-233 SR 450 mg Postprandial	7.3 ± 10.3	3.0 ± 0.0	16.8 ± 25.8	33.3
DVS-233 SR 600 mg Postprandial	0.0	-	0.0	0.0
DVS-233 SR 750 mg Postprandial	42.2 ± 32.5	2.0 ± 1.2	76.1 ± 44.4	100.0
DVS-233 SR 900 mg Postprandial	44.2 ± 29.7	3.6 ± 2.3	141.9 ± 102.4	83.3
DVS-233 SR 750 mg Fasting	18.7 ± 31.6	4.5 ± 2.4	75.6 ± 142.2	50.0
p-Values from 1-Factor ANOVA	0.001	0.169	0.112	-

a: Mean ± standard deviation.
Abbreviations: VAS = visual analogue scale; ER = extended release; DVS-233 SR = desvenlafaxine sustained release; ANOVA = analysis of variance.

The VAS Emax and AURC increased with increasing DVS-233 SR dose with the exception of the 600-mg dose group, for which no subjects reported a single VAS score above 0 mm. The venlafaxine ER 150-mg dose group reported a mean VAS E_{max} similar to the mean for subjects receiving DVS-233 SR 225 mg to 450 mg; the mean VAS AURC was higher for venlafaxine ER 150 mg than for DVS-233 SR doses of 600 mg or less, with an exception at the 225-mg dose group. Comparing DVS-233 SR 750 mg fasting versus postprandial administrations, the fasting administration produced a

slightly lower mean VAS E_{max}, but the mean VAS AURCs were similar for the 2 treatments.

Safety Summary: The sponsor reported that TEAEs were more common at DVS-233 SR doses of 750 mg (fed and fasted) and 900 mg than at lower doses. In fed subjects receiving 750-mg and 900-mg doses, the incidences of TEAEs were 100% and 83.3%, respectively, compared with 33.3% in subjects who received 150-mg, 225-mg, 300-mg, or 450-mg doses. In fasted subjects receiving the 750-mg dose, the incidence of TEAEs was 66.7%. TEAEs occurred in 31.3% of subjects taking venlafaxine ER and in only 6.3% of those taking placebo. The sponsor reported that no adverse events were observed in subjects who received the 600-mg dose.

The sponsor reported that the most common TEAE across all groups was nausea. There were no reports of vomiting at DVS-233 SR doses below 750 mg, while vomiting occurred at doses of 750 mg (40% of fed subjects and 16.7% of fasted subjects at this dose) and 900 mg (66.7%). Severe nausea was reported by 16.7% of fasted subjects at the 750-mg dose level and by 33.3% of subjects at the 900-mg dose level, compared with 6.3% of subjects receiving venlafaxine ER 150 mg. DVS-233 SR 150 mg produced a lower incidence of nausea and vomiting than did venlafaxine ER 150 mg (16.7% versus 25.0% for nausea and 0% versus 6.3% for vomiting, DVS-233 SR versus venlafaxine ER, respectively). Dizziness, feeling drunk, and paresthesias were reported at doses of DVS-233 SR greater than 450 mg (40.0% at 750 mg in fed subjects, 50.0% at 750 mg in fasted subjects, and 33.3% at 900 mg) while only 16.7% of subjects receiving DVS-233 SR 150 mg experienced these symptoms.

The sponsor reported that there were no clinically important changes in vital sign measurements after treatment, but changes in systolic and diastolic blood pressure and pulse were observed in some treatment groups. There were no significant changes in systolic blood pressure compared with placebo at any observation time after administration of 150-, 225-, 450-, 600- and 750-mg DVS-233 SR.

The sponsor reported that the linear trend analysis of vital sign parameters showed a relationship between dose and systolic blood pressure from approximately 2 to 24 hours postdose. The maximum estimated increase from placebo in systolic blood pressure occurred at 4 hours postdose and was 14.3 mm Hg for 900 mg of DVS-233 SR. Visual inspection of this data does not show an apparent dose related increase in systolic blood pressure at 4 hours postdose. For diastolic blood pressure, the linear trend showed a relationship between dose and diastolic blood pressure from approximately 2 to 24 hours postdose. The maximum estimated change from placebo in diastolic blood pressure occurred at 6 hours postdose and was 16.1 mm Hg for 900 mg of DVS-233 SR.

Diastolic Blood Pressure (Supine) (mm Hg); by Dose Level

Dose (mg)	n	Baseline Day 1, h -1	t_{max} Day 1 h 8	Delta Day 1 h 8
DVS 150	6	61.00 ± 10.13 [a] (42/68)	66.00 ± 9.44 (47/72)	5.00 ± 4.35 (1/12)
DVS 225	6	66.56 ± 12.23 (48/81)	66.50 ± 17.38 (45/90)	-0.05 ± 8.66 (-13/10)
DVS 300	6	63.89 ± 12.26 (54/87)	65.33 ± 8.21 (57/77)	1.45 ± 17.96 (-30/18)
DVS 450	6	58.22 ± 1.59 (57/61)	64.17 ± 4.26 (60/72)	5.94 ± 4.84 (1/14)
DVS 600	6	60.00 ± 8.06 (45/68)	73.17 ± 5.71 (64/80)	13.17 ± 7.44 (6/26)
DVS 750	5	59.00 ± 9.96 (46/72)	64.80 ± 9.34 (49/73)	5.80 ± 17.85 (-23/21)
DVS 750 Fasted	6	63.45 ± 7.20 (56/73)	69.50 ± 8.71 (57/81)	6.06 ± 5.78 (-3/15)
DVS 900	6	66.44 ± 7.14 (56/78)	71.33 ± 8.89 (55/79)	4.89 ± 10.71 (-14/14)
VEN 150	16	54.17 ± 7.73 (43/70)	62.06 ± 7.34 (50/76)	7.90 ± 8.40 (-7/19)
Placebo	16	61.15 ± 11.09 (35/79)	61.25 ± 7.97 (44/72)	0.10 ± 9.99 (-24/11)

a: Mean ± Standard Deviation (Min/Max)

Systolic Blood Pressure (Supine)(mm Hg); by Dose Level

Dose (mg)	n	Baseline Day 1, h -1	t_{max} Day 1 h 8	Delta Day 1 h 8
DVS 150	6	110.67 ± 5.11 * (102/115)	123.83 ± 8.23 (115/136)	13.17 ± 11.89 (1/28)
DVS 225	6	111.11 ± 10.83 (96/126)	129.50 ± 3.83 (126/137)	18.39 ± 9.05 (9/33)
DVS 300	6	119.28 ± 9.76 (112/138)	123.17 ± 13.70 (102/139)	3.89 ± 16.55 (-14/25)
DVS 450	6	105.22 ± 5.37 (95/112)	115.83 ± 7.41 (105/124)	10.61 ± 7.57 (-1/19)
DVS 600	6	114.28 ± 5.07 (106/120)	126.50 ± 10.99 (114/140)	12.22 ± 9.38 (2/22)
DVS 750	5	115.47 ± 13.20 (102/129)	127.60 ± 14.24 (104/139)	12.13 ± 9.35 (2/23)
DVS 750 Fasted	6	119.39 ± 10.98 (108/137)	131.67 ± 12.58 (119/149)	12.28 ± 7.50 (1/23)
DVS 900	6	109.72 ± 8.50 (101/124)	125.30 ± 5.61 (120/136)	15.78 ± 4.56 (9/19)
VEN 150	16	110.56 ± 5.32 (102/123)	126.25 ± 14.12 (104/140)	13.62 ± 9.25 (-3/29)
PBO	16	110.69 ± 5.93 (103/121)	120.06 ± 11.43 (107/137)	9.37 ± 10.24 (-7/23)

a: Mean ± Standard Deviation (Min/Max)

A linear relationship between dose and pulse was shown at 4, 6, and 12 hours postdose. Pulse significantly increased from placebo at 4, 6, and 12 hours postdose after 900 mg and at 4 hour postdose after 750 mg of DVS-233 SR. The maximum estimated change from placebo occurred at 6 hours and was 11 beats/min for 900 mg of DVS-233 SR.

Pulse (Supine) (bpm); by Dose Level

Dose (mg)	n	Baseline Day 1, h -1	t_{max} Day 1 h 8	Delta Day 1 h 8
DVS 150	6	63.00 ± 12.38 * (41/75)	59.67 ± 10.31 (42/70)	-3.34 ± 8.47 (-13/11)
DVS 225	6	63.22 ± 11.14 (52/84)	64.83 ± 13.39 (48/84)	1.61 ± 4.94 (-4/10)
DVS 300	6	61.39 ± 5.60 (54/69)	61.50 ± 4.85 (57/69)	0.11 ± 8.28 (-11/10)
DVS 450	6	59.61 ± 7.66 (46/67)	63.17 ± 10.44 (50/80)	3.56 ± 10.80 (-7/24)
DVS 600	6	54.39 ± 10.71 (43/70)	61.50 ± 9.44 (51/77)	7.11 ± 6.15 (-2/17)
DVS 750	5	60.20 ± 10.93 (51/74)	67.20 ± 6.14 (61/76)	7.00 ± 10.85 (-9/20)
DVS 750 Fasted	6	60.78 ± 11.03 (44/73)	64.17 ± 8.18 (54/76)	3.39 ± 12.90 (-9/22)
DVS 900	6	60.17 ± 4.49 (55/69)	68.67 ± 7.47 (59/80)	8.50 ± 10.48 (-10/20)
VEN 150	16	59.63 ± 6.96 (48/70)	63.25 ± 8.13 (52/84)	3.62 ± 5.29 (-7/14)
Placebo	16	52.69 ± 11.01 (41/89)	67.63 ± 9.99 (53/91)	4.94 ± 7.07 (-9/15)

a: Mean ± Standard Deviation (Min/Max)

Conclusion: Following administration of DVS-233 SR, desvenlafaxine was slowly absorbed with mean Tmax occurring between 5 and 11 hours after dose administration,

and desvenlafaxine was slowly eliminated with a mean T ½ of 9 to 11 hours. Higher than expected C_{max} and AUC values in the postprandial DVS-233 SR 750-mg treatment group produced a slight nonlinearity (10% to 15%) in the increases in desvenlafaxine C_{max} and AUC with increasing dose over the range of 150 to 900 mg.

DVS SR 750 mg and 900 mg produced higher mean nausea VAS E_{max} scores than the lower doses and more subjects reported at least 1 VAS score of at least 10 mm for DVS SR 750 mg and 900 mg than for the lower doses. The sponsor reported that TEAEs were more common at DVS-233 SR doses of 750 mg (fed and fasted) and 900 mg than at lower doses of DVS-233 SR. In fed subjects receiving 750-mg and 900-mg doses, the incidence of TEAEs was 100% and 83.3%, respectively, compared with 33.3% in subjects who received 150 mg, 225 mg, 300 mg, or 450 mg. In fasted subjects receiving 750-mg doses, the incidence of TEAEs was 66.7%. TEAEs occurred in 31.3% of subjects taking venlafaxine ER and in only 6.3% of those taking placebo. The sponsor reported that the linear trend analysis of vital sign parameters showed a relationship between dose and systolic and diastolic blood pressure from approximately 2 to 24 hours postdose.

The sponsor reported that no clinically relevant findings in ECG parameters were identified. Linear trend analysis showed a significant decrease in QT interval at 4 hours postdose in the 600-, 750 (fasted)- and 900-mg groups compared with placebo; however, these decreases were reported not to be clinically significant. There were no significant trends observed for heart rate, PR, QRS and QTc intervals (machine-read, Bazett formula).

Reviewer's comments: *The pharmacokinetics of desvelafaxine after administration of DVS SR appears to be linear at lower doses but becomes nonlinear at doses greater than 600 mg. The most common adverse event was reported to be nausea. The relationship between dose and vital signs (BP, Pulse) and QTc is being reviewed by the Pharmacometric group in the Office of Clinical Pharmacology.*

Attachments

ST 8-2. PHARMACOKINETIC PARAMETERS OF VENLAFAXINE IN HEALTHY SUBJECTS RECEIVING PLACEBO, VENLAFAXINE, OR DESVENLAFAXINE

Protocol 060003-170-FR

17:28 Monday, August 4, 2003

	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	t1/2 (h)	AUCt - (ng*h/mL) -	AUC	Cl/F (L/h/kg)	Vz/F (L/kg)
VEN ER 150 mg								
3	59.7	4.0	0.065	10.63	788	942	2.49	38.20
6	106.6	6.0	0.055	12.61	1586	1702	1.10	20.05
14	64.3	4.0	0.055	12.56	716	869	2.01	36.39
16	36.3	6.0	0.079	8.76	413	496	4.45	56.23
23	85.0	6.0	0.089	7.76	966	1038	1.72	19.27
28	68.4	6.0	0.096	7.25	941	1002	2.20	23.04
35	49.2	6.0	0.089	7.79	597	672	3.10	34.84
37	29.8	6.0	0.037	18.77	356	500	3.57	96.68
41	39.0	4.0	0.103	6.72	401	454	4.65	45.16
46	75.4	6.0	0.062	11.24	1215	1299	1.80	29.26
51	25.3	6.0	0.041	16.79	325	463	4.63	112.20
59	62.8	6.0	0.043	16.05	647	816	2.87	66.56
62	113.4	4.0	0.086	8.07	1622	1711	1.37	15.96
68	37.4	6.0	0.114	6.10	401	445	4.88	42.93
71	88.8	6.0	0.069	10.10	1368	1447	1.23	17.99
80	59.3	6.0	0.074	9.36	850	920	2.51	33.87
MEAN	62.5	5.5	0.072	10.66	825	923	2.79	43.04
S.D.	26.4	0.9	0.023	3.80	431	429	1.30	27.88
% CV	42.2	16.3	31.6	35.7	52.3	46.5	46.53	64.77
GEO MN	57.2	5.4	0.069	10.09	723	834	2.50	36.44
MIN	25.3	4.0	0.037	6.10	325	445	1.10	15.96
MAX	113.4	6.0	0.114	18.77	1622	1711	4.88	112.20

. DATA NOT AVAILABLE.
* SUBJECT WAS EXCLUDED FROM SUMMARY STATISTICS DUE TO A VOMITING AE AND LOW PLASMA CONCENTRATIONS.

ST 8-6. STATISTICAL COMPARISONS OF DESVENLAFAXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS RECEIVING PLACEBO, VENLAFAXINE, OR DESVENLAFAXINE

Protocol 060003-170-FR

17:28 Monday
August 4, 2003

TREATMENT		CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	t1/2 (h)	AUCt - (ng*h/mL) -	AUC	Cl/F (L/h/kg)	Vz/F (L/kg)
VEN ER 150 mg									
	MEAN	171.9	7.9	0.058	12.44	4370	4602	0.47	8.62
	S.D.	41.2	1.0	0.013	2.67	1020	963	0.10	3.36
	% CV	23.9	12.6	21.8	21.4	23.3	20.9	21.6	38.9
	GEOMETRIC MEAN	166.4	7.9	0.057	12.18	4251	4503	0.46	8.14
DVS-233 SR 150 mg									
	MEAN	216.0	5.2	0.077	9.14	4874	5004	0.43	5.47
	S.D.	80.9	2.9	0.011	1.46	1375	1379	0.15	1.53
	% CV	37.4	55.3	13.7	16.0	28.2	27.6	35.8	28.0
	GEOMETRIC MEAN	203.5	4.5	0.077	9.05	4705	4838	0.41	5.30
DVS-233 SR 225 mg									
	MEAN	431.3	7.5	0.064	11.33	10311	10601	0.31	4.92
	S.D.	104.7	4.5	0.014	2.41	2885	3030	0.06	0.42
	% CV	24.3	59.5	22.6	21.3	28.0	28.6	19.4	8.5
	GEOMETRIC MEAN	421.0	6.6	0.062	11.11	9931	10202	0.31	4.90
DVS-233 SR 300 mg									
	MEAN	445.8	10.5	0.068	10.44	14197	14554	0.30	4.33
	S.D.	32.1	9.9	0.015	1.80	3050	3151	0.08	0.93
	% CV	7.2	94.4	21.2	17.3	21.5	21.7	27.4	21.4
	GEOMETRIC MEAN	444.9	7.1	0.067	10.29	13913	14258	0.29	4.25
DVS-233 SR 450 mg									
	MEAN	821.8	5.0	0.069	10.17	18352	18580	0.36	5.19
	S.D.	157.8	1.1	0.006	0.93	3621	3680	0.06	0.73
	% CV	19.2	21.9	9.3	9.1	19.7	19.8	15.6	14.0
	GEOMETRIC MEAN	807.8	4.9	0.068	10.13	18058	18278	0.35	5.14
DVS-233 SR 600 mg									
	MEAN	1098.6	5.3	0.069	10.22	26565	26920	0.33	4.77
	S.D.	195.2	1.5	0.008	1.13	7682	7932	0.07	0.81
	% CV	17.8	28.2	11.6	11.1	28.9	29.5	22.2	17.1
	GEOMETRIC MEAN	1084.3	5.2	0.068	10.17	25782	26098	0.32	4.70

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Table 8-6 - Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters
In Healthy Subjects Receiving Placebo, Venlafaxine, or Desvenlafaxine

Protocol 060003-170-FR

17:28 Monday
August 4, 2003

TREATMENT		CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	t1/2 (h)	AUCt - (ng*h/mL) -	AUC	Cl/F (L/h/kg)	Vz/F (L/kg)
DVS-233 SR 750 mg									
	MEAN	1905.9	6.0	0.070	9.89	41327	41816	0.26	3.70
	S.D.	431.2	1.6	0.006	0.76	6262	6347	0.03	0.49
	% CV	22.6	27.2	8.2	7.7	15.2	15.2	12.2	13.4
	GEOMETRIC MEAN	1868.5	5.8	0.070	9.87	40993	41478	0.26	3.68
DVS-233 SR 900 mg									
	MEAN	1572.2	7.3	0.073	9.61	38206	38546	0.32	4.55
	S.D.	336.2	1.0	0.007	0.96	8652	8646	0.11	2.07
	% CV	21.4	13.2	9.6	10.0	22.6	22.4	34.7	45.6
	GEOMETRIC MEAN	1540.9	7.2	0.072	9.58	37409	37758	0.31	4.26
DVS-233 SR 750 mg (FASTED)									
	MEAN	1683.4	6.8	0.074	9.53	36422	36800	0.29	3.99
	S.D.	309.9	1.0	0.009	1.17	6116	6214	0.08	1.05
	% CV	18.4	14.4	12.8	12.3	16.8	16.9	26.5	26.3
	GEOMETRIC MEAN	1658.6	6.8	0.073	9.47	35980	36349	0.28	3.88
SOURCE OF VARIATION	P-VALUES FROM A ONE FACTOR ANALYSIS OF VARIANCE OF ALL DESVENLAFAXINE TREATMENTS #								
DOSE		.015	.661	.408	.408	.056	.063	.144	.156

BEFORE STATISTICAL COMPARISON, DOSE DEPENDENT PARAMETERS (Cmax, AUCT, AND AUCI WERE NORMALISED TO THE 150 MG DOSE.
* SUBJECTS WERE EXCLUDED FROM SUMMARY STATISTICS AND STATISTICAL ANALYSIS DUE TO A VOMITING AE AND LOW PLASMA CONCENTRATIONS.

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ST 8-2. PHARMACOKINETIC PARAMETERS OF VENLAFAXINE IN HEALTHY SUBJECTS RECEIVING PLACEBO, VENLAFAXINE, OR DESVENLAFAXINE

Protocol 060003-170-FR 17:28 Monday, August 4, 2003

	CMAX (ng/mL)	TMAX (h)	LAMBDA (1/h)	t1/2 (h)	AUCt - (ng*h/mL) -	AUC	Cl/F (L/h/kg)	Vz/F (L/kg)
VEN ER 150 mg								
3	59.7	4.0	0.065	10.63	788	942	2.49	38.20
6	106.6	6.0	0.055	12.61	1586	1702	1.10	20.05
14	64.3	4.0	0.055	12.56	716	869	2.01	36.39
16	36.3	6.0	0.079	8.76	413	496	4.45	56.23
23	85.0	6.0	0.089	7.76	966	1038	1.72	19.27
28	68.4	6.0	0.096	7.25	941	1001	2.20	23.04
35	49.2	6.0	0.089	7.79	597	672	3.10	34.84
37	29.8	6.0	0.037	18.77	356	500	3.57	96.68
41	39.0	4.0	0.103	6.72	401	454	4.65	45.16
46	75.4	6.0	0.062	11.24	1215	1299	1.80	29.26
51	25.3	6.0	0.041	16.79	325	463	4.63	112.20
59	62.8	6.0	0.043	16.05	647	816	2.87	66.56
62	113.4	4.0	0.086	8.07	1622 *	1711	1.37	15.96
68	37.4	6.0	0.114	6.10	401	445	4.88	42.93
71	88.8	6.0	0.069	10.10	1368	1447	1.23	17.99
80	59.3	6.0	0.074	9.36	850	920	2.51	33.87
MEAN	62.5	5.5	0.072	10.66	825	923	2.79	43.04
S.D.	26.4	0.9	0.023	3.80	431	429	1.30	27.88
% CV	42.2	16.3	31.6	35.7	52.3	46.5	46.53	64.77
GEO MN	57.2	5.4	0.069	10.09	723	834	2.50	36.44
MIN	25.3	4.0	0.037	6.10	325	445	1.10	15.96
MAX	113.4	6.0	0.114	18.77	1622	1711	4.88	112.20

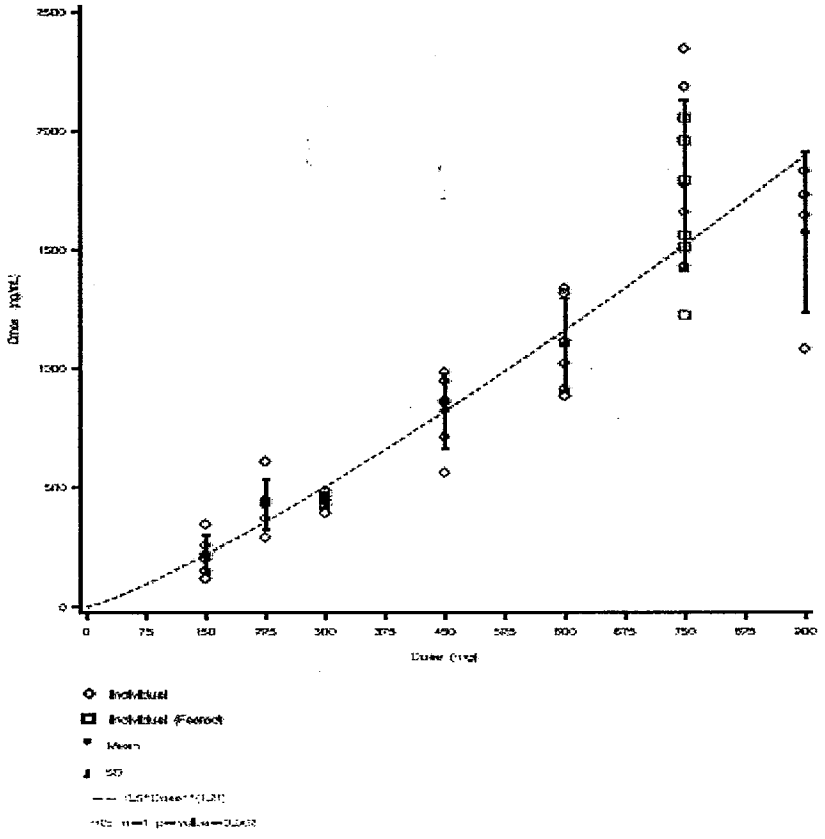
. DATA NOT AVAILABLE.
* SUBJECT WAS EXCLUDED FROM SUMMARY STATISTICS DUE TO A VOMITING AE AND LOW PLASMA CONCENTRATIONS.

Table 7.2-1: Demographic and Baseline Characteristics

Characteristic	DVS-233 SR 150 mg (n = 6)	DVS-233 SR 225 mg (n = 6)	DVS-233 SR 300 mg (n = 6)	DVS-233 SR 450 mg (n = 6)	DVS-233 SR 600 mg (n = 6)	DVS-233 SR 750 mg (n = 5)	DVS-233 SR 750 mg (Fasted) (n = 6)	DVS-233 SR 900 mg (n = 6)	Ven ER 150 mg (n = 16)	Placebo (n = 16)	Total (n = 79)
Age (years)											
Mean	31.5	26.2	27.5	28.5	27.0	23.6	24.3	27.5	27.6	27.9	27.4
SD	8.3	4.6	7.6	5.6	4.7	4.0	3.3	9.0	7.2	6.9	6.5
Min	20.0	19.0	19.0	24.0	22.0	20.0	20.0	18.0	18.0	19.0	18.0
Max	42.0	32.0	40.0	39.0	34.0	30.0	29.0	42.0	41.0	41.0	42.0
Median	31.5	27.0	26.0	27.0	25.5	22.0	24.5	25.0	25.5	26.5	26.0
Sex, n (%)											
Male	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (100)	6 (100)	6 (100)	16 (100)	16 (100)	79 (100)
Ethnic origin, n (%)											
White	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (100)	6 (100)	6 (100)	16 (100)	16 (100)	79 (100)
Height (cm)											
Mean	178.2	177.7	178.3	173.7	174.3	171.0	176.0	182.2	176.6	178.1	176.9
SD	7.9	7.4	5.9	4.8	6.1	5.5	6.0	3.8	6.0	10.1	7.2
Min	171.0	168.0	171.0	169.0	167.0	165.0	170.0	178.0	168.0	163.0	163.0
Max	190.0	188.0	188.0	182.0	183.0	176.0	185.0	188.0	187.0	197.0	197.0
Median	175.0	178.0	178.5	173.5	173.0	174.0	175.0	182.5	175.0	177.0	176.0
Weight (kg)											
Mean	76.7	72.8	73.8	70.3	72.0	72.2	72.8	77.5	72.3	74.8	73.6
SD	7.5	11.2	8.2	6.7	6.4	7.4	6.8	7.7	8.3	10.6	8.4
Min	70.0	60.0	64.0	60.0	62.0	64.0	64.0	68.0	64.0	61.0	60.0
Max	90.0	90.0	85.0	78.0	80.0	80.0	80.0	86.0	86.0	98.0	98.0
Median	74.0	72.0	72.5	72.0	71.0	70.0	73.0	77.0	69.5	71.5	72.0

Abbreviations: DVS-233 SR = desvenlafaxine sustained release; Ven ER = venlafaxine extended release; SD = standard deviation; Min = minimum; Max = maximum.

SF 8-3. INDIVIDUAL C_{max} VALUES FOR EACH SUBJECT RECEIVING POSTPRANDIAL ADMINISTRATION OF DVS-233 SR (150 TO 900 mg) ALONG WITH THE EXPONENTIAL REGRESSION RESULTS



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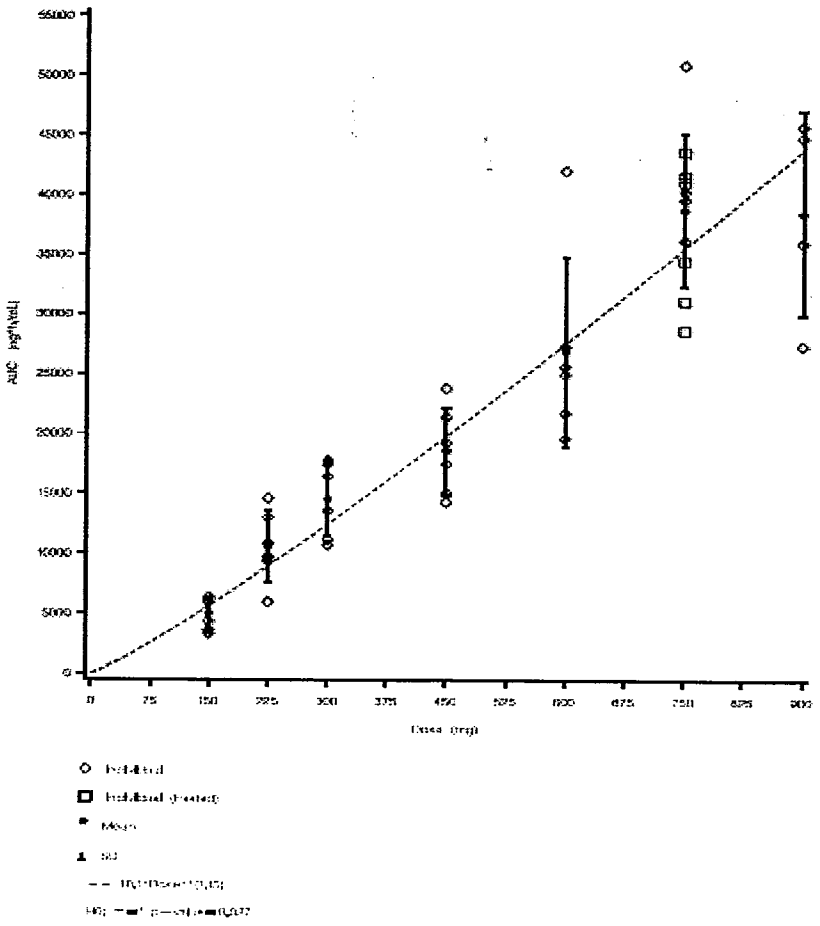
SF 8-4. DESVENLAFAXINE AUC AFTER RECEIVING A SINGLE DOSE OF DVS-233 SR



Study Title: An Ascending Multiple Dose Study Of The Safety, Pharmacokinetics, And Pharmacodynamics Of DVS-233 SR in Healthy Subjects (0600d3-171-US; CSR 46584)

Objective: The primary objective was to assess the safety and tolerability of ascending multiple oral doses of a sustained-release (SR) formulation of desvenlafaxine succinate monohydrate (DVS) in healthy subjects. The secondary objective was to assess the preliminary pharmacokinetics and pharmacodynamics of ascending multiple oral doses of DVS SR.

Study Design: This was a double-blind, placebo-controlled, inpatient, sequential-group, ascending multiple oral dose study conducted with healthy subjects. Each subject participated in only 1 dose group and received multiple doses of either DVS SR or placebo. Each dose level was evaluated in 12 subjects (9 subjects receiving DVS SR and 3 receiving placebo). Test article was given with 240 mL of room temperature water with the subject in an upright position. Subjects remained sitting for 2 hours after dose administration on day 1, day 7, and day 14, except at the times they needed to be supine for vital signs collection. No strenuous exercise was permitted for the entire study period. A medium-fat breakfast was served and completed within 30 minutes before the administration of test article. The following table presents the batch numbers for the study medication.

Study Medications Batch Numbers

Study Medication	Batch Number	Formulation Number	Strength
Desvenlafaxine SR 75 mg tablet	2001B0139	0931580A	mg/tablet
Placebo tablets	2001B0236	0931645A	NA

Abbreviations: NA = not applicable.

DVS SR doses of 300 mg, 450 mg, and 600 mg q24h, administered for 14 days, were evaluated sequentially.

Analytical Methods: Plasma was assayed for desvenlafaxine levels using a validated high-performance liquid chromatography method with fluorescence detection. Based on a 1.0-mL plasma sample, the method has a minimum quantifiable concentration of 5.0 ng/mL for desvenlafaxine. The performance of the desvenlafaxine assays 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 Desvenlafaxine/Plasma
Linear range (ng/mL)	5.0-500
Sensitivity (ng/mL)	5.0

Source: Reference 4

Table 6.5.2-2: Summary of Assay Validation and In-Process Performance for Plasma Samples

Assay Standards/QCs	Compound/Matrix Desvenlafaxine/Plasma	
	Interday	Intraday
Validation standards/QCs[a]		
Accuracy (%)	–1.7, 3.0	–2.0, 5.3
Precision (%)	0.0, 4.7	0.6, 3.3
In-process standards[a]		
Accuracy (%)	–6.8, 5.6	-
Precision (%)	1.4, 4.4	-
In-process QCs[a]		
Accuracy (%)	5.7, 8.1	-
Precision (%)	5.9, 10.8	-

a: Values are ranges of accuracy and precision.
Abbreviation: QCs = quality controls.

Data Analysis: The desvenlafaxine plasma concentration data for each subject were analyzed by using model-independent methods. For the multiple-dose pharmacokinetic analysis, the area under the steady state plasma concentration versus time curve (AUC_{ss}) estimated over the dose administration interval (τ = 24h) was calculated by using the log-trapezoidal rule with the observed data; Cl/F was calculated as: $Cl/F = Dose/AUC_{ss}$. If all plasma concentrations for desvenlafaxine were zero, the C_{max}, AUC_T, AUC, and/or AUC_{ss} were set equal to zero, and the other pharmacokinetic parameters were not determined.

The extent of nausea experienced by each subject was evaluated using a 100-mm VAS (Visual Analogue Scale) at specified times during the study. Each subject's cognitive performance was assessed by the (Digit Symbol Substitution Test) DSST (a pencil and paper test measured over 90 seconds) and by a short- and long-term memory test (immediate and delayed free recall of a 20-word list). DSST was assessed before dose administration and at 2 hours and 7 hours after dose administration on study days 1 and 13. Memory was assessed 3 hours after dose administration only on days 1 and 13. DSST is a test that measures information processing and motor speed.

The statistical comparisons of mean desvenlafaxine plasma concentrations at each sampling time and pharmacokinetic parameters of desvenlafaxine were compared among the different treatments by using a 1-factor ANOVA. Additionally, the linear dose proportionalities of the C_{max}, AUC, and AUC_{ss} were assessed by using the following exponential regression model that measures the degree of nonlinear proportionality:

$Cmax \text{ or } AUC = a*Dose^m$

A = Coefficient
m= exponent of the regression mode

The statistical comparisons of the nausea VAS raw scores and the VAS pharmacodynamic parameters among the different treatments were analyzed using 1-factor ANOVA rather than ANCOVA because all baseline values were < 5 mm.

Results: Thirty-six (36) male subjects were enrolled in this study, 27 received DVS SR and 9 received placebo. Of the 27 subjects who received active treatment, there were 9 in each of 3 treatment groups (300-mg, 450-mg, and 600-mg groups). All 36 subjects were valid for safety analysis. Twenty-one (21) subjects completed the study. The demographics of the subjects who participated in the study are provided in the following table.

Demographics and Baseline Characteristics

Characteristic	DVS SR 300 mg (n = 9)	DVS SR 450 mg (n = 9)	DVS SR 600 mg (n = 9)	Placebo (n = 9)	Total (n = 36)
Age (years)					
Mean ± SD	34.0 ± 5.4	34.9 ± 7.4	32.9 ± 4.7	34.7 ± 6.6	34.1 ± 5.9
Minimum, Maximum	25.0, 43.0	23.0, 45.0	24.0, 38.0	27.0, 45.0	23.0, 45.0
Median	33.0	33.0	34.0	32.0	33.0
Sex, n (%)					
Male	9 (100)	9 (100)	9 (100)	9 (100)	36 (100)
Ethnic origin, n (%)					
Black	3 (33)	8 (89)	2 (22)	3 (33)	16 (44)
Other	1 (11)	1 (11)	3 (33)	1 (11)	6 (17)
White	5 (56)	0	4 (44)	5 (56)	14 (39)
Height (cm)					
Mean ± SD	180.1 ± 7.8	181.9 ± 7.2	179.0 ± 8.8	179.1 ± 8.6	180.0 ± 7.9
Minimum, Maximum	170.6, 195.7	169.3, 194.1	169.7, 196.3	169.3, 191.9	169.3, 196.3
Median	177.9	182.5	179.3	174.5	180.0
Weight (kg)					
Mean ± SD	83.0 ± 10.3	80.8 ± 10.1	79.6 ± 13.3	81.7 ± 6.3	81.3 ± 9.9
Minimum, Maximum	75.8, 107.3	67.6, 101.1	66.6, 99.2	69.4, 88.6	66.6, 107.3
Median	79.6	81.0	71.7	83.7	81.0

Abbreviations: DVS SR = desvenlafaxine – sustained release; SD = standard deviation.

Summary of the single-dose pharmacokinetic parameters of DVS SR at all 3 dose levels are contained in the following table.

Desvenlafaxine Single Dose Pharmacokinetic Parameters

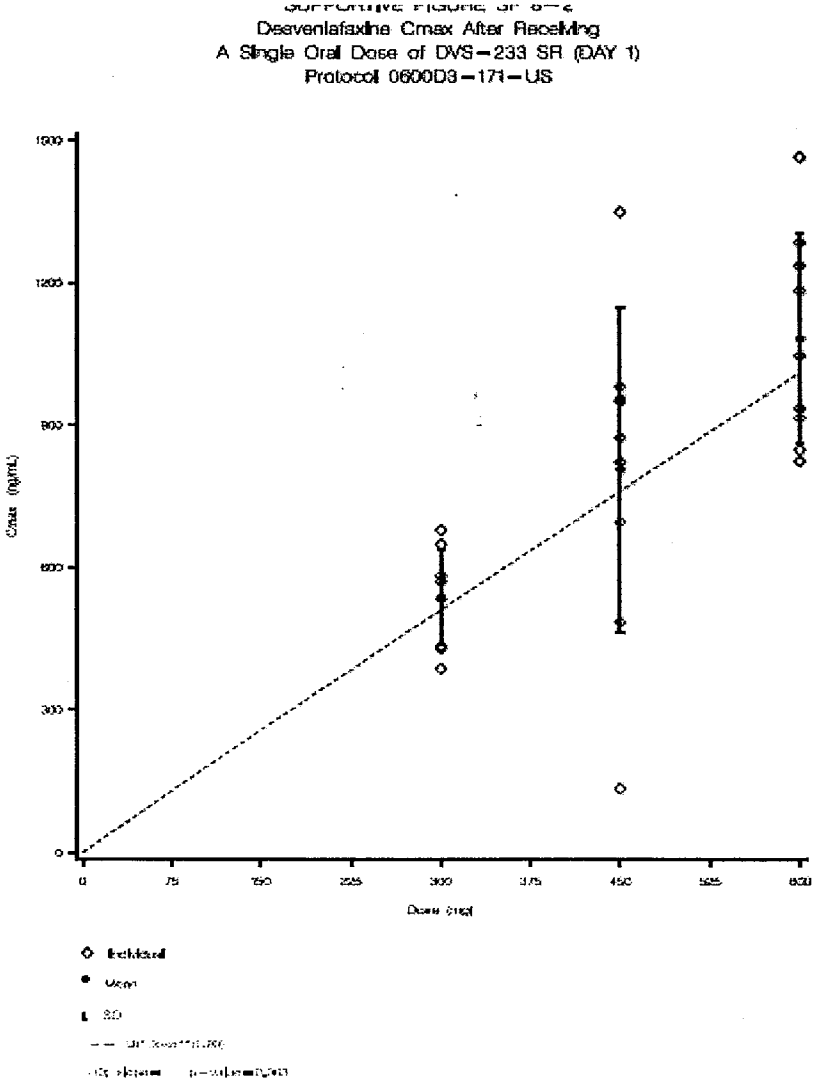
Parameters Dosage	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-24} (ng•h/mL)	AUC (ng•h/mL)	Cl/F (L/h/kg)
DVS SR 300 mg						
Mean ± SD	537 ± 101	6.7 ± 2.4	17.2 ± 8.0	8843 ± 2053	16396 ± 5220	0.27 ± 0.19
%CV	18.8	36.0	46.5	23.2	31.8	71.1
Min – Max	386 – 679	4 – 12	6.5 – 31.6	4398 – 11392	4862 – 21858	0.17 – 0.78
DVS SR 450 mg						
Mean ± SD	806 ± 342	8.7 ± 1.7	14.6 ± 8.3	13716 ± 5526	23500 ± 12356	0.34 ± 0.23
%CV	42.5	20.0	56.5	40.3	52.6	67.8
Min – Max	136 – 1349	6 – 10	2.9 – 28.5	2560 – 21343	5449 – 45498	0.12 – 0.82
DVS SR 600 mg						
Mean ± SD	1083 ± 222	7.1 ± 1.3	17.7 ± 5.9	17829 ± 2703	34315 ± 9352	0.24 ± 0.06
%CV	20.5	17.8	33.5	15.2	27.3	24.7
Min – Max	825 – 1465	6 – 10	9.6 – 25.97	14121 – 21270	20445 – 49607	0.18 – 0.35
p-Values from the 1-factor ANOVA with log-transformed parameters[a]						
	0.756	0.059	0.418	0.888	0.639	0.635

a: Before statistical comparisons, dose-dependent parameters (C_{max}, AUC_{0-24}, and AUC) were dose normalized to the 300-mg dose.

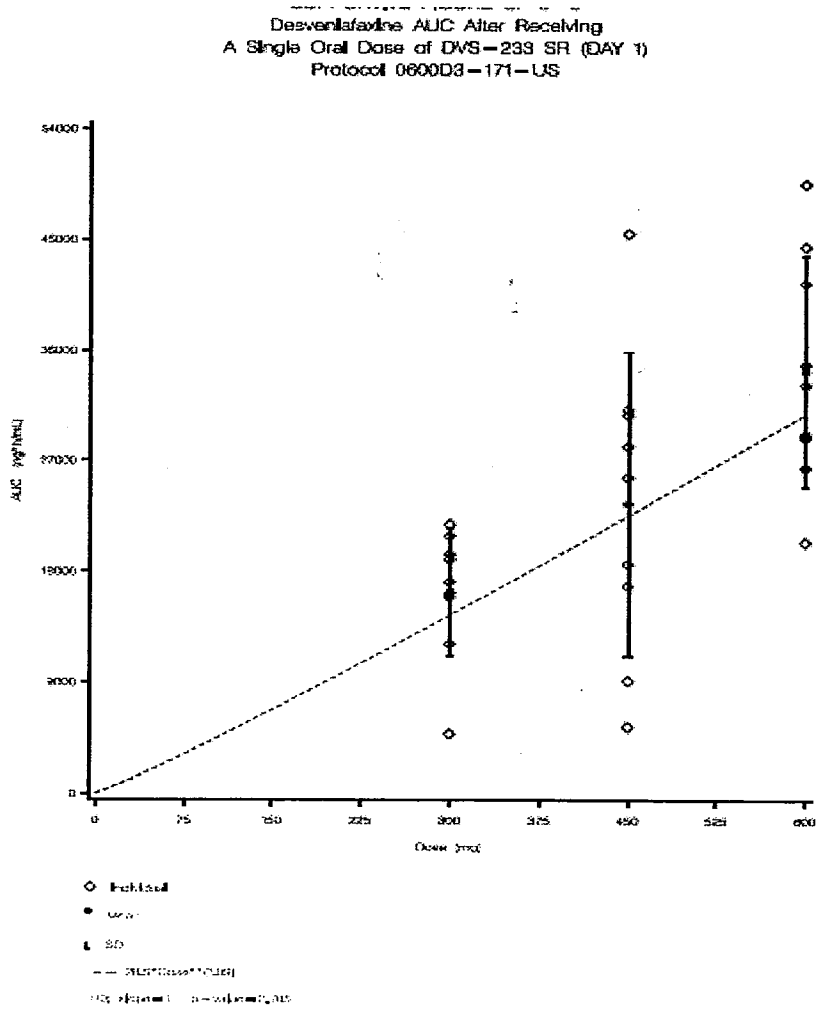
Following administration of DVS SR, desvenlafaxine was slowly absorbed with mean Tmax occurring between 6 and 8 hours after dose administration and was slowly eliminated with a mean T ½ of 15 to 18 hours. No significant differences in any of the pharmacokinetic parameters were found among the doses.

Linear dose-proportional increases in mean Cmax and AUC were noted in the 3 dose groups as shown in the following figures.

Desvenlafaxine Cmax After Receiving A Single Oral Dose of DVS-233 SR (Day 1)



Desvenlafaxine AUC After Receiving A Single Oral Dose of DVS-233 SR (Day 1)



Desvenlafaxine trough plasma concentrations were taken on days 3, 4, 5, 7, 10, and 13 and were compared to assess desvenlafaxine steady-state conditions. Statistical analysis showed no significant differences among the dose normalized trough concentrations on any of the days. Examination of the trough plasma concentrations indicated that pharmacokinetic steady-state was reached by day 4 or day 5. The following contains the mean trough concentrations.

Statistical Comparisons of Desvenlafaxine Trough Concentrations in Healthy Subjects Receiving Multiple Oral Doses Q24h

SUBJECT	(UNIT = ng/mL) DAY					
	3	4	5	7	10	13
DVS-233 SR 300 mg Q24H						
MEAN	410.9	456.6	483.2	482.4	480.2	487.3
S.D.	118.6	138.7	159.8	145.3	110.2	154.6
% CV	28.9	30.6	33.1	31.4	24.0	31.7
DVS-233 SR 450 mg Q24H						
MEAN	624.5	690.0	695.9	685.7	625.4	675.5
S.D.	241.7	217.6	239.6	294.1	435.7	347.5
% CV	38.7	31.5	34.4	42.9	66.6	51.4
DVS-233 SR 600 mg Q24H						
MEAN	820.1	841.8	899.2	914.3	.	.
S.D.	134.4	194.8	243.6	156.6	.	.
% CV	16.4	23.1	27.1	17.1	.	.
P-VALUES FROM A ONE FACTOR ANALYSIS OF VARIANCE @						
SOURCE OF VARIATION						
DOSE	0.993	0.779	0.880	0.996	0.870	0.699

@ PRIOR TO STATISTICAL COMPARISON, PLASMA CONCENTRATIONS WERE NORMALIZED TO THE 300 MG DOSE.

The following table contains the statistical comparisons among the treatments. And the summary of the pharmacokinetic parameters of desvenlafaxine SR multiple dose (q24h) at all 3 dose levels.

Desvenlafaxine Multiple Dose (q24h) Pharmacokinetic Parameters

Dosage	C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	$t_{1/2}$ (h)	AUC_{ss} (ng•h/mL)	CL/F (L/h/kg)
DVS SR 300 mg (q24h)						
Mean ± SD	807 ± 141	4.6 ± 1.1	418 ± 94	11.1 ± 2.6	14831 ± 2894	0.26 ± 0.06
%CV	17.5	4.4	22.4	23.8	19.5	22.9
Min – Max	566 – 1067	3 – 6	268 – 567	7.8 – 15.0	10856 – 18429	0.16 – 0.35
DVS SR 450 mg (q24h)						
Mean ± SD	1369 ± 292	7.6 ± 5.7	698 ± 204	11.5 ± 2.2	24073 ± 5880	0.26 ± 0.07
%CV	21.4	75.0	29.2	19.0	24.4	28.4
Min – Max	959 – 1677	3 – 20	433 – 902	8.9 – 15.3	16649 – 29915	0.17 – 0.35
p-Values from the 1-factor ANOVA with log-transformed parameters[a]						
	0.228	0.118	0.519	0.711	0.556	0.963

a: Prior to statistical comparisons, dose-dependent parameters (C_{max}, C_{min}, and AUC_{ss}) were dose-normalized to the 300-mg dose.

Following multiple-dose administration of DVS SR 300 and 450 mg q24h desvenlafaxine was absorbed with mean Tmax occurring approximately 5 to 8 hours after administration and was eliminated with mean $t_{1/2}$ of 11 to 12 hours. There were no significant differences in any of the desvenlafaxine pharmacokinetic parameters between the 2 dose groups (300 mg and 450 mg q24h).

Pharmacodynamic Results: Summary of the mean VAS nausea ratings are provided in the following table.

Nausea VAS Parameters

Dosage	E_{max} (mm)	t_{Emax} (h)	AURC (mm•h)	VAS ≥ 10 mm (% of subjects)
Day 1 : Single Dose				
Placebo	6 ± 15[a]	12.5 ± 16.3	55 ± 162	11.1
DVS SR 300 mg	6 ± 8	3.3 ± 1.0	19 ± 34	33.3
DVS SR 450 mg	21 ± 24	6.7 ± 8.6	137 ± 203	55.6
DVS SR 600 mg	13 ± 18	4.8 ± 2.3	75 ± 105	44.4
p-Values from the 1-factor ANOVA	0.222	0.410	0.361	
Day14: Multiple Dose (q24h)[b]				
Placebo	0 ± 0	NA	0 ± 0	0.0
DVS SR 300 mg	0 ± 0	NA	0 ± 0	0.0
DVS SR 450 mg	2 ± 6	1 ± NA	16 ± 48	11.1
p-Values from the 1-factor ANOVA	0.480	NA	0.480	

a: Mean ± SD.
b: Data are not available for the DVS SR 600-mg dose because all subjects had discontinued by this day.

The sponsor reported that on day 1, the 450-mg dose group had the highest nausea scores with a mean E_{max} of 21 mm and with 56% of the subjects having nausea scores greater than 10 mm. There were no significant differences among the dosage levels and placebo. In the 300-mg dose group, no subjects had a nausea VAS score ≥ 10 mm after the first day of dosing. In the 450-mg dose group, no subject had a nausea VAS score ≥ 10 mm after the seventh day of dosing.

A summary of the Digit Symbol Substitution Test (DSST) is contained in the following table

Summary of DSST Results

	Day 1			Day 13[a]		
Dosage	0 h (Baseline)	2 h	7 h	0 h	2 h	7 h
Placebo	30 ± 11[b]	29 ± 13	30 ± 12	30 ± 14	28 ± 17	27 ± 12
DVS SR 300 mg	34 ± 11	37 ± 10	40 ± 11	41 ± 10	37 ± 9	37 ± 11
DVS SR 450 mg	33 ± 6	33 ± 9	34 ± 9	32 ± 9	30 ± 10	34 ± 9
DVS SR 600 mg	34 ± 10	35 ± 15	34 ± 15	NA	NA	NA
p-Values from a 1-factor ANCOVA						
Baseline		0.001	0.001	0.001	0.001	0.001
Treatment	0.784	0.435	0.035	0.006	0.120	0.065
Pairwise Comparisons of Significant Treatment Effects						
300 mg vs 450 mg			0.022	0.002		
300 mg vs 600 mg			0.009	NA		
300 mg vs placebo			0.027	0.019		
450 mg vs 600 mg			0.704	NA		
450 mg vs placebo			0.943	0.598		
600 mg vs placebo			0.655	NA		

a: Data not available for the DVS SR 600-mg dose because all subjects had discontinued by this day.
b: Mean ± SD

The sponsor reported that on day 1 predose (baseline), there was no significant difference in the mean DSST scores among all 3 dose groups and the placebo group. After treatment, the 300-mg dose group scored higher (range 37 to 41), whereas, the 450-mg, 600-mg, and placebo dose groups produced similar scores (range 27 to 35). All pairwise comparisons are exploratory, but they indicate that the 300-mg dose group performed significantly better than the placebo group on day 1 (hour 7) and day 13 (predose). For day 1 (hour 2), day 13 (hour 2), and day 13 (hour 7), the 300-mg group produced higher mean DSST scores than the placebo group, but these differences did not attain statistical significance.

Summary of the results of the immediate and delayed word recall along with the percent retained (delayed word recall divided by immediate word recall) are presented in the following tables

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Summary of Immediate and Delayed Word Recall Results

	Immediate Word Recall			Delayed Word Recall		
	Day 1		Day 13[a]	Day 1		Day 13[a]
Dosage	−12 h (Baseline)	3 h	3 h	−12 h (Baseline)	3 h	3 h
Placebo	10 ± 3[b]	11 ± 5	10 ± 5	9 ± 4	9 ± 6	8 ± 6
DVS SR 300 mg	12 ± 4	12 ± 4	13 ± 3	9 ± 5	9 ± 6	11 ± 4
DVS SR 450 mg	9 ± 2	8 ± 2	9 ± 2	7 ± 2	5 ± 2	8 ± 3
DVS SR 600 mg	11 ± 4	10 ± 4	NA	8 ± 3	7 ± 6	NA
p-Values from a 1-factor ANCOVA						
Baseline		0.002	0.001		0.001	0.001
Treatment	0.286	0.662	0.458	0.617	0.510	0.300

a: Data not available for DVS SR 600-mg group because all subjects had discontinued by this date.
b: Mean ± SD

Summary of Percent of Words Retained Results

	Day 1		Day 13[a]
Dosage	−12 h (Baseline)	3 h	3 h
Placebo	86 ± 20[b]	76 ± 32	72 ± 18
DVS SR 300 mg	78 ± 21	68 ± 28	86 ± 12
DVS SR 450 mg	83 ± 19	54 ± 21	79 ± 11
DVS SR 600 mg	78 ± 12	59 ± 34	NA
p-Values from a 1-factor ANCOVA			
Baseline		0.429	0.025
Treatment	0.739	0.494	0.214

a: Data not available for the DVS SR 600-mg group because all subjects had discontinued by this date.
b: Mean ± SD

There were no significant differences among the 3 dosage groups and the placebo group in terms of the immediate word recall, delayed word recall, and percent of words retained. The percent of words retained averaged from 54% to 86%.

Safety Summary: The sponsor reported that there was an apparent increase in the number of TEAEs across treatment groups. The most frequently reported TEAEs (> 30%) seen in the 300-mg dose group were hypertension and nausea. In the 450-mg dose group, the most common TEAEs were constipation, headache, hypertension, nausea, and tachycardia, and in the 600-mg dose group, the most common TEAEs were abnormal dreams, anorexia, application site reaction (chest wall irritation due to ECG electrodes), asthenia, constipation, dizziness, euphoria, hypertension, nausea, postural (orthostatic) hypotension, tachycardia, and twitching. In the 600-mg dose group, the investigator reported 6 of 9 subjects with postural hypotension and 9 of 9 subjects with tachycardia. The sponsor reported that postural hypotension was not reported as an AE by any subject at the lower doses.

The sponsor reported that there were increases in systolic and diastolic blood pressures over the 14-day trial. The mean increase from baseline in systolic blood pressure for the 300-mg group was 12.3 ± 12.4 mm Hg (mean ± standard deviation), whereas the 450-mg group at the same time had a mean increase from baseline of 15.1 ± 10.7 mm Hg. For diastolic pressure, the 300-mg group had a mean increase from baseline of 4.4 ± 9.1 mm Hg, whereas the 450-mg group had an increase from baseline of 9.6 ± 8.8 mm Hg. By day 14 at hour 8, pulse rate in the 300-mg group had a minor increase from baseline of 6.5 ± 7.0 beats per minute (bpm) while pulse rate in the 450-mg group increased from baseline by 15.0 ± 6.2 bpm. Changes in blood pressure values in response to the 600-mg dose of DVS SR varied among subjects. Some showed a decrease in supine blood pressure and others exhibited an increase in supine blood pressure. On day 8, terminated the study because of significant postural hypotension observed in the 600-mg cohort. Postural hypotension was reported in 6 of the 9 subjects receiving 600 mg DVS SR.

Summary: The pharmacokinetics of DVS SR were evaluated in this study after single and multiple doses of 300 mg, 450 mg, and 600 mg q24h. Following single- or multiple-dose administration of DVS SR, desvenlafaxine was slowly absorbed with Tmax occurring approximately 5 to 8 hours after administration and was slowly eliminated with a mean T ½ of 11 to 18 hours. At each dose level, trough plasma concentrations indicated that pharmacokinetic steady state was reached by day 4 or 5 of the multiple-dose (q24h) regimen. The plasma concentrations appeared to increase in a linearly dose-proportional manner over the studied dose range as indicated by the approximately linear dose-proportional increases in C_{max} and AUC.

For DVS SR, there were no significant differences among the 3 dosage levels and placebo in terms of the immediate word recall, delayed word recall, and percent of words retained. There were no statistically significant differences among the treatment groups in nausea VAS profile; however, the maximum VAS score was higher for the 450-mg and the 600-mg dose groups than for the 300-mg group and the placebo group. The most common (frequency > 30%) TEAEs seen at the 300-mg dose group were hypertension and nausea. In the 450-mg dose group, the most common TEAEs were constipation, headache, hypertension, nausea, and tachycardia, and in the 600-mg dose group, they

were abnormal dreams, anorexia, application site reaction, asthenia, constipation, dizziness, euphoria, hypertension, nausea, postural hypotension, tachycardia, and twitching.

Reviewer Comments: *The reviewer agrees with the sponsor's evaluation of the pharmacokinetic of DVS SR. Significant accumulation was not observed when DVS 300 mg was administered every 24 hours for 14 days. The accumulation index was calculated to be about 1.3 when day1 and day 14 data are compared. Nausea and hypertension appeared to be the most frequently reported adverse events.*

Attachments

ST 8-4. STATISTICAL COMPARISONS OF DESVENLAFAXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS RECEIVING A SINGLE ORAL DOSE OF DVS-233 SR (DAY 1)

SUPPORTIVE TABLE ST 8-4 - Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters In Healthy Subjects Receiving A Single Oral Dose of DVS-233 SR (Day 1)

Protocol 060003-171-US

14:02 Thursday
February 26, 2009

	Cmax (ng/mL)	Tmax (h)	LAMBDA (1/h)	t1/2 (h)	AUCt = (ng*h/mL) =	AUC	CL/F (L/h/kg)	Vz/F (L/kg)
DVS-233 SR 300 mg Q24H								
MEAN	537	6.7	0.049	17.3	9843	16396	0.27	5.58
S.D.	101	2.4	0.025	8.0	2053	5220	0.13	1.59
% CV	18.8	35.0	50.8	46.5	21.2	31.8	71.1	28.4
GEO. MEAN	529	6.3	0.044	15.7	9574	15239	0.24	5.39
DVS-233 SR 450 mg Q24H								
MEAN	806	8.7	0.075	14.6	13715	23500	0.34	6.41
S.D.	342	1.7	0.068	8.3	5526	12356	0.33	6.47
% CV	42.5	20.0	90.5	56.8	40.3	52.6	97.8	101.0
GEO. MEAN	699	8.5	0.057	12.1	12852	19938	0.28	4.90
DVS-233 SR 600 mg Q24H								
MEAN	1083	7.4	0.044	17.7	17829	34315	0.34	5.69
S.D.	293	1.3	0.017	5.9	2703	9352	0.06	1.26
% CV	26.5	17.8	38.5	33.5	15.2	27.3	24.7	22.2
GEO. MEAN	1063	7.0	0.041	16.7	17645	33173	0.33	5.55
P-VALUES FROM A ONE FACTOR ANALYSIS OF VARIANCE @ SOURCE OF VARIATION								
DOSE	0.756	0.059	0.418	0.418	0.889	0.639	0.659	0.831

@ PRIOR TO STATISTICAL COMPARISON, DOSE-DEPENDENT PARAMETERS (CMAX, AUCT, AUC) WERE NORMALIZED TO THE 300 MG DOSE.

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ST 8-9. PHARMACOKINETIC PARAMETERS OF DESVENLAFAXINE IN HEALTHY SUBJECTS RECEIVING MULTIPLE ORAL DOSES OF DVS-233 SR Q24H (DAY 14)

SUPPORTIVE TABLE ST 8-9 - Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving Multiple Oral Doses of DVS-233 SR Q24H (Day 14)

Protocol 080003-171-US

14:02 Thursday
February 20, 2003

TREATMENT	SUBJECT	Cmax (ng/mL)	Tmax (h)	LAMBDA (1/h)	t1/2 (h)	Cmin (ng/mL)	Cmean (ng/mL)	AUCss (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)	Rf
DVS-233 SR 300 mg Q24H											
	1	714	4.0	0.081	8.6	393	518	12420	0.30	3.67	0.62
	2	783	4.0	0.065	10.6	423	602	14438	0.27	4.15	0.60
	4	1067	4.0	0.046	15.0	476	767	18397	0.20	4.37	0.77
	6	753	4.0	0.057	12.4	337	508	12197	0.27	4.65	0.82
	7	805	4.0	0.056	12.3	468	684	16408	0.24	4.38	0.49
	8	907	3.0	0.049	14.1	567	768	18429	0.21	4.22	0.44
	9	566	6.0	0.089	7.8	258	452	10856	0.35	3.91	0.66
	10	903	6.0	0.053	13.0	492	725	17391	0.16	3.01	0.57
	12	762	6.0	0.085	8.2	334	539	12941	0.31	3.62	0.79
	MEAN	807	4.6	0.065	11.1	418	618	14831	0.25	3.92	0.64
	S.D.	141	1.1	0.015	2.6	94	121	2894	0.06	0.43	0.13
	% CV	17.5	24.8	24.2	23.8	22.4	19.5	19.5	22.9	11.0	20.7
	GEO. MEAN	796	4.4	0.064	10.8	408	607	14577	0.25	3.90	0.63
	MIN	566	3.0	0.046	7.8	258	452	10856	0.16	3.01	0.44
	MAX	1067	6.0	0.089	15.0	567	768	18429	0.35	4.37	0.82
DVS-233 SR 450 mg Q24H											
	15	959	6.0	0.078	8.9	433	694	16649	0.35	4.45	0.76
	18	1403	20.0	0.076	9.1	539	795	19074	0.28	3.68	1.00
	19	1598	7.0	0.055	12.6	815	1215	29166	0.19	3.46	0.59
	20	1677	3.0	0.061	11.3	803	1155	27728	0.24	3.91	0.76
	22	1516	7.0	0.045	15.3	902	1246	29915	0.17	3.76	0.49
	23	962	6.0	0.060	11.5	481	746	17892	0.35	5.90	0.64
	24	1465	4.0	0.060	11.5	851	1170	28069	0.22	3.59	0.53
	MEAN	1369	7.6	0.062	11.5	698	1003	24073	0.25	4.10	0.69
	S.D.	292	5.7	0.011	2.2	204	245	5880	0.07	0.85	0.20
	% CV	21.4	75.0	18.3	19.0	29.2	24.4	24.4	28.4	20.7	29.0
	GEO. MEAN	1339	6.4	0.061	11.3	670	976	23418	0.25	4.04	0.67
	MIN	959	3.0	0.045	8.9	433	694	16649	0.17	3.46	0.49
	MAX	1677	20.0	0.078	15.3	902	1246	29915	0.35	5.90	1.00

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ST 8-10. STATISTICAL COMPARISONS OF DESVENLAFAXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS RECEIVING MULTIPLE ORAL DOSES OF DVS-233 SR Q24H (DAY 14)

SUPPORTIVE TABLE ST 8-10 - Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters
In Healthy Subjects Receiving Multiple Oral Doses of DVS-233 SR Q24H (Day 14)

Protocol 060083-171-US

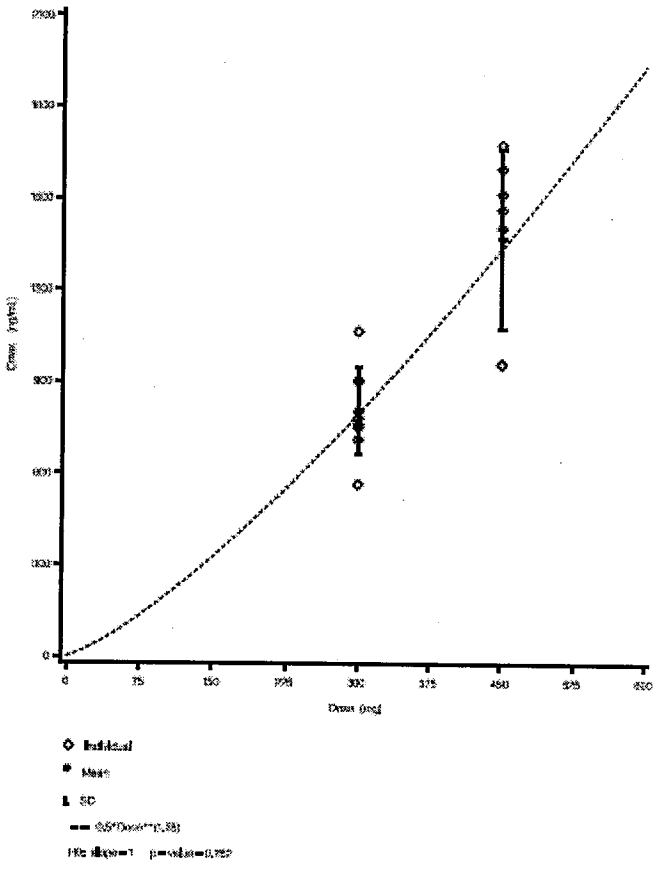
14:02 Thursday
February 20, 2003

	Cmax (ng/mL)	Tmax (h)	LAMBDA (1/h)	t1/2 (h)	Cmin (ng/mL)	Cmean (ng/mL)	AUCss (ng*h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)	Rf
DVS-233 SR 300 mg Q24H										
MEAN	697	4.6	0.066	11.1	418	518	14831	0.26	3.92	0.64
S.D.	141	1.1	0.016	2.6	94	121	2894	0.06	0.43	0.13
% CV	17.5	24.0	24.2	23.8	22.4	19.5	19.5	22.9	11.0	20.7
GEO. MEAN	796	4.4	0.064	10.8	408	507	14577	0.25	3.90	0.63
DVS-233 SR 450 mg Q24H										
MEAN	1369	7.6	0.062	11.5	698	1003	24073	0.26	4.10	0.69
S.D.	293	5.7	0.011	2.2	204	245	5886	0.07	0.85	0.20
% CV	21.4	75.0	18.3	19.0	29.2	24.4	24.4	28.4	20.7	29.0
GEO. MEAN	1339	6.4	0.061	11.3	670	976	23418	0.25	4.04	0.67
P-VALUES FROM A ONE FACTOR ANALYSIS OF VARIANCE @ SOURCE OF VARIATION										
DOSE	0.282	0.218	0.711	0.711	0.519	0.556	0.556	0.963	0.644	0.582

PRIOR TO STATISTICAL COMPARISON, DOSE-DEPENDENT PARAMETERS (Cmax, Cmin, Cmean, AUCss) WERE NORMALIZED TO THE 300 MG DOSE.

SF 8-5. DESVENLAFAXINE C_{max} AFTER RECEIVING MULTIPLE ORAL DOSES OF DVS-233 SR Q24H (DAY 14)

SUPPORTIVE FIGURE SF 8–5
Desvenlafaxine Cmax After Receiving
Multiple Oral Doses of DVS–233 SR Q24H (DAY 14)
Protocol 060003–171–US



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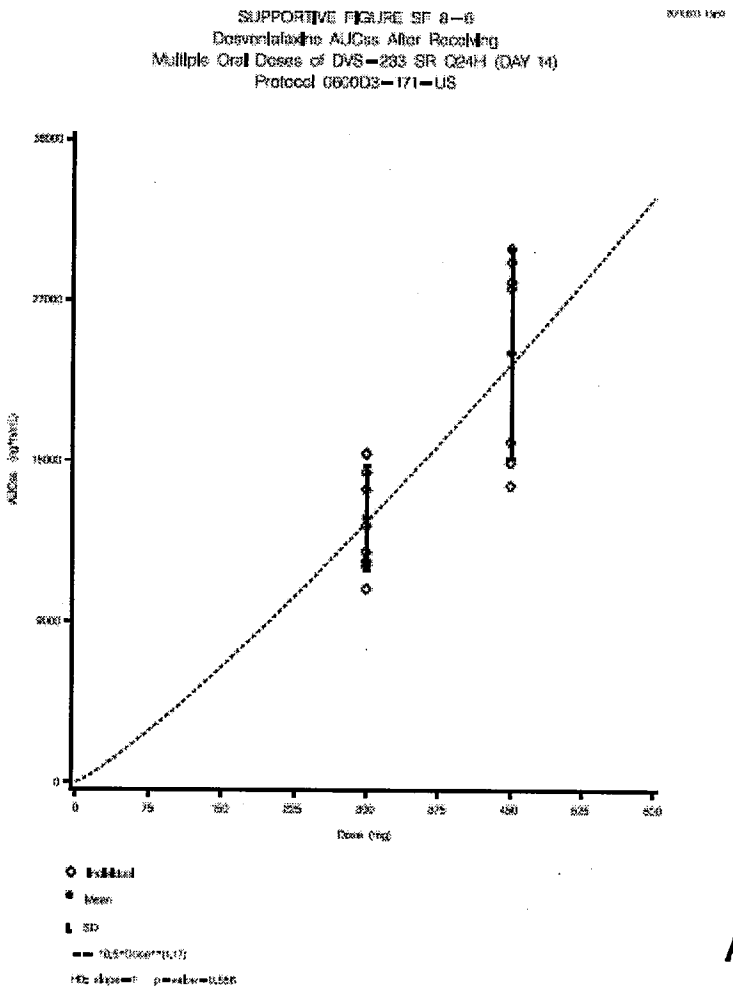
SF 8-6. DESVENLAFAXINE AUC_{ss} AFTER RECEIVING MULTIPLE ORAL DOSES OF DVS-233 SR Q24H (DAY 14)



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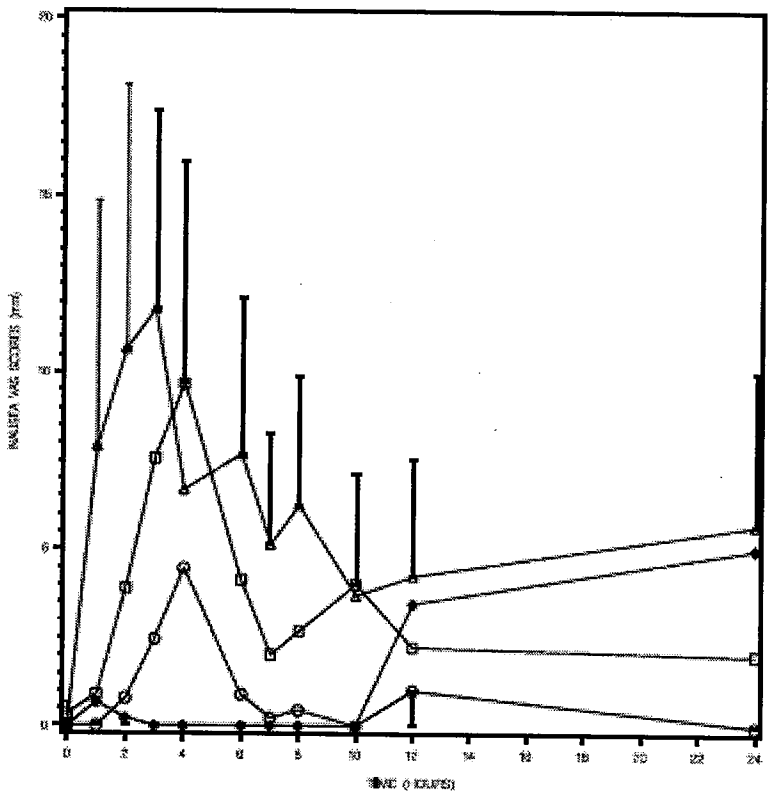
SUPPORTIVE FIGURE ST 8—7

Mean Nausea VAS Scores In

In Healthy Subjects Receiving a Single Oral Dose of DVS—233 SR (Day 1)

Protocol 0600D3—171—US



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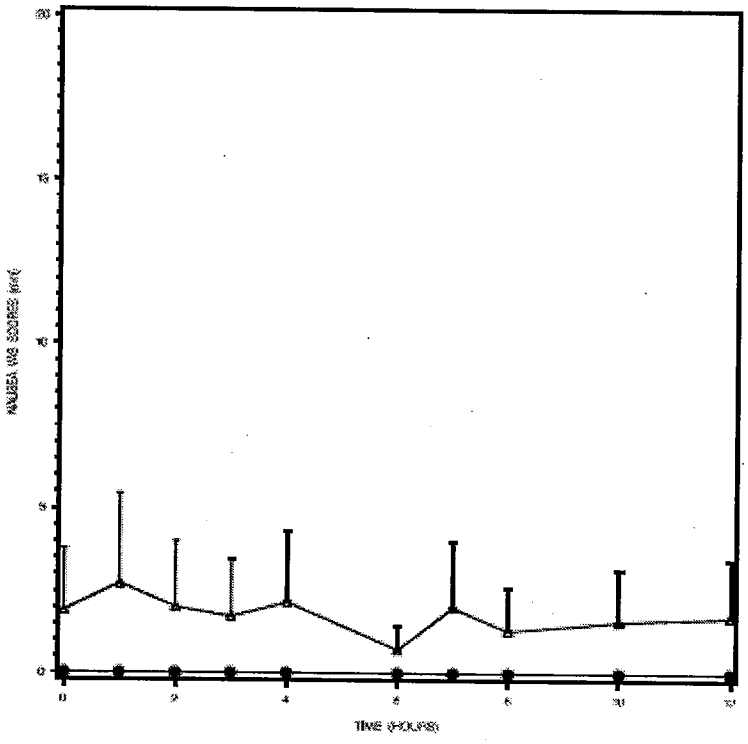
SUPPORTIVE FIGURE SF 5–5

Mean Nausea VAS Scores In

In Healthy Subjects Receiving Multiple Oral Doses of DVS–233 SR Q24H (Day 14)

Protocol 0600D3–171–US



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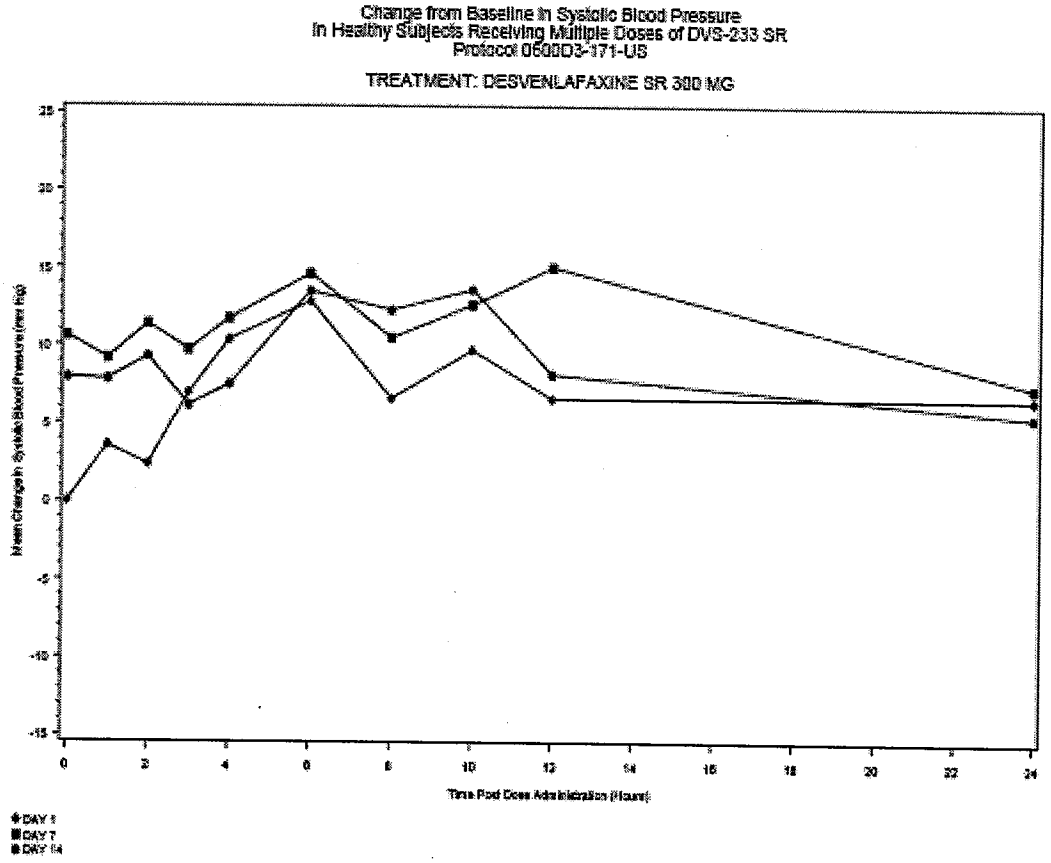

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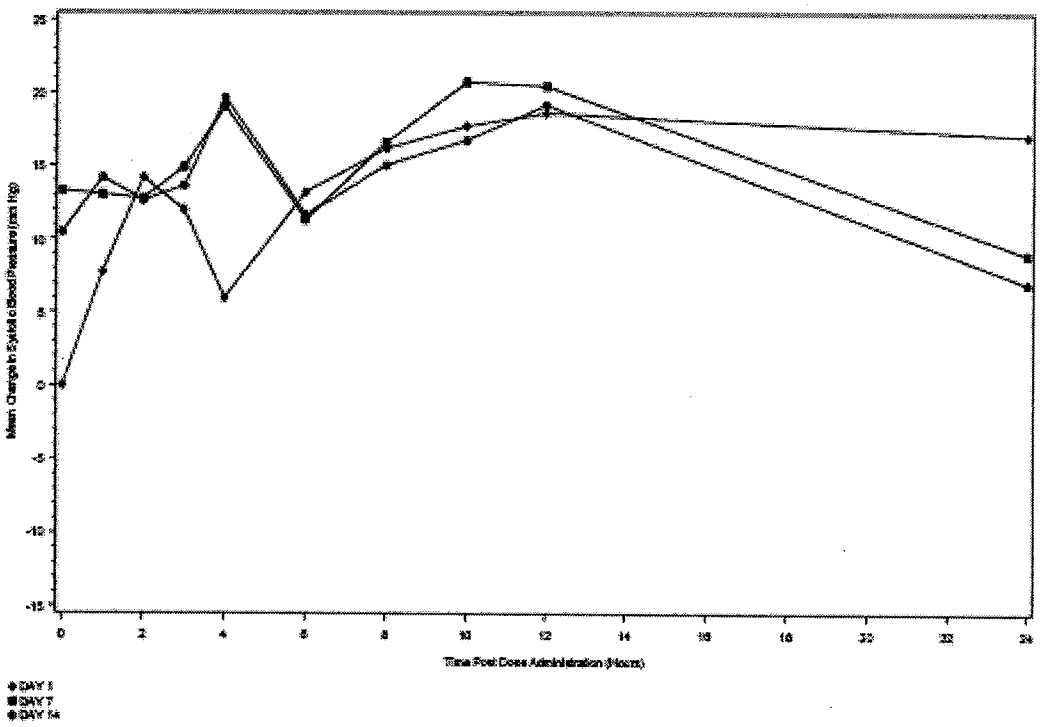
Change from Baseline in Systolic Blood Pressure
In Healthy Subjects Receiving Multiple Doses of DVS-233 SR
Protocol 0600D3-171-US

TREATMENT: DESVENLAFAXINE SR 450 MG



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