

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

Phenotype	Subject	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₇ (h*ng/mL)	AUC (h*ng/mL)	AUC Extrap (%)	t _{1/2} (h)	VF (L)	VF (L/kg)	CLF (L/h)	CLF (L/h/kg)
PM	5	445.90	6.0	8072.5	8118.9	0.57	12.56	223.3	3.17	12.32	0.175
	6	255.80	6.0	2393.5	8109.5	70.49	19.45	346.0	6.01	12.33	0.214
	7	185.50	6.0	6093.4	6218.9	2.02	10.38	240.8	3.56	16.08	0.238
	15	119.20	4.0	1684.9	1740.9	3.22	9.67	801.1	7.85	57.44	0.563
	26	211.50	10.0	4326.2	4363.8	0.86	8.34	275.6	3.66	22.92	0.304
	39	216.80	12.0	6113.8	6224.4	1.78	11.02	255.4	3.20	16.07	0.201
	49	312.70	6.0	7117.5	7170.0	0.73	8.56	172.2	3.13	13.95	0.254
N	7	7	7	7	7	7	7	7	7	7	7
Mean	249.63	7.1	5114.5	5992.3	11.38	11.43	330.6	4.37	21.59	0.278	
SD	105.04	2.8	2398.1	2281.2	26.08	3.82	214.1	1.84	16.22	0.132	
SE	39.70	1.1	906.4	862.2	9.86	1.45	80.9	0.70	6.13	0.050	
Min	119.20	4.0	1684.9	1740.9	0.57	8.34	172.2	3.13	12.32	0.175	
Median	216.80	6.0	6093.4	6224.4	1.78	10.38	255.4	3.56	16.07	0.238	
Max	445.90	12.0	8072.5	8118.9	70.49	19.45	801.1	7.85	57.44	0.563	
CV%	42.1	39.1	46.9	38.1	229.2	33.5	64.7	42.1	75.1	47.4	
Geometric Mean	231.99	6.7	4499.6	5428.0	2.25	10.98	291.9	4.10	18.42	0.259	

3.2.5. GENOMICS REVIEW

NDA (Serial Number): 21-992

Sponsor: Wyeth

Drug: PRISTIQ (desvenlafaxine) XR

Formulation: Oral tablets

Proposed Indication: major depressive disorder, vasomotor symptoms associated with menopause,

Review Due Date: 1/7/2008

Material Submitted: Pharmacogenomics evaluations in four different clinical studies

Reviewer: Silvana Borges, M.D.

Background:

Sponsor: Desvenlafaxine is primarily metabolized by phase 2 enzymes to form a glucuronide conjugate, and to a lesser extent by CYP3A4 to form N,O-didesmethylvenlafaxine (NODV). After single-dose administration of DVS SR, approximately 50% of the administered dose is recovered in the urine as unchanged desvenlafaxine. Approximately 25% is excreted as the glucuronide conjugate of desvenlafaxine and 5% or less as the oxidative metabolite. In vitro evidence indicates that desvenlafaxine is a weak inhibitor of the CYP2D6 enzyme.

Comments from reviewer:

The sponsor conducted four clinical studies to evaluate the potential of desvenlafaxine (DVS) for drug-drug interactions with respect to CYP2D6 substrates and CYP2D6 status:

- 1) Study 3151A1-198-US: to evaluate the effect of multiple doses of 100 mg DVS SR on the pharmacokinetics of desipramine (a CYP2D6 substrate) when coadministered to healthy subjects.
- 2) Study 3151A1-401-US: to evaluate the effects of multiple doses of DVS SR and duloxetine on the PK of a single dose of desipramine in healthy subjects.
- 3) Study 3151A1-900-US: to evaluate the effects of multiple doses of DVS SR and paroxetine on the pharmacokinetics (PK) of a single dose of desipramine in healthy subjects.
- 4) Study 3151A1-901-US: To determine if the relative difference in PK between EMs and PMs was the same for DVS SR and venlafaxine ER when a single dose of each was administered.

In order to identify the effect of CYP2D6 genetic polymorphisms on the pharmacokinetics of desipramine and DVS, the sponsor genotyped for CYP2D6 in all four studies.

Collection of DNA. There is no sufficient information about the conditions of blood collection, storage of the blood samples before DNA extraction and DNA extraction procedures. Blood is usually collected in tubes with anticoagulants such as EDTA, Citrate or Heparin. DNA in a blood sample is susceptible to degradation unless properly stored. Although the sponsor mentioned that the blood samples were stored and transported at 4 °C, there is no information about the time elapsed between blood collection and DNA extraction.

CYP2D6 genotyping. Being CYP2D6 a highly polymorphic enzyme, with more than 70 alleles and allelic variants described, it is always a challenge to select a small number of alleles that allows efficient testing and yet considers the CYP2D6 allelic frequencies in different racial groups. There is no full agreement in the scientific community to what the list of recommended alleles is for each racial group and that list is also different according to the type and goals of the studies. In this case, the sponsor studied 14 alleles (*1, *2, *2xN (gene duplication), *3 to *8, *10, *17, *29, *40, and *41), which are appropriate for the racial and ethnic distribution of the studied population. The sponsor also made a proper selection of defining nucleotide polymorphisms for the identification of each allele and performed an adequate quality control. However, although the sponsor refers to their report on the genotyping method validation, there is no summary information about the genotyping procedures included in these studies.

CYP2D6 genotyping results. There is no detailed information of the genotyping results in study 3151A1-198-US (see conclusions and recommendations). In studies 3151A1-401-US and 3151A1-901-US the genotypes are correctly reported according to the identified defining nucleotide polymorphisms. In study 3151A1-900-US there is an incorrect genotype assignment of subjects 1 (should be *1xN/*29) and 14 (could be either *1xN/*4 or *1/*4xN), although these miscalls would not affect the predicted phenotype.

CYP2D6 phenotype prediction. The sponsor designed a table to predict the CYP2D6 phenotype for each possible CYP2D6 allelic combination. Although it is still controversial whether such prediction could be made, the prediction approach presented by the sponsor is reasonable and similar to the prediction table provided in the package insert of the only FDA approved CYP2D6 test. However, the sponsor omitted *1xN (a duplication that has been previously described as having a frequency similar to *2xN in some studies). In the phenotype prediction table of study 3151A1-900-US (page 69) the genotypes CYP2D6*41/*3 to *7 and CYP2D6*41/*41 are inaccurately assigned the PM instead of the IM phenotype.

Conclusions and Recommendations:

The CYP2D6 genotyping procedures are overall adequate, with the following recommendations:

- Provide more information about conditions for blood collection, time elapsed between blood collection and DNA extraction and DNA extraction methods
- Provide a summary of the genotyping methods
- Provide a listing of the nucleotide(s) identified at each defining polymorphic position for all CYP2D6 alleles tested in all participants in study 3151A1-198-US.

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/s/

Kofi Kumi
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Raman Baweja
1/28/2008 02:59:56 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-992
Generic Name:	Desvenlafaxine Succinate Sustained Release (SR) Tablets
Trade Name:	TBD
Strength and Dosage Form:	100 mg and 200 mg Oral Tablets
Indication:	Treatment of Major Depressive Disorder (MDD)
Sponsor:	Wyeth Pharmaceuticals Inc.
Submission Type:	Original NDA (NME)
Submission Dates:	12/22/05, 1/13/06, 2/1/06, 3/7/06, 5/10/06, 6/26/06, 9/14/06
OCP Division:	DCP1 (HFD-860)
OND Division:	DPP (HFD-130)
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

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1. Executive Summary

1.1 Recommendations

Based on the review of the data submitted to the Clinical Pharmacology and Biopharmaceutics section of NDA 21-992 to fulfill section 320 and 201.5 of 21CFR, the Office of Clinical Pharmacology supports a recommendation for approval of DVS SR provided a satisfactory agreement is reached between the applicant and the Agency regarding 1) language in the package insert 2) specifications for the in vitro release test and the following comments.

- 1a) Dose for patients with moderate, severe and end-stage renal disease should be reduced to half (50 mg per day) of the standard dose for patients with normal renal function.
- 1b) Patients with moderate, severe and end-stage renal disease should not be administered DVS SR until a 50 mg dose is commercially available
- 1c) Patients with renal impairment should not have their dose escalated higher.

- 2) 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".

- 3) Language indicating that "hypertension was observed" should be added to the label as a warning.

- 4) It is recommended that the following dissolution method and specification be adopted for the strengths (100 and 200 mg) of DVS SR

Method:

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

Time	Criteria (% LC Released)
2 hours	—
4 hours	—
8 hours	—
12 hours	—
24 hours	NLT (

1.2 Phase 4 Commitments

There are no Phase 4 commitments from OCP

1.3 Comments to Medical Division

1. OCP Labeling recommendations are incorporated into the label attached under Appendices: Package Insert.
2. Based on the Level A IVIVC information submitted, the multiple point dissolution specification as recommended above under “Recommendations” should be adopted as dissolution specification.
3. The evaluation of dissolution specification based on Quality By Design (QBD) principles is ongoing. The appropriateness of setting a t_{90} time point dissolution specification is being evaluated by both OCP and ONDQA. When the evaluation is completed, a decision as to adopting a t_{90} time point specification will be conveyed.

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Regulatory Background: Desvenlafaxine succinate (O-desmethylvenlafaxine succinate monohydrate) is a salt form of the major active metabolite of venlafaxine, which is approved under trade name, Effexor[®] XR Extended Release Capsules and Effexor[®] Tablets. Desvenlafaxine succinate (DVS) has been developed as a sustained release product.

Therapeutic Indication and Dosing Regimen: Desvenlafaxine succinate is a potent and selective serotonin and norepinephrine reuptake inhibitor (sSNRI). Desvenlafaxine sustained release (DVS SR) is being evaluated for the treatment of major depressive disorder (MDD). The recommended dose for DVS SR is 100 mg once daily, with or without food. Subjects not responding to the initial 100 mg per day dose may benefit from a dose increase to 200 mg/day. There is no evidence that doses greater than 200 mg/day confer any additional benefit. OCP is recommending that the dose for moderate, severe renal and End Stage Renal Disease (ESRD) patients be half of the recommended dose. OCP is recommending that DVS should not be administered to moderate, severe and renal impaired patients until a 50 mg dose is commercially available. It is also recommended that the doses for renal impaired patients should not be escalated to 200 mg.

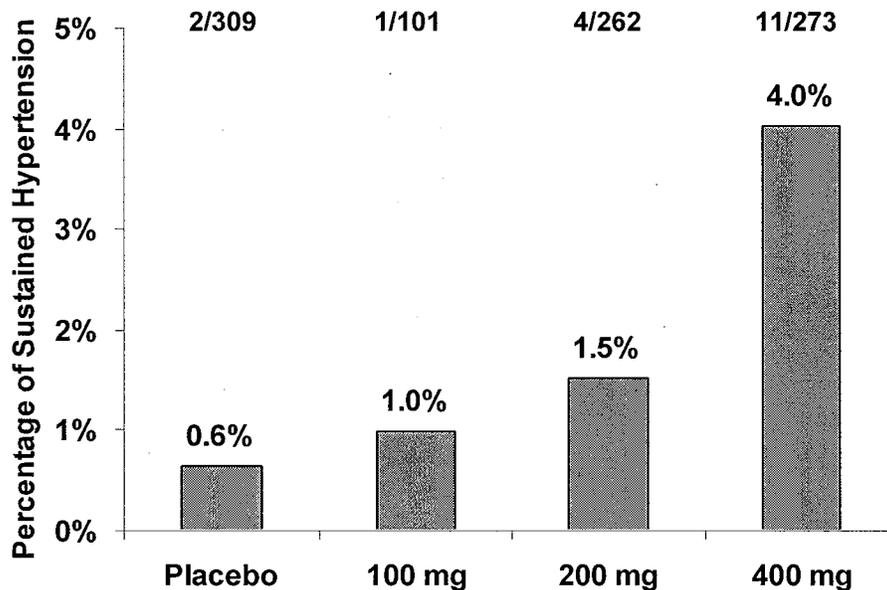
Exposure-Response

Efficacy: The applicant developed a pharmacokinetic/pharmacodynamic (PK/PD) relationship between desvenlafaxine plasma exposure and change from baseline on the HAM-D17 total score. 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. Although the linear regression analysis predicted increases in the change from baseline in the HAM-D17 score as desvenlafaxine plasma concentrations and AUC increased, small adjusted R-square values indicated that these analyses predicted only a small portion of the variability (6% and 3%) in HAM-D17 scores observed between subjects. While these analyses predict dose-concentration effects, the efficacy findings of the fixed-dose studies did not show that higher doses of DVS SR provided greater efficacy. In a pivotal efficacy study (study 306), there was no evidence of a dose-response effect at the final on-therapy evaluation for the change from baseline on the HAM-D17 ($p=0.251$).

Safety: Independent analysis to explore the relationship between desvenlafaxine dose and sustained hypertension was conducted by OCP. 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. With the same definition of sustained hypertension as in venlafaxine's (the parent compound for desvenlafaxine) product label, desvenlafaxine was also found to cause sustained hypertension in a dose dependent manner.

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Fig 1: Dose Dependent Sustained Hypertension



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 applicant's analysis treated blood pressure as a continuous variable and evaluated whether blood pressure change is related to dose or not.

The sponsor reported that, in the short-term (8 week) fixed-dose studies, the following Treatment Emergent Adverse Events (TEAEs) were reported at a higher incidence in the 400 mg group than either the 100 or 200 mg groups and appeared to show a dose-related trend: asthenia, chills, nausea, dry mouth, vomiting, sweating, abnormal ejaculation/orgasm (men), anorgasmia (men), and impotence (men).

DVS effect on QT or QTc Interval: The applicant reported that based on the primary variables of QTcF and QTcN, the thorough QTc study was negative for a DVS SR effect on QTc. Therefore, the results of the thorough QTc study indicated that DVS SR has a low potential to prolong the QT interval. OCP agreed with these 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.

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 t_{max} (postdose hour 1) and the t_{max} of the 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.

Intrinsic Factors

Renal Impairment: Compared with values in age-matched healthy subjects, increases in AUC of approximately 56%, 108% and 116% were observed in subjects with moderate, severe renal impairment and ESRD, respectively. Compared with values in age-matched healthy subjects, increases in C_{max} of 10%, 25% and 43% were observed in subjects with moderate, severe renal impairment and ESRD, respectively. Only small amounts of desvenlafaxine were removed during 4 hours of dialysate with recovery in dialysate fluid ranging from 0.4% to 4.12% of the total dose of 100mg.

It is recommended that the dose for moderate, severe and ESRD patients be reduced in half. DVS SR should not be given to patients with moderate, severe and renal impairment and ESRD until a 50 mg dose is commercially available. Care should be taken when treating patients with mild renal impairment with DVS SR. Patients with mild renal impairment could be administered the recommended dose of 100 mg/day. Dose escalation for patients with any category of renal impairment is not recommended.

These recommendations for dosing in renal impaired patients are based on the following:

- a) There is at least a 50% increase in AUC for moderate, severe renal impaired and ESRD patients. And a 10 to 43% increase in C_{max} for these categories of renal impaired patients.
- b) Accumulation after multiple dosing was calculated to be 1.6.
- c) Every other day (QOD) dosing would potentially pose compliance problems.
- d) Renal impaired patients are prone to have high blood pressure and hypertension is a concern after dosing with DVS SR.
- e) DVS SR is recommended to be taken whole and not broken in half or chewed. Therefore, a 50 mg strength is needed for administration to moderate, severe renal impaired and ESRD patients.
- f) Alternative anti-depression medications are commercially available.

Hepatic Impairment: No dosage adjustment is recommended for all categories of patients with hepatic impairment. But dose escalation to 200 mg/day is not recommended for patients with all categories of hepatic impairment. An increase in exposure (AUC ≈ 35% increase) after administration of DVS SR 100 mg to patients with hepatic impairment was seen in patients with moderate to severe hepatic impairment (Child-Pugh B and C category).

Age: In a trial in healthy subjects administered doses up to 300 mg, there was an age dependent decrease in desvenlafaxine clearance, resulting in about 25% increase in C_{max} and about 54% increase in AUC values in subjects greater than 75 years of age as compared with subjects 18 - 45 years of age. Sixty-five to seventy-five year old subjects had about 5% higher desvenlafaxine C_{max} and about 32% higher AUC than

young subjects. No dosage adjustment is recommended, however, care should be taken when the elderly are treated with DVS. The dose for elderly patients (≥ 75 years) should not be escalated to 200 mg.

Gender: In a trial of healthy subjects administered doses up to of 300 mg, women had an 18-37% higher C_{max} and a 6-17 % higher AUC than age-matched men. No adjustment of dosage on the basis of gender is recommended

Race: No differences were seen in the pharmacokinetics of desvenlafaxine between different races.

Extrinsic Factors

In vitro metabolism: Minor metabolism occurs through CYP3A4, and in vitro studies show no evidence for induction of the CYP3A4 enzyme pathway. In addition, no significant inhibition was seen on the activities of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 at desvenlafaxine concentrations up to 100 μM . Based on in vitro data, desvenlafaxine was not a substrate of P-gp efflux and did not inhibit the P-gp-mediated efflux. Therefore, it is unlikely that smoking, diet or use of herbal substances would alter the pharmacokinetics of desvenlafaxine.

Effect of DVS on other drugs

Desipramine: Desipramine exposure, as measured by C_{max} and AUC, increased by 50% and 83%, respectively, during coadministration of desipramine and DVS SR. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 may result in higher concentrations of that drug. It is recommended that desipramine should not be co-administered with DVS SR. If it is necessary to co-administer desipramine with DVS-SR, then, the dose of desipramine should be reduced in half.

Midazolam: After administration of a single oral 4-mg dose of midazolam with steady state 400-mg dosing of DVS SR, approximately 16% decrease in mean C_{max} and a 31% decrease in mean AUC of midazolam were observed when compared with the midazolam-alone treatment. A dosage adjustment for midazolam or CYP 3A substrates is not recommended when co-administered with desvenlafaxine.

Alcohol: In a pharmacodynamic drug interaction study with DVS and alcohol, desvenlafaxine did not increase the impairment of mental and motor skills caused by alcohol. However, patients should be advised to avoid alcohol while taking desvenlafaxine.

Effect of other drugs on DVS

Ketoconazole: Ketoconazole (200 mg BID) increased the AUC of desvenlafaxine (400 mg single dose) by about 43%; C_{max} were comparable between treatments. Concomitant use of desvenlafaxine with potent inhibitors of CYP3A4 could result in higher concentrations of desvenlafaxine. Therefore, caution should be exercised when potent inhibitors of CYP3A4 are concomitantly administered with desvenlafaxine.

Pharmacokinetics and Bioavailability

Pharmacokinetics: The pharmacokinetics of desvenlafaxine after administration of DVS SR is linear at doses up to 600 mg. Following multiple-dose administration of DVS SR, desvenlafaxine Mean \pm SD T_{max} occurred approximately 7.4 ± 3.3 hours after administration and a mean $T_{1/2}$ of 10.6 ± 3.1 hours. Trough plasma concentrations indicated that pharmacokinetic steady state was reached by day 4 or 5 of the multiple-dose (q24h) regimen and accumulation was about 1.6. No significant difference was found in the pharmacokinetic of desvenlafaxine in MDD patients compared to healthy subjects.

ADME: The absolute oral bioavailability of DVS SR is about 80%. The plasma protein-binding of desvenlafaxine was low ($29.9\% \pm 12.1\%$) and independent of drug concentration at values of 0.04 to 0.20 $\mu\text{g/mL}$. Following a single oral administration of desvenlafaxine to healthy volunteers the major compound-related components in plasma were unchanged desvenlafaxine (about 46%) and its O-glucuronide (about 19%). Glucuronidation of desvenlafaxine represented the major metabolic pathway. Urinary recovery of conjugated and unconjugated desvenlafaxine and NODV accounted for 69% of the dose of DVS SR after oral administration. Of the amount of the dose excreted in urine after oral administration, 19% was excreted as conjugated desvenlafaxine and 46% was excreted as unconjugated desvenlafaxine. The excretion of NODV accounted for only 3.5% of the dose of desvenlafaxine eliminated in urine.

Food Effect: Administration of DVS SR with food had a minimal effect on drug absorption, resulting in an approximate 1-hour delay in T_{max} . About a 16% increase in C_{max} was observed when DVS SR was administered after a high-fat meal; AUCs were comparable. Food is not expected to have significant clinical effect on the absorption of DVS from DVS SR. DVS SR can be administered without regard to food.

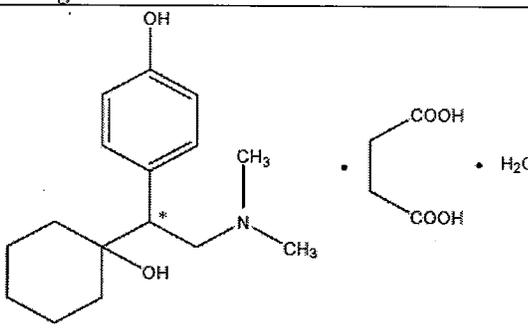
Bioequivalence: The proposed to be marketed formulation is quantitatively and qualitatively identical to the clinical formulation except for a minor change in the color and the debossing of the tablets. The 200 mg to-be-marketed formulation was bioequivalent to the clinical-trial formulation. The dissolution profiles between formulations are similar.

IVIVC: A Level A In Vitro/In Vivo Correlation (IVIVC) was demonstrated for desvenlafaxine succinate tablets. The IVIVC formed the basis for dissolution specification during clinical phases of product development including stability assessment. The correlation led to a multipoint dissolution specification, which provided measurements of the sustained release product performance.

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The chemical structure of Desvenlafaxine Succinate (DVS-233, DVS) Drug Substance is provided in the following figure.

Fig 2: Chemical Structure of desvenlafaxine succinate drug substance

Type	Designation
Structural Formula	 <p>* Denotes chiral center, the compound is racemic.</p>
Empirical (Molecular) Formula	$C_{16}H_{25}NO_2 \cdot C_4H_6O_4 \cdot H_2O$
Molecular Weight	399.48 (as the succinate, monohydrate) 263.38 (as the free base)

2.1.2. What are the proposed mechanism (s) of action and therapeutic indication(s)?

Desvenlafaxine succinate is a potent and 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 sustained release (DVS SR) is being evaluated for the treatment of major depressive disorder (MDD). DVS SR tablets are also being evaluated for the treatment of vasomotor symptoms (VMS) associated with menopause. However, the focus for this application is on the MDD indication.

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

The proposed commercial Desvenlafaxine succinate (DVS) extended-release tablets are 100 mg, reddish-orange, square pyramid tablet and 200 mg, _____ DVS SR tablets are to be administered orally. The recommended dose for DVS SR is 100 mg once daily, with or without food. Individual patients may benefit from an increase in dose to 200 mg/day. In clinical trials, no additional benefit was demonstrated at doses greater than 100 mg.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The DVS submission includes clinical study reports for 19 phase 1 studies, 1 phase 2 MDD study and 7 phase 3 MDD studies. In healthy subjects, the pharmacokinetic profile was examined after single doses up to 900 mg and multiple doses up to 600 mg once daily for 14 doses. In phase 2 and 3 studies, sparse sampling was conducted to permit population pharmacokinetic modeling to determine pharmacokinetics in patients. Seven short term DVS SR studies were designed to evaluate the efficacy of DVS SR in doses of 100, 200 or 400 mg/day. The sponsor reported that DVS SR was shown to be effective in a dose range of 100 to 400 mg/day in 2 pivotal clinical safety and efficacy studies- 306 and 308. All of the efficacy studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in adults with MDD. After the screening period, subjects were to be treated during an 8-week double-blind period with doses of DVS SR ranging from 100 to 400 mg/day, varying by study. At the end of the study, up to 2 weeks were allowed for tapering of the test article. The following table contains the study design for the Phases 2 and 3 studies.

Table 3: Phase 2 and 3 Studies With DVS SR in MDD

Study Number	Type of Study	Study Objective(s)	Study Design and Type of Control	Test Product; Dose Regimen ^a	Number of Subjects Randomized (R); Safety (S); Efficacy (E)	Duration of Treatment
Controlled Clinical Studies						
<i>Fixed-dose Studies</i>						
0600D3-223-FR/PL/US/ZA	Efficacy in MDD	Efficacy, safety, population PK	Randomized double-blind, placebo-controlled, fixed-dose	DVS SR tablets; 200 or 400 mg/day	R=227 S=222 E=213	8 weeks, plus 1-week taper
3151A1-306-US	Efficacy in MDD	Efficacy, safety, population PK	Randomized double-blind, placebo-controlled, fixed-dose	DVS SR tablets; 100, 200, or 400 mg/day	R=480 S=470 E=461	8 weeks, plus 2-week taper, or go into study 303
3151A1-308-EU/WW	Efficacy in MDD	Efficacy, safety	Randomized double-blind, placebo-controlled, fixed-dose	DVS SR tablets; 200 or 400 mg/day	R=375 S=373 E=369	8 weeks, plus 2-week taper, or go into study 303
<i>Flexible-dose Studies</i>						
3151A1-304-US	Efficacy in MDD	Efficacy, safety	Randomized double-blind, placebo-controlled, flexible-dose	DVS SR tablets; 100 or 200 mg/day	R=247 S=238 E=234	8 weeks, plus up to 1-week taper, or go into study 303
3151A1-309-EU	Efficacy in MDD	Efficacy, safety	Randomized double-blind, placebo-controlled, flexible-dose, ven ER comparator	DVS SR tablets; 200 or 400 mg/day Ven ER 75 or 150 mg/day	R=369 S=364 E=363	8 weeks, plus 2-week taper, or go into study 303
3151A1-317-US	Efficacy in MDD	Efficacy, safety	Randomized double-blind, placebo-controlled, flexible-dose, ven ER comparator	DVS SR tablets; 200 or 400 mg/day Ven ER 150 or 225 mg/day	R=369 S=356 E=350	8 weeks, plus 2-week taper, or go into study 303

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Table 4: Phase 2 and 3 Studies With DVS SR in MDD (contd.)

Study Number	Type of Study	Study Objective(s)	Study Design and Type of Control	Test Product; Dose Regimen*	Number of Subjects Randomized (R); Safety (S); Efficacy (E)	Duration of Treatment
3151A1-320-US	Efficacy in MDD	Efficacy, safety	Randomized double-blind, placebo-controlled, flexible-dose	DVS SR tablets; 200 or 400 mg/day	R=244 S=235 E=235	8 weeks, plus 2-week taper, or go into study 303
Uncontrolled Clinical Studies						
3151A1-318-US	Safety in MDD	Long-term safety, efficacy	Open-label long-term safety, flexible-dose	DVS SR tablets; 200 or 400 mg/day	R=108 S=104 E=99	12 months, plus 1 to 2-week taper
Other Clinical Studies						
3151A1-302-EU/WW	Efficacy in MDD	Long-term efficacy (relapse prevention), safety	Open-label phase followed by randomized double-blind, placebo-controlled, flexible-dose phase. During double-blind phase, dose can be decreased, but not increased.	DVS SR tablets; 200 or 400 mg/day	Open label R=603 S=593 E=575 Double-blind (Ongoing)	12-week open-label, 6-month double-blind, plus 1 to 2-week taper
3151A1-303-EU/WW	Safety in MDD	Long-term safety, efficacy	Open-label long-term safety, flexible-dose	DVS SR tablets; 200 or 400 mg/day	As of 30 Sep 2005: S=1393	10 months, plus 1 to 2-week taper
3151A1-307-US	Safety in MDD	Long-term safety, efficacy in elderly, population PK	Open-label long-term safety, flexible-dose	DVS SR tablets; 100 or 200 mg/day	As of 30 Sep 2005: S=52	6 months, plus up to 1-week taper

DVS SR = desvenlafaxine succinate sustained release; MDD = major depressive disorder; Ven ER = venlafaxine extended release .

2.2.2. What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers and how are they measured in clinical pharmacology and clinical studies

The primary criterion to establish the efficacy of DVS SR was the change from baseline (decrease indicating improvement) on the Hamilton Rating Scale for Depression, 17-item questionnaire (HAM-D17) score at the final on-therapy evaluation. The final on-therapy evaluation was at day 56 in the two 8-week randomized, double blind, placebo-controlled, fixed dose studies in adult outpatients (studies 306 and 308) that were the pivotal efficacy studies of DVS SR in the treatment of major depression. The key secondary endpoint was the mean change (decrease indicating improvement) in the Clinical Global Impressions Scale-Improvement item (CGI-I) at the final on-therapy evaluation. Both of these questionnaires are well-established and validated clinician-rated scales. The analyses of the HAM-D-17 and CGI-I were done using the last-observation-carried-forward (LOCF) technique and the observed-case analysis on the intent to-treat (ITT) population. The table lists the efficacy variables for the 7 short-term DVS SR studies.

Table 5: Efficacy Variables in DVS SR MDD Studies

Study/Type of Variable	Efficacy Variable
223	
Primary efficacy variable	HAM-D ₁₇ total score
Key secondary efficacy variables	CGI-I score HAM-D ₆ subscale total score ^a Percentage of subjects with HAM-D ₁₇ total score ≤7 MADRS total score
Selected secondary efficacy variables	Percentage of responders based on CGI-I ^b Percentage of responders based on HAM-D ₁₇ ^c
Health outcomes assessments	None
304, 306, 308, 309, 317, and 320	
Primary efficacy variable	HAM-D ₁₇ total score
Key secondary efficacy variable	CGI-I score
Selected secondary efficacy variables	Percentage of responders based on CGI-I ^b Percentage of responders based on HAM-D ₁₇ ^c Remission defined as HAM-D ₁₇ ≤7 MADRS total score

CGI-I=Clinical Global Impressions-Improvement; HAM-D₁₇=Hamilton Rating Scale for Depression, 17-item; MADRS=Montgomery and Asberg Depression Rating Scale; MDD=major depressive disorder.

- HAM-D₆ Bech version: HAM-D items 1, 2, 7, 8, 10, and 13 per Bech P, Gram LF, Dein E, Jacobsen O, Vitger J, Bolwig TG. Quantitative rating of depressive states. *Acta Psychiatr Scand.* 1975;51(3):161-70.
- Responders were those with scores of 1 (very much improved) or 2 (much improved).
- Decrease of 50% or more from baseline.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Yes, the active moieties in the plasma and other biological fluids were appropriately measured. The analytical methods developed for the determination desvenlafaxine and its metabolites are acceptable.

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. 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. The long-term stability of desvenlafaxine and desvenlafaxine enantiomers in plasma and urine samples was also evaluated. The precision and accuracy for DVS methods was less than 15% of nominal values (Refer to analytical section).

2.2.4 Exposure-response

2.2.4.1. What are the characteristics of the exposure response relationships (dose-response, concentration response) for efficacy?

The applicant developed a pharmacokinetic/pharmacodynamic(PK/PD) relationship between desvenlafaxine plasma exposure and change from baseline on the HAM-D17 total score. 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 pharmacometric reviewer (Dr. Yaning Wang) conducted independent analysis and confirmed the applicant's overall results. The reviewer concluded that the small proportion of variability in HAM-D17 total score explained by the desvenlafaxine exposure suggested that the other unidentified factors also contributed 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.

Based on the efficacy data in the short-term studies and the safety data across all studies, the recommended starting dose is 100 mg once daily. While the relationship between dose and antidepressant response has not been conclusively established, subjects not responding to the initial 100 mg per day dose may benefit from a dose increase to 200 mg/day. There is no evidence that doses greater than 200 mg/day confer any additional benefit.

Information regarding dose effect was obtained by evaluating desvenlafaxine concentrations in relation to HAM-D17 scores using data from study 306, a fixed-dose, placebo-controlled study. The 3 doses of DVS SR in this study were 100 mg, 200 mg, and 400 mg. For subjects who had plasma samples, a concentration-effect analysis was performed for the change from baseline on the HAM-D17 total score determined at the final on-therapy evaluation in relation to the desvenlafaxine plasma concentration. Linear regression (with the change from baseline on the HAM-D17 total score as the response variable) and logistic regression (with the HAM-D17 response as the response variable) were used for these analyses. An exploratory analysis was performed in which the HAM-D17 was regressed on AUC for 1 dose administration interval based on the final Bayesian estimates of clearance obtained for subjects included in the population analysis

and the final dose amount administered to subjects. Only subjects with plasma desvenlafaxine concentration and AUC data were included in the analysis. The results of these analyses are briefly summarized below.

Of the 461 subjects in the ITT population in study 306, plasma samples were obtained from 395 subjects and these data were used in the linear regression model. Desvenlafaxine plasma concentration values were set to zero for placebo-treated subjects. The results showed significance for the concentration term in the model with a p-value of <0.001. These results suggest that with higher concentrations of desvenlafaxine, a greater drop in HAM D17 scores could be expected. The results should be interpreted with caution, however, since the plasma concentration data only explained a small amount (6%) of the variability in the HAM-D17 data.

Because the linear regression model using concentrations of desvenlafaxine only explained a small amount of the variability in the data, a linear regression analysis using AUC as the exploratory variable was also conducted. Predicted AUC values available from 293 subjects treated with any dose of desvenlafaxine were included in the analysis. AUC values were set to zero for placebo-treated subjects. Also included in the model were baseline HAM-D17 score as a covariate and the study center as a factor. The results showed significance for the AUC term with a p-value of <0.001. Higher values of AUC were associated with smaller HAM-D17 scores. Again, AUC values only explained a small portion (3%) of the variability in the HAM-D17 data. In the logistic regression model, subjects were classified as responders if they achieved a decrease of 50% or greater in the HAM-D17 total score at baseline. Data from the 395 ITT subjects with plasma samples were included in the analysis. The HAM-D17 response was modeled as a function of the desvenlafaxine plasma concentration with baseline HAM-D17 scores as a covariate, and study center as a factor. The test showed significance for the concentration term with a p-value of <0.001, with higher concentrations of desvenlafaxine being associated with higher odds of HAM-D17 response. The odds ratio for desvenlafaxine plasma concentration was 1.001 (CL, 1.001, 1.002).

Although the linear regression analysis predicted increases in the change from baseline in the HAM-D17 score as desvenlafaxine plasma concentrations and AUC increased, small adjusted R-square values indicated that these analyses predicted only a small portion of the variability (6% and 3%) in HAM-D17 scores observed between subjects. While these analyses predict dose-concentration effects, the efficacy findings of the fixed-dose studies did not show that higher doses of DVS SR provided greater efficacy. In study 306, there was no evidence of a dose-response effect at the final on-therapy evaluation for the change from baseline on the HAM-D17 (p=0.251).

2.2.4.2 What are the characteristics of the exposure-response (dose-response, concentration-response) for safety?

With the same definition of sustained hypertension as in venlafaxine's (the parent compound for desvenlafaxine) 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.

The pharmacometric reviewer conducted independent analysis to explore the relationship between desvenlafaxine and sustained hypertension. 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 pharmacometric 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) \geq 90 mm Hg and \geq 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. A clear

dose dependent relationship was demonstrated by both the frequency summary (0X) and the results from logistic modeling (0Y).

Fig 3

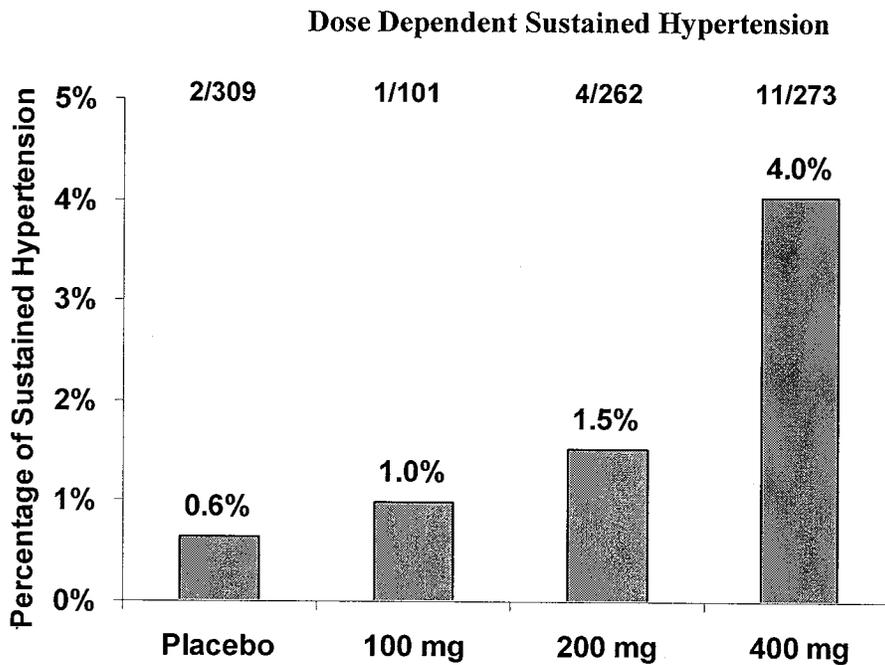


Table 6: Logistic Modeling Results for Sustained Hypertension

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	

The applicant reported that, in the short-term (8 week) fixed-dose studies, the following Treatment Emergent Adverse Events (TEAEs) were reported at a higher incidence in the 400 mg group than either the 100 or 200 mg groups and appeared to show a dose-related trend: asthenia, chills, nausea, dry mouth, vomiting, sweating, abnormal ejaculation/orgasm (men), anorgasmia (men), and impotence (men). The sponsor reported that in the short-term (8 weeks, fixed- and flexible-dose) studies, and long-term (6 to 12 months) studies, DVS SR treatment was associated with increases from baseline in mean serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. The sponsor reported that in the short-term fixed-dose studies, subjects treated with 400 mg of DVS SR showed significant mean increases from baseline in AST/SGOT values but the increases did not differ significantly from the decreases observed in placebo-treated subjects. Small increases from baseline in mean AST/SGOT values were also observed in the 100-mg and 200-mg dose groups but the increases did not differ significantly from baseline. The small increase from baseline in mean AST/SGOT value in the 200-mg group differed significantly from the mean decrease observed in the placebo group at the final on-therapy evaluation. The increases in mean AST/SGOT values observed in DVS SR-treated subjects were not dose-related and ranged in magnitude from 0.9 to 2.1 mU/mL at the final on-therapy evaluation. The sponsor reported that in the short-term, fixed-dose studies, dose-related increases from baseline in mean GGT values were observed in DVS SR-treated subjects.

The visual analogue scale (VAS) for nausea was administered in some phase I studies. With the exception of one study, which involved multiple-dose administration, these studies examined the effects of single doses of DVS SR. Indices computed from the VAS included Emax, the time of the maximum level of nausea (TEmax), and the area under the response (VAS nausea) curve (AURC). Nausea effects were evident primarily on Emax rather than AURC. The TEmax usually occurred from 2 to 9 hours after DVS SR administration. At the completion of the multiple dose regimen, no subjects in the 300-mg dose group and 1 subject in the 450-mg dose group had a VAS score greater than zero.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The applicant reported that based on the primary variables of QTcF and QTcN, the thorough QTc study was negative for a DVS SR effect on QTc. Therefore, the results of the thorough QTc study indicated that DVS SR has a low potential to prolong the QT interval. The pharmacometric reviewer agreed with this conclusions.

The primary objective of the QT study (study no. 193) 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. The study 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). Three 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.

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.

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 moxifloxacin plasma concentrations in relation to QTc data.

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 post dose 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 than 10 ms.

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.

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Table 7: Mean and 90% CI Estimates of Change from Baseline in QTcF After Administration of DVS

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

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2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The recommended dose for DVS SR is 100 mg once daily, with or without food. Based on the efficacy data in the short-term studies and the safety data across all studies, the recommended starting dose is 100 mg once daily. While the relationship between dose and antidepressant response has not been conclusively established, subjects not responding to the initial 100 mg per day dose may benefit from a dose increase to 200 mg/day. There is no evidence that doses greater than 200 mg/day confer any additional benefit.

2.2.5 What are the Pharmacokinetic Characteristics of the drug and its major metabolite?

The pharmacokinetic profile has been examined after single-doses of up to 900 mg and multiple doses of up to 450 mg once daily for up to 14 doses in healthy subjects. In a Phase 2 study and Phase 3 studies sparse sampling in patients to permit population pharmacokinetic modeling was undertaken. In addition, desvenlafaxine pharmacokinetic parameters from 399 Phase 1 subjects have been pooled to examine the potential effects of the intrinsic factors of age, sex, body weight, and race on desvenlafaxine pharmacokinetics. Desvenlafaxine is conjugated to inactive metabolites.

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters of DVS?

The pharmacokinetics of desvenlafaxine after administration of DVS SR appears to be linear at doses up to 600 mg. Higher than expected C_{max} and AUC values in the postprandial DVS SR 750-mg treatment produced nonlinearity in the increases in desvenlafaxine C_{max} and AUC with increasing dose. The pharmacokinetics of DVS SR was evaluated in a study after multiple doses of 300 mg and 450 mg q 24h. Following multiple-dose administration of DVS SR, desvenlafaxine was slowly absorbed with mean \pm SD T_{max} of 5.9 \pm 4.0 hours after administration and was slowly eliminated with a mean \pm SD T_{1/2} of 11.3 \pm 2.4 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 and accumulation was about 1.6. The pharmacokinetic parameters in healthy subjects are provided in the following table.

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Table 8: Desvenlafaxine Pharmacokinetic Parameters in Healthy Subjects from Individual Studies

Study Number Treatment	n	C _{max} (ng/mL)	t _{max} (h)	AUC (ng•h/mL)	t _{1/2} (h)	C _l /F (L/h/kg)	V _z /F (L/kg)
DVS SR Healthy Subject Pharmacokinetic and Initial Tolerability Studies							
0600-D3-170-FR^a							
Venlafaxine ER 150 mg (fed)	16	172 ± 41	7.9 ± 1.0	4602 ± 963	12.4 ± 2.7	0.47 ± 0.10	8.62 ± 3.36
DVS SR 150 mg (fed)	6	216 ± 81	5.2 ± 2.9	5004 ± 1379	9.1 ± 1.5	0.43 ± 0.15	5.47 ± 1.53
DVS SR 225 mg (fed)	6	431 ± 105	7.5 ± 4.5	10601 ± 3030	11.3 ± 2.4	0.31 ± 0.06	4.92 ± 0.42
DVS SR 300 mg (fed)	6	446 ± 32	10.5 ± 9.9	14554 ± 3151	10.4 ± 1.8	0.30 ± 0.08	4.33 ± 0.93
DVS SR 450 mg (fed)	6	822 ± 158	5.0 ± 1.1	18580 ± 3680	10.2 ± 0.9	0.36 ± 0.06	5.19 ± 0.73
DVS SR 600 mg (fed)	6	1099 ± 195	5.3 ± 1.5	26920 ± 7932	10.2 ± 1.1	0.33 ± 0.07	4.77 ± 0.81
DVS SR 750 mg (fed)	4	1906 ± 431	6.0 ± 1.6	41816 ± 6347	9.9 ± 0.8	0.26 ± 0.03	3.70 ± 0.49
DVS SR 750 mg (fasting)	6	1683 ± 310	6.8 ± 1.0	36800 ± 6214	9.5 ± 1.2	0.29 ± 0.08	3.99 ± 1.05
DVS SR 900 mg (fed)	4	1572 ± 336	7.3 ± 1.0	38546 ± 8646	9.6 ± 1.0	0.32 ± 0.11	4.55 ± 2.07
0600D3-171-US^{a,b}							
DVS SR 300 mg ^a	9	537 ± 101	6.7 ± 2.4	16396 ± 5220	17.2 ± 8.0	0.27 ± 0.19	5.58 ± 1.59
DVS SR 300 mg q24h ^b	9	807 ± 141	4.6 ± 1.1	14831 ± 2894	11.1 ± 2.6	0.26 ± 0.06	3.92 ± 0.43
DVS SR 450 mg ^a	9	806 ± 342	8.7 ± 1.7	23500 ± 12360	14.6 ± 8.3	0.34 ± 0.23	6.41 ± 6.47
DVS SR 450 mg q24h ^b	9	1369 ± 292	7.6 ± 5.7	24073 ± 5880	11.5 ± 2.2	0.26 ± 0.07	4.10 ± 0.85
DVS SR 600 mg ^a	9	1083 ± 222	7.1 ± 1.3	34315 ± 9352	17.7 ± 5.9	0.24 ± 0.06	5.69 ± 1.26
DVS SR 600 mg q24h ^b	0	NA	NA	NA	NA	NA	NA
0600-D3-172-US^a							
DVS SR 1 x 100 mg	21	238 ± 44.5	7.5 ± 2.0	5560 ± 1378	11.2 ± 1.5	0.25 ± 0.08	3.94 ± 1.32
DVS SR 3 x 100 mg	20	712 ± 129.1	7.2 ± 1.8	16594 ± 3553	11.0 ± 1.6	0.24 ± 0.05	3.71 ± 0.57
DVS SR 6 x 100 mg	19	1422 ± 200.5	8.3 ± 1.9	35517 ± 6865	11.2 ± 1.8	0.22 ± 0.05	3.51 ± 0.52

^aSingle Dose Administration

^bMultiple Dose Administration

The following table presents the pooled data for pharmacokinetic parameters of desvenlafaxine after single and multiple dose administration, dose-normalized to 100 mg, for healthy subjects who participated in phase I studies of DVS SR.

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Table 9: Pooled Desvenlafaxine Pharmacokinetic Parameters (Normalized to 100 mg) from Healthy Subjects in Phase 1 Studies of DVS SR

Parameter (units)	n	Single-Dose Mean ± SD	n	Steady-State Mean ± SD
C _{max} (ng/mL)	399	204.9 ± 60.8	16	284.3 ± 56.5
t _{max} (h)	398	7.4 ± 3.3	16	5.9 ± 4.0
AUC (ng•h/mL)	397	5044 ± 1601	16	-
AUC _{0-24h} (ng•h/mL)	398	4795 ± 1624	-	5121 ± 1106
t _{1/2} (h)	397	10.6 ± 3.1	16	11.3 ± 2.4
Cl (L/h)	397	22.9 ± 11.3	16	20.4 ± 4.5
Cl (L/h/kg)	397	0.31 ± 0.15	16	0.26 ± 0.06
CL _r (L/h)	48	10.1 ± 4.01	-	-
CL _r (mL/min)	48	168.1 ± 66.8	-	-
A _e (%-dose)	48	60.6 ± 13.8	-	-

Abbreviations: A_e=amount of drug excreted in urine; AUC area under the single-dose serum concentration-versus-time curve; AUC₀₋₂₄=area under the steady-state serum concentration-versus-time over a full day; Cl=clearance; CL_r=renal clearance; C_{max}=peak concentration; CV=coefficient of variation; SD=standard deviation; t_{1/2}=terminal elimination half-life; V_{ss}=apparent steady-state volume of distribution.

2.2.5.2 How does the PK of the drug and its major metabolites in healthy volunteers compare to that in patients?

In the population pharmacokinetic analysis conducted using data from healthy subjects and MDD patients, no difference was found in the CL/F of desvenlafaxine in MDD patients compared to healthy subjects. Also, clearance values from the population pharmacokinetic analysis were similar to the values from the pooled data for the phase 1 studies.

The pharmacokinetics of DVS in major depressive disorder (MDD) patients was evaluated using population pharmacokinetic analysis. 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 formulation. Creatinine clearance (CRCL) and body weight were shown to be the major factors affecting desvenlafaxine CL/F in the population PK analysis. In addition, body weight was shown to be the primary factor affecting desvenlafaxine V/F.

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. The following table provides the Population Pharmacokinetic Parameters of Desvenlafaxine in MDD patients.

Table 10: Population Pharmacokinetic Parameters of Desvenlafaxine in MDD Patients Obtained From the Final Model

Parameters	Mean ^a	BSV (%) ^b	BOV (%) ^c
CL _r /F (L/hr) ^{d,e}	8.12 (17)	12 (11)	3.2 fixed
CL _m /F (L/hr) ^{d,e}	11.4 (13)	-	-
V/F (L) ^{d,e}	323 (6)	22 (17)	9.5 fixed
K _a (hr ⁻¹)	0.514 fixed	61.1 fixed	The same as BSV
D ₂ (hr)	24.2 fixed	23.9 fixed	0. fixed
EE1 ^f	1.61 fixed	111 fixed	0. fixed
T _{lag} (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 (variance) ^{1/2} *100 and its precision as % CV for all PK parameters except EE1 which is calculated as (variance) ^{1/2} ^c BOV = between occasion variability calculated the same way as BSV ^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 Correlation between CL/F and V/F is 0.43, calculated as covariance ₁₂ ÷ (variance ₁ *variance ₂) ^{1/2} *100, where variance ₁ and variance ₂ are variances of random effects for the two parameters and covariance ₁₂ is their covariance ^f F1 = exp(EE1)/(1+exp(EE1)) = 83 %, F2 = 1 - F1 = 17 %			

2.2.5.3. What are the general ADME (Absorption, Distribution, Metabolism and Elimination) Characteristics of DVS SR?

Absorption

Bioavailability: The absolute oral bioavailability of DVS SR is about 80%. Peak plasma concentrations were observed 6 to 10 hours after oral administration of DVS SR. The following table contains the pharmacokinetic parameters after administration of DVS as an intravenous (IV) solution and DVS SR oral tablet.

Table 11 Pharmacokinetic Parameters for Desvenlafaxine

Treatment		Cmax (ng/mL)	Tmax (h)	T _{1/2} (h)	AUC (ng*h/mL)	F (%)
DVS IV (50 mg/60 min)	Mean ± SD (%CV)	232 ± 53 (23%)	1	9.8 ± 2.1 (21%)	2442 ± 585 (24%)	N/A
DVS SR, oral 100 mg	Mean ± SD (%CV)	160 ± 42 (27%)	6.4 ± 2.1 (33%)	10.4 ± 2.0 (19%)	3993 ± 1271 (32%)	80.5 ± 16 (20%)

Food Effect: Administration of DVS SR with food had a minimal effect on drug absorption, resulting in an approximate 1-hour delay in Tmax. Both Cmax and AUC of DVS met the 90% confidence interval criteria for bioequivalence when low, medium and high fat meals and fasting conditions were compared. About a 16% increase in Cmax was observed when DVS SR was administered after a high-fat meal; AUCs were comparable. Food is not expected to have significant clinical effect on the absorption of DVS from DVS SR. DVS SR can be administered without regard to food.

The effect of food was evaluated in a single-dose, open-label, randomized, 4-period, 4-sequence, crossover, inpatient study. The highest strength of DVS SR (200-mg) tablet was administered orally. Subjects received a single dose of DVS SR under 4 dosing conditions. Each dose was separated by a washout interval of at least 4 days. Subjects were randomly assigned to a sequence of the following treatments:

- Treatment A: Single 200-mg dose of DVS SR under fasting conditions.
- Treatment B: Single 200-mg dose of DVS SR administered 5 minutes after completion of a low-fat breakfast.
- Treatment C: Single 200-mg dose of DVS SR administered 5 minutes after completion of a medium-fat breakfast.
- Treatment D: Single 200-mg dose of DVS SR administered 5 minutes after completion of a high-fat breakfast.

The fasted arm was preceded by an overnight fast of at least 10 hours.

The following table contains the statistical comparisons of Desvenlafaxine pharmacokinetic parameters after administration of 4 different types of meals.

Table 12: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters

4-Period Crossover Analysis of Variance of Log-Transformed Data			Treatment ^a		
Effect		p-Value	Low-Fat Relative Bioavail. 90% C.L.	Medium-Fat Relative Bioavail. 90% C.L.	High-Fat Relative Bioavail. 90% C.L.
C_{max} (ng/mL) ^b	Sequence	0.077	101.1%-117.2%	98.6%-114.5%	107.8%-125.05%
	Treatment	0.013			
	Period	0.860			
AUC (ng·h/mL) ^c	Sequence	0.282	99% 90.9%-108.3%	105% 96.4%-114.9%	96% 88.2%-105.1%
	Treatment	0.411			
	Period	0.354			
AUC _T (ng·h/mL) ^c	Sequence	0.228	99% 91.1%-108.6%	105% 95.9%-114.4%	97% 88.5%-105.6%
	Treatment	0.512			
	Period	0.370			

Abbreviations: AUC=area under the concentration-versus-time curve; AUC_T=area under the concentration-versus-time curve to the last quantifiable concentration at time T; Bioavail.=bioavailability; C.L.= confidence limits.

a. Compared with fasting treatment.

Effect of Pgp Transporter: DVS was shown not to be a substrate for Pgp or an inhibitor of Pgp using Caco-2 monolayers. Due to the lowest in vitro inhibition of P-gp activity, DVS is not likely to engage in clinical drug-drug interactions via inhibition of P-gp.

In vitro studies were conducted to examine whether DVS is a substrate or inhibitor of Pgp. To evaluate whether DVS and five other anti-depressants (venlafaxine, S, S-duloxetine, paroxetine, bupropion and amitryptine) are substrates of P-glycoprotein (P-gp) using Caco-2 cell monolayers. To determine the rates of permeation, DVS and comparators were added to either apical or basolateral compartments at concentrations of 5, 25, and 100 μM. To evaluate the involvement of P-gp, DVS or comparators (5 μM) were added to the apical or basolateral compartment in the absence or presence of verapamil (100 μM), a known inhibitor of p-glycoprotein. The inhibitor (verapamil) was added to the apical compartment. ³[H]-Digoxin (5 μM), a known P-gp substrate, was used as a positive control in the presence or absence of verapamil (100 μM) to verify P-gp activity in Caco-2 monolayers. The following table contains the permeability of DVS and comparators in Caco-2 monolayers.

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Table 13: Permeability of DVS and Comparators in Caco-2 Monolayers

Compound	Conc. (μM)	$P_{\text{app}}(\text{AB}), \times 10^{-6} \text{ cm/sec}$ (Mean \pm SD)	$P_{\text{app}}(\text{BA}), \times 10^{-6} \text{ cm/sec}$ (Mean \pm SD)	BA/AB Ratio
DVS-233	5	9.90 \pm 0.41	15.1 \pm 1.26	1.5
	25	8.18 \pm 0.23	12.4 \pm 0.38	1.5
	100	7.27 \pm 0.33	9.54 \pm 0.59	1.3
Venlafaxine	5	4.62 \pm 0.65	6.84 \pm 0.50	1.5
	25	4.75 \pm 0.53	6.50 \pm 0.77	1.4
	100	4.81 \pm 0.27	5.39 \pm 0.28	1.1
Bupropion	5	5.09 \pm 1.68	7.96 \pm 1.42	1.6
	25	4.15 \pm 0.41	8.84 \pm 1.02	2.1
	100	5.74 \pm 0.72	7.47 \pm 0.98	1.3
Paroxetine	5	0.17 \pm 0.02	1.26 \pm 0.37	7.7
	25	0.53 \pm 0.06	2.13 \pm 0.15	4.0
	100	1.64 \pm 0.21	4.51 \pm 0.83	2.8
+ verapamil (100 μM)	5	0.43 \pm 0.02	1.39 \pm 0.67	3.2
Duloxetine	5	0.36 \pm 0.02	0.93 \pm 0.44	2.6
	25	0.52 \pm 0.07	2.05 \pm 0.13	3.9
	100	1.69 \pm 0.18	3.76 \pm 0.25	2.2
+ verapamil (100 μM)	5	0.78 \pm 0.12	0.75 \pm 0.05	1.0
Amitriptyline	5	0.98 \pm 0.09	2.42 \pm 0.30	2.5
	25	1.94 \pm 0.17	3.64 \pm 0.18	1.9
	100	3.10 \pm 0.45	4.71 \pm 0.38	1.5
+ verapamil (100 μM)	5	1.03 \pm 0.10	0.90 \pm 0.15	0.9
Digoxin	5	0.70 \pm 0.01	17.7 \pm 0.58	25
+ verapamil (100 μM)	5	4.58 \pm 0.33	6.59 \pm 0.19	1.4

Incubations were performed for 2 hours at 37°C with DVS-233 or comparator antidepressants administered in the apical (AB) or basolateral (BA) compartment. Results are mean \pm SD of n = 3 inserts.

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Table 14: Inhibition of P-gp mediated Digoxin Efflux in Caco-2 Monolayers in the Absence or Presence of DVS and Venlafaxine

DVS-233 (μM)	P_{app} (A to B), x 10 ⁻⁶ cm/sec (Mean \pm SD)	P_{app} (B to A), x 10 ⁻⁶ cm/sec (Mean \pm SD)	P_{app} (B to A)/ P_{app} (A to B) Ratio	% Control
0	0.290 \pm 0.014	8.39 \pm 0.78	28.9 \pm 1.5	100
1	0.287 \pm 0.048	7.73 \pm 0.50	27.3 \pm 2.7	92.1 \pm 4.8
2.5	0.264 \pm 0.011	7.69 \pm 0.26	29.1 \pm 2.1	92.2 \pm 10
10	0.272 \pm 0.013	7.49 \pm 0.26	27.6 \pm 1.9	89.6 \pm 7.1
25	0.273 \pm 0.009	7.49 \pm 0.21	27.5 \pm 1.4	89.5 \pm 7.9
50	0.264 \pm 0.006	7.16 \pm 0.91	27.2 \pm 3.9	85.5 \pm 13
100	0.288 \pm 0.032	8.00 \pm 0.66	28.1 \pm 4.7	96.3 \pm 18
250	0.276 \pm 0.013	7.55 \pm 0.39	27.4 \pm 0.9	90.1 \pm 5.7

Venlafaxine (μM)	P_{app} (A to B), x 10 ⁻⁶ cm/sec (Mean \pm SD)	P_{app} (B to A), x 10 ⁻⁶ cm/sec (Mean \pm SD)	P_{app} (B to A)/ P_{app} (A to B) Ratio	% Control
0	0.218 \pm 0.069	7.78 \pm 1.76	36.5 \pm 4.2	100
1	0.213 \pm 0.068	7.65 \pm 2.30	36.5 \pm 5.7	97.5 \pm 12
2.5	0.214 \pm 0.064	7.32 \pm 1.74	34.8 \pm 2.7	93.8 \pm 5.3
10	0.218 \pm 0.071	6.62 \pm 1.62	31.1 \pm 3.2	84.3 \pm 2.5
25	0.216 \pm 0.069	7.15 \pm 1.78	33.8 \pm 3.6	91.4 \pm 2.8
50	0.321 \pm 0.201	6.30 \pm 1.31	23.6 \pm 9.8	79.9 \pm 7.7
100	0.255 \pm 0.041	6.84 \pm 1.28	26.8 \pm 1.9	87.6 \pm 4.5
250	0.293 \pm 0.072	6.51 \pm 1.05	22.6 \pm 2.4	83.2 \pm 6.9

Results are mean \pm SD of three determinations each conducted on a separate day

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Table 15: Inhibition of P-gp mediated Digoxin Efflux in Caco-2 Monolayers in the Absence or Presence of Verapamil

Verapamil (μM)	P_{app} (A to B), $\times 10^{-6}$ cm/sec (Mean \pm SD)	P_{app} (B to A), $\times 10^{-6}$ cm/sec (Mean \pm SD)	P_{app} (B to A)/ P_{app} (A to B) Ratio	% Control
0	0.290 \pm 0.014	8.39 \pm 0.78	28.9 \pm 1.5	100
1	0.331 \pm 0.006	7.21 \pm 0.26	21.8 \pm 0.8	85.6 \pm 11
2.5	0.430 \pm 0.004	7.59 \pm 0.33	17.6 \pm 0.7	89.2 \pm 12
10	0.813 \pm 0.025	4.84 \pm 0.13	6.0 \pm 0.2	50.0 \pm 5.6
25	1.25 \pm 0.121	4.11 \pm 0.11	3.3 \pm 0.2	35.5 \pm 3.0
50	1.62 \pm 0.088	3.00 \pm 0.11	1.9 \pm 0.0	17.1 \pm 2.0
100	1.94 \pm 0.079	2.90 \pm 0.12	1.5 \pm 0.1	12.0 \pm 2.5
250	2.25 \pm 0.153	3.04 \pm 0.41	1.4 \pm 0.2	9.6 \pm 6.0

Results are mean \pm SD of three determinations each conducted on a separate day

Distribution

The plasma protein-binding of desvenlafaxine was low (29.9% \pm 12.1%) and independent of drug concentration at values of 0.04 to 0.20 $\mu\text{g}/\text{mL}$. The desvenlafaxine volume of distribution at steady-state after intravenous administration was 3.4 L/kg.

Metabolism

Mass Balance: In a mass balance study using ^{14}C -labeled Venlafaxine, over 92% of the dose was recovered in urine. The metabolite Wy-45,233 (DVS) was 5-fold greater than venlafaxine. The primary route of excretion for dose-related material is via the kidneys into the urine. By 48 hours after dosing, 87% of the dose had appeared in the urine. Seventy-two percent of the dose was present in the urine as products of O-demethylation. Of this, 29.4% of the dose escaped further metabolism and appeared in the urine as DVS. Another 26.4% of the dose was conjugated to form DVS glucuronide. Approximately 10% of dose forms N-desmethyl DVS and 6% conjugated to form N-desmethyl DVS

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Table 16; Urinary Metabolites Excreted by 9 Male Subjects up to 48 hr Following a Single Oral 50 mg Dose of [¹⁴C]Venlafaxine, as the Hydrochloride Salt^a

Subject	Venlafaxine	Percent of Administered Dose		Hy-46,689	Gluc.	A ^b	B ^c	Hy-46,965	Hy-45,494	Other ^d
		Hy-45,233	Gluc.							
1										
2										
3										
4										
5										
6										
7										
8										
10										
Mean	4.7	29.4	26.4	9.8	6.2	2.7	2.2	1.0	1.0	0.9
±SD	3.1	5.0	9.0	2.7	1.3	1.5	0.8	0.6	1.6	0.4

^aSubject 9 was excluded due to a missing urine sample.

^bMetabolite A was an unidentified conjugate.

^cMetabolite B was an unidentified metabolite, not a glucuronide or sulfate conjugate.

^dOther - the sum of minor unidentified metabolite peaks.

Moieties after oral administration of Desvenlafaxine SR: Following a single oral administrations of desvenlafaxine to healthy volunteers the major compound-related components in plasma were unchanged desvenlafaxine (about 46%) and its O-glucuronide (about 19%). Minor metabolites, N-desmethyl desvenlafaxine and the O-glucuronide of N-desmethyl desvenlafaxine, were also detected. Glucuronidation of desvenlafaxine represented the major metabolic pathway. Minor metabolites (NODV and NODV-O-glucuronide) were present at concentrations less than 1% that of desvenlafaxine plasma concentrations.

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Table 17: Metabolites of Desvenlafaxine Observed by LC/MS in Human Plasma

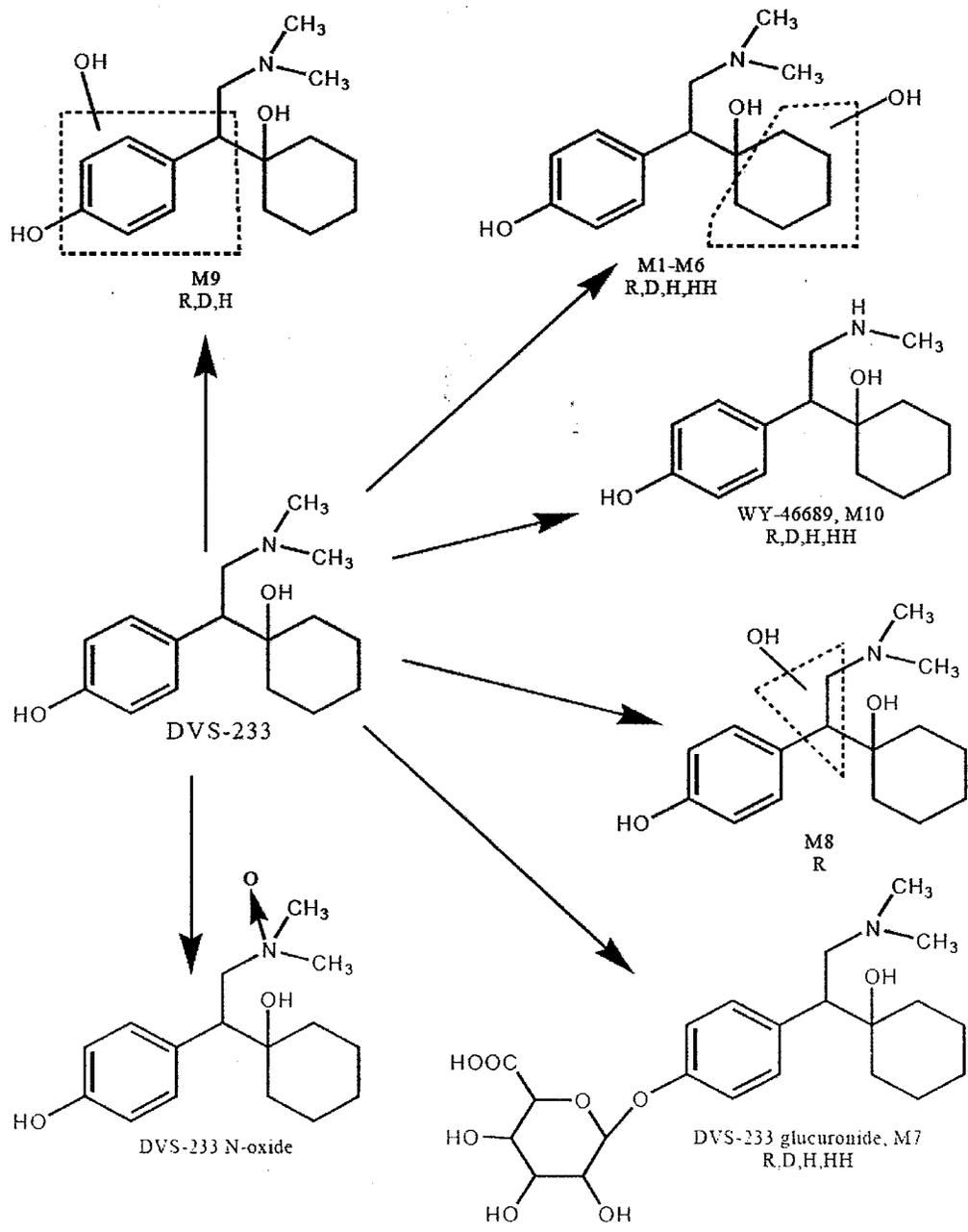
Metabolite	Retention Time (min) ^a	[M+H] ⁺	Site of Metabolism	Metabolite Name
M13	14.1	426	Dimethylamino group and Phenol -OH group	N-Desmethyl Desvenlafaxine O-Glucuronide
M7	15.6	440	Phenol -OH group	Desvenlafaxine O-Glucuronide
M10	33.0	250	Dimethylamino group	N-Desmethyl Desvenlafaxine (WY-46689)
Desvenlafaxine	34.1	264	None	Desvenlafaxine

In vitro metabolism: In vitro incubations with desvenlafaxine indicated that glucuronidation and N-demethylation were the primary metabolic pathways in human microsomes, as well as in cryopreserved human hepatocytes. The results of in vitro uridine-5'-diphosphoglucuronosyl-transferase (UGT) isozyme analysis indicate that the human UGT isozymes capable of metabolizing desvenlafaxine include UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17. The CYP isozyme involved in the metabolism of desvenlafaxine to NODV in human liver microsomes was determined to be CYP3A4. This is a minor metabolic pathway.

The CYP450 isozymes involved in the metabolism of DVS-233 to its microsomal metabolites were investigated in vitro. The approaches utilized were chemical inhibition studies in human liver microsomes, metabolism by recombinant expressed human CYP450 isozymes, human liver microsomes and cryopreserved human hepatocytes. The metabolic scheme is provided in the figure below

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Fig 4: Primary DVS Metabolites And Reaction Products Detected Using Cryopreserved Human Hepatocytes (HH) And Liver Microsomes From Rat (R), Dog (D) And Human (H)



DVS did not significantly inhibit the CYP P450 activity in vitro.

Table 18: Estimated IC₅₀ Values (μM) for the inhibition of CYP Enzymes by DVS and Comparators in Human Liver Microsomes

P450	DVS-233	Venlafaxine	S,S Duloxetine	Paroxetine	Sertraline	Bupropion
CYP1A2	130 ± 88	NC	NC	80 ± 10	61 ± 7	160 ± 29
CYP2A6	NC	NC	270 ± 78	210 ± 29	51 ± 2	NC
CYP2C19	NC	NC	49 ± 8	70 ± 14	27 ± 3	43 ± 9
CYP2C8	NC	NC	180 ± 91	NC	350 ± 150	NC
CYP2C9	NC	NC	NC	63 ± 5	120 ± 19	NC
CYP2D6	NC	69 ± 3	6.0 ± 0.6	2.0 ± 1	5.0 ± 0.6	28 ± 5
CYP3A (mdz)	NC	NC	89 ± 13	32 ± 9	26 ± 3	120 ± 22
CYP3A (test)	NC	NC	54 ± 4	59 ± 14	41 ± 7	270 ± 90

Values are mean ± SD of three separate determinations each performed in triplicate

NC. Not calculated due to lack of inhibition at 100 μM

mdz. Midazolam

test. Testosterone

Table 19: K_i Values and Mode of Inhibition for the Inhibition of CYP Enzymes by DVS-233 and Comparators in Human Microsomes

	CYP2D6	CYP2C19	CYP3A ^a	CYP3A ^b
DVS-233	> 300	ND	ND	ND
Venlafaxine	93 (competitive)	ND	ND	ND
S, S Duloxetine	4.5 (competitive)	24 (competitive)	28 (mixed)	26 ^c
Paroxetine	4.5 (competitive)	78 (mixed)	25 (non-competitive)	46 ^c
Sertraline	3.8 (competitive)	28 (mixed)	43 (non-competitive)	23 ^c
Bupropion	28 (competitive)	13 (competitive)	ND	ND

Values are mean of two separate determinations each performed in duplicate

ND. Not determined due to minimal or no inhibition in IC₅₀ studies

a. Midazolam-1'-hydroxylation

b. Testosterone-6β-hydroxylation

c. K_i was only an estimate due to autoactivation (homotropic cooperativity) kinetics for testosterone 6β-hydroxylation. Mode of inhibition was not determined.

Elimination

The results of the absorption, distribution, metabolism, and excretion study conducted with a single 50-mg oral dose of [¹⁴C]-venlafaxine indicated the major metabolite of venlafaxine was desvenlafaxine. During the first 48 hours, when 87% of the radioactive dose had appeared in urine, 83% of radioactivity in urine (72% of total dose) was identified as desvenlafaxine or its metabolites (NODV or the glucuronide of desvenlafaxine or NODV). The major finding after oral administration of single doses of [¹⁴C]-venlafaxine was that 92% of the dose was excreted in the urine (~2% in the feces) over a 120-hour period. Less than 1% of the dose was excreted in urine as unknown metabolites that could potentially be metabolites of venlafaxine. Because fecal elimination is low after oral administration of [¹⁴C]-venlafaxine (<2%), it suggests that the majority of the elimination of desvenlafaxine will occur by renal excretion after oral administration of DVS SR.

The results of the absolute bioavailability study of DVS SR showed that urinary recovery of conjugated and unconjugated desvenlafaxine and NODV accounted for 69% of the dose of DVS SR after oral administration. Of the amount of the dose excreted in urine after oral administration, 19% was excreted as conjugated desvenlafaxine and 46% was excreted as unconjugated desvenlafaxine. The excretion of conjugated and unconjugated NODV accounted for only 3.5% of the dose of desvenlafaxine eliminated in urine.

2.2.5.4. Based on PK parameters, what is the degree of linearity or nonlinearity?

The pharmacokinetics of desvenlafaxine was demonstrated to be linear over the dose range of 100 to 600 mg in a single dose study. The single-dose pharmacokinetics predicts the multiple-dose pharmacokinetics.

Dose proportionality was evaluated in a randomized, single dose, open-label, 3-treatment crossover study between doses of 100 and 900 mg. And in a multiple dose study between doses of 300 to 600 mg administered every day. The pharmacokinetic results indicated that desvenlafaxine exhibits linear dose proportionality over the single-dose range of 100 to 600 mg and over the steady-state dose range of 300 to 450 mg/day. Statistical comparisons of mean plasma concentrations at each sample collection time and mean pharmacokinetic parameters were made by using ANOVA. Additionally, an exponential regression (eg, $AUC = \alpha \cdot Dose^\beta$) was used to evaluate the dose-proportionality relationship. The linear dose-proportionality was supported by the lack of statistically significant differences among doses in total CI/F and dose-normalized AUC.

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Table 20: Desvenlafaxine Pharmacokinetic Parameters

Treatment	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} (h)	AUC (ng·h/mL)	Cl/F (L/h/kg)
100 mg ^a	238 ± 44.5	7.52 ± 1.99	11.2 ± 1.5	5560 ± 1378	0.246 ± 0.082
	234	7.28	11.1	5376	0.236
300 mg	712 ± 129.1	7.20 ± 1.77	11.0 ± 1.6	16594 ± 3553	0.238 ± 0.049
	701	7.01	10.9	16215	0.233
600 mg	1422 ± 200.5	8.32 ± 1.92	11.2 ± 1.8	35517 ± 6865	0.223 ± 0.045
	1409	8.11	11.0	34880	0.218
<i>3-Period Crossover Analysis of Variance of Log-Transformed Data^b</i>					
Sequence	<0.001	0.735	0.008	<0.001	<0.001
Subject (sequence)	<0.001	0.367	<0.001	<0.001	<0.001
Treatment	0.759	0.226	0.670	0.121	0.121
Period	0.960	0.894	0.767	0.564	0.564

a: Mean±SD and geometric mean.

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

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

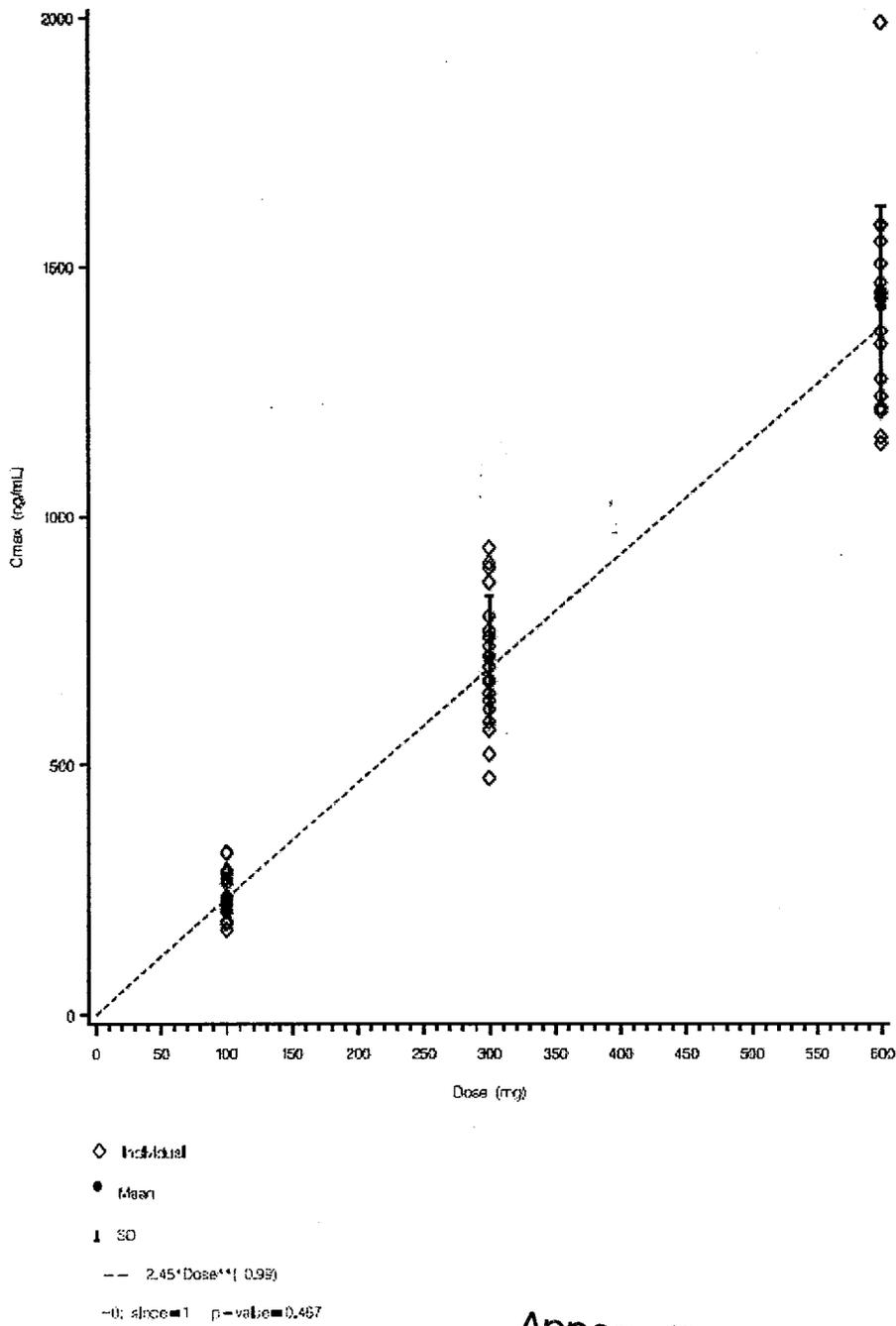
Table 21: Power Model for Desvenlafaxine Pharmacokinetic Parameters

Parameter	Model	95% CI for the exponent	p-Value (exponent = 1)
C _{max}	C _{max} = 2.45·(Dose) ^{0.99}	0.95, 1.02	0.467
AUC	AUC = 49.25·(Dose) ^{1.01}	0.99, 1.04	0.341

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

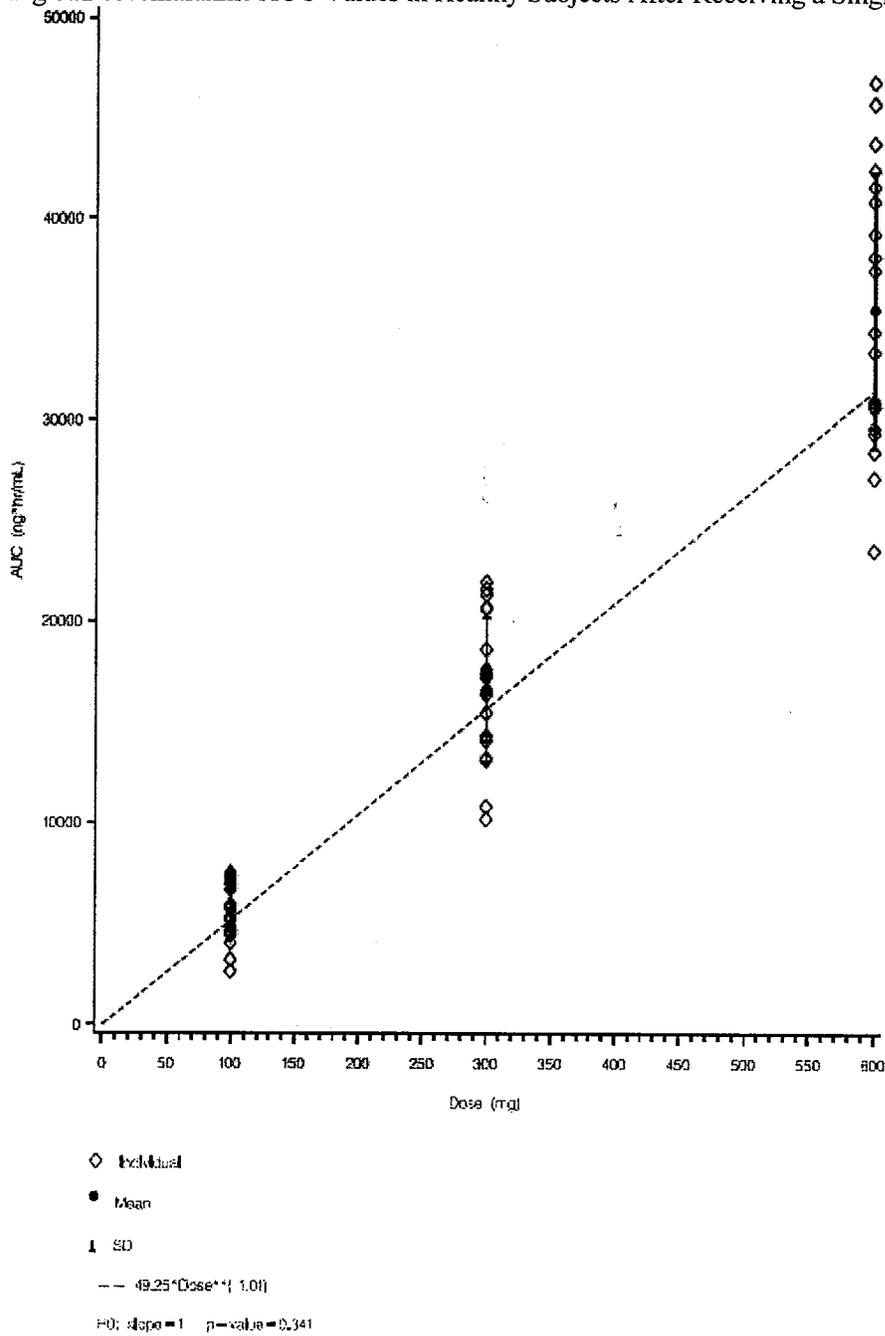
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Fig 5: Desvenlafaxine Cmax Values in Healthy Subjects After Receiving a Single Dose of DVS SR



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Fig 6: Desvenlafaxine AUC Values in Healthy Subjects After Receiving a Single Dose of DVS SR



2.2.5.5 Does the PK parameters change with time following chronic dosing?

The desvenlafaxine C_{max} and AUC values increased in a linear dose-proportional manner after single doses of 300- to 600-mg of DVS and after multiple doses of 300- to 450-mg of DVS per 24 hours. Accumulation of DVS following multiple dosing of DVS SR is predictable from single dose data and is 1.6. Examination of trough plasma concentrations indicated that pharmacokinetic steady state was reached by day 4 or 5 of multiple dosing. The pharmacokinetic parameters of desvenlafaxine administered in oral doses of 300 mg, 450 mg, and 600 mg daily after a light breakfast for 14 days are summarized in the following table

Table 22: Summary of Desvenlafaxine Pharmacokinetic Parameters After Multiple Oral Daily Doses of 300 mg, 450 mg and 600 mg of DVS SR in Healthy Subjects

Dose (mg)	Single Dose (Day 1)			Multiple Dose (Day 14)		
	C _{max} ^a (ng/mL)	t _{max} (h)	AUC (ng•h/mL)	C _{max} (ng/mL)	t _{max} (h)	AUC _{ss} (ng•h/mL)
300	537 ± 101	6.7 ± 2.4	16396 ± 5220	807 ± 141	4.6 ± 1.1	14831 ± 2894
450	806 ± 342	8.7 ± 1.7	23500 ± 12356	1369 ± 292	7.6 ± 5.7	24073 ± 5880
600 ^b	1083 ± 222	7.1 ± 1.3	34315 ± 9352	NA ^b	NA	NA
p-Values from the 1-factor ANOVA with log-transformed parameters						
	0.756	0.059	0.639	0.202	0.118	0.556

Abbreviations: AUC=area under the concentration curve-versus-time; AUC_{ss}=AUC during a single dosing interval at steady state; Cl/F=apparent oral dose clearance; C_{max}=peak concentration; NA=not available; SD=standard deviation; t_{1/2}=terminal-phase elimination half-life; t_{max}=time to peak concentration.

a. Mean ± SD.

b. The 600-mg cohort was withdrawn before day 14.

2.2.5.6 What is the variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In the population pharmacokinetic analysis, between subject variability (BSV) and between occasion variability (BOV) on clearance was determined to be 30% and 9.7%, respectively.

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2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and what is the impact of any differences in exposure on efficacy or safety? Based upon what is known about exposure-response relationships and their variability and the groups studied, what dosage regimen adjustments, if any, are recommended for each of these groups?

2.3.1.1 Effect of Renal Impairment

Dosage adjustments is recommended for patients with moderate, severe renal impairment and ESRD patients. Dialysis does not significantly affect the concentrations of DVS. It is recommended that the dose for moderate, severe and ESRD patients be reduced in half.

Care should be taken when treating patients with mild renal impairment with DVS SR.

Patients with mild renal impairment could be administered the recommended dose of 100 mg/day.

DVS SR should not be administered to moderate, severe renal impaired and ESRD patients until a 50 mg strength is commercially available

Dose escalation to 200 mg/day for patients with renal impairment is not recommended.

There was no statistically significant difference in C_{max} but AUCT, AUC, and CL/F of desvenlafaxine were significantly different across healthy and all renal impairment groups. Compared with values in age-matched healthy subjects, increases in AUC of approximately 108% and 116% were observed in subjects with severe renal impairment and ESRD, respectively. The renal clearance of desvenlafaxine decreased as the degree of renal impairment increased. Only small amounts of desvenlafaxine were removed during 4 hours of dialysate with recovery in dialysate fluid ranging from 0.4% to 4.12% of the total dose of 100mg.

The pharmacokinetics of desvenlafaxine in subjects with mild, moderate or severe renal impairment or ESRD were compared with values obtained from aged-matched healthy subjects after oral administration of 100 mg of DVS SR. The study was an open-label, single-dose, inpatient, nonrandomized trial. Subjects with mild, moderate, or severe renal impairment or end-stage renal disease (ESRD) or healthy subjects aged 18 to 65 years were eligible for enrollment. Healthy subjects had 24-hour creatinine clearance > 80 mL/min, obtained during the screening period. Subjects with ESRD had to be on dialysis for at least 30 days before day -1. Subjects with ESRD could include those who had received and rejected renal transplants. Subjects with severe renal impairment had a 24-hour creatinine clearance < 30 mL/min obtained during screening. Subjects with mild or moderate renal impairment had a 24-hour creatinine clearance of 50 to 80 mL/min or 30 to 50 mL/min, respectively, obtained during screening. A single dose of DVS SR (100 mg) was administered orally on day 1 with 240 mL of room-temperature water after an overnight fast of at least 10 hours. Blood and urine samples for PK analysis were collected at specified time points. Dialysate samples were collected before dialysis and after the start of dialysis.

The mean C_{max} of desvenlafaxine was similar in subjects with mild and moderate renal impairment and was about 10% higher than the mean C_{max} in healthy subjects. Increases in C_{max} of desvenlafaxine were noticeable in subjects with severe and ESRD renal impairment. Twenty-five percent (25%) and 43% higher C_{max} values of desvenlafaxine were observed in subjects with severe renal impairment and ESRD, respectively. The mean AUC for desvenlafaxine was 42%, 56%, 108%, and 116% higher in subjects with mild, moderate, severe, and ESRD renal impairment, respectively, as compared with healthy subjects. The urinary recovery of unconjugated desvenlafaxine decreased in subjects with moderate and severe renal impairment by 26% and 45%, respectively. Urinary recovery of conjugated desvenlafaxine increased from 14.3% and 15.8% in healthy subjects and those with mild renal impairment, respectively, to 32.6% and 31.6% in subjects with moderate and severe renal impairment, respectively. All subjects with ESRD had dialysis on either day 2 or 3 of the study. The recovery of desvenlafaxine ranged from 0.40% to 4.12% of

the total dose of 100 mg during the 4 hours of dialysis. The pharmacokinetic parameters for desvenlafaxine and the statistical analysis are provided in the following tables

Table 23: Summary of Pharmacokinetic Parameters for Desvenlafaxine Following Single Oral Administration of DVS SR 100 mg to Subjects With Renal Impairment and Healthy Subjects

Subject Group	Variables	C _{max} (ng/mL)	t _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC (ng·hr/mL)	t _{1/2} (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)	CL _R (L/hr/kg)
Healthy (N=8)	Mean±SD	205.83 ± 75.58	9.76 ± 7.12	4862 ± 2210	4985 ± 2235	11.09 ± 1.45	0.336 ± 0.216	5.04 ± 2.54	0.094 ± 0.018
	%CV	37%	73%	45%	45%	13%	64%	50%	19%
	Geo. Mean	193.55	7.96	4218	4356	11.00	0.288	4.58	0.093
	Min - Max	112.17 - 331.22	4.00 - 24.00	1488 - 7002	1615 - 7216	8.20 - 12.83	0.159 - 0.698	2.66 - 9.67	0.063 - 0.117
Mild renal impairment (N=9)	Mean±SD	217.41 ± 58.12	6.67 ± 5.57	6276 ± 2068	6423 ± 2080	13.50 ± 3.26	0.210 ± 0.042	3.95 ± 0.71	0.071 ± 0.031
	%CV	27%	84%	33%	32%	24%	20%	18%	44%
	Geo. Mean	210.57	5.20	6029	6177	13.16	0.206	3.90	0.065
	Min - Max	144.82 - 321.49	2.00 - 20.00	4589 - 11047	4684 - 11205	9.89 - 18.76	0.123 - 0.254	3.29 - 5.64	0.031 - 0.133
Moderate renal impairment (N=8)	Mean±SD	222.06 ± 71.46	9.25 ± 3.85	7725 ± 5457	7960 ± 5750	15.48 ± 6.50	0.196 ± 0.090	3.88 ± 1.31	0.042 ± 0.010
	%CV	32%	42%	71%	72%	42%	46%	34%	25%
	Geo. Mean	212.54	8.54	6617	6789	14.60	0.176	3.71	0.041
	Min - Max	140.18 - 353.41	4.00 - 16.00	3539 - 20531	3676 - 21522	9.95 - 30.60	0.059 - 0.367	2.62 - 6.67	0.024 - 0.054
Severe renal impairment (N=7)	Mean±SD	245.71 ± 41.97	9.14 ± 4.88	9362 ± 2794	9516 ± 2827	17.58 ± 4.18	0.152 ± 0.067	3.65 ± 1.18	0.023 ± 0.012
	%CV	17%	53%	30%	30%	24%	44%	32%	53%
	Geo. Mean	242.80	8.40	8923	9081	17.22	0.141	3.50	0.020
	Min - Max	206.84 - 315.76	6.00 - 20.00	4434 - 12286	4603 - 12592	13.83 - 26.28	0.094 - 0.272	2.40 - 5.42	0.009 - 0.043
ESRD renal impairment (N=9)	Mean±SD	311.33 ± 172.05	10.22 ± 5.24	10307 ± 4611	10584 ± 4718	22.83 ± 7.73	0.139 ± 0.091	3.92 ± 1.04	NA
	%CV	55%	51%	45%	45%	34%	66%	27%	
	Geo. Mean	276.07	9.01	9143	9392	21.58	0.122	3.79	
	Min - Max	150.17 - 674.41	4.00 - 20.00	2574 - 16889	2627 - 17614	10.37 - 35.57	0.057 - 0.370	2.33 - 5.54	

Abbreviations: NA: not available

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Table 24: Statistical Analysis of Pharmacokinetic Parameters for Desvenlafaxine Following Single Oral Administration of DVS SR 100 mg to Subjects With Renal Impairment and Healthy Subjects

Parameter	p-value	Variables	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment	ESRD Renal Impairment
C_{max} (ng/mL)	.279	Ratio of means ^a 90% CI ^b	109 81.4-145	110 81.5-148	125 92.1-171	143 107-191
AUC_T (ng•hr/mL)	.023	Ratio of means ^a 90% CI ^b	143 94.7-216	157 103-239	212 137-328	217 144-327
AUC (ng•hr/mL)	.023	Ratio of means ^a 90% CI ^b	142 94.4-213	156 103-237	208 135-322	216 143-324
CL/F (L/hr/kg)	.005	Ratio of means ^a 90% CI ^b	71.2 48.8-104	61.1 41.4-90.2	48.8 32.6-73.0	42.2 28.9-61.6

Abbreviations: CI = confidence interval; ESRD = end stage renal disease. Source: Statistical Appendix

a. Ratio of geometric least square means with Healthy Subjects as reference.

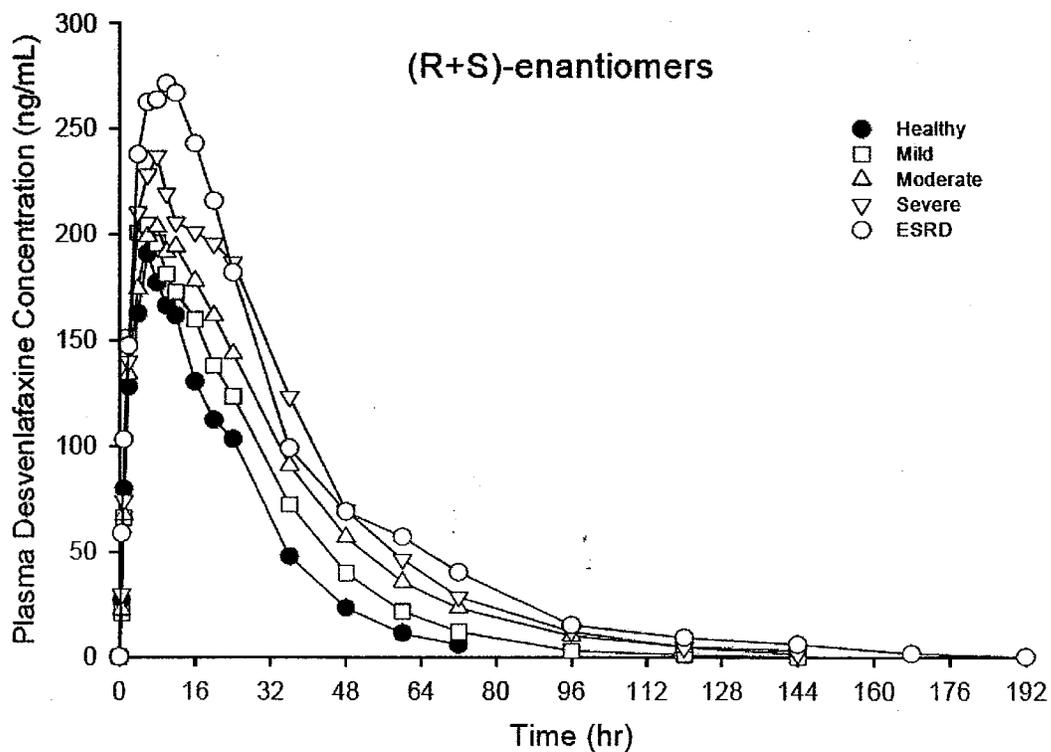
Table 25: Summary of Urinary Excretion of Unconjugated and Conjugated Desvenlafaxine Following Single Oral Administration of DVS SR 100 mg to Subjects With Renal Impairment and Healthy Subjects.

Subject Group	Variables	Unconjugated (R+S) Desvenlafaxine (% Dose)	Conjugated (R+S) Desvenlafaxine ^a (% Dose)
Healthy (N=8)	Mean±SD	33.6 ± 11.4	14.3 ± 8.1
	%CV	34%	57%
Mild renal impairment (N=9)	Mean±SD	33.3 ± 12.7	15.8 ± 10.0
	%CV	38%	61%
Moderate renal impairment (N=8)	Mean±SD	24.8 ± 10.0	32.6 ± 12.2
	%CV	39%	38%
Severe renal impairment (N=7)	Mean±SD	18.5 ± 13.3	31.6 ± 11.8
	%CV	72%	37%

Abbreviation: %CV= coefficient of variation; SD=standard deviation

a. Conjugated (R+S) desvenlafaxine is calculated as the Total (R+S)-enantiomer minus Unconjugated (R+S)-enantiomer of desvenlafaxine.

Fig 7: Mean Plasma Concentrations of Desvenlafaxine After Single Oral Administration of 100 mg of DVS SR to Healthy Subjects and Subjects With Renal Impairment



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2.3.1.2. Hepatic Impairment

No dosage adjustment is recommended for patients with hepatic impairment. However, it is suggested that care should be taken when treating patients with hepatic impairment of the Child Pugh B and C category. In accordance with the recommendations of the FDA Guidance on Studies in Hepatic Impaired Patients, no dosage adjustment is recommended for all categories of patients with hepatic impairment because the highest increase in exposure (AUC \approx 35% increase) after administration of DVS SR 100 mg to patients with hepatic impairment was seen in patients with hepatic impairment of Child-Pugh B and C category. Dose escalation to 200 mg is not recommended.

The pharmacokinetics of desvenlafaxine in subjects with chronic hepatic impairment, defined using Child-Pugh A, B, and C categories, were compared with values obtained from age-matched healthy subjects after oral administration of 100 mg of DVS SR. This was an open-label, single-dose, parallel-group, inpatient, nonrandomized study conducted in subjects with chronic hepatic impairment and in healthy adults matched by age, sex, weight, and, if possible, smoking habit. Each subject received the test article with 240 mL of room temperature water. The test article was administered as 1 x 100-mg tablet of DVS SR (orally) after an overnight fast of at least 8 hours. The pharmacokinetics of desvenlafaxine were examined. The following table summarizes the pharmacokinetic parameters for desvenlafaxine after oral administration of 100 mg of DVS SR in subjects with hepatic impairment and healthy subjects.

Table 26: Pharmacokinetic Parameters of Desvenlafaxine After Single Oral Administration of 100 mg SR to Subjects With Hepatic Impairment and Healthy Subjects

Subject Group	Variables	C_{max} (ng/mL)	T_{max} (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/hr/kg)	V_z/F (L/kg)	Cl_R (L/hr/kg)
Healthy (n = 12)	Mean \pm SD	183.26 \pm 50.69	8.17 \pm 3.95	5003 \pm 1496	5143 \pm 1529	9.99 \pm 1.63	0.267 \pm 0.048	3.81 \pm 0.77	0.124 \pm 0.028
	%CV	28%	48%	30%	30%	16%	18%	20%	23%
	Geo. Mean	176.61	7.19	4792	4931	9.87	0.263	3.74	0.120
	Min - Max	106.41 - 262.35	2.00 - 16.00	2709 - 7268	2854 - 7473	7.84 - 13.64	0.197 - 0.340	2.94 - 5.11	0.081 - 0.169
Child-Pugh A (n = 8)	Mean \pm SD	226.45 \pm 54.04	7.50 \pm 3.66	5233 \pm 2086	5365 \pm 2141	9.58 \pm 1.80	0.273 \pm 0.070	3.74 \pm 1.20	0.104 \pm 0.038
	%CV	24%	49%	40%	40%	19%	26%	32%	36%
	Geo. Mean	220.55	6.93	4906	5035	9.43	0.264	3.59	0.098
	Min - Max	157.41 - 290.92	4.00 - 16.00	2873 - 9507	3020 - 9818	7.41 - 12.45	0.152 - 0.387	2.37 - 6.28	0.059 - 0.171
Child-Pugh B (n = 8)	Mean \pm SD	210.00 \pm 62.73	9.75 \pm 4.46	6963 \pm 3208	7254 \pm 3484	13.44 \pm 6.44	0.235 \pm 0.126	4.00 \pm 1.60	0.117 \pm 0.049
	%CV	30%	46%	46%	48%	48%	54%	40%	42%
	Geo. Mean	201.61	8.85	6229	6447	12.52	0.209	3.78	0.109
	Min - Max	125.08 - 296.11	4.00 - 16.00	3163 - 10895	3261 - 12353	8.76 - 28.87	0.098 - 0.457	2.34 - 7.44	0.067 - 0.217
Child-Pugh C (n = 8)	Mean \pm SD	215.98 \pm 50.29	8.75 \pm 3.20	7246 \pm 3161	7439 \pm 3212	13.96 \pm 1.86	0.200 \pm 0.132	3.85 \pm 2.23	0.077 \pm 0.029
	%CV	23%	37%	44%	43%	13%	66%	58%	38%
	Geo. Mean	209.46	8.17	6482	6679	13.85	0.169	3.39	0.072
	Min - Max	109.76 - 274.06	4.00 - 12.00	1979 - 12274	2098 - 12544	11.34 - 17.32	0.077 - 0.457	1.58 - 7.47	0.041 - 0.125

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

Table 27: Statistical Analysis of Pharmacokinetic Parameters of Desvenlafaxine After Single Oral Administration of DVS SR 100 mg to Subjects with Hepatic Impairment and Healthy Subjects

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

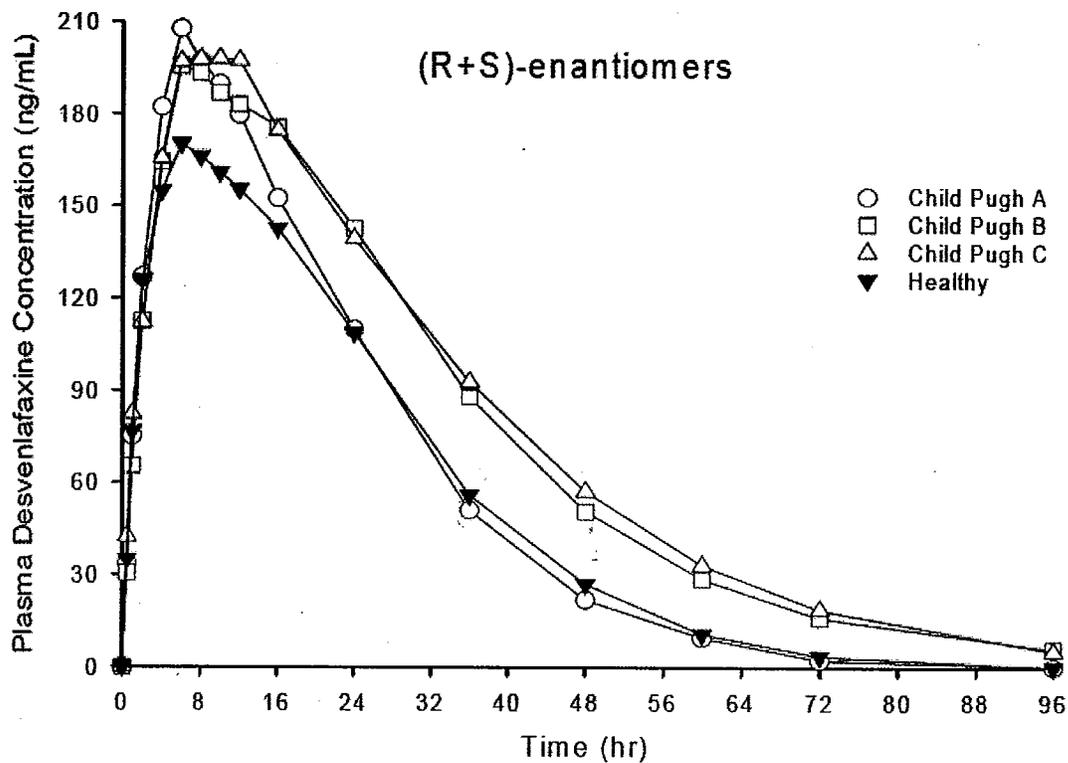
a. Ratio of geometric least square means with healthy subjects as reference.

b. 90% confidence interval.

Based on apriori statistical criterion of detecting a 50% difference in the primary pharmacokinetic parameters, there were no statistically significant differences in the C_{max} , AUC_T , AUC, or Cl/F of desvenlafaxine between the subjects with Child-Pugh A, B, or C hepatic impairment and healthy subjects. The C_{max} of desvenlafaxine was up to 14% to 25% higher for hepatic impairment than in healthy subjects. The mean AUC values of desvenlafaxine were similar for subjects with Child-Pugh A hepatic impairment and healthy subjects; however, there was a 31% and 35% higher mean AUC for desvenlafaxine in subjects with Child-Pugh B and Child-Pugh C hepatic impairment, respectively, compared with healthy. The mean $T_{1/2}$ was similar for healthy subjects and those with Child-Pugh A hepatic impairment and up to 42% longer in subjects with Child-Pugh B and Child-Pugh C hepatic impairment.

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Fig 8: Mean Plasma Concentrations of Desvenlafaxine After Single Oral Administration of 100 mg of DVS SR to Healthy Subjects and Subjects With Hepatic Impairment



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2.3.1.3 Effects of Age

In a phase 1 trial of healthy subjects administered doses up to 300 mg, there was an age dependent decrease in desvenlafaxine clearance, resulting in about 25% increase in C_{max} and about 54% increase in AUC values in subjects greater than 75 years of age as compared with subjects 18 - 45 years of age. The 65 to 75 year old subjects had about 5% higher desvenlafaxine C_{max} and about 32% higher AUC than young subjects. In the population pharmacokinetic analysis, age was determined to be a significant factor on CL/F of desvenlafaxine. No dosage adjustment is recommended, however, care should be taken when treating the elderly.

The effect of age on pharmacokinetic properties was examined based on individual results from a phase 1 study that was conducted specifically to evaluate the effect of age. The phase 1 study examined the pharmacokinetics in subjects aged 18 to 45 years (Young), 65 to 75 years (Young elderly) and subjects older than 75 years (elderly). There was a significant decrease in desvenlafaxine clearance with increasing age, which resulted in a higher C_{max} and AUC values in elderly subjects.

Table 28: Desvenlafaxine Pharmacokinetic Parameters (Phase 1 Study)

Age/Sex Group	n	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} (h)	AUC (ng•h/mL)	CL/F (L/h/kg)	CL _r (mL/min)
Young Men	8	411 ± 93 ^a	7.3 ± 2.1	11.8 ± 4.5	9702 ± 4134	0.28 ± 0.11	121 ± 35
		402	7.0	11.1	8713	0.26	117
Young Women	8	562 ± 133	5.8 ± 0.7	9.2 ± 0.9	10237 ± 2249	0.32 ± 0.05	113 ± 44
		549	5.7	9.1	9913	0.32	100
Young-Elderly Men	7	450 ± 61	9.7 ± 2.9	11.1 ± 1.7	12037 ± 3284	0.23 ± 0.05	105 ± 26
		446	9.3	11.0	11425	0.22	102
Young-Elderly Women	8	566 ± 140	6.3 ± 1.7	11.1 ± 3.4	14126 ± 5342	0.24 ± 0.06	102 ± 29
		551	6.0	10.7	13065	0.23	98
Elderly Men	9	582 ± 135	8.7 ± 2.6	11.7 ± 1.9	14941 ± 4660	0.19 ± 0.04	91 ± 44
		569	8.3	11.6	13994	0.18	82
Elderly Women	8	688 ± 132	8.5 ± 3.2	10.6 ± 1.3	15851 ± 4669	0.22 ± 0.07	83 ± 21
		678	7.9	10.6	14899	0.21	81
<i>2-Factor Analysis of Variance of Log-Transformed Data</i>							
Age		0.001	0.060	0.433	0.001	<0.001	0.119
Sex		<0.001	0.011	0.091	0.288	0.096	0.555
Age/Sex		0.633	0.200	0.543	0.934	0.713	0.870

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

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Fig 9: Age vs Dose-Normalized C_{max} in Healthy Subjects Receiving Single Dose of DVS SR (Dose normalized to 200 mg)

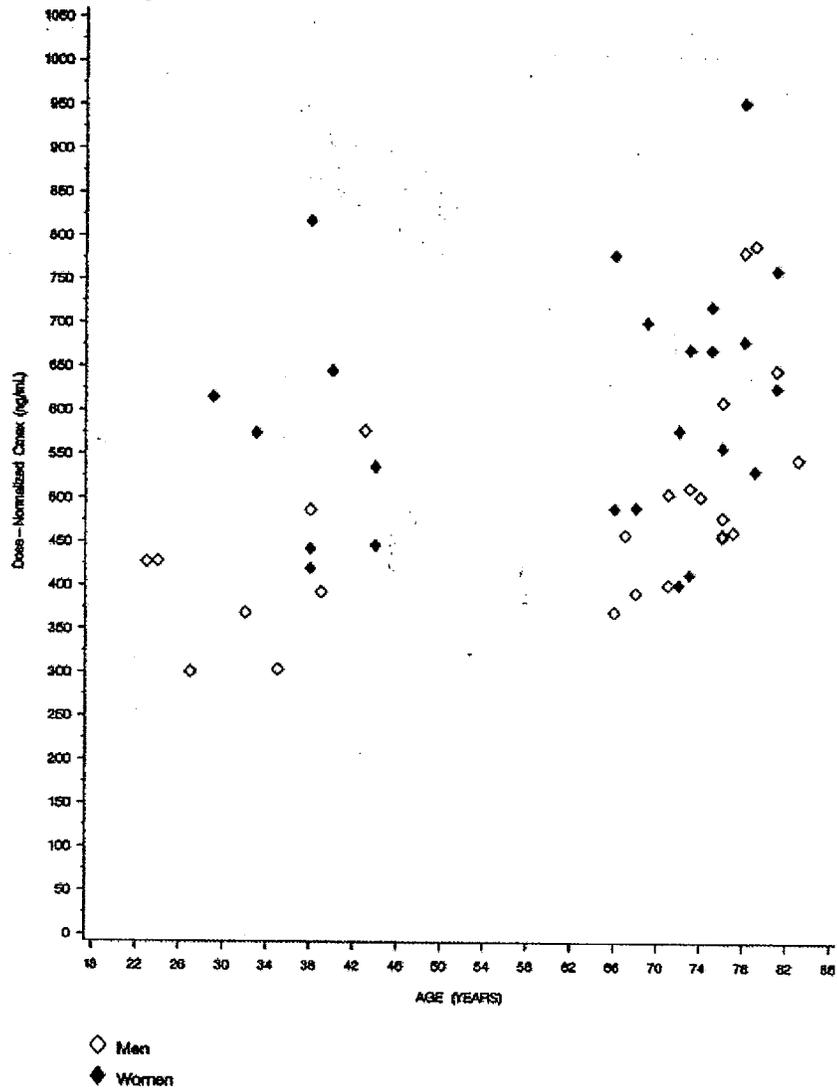
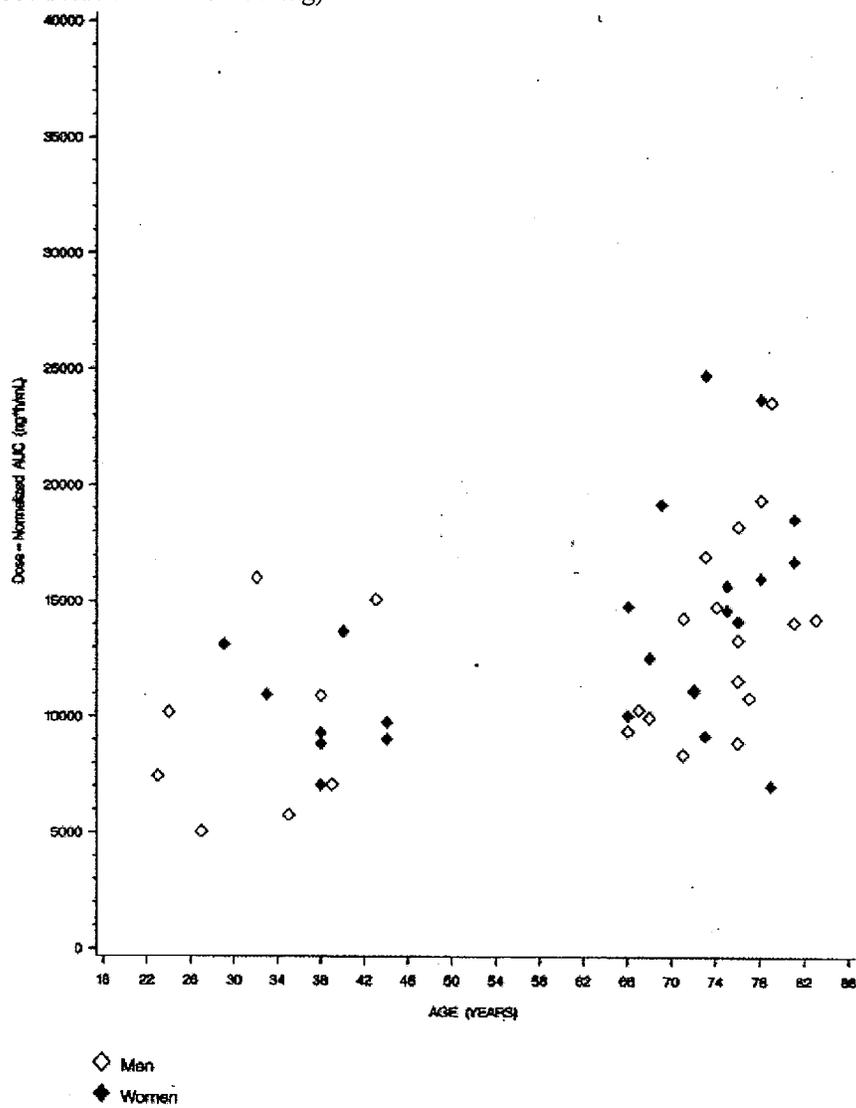


Fig 10: Age vs Dose-Normalized AUC in Healthy Subjects Receiving a Single Dose of DVS SR (Dose Normalized to 200 mg)



2.3.1.4. Effect of Gender:

In a trial of healthy subjects administered doses up to of 300 mg, women had an 18-37% higher C_{max} and a 6-17 % higher AUC than age-matched men. No adjustment of dosage on the basis of gender is recommended.

An open label, nonrandomized, single-dose, inpatient study of a single oral dose of DVS SR 200 or 300 mg was conducted in healthy young (18 to 45 years), young-elderly (65 to 75 years), and elderly (older than 75 years) men and women. Based on the results of the phase 1 study (Table 28 on page 47), there were small to moderate differences between the pharmacokinetics of desvenlafaxine for men and women after 200- or 300-mg single oral doses. In data from pooled Phase 1 studies, C_{max} was higher in female than males but mean AUC was similar. Body weight contributed to observed differences in the pharmacokinetic parameters in men and women. There was an inverse relationship between body weight and C_{max}, and between body weight and AUC. In the population pharmacokinetic analysis, body weight was determined to be a significant factor on the pharmacokinetics of desvenlafaxine. The conclusions from the phase 1 study are consistent with those obtained from the population pharmacokinetic analysis. The following figures are from pooled Phase 1 data.

Fig 11: Dose Normalized (100 mg) Desvenlafaxine C_{max} After a Single Dose of DVS SR in Healthy Subjects Stratified by Sex (Pooled Phase 1 Data)

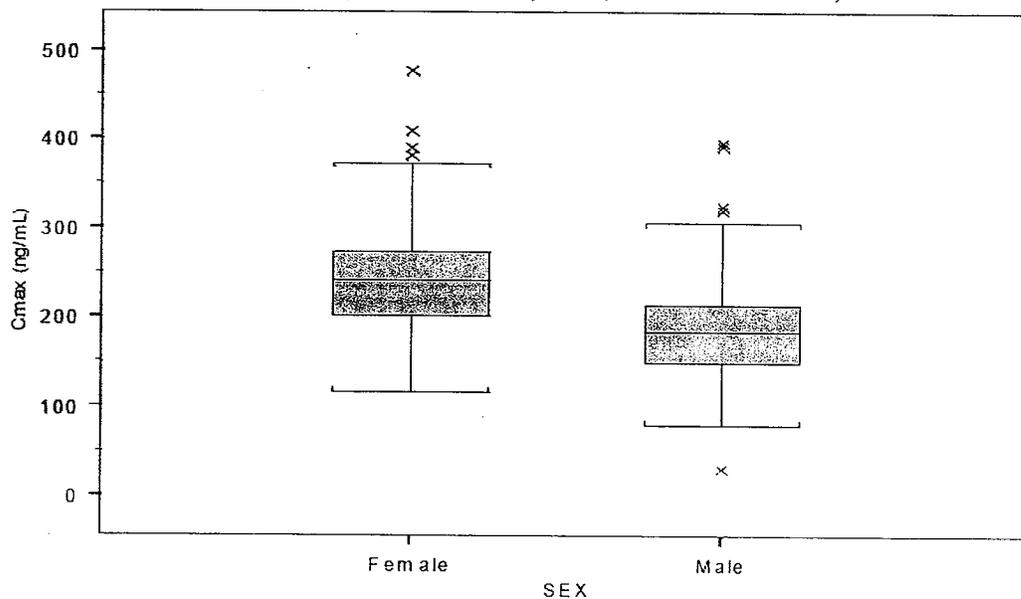
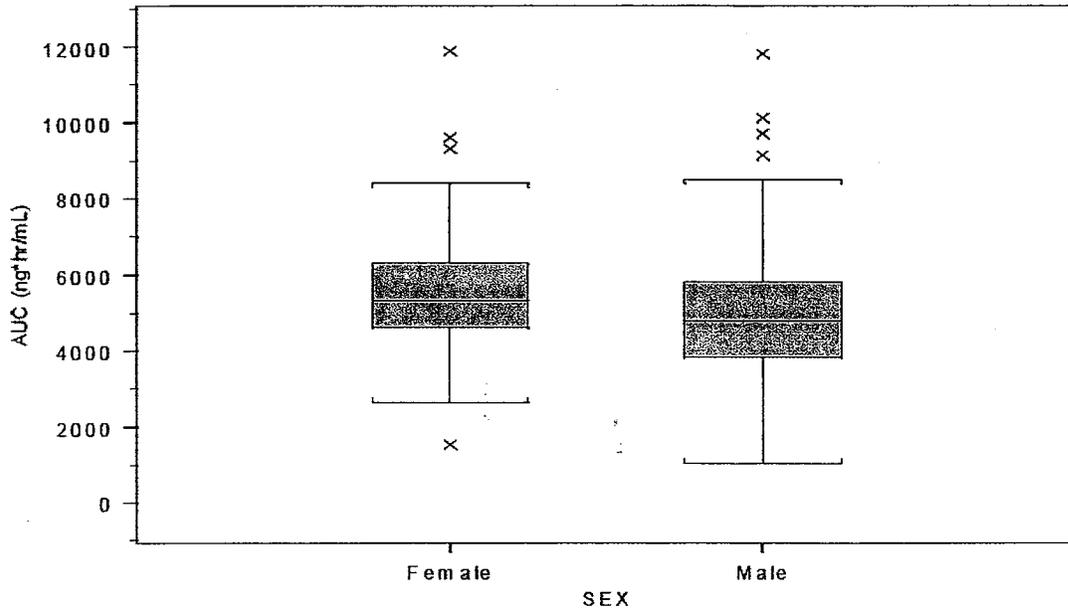


Fig 12: Dose Normalized (100 mg) Desvenlafaxine AUC After a Single Dose of DVS SR in Healthy Subjects Stratified By Sex (Pooled Phase 1 Data)



2.3.1.5. Effect of Race

No differences were seen when the pharmacokinetic profile of desvenlafaxine was analyzed by race. In the population pharmacokinetic analysis, race was not determined to be a factor on the Cl/F and V/F of desvenlafaxine.

Race, as an intrinsic factor was evaluated using two methodologies: 1) pooling of all phase 1 data; 2) employing population pharmacokinetic (PK) methodology on phase 1 through 3 data. The pooling of desvenlafaxine pharmacokinetic data from all phase 1 healthy subjects included subjects aged 18 to 83 years. The following tables provide the distribution of subjects and the mean C_{max}, AUC, and Cl/F for healthy white and black subjects from pooled phase 1 data.

Table 29: Distribution of Subjects by Race in Phase 1 Studies

Race	n	Percent
Asian	6	1.06
Black	151	26.63
Hispanic	6	1.06
White	370	65.26
Other	34	6.00

Table 30: Mean (SD) C_{max}, AUC and Cl/F for Healthy White and Black Subjects From Pooled Phase 1 Data

Race	n	C _{max} (ng/mL) ^a	AUC (ng-h/mL) ^a	Cl/F (L/h/kg)
White	263	203 (61)	4980 (1616)	0.316 (0.149)
Black	97	205 (57)	5130 (1610)	0.299 (0.162)

a. C_{max} and AUC values are dose-normalized to 100 mg of DVS SR.

The following figures (Figs 13 and 14) show the distributions of C_{max}, AUC, and Cl/F, respectively, by race for subjects participating in DVS SR phase 1 studies.

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Fig 13: Distribution of Dose-Normalized (100 mg) Cmax by Race for Subjects Participating in DVS SR Phase 1 Studies

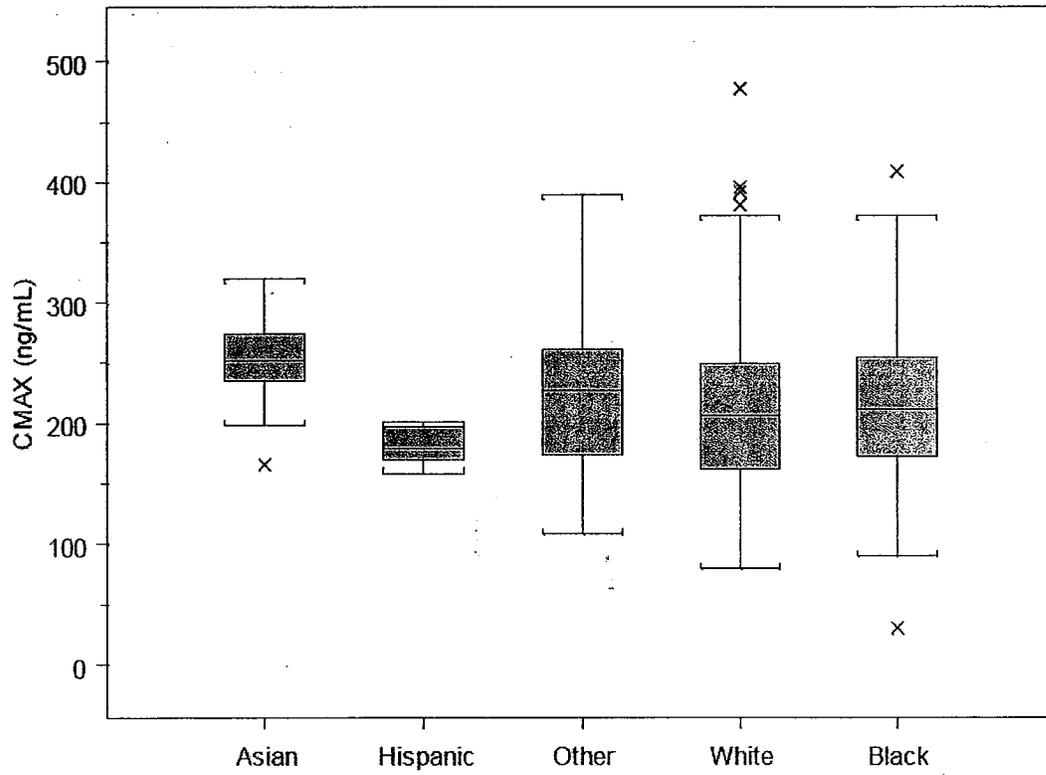
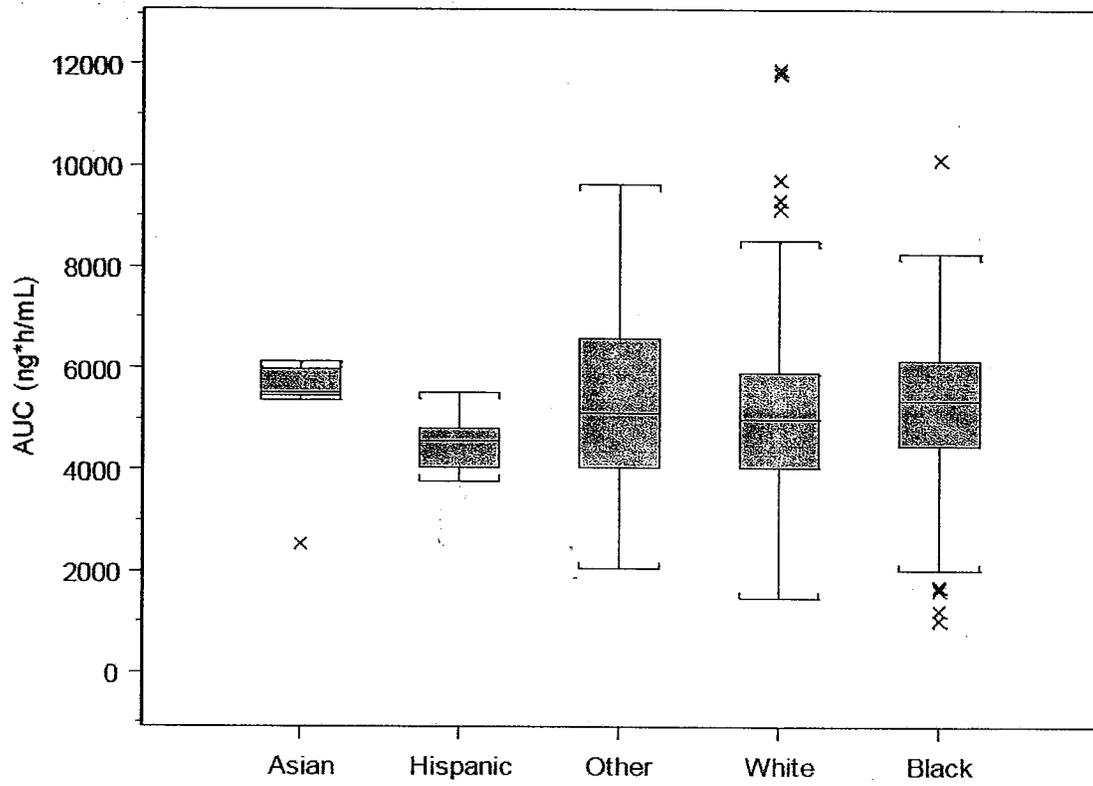


Fig 14: Distribution of Dose Normalized (100 mg) AUC by Race for Subjects Participating in DVS SR Phase 1 Studies



2.4 Extrinsic Factors

2.4.1. What Extrinsic Factors (Such as Herbal Products, Diet, Smoking and Alcohol) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Minor metabolism occurs through CYP3A4, and in vitro studies show no evidence for induction of the CYP3A4 enzyme pathway. In addition, no significant inhibition was seen on the activities of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 at desvenlafaxine concentrations up to 100 μ M. Based on in vitro data, desvenlafaxine was not a substrate of P-gp efflux and did not inhibit the P-gp-mediated efflux. Therefore, it is unlikely that smoking, diet or use of herbal substances would alter the pharmacokinetics of desvenlafaxine.

In a pharmacodynamic drug interaction study with DVS and alcohol, desvenlafaxine does not increase the impairment of mental and motor skills caused by alcohol. However, patients should be advised to avoid alcohol while taking desvenlafaxine.

The primary objective of the study was to assess the potential pharmacodynamic interaction of coadministration of DVS SR and ethanol in healthy subjects. Pharmacodynamic tests did not suggest any clinically relevant potentiation of ethanol impairments by desvenlafaxine 400 mg at steady state at a blood alcohol concentration (BAC) of approximately 0.4 g/L or below. Although the potentiation of ethanol cannot be completely ruled out, the study suggested that no clinically significant effect occurred when DVS SR was coadministered with ethanol.

2.4.2 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?

Pharmacokinetic drug interaction studies with desipramine, midazolam and ketoconazole were conducted.

2.4.2.1. Desipramine

It is recommended that desipramine is not co-administered with DVS SR. However, if it is necessary to co-administer DVS SR with desipramine, it is recommended that desipramine dose be reduced in half.

Desipramine exposure, as measured by C_{max} and AUC, increased by 50% and 83%, respectively, during coadministration of desipramine and DVS SR. Observed changes in desipramine pharmacokinetics (increases in AUC and C_{max}), when DVS SR is administered concomitantly, suggests that desvenlafaxine is a potential inhibitor of the CYP2D6 isozyme. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 may result in higher concentrations of that drug.

The study was an open-label, 2-period, sequential, inpatient trial. The study consisted of 2 treatment periods: administration of desipramine alone, and co-administration of DVS-233 SR and desipramine. In period 1, a single dose of desipramine was administered, followed by period 2 where a single dose of desipramine was co-administered following titration of DVS SR to steady state. Blood and urine samples were collected for determination of desipramine and 2-hydroxydesipramine concentrations at specified times.

Table 31: Pharmacokinetic Parameters for Desipramine following Administration of Desipramine 50 mg without and with Coadministration of DVS SR to Healthy Subjects

Treatment	Variables	C_{max} (ng/mL)	t_{max} (h)	AUC (ng*h/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)
Desipramine 50 mg (n=28 ^a)	Mean±SD	20.8±7.24	6.64±1.79	642±350	21.7±7.30	1.38±1.03
	%CV	34.8	27.0	54.5	33.6	75
	Geo. Mean	19.5	6.40	558	20.8	1.16
	Min-Max	7.86–34.1	3.00–12.03	135–1682	10.8–50.4	0.45–5.91
Desipramine 50 mg+DVS SR (n=23 ^{a,b})	Mean±SD	31.2±8.26	6.61±2.25	1176±477	28.2±7.86	0.65±0.34
	%CV	26.5	34.0	40.6	27.9	53.4
	Geo. Mean	30.2	6.18	1093	27.2	0.589
	Min-Max	18.2–47.2	3.00–12.00	395–2785	13.3–54.0	0.27–2.02

Abbreviations: C_{max} =peak concentration; CV=coefficient of variation; Geo. Mean=geometric mean; Min=minimum; Max=maximum; SD=standard deviation; $t_{1/2}$ =terminal phase elimination half-life; t_{max} =time at which peak concentration occurs.

Table 32: Pharmacokinetics Parameters (Urine) for Desipramine Following Administration of Desipramine 50mg without and with Co-administration of DVS SR to Healthy Subjects

Treatment	Variables	Ae (mg)	Ae (%)	CL _R (L/h)
Desipramine 50 mg (n=27 ^a)	Mean±SD	0.59±0.71	1.17±1.43	0.89±0.49
	%CV	122	122	55.2
	Geo. Mean	0.43	0.86	0.81
	Min-Max	0.08–3.96	0.17–7.92	0.35–2.96
Desipramine 50 mg + DVS SR (n=20 ^b)	Mean±SD	0.98±0.33	1.95±0.67	0.95±0.22
	%CV	33.9	34.0	23.4
	Geo. Mean	0.91	1.82	0.92
	Min-Max	0.28–1.55	0.56–3.11	0.53–1.28

Abbreviations: Ae=total urinary recovery amount; Ae%=total urinary recovery percentage; CL_R=renal clearance; CV=coefficient of variation; Geo. Mean=geometric mean; Min=minimum; Max=maximum; SD=standard deviation.

Table 33: Desipramine Ratio of Means (90% Confidence Interval)

Analyte	Parameter	Ratio of Mean ^a	90% CI
Desipramine	C _{max} (ng/mL)	152	140 - 165
	AUC (ng*h/mL)	190	175 - 208

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

C_{max} =maximum concentration.

a. Ratio of geometric least square means.

2.4.2.2 Midazolam

After administration of a single oral 4-mg dose of midazolam with steady state 400-mg dosing of DVS SR, an approximately 16% decrease in mean C_{max} and a 31% decrease in mean AUC of midazolam were observed when compared with the midazolam-alone treatment. A dosage adjustment for midazolam or CYP 3A substrates is not recommended when co-administered with desvenlafaxine.

The study was an open-label, 2-period, sequential inpatient trial. The study consisted of 2 treatment periods: administration of midazolam alone for 1 day and coadministration of DVS SR and midazolam after titration of DVS SR to steady state. DVS SR 100-mg tablets was given orally and titrated from 100 mg once daily on day 1 of period 2 up to 400 mg once daily by day 8 of period 2. Midazolam liquid was given orally in a single dose of 4 mg (2 mg/mL). The pharmacokinetic parameters and statistical analysis are presented in the following tables.

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Table 34: Pharmacokinetic Parameters for Midazolam and 1'-Hydroxymidazolam After Single Oral Administration of 4 mg of Midazolam Alone or With Multiple Oral Administration of 400 mg of DVS SR to Healthy Subjects

Analyte	Treatment (n=24)	C _{max} (ng/mL)	t _{max} (h)	AUC _T (ng•h/mL)	AUC (ng•h/mL)	t _{1/2} (h)	Cl/F (L/h/kg)	V _d /F (L/kg)
Midazolam	Midazolam alone	20.1 ±9.02 ^a	0.55 ±0.25	44.52 ±19.78	45.72 ±20.31	4.29 ±1.63	1.31 ±0.54	7.54 ±3.54
	Midazolam + DVS SR	16.5 ±6.24	0.45 ±0.16	30.62 ±12.81	31.41 ±13.03	3.79 ±1.75	1.89 ±0.76	9.36 ±4.85
	1'-Hydroxy-midazolam alone	9.73 ±4.3	0.58 ±0.23	18.94 ±6.39	19.99 ±6.42 ^b	4.72 ±2.15 ^b	--	--
1'-Hydroxy-midazolam	Midazolam + DVS SR	9.27 ±3.29	0.49 ±0.14	16.33 ±4.83	17.44 ±5.56 ^c	5.51 ±4.30 ^c	--	--

AUC= Area under the drug concentration-versus-time curve, calculated as $AUC_T + C_T/\lambda_z$; AUC_T=area under the concentration-versus-time curve to the last observable concentration (C_T) at time T; Cl/F=apparent oral dose clearance (dose/AUC); C_{max}=peak concentration; t_{1/2}=terminal-phase elimination half-life ($0.693/\lambda_z$); t_{max}=time to peak concentration; SD=standard deviation; V_d/F=apparent volume of distribution.

- a. Mean±SD.
- b. n=22.
- c. n=15.

Table 35: Statistical Analysis of Pharmacokinetic Parameters for Midazolam After Single Oral Administration of Midazolam 4 mg Alone or With Multiple Oral Administration of DVS SR 400 mg to Healthy Subjects

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

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

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

2.4.2.3 Ketoconazole

An increase in the concentrations of desvenlafaxine occurred after concomitant administration of DVS SR with the CYP3A4 inhibitor ketoconazole. In a clinical study, ketoconazole (200 mg BID) increased the AUC of desvenlafaxine (400 mg single dose) by about 43%; C_{max} were comparable between treatments. Concomitant use of desvenlafaxine with potent inhibitors of CYP3A4 could result in higher concentrations of desvenlafaxine. Therefore, caution should be exercised when potent inhibitors of CYP3A4 are concomitantly administered with desvenlafaxine. Dosage adjustment is not recommended when DVS SR is co-administered with ketoconazole or other CYP 3A inhibitors.

The clinical study was an open-label, nonrandomized, 2-period, sequential, inpatient trial. On study day 1 of period 1, each subject received 400 mg (2 tablets each containing 200 mg) DVS SR approximately 10 minutes after a low-fat breakfast. Study period 2 included study days 5 through 12. After a washout period of 4 days subjects were administered 200 mg ketoconazole every 12 hours under fed conditions for 8 consecutive days (study days 5 to 12). On study day 9, the morning dose of 200 mg ketoconazole was coadministered with 400 mg of DVS SR approximately 10 minutes after a low-fat breakfast. In all instances, the test articles were administered with 240 mL of room-temperature water. A baseline ketoconazole blood sample was collected before ketoconazole administration on study day 5. Descriptive statistics and the ratio of means for the pharmacokinetic parameters of desvenlafaxine are provided in the following tables

Table 36: Pharmacokinetic Parameters of Desvenlafaxine After Single Oral Administration of 400 mg of DVS SR to Healthy Subjects

Subject Group	Variables	C _{max} (ng/mL)	t _{max} (h)	AUC _T (ng•h/mL)	AUC (ng•h/mL)	t _{1/2} (h)	Cl/F (L/h/kg)	V _F (L/kg)	CL _R (L/h/kg)
DVS (N=14)	Mean±SD	819±161	7.30±3.31	21784±4310	21942±4321	9.79±0.98	0.255±0.045	3.59±0.63	0.117±0.035
	%CV	19.7%	45.3%	19.8%	19.7%	10.0%	17.8%	17.6%	30.0%
	Geo. mean	804	6.73	21398	21557	9.75	0.251	3.54	0.111
	Min-Max	562-1105	4.00-16.03	15568-31485	15607-31654	8.14-11.36	0.174-0.333	2.71-4.78	0.049-0.165
DVS+KETO (N=13)	Mean±SD	884±185	8.15±4.27	30820±6260	31245±6463	13.49±1.47	0.181±0.033	3.50±0.60	0.092±0.017
	%CV	21.0%	52.4%	20.3%	20.7%	10.9%	18.3%	17.1%	19.0%
	Geo. mean	865	8.65	30301	30702	13.42	0.178	3.45	0.090
	Min - Max	631 - 1192	4.00 - 16.00	23914 - 47640	24079 - 48697	10.94 - 16.2	0.113 - 0.229	2.32 - 4.85	0.061 - 0.124

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

Table 37: Statistical Analysis of Pharmacokinetic Parameters of Desvenlafaxine After Single Oral Administration of DVS SR Alone and with Ketoconazole to Healthy Volunteers

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

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

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

b. 90% confidence interval

2.4.2.4 *Is there an in vitro basis to suspect drug-drug interaction?*

There does not seem to be an in vitro basis for drug-drug interactions. The plasma protein binding of desvenlafaxine in humans is low ($29.8\% \pm 12.1\%$), and independent of drug concentrations. Only minor metabolism occurs through CYP3A4, and in vitro studies show no evidence for induction of the CYP3A4 enzyme pathway. In addition, no significant inhibition was seen on the activities of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 at desvenlafaxine concentrations up to 100 μ M. Based on in vitro data, desvenlafaxine was not a substrate of P-gp efflux and did not inhibit the P-gp-mediated efflux. It is unlikely that UGT-mediated drug interactions would occur with desvenlafaxine because glucuronidation of desvenlafaxine is substantially less than 50% of the total drug elimination and the multiple UGT enzymes are involved in desvenlafaxine glucuronidation.

2.4.2.5 *Is Desvenlafaxine A Substrate, Inhibitor or Inducer of CYP?*

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms, including UGT 1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17) and to a minor extent through oxidative metabolism. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. In vitro, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, 2C19 and CYP3A4 isozymes. In vitro studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. DVS-233 does not induce CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5.

2.4.2.5 *Is Desvenlafaxine a Substrate and/or inhibitor of P-glycoprotein (P-gp) transport process?*

Desvenlafaxine is not a substrate or an inhibitor of P-gp in vitro.

2.5 General Biopharmaceutics

2.5.1 What are the general solubility and permeability characteristics of DVS?

Solubility: Desvenlafaxine succinate has two pKa's at 8.34 (dimethylamino group) and 10.11 (phenolic group), respectively. Desvenlafaxine succinate has a pH dependent solubility. It is reported to have an equilibrium solubility of 32 mg/mL in aqueous buffer (pH 4.6), with a higher solubility (>133 mg/mL) at pH <2.5 and lower solubility (<1.0 mg/mL) at pH >8.

Table 38: pH Solubility Profile for Desvenlafaxine Succinate

pH	1.3	2.8	3.8	4.7	5.0	6.5	6.9	7.3	8.2	9.0
Solubility (mg/mL) ^a	>134	65.6	37.6	28.0	34.0	34.6	30.5	13.6	1.04	0.58

a. Expressed as mg/mL free base.

The sponsor reported that the highest DVS formulation strength (200 mg) has a dissolving volume of ~ 3 to 15 mL based on aqueous solubility under physiologically relevant pH conditions. The minimal dissolving volume is significantly less than the BCS Guidance specified volume of 250 mL.

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

The site-specific intestinal absorption of DVS (50 µg/mL) was evaluated using rat perfusion model by cannulating rat duodenum-jejunum, ileum, and proximal colon segments and using Metoprolol as the control. The ileum segment was found to be the best site for the absorption of DVS-233. The permeability ratios of DVS versus Metoprolol were found to be 0.36, 0.54, and 0.11 in duodenum-jejunum, ileum, and colon respectively.

Table 39: Intestinal Absorption of DVS Using Rat Perfusion Model

GI Segment	DVS-233		Metoprolol	
	Mean P_{eff} (µm/sec)	SD	Mean P_{eff} (µm/sec)	SD
Duodenum-Jejunum	0.0912	0.0067	0.2500	0.0113
Ileum	0.1730	0.0220	0.3220	0.0072
Colon	0.0062	0.0031	0.0583	0.0087

The pH distribution coefficients for DVS are provided in the following table

Table 40: pH Distribution Co-Efficients for DVS

pH	1.2	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0
Log D ^a	-1.14	-1.38	-2.04	-1.71	-1.58	-1.04	0.21	0.83	1.65

2.5.2 Is the proposed to-be-marketed formulation of desvenlafaxine bioequivalent to the formulation used in the primary bioavailability and clinical trials?

The proposed to be marketed formulation is quantitatively and qualitatively identical to the clinical formulation except for a minor change in the color and the debossing of the tablets. The 200 mg to-be-marketed formulation (TBM) formulation was bioequivalent to the clinical-trial formulation for both AUC and Cmax. The dissolution profiles are similar. A Level A In Vitro/In Vivo Correlation (IVIVC) has been demonstrated for desvenlafaxine succinate tablets. The following tables are representative formulations for the proposed commercial tablets and the linkage between bio-batches.

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Table 41: Quantitative Composition of 100 mg DVS SR

Ingredient	Reference to Standards	Function	Theoretical Unit Dose mg/tablet
DVS-233 ^a	In-house		
Hypromellose	USP/Ph. Eur. ^c		
Microcrystalline Cellulose	NF/Ph. Eur.		
Microcrystalline Cellulose	NF/Ph. Eur.		
Talc	USP/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
Total Core Tablet Weight			
	<i>Film Coat</i>		
	In-house		
	USP/Ph. Eur.		
Total Film Coated Tablet Weight			

- a. _____ of theory.
- b. DVS-233 contains _____ as base.
- c. Tested against design space criteria as presented in drug product section P.4.1, Table P.4.1-2.

Table 42: Quantitative Composition of 200 mg DVS SR

Ingredient	Reference to Standards	Function	Theoretical Unit Dose mg/tablet
DVS-233 ^a	In-house	Active	
Hypromellose	USP/Ph. Eur. ^c		
Microcrystalline Cellulose	NF/Ph. Eur.		
Talc	USP/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
Total Core Tablet Weight			
	<i>Film Coat</i>		
	In-house		
	USP/Ph. Eur. C		
Total Film Coated Tablet Weight			

- a. _____
 b. DVS-233 contains _____ as base.
 c. Tested against design space criteria as presented in drug product section P.4.1, Table P.4.1-2.
 d. _____

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

Bioequivalence was demonstrated between the 200 mg DVS SR tablets manufactured at the Puerto Rico (PR) and the Canadian (CAN) site. The commercial product would be manufactured at PR site. Tablets manufactured at the CAN site were used in the clinical and bio-studies. The 50, 100 and 200 mg tablets used in phase 1 studies were demonstrated to be bioequivalent to a prototype DVS SR 75 mg. A Level A IVIVC was developed and was used to demonstrate that similar exposure would be achieved when the commercial instead of the formulations used in the pivotal bioavailability and clinical studies are administered. The Level A IVIVC was reviewed and determined to be acceptable. The following tables provide the pharmacokinetic results from the pivotal bioequivalence study using the 200 mg formulation and summary of the linkages between desvenlafaxine formulations used in various studies.

Table 43: Results of Pharmacokinetic Analysis of Desvenlafaxine for Pivotal Bioequivalence Study Using 200 mg Formulations

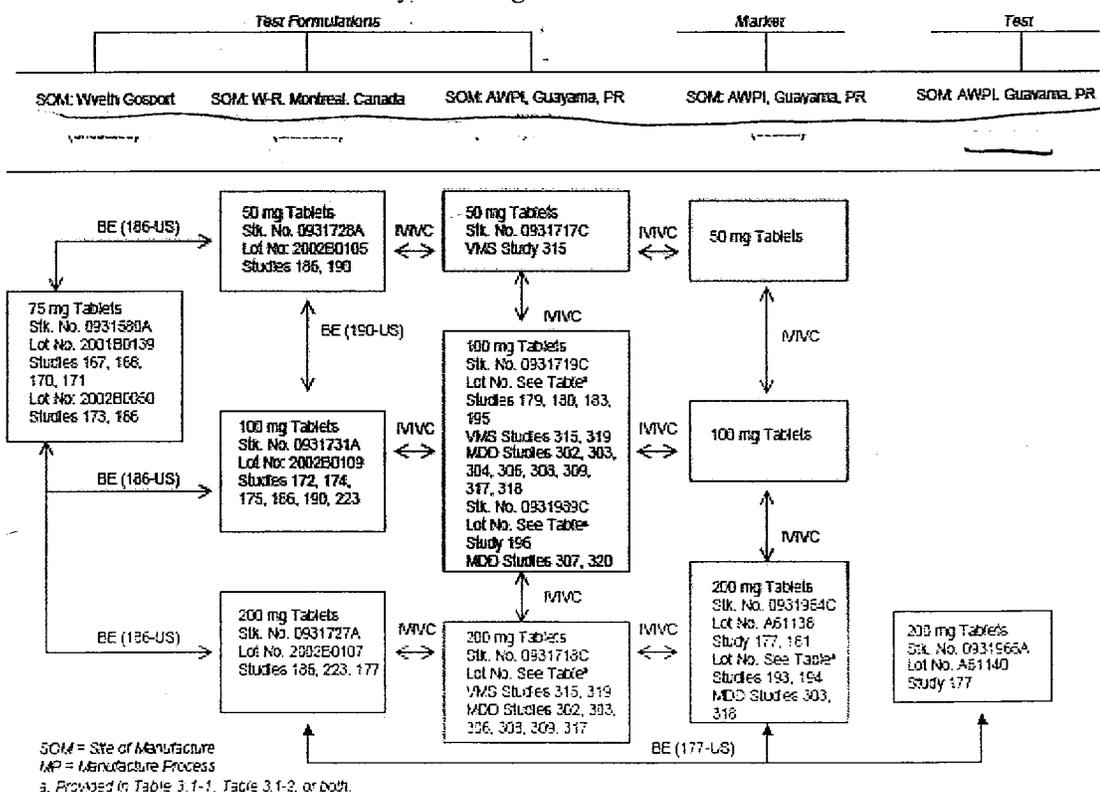
DVS SR 200-mg Product	C _{max} (ng/mL)	t _{max} (h)	AUC _T (ng•h/mL)	AUC (ng•h/mL)
CAN (clinical-trial formulation)	324±99 ^a	7.1±3.6	8332±2873	8540±2989
PR (TBM formulation)	330±75	8.8±5.4	8780±2448	8984±2536
PR fast-release	390±97	6.4±2.5	8706±2474	8870±2547

Relative Bioavailability 90% Confidence Limits (Reference=DVS SR 200 mg CAN Formulation)				
PR	94-108%	--	94-119%	94-119%
PR fast-release	115-132%	--	96-118%	96-117%

Abbreviations: AUC=area under the concentration-versus-time curve; AUC_T=area under the concentration-versus-time curve to the last quantifiable concentration at time T; C_{max}=peak concentration; CAN=Montreal, Canada, formulation (reference); DVS=desvenlafaxine succinate; PR=Puerto Rico formulation; PR fast-release=Puerto Rico fast-dissolving formulation; SR=sustained release; TBM=to be marketed; t_{max}=time to peak concentration.

a. Mean ± standard deviation.

Table 44: Summary of Linkages Between DVS Formulations



Two level A IVIVCs have been established, one each for the low and high strength SR tablets. For the low strength SR tablet (50 mg), which contains HPMC, the in vitro release was independent of the dissolution conditions. The high strength SR tablet (200 mg) contains and its dissolution was dependent on dissolution conditions. DVS tablets have been manufactured in strengths of 50, 75, 100 and 200 mg. The major difference among the various strength SR tablets is

Plasma DVS concentration-time profile data from DVS SR tablets and their respective in vitro dissolution profiles were used to develop two Level A IVIVCs. A single Level A IVIVC was not possible for the DVS-SR tablets

The dissolution data for the 50 mg SR tablets were used to estimate the plasma DVS concentration-time profile in order to assess the internal predictability of the IVIVC. External predictability was evaluated using data from the 75 and 100 mg SR tablets which were administered in the same study as the 50 mg SR tablet. The correlations were used to determine that dissolution could be set about the mean dissolution profile of a DVS SR tablet, and would predict bioequivalence with respect to Cmax and AUC of SR tablets with in vitro release at the limits of dissolution.

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Table 45: Validation of DVS SR Tablet Level A IVIVC Model Developed and Validated Without Normalization of Plasma Desvenlafaxine Concentration-Time Data Across Studies

Internal Predictability						
Batch	Observed AUC	Predicted AUC	Absolute % PE	Observed C _{max}	Predicted C _{max}	Absolute % PE
1x200 mg A61140 <u>Study 177</u>	8870	9065	2.20	362	341	5.62
1x200 mg A61138 <u>Study 177</u>	8984	9178	2.16	314	307	2.01
	Average % PE		2.18	Average % PE		3.81
External Predictability						
Batch	Observed AUC	Predicted AUC	Absolute % PE	Observed C _{max}	Predicted C _{max}	Absolute % PE
1x200 mg 2002B0107 <u>Study 177</u>	8540	8722	2.13	308	309	0.36
2x50 mg 2002B0105 <u>Study 186</u>	4695	4843	3.16	169	155	8.00
1x100 mg 2002B0109 <u>Study 186</u>	4542	4677	2.96	173	157	9.53

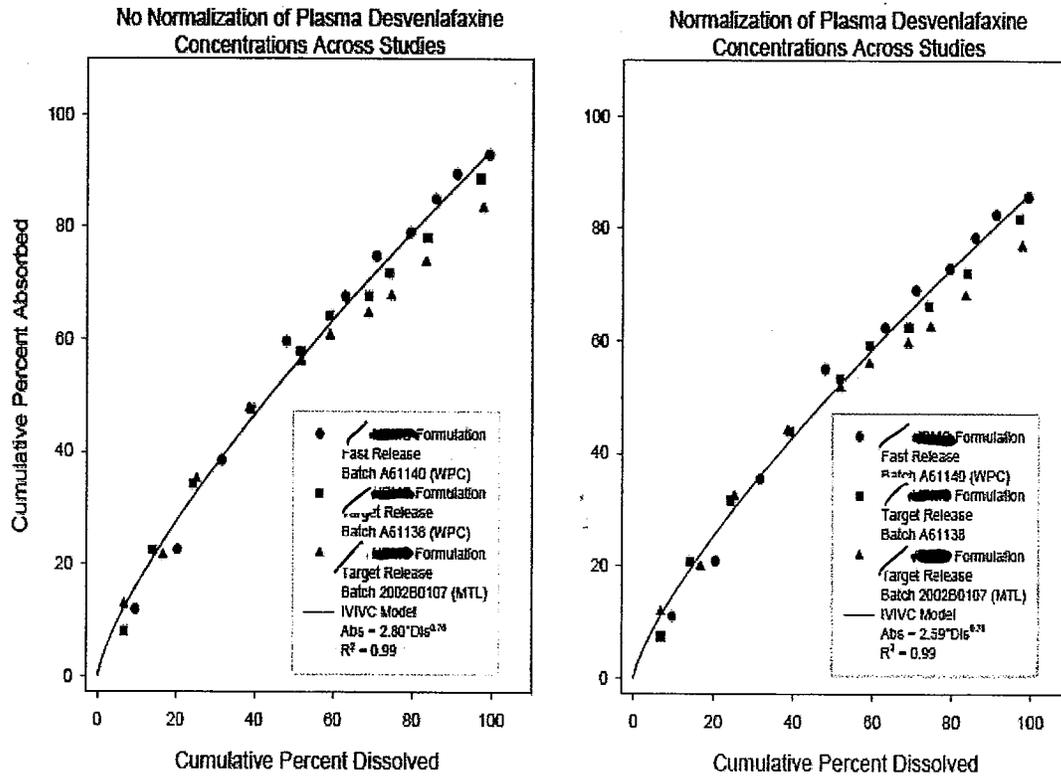
Internal Validation Criteria: Average %PE < 10% and no individual %PE > 15%

External Validation Criteria: No individual %PE > 10%

AUC units: ng·hr/mL

C_{max} units: ng/mL

Fig 15: Absorption of Desvenlafaxine versus Dissolution of Desvenlafaxine Succinate Relationships for 200 mg DVS-233 Extended Release Tablets



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2.5.3. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of DVS SR in relation to meals or meal types.

Following administration with low, medium, and high-fat meals, increases in C_{max} of approximately 16% (observed confidence interval: 107.1 -125.1%) were observed only following a high-fat meal. There was no statistically significant change in AUC values for any of the meals. Based on bioequivalence standards (90% CI: 80 -125%), AUC values were similar between the fasted and all fed conditions. DVS SR can be administered without regard to food.

A pivotal food-effect study was undertaken to examine the effects of low-, medium-, and high-fat meals on desvenlafaxine pharmacokinetic parameters after administration of DVS SR tablets manufactured in Guayama, Puerto Rico, the commercial manufacturing site. The highest strength of DVS SR (200-mg) tablet was administered orally. Subjects received a single dose of desvenlafaxine SR under 4 dosing conditions. The study had at least 29 subjects complete each of the 4 treatment conditions (fasted, low-fat, medium-fat, and high-fat). Each dose was separated by a washout interval of at least 4 days. Subjects were randomly assigned to a sequence of the following treatments:

- Treatment A: Single 200-mg dose of DVS SR under fasting conditions.
- Treatment B: Single 200-mg dose of DVS SR administered 5 minutes after completion of a low-fat breakfast.
- Treatment C: Single 200-mg dose of DVS SR administered 5 minutes after completion of a medium-fat breakfast.
- Treatment D: Single 200-mg dose of DVS SR administered 5 minutes after completion of a high-fat breakfast.

The fasted arm was preceded by an overnight fast of at least 10 hours. All breakfasts were consumed in their entirety over 25 minutes

The statistical comparison is provided of the various types of food with fasting conditions is provided in the following table.

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Table 46: Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters

4-Period Crossover Analysis of Variance of Log-Transformed Data			Treatment ^a		
Effect		p-Value	Low-Fat Relative Bioavail. 90% C.L.	Medium-Fat Relative Bioavail. 90% C.L.	High-Fat Relative Bioavail. 90% C.L.
C_{max} (ng/mL) ^b	Sequence	0.077	101.1%-117.2%	98.6%-114.5%	107.8%-125.05%
	Treatment	0.013			
	Period	0.860			
AUC (ng·h/mL) ^c	Sequence	0.282	99%	105%	96%
	Treatment	0.411	90.9%-108.3%	96.4%-114.9%	88.2%-105.1%
	Period	0.354			
AUC _T (ng·h/mL) ^c	Sequence	0.228	99%	105%	97%
	Treatment	0.512	91.1%-108.6%	95.9%-114.4%	88.5%-105.6%
	Period	0.370			

Abbreviations: AUC=area under the concentration-versus-time curve; AUC_T=area under the concentration-versus-time curve to the last quantifiable concentration at time T; Bioavail.=bioavailability; C.L.= confidence limits.

a. Compared with fasting treatment.

b. Subject 181-001-000022 (low-fat treatment) was excluded.

c. Subjects 181-001-000022 (low-fat treatment) and 181-001-000005 (fasting treatment) were excluded.

2.5.4. When would a fed BE study be appropriate and was one conducted?

It is recommended that DVS SR be taken without regard to food. Therefore, a fed BE study is not recommended. The sponsor did not conduct a fed BE study.

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Fig 16: Dissolution Profiles of DVS from DVS SR 50, 75 and 100 mg Tablets Used in Bioavailability Studies (Studies 167, 186, 190)

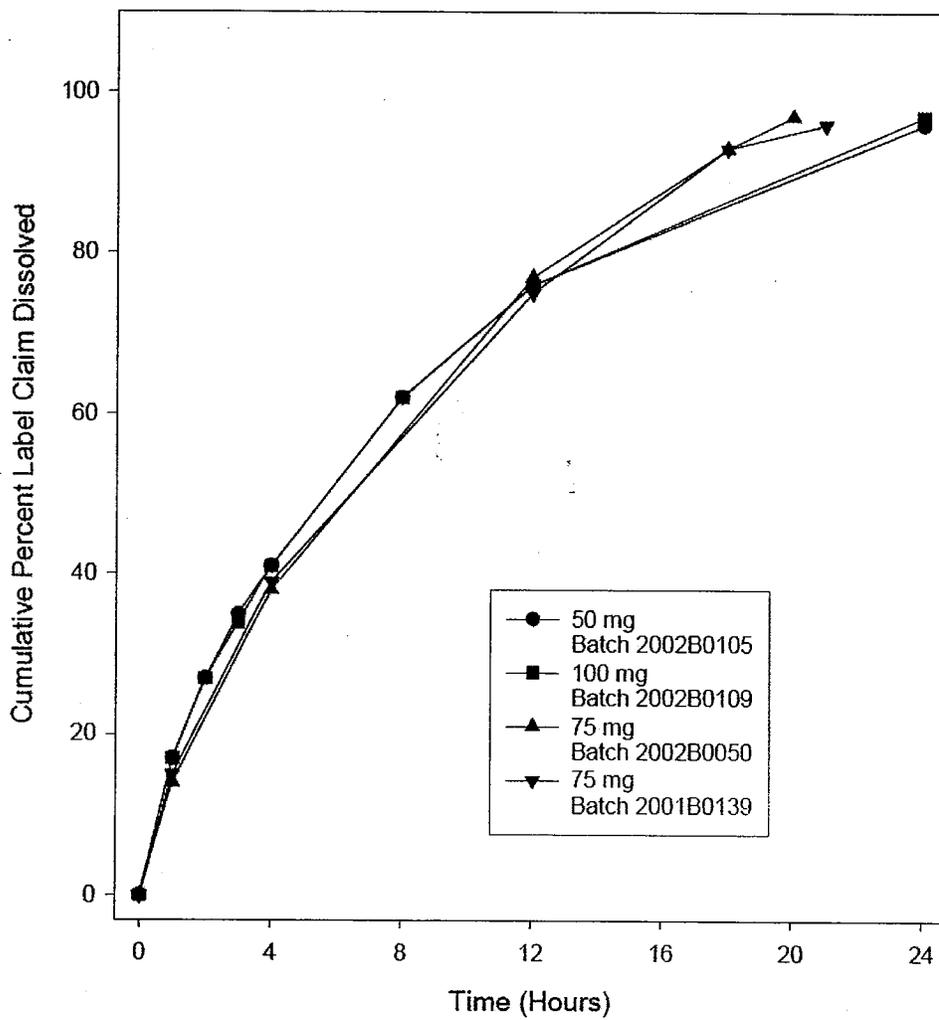


Fig 17: Dissolution Profiles of DVS from DVS SR 200 mg Tablets Used in Bioavailability Study (Pivotal Study 177)

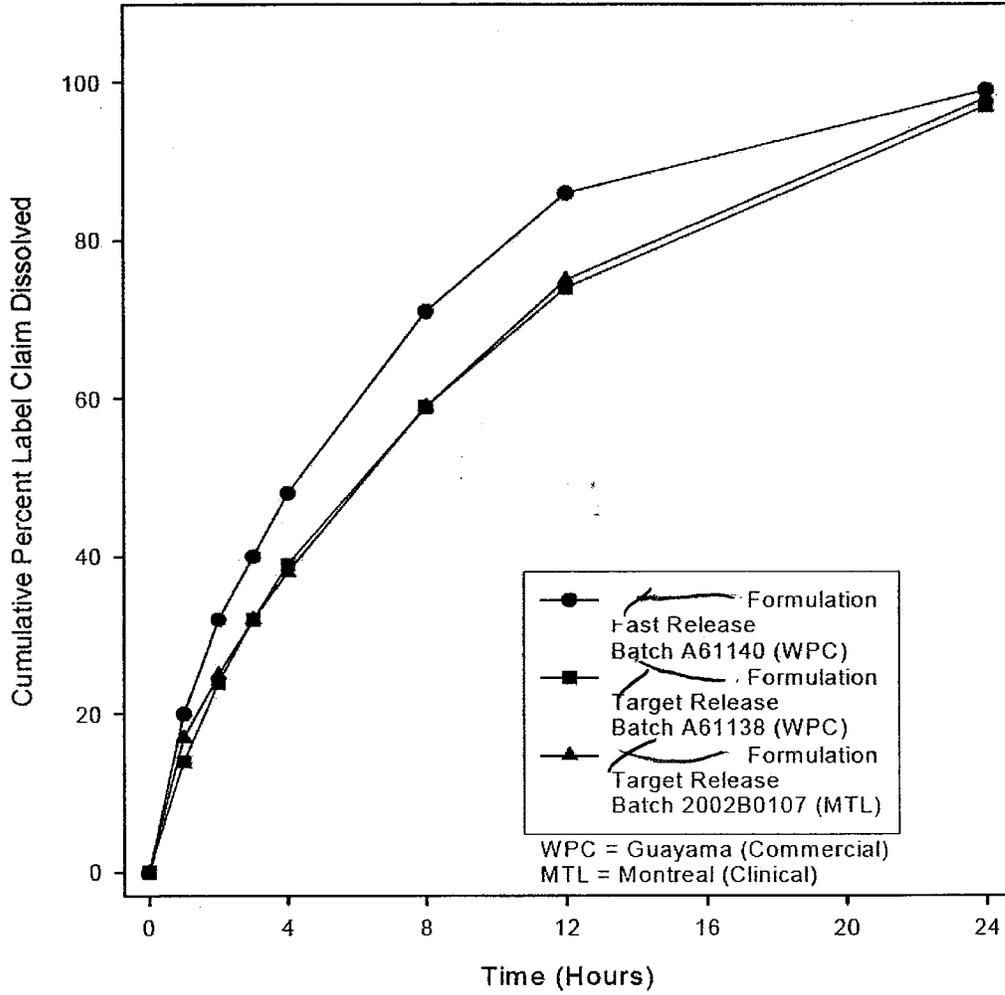


Fig 18: Absorption of DVS versus Dissolution of DVS Relationship for DVS SR 50 mg Tablets

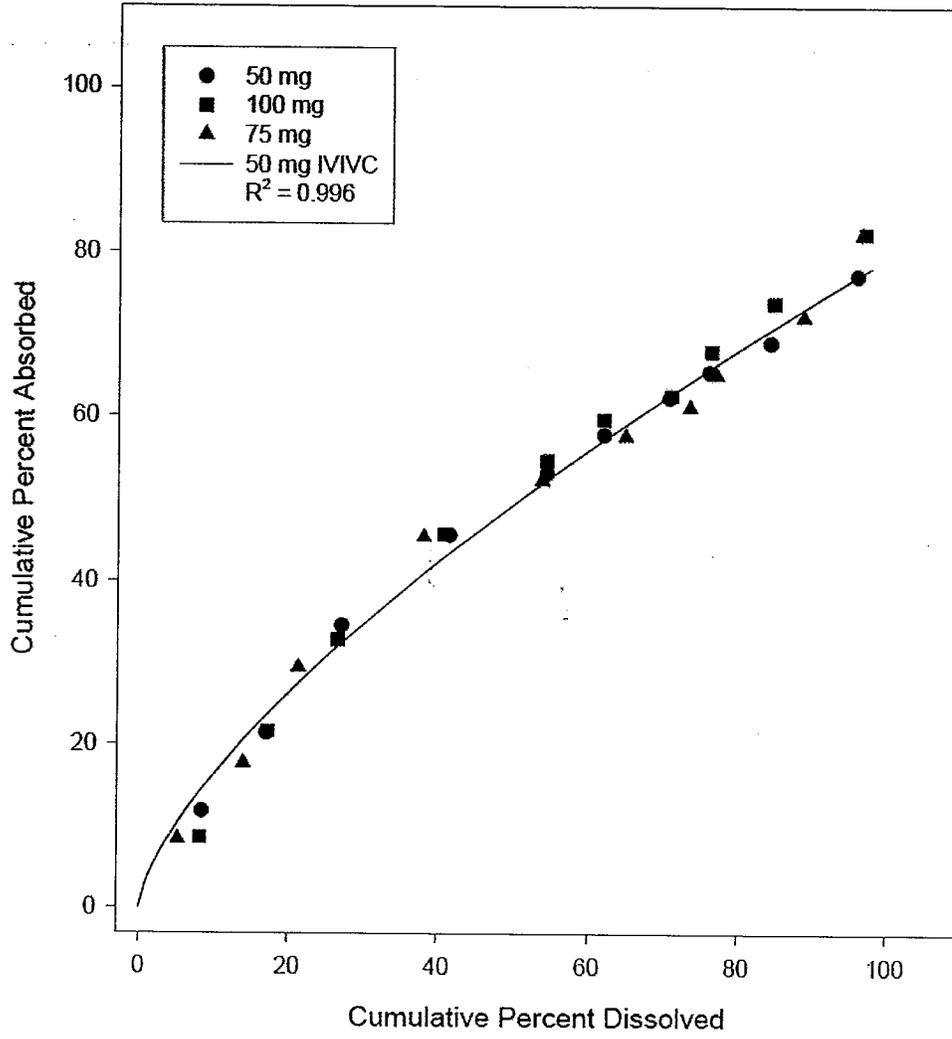


Fig 19: Absorption of DVS versus Dissolution of DVS Relationship for DVS SR 200 mg Tablets

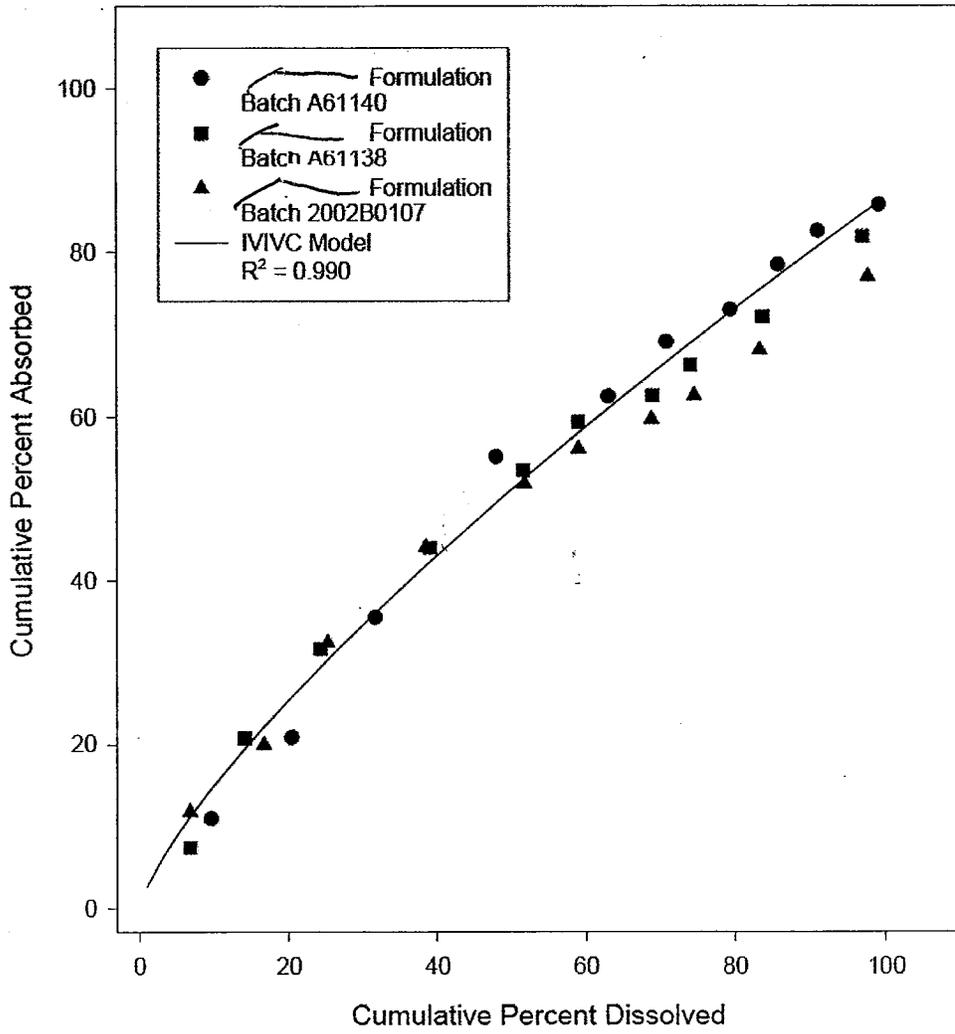


Table 47

6.3 Dissolution of DVS-233 SR 50 mg Tablets: Evaluation of pH			
Batch A35065			
Media	Time (hr)	AVG (%)	Range (%)
			
0.9% NaCl	2	26	
	4	42	
	8	63	
	12	77	
	24	97	
Dissolution conditions: USP apparatus 1 (baskets), 100 rpm, 0.9 L of media, 37°C Reference media: 0.9% NaCl.			

Table 48

6.4 Dissolution of DVS-233 SR 200 mg Tablets: Evaluation of pH							
Media	Time (hr)	Batch A61140		Batch A61138		Batch A43079	
		AVG (%)	Range (%)	AVG (%)	Range (%)	AVG (%)	Range (%)



0.9% NaCl	2	32	[24	[25	[
	4	48		39		39	
	8	71		59		60	
	12	86		74		76	
	24	99		97		97	
Dissolution conditions: USP apparatus 1 (baskets), 100 rpm, 0.9L of media, 37°C Reference media: 0.9% NaCl within each batch							

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations and is the validation complete and acceptable?

High-performance liquid chromatography (HPLC) methods with fluorescence detection were developed and used for the quantitation of desvenlafaxine in human plasma. HPLC/ultraviolet (UV) methods were also developed for the quantitation of unconjugated and total (conjugated and unconjugated) desvenlafaxine in human urine. These liquid chromatography (LC)/fluorescence and LC/UV methods also detect venlafaxine, N-desmethylvenlafaxine (NDV; metabolite specific to venlafaxine), and NODV (metabolite common to both venlafaxine and desvenlafaxine). A liquid chromatography/tandem mass spectrometry (LC/MS/MS) method was developed, validated, and used for the quantitation of desvenlafaxine, along with venlafaxine, if administered. LC/MS/MS methods for the quantitation of unconjugated and total (conjugated and unconjugated) desvenlafaxine in human urine were also developed and used. These LC/MS/MS methods also detect venlafaxine, NDV, and NODV. An LC/MS/MS method was validated and used for the quantification of desvenlafaxine in human dialysate. Methods of LC/MS/MS were developed, validated, and used for the determination of desvenlafaxine enantiomeric ratios (S:R) in human plasma. LC/MS/MS methods were developed, validated, and used in the quantification of the (R)- and (S)-enantiomers in plasma and urine. A summary of assay performance with the accuracy (% bias) and precision (% coefficient of variation) of the assay quality control samples for the plasma and urine assays for each study are contained in the following tables. The assay performance was acceptable.

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