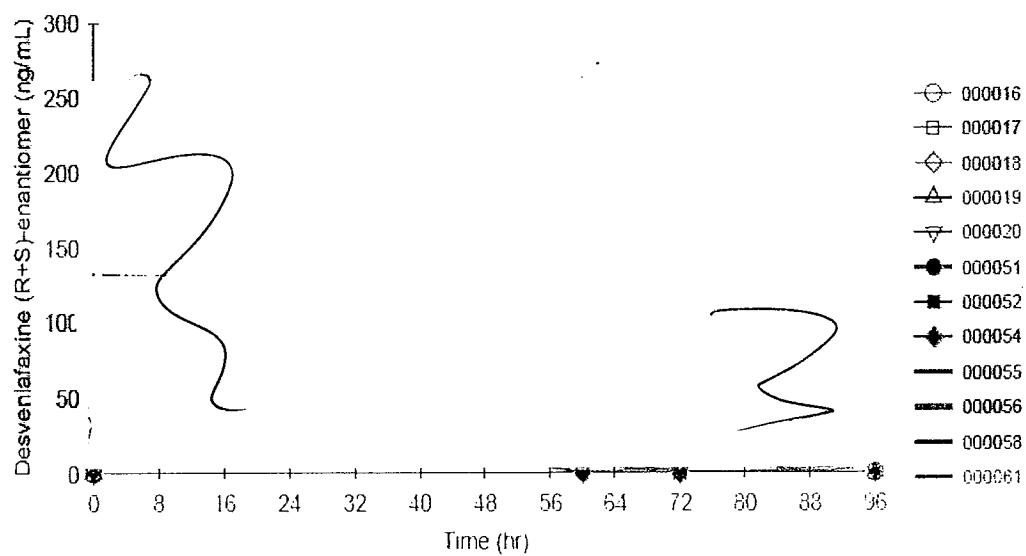


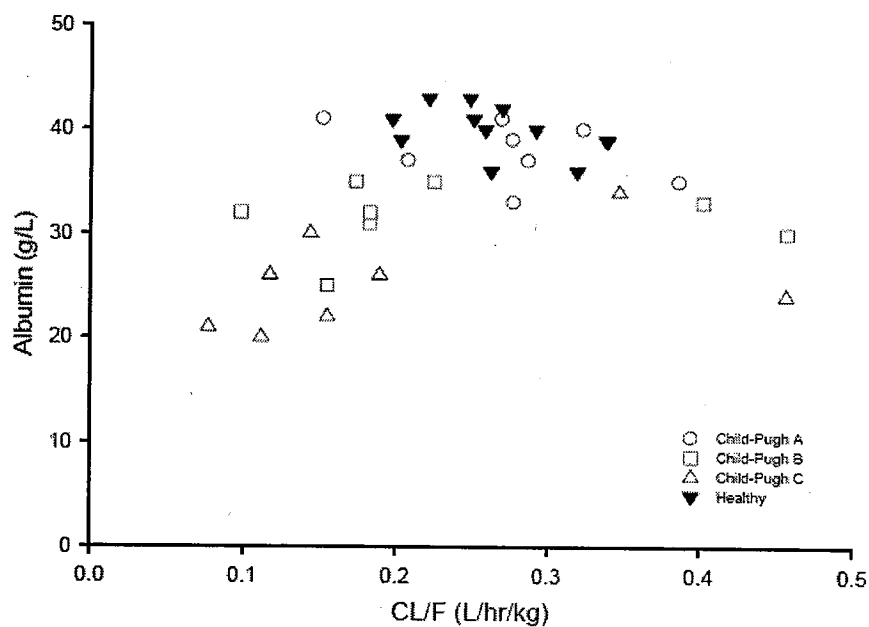
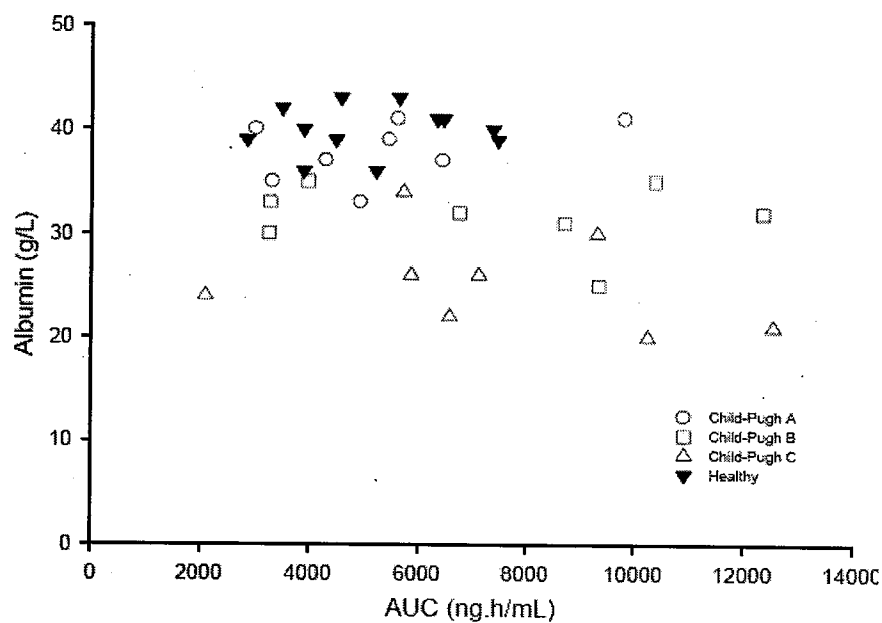
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SF 8-12. Individual plasma concentration-time profiles of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to healthy subjects

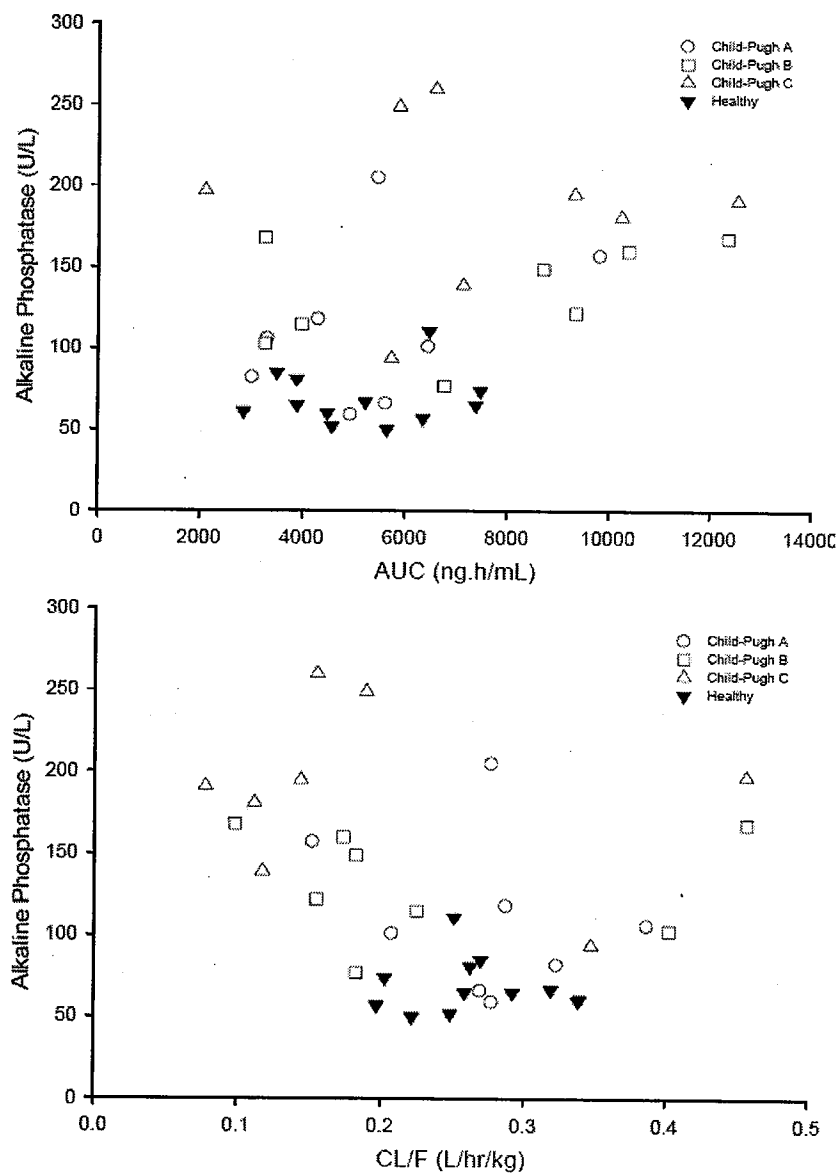
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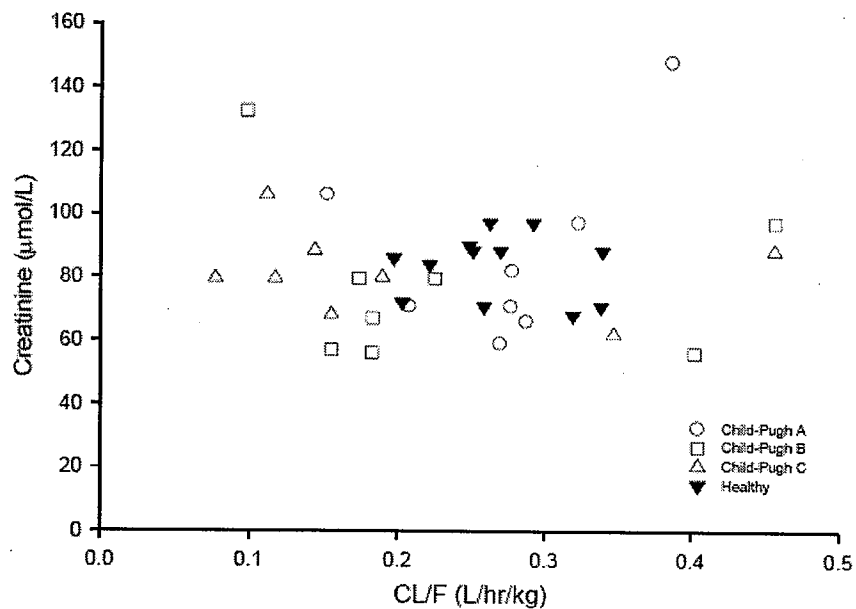
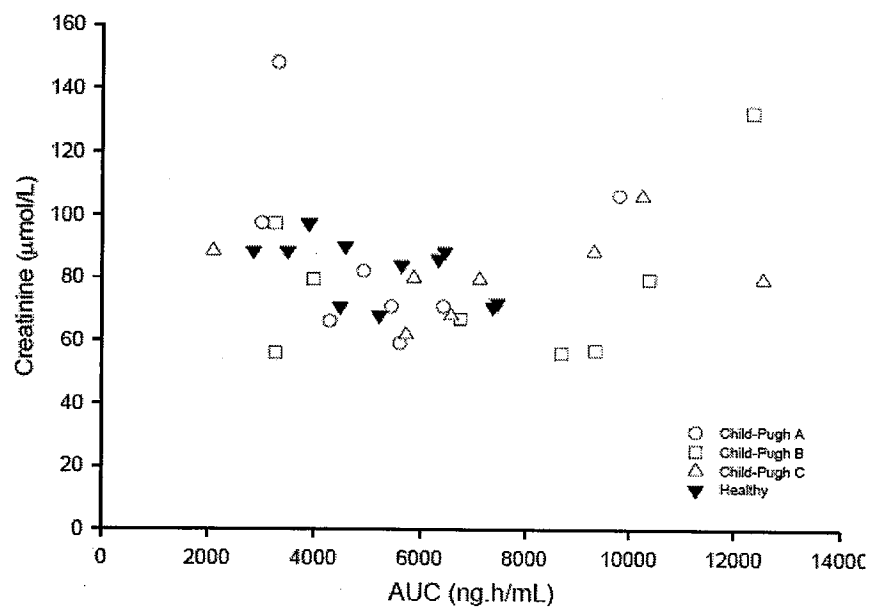
SF 8-13. Plot of albumin and area under the curve (AUC) and oral clearance (CL/F) of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with hepatic impairment (Child Pugh A, B, C) and healthy subjects



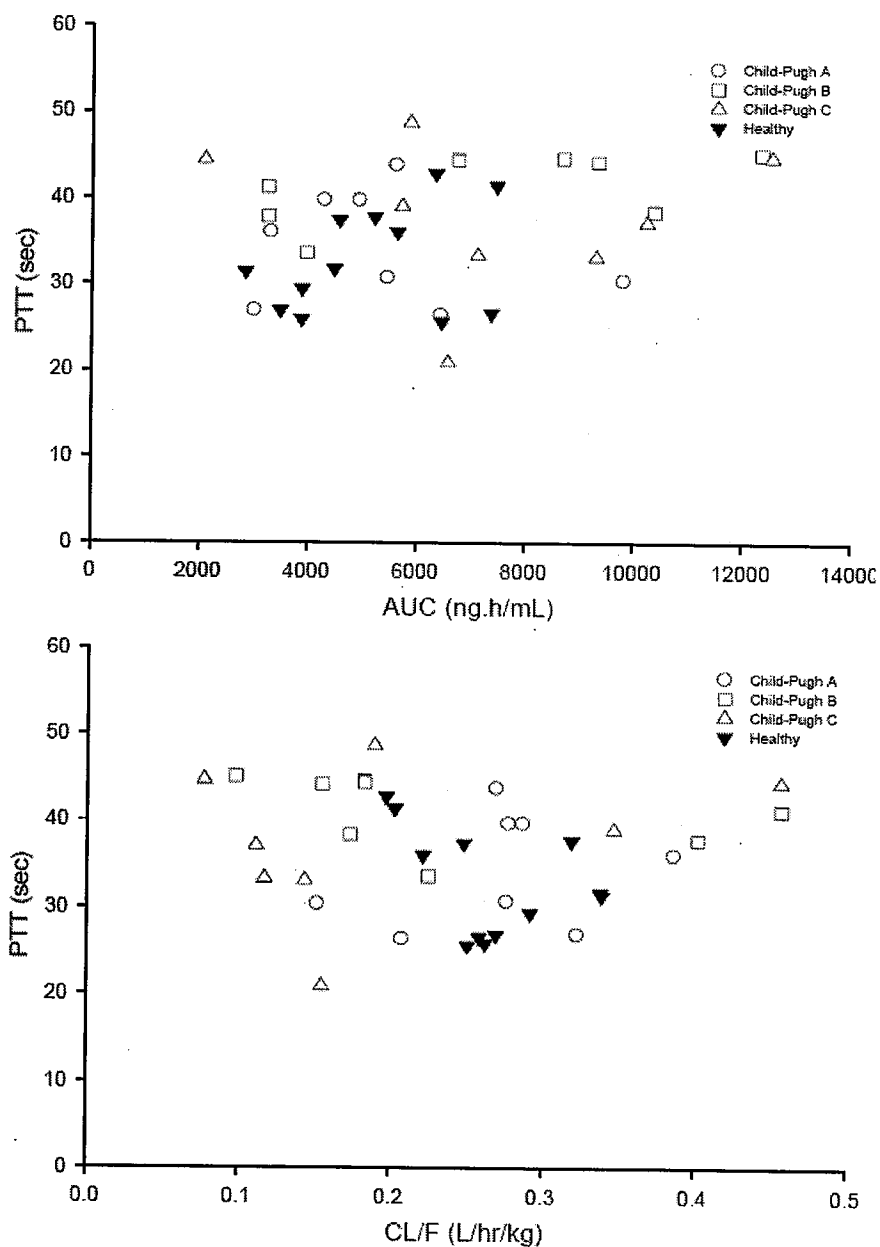
SF 8-14. Plot of alkaline phosphatase and area under the curve (AUC) and oral clearance (CL/F) of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with hepatic impairment (Child Pugh A, B, C) and healthy subjects



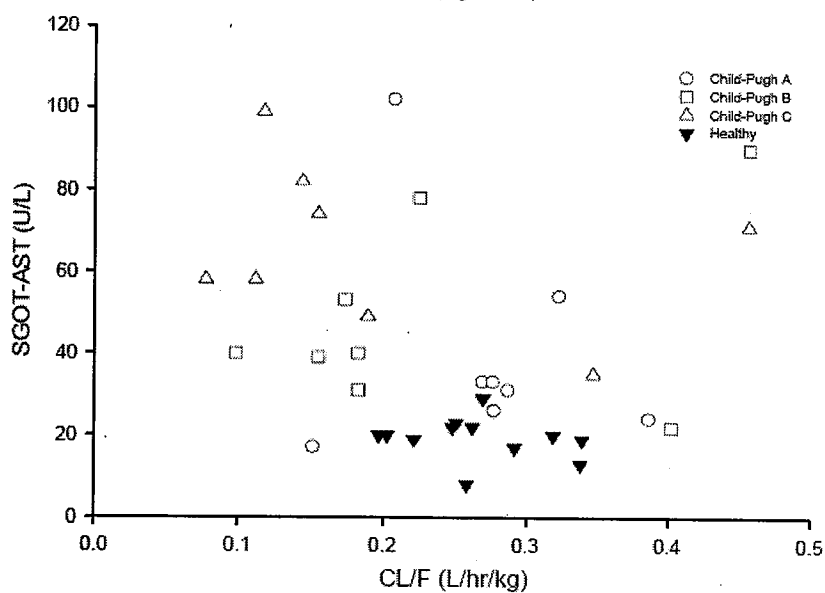
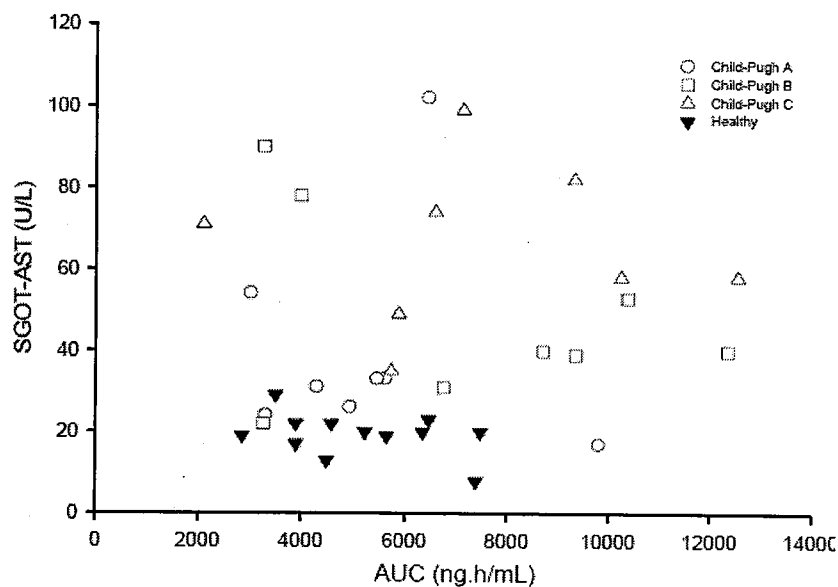
SF 8-15. Plot of creatinine and area under the curve (AUC) and oral clearance (CL/F) of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with hepatic impairment (Child Pugh A, B, C) and healthy subjects



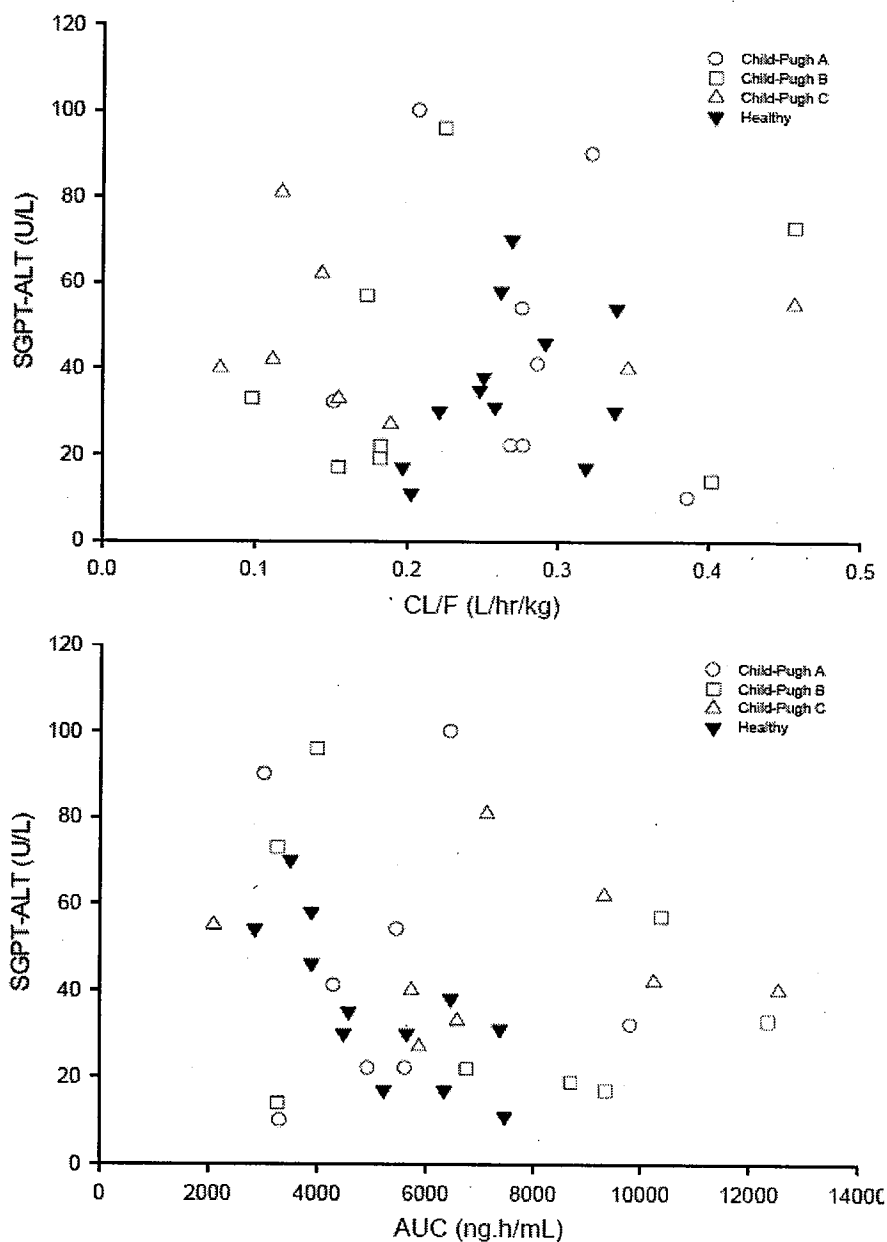
SF 8-16. Plot of partial thromboplastin time (PTT) and area under the curve (AUC) and oral clearance (CL/F) of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with hepatic impairment (Child Pugh A, B, C) and healthy subjects



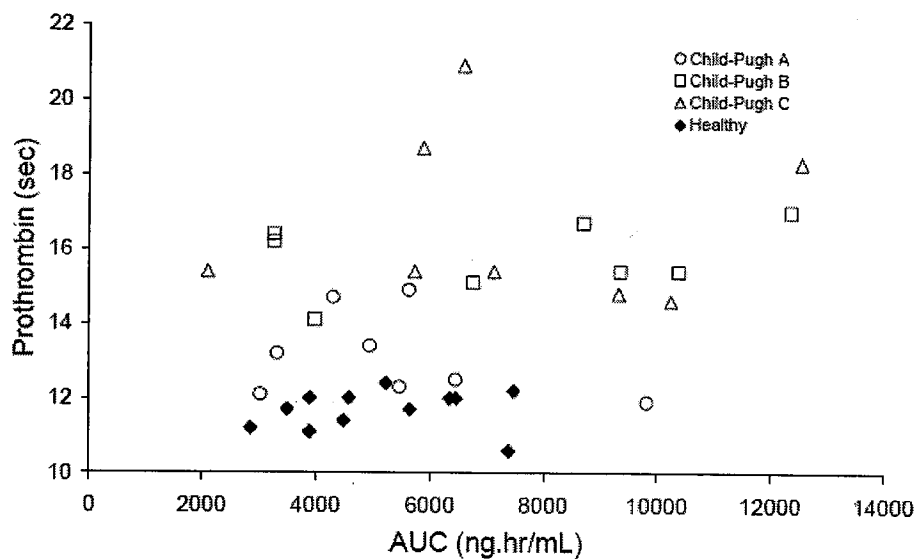
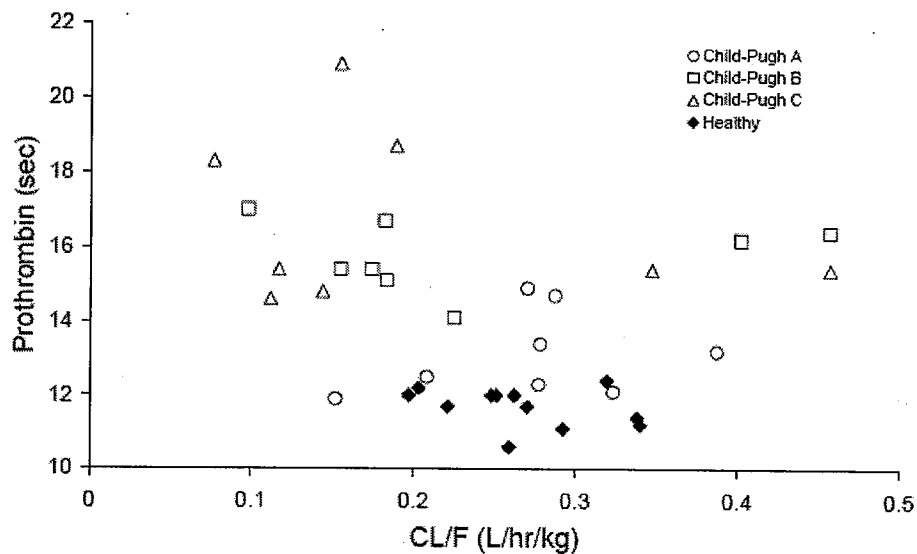
SF 8-17. Plot of aspartate transferase (SGOT-AST) and area under the curve (AUC) and oral clearance (CL/F) of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with hepatic impairment (Child Pugh A, B, C) and healthy subjects



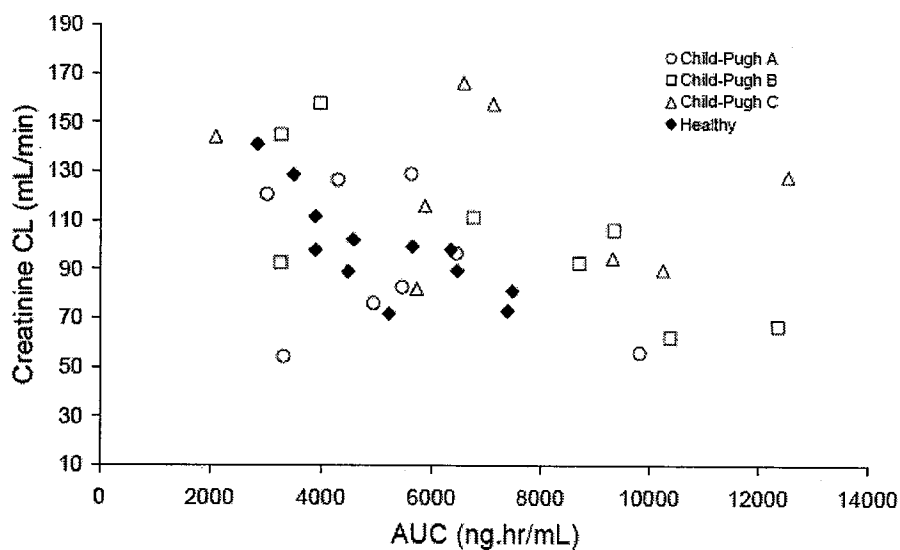
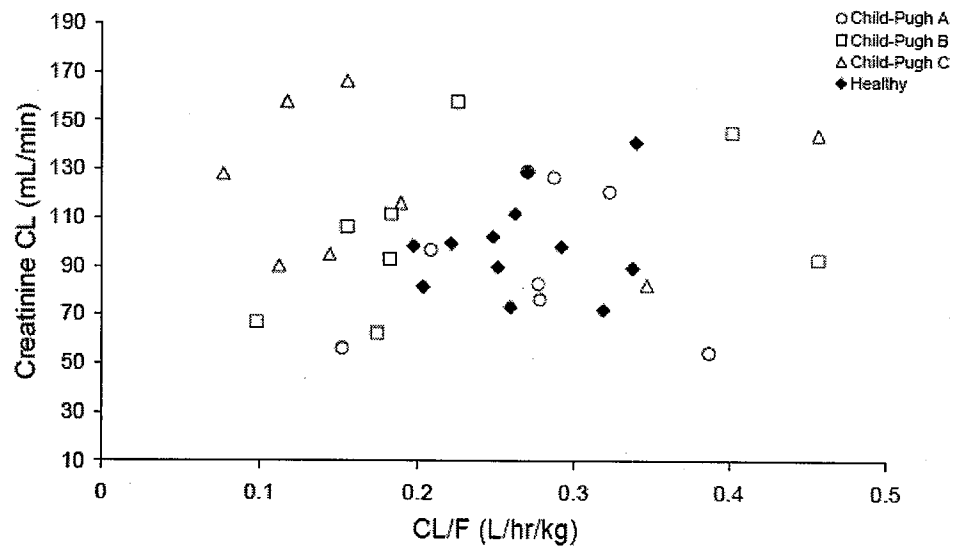
SF 8-18. Plot of alanine transferase (SGPT-ALT) and area under the curve (AUC) and oral clearance (CL/F) of (R+S)-enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with hepatic impairment (Child Pugh A, B, C) and healthy subjects



SF 8-19. Plot of prothrombin time (PT) and area under the curve (AUC) and oral clearance (CL/F) of (R+S) enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with hepat impairment (Child Pugh A, B, C) and healthy subjects



SF 8-20. Plot of creatinine clearance (CL_{CR}) and area under the curve (AUC) and oral clearance (CL/F) of (R+S) enantiomers of desvenlafaxine following single oral administration of DVS SR 100 mg to subjects with hepatic impairment (Child Pugh A, B, C) and healthy subjects



Title (Protocol 3151A1-181-US): An Open-Label, Randomized, Single-Dose, 4-Period Crossover Study To Determine The Effect Of A Low-Fat, Medium-Fat, And High fat Meal In Relationship To Fasting On The Relative Bioavailability, Pharmacokinetic Profile, Safety And Tolerability Of DVS-233 SR In Healthy Adults.

Objective: The primary objective was to assess the effect of a low-fat, medium-fat, and high-fat meal (breakfast) on the relative bioavailability and pharmacokinetic (PK) profile of desvenlafaxine succinate sustained-release formulation (DVS SR) after a single oral dose in healthy subjects. The secondary objective was to obtain additional safety and tolerability data on DVS SR when administered under different conditions to healthy subjects.

Study Design: This study was a single-dose, open-label, randomized, 4-period, 4-sequence, crossover, inpatient study. Men or nonlactating, nonpregnant women aged 18 to 45 years, inclusive were enrolled in the study. Women of childbearing potential (WOCBP) had to have a negative serum pregnancy test result within 48 hours before the start of test article administration. Body mass index of 18 to 30 kg/m² and body weight \geq 60 kg. Nonsmoker or smoker of fewer than 10 cigarettes (half a pack) per day. Ability to abstain from smoking, caffeine-containing products, alcohol, grapefruit juice, and grapefruit-containing products. The highest strength of DVS SR (200-mg) tablet (batch A61138) was administered orally. Subjects received a single dose of desvenlafaxine 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. All breakfasts were consumed in their entirety over 25 minutes.

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

Analytical Method: Concentrations of (S)- and (R)-desvenlafaxine were determined in sodium heparinized human plasma using the validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. The linear range of the assay was 2.5 to 350 ng/mL and the lower limit of quantitation (LLQ) was 2.5 ng/mL. The precision (CV) of

QC1, QC2, and QC3 samples was $\leq 7.5\%$ for (S)-DVS-233 and $\leq 6.5\%$ for (R)-DVS-233. The accuracy (%Dev) of the QC samples ranged from -9.3 to -6.6% for (S)-DVS-233 and from -10.3 to -4.1% for (R)-DVS-233. The CV of the standards was $\leq 5.4\%$ for (S)-DVS-233 and $\leq 4.5\%$ for (R)-DVS-233. The %Dev of the standards ranged from -2.0 to 1.8% for (S)-DVS-233 and from -1.9 to 1.7% for (R)-DVS-233. The r^2 values were ≥ 0.9949 for the determination of (S)-DVS-233 in human plasma and ≥ 0.9954 for the determination of (R)-DVS-233 in human plasma.

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

Results: A total of 33 healthy subjects (16 female subjects and 17 male subjects) ranging in age from 18 to 45 years (mean, 33.61 years) enrolled in the study. The subjects were black (52%), white (42%), or Asian (6%).

Summary descriptive statistics for PK parameter values for (R)-, (S)-, and (R+S)-enantiomers of desvenlafaxine, respectively, in the fasting, lowfat, medium-fat, and high-fat states are provided in the following tables. In addition, the corresponding statistical comparisons of PK parameters of (R+S)-desvenlafaxine, including the geometric mean relative bioavailability and 90% confidence limits are also provided

Table 8.1-1: Descriptive Statistics for Pharmacokinetic Parameters for (R)-Desvenlafaxine: Mean \pm SD (CV%)
[Geometric Mean]

| Parameter | Treatment | | | |
|----------------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------|
| | Fasting | Low-Fat | Medium-Fat | High-Fat |
| C_{max} (ng/mL) | 209 \pm 54.44 (26) [202] | 224 \pm 56.56 (25) [217] | 223 \pm 58.10 (26) [215] | 242 \pm 59.12 (24) [233] |
| t_{max} (h) ^a | 6.00 (4.00, 24.00) | 10.00 (4.00, 16.00) | 7.00 (4.00, 16.00) | 8.00 (4.00, 12.00) |
| $t_{1/2}$ (h) | 11.12 \pm 2.63 (24) [10.86] | 10.78 \pm 1.99 (19) [10.60] | 11.20 \pm 4.81 (43) [10.66] | 10.66 \pm 2.40 (22) [10.41] |
| AUC_T (ng \cdot h/mL) | 5275 \pm 1420 (27) [5033] | 5245 \pm 1215 (23) [5070] | 5433 \pm 1160 (21) [5288] | 5100 \pm 1292 (25) [4898] |
| AUC_{∞} (ng \cdot h/mL) | 5503 \pm 1441 (26) [5259] | 5348 \pm 1257 (23) [5168] | 5588 \pm 1284 (23) [5423] | 5200 \pm 1353 (26) [4989] |
| CL/F (L/h) | 20.67 \pm 11.10 (54) [19.19] | 20.33 \pm 8.31 (41) [19.35] | 19.6 \pm 6.49 (34) [18.44] | 21.27 \pm 9.37 (44) [20.05] |
| CL/F (L/h/kg) | 0.28 \pm 0.15 (55) [0.26] | 0.28 \pm 0.10 (37) [0.26] | 0.27 \pm 0.08 (31) [0.26] | 0.29 \pm 0.12 (43) [0.27] |

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; CL/F=apparent oral-dose clearance; C_{max} =peak concentration; CV=coefficient of variation; SD=standard deviation; $t_{1/2}$ =apparent terminal half-life; t_{max} =time to peak concentration.

a. Median (minimum, maximum) for t_{max} .

Table 8.1-2: Descriptive Statistics for Pharmacokinetic Parameters for (S)-Desvenlafaxine: Mean±SD (CV%)
[Geometric Mean]

| Parameter | Treatment | | | |
|----------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| | Fasting | Low-Fat | Medium-Fat | High-Fat |
| C_{max} (ng/mL) | 225±57.04 (25) [218] | 241±62.67 (26) [233] | 240±60.71 (25) [232] | 259±64.01 (25) [250] |
| t_{max} (h) ^a | 6.00 (4.00, 24.00) | 10.00 (4.00, 24.00) | 8.00 (4.00, 12.00) | 8.00 (6.00, 12.00) |
| $t_{1/2}$ (h) | 11.01±2.81 (26) [10.75] | 10.50±1.69 (16) [10.37] | 10.93±4.56 (42) [10.45] | 10.31±1.92 (19) [10.14] |
| AUC_T (ng·h/mL) | 5610±1507 (27) [5360] | 5578±1282 (23) [5391] | 5765±1227 (21) [5809] | 5403±1347 (25) [5187] |
| AUC (ng·h/mL) | 5859±1539 (26) [5603] | 5674±1308 (23) [5483] | 5911±1321 (22) [5740] | 5491±1388 (25) [5269] |
| Cl/F (L/h) | 19.28±9.13 (47) [18.05] | 19.20±8.15 (42) [18.24] | 18.12±6.36 (35) [17.42] | 20.17±9.07 (45) [18.98] |
| Cl/F (L/h/kg) | 0.26±0.12 (47) [0.25] | 0.26±0.10 (39) [0.25] | 0.25±0.08 (32) [0.24] | 0.27±0.12 (43) [0.26] |

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; Cl/F=apparent oral-dose clearance; C_{max} =peak concentration; CV=coefficient of variation; SD=standard deviation; $t_{1/2}$ =apparent terminal half-life; t_{max} =time to peak concentration.

a. Median (minimum, maximum) for t_{max} .

Table 8.1-3: Descriptive Statistics for Pharmacokinetic Parameters for Racemic Mixture (R+S)-Desvenlafaxine: Mean±SD (CV%) [Geometric Mean]

| Parameter | Treatment | | | |
|----------------------------|--------------------------------------|--------------------------------------|-------------------------|-------------------------|
| | Fasting | Low-Fat | Medium-Fat | High-Fat |
| C_{max} (ng/mL) | 433±111 (26) [419] | 471±117 (25) [455] ^a | 463±118 (26) [447] | 500±121 (24) [483] |
| t_{max} (h) ^a | 6.00 (4.00, 24.00) | 10.00 (4.00, 16.00) ^a | 8.00 (4.00, 16.00) | 8.00 (6.00, 12.00) |
| $t_{1/2}$ (h) | 10.73±1.69 (16) [10.60] ^b | 10.64±1.74 (16) [10.49] ^a | 11.04±4.68 (42) [10.53] | 10.39±2.13 (21) [10.18] |
| AUC_T (ng·h/mL) | 11019±2863 (26) [10541] ^b | 10797±2496 (23) [10434] ^a | 11200±2346 (21) [10907] | 10507±2609 (25) [10096] |
| AUC (ng·h/mL) | 11245±2936 (26) [10759] ^b | 10995±2558 (23) [10624] ^a | 11496±2562 (22) [11170] | 10683±2703 (25) [10259] |
| Cl/F (L/h) | 19.90±9.91 (50) [18.59] ^a | 19.81±8.32 (42) [18.83] ^a | 18.6±6.38 (34) [17.90] | 20.68±9.18 (44) [19.50] |
| Cl/F (L/h/kg) | 0.27±0.14 (50) [0.25] ^a | 0.27±0.10 (39) [0.25] ^a | 0.26±0.08 (31) [0.25] | 0.28±0.12 (43) [0.26] |

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; Cl/F=apparent oral-dose clearance; C_{max} =peak concentration; CV=coefficient of variation; SD=standard deviation; $t_{1/2}$ =apparent terminal half-life; t_{max} =time to peak concentration.

a. Median (minimum, maximum) for t_{max} .

b. Subject 181-001-000005 (fasting treatment) was excluded.

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

Table 8.1-4: Statistical Comparisons of Racemic Mixture Desvenlafaxine Pharmacokinetic Parameters

| 4-Period Crossover Analysis of Variance of Log-Transformed Data | | | Treatment ^a | | |
|---|-----------|---------|---|--|--|
| Effect | | p-Value | Low-Fat Relative Bioavail. 90% C.I. | Medium-Fat Relative Bioavail. 90% C.I. | High-Fat Relative Bioavail. 90% C.I. |
| | | | 109% | 106% | 116% |
| C_{max} (ng/mL) ^b | Sequence | 0.077 | 101.1%-117.2% | 98.6%-114.5% | 107.8%-125.05% |
| | Treatment | 0.613 | | | |
| | 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.I.= confidence limits.

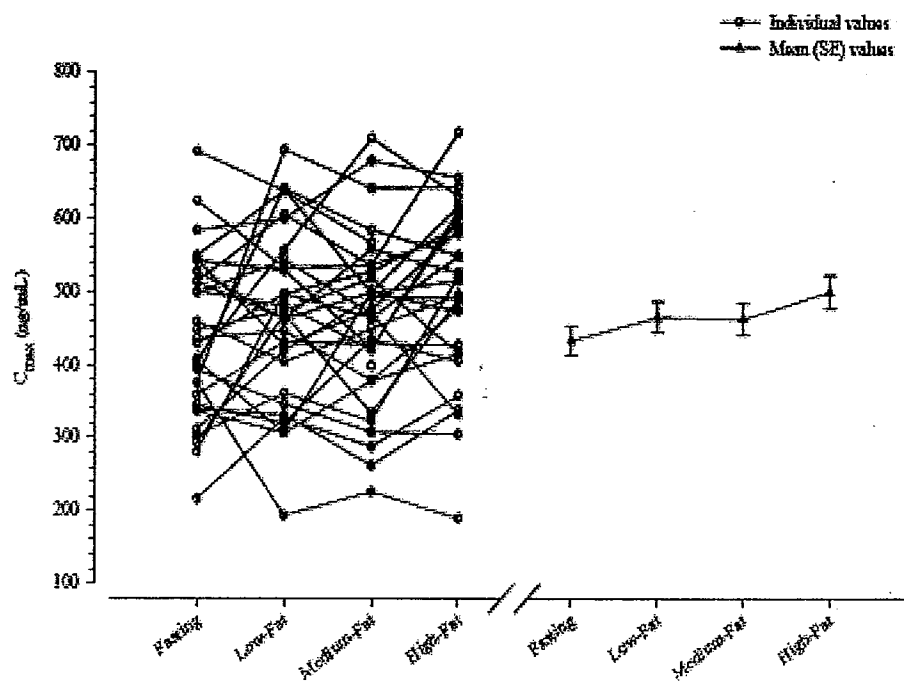
a. Compared with fasting treatment.

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

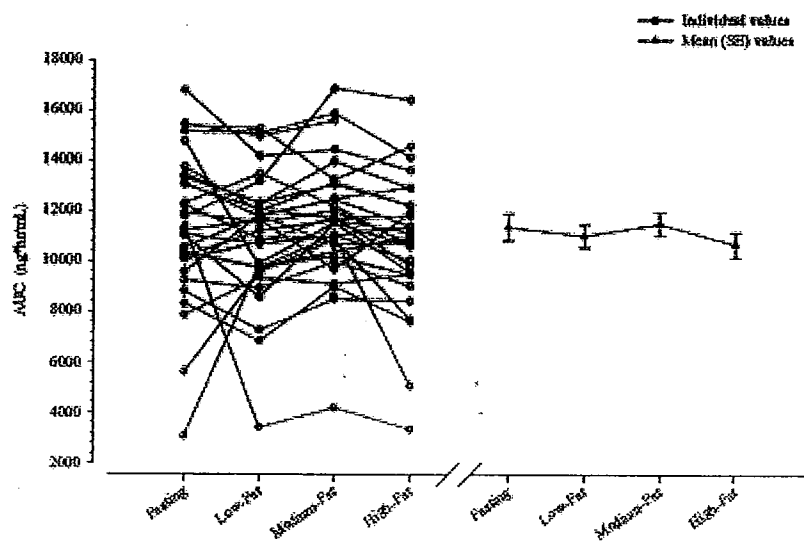
c. Subjects 181-001-000022 (low-fat treatment) and 181-001-000005 (fasting treatment) were excluded.

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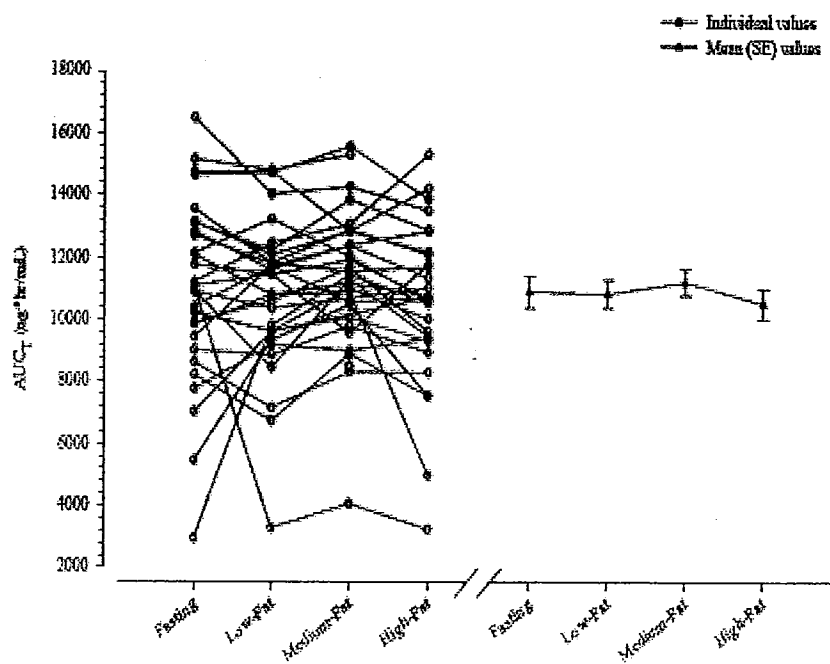
SF 8-2. (R+S)-Desvenlafaxine C_{max} in Subjects Receiving a Single 200-mg Dose of DV5 SR



SP 8-3. (R+S)-Desvenlafaxine AUC in Subjects Receiving a Single 200-mg Dose of DVS SR



SF 8-4. (R+S)-Desvenlafaxine AUC_T in Subjects Receiving a Single 200-mg Dose of DVS SR



After administration of DVS SR, concentrations of (R)-, (S)-, and (R+S)-enantiomers of desvenlafaxine were measurable in most subjects by 30 minutes after dosing for both fasting and fed conditions. After administration of DVS SR under fasting conditions, the median T_{max} occurred at approximately 6 hours after dose administration for (R)-, (S)-, and (R+S)-enantiomers of desvenlafaxine. Median T_{max} values were delayed by approximately 2 hours when DVS SR was administered after low-fat, medium fat, and high-fat meals. The delay in T_{max} under fed conditions resulted in peak concentrations for both enantiomers and racemic desvenlafaxine occurring 8 to 10 hours after administration of DVS SR. C_l/F and T_{1/2} values for (R)-, (S)-, and (R+S)-enantiomers of desvenlafaxine were not altered by administration with food. AUC and C_{max} were not significantly altered after administration with a meal.

Safety Summary: Thirty (30) of 33 subjects (91%) had AEs. The number of subjects reporting AEs for the fasting, high-fat, low-fat, and medium-fat treatments was the same as the number reporting treatment emergent AEs (TEAEs). Eight (8) subjects reported AEs during a washout period, and 4 subjects reported AEs during the follow-up period. Mild TEAEs were reported most frequently (fasting [37% of subjects], low-fat [32%], medium fat [47%], and high-fat [47%]). Moderate TEAEs were reported for the fasting (10%), low-fat (19%), medium-fat (13%), and high-fat (10%) meal conditions. The only severe TEAE was the SAE of cellulitis and sepsis in the fasting condition. The investigator considered this not related to the test drug.

In individual treatment groups, nausea occurred most frequently (fasting [27% of subjects], low-fat [29%], medium-fat [33%], and high-fat [17%]). Other frequently reported TEAEs (>10%) were asthenia (medium-fat [23%] and high-fat [17%]), dizziness (fasting [17%]), and somnolence (low-fat [13%] and medium-fat [13%]).

Conclusions: The pharmacokinetics of (R)-, (S)-, and (R+S)-enantiomers of desvenlafaxine were examined after single-dose administration of 200 mg of DVS SR under fasting, low-fat, medium-fat, and high-fat meal conditions. Plasma concentrations of (R)- and (S)-enantiomers and the PK parameters for the (R)- and (S)-enantiomers were similar. With the exception of C_{max} under high-fat meal conditions, both C_{max} and AUC for the racemic mixture of desvenlafaxine met bioequivalence test criteria (90% confidence interval entirely within 80% to 125% limits). The upper limit of the 90% confidence interval for C_{max} under high-fat treatment exceeded 125% (CI=108% to 125.05%). Food is not a significant factor in administration of DVS SR.

Reviewer's comments: *The reviewer agrees with the sponsor that food does not significantly affect the exposure of desvenlafaxine after administration of DVS SR.*

Attachments

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ST 8-9. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 224 | 10.00 | 11.73 | 5188 | 5288 |
| 2 | 145 | 8.00 | 13.10 | 5020 | 5222 |
| 4 | 218 | 10.00 | 11.51 | 5235 | 5328 |
| 5 | 174 | 8.00 | NC | 3421 | NC |
| 6 | 191 | 4.00 | 9.83 | 5635 | 5710 |
| 7 | 182 | 6.00 | 12.23 | 5393 | 5565 |
| 8 | 237 | 6.00 | 10.46 | 5855 | 5933 |
| 9 | 162 | 6.00 | 10.10 | 3604 | 3644 |
| 10 | 243 | 4.00 | 14.43 | 7578 | 7932 |
| 11 | 210 | 12.00 | 12.64 | 6296 | 6464 |
| 12 | 188 | 4.00 | 12.02 | 4251 | 4350 |
| 13 | 180 | 24.00 | 11.96 | 7186 | 7430 |
| 14 | 199 | 16.00 | 9.92 | 6372 | 6477 |
| 15 | 260 | 8.00 | 7.02 | 3986 | 4035 |
| 16 | 289 | 6.00 | 9.05 | 4630 | 4689 |
| 17 | 236 | 4.00 | 10.41 | 6057 | 6163 |
| 19 | 131 | 4.00 | 7.32 | 1318 | 1363 |
| 21 | 250 | 8.00 | 9.37 | 5479 | 5544 |
| 22 | 194 | 6.00 | 9.65 | 6107 | 6219 |
| 23 | 345 | 6.00 | 11.85 | 7204 | 7331 |
| 24 | 305 | 8.00 | 11.23 | 6739 | 6844 |
| 25 | 263 | 4.00 | 10.70 | 7924 | 8056 |
| 26 | 252 | 10.00 | 8.89 | 4933 | 5007 |
| 27 | 149 | 12.00 | 13.63 | 5521 | 5810 |

ST 8-9. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | AUC_t (ng·h/mL) | AUC (ng·h/mL) |
|---------|-------------------|---------------|---------------|-------------------|-----------------|
| 28 | 160 | 6.00 | 11.40 | 4081 | 4159 |
| 1003 | 150 | 8.00 | 10.25 | 4827 | 4915 |
| 1004 | 160 | 6.00 | 9.21 | 5258 | 5301 |
| 1005 | 108 | 8.00 | 13.93 | 2906 | 3069 |
| 1018 | 247 | 4.00 | 9.30 | 5087 | 5131 |
| 1020 | 207 | 6.00 | 9.16 | 5170 | 5221 |

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ST 8-10. Descriptive Statistics for Pharmacokinetic Parameters of (R)-Desvenlafaxine for Fasting Treatment

| | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | AUC_0 (ng*h/mL) | AUC_{∞} (ng*h/mL) |
|----------------|-------------------|---------------|---------------|-------------------|--------------------------|
| N | 30 | 30 | 29 | 30 | 29 |
| Mean | 209 | 7.73 | 10.77 | 3275 | 3434 |
| SD | 54.44 | 4.19 | 1.83 | 1420 | 1442 |
| SE | 9.94 | 0.77 | 0.34 | 259 | 268 |
| Min | 108 | 4.00 | 7.02 | 1318 | 1363 |
| Median | 203 | 6.00 | 10.46 | 3246 | 3328 |
| Max | 345 | 24.00 | 14.43 | 7924 | 8036 |
| CV% | 26 | 54 | 17 | 27 | 26 |
| Geometric Mean | 202 | 6.96 | 10.61 | 3033 | 3210 |

NC - Not calculated

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ST 8-11. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | CLF (L/h) | CLF (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|---------|-----------|--------------|----------------------|-------------------------|
| 1 | 18.91 | 0.23 | 320 | 3.94 |
| 2 | 19.15 | 0.21 | 362 | 3.90 |
| 4 | 18.77 | 0.18 | 312 | 3.03 |
| 5 | NC | NC | NC | NC |
| 6 | 17.51 | 0.27 | 249 | 3.85 |
| 7 | 17.97 | 0.22 | 317 | 3.89 |
| 8 | 16.85 | 0.25 | 254 | 3.75 |
| 9 | 27.45 | 0.35 | 400 | 5.08 |
| 10 | 12.61 | 0.20 | 262 | 4.06 |
| 11 | 15.47 | 0.25 | 282 | 4.55 |
| 12 | 22.99 | 0.27 | 399 | 4.68 |
| 13 | 13.42 | 0.18 | 232 | 3.07 |
| 14 | 15.44 | 0.24 | 221 | 3.43 |
| 15 | 24.78 | 0.40 | 251 | 4.01 |
| 16 | 21.28 | 0.27 | 278 | 3.50 |
| 17 | 16.22 | 0.27 | 244 | 4.12 |
| 19 | 73.37 | 1.04 | 774 | 10.97 |
| 21 | 18.04 | 0.26 | 244 | 3.48 |
| 22 | 16.08 | 0.29 | 224 | 3.58 |
| 23 | 13.64 | 0.25 | 233 | 4.27 |
| 24 | 14.61 | 0.21 | 237 | 3.32 |
| 25 | 12.41 | 0.23 | 192 | 3.58 |
| 26 | 19.97 | 0.27 | 256 | 3.47 |
| 27 | 17.21 | 0.18 | 338 | 3.53 |

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ST 8-11. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | C ₀ F (L/h) | C ₀ F (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|---------|------------------------|---------------------------|----------------------|-------------------------|
| 28 | 24.04 | 0.25 | 395 | 4.12 |
| 1023 | 20.34 | 0.28 | 301 | 4.21 |
| 1004 | 18.87 | 0.22 | 251 | 2.86 |
| 1005 | 33.23 | 0.36 | 668 | 7.23 |
| 1018 | 19.49 | 0.32 | 262 | 4.23 |
| 1020 | 19.15 | 0.23 | 253 | 3.69 |

NC - Not calculated

ST 8-12. Descriptive Statistics for Pharmacokinetic Parameters of (R)-Desvenlafaxine for Fasting Treatment

| | C ₀ F (L/h) | C ₀ F (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|----------------|------------------------|---------------------------|----------------------|-------------------------|
| N | 29 | 29 | 29 | 29 |
| Mean | 20.67 | 0.28 | 311 | 4.38 |
| SD | 11.10 | 0.15 | 127 | 1.54 |
| SE | 2.06 | 0.03 | 23.62 | 0.29 |
| Min | 12.43 | 0.18 | 192 | 2.86 |
| Median | 18.77 | 0.25 | 262 | 3.90 |
| Max | 73.37 | 1.04 | 774 | 10.97 |
| CV% | 54 | 53 | 41 | 37 |
| Geometric Mean | 19.19 | 0.26 | 294 | 4.01 |

NC - Not calculated

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ST 8-13. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-t} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 237 | 10.00 | 11.24 | 4910 | 4994 |
| 2 | 236 | 10.00 | 14.63 | 5556 | 5795 |
| 4 | 197 | 12.00 | 14.53 | 5168 | 5362 |
| 5 | 210 | 6.00 | 11.31 | 4640 | 4722 |
| 6 | 301 | 10.00 | 10.68 | 5441 | 5493 |
| 7 | 93.80 | 4.00 | 12.93 | 1620 | 1679 |
| 8 | 259 | 6.00 | 10.55 | 5272 | 5328 |
| 9 | 151 | 6.00 | 10.88 | 4287 | 4357 |
| 10 | 247 | 12.00 | 14.00 | 7608 | 7929 |
| 11 | 241 | 6.00 | 11.38 | 5773 | 5914 |
| 12 | 166 | 12.00 | 9.22 | 4198 | 4232 |
| 13 | 337 | 10.00 | 12.81 | 7290 | 7499 |
| 14 | 263 | 12.00 | 9.47 | 5931 | 5979 |
| 15 | 208 | 6.00 | 6.54 | 3302 | 3347 |
| 16 | 298 | 6.00 | 9.66 | 5844 | 5894 |
| 17 | 280 | 10.00 | 10.43 | 5618 | 5708 |
| 18 | 225 | 10.00 | 10.31 | 5138 | 5210 |
| 19 | 230 | 8.00 | 7.71 | 4337 | 4378 |
| 21 | 248 | 10.00 | 10.63 | 5973 | 6053 |
| 22 | 146 | 4.00 | 8.73 | 5579 | 5663 |
| 23 | 307 | 8.00 | 9.38 | 7056 | 7116 |
| 24 | 258 | 8.00 | 10.75 | 5885 | 5933 |
| 25 | 305 | 10.00 | 10.47 | 6773 | 6841 |

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ST 8-13. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _T (ng•h/mL) | AUC (ng•h/mL) |
|---------|--------------------------|----------------------|----------------------|----------------------------|---------------|
| 26 | 223 | 12.00 | 8.78 | 5570 | 5611 |
| 27 | 174 | 8.00 | 14.92 | 6140 | 6327 |
| 28 | 157 | 10.00 | 10.21 | 3343 | 3387 |
| 1003 | 202 | 6.00 | 10.24 | 5171 | 5256 |
| 1004 | 147 | 4.00 | 9.81 | 4042 | 4094 |
| 1005 | 166 | 16.00 | 12.84 | 4953 | 5121 |
| 1018 | 228 | 10.00 | 8.97 | 4814 | 4882 |
| 1020 | 211 | 8.00 | 10.11 | 5332 | 5439 |

ST 8-14. Descriptive Statistics for Pharmacokinetic Parameters of (R)-Desvenlafaxine for Low-Fat Treatment

| | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _T (ng•h/mL) | AUC (ng•h/mL) |
|----------------|--------------------------|----------------------|----------------------|----------------------------|---------------|
| N | 31 | 31 | 31 | 31 | 31 |
| Mean | 224 | 8.71 | 10.78 | 5245 | 5348 |
| SD | 56.16 | 2.85 | 1.99 | 1215 | 1257 |
| SE | 10.16 | 0.51 | 0.36 | 218 | 236 |
| Min | 93.80 | 4.00 | 6.54 | 1620 | 1679 |
| Median | 228 | 10.00 | 10.47 | 5352 | 5439 |
| Max | 337 | 16.00 | 14.92 | 7608 | 7929 |
| CV% | 25 | 33 | 18 | 23 | 23 |
| Geometric Mean | 217 | 8.22 | 10.60 | 5070 | 5168 |

ST 8-15. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | CL/F (L/h) | CL/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 1 | 20.03 | 0.25 | 325 | 4.00 |
| 2 | 17.26 | 0.19 | 364 | 3.92 |
| 4 | 18.63 | 0.18 | 391 | 3.80 |
| 5 | 21.18 | 0.25 | 346 | 4.09 |
| 6 | 18.20 | 0.28 | 280 | 4.34 |
| 7 | 59.56 | 0.73 | 1111 | 13.65 |
| 8 | 18.79 | 0.28 | 286 | 4.22 |
| 9 | 22.95 | 0.29 | 360 | 4.57 |
| 10 | 12.61 | 0.20 | 255 | 3.94 |
| 11 | 16.93 | 0.27 | 278 | 4.48 |
| 12 | 23.63 | 0.28 | 314 | 3.69 |
| 13 | 13.33 | 0.18 | 246 | 3.27 |
| 14 | 16.73 | 0.26 | 229 | 3.55 |
| 15 | 29.83 | 0.48 | 282 | 4.90 |
| 16 | 16.97 | 0.21 | 237 | 2.98 |
| 17 | 17.52 | 0.30 | 264 | 4.45 |
| 18 | 19.19 | 0.23 | 286 | 4.10 |
| 19 | 22.84 | 0.32 | 254 | 3.60 |
| 21 | 16.49 | 0.24 | 253 | 3.62 |
| 22 | 17.66 | 0.31 | 223 | 3.96 |
| 23 | 14.05 | 0.26 | 190 | 3.48 |
| 24 | 16.70 | 0.23 | 259 | 3.64 |
| 25 | 14.62 | 0.27 | 221 | 4.12 |

ST 8-15. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | CLF (L/h) | CLF (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|-----------|--------------|-----------------------|--------------------------|
| 26 | 17.82 | 0.24 | 226 | 3.06 |
| 27 | 15.32 | 0.16 | 330 | 3.44 |
| 28 | 29.52 | 0.31 | 435 | 4.53 |
| 1003 | 19.02 | 0.27 | 281 | 3.94 |
| 1004 | 24.43 | 0.28 | 346 | 3.93 |
| 1005 | 19.53 | 0.21 | 362 | 3.91 |
| 1018 | 20.48 | 0.33 | 265 | 4.29 |
| 1020 | 18.39 | 0.22 | 268 | 3.28 |

ST 8-16. Descriptive Statistics for Pharmacokinetic Parameters of (R)-Desvenlafaxine for Low-Fat Treatment

| | CLF (L/h) | CLF (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|----------------|-----------|--------------|-----------------------|--------------------------|
| N | 31 | 31 | 31 | 31 |
| Mean | 20.33 | 0.28 | 315 | 4.21 |
| SD | 8.31 | 0.10 | 158 | 1.81 |
| SE | 1.49 | 0.02 | 28.41 | 0.32 |
| Min | 12.61 | 0.16 | 190 | 2.98 |
| Median | 18.39 | 0.27 | 280 | 3.94 |
| Max | 59.56 | 0.73 | 1111 | 13.63 |
| CV% | 41 | 37 | 50 | 43 |
| Geometric Mean | 19.35 | 0.26 | 296 | 4.03 |

ST 8-17. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 239 | 10.00 | 11.25 | 5155 | 5243 |
| 2 | 167 | 6.00 | 14.40 | 5754 | 6032 |
| 3 | 191 | 4.00 | 11.76 | 4080 | 4154 |
| 6 | 277 | 3.00 | 9.53 | 5662 | 5708 |
| 7 | 109 | 4.00 | 11.63 | 2008 | 2071 |
| 8 | 227 | 6.00 | 10.52 | 5304 | 5366 |
| 9 | 204 | 10.00 | 9.93 | 4190 | 4234 |
| 10 | 206 | 4.00 | 13.32 | 6355 | 6799 |
| 11 | 251 | 6.00 | 10.95 | 5693 | 5769 |
| 12 | 145 | 10.00 | 10.86 | 4563 | 4656 |
| 13 | 311 | 3.00 | 12.32 | 7657 | 7832 |
| 14 | 347 | 10.00 | 9.47 | 6780 | 6839 |
| 15 | 236 | 6.00 | 6.87 | 4321 | 4378 |
| 16 | 339 | 3.00 | 9.13 | 6167 | 6208 |
| 17 | 253 | 3.00 | 10.17 | 3973 | 6060 |
| 19 | 311 | 4.00 | 8.67 | 5036 | 5072 |
| 20 | 222 | 6.00 | 7.97 | 4306 | 4345 |
| 21 | 196 | 3.00 | 9.75 | 5386 | 5448 |
| 22 | 241 | 6.00 | 8.15 | 5914 | 5963 |
| 23 | 272 | 4.00 | 10.71 | 7337 | 7448 |
| 24 | 256 | 6.00 | 11.60 | 6367 | 6514 |
| 25 | 238 | 3.00 | 9.29 | 6849 | 6921 |
| 26 | 238 | 10.00 | 7.72 | 5096 | 5054 |

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ST 8-17. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _τ (ng•h/mL) | AUC (ng•h/mL) |
|---------|--------------------------|----------------------|----------------------|----------------------------|---------------|
| 27 | 138 | 8.00 | 35.00 | 6463 | 6402 |
| 28 | 134 | 4.00 | 10.47 | 3896 | 3976 |
| 1003 | 234 | 10.00 | 10.22 | 5650 | 5769 |
| 1004 | 179 | 4.00 | 10.88 | 5401 | 5507 |
| 1005 | 148 | 16.00 | 13.48 | 5555 | 5845 |
| 1018 | 276 | 10.00 | 9.94 | 5533 | 5580 |
| 1020 | 180 | 6.00 | 9.78 | 4459 | 4508 |

ST 8-18. Descriptive Statistics for Pharmacokinetic Parameters of (R)-Desvenlafaxine for Medium-Fat Treatment

| | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _τ (ng•h/mL) | AUC (ng•h/mL) |
|----------------|--------------------------|----------------------|----------------------|----------------------------|---------------|
| N | 30 | 30 | 30 | 30 | 30 |
| Mean | 223 | 7.27 | 11.20 | 5433 | 5588 |
| SD | 58.10 | 2.75 | 4.81 | 1160 | 1284 |
| SE | 10.61 | 0.50 | 0.88 | 212 | 234 |
| Min | 109 | 4.00 | 6.87 | 2008 | 2071 |
| Median | 227 | 7.00 | 10.35 | 5544 | 5644 |
| Max | 347 | 16.00 | 35.00 | 7657 | 8402 |
| CV% | 26 | 38 | 43 | 21 | 23 |
| Geometric Mean | 215 | 6.79 | 10.66 | 5233 | 5423 |

ST 8-19. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | CLF (L/h) | CLF (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|---------|-----------|--------------|----------------------|-------------------------|
| 1 | 19.07 | 0.33 | 310 | 3.81 |
| 2 | 16.38 | 0.18 | 344 | 3.71 |
| 3 | 24.07 | 0.38 | 409 | 6.49 |
| 6 | 17.52 | 0.27 | 241 | 3.73 |
| 7 | 48.28 | 0.59 | 810 | 9.93 |
| 8 | 18.64 | 0.27 | 283 | 4.17 |
| 9 | 23.62 | 0.30 | 338 | 4.29 |
| 10 | 14.71 | 0.23 | 287 | 4.44 |
| 11 | 17.33 | 0.28 | 274 | 4.42 |
| 12 | 21.48 | 0.25 | 336 | 3.95 |
| 13 | 12.77 | 0.17 | 227 | 3.01 |
| 14 | 14.62 | 0.23 | 200 | 3.30 |
| 15 | 22.84 | 0.36 | 226 | 3.61 |
| 16 | 16.11 | 0.20 | 212 | 2.67 |
| 17 | 16.30 | 0.28 | 242 | 4.08 |
| 19 | 19.71 | 0.28 | 247 | 3.49 |
| 20 | 23.01 | 0.36 | 264 | 4.12 |
| 21 | 18.35 | 0.26 | 258 | 3.70 |
| 22 | 16.77 | 0.30 | 197 | 3.21 |
| 23 | 13.43 | 0.25 | 308 | 3.30 |
| 24 | 13.35 | 0.22 | 257 | 3.62 |
| 25 | 14.45 | 0.27 | 194 | 3.61 |
| 26 | 19.79 | 0.27 | 220 | 2.59 |

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ST 8-19. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C ₁ F (L/h) | C ₁ F (L/kg) | V _d F (L) | V _d F (L/kg) |
|---------|------------------------|-------------------------|----------------------|-------------------------|
| 27 | 11.90 | 0.12 | 601 | 6.27 |
| 28 | 23.15 | 0.26 | 380 | 3.96 |
| 1003 | 17.52 | 0.25 | 258 | 3.62 |
| 1004 | 18.16 | 0.21 | 285 | 3.25 |
| 1005 | 17.11 | 0.19 | 333 | 3.60 |
| 1018 | 17.92 | 0.29 | 257 | 4.16 |
| 1020 | 22.18 | 0.27 | 313 | 3.83 |

ST 8-20. Descriptive Statistics for Pharmacokinetic Parameters of (R)-Desvenlafaxine for Medium-Fat Treatment

| | C ₁ F (L/h) | C ₁ F (L/kg) | V _d F (L) | V _d F (L/kg) |
|----------------|------------------------|-------------------------|----------------------|-------------------------|
| N | 30 | 30 | 30 | 30 |
| Mean | 19.16 | 0.27 | 300 | 4.10 |
| SD | 6.49 | 0.08 | 136 | 1.36 |
| SE | 1.18 | 0.02 | 22.59 | 0.25 |
| Min | 11.90 | 0.12 | 194 | 2.67 |
| Median | 17.72 | 0.27 | 261 | 3.76 |
| Max | 48.78 | 0.59 | 510 | 9.95 |
| CV% | 34 | 27 | 42 | 32 |
| Geometric Mean | 13.44 | 0.16 | 234 | 3.95 |

ST 8-21. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng•h/mL) | AUC (ng•h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 305 | 10.00 | 10.80 | 4716 | 4801 |
| 2 | 244 | 6.00 | 14.34 | 5334 | 5737 |
| 4 | 247 | 10.00 | 14.38 | 5332 | 5739 |
| 5 | 204 | 6.00 | 12.81 | 5304 | 5343 |
| 6 | 267 | 10.00 | 8.69 | 5085 | 5148 |
| 7 | 90.60 | 6.00 | 11.21 | 1580 | 1627 |
| 8 | 160 | 6.00 | 9.43 | 2434 | 2470 |
| 9 | 193 | 12.00 | 10.59 | 4377 | 4423 |
| 10 | 302 | 10.00 | 13.45 | 7236 | 7442 |
| 11 | 286 | 10.00 | 10.56 | 5731 | 5804 |
| 12 | 142 | 6.00 | 9.18 | 4309 | 4239 |
| 13 | 304 | 10.00 | 12.44 | 6782 | 6937 |
| 14 | 330 | 6.00 | 9.14 | 6344 | 6385 |
| 15 | 282 | 10.00 | 6.18 | 3689 | 3722 |
| 16 | 318 | 8.00 | 9.19 | 5606 | 5645 |
| 17 | 330 | 4.00 | 8.98 | 5637 | 5706 |
| 19 | 255 | 10.00 | 7.01 | 4618 | 4646 |
| 21 | 280 | 10.00 | 8.33 | 4725 | 4775 |
| 22 | 301 | 8.00 | 8.90 | 6152 | 6201 |
| 24 | 284 | 6.00 | 12.28 | 6064 | 6169 |
| 25 | 246 | 6.00 | 9.28 | 6421 | 5481 |
| 26 | 228 | 10.00 | 9.15 | 5081 | 5119 |
| 27 | 247 | 8.00 | 17.46 | 7561 | 8170 |

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ST 8-21. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | $AUC_0-\infty$ (ng·h/mL) | AUC (ng·h/mL) |
|---------|-------------------|---------------|---------------|--------------------------|-----------------|
| 28 | 161 | 8.00 | 10.39 | 3907 | 3966 |
| 1003 | 240 | 8.00 | 11.26 | 4724 | 4830 |
| 1004 | 199 | 6.00 | 10.55 | 4496 | 4582 |
| 1005 | 177 | 6.00 | 13.05 | 3993 | 4108 |
| 1018 | 258 | 10.00 | 9.27 | 5005 | 5040 |
| 1020 | 228 | 8.00 | 9.98 | 5479 | 5557 |

ST 8-22. Descriptive Statistics for Pharmacokinetic Parameters of (R)-Desvenlafaxine for High-Fat Treatment

| | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | $AUC_0-\infty$ (ng·h/mL) | AUC (ng·h/mL) |
|----------------|-------------------|---------------|---------------|--------------------------|-----------------|
| N | 29 | 29 | 29 | 29 | 29 |
| Mean | 242 | 8.07 | 10.66 | 5100 | 5200 |
| SD | 59.12 | 2.03 | 2.40 | 1292 | 1353 |
| SE | 10.98 | 0.38 | 0.44 | 242 | 251 |
| Min | 90.80 | 4.00 | 6.18 | 1580 | 1627 |
| Median | 247 | 8.00 | 10.56 | 5085 | 5148 |
| Max | 330 | 12.00 | 17.46 | 7561 | 8170 |
| CV% | 24 | 25 | 22 | 25 | 26 |
| Geometric Mean | 233 | 7.81 | 10.41 | 4898 | 4989 |

ST 8-23. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 1 | 20.83 | 0.26 | 325 | 4.00 |
| 2 | 17.37 | 0.19 | 339 | 3.87 |
| 4 | 17.43 | 0.17 | 361 | 3.51 |
| 5 | 18.71 | 0.22 | 346 | 4.09 |
| 6 | 19.42 | 0.30 | 244 | 3.77 |
| 7 | 61.48 | 0.76 | 994 | 12.21 |
| 8 | 40.48 | 0.60 | 551 | 8.12 |
| 9 | 22.61 | 0.29 | 345 | 4.38 |
| 10 | 13.44 | 0.21 | 261 | 4.04 |
| 11 | 17.23 | 0.28 | 263 | 4.23 |
| 12 | 23.39 | 0.28 | 312 | 3.67 |
| 13 | 14.42 | 0.19 | 259 | 3.43 |
| 14 | 15.66 | 0.24 | 206 | 3.21 |
| 15 | 26.86 | 0.43 | 240 | 3.83 |
| 16 | 17.71 | 0.22 | 235 | 2.96 |
| 17 | 17.53 | 0.30 | 227 | 3.83 |
| 19 | 11.52 | 0.30 | 218 | 3.08 |
| 21 | 10.94 | 0.30 | 258 | 3.69 |
| 22 | 16.13 | 0.29 | 207 | 3.68 |
| 24 | 16.21 | 0.23 | 287 | 4.03 |
| 25 | 15.43 | 0.29 | 207 | 3.86 |
| 26 | 19.54 | 0.26 | 218 | 3.49 |
| 27 | 12.24 | 0.13 | 308 | 3.22 |

ST 8-23. Pharmacokinetic Parameters of (R)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | C ₀ F (L/h) | C ₀ F (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|---------|------------------------|---------------------------|----------------------|-------------------------|
| 28 | 15.21 | 0.26 | 383 | 4.01 |
| 1003 | 20.70 | 0.29 | 336 | 4.71 |
| 1004 | 21.92 | 0.25 | 346 | 3.95 |
| 1005 | 24.34 | 0.26 | 438 | 4.96 |
| 1018 | 19.84 | 0.32 | 265 | 4.29 |
| 1020 | 18.00 | 0.22 | 259 | 3.17 |

ST 8-24. Descriptive Statistics for Pharmacokinetic Parameters of (R)-Desvenlafaxine for High-Fat Treatment

| | C ₀ F (L/h) | C ₀ F (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|----------------|------------------------|---------------------------|----------------------|-------------------------|
| N | 29 | 29 | 29 | 29 |
| Mean | 21.27 | 0.29 | 331 | 4.25 |
| SD | 9.37 | 0.12 | 151 | 1.79 |
| SE | 1.74 | 0.02 | 28.07 | 0.33 |
| Min | 12.24 | 0.13 | 206 | 2.96 |
| Median | 19.42 | 0.26 | 265 | 3.86 |
| Max | 61.48 | 0.76 | 994 | 12.21 |
| CV% | 44 | 43 | 47 | 42 |
| Geometric Mean | 20.95 | 0.27 | 301 | 4.05 |

ST 8-33. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 225 | 8.00 | 10.67 | 5004 | 5068 |
| 2 | 149 | 8.00 | 12.27 | 4814 | 4968 |
| 4 | 241 | 10.00 | 11.31 | 5663 | 5755 |
| 5 | 185 | 8.00 | NC | 3612 | NC |
| 6 | 206 | 4.00 | 10.34 | 6117 | 6214 |
| 7 | 194 | 6.00 | 10.88 | 5638 | 5778 |
| 8 | 261 | 6.00 | 9.91 | 6225 | 6293 |
| 9 | 183 | 6.00 | 10.19 | 4166 | 4213 |
| 10 | 257 | 4.00 | 13.73 | 7180 | 7453 |
| 11 | 219 | 12.00 | 11.14 | 6409 | 6550 |
| 12 | 205 | 4.00 | 12.80 | 4764 | 4886 |
| 13 | 195 | 24.00 | 11.40 | 7466 | 7691 |
| 14 | 211 | 12.00 | 9.60 | 6730 | 6823 |
| 15 | 283 | 8.00 | 6.77 | 4238 | 4281 |
| 16 | 295 | 6.00 | 10.10 | 4809 | 4877 |
| 17 | 278 | 4.00 | 12.22 | 7082 | 7248 |
| 19 | 159 | 4.00 | 7.67 | 1634 | 1702 |
| 21 | 282 | 8.00 | 10.16 | 6654 | 6765 |
| 22 | 212 | 6.00 | 10.74 | 6703 | 6855 |
| 23 | 347 | 6.00 | 11.67 | 7959 | 8113 |
| 24 | 319 | 8.00 | 10.18 | 6812 | 6884 |
| 25 | 266 | 4.00 | 10.45 | 8572 | 8716 |
| 26 | 275 | 10.00 | 8.94 | 5469 | 5552 |

ST 8-33. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | AUC_T (ng \cdot h/mL) | AUC (ng \cdot h/mL) |
|---------|-------------------|---------------|---------------|---------------------------|-------------------------|
| 27 | 157 | 10.00 | 13.00 | 5691 | 5956 |
| 28 | 179 | 6.00 | 11.79 | 4533 | 4632 |
| 1003 | 162 | 8.00 | 9.35 | 5076 | 5145 |
| 1004 | 176 | 6.00 | 8.63 | 5657 | 5689 |
| 1005 | 108 | 8.00 | 11.71 | 2555 | 2600 |
| 1018 | 266 | 4.00 | 8.85 | 5152 | 5184 |
| 1020 | 229 | 6.00 | 10.51 | 5925 | 6006 |

NC - Not calculated

ST 8-34. Descriptive Statistics for Pharmacokinetic Parameters of (S)-Desvenlafaxine for Fasting Treatment

| | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | AUC_T (ng \cdot h/mL) | AUC (ng \cdot h/mL) |
|----------------|-------------------|---------------|---------------|---------------------------|-------------------------|
| N | 30 | 30 | 29 | 30 | 29 |
| Mean | 225 | 7.47 | 10.58 | 5610 | 5790 |
| SD | 57.04 | 3.89 | 1.55 | 1507 | 1519 |
| SE | 10.41 | 0.71 | 0.29 | 275 | 282 |
| Min | 103 | 4.00 | 6.77 | 1634 | 1702 |
| Median | 216 | 6.00 | 10.51 | 5660 | 5778 |
| Max | 347 | 24.00 | 13.73 | 8572 | 8716 |
| CV% | 25 | 52 | 15 | 27 | 26 |
| Geometric Mean | 218 | 6.80 | 10.46 | 5580 | 5540 |

NC - Not calculated

ST 8-35. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 1 | 19.73 | 0.24 | 304 | 3.74 |
| 2 | 20.13 | 0.22 | 356 | 3.84 |
| 4 | 17.38 | 0.17 | 284 | 2.76 |
| 5 | NC | NC | NC | NC |
| 6 | 16.09 | 0.25 | 240 | 3.72 |
| 7 | 17.31 | 0.21 | 272 | 3.34 |
| 8 | 15.89 | 0.23 | 227 | 3.35 |
| 9 | 23.74 | 0.30 | 349 | 4.43 |
| 10 | 13.42 | 0.21 | 266 | 4.11 |
| 11 | 15.27 | 0.25 | 245 | 3.96 |
| 12 | 20.47 | 0.24 | 378 | 4.44 |
| 13 | 13.00 | 0.17 | 214 | 2.84 |
| 14 | 14.66 | 0.23 | 203 | 3.15 |
| 15 | 23.36 | 0.37 | 228 | 3.65 |
| 16 | 20.50 | 0.26 | 259 | 3.76 |
| 17 | 13.80 | 0.23 | 241 | 4.08 |
| 19 | 58.76 | 0.83 | 650 | 9.21 |
| 21 | 14.78 | 0.21 | 217 | 3.10 |
| 22 | 14.59 | 0.26 | 226 | 4.02 |
| 23 | 12.33 | 0.23 | 207 | 3.79 |
| 24 | 14.51 | 0.20 | 213 | 2.99 |
| 25 | 11.47 | 0.21 | 173 | 3.23 |
| 26 | 18.01 | 0.24 | 232 | 3.15 |

ST 8-35. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | C ₁ F (L/h) | C ₁ F (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|---------|------------------------|---------------------------|----------------------|-------------------------|
| 27 | 16.79 | 0.18 | 315 | 3.29 |
| 28 | 21.59 | 0.22 | 367 | 3.82 |
| 1003 | 19.44 | 0.27 | 262 | 3.67 |
| 1004 | 17.58 | 0.30 | 319 | 2.50 |
| 1005 | 38.47 | 0.42 | 610 | 7.03 |
| 1018 | 19.29 | 0.31 | 246 | 3.99 |
| 1020 | 16.65 | 0.20 | 213 | 3.09 |

NC - Not calculated

ST 8-36. Descriptive Statistics for Pharmacokinetic Parameters of (S)-Desvenlafaxine for Fasting Treatment

| | C ₁ F (L/h) | C ₁ F (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|------------------|------------------------|---------------------------|----------------------|-------------------------|
| N | 29 | 29 | 29 | 29 |
| Mean | 19.28 | 0.26 | 287 | 3.86 |
| SD | 9.13 | 0.12 | 113 | 1.31 |
| SE | 1.70 | 0.02 | 21.03 | 0.24 |
| N _{est} | 11.47 | 0.17 | 173 | 2.50 |
| Median | 17.31 | 0.23 | 246 | 3.72 |
| Max | 38.76 | 0.83 | 630 | 9.21 |
| CV% | 47 | 47 | 39 | 34 |
| Geometric Mean | 18.35 | 0.25 | 273 | 3.72 |

NC - Not calculated

ST 8-37. Pharmacokinetic Parameters of (S)-Desvendafaxine by Subject for Low-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 237 | 10.00 | 10.70 | 4709 | 4773 |
| 2 | 233 | 10.00 | 13.51 | 5233 | 5404 |
| 4 | 208 | 10.00 | 12.46 | 5188 | 5331 |
| 5 | 221 | 6.00 | 11.01 | 4975 | 5055 |
| 6 | 340 | 10.00 | 10.03 | 5895 | 6054 |
| 7 | 99.80 | 4.00 | 12.89 | 1639 | 1712 |
| 8 | 284 | 6.00 | 10.00 | 5515 | 5556 |
| 9 | 169 | 6.00 | 10.90 | 4892 | 4974 |
| 10 | 234 | 12.00 | 11.94 | 7149 | 7349 |
| 11 | 256 | 6.00 | 11.12 | 6008 | 6140 |
| 12 | 180 | 12.00 | 9.67 | 4655 | 4695 |
| 13 | 357 | 10.00 | 11.71 | 7433 | 7583 |
| 14 | 294 | 12.00 | 8.69 | 6290 | 6323 |
| 15 | 219 | 6.00 | 6.14 | 3437 | 3474 |
| 16 | 301 | 6.00 | 9.35 | 5889 | 5930 |
| 17 | 325 | 10.00 | 12.71 | 6464 | 6616 |
| 18 | 265 | 10.00 | 10.27 | 6418 | 6526 |
| 19 | 267 | 6.00 | 8.43 | 5466 | 5544 |
| 21 | 281 | 10.00 | 11.75 | 7247 | 7400 |
| 22 | 160 | 24.00 | 8.77 | 6011 | 6104 |
| 23 | 331 | 12.00 | 9.78 | 7757 | 7842 |
| 24 | 274 | 6.00 | 10.30 | 5824 | 6011 |
| 25 | 333 | 10.00 | 10.19 | 7246 | 7367 |

ST 8-37. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | AUC_T (ng \cdot h/mL) | AUC (ng \cdot h/mL) |
|---------|-------------------|---------------|---------------|---------------------------|-------------------------|
| 26 | 239 | 12.00 | 8.98 | 6130 | 6182 |
| 27 | 187 | 8.00 | 14.37 | 6305 | 6653 |
| 28 | 174 | 10.00 | 11.17 | 3815 | 3876 |
| 1003 | 217 | 6.00 | 9.76 | 5423 | 5499 |
| 1004 | 160 | 4.00 | 9.82 | 4408 | 4463 |
| 1005 | 161 | 16.00 | 10.61 | 4381 | 4454 |
| 1018 | 234 | 10.00 | 8.39 | 4804 | 4853 |
| 1020 | 235 | 8.00 | 10.19 | 6085 | 6195 |

ST 8-38. Descriptive Statistics for Pharmacokinetic Parameters of (S)-Desvenlafaxine for Low-Fat Treatment

| | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | AUC_T (ng \cdot h/mL) | AUC (ng \cdot h/mL) |
|----------------|-------------------|---------------|---------------|---------------------------|-------------------------|
| N | 31 | 31 | 31 | 31 | 31 |
| Mean | 241 | 9.42 | 10.50 | 5578 | 5674 |
| SD | 62.67 | 3.84 | 1.69 | 1282 | 1308 |
| SE | 11.26 | 0.69 | 0.30 | 230 | 235 |
| Min | 99.80 | 4.00 | 6.14 | 3659 | 1712 |
| Median | 235 | 10.00 | 10.27 | 5889 | 5930 |
| Max | 357 | 24.00 | 14.17 | 7757 | 7842 |
| CV% | 26 | 41 | 16 | 23 | 23 |
| Geometric Mean | 233 | 8.73 | 10.17 | 5381 | 5483 |

ST 8-39. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 1 | 20.95 | 0.26 | 323 | 3.98 |
| 2 | 18.50 | 0.20 | 361 | 3.89 |
| 4 | 18.76 | 0.18 | 337 | 3.28 |
| 5 | 19.78 | 0.23 | 314 | 3.71 |
| 6 | 16.52 | 0.26 | 239 | 3.70 |
| 7 | 28.40 | 0.72 | 1086 | 13.34 |
| 8 | 18.00 | 0.27 | 260 | 3.83 |
| 9 | 20.11 | 0.26 | 316 | 4.01 |
| 10 | 13.61 | 0.21 | 234 | 3.63 |
| 11 | 16.29 | 0.26 | 261 | 4.21 |
| 12 | 21.30 | 0.25 | 297 | 3.49 |
| 13 | 13.19 | 0.17 | 223 | 2.96 |
| 14 | 15.82 | 0.25 | 198 | 3.08 |
| 15 | 28.78 | 0.46 | 255 | 4.07 |
| 16 | 16.86 | 0.21 | 227 | 2.86 |
| 17 | 15.11 | 0.26 | 277 | 4.68 |
| 18 | 15.32 | 0.22 | 227 | 3.26 |
| 19 | 18.04 | 0.26 | 219 | 3.11 |
| 21 | 13.51 | 0.19 | 229 | 3.28 |
| 22 | 16.38 | 0.28 | 207 | 3.68 |
| 23 | 12.75 | 0.23 | 180 | 3.30 |
| 24 | 16.64 | 0.23 | 247 | 3.47 |
| 25 | 13.69 | 0.26 | 201 | 3.75 |

ST 8-39. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 26 | 16.18 | 0.22 | 210 | 2.84 |
| 27 | 15.05 | 0.16 | 312 | 3.23 |
| 28 | 25.80 | 0.27 | 416 | 4.33 |
| 1003 | 18.19 | 0.25 | 256 | 3.59 |
| 1004 | 22.40 | 0.26 | 317 | 3.62 |
| 1005 | 22.45 | 0.24 | 344 | 3.72 |
| 1018 | 20.61 | 0.33 | 249 | 4.03 |
| 1020 | 16.14 | 0.20 | 237 | 2.90 |

ST 8-40. Descriptive Statistics for Pharmacokinetic Parameters of (S)-Desvenlafaxine for Low-Fat Treatment

| | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|----------------|------------|---------------|-----------------------|--------------------------|
| N | 31 | 31 | 31 | 31 |
| Mean | 19.20 | 0.26 | 292 | 3.90 |
| SD | 8.15 | 0.19 | 157 | 1.81 |
| SE | 1.46 | 0.02 | 28.24 | 0.32 |
| Min | 12.75 | 0.16 | 189 | 2.84 |
| Median | 16.86 | 0.25 | 255 | 3.63 |
| Max | 28.40 | 0.72 | 1086 | 13.34 |
| CV% | 42 | 39 | 54 | 46 |
| Geometric Mean | 18.24 | 0.25 | 273 | 3.71 |

ST 8-41. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 259 | 10.00 | 10.49 | 4903 | 4938 |
| 2 | 167 | 6.00 | 13.24 | 5405 | 5604 |
| 3 | 208 | 4.00 | 11.73 | 4397 | 4475 |
| 6 | 307 | 8.00 | 9.54 | 6245 | 6296 |
| 7 | 117 | 4.00 | 11.04 | 3052 | 2105 |
| 8 | 243 | 6.00 | 9.51 | 3593 | 5642 |
| 9 | 231 | 10.00 | 10.00 | 4811 | 4862 |
| 10 | 215 | 4.00 | 12.19 | 6286 | 6446 |
| 11 | 276 | 6.00 | 11.06 | 3855 | 5932 |
| 12 | 163 | 10.00 | 11.42 | 5219 | 5341 |
| 13 | 330 | 8.00 | 11.10 | 7912 | 8034 |
| 14 | 363 | 10.00 | 9.74 | 7062 | 7119 |
| 15 | 249 | 10.00 | 6.68 | 4563 | 4619 |
| 16 | 340 | 8.00 | 3.84 | 6208 | 6243 |
| 17 | 283 | 8.00 | 10.93 | 6855 | 6979 |
| 19 | 257 | 10.00 | 9.31 | 6405 | 6467 |
| 20 | 229 | 6.00 | 7.46 | 4199 | 4229 |
| 21 | 227 | 8.00 | 10.55 | 6537 | 6744 |
| 22 | 258 | 6.00 | 8.44 | 6477 | 6538 |
| 23 | 295 | 4.00 | 11.29 | 7978 | 8143 |
| 24 | 280 | 6.00 | 10.67 | 6510 | 6625 |
| 25 | 260 | 8.00 | 8.98 | 7450 | 7512 |
| 26 | 261 | 10.00 | 8.18 | 5561 | 5624 |

ST 8-41. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _r (ng*h/mL) | AUC (ng*h/mL) |
|---------|--------------------------|----------------------|----------------------|----------------------------|---------------|
| 27 | 165 | 8.00 | 33.93 | 6603 | 8459 |
| 28 | 138 | 4.00 | 10.49 | 4419 | 4518 |
| 1003 | 238 | 10.00 | 9.59 | 6008 | 6053 |
| 1004 | 199 | 4.00 | 10.86 | 5888 | 6005 |
| 1005 | 142 | 12.00 | 10.80 | 4913 | 5041 |
| 1018 | 282 | 10.00 | 9.34 | 5445 | 5532 |
| 1020 | 199 | 6.00 | 10.36 | 5105 | 5177 |

ST 8-42. Descriptive Statistics for Pharmacokinetic Parameters of (S)-Desvenlafaxine for Medium-Fat Treatment

| | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _r (ng*h/mL) | AUC (ng*h/mL) |
|----------------|--------------------------|----------------------|----------------------|----------------------------|---------------|
| N | 30 | 30 | 30 | 30 | 30 |
| Mean | 240 | 7.47 | 10.53 | 5765 | 5911 |
| SD | 60.71 | 1.40 | 4.56 | 1227 | 1321 |
| SE | 11.08 | 0.44 | 0.83 | 234 | 241 |
| Min | 117 | 4.00 | 6.68 | 2052 | 2105 |
| Median | 253 | 8.00 | 10.49 | 5872 | 5969 |
| Max | 363 | 12.00 | 33.93 | 7978 | 8459 |
| CV% | 25 | 12 | 42 | 21 | 22 |
| Geometric Mean | 232 | 7.06 | 10.45 | 5608 | 5740 |

ST 8-43. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | CLF (L/h) | CLF (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|---------|-----------|--------------|----------------------|-------------------------|
| 1 | 26.17 | 0.25 | 305 | 3.76 |
| 2 | 17.84 | 0.19 | 341 | 3.67 |
| 3 | 22.35 | 0.35 | 378 | 6.01 |
| 6 | 15.88 | 0.25 | 219 | 3.38 |
| 7 | 47.51 | 0.58 | 757 | 9.30 |
| 8 | 17.72 | 0.26 | 243 | 3.59 |
| 9 | 20.57 | 0.26 | 297 | 3.76 |
| 10 | 15.51 | 0.24 | 273 | 4.22 |
| 11 | 16.86 | 0.27 | 269 | 4.34 |
| 12 | 18.72 | 0.22 | 308 | 3.62 |
| 13 | 12.45 | 0.17 | 199 | 2.64 |
| 14 | 14.05 | 0.22 | 197 | 3.06 |
| 15 | 21.65 | 0.35 | 299 | 3.33 |
| 16 | 16.02 | 0.20 | 204 | 2.57 |
| 17 | 14.33 | 0.24 | 226 | 3.82 |
| 19 | 15.46 | 0.22 | 268 | 2.94 |
| 20 | 13.65 | 0.17 | 254 | 3.96 |
| 21 | 14.33 | 0.21 | 226 | 3.23 |
| 22 | 15.30 | 0.17 | 186 | 3.31 |
| 23 | 12.28 | 0.22 | 209 | 3.66 |
| 24 | 15.09 | 0.21 | 232 | 3.26 |
| 25 | 13.31 | 0.25 | 173 | 3.23 |
| 26 | 17.78 | 0.24 | 210 | 2.85 |

ST 8-43. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C ₁ F (L/h) | C ₁ F (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|---------|------------------------|---------------------------|----------------------|-------------------------|
| 27 | 11.82 | 0.12 | 579 | 6.04 |
| 38 | 22.14 | 0.23 | 335 | 3.49 |
| 1003 | 16.32 | 0.23 | 229 | 3.20 |
| 1094 | 16.65 | 0.19 | 261 | 2.98 |
| 1005 | 19.84 | 0.21 | 309 | 3.33 |
| 1018 | 18.08 | 0.29 | 244 | 3.94 |
| 1020 | 19.32 | 0.24 | 289 | 3.53 |

ST 8-44. Descriptive Statistics for Pharmacokinetic Parameters of (S)-Desvenlafaxine for Medium-Fat Treatment

| | C ₁ F (L/h) | C ₁ F (L/h/kg) | V _d F (L) | V _d F (L/kg) |
|----------------|------------------------|---------------------------|----------------------|-------------------------|
| N | 30 | 30 | 30 | 30 |
| Mean | 18.12 | 0.25 | 279 | 3.80 |
| SD | 6.36 | 0.08 | 120 | 1.30 |
| SE | 1.15 | 0.01 | 21.84 | 0.24 |
| Min | 11.82 | 0.12 | 173 | 2.57 |
| Median | 16.76 | 0.24 | 243 | 3.51 |
| Max | 47.51 | 0.38 | 757 | 9.30 |
| CV% | 35 | 32 | 43 | 34 |
| Geometric Mean | 17.42 | 0.24 | 263 | 3.66 |

ST 8-45. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | $AUC_{0-\infty}$ (ng \cdot h/mL) | AUC (ng \cdot h/mL) |
|---------|-------------------|---------------|---------------|------------------------------------|-------------------------|
| 1 | 211 | 10.00 | 9.98 | 4593 | 4652 |
| 2 | 245 | 6.00 | 13.29 | 5225 | 5386 |
| 4 | 248 | 10.00 | 12.69 | 5476 | 5629 |
| 5 | 223 | 6.00 | 12.40 | 5498 | 5636 |
| 6 | 282 | 10.00 | 9.01 | 5583 | 5617 |
| 7 | 98.60 | 6.00 | 10.33 | 1655 | 1691 |
| 8 | 172 | 6.00 | 11.74 | 2538 | 2592 |
| 9 | 212 | 12.00 | 10.32 | 5004 | 5054 |
| 10 | 309 | 10.00 | 13.07 | 6978 | 7132 |
| 11 | 303 | 10.00 | 10.23 | 5936 | 6001 |
| 12 | 163 | 6.00 | 9.34 | 4730 | 4778 |
| 13 | 339 | 10.00 | 11.40 | 7073 | 7189 |
| 14 | 323 | 10.00 | 8.06 | 6498 | 6554 |
| 15 | 302 | 10.00 | 5.86 | 3845 | 3871 |
| 16 | 338 | 8.00 | 8.88 | 5721 | 5754 |
| 17 | 391 | 8.00 | 9.43 | 6509 | 6548 |
| 19 | 293 | 10.00 | 8.60 | 5886 | 5921 |
| 21 | 322 | 10.00 | 9.43 | 5830 | 5881 |
| 22 | 316 | 8.00 | 9.53 | 6670 | 6734 |
| 24 | 285 | 6.00 | 9.62 | 6012 | 6063 |
| 25 | 269 | 6.00 | 9.11 | 7087 | 7130 |
| 26 | 245 | 10.00 | 9.18 | 5602 | 5644 |
| 27 | 274 | 8.00 | 15.58 | 7751 | 8275 |

ST 8-46. Descriptive Statistics for Pharmacokinetic Parameters of (S)-Desvenlafaxine for High-Fat Treatment

| | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | AUC_0-8 (ng·h/mL) | AUC (ng·h/mL) |
|----------------|-------------------|---------------|---------------|---------------------|-----------------|
| N | 29 | 29 | 29 | 29 | 29 |
| Mean | 239 | 8.34 | 10.31 | 5403 | 5491 |
| SD | 64.91 | 1.86 | 1.92 | 1347 | 1388 |
| SE | 11.89 | 0.34 | 0.36 | 250 | 258 |
| Min | 98.60 | 6.00 | 5.86 | 1655 | 1695 |
| Median | 268 | 8.00 | 10.08 | 5583 | 5636 |
| Max | 391 | 11.00 | 15.38 | 7751 | 8275 |
| CV% | 25 | 22 | 19 | 25 | 25 |
| Geometric Mean | 250 | 8.14 | 10.14 | 5187 | 5269 |

ST 8-45. Pharmacokinetic Parameters of (S)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | C_{max} (ng/mL) | t_{max} (h) | $t_{1/2}$ (h) | AUC_0-8 (ng·h/mL) | AUC (ng·h/mL) |
|---------|-------------------|---------------|---------------|---------------------|-----------------|
| 18 | 177 | 8.00 | 11.05 | 4375 | 4452 |
| 1003 | 251 | 8.00 | 10.90 | 4885 | 4995 |
| 1004 | 216 | 6.00 | 10.86 | 4942 | 5013 |
| 1005 | 181 | 6.00 | 10.96 | 3539 | 3590 |
| 1018 | 268 | 10.00 | 8.48 | 4977 | 5029 |
| 1020 | 249 | 8.00 | 10.08 | 6286 | 6385 |

ST 8-48. Descriptive Statistics for Pharmacokinetic Parameters of (S)-Desvenlafaxine for High-Fat Treatment

| | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|----------------|------------|---------------|-----------------------|--------------------------|
| N | 29 | 29 | 29 | 29 |
| Mean | 20.17 | 0.27 | 299 | 3.97 |
| SD | 9.07 | 0.12 | 148 | 1.84 |
| SE | 1.68 | 0.02 | 27.54 | 0.34 |
| Min | 12.06 | 0.13 | 177 | 2.73 |
| Median | 17.74 | 0.24 | 246 | 3.57 |
| Max | 38.99 | 0.72 | 897 | 11.01 |
| CV% | 45 | 43 | 50 | 46 |
| Geometric Mean | 18.58 | 0.26 | 278 | 3.73 |

ST 8-49. Plasma Concentrations of (R+S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | Concentration (ng/mL) over Nominal Time (h) | | | | | | | | | | | | | | |
|---------|---|------|------|------|------|------|------|-------|-------|-------|-------|-------|-------|-------|-------|
| | 0.00 | 0.50 | 1.00 | 2.00 | 4.00 | 6.00 | 8.00 | 10.00 | 12.00 | 16.00 | 24.00 | 36.00 | 48.00 | 60.00 | 72.00 |
| 1 | | | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | | | | |
| 6 | | | | | | | | | | | | | | | |
| 7 | | | | | | | | | | | | | | | |
| 8 | | | | | | | | | | | | | | | |
| 9 | | | | | | | | | | | | | | | |
| 10 | | | | | | | | | | | | | | | |
| 11 | | | | | | | | | | | | | | | |

ST 8-57. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 448 | 8.00 | 11.21 | 10192 | 10355 |
| 2 | 294 | 8.00 | 12.70 | 9835 | 10190 |
| 4 | 459 | 10.00 | 11.41 | 10898 | 11083 |
| 5 | 359 | 8.00 | NC | 7033 * | NC |
| 6 | 397 | 4.00 | 10.10 | 11753 | 11924 |
| 7 | 376 | 6.00 | 11.87 | 11031 | 11351 |
| 8 | 498 | 6.00 | 10.18 | 12081 | 12228 |
| 9 | 345 | 6.00 | 10.15 | 7770 | 7857 |
| 10 | 500 | 4.00 | 14.10 | 14758 | 15384 |
| 11 | 429 | 12.00 | 12.45 | 12705 | 13028 |
| 12 | 393 | 4.00 | 12.66 | 9015 | 9240 |
| 13 | 375 | 24.00 | 11.75 | 14652 | 15144 |
| 14 | 408 | 16.00 | 9.76 | 13102 | 13300 |
| 15 | 543 | 8.00 | 6.90 | 8224 | 8316 |
| 16 | 584 | 6.00 | 9.96 | 9440 | 9583 |
| 17 | 514 | 4.00 | 11.95 | 13139 | 13425 |
| 19 | 281 | 4.00 | 7.52 | 2952 | 3065 |
| 21 | 543 | 8.00 | 9.83 | 12133 | 12368 |
| 22 | 406 | 6.00 | 10.57 | 12810 | 13083 |
| 23 | 692 | 6.00 | 11.42 | 15154 | 15437 |
| 24 | 624 | 8.00 | 10.51 | 13552 | 13735 |
| 25 | 549 | 4.00 | 10.53 | 16498 | 16771 |
| 26 | 527 | 10.00 | 8.91 | 10401 | 10559 |
| 27 | 303 | 10.00 | 13.31 | 11212 | 11795 |

ST 8-57. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng•h/mL) | AUC (ng•h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 28 | 339 | 6.00 | 11.60 | 8615 | 8791 |
| 1003 | 312 | 8.00 | 9.80 | 9903 | 10080 |
| 1004 | 336 | 6.00 | 8.92 | 10915 | 10990 |
| 1005 | 216 | 8.00 | 12.89 | 5462 | 5606 |
| 1018 | 513 | 4.00 | 8.99 | 10239 | 10314 |
| 1020 | 436 | 6.00 | 9.30 | 11095 | 11219 |

Note: Extrapolated portion of AUC >30%.

* Subject 5 excluded.

ST 8-58. Descriptive Statistics for Pharmacokinetic Parameters of (R+S)-Desvenlafaxine for Fasting Treatment

| | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng•h/mL) ^a | AUC (ng•h/mL) |
|----------------|--------------------------|----------------------|----------------------|---|---------------|
| N | 30 | 30 | 29 | 29 | 29 |
| Mean | 433 | 7.60 | 10.73 | 11009 | 11245 |
| SD | 311 | 4.12 | 1.69 | 2863 | 2936 |
| SE | 20.30 | 0.73 | 0.31 | 532 | 545 |
| Min | 216 | 4.00 | 6.90 | 2952 | 3065 |
| Median | 419 | 6.00 | 10.53 | 11031 | 11219 |
| Max | 692 | 24.00 | 14.10 | 16496 | 16771 |
| CV% | 26 | 34 | 16 | 26 | 26 |
| Geometric Mean | 419 | 6.87 | 10.60 | 10541 | 10709 |

Note: Extrapolated portion of AUC >30%.

* Subject 5 excluded.

ST 8-59. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | CL/F (L/h) | CL/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 1 | 19.31 | 0.24 | 312 | 3.85 |
| 2 | 19.63 | 0.21 | 360 | 3.88 |
| 4 | 18.05 | 0.18 | 297 | 2.89 |
| 5 | NC | NC | NC | NC |
| 6 | 16.77 | 0.26 | 245 | 3.78 |
| 7 | 17.62 | 0.22 | 302 | 3.71 |
| 8 | 16.36 | 0.24 | 240 | 3.54 |
| 9 | 33.46 | 0.32 | 373 | 4.73 |
| 10 | 13.00 | 0.20 | 264 | 4.09 |
| 11 | 15.35 | 0.25 | 276 | 4.45 |
| 12 | 21.64 | 0.25 | 395 | 4.64 |
| 13 | 13.21 | 0.18 | 224 | 2.97 |
| 14 | 15.04 | 0.23 | 212 | 3.29 |
| 15 | 24.05 | 0.38 | 239 | 3.82 |
| 16 | 20.87 | 0.26 | 300 | 3.78 |
| 17 | 14.90 | 0.25 | 257 | 4.34 |
| 19 | 65.26 | 0.92 | 708 | 10.03 |
| 21 | 16.25 | 0.23 | 230 | 3.30 |
| 22 | 35.29 | 0.27 | 233 | 4.15 |
| 23 | 12.96 | 0.24 | 213 | 3.91 |
| 24 | 14.56 | 0.20 | 221 | 3.10 |
| 26 | 18.94 | 0.26 | 241 | 3.30 |
| 27 | 17.00 | 0.18 | 326 | 3.41 |

ST 8-59. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Fasting Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 28 | 22.75 | 0.24 | 381 | 3.97 |
| 1003 | 19.88 | 0.28 | 281 | 3.94 |
| 1004 | 18.30 | 0.21 | 234 | 2.67 |
| 1005 | 35.67 | 0.39 | 663 | 7.18 |
| 1018 | 19.39 | 0.31 | 252 | 4.07 |
| 1020 | 17.83 | 0.22 | 239 | 2.92 |

NC - Not calculated.

ST 8-60. Descriptive Statistics for Pharmacokinetic Parameters of (R+S)-Desvenlafaxine for Fasting Treatment

| | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|----------------|------------|---------------|-----------------------|--------------------------|
| N | 29 | 29 | 29 | 29 |
| Mean | 19.90 | 0.27 | 360 | 4.04 |
| SD | 9.91 | 0.14 | 130 | 1.42 |
| SE | 1.84 | 0.03 | 22.27 | 0.26 |
| Mean | 11.93 | 0.18 | 181 | 2.67 |
| Median | 17.83 | 0.24 | 257 | 3.82 |
| Max | 65.26 | 0.92 | 708 | 10.03 |
| CV% | 50 | 50 | 40 | 35 |
| Geometric Mean | 18.59 | 0.25 | 284 | 3.38 |

NC - Not calculated.

ST 8-61. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|--------------------|
| 1 | 474 | 10.00 | 10.57 | 9620 | 9762 |
| 2 | 469 | 10.00 | 14.09 | 10790 | 11199 |
| 4 | 404 | 12.00 | 12.74 | 10356 | 10673 |
| 5 | 431 | 6.00 | 11.15 | 9615 | 9777 |
| 6 | 641 | 10.00 | 9.92 | 11436 | 11543 |
| 7 | 194 | 4.00 | 12.91 | 3279 | 3391 |
| 8 | 543 | 6.00 | 10.27 | 10786 | 10877 |
| 9 | 320 | 6.00 | 10.89 | 9180 | 9331 |
| 10 | 481 | 12.00 | 12.77 | 14758 | 15265 |
| 11 | 497 | 6.00 | 11.25 | 11781 | 12054 |
| 12 | 346 | 12.00 | 9.30 | 8853 | 8926 |
| 13 | 694 | 10.00 | 12.26 | 14724 | 15081 |
| 14 | 557 | 12.00 | 9.08 | 12221 | 12302 |
| 15 | 427 | 6.00 | 6.33 | 6740 | 6821 |
| 16 | 599 | 6.00 | 9.51 | 11734 | 11824 |
| 17 | 605 | 10.00 | 11.09 | 12083 | 12311 |
| 18 | 490 | 10.00 | 10.58 | 11557 | 11741 |
| 19 | 497 | 3.00 | 8.13 | 9804 | 9922 |
| 21 | 529 | 10.00 | 11.37 | 13220 | 13465 |
| 22 | 507 ^a | 4.00 ^a | 8.75 ^a | 11590 ^a | 11768 ^a |
| 23 | 637 | 12.00 | 9.60 | 14813 | 14958 |
| 24 | 552 | 8.00 | 10.55 | 11810 | 12000 |
| 25 | 638 | 10.00 | 10.33 | 14019 | 14148 |
| 26 | 462 | 12.00 | 8.89 | 11669 | 11793 |

ST 8-61. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng•h/mL) | AUC (ng•h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 27 | 361 | 8.00 | 14.65 | 12443 | 13180 |
| 28 | 331 | 10.00 | 10.40 | 7158 | 7260 |
| 1003 | 419 | 6.00 | 9.99 | 10594 | 10755 |
| 1004 | 307 | 4.00 | 9.82 | 8450 | 8559 |
| 1005 | 327 | 16.00 | 11.83 | 9336 | 9571 |
| 1018 | 462 | 10.00 | 8.68 | 9619 | 9735 |
| 1020 | 446 | 8.00 | 10.15 | 11437 | 11634 |

* Subject 22 excluded

ST 8-62. Descriptive Statistics for Pharmacokinetic Parameters of (R+S)-Desvenlafaxine for Low-Fat Treatment

| | C _{max} (ng/mL) * | t _{max} (h) * | t _{1/2} (h) * | AUC _{0-∞} (ng•h/mL) * | AUC (ng•h/mL) * |
|----------------|----------------------------|------------------------|------------------------|--------------------------------|-----------------|
| N | 30 | 30 | 30 | 30 | 30 |
| Mean | 471 | 9.00 | 10.64 | 10797 | 10895 |
| SD | 117 | 2.82 | 1.74 | 2496 | 2558 |
| SE | 21.34 | 0.51 | 0.32 | 456 | 467 |
| Min | 194 | 4.00 | 6.33 | 3279 | 3391 |
| Median | 472 | 10.00 | 10.46 | 11113 | 11371 |
| Max | 694 | 16.00 | 14.65 | 14813 | 15265 |
| CV% | 25 | 31 | 16 | 23 | 23 |
| Geometric Mean | 455 | 8.34 | 10.49 | 10434 | 10624 |

* Subject 22 excluded

ST 8-63. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|--------------------|-------------------|-----------------------|--------------------------|
| 1 | 20.49 | 0.25 | 313 | 3.85 |
| 2 | 17.86 | 0.19 | 363 | 3.91 |
| 4 | 18.74 | 0.18 | 344 | 3.35 |
| 5 | 20.46 | 0.24 | 329 | 3.89 |
| 6 | 17.33 | 0.27 | 248 | 3.84 |
| 7 | 58.98 | 0.72 | 1099 | 13.50 |
| 8 | 18.39 | 0.27 | 273 | 4.02 |
| 9 | 21.43 | 0.27 | 337 | 4.27 |
| 10 | 13.10 | 0.20 | 241 | 3.74 |
| 11 | 16.59 | 0.27 | 269 | 4.34 |
| 12 | 22.41 | 0.26 | 309 | 3.53 |
| 13 | 13.26 | 0.18 | 235 | 3.11 |
| 14 | 16.26 | 0.25 | 213 | 3.31 |
| 15 | 29.32 | 0.47 | 268 | 4.28 |
| 16 | 16.91 | 0.21 | 232 | 2.92 |
| 17 | 16.23 | 0.27 | 260 | 4.39 |
| 18 | 17.03 | 0.24 | 260 | 3.74 |
| 19 | 20.16 | 0.29 | 236 | 3.35 |
| 21 | 14.85 | 0.21 | 244 | 3.49 |
| 22 | 17.00 ^a | 0.30 ^a | 215 ^a | 3.83 ^a |
| 23 | 13.37 | 0.24 | 185 | 3.39 |
| 24 | 16.67 | 0.23 | 253 | 3.56 |
| 25 | 14.14 | 0.26 | 211 | 3.93 |
| 26 | 16.96 | 0.23 | 217 | 2.95 |

ST 8-63. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Low-Fat Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 27 | 15.17 | 0.16 | 321 | 3.35 |
| 28 | 27.55 | 0.29 | 413 | 4.30 |
| 1003 | 18.60 | 0.26 | 268 | 3.76 |
| 1004 | 23.37 | 0.27 | 331 | 3.78 |
| 1005 | 30.90 | 0.23 | 356 | 3.85 |
| 1018 | 30.54 | 0.33 | 257 | 4.16 |
| 1020 | 17.19 | 0.21 | 352 | 3.68 |

* Subject 22 excluded

ST 8-64. Descriptive Statistics for Pharmacokinetic Parameters of (R+S)-Desvenlafaxine for Low-Fat Treatment

| | Cl/F (L/h) * | Cl/F (L/h/kg) * | V _d /F (L) * | V _d /F (L/kg) * |
|----------------|--------------|-----------------|-------------------------|----------------------------|
| N | 30 | 30 | 30 | 30 |
| Mean | 19.81 | 0.27 | 304 | 4.05 |
| SD | 8.32 | 0.10 | 159 | 1.84 |
| SE | 1.52 | 0.02 | 29.04 | 0.34 |
| Min | 13.10 | 0.16 | 185 | 2.92 |
| Median | 17.59 | 0.25 | 264 | 3.77 |
| Max | 58.98 | 0.72 | 1089 | 11.50 |
| CV % | 42 | 38 | 52 | 46 |
| Geometric Mean | 18.81 | 0.25 | 235 | 3.24 |

* Subject 22 excluded

ST 8-65. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1 | 518 | 10.00 | 10.74 | 10039 | 10189 |
| 2 | 334 | 6.00 | 13.84 | 11160 | 11613 |
| 3 | 399 | 4.00 | 11.75 | 8477 | 8629 |
| 6 | 584 | 8.00 | 9.53 | 11908 | 12004 |
| 7 | 236 | 4.00 | 11.33 | 4061 | 4176 |
| 8 | 470 | 6.00 | 9.80 | 10898 | 11006 |
| 9 | 435 | 10.00 | 9.96 | 9001 | 9086 |
| 10 | 421 | 4.00 | 12.88 | 12843 | 13243 |
| 11 | 527 | 6.00 | 11.00 | 11548 | 11702 |
| 12 | 308 | 10.00 | 11.07 | 9782 | 9995 |
| 13 | 641 | 8.00 | 11.70 | 15570 | 15866 |
| 14 | 719 | 10.00 | 9.44 | 13843 | 13957 |
| 15 | 475 | 10.00 | 6.77 | 8885 | 8998 |
| 16 | 679 | 8.00 | 8.99 | 12375 | 12451 |
| 17 | 536 | 8.00 | 10.84 | 12029 | 13045 |
| 18 | 464 | 6.00 | 9.66 | 11442 | 11541 |
| 20 | 451 | 6.00 | 7.72 | 8366 | 8575 |
| 21 | 423 | 8.00 | 10.20 | 12024 | 12183 |
| 22 | 489 | 6.00 | 8.31 | 12391 | 12501 |
| 23 | 567 | 4.00 | 11.02 | 15306 | 15581 |
| 24 | 536 | 6.00 | 11.14 | 12877 | 13138 |
| 25 | 488 | 8.00 | 9.25 | 14270 | 14435 |
| 26 | 489 | 10.00 | 7.82 | 10567 | 10576 |
| 27 | 323 | 8.00 | 14.46 | 13086 | 13358 |

ST 8-65. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 28 | 262 | 4.00 | 10.48 | 8315 | 8494 |
| 1003 | 492 | 10.00 | 9.87 | 11658 | 11762 |
| 1004 | 378 | 4.00 | 10.87 | 11290 | 11512 |
| 1005 | 288 | 16.00 | 12.29 | 10470 | 10879 |
| 1018 | 558 | 10.00 | 8.92 | 11005 | 11047 |
| 1020 | 379 | 6.90 | 10.09 | 9564 | 9685 |

ST 8-66. Descriptive Statistics for Pharmacokinetic Parameters of (R+S)-Desvenlafaxine for Medium-Fat Treatment

| | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | AUC (ng·h/mL) |
|----------------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| N | 30 | 30 | 30 | 30 | 30 |
| Mean | 463 | 7.47 | 11.04 | 11290 | 11496 |
| SD | 118 | 2.73 | 4.68 | 2346 | 2562 |
| SE | 21.62 | 0.50 | 0.86 | 428 | 468 |
| Min | 226 | 4.00 | 5.77 | 4061 | 4176 |
| Median | 473 | 8.00 | 10.34 | 11366 | 11538 |
| Max | 710 | 16.00 | 24.46 | 15570 | 16859 |
| CV% | 26 | 37 | 42 | 21 | 22 |
| Geometric Mean | 447 | 7.01 | 10.53 | 10907 | 11170 |

ST 8-67. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | C ₁ F (L/h) | C ₁ F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------------------|---------------------------|-----------------------|--------------------------|
| 1 | 19.61 | 0.24 | 304 | 3.74 |
| 2 | 17.19 | 0.19 | 343 | 3.70 |
| 3 | 23.18 | 0.37 | 393 | 6.24 |
| 6 | 16.66 | 0.26 | 229 | 3.55 |
| 7 | 47.89 | 0.79 | 783 | 9.62 |
| 8 | 18.17 | 0.27 | 257 | 3.78 |
| 9 | 21.99 | 0.28 | 316 | 4.01 |
| 10 | 15.10 | 0.23 | 281 | 4.34 |
| 11 | 17.09 | 0.28 | 271 | 4.38 |
| 12 | 20.01 | 0.23 | 320 | 3.75 |
| 13 | 12.61 | 0.17 | 213 | 2.82 |
| 14 | 14.33 | 0.22 | 195 | 3.03 |
| 15 | 22.23 | 0.36 | 217 | 3.47 |
| 16 | 16.06 | 0.20 | 208 | 2.62 |
| 17 | 15.33 | 0.26 | 240 | 4.05 |
| 19 | 17.33 | 0.25 | 226 | 3.21 |
| 20 | 21.52 | 0.36 | 260 | 4.05 |
| 21 | 16.40 | 0.24 | 241 | 3.46 |
| 22 | 16.09 | 0.28 | 192 | 3.41 |
| 23 | 12.83 | 0.23 | 204 | 3.73 |
| 24 | 15.22 | 0.21 | 245 | 3.44 |
| 25 | 11.86 | 0.26 | 185 | 3.45 |
| 26 | 18.73 | 0.25 | 211 | 2.86 |
| 27 | 11.86 | 0.12 | 590 | 6.16 |

ST 8-67. Pharmacokinetic Parameters of (R:S)-Desvenlafaxine by Subject for Medium-Fat Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 28 | 23.55 | 0.25 | 356 | 3.71 |
| 1003 | 17.09 | 0.24 | 242 | 3.39 |
| 1004 | 17.37 | 0.20 | 272 | 3.11 |
| 1005 | 13.38 | 0.20 | 326 | 3.53 |
| 1018 | 18.10 | 0.29 | 233 | 3.77 |
| 1029 | 20.65 | 0.25 | 301 | 3.68 |

ST 8-68. Descriptive Statistics for Pharmacokinetic Parameters of (R:S)-Desvenlafaxine for Medium-Fat Treatment

| | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|----------------|------------|---------------|-----------------------|--------------------------|
| N | 30 | 30 | 30 | 30 |
| Mean | 18.60 | 0.26 | 288 | 3.94 |
| SD | 5.38 | 0.08 | 123 | 1.33 |
| SE | 1.16 | 0.01 | 22.43 | 0.24 |
| Min | 11.86 | 0.12 | 185 | 2.62 |
| Median | 17.26 | 0.25 | 251 | 3.69 |
| Max | 47.89 | 0.59 | 783 | 9.62 |
| CV% | 34 | 31 | 43 | 34 |
| Geometric Mean | 17.90 | 0.25 | 272 | 3.79 |

ST 8-69. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _r (ng•h/mL) | AUC (ng•h/mL) |
|---------|--------------------------|----------------------|----------------------|----------------------------|---------------|
| 1 | 416 | 10.00 | 10.47 | 9310 | 9452 |
| 2 | 489 | 6.00 | 13.85 | 10759 | 11142 |
| 4 | 495 | 10.00 | 14.02 | 11008 | 11380 |
| 5 | 427 | 6.00 | 13.41 | 10702 | 10976 |
| 6 | 549 | 10.00 | 8.29 | 10689 | 10721 |
| 7 | 189 | 6.00 | 10.86 | 3235 | 3322 |
| 8 | 332 | 6.00 | 10.47 | 4973 | 5062 |
| 9 | 405 | 12.00 | 10.44 | 9381 | 9477 |
| 10 | 611 | 10.00 | 11.19 | 14215 | 14572 |
| 11 | 589 | 10.00 | 10.39 | 11667 | 11805 |
| 12 | 305 | 6.00 | 9.27 | 5930 | 5918 |
| 13 | 643 | 10.00 | 11.73 | 13855 | 14121 |
| 14 | 630 | 6.00 | 8.21 | 12864 | 12901 |
| 15 | 584 | 10.00 | 6.04 | 7534 | 7594 |
| 16 | 658 | 8.00 | 9.03 | 11328 | 11369 |
| 17 | 718 | 3.00 | 8.49 | 12170 | 12305 |
| 19 | 548 | 10.00 | 7.59 | 10505 | 10598 |
| 21 | 602 | 10.00 | 8.59 | 10574 | 10621 |
| 22 | 617 | 8.00 | 9.40 | 12822 | 12936 |
| 24 | 579 | 6.00 | 11.14 | 12077 | 12234 |
| 25 | 515 | 6.00 | 9.19 | 13489 | 13612 |
| 26 | 473 | 10.00 | 9.17 | 10683 | 10763 |
| 27 | 521 | 8.00 | 15.88 | 15312 | 16460 |
| 28 | 338 | 8.00 | 10.84 | 8283 | 8417 |

ST 8-69. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng•h/mL) | AUC (ng•h/mL) |
|---------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| 1003 | 491 | 3.00 | 11.08 | 5609 | 9836 |
| 1004 | 415 | 6.00 | 10.90 | 9437 | 9575 |
| 1005 | 358 | 6.00 | 12.07 | 7334 | 7666 |
| 1018 | 526 | 10.00 | 8.38 | 10001 | 10932 |
| 1020 | 477 | 3.00 | 10.03 | 11765 | 11942 |

ST 8-70. Descriptive Statistics for Pharmacokinetic Parameters of (R+S)-Desvenlafaxine for High-Fat Treatment

| | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _{0-∞} (ng•h/mL) | AUC (ng•h/mL) |
|----------------|--------------------------|----------------------|----------------------|------------------------------|---------------|
| N | 29 | 29 | 29 | 29 | 29 |
| Mean | 590 | 8.21 | 10.39 | 10507 | 10683 |
| SD | 121 | 1.88 | 2.13 | 2668 | 2503 |
| SE | 22.53 | 0.35 | 0.40 | 485 | 502 |
| Min | 189 | 6.00 | 6.04 | 3235 | 3322 |
| Median | 515 | 3.00 | 10.42 | 10689 | 10763 |
| Max | 718 | 12.00 | 15.88 | 15312 | 16400 |
| CV% | 24 | 23 | 21 | 25 | 23 |
| Geometric Mean | 483 | 3.00 | 10.18 | 10096 | 10259 |

ST 8-71. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 1 | 21.16 | 0.26 | 318 | 3.92 |
| 2 | 17.95 | 0.19 | 359 | 3.86 |
| 4 | 17.58 | 0.17 | 336 | 3.45 |
| 5 | 18.23 | 0.22 | 326 | 3.86 |
| 6 | 18.66 | 0.29 | 223 | 3.45 |
| 7 | 60.21 | 0.74 | 944 | 11.59 |
| 8 | 39.51 | 0.58 | 597 | 8.80 |
| 9 | 21.10 | 0.27 | 318 | 4.04 |
| 10 | 13.72 | 0.21 | 261 | 4.04 |
| 11 | 16.94 | 0.27 | 254 | 4.10 |
| 12 | 23.18 | 0.26 | 297 | 3.48 |
| 13 | 14.16 | 0.19 | 240 | 3.18 |
| 14 | 15.50 | 0.24 | 184 | 2.85 |
| 15 | 16.34 | 0.42 | 229 | 3.66 |
| 16 | 17.55 | 0.22 | 229 | 2.88 |
| 17 | 16.39 | 0.28 | 201 | 3.39 |
| 19 | 18.87 | 0.27 | 207 | 2.93 |
| 21 | 18.83 | 0.27 | 233 | 3.34 |
| 22 | 15.46 | 0.28 | 210 | 3.73 |
| 24 | 16.35 | 0.23 | 263 | 3.69 |
| 25 | 14.69 | 0.27 | 195 | 3.63 |
| 26 | 18.58 | 0.25 | 246 | 3.33 |
| 27 | 17.20 | 0.13 | 279 | 2.92 |
| 28 | 13.74 | 0.25 | 371 | 3.87 |

ST 8-71. Pharmacokinetic Parameters of (R+S)-Desvenlafaxine by Subject for High-Fat Treatment

| Subject | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|---------|------------|---------------|-----------------------|--------------------------|
| 1003 | 20.35 | 0.29 | 325 | 4.56 |
| 1004 | 20.89 | 0.24 | 329 | 3.75 |
| 1005 | 23.99 | 0.33 | 453 | 4.90 |
| 1018 | 19.94 | 0.32 | 241 | 3.90 |
| 1020 | 16.75 | 0.20 | 242 | 2.96 |

ST 8-72. Descriptive Statistics for Pharmacokinetic Parameters of (R+S)-Desvenlafaxine for High-Fat Treatment

| | Cl/F (L/h) | Cl/F (L/h/kg) | V _d /F (L) | V _d /F (L/kg) |
|----------------|------------|---------------|-----------------------|--------------------------|
| N | 29 | 29 | 29 | 29 |
| Mean | 20.68 | 0.28 | 308 | 4.07 |
| SD | 9.18 | 0.12 | 150 | 1.80 |
| SE | 1.70 | 0.02 | 27.83 | 0.33 |
| Min | 12.20 | 0.13 | 184 | 2.85 |
| Median | 18.58 | 0.26 | 261 | 3.69 |
| Max | 60.21 | 0.74 | 844 | 11.39 |
| CV% | 44 | 43 | 49 | 44 |
| Geometric Mean | 19.50 | 0.26 | 286 | 3.35 |

Study Title (Protocol 3151A1-183-US, CSR-58919): An Open Label 2-Period Sequential Drug Interaction Study To Evaluate The Effect Of Multiple Doses Of DVS-233 SR On The Pharmacokinetics Of Desipramine (A CYP2D6 Substrate) When Coadministered In Healthy Subjects

Objectives: The primary objective of this study was to evaluate the effect of multiple doses of DVS-233 SR on the pharmacokinetics of desipramine (a CYP2D6 substrate) when administered concomitantly in healthy subjects. The secondary objective of this study was to assess safety and tolerability of DVS-233 SR and desipramine when administered concomitantly to healthy subjects.

Study Design: This was an open-label, 2-period, sequential, inpatient study that was performed in 30 healthy subjects, aged 18 to 45 years (mean \pm SD age and weight were 31.2 ± 5.7 years and 78.9 ± 8.1 kg, respectively). This 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. The following table provides test article administration schedule. Test article was always administered with approximately 240 mL of water.

Test Article Administration

| Period | Study Day | Dose Regimen |
|--------|-----------|--|
| 1 | 1 | Single oral dose desipramine 50-mg tablet |
| 2 | 7 | 100 mg DVS SR |
| 2 | 8-9 | 200 mg DVS SR |
| 2 | 10-13 | 400 mg DVS SR |
| 2 | 14 | 400 mg DVS SR and Single oral desipramine 50-mg tablet coadministered |
| 2 | 15-18 | 400 mg DVS SR |
| 2 | 19-20 | 200 mg DVS SR |
| 2 | 21 | 100 mg DVS SR |

The formulation, strength and batch number of the study drug are A43077, 100 to 400 mg and 0931719C, respectively. The dosage of desipramine was 50 mg and was commercially available.

Blood samples were collected for determination of desipramine and 2-hydroxydesipramine concentrations starting on study day 1 in period 1 and starting on study day 14 in period 2 at the following time points: before (0 hour) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after test article administration. Blood samples were collected on study days 12, 13, and 14 for evaluation of desvenlafaxine

steady-state. Urine samples were collected for determination of desipramine and 2-hydroxydesipramine concentrations on study days 1 through 6 (period 1) and on study days 14 through 19 (period 2) at the following time intervals: before (-2 to 0 hour) and at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 hours after test article administration. The required specimen for analysis of whole blood samples for CYP2D6 genotyping was purified genomic DNA (8 ng/ μ L) or one 6-mL Vacutainer tube with ethylenediamine tetraacetic acid (EDTA) or acid citrate dextrose (ACD) preservative.

Analytical Method: Desvenlafaxine plasma concentrations, and desipramine and 2-hydroxydesipramine concentrations in sodium heparin-treated plasma and in urine were measured using a validated liquid chromatography-mass spectroscopy method with mass spectroscopy detection (LC/MS/MS). The performance of the desvenlafaxine assay during plasma samples from this study is summarized in the following tables.

Assay Range and Sensitivity for Desvenlafaxine in Plasma Samples

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

Analytical Summary for Desvenlafaxine Assays

| Analyte | High QC ^a (375.0 ng/mL) | | | Medium QC (45.0 ng/mL) | | | Low QC (5.0 ng/mL) | | |
|---------|------------------------------------|------|--------|------------------------|------|--------|--------------------|------|--------|
| | Conc. | CV% | Bias % | Conc. | CV% | Bias % | Conc. | CV% | Bias % |
| Desven | 333.4 | 3.20 | -11.1 | 40.2 | 6.04 | -10.6 | 4.49 | 7.23 | -10.3 |

Abbreviations: Conc=concentration; CV=coefficient of variation; Desven = Desvenlafaxine; QC=Quality Control.

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

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

Analytical Summary of Desipramine and 2-Hydroxydesipramine Assays

| Analyte | High CS ^a (80 ng/mL) | | | Medium CS (8 ng/mL) | | | Low CS (0.5 ng/mL) | | |
|----------------------|---------------------------------|------|--------|---------------------|------|--------|--------------------|------|--------|
| | Conc. | CV% | Bias % | Conc. | CV% | Bias % | Conc. | CV% | Bias % |
| Desvenlafaxine | 79.0 | 3.32 | -1.19 | 7.76 | 5.78 | -3.01 | 0.493 | 9.56 | -1.32 |
| 2-Hydroxydesipramine | 79.8 | 4.13 | -0.202 | 7.93 | 9.21 | -0.881 | 0.478 | 12.4 | -4.40 |

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

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

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

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

Analytical Summary Of Desipramine And 2-HydroDesipramine Assays

| Analyte | High CS ^a (80 ng/mL) | | | Medium CS (8 ng/mL) | | | Low CS (0.5 ng/mL) | | |
|--------------------|---------------------------------|------|--------|---------------------|------|--------|--------------------|------|--------|
| | Conc. | CV% | Bias % | Conc. | CV% | Bias % | Conc. | CV% | Bias % |
| Desvenlafaxine | 79.0 | 3.32 | -1.19 | 7.76 | 5.78 | -3.01 | 0.493 | 9.56 | -1.32 |
| 2-Hydrodesipramine | 79.8 | 4.13 | -0.202 | 7.93 | 9.21 | -0.881 | 0.478 | 12.4 | -4.40 |

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

The performance of the desipramine and 2-hydroxydesipramine assays during analysis of urine samples from this study

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

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

Analytical Summary of Desipramine Assay

| Analyte | High CS ^a (2500 ng/mL) | | | Medium CS (250 ng/mL) | | | Low CS (10 ng/mL) | | |
|-------------|-----------------------------------|------|--------|-----------------------|------|--------|-------------------|------|--------|
| | Conc. | CV% | Bias % | Conc. | CV% | Bias % | Conc. | CV% | Bias % |
| Desipramine | 2040 | 5.88 | 2.19 | 140 | 8.25 | -6.67 | 26.5 | 5.51 | 6.18 |

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

Analytical Summary of 2-Hydroxydesipramine Assay

| Analyte | High CS (25000 ng/mL) | | | Medium CS (2500 ng/mL) | | | Low CS (100 ng/mL) | | |
|----------------------|-----------------------|------|--------|------------------------|------|--------|--------------------|------|--------|
| | Conc. | CV% | Bias % | Conc. | CV% | Bias % | Conc. | CV% | Bias % |
| 2-Hydroxydesipramine | 20100 | 9.83 | 0.518 | 1340 | 10.0 | -10.9 | 254 | 9.68 | 1.76 |

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

Data Analysis: A model-independent PK method of analysis was used to analyze plasma concentrations and urinary excretion data of desipramine and 2-hydroxydesipramine. CYP2D6 gene polymorphism yielding EM, IM, UM, and PM status/activity was characterized via genotyping assay of CYP2D6 alleles *1, *2, duplication gene *2XN, *3 to *8, *10, *17, *29 and *40. CYP2D6 genotyping was used to evaluate the potential impact of genetic polymorphism for any outliers (characterized by EM, IM, UM, and PM status), with respect to pharmacokinetics of desipramine, when given simultaneously with DVS SR. The plasma concentration data and PK parameters for desipramine and 2-hydroxydesipramine were compared between the monotherapy (ie, desipramine administered alone) and the combination therapy by using a 1-factor analysis of variance with subject as a random effect. Additionally, the geometric mean relative bioavailability of desipramine C_{max} and AUC and their 90% confidence limits were calculated to estimate the magnitude of the effect of DVS SR on the PK profile of desipramine (using desipramine monotherapy as the reference treatment).

Results: Thirty male subjects were enrolled and 23 subjects would complete the study. Seven subjects discontinued from the study: 5 because of AEs; 1 because of aggressive and threatening behavior, and 1 (3.3%) withdrew consent.

Mean desipramine plasma concentrations with and without concomitant administration of DVS SR are provided in the Attachments. Summary of the mean PK parameters for desipramine on plasma and urine are provided in the following tables. The results of statistical evaluation for desipramine with and without coadministration of DVS SR are also provided in the following table.

Whether desipramine is administered alone or in combination with DVS SR, desipramine plasma concentrations peaked at similar times. Mean C_{max} after concomitant administration of desipramine and DVS SR was about 50% higher than C_{max} when desipramine was administered alone. Ratio of means (90% confidence interval) for C_{max} was 152% (140% to 165%). AUC following concomitant administration of desipramine and DVS SR was approximately 83% higher than AUC when desipramine was administered alone. Ratio of means (90% confidence interval) for AUC was 190% (175% to 208%). Mean apparent clearance (Cl/F) decreased approximately 54% while mean renal clearance (CL_R) was approximately similar, showing a 7% increase with concomitant administration of desipramine and DVS SR. Mean urinary recovery (A_e %) increased approximately 66% with concomitant administration.

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Summary of 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.

Summary of 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.

Summary of the mean PK parameters for 2-hydroxydesipramine in plasma and urine, respectively, with and without coadministration of DVS SR are provided in the following table. The 2-hydroxydesipramine C_{max} after concomitant administration of desipramine and DVS SR was approximately 19% lower than C_{max} when desipramine was administered without DVS SR. Ratio of means (90% confidence interval) for C_{max} was 82% (76% to 88%). Coadministration of DVS SR increased the mean 2-hydroxydesipramine AUC by 24%. Ratio of means (90% confidence interval) for AUC was 124% (119% to 130%). The ratio of AUC for 2-hydroxydesipramine to desipramine changed from 0.65 to 0.41 after concomitant administration of DVS SR. Mean urinary recovery (Ae %) of 2-hydroxydesipramine remained constant with or without concomitant administration of DVS SR. Renal clearance (CL_R) of 2-hydroxydesipramine decreased approximately 20% during concomitant administration of desipramine and DVS SR.

Summary of Pharmacokinetic Parameters for 2-Hydroxydesipramine following Administration of Desipramine 50 mg without and with Co-Administration of DVS SR to Healthy Subjects

| Treatment | Variables | C _{max} (ng/mL) | t _{max} (h) | AUC (ng*h/mL) | t _{1/2} (h) | AUC Ratio* |
|--|-----------|-----------------------------|-------------------------|------------------|-------------------------|---------------|
| Desipramine 50 mg (n=28 ^a) | Mean±SD | 13.4±4.63 | 4.51±1.94 | 338±87 | 21.9±6.69 | 0.65±0.32 |
| | %CV | 34.6 | 43.0 | 25.6 | 30.5 | 48.7 |
| | Geo. Mean | 12.6 | 4.10 | 328 | 21.0 | 0.59 |
| | Min-Max | 6.33–26.2 | 2.00–8.03 | 219–601 | 10.6–42.4 | 0.20–1.62 |
| Desipramine 50 mg + DVS SR (n=23 ^{a, b}) | Mean±SD | 10.8±3.69 | 5.31±1.89 | 420±99 | 30.8±10.5 | 0.41±0.18 |
| | %CV | 34.2 | 35.7 | 23.5 | 34.2 | 43.5 |
| | Geo. Mean | 10.2 | 4.97 | 409 | 29.5 | 0.38 |
| | Min-Max | 4.04–21.6 | 3.00–8.02 | 253–700 | 15.5–70.8 | 0.13–0.95 |

Abbreviations: AUC=total area under the concentration-time curve; 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 peak concentration occurs.

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Summary of Pharmacokinetic Parameters (Urine) for 2-Hydroxydesipramine following Administration of Desipramine 50 mg 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 | 17.5±2.60 | 34.9±5.21 | 56.1±16.1 |
| | %CV | 14.9 | 14.9 | 28.6 |
| | Geo. Mean | 17.3 | 34.5 | 54.0 |
| | Min-Max | 12.8–22.7 | 25.6–45.4 | 28.5–95.9 |
| Desipramine 50 mg + DVS SR (n=20 ^b) | Mean±SD | 17.3±2.57 | 34.7±5.15 | 44.7±11.7 |
| | %CV | 14.8 | 14.8 | 26.1 |
| | Geo. Mean | 17.2 | 34.3 | 43.3 |
| | Min-Max | 12.4–22.8 | 24.9–45.7 | 27.3–74.2 |

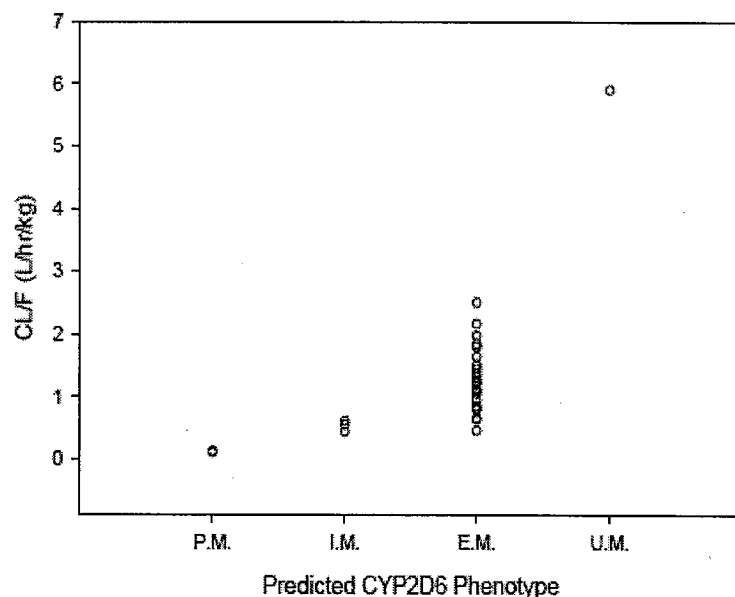
Pharmacogenomics

Results of pharmacogenomic testing for CYP2D6 genotype are provided in the Attachment. Subjects 16 and 19 were classified as poor metabolizers for the CYP2D6 phenotype and had the slowest desipramine observed Cl/F of 0.10 and 0.13 L/h/kg, respectively. These values are approximately one-tenth of the mean value for Cl/F of 1.38 L/h/kg (desipramine without DVS SR). In addition, these 2 subjects had 40% or greater of the AUC extrapolated past the last sampling time indicating that the sampling period of 120 hours was insufficient to characterize the PK profile for these 2 subjects, and therefore, statistics for AUC, $t_{1/2}$, V_z/F , and clearance values were excluded from these subjects. The following figure presents desipramine Cl/F in subjects receiving desipramine without DVS SR by CYP2D6 phenotype.

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Desipramine Apparent Clearance (Cl/F) in Subjects Receiving Desipramine 50 mg without DVS SR According to Genotype

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P.M.: Poor metabolizer.
I.M.: Intermediate metabolizer.
E.M.: Extensive metabolizer.
U.M.: Ultra-rapid metabolize

Safety Summary

The most frequently reported TEAEs ($\geq 10\%$) across all treatment periods were headache, vasodilatation, diarrhea, dry mouth, nausea, anxiety, dizziness, somnolence, tremor, abnormal vision, and impotence. The most frequently reported TEAEs after administration of a single desipramine dose were dizziness and somnolence, each reported in 3 of 30 (10%) subjects. The most frequently reported TEAEs during DVS SR titration in period 2 were dizziness and somnolence, each reported in 8 of 30 (26.7%) subjects; headache, vasodilatation, diarrhea, and nausea, each reported in 5 of 30 (16.7%) subjects; dry mouth and anxiety each reported in 4/30 (13.3%); and subjects; tremors, impotence, and abnormal vision, each reported in 3 of 30 (10%) subjects. All TEAEs were rated as mild or moderate in severity with the exception of 2 severe TEAEs during period 2 (DVS SR titration). Subject 183-001-000011, who reported a mild headache during DVS SR titration, also reported a severe headache during DVS SR taper that resolved in 11 hours after treatment with acetaminophen. Subject 183-001-000010 had hypertension that was described as severe.

The sponsor reported that there were significant increases in mean supine systolic BP after both treatments. Mean supine systolic BP was significantly increased from 4 to 24 hours after desipramine alone, with a maximum increase of 6.67 mm Hg 4 hours after test article administration. Mean supine systolic BP was also significantly increased after combined desipramine and DVS SR administration from 2 to 4 hours after test article administration, with a maximum mean increase of 10.02 mm Hg 4 hours after test article administration. The differences between the treatment groups were significant only at 4 hours after test article administration. Mean supine diastolic BP was significantly

increased at a single time point after desipramine administration: an increase of 3.09 mm Hg 24 hours after test article administration. Both significant increases and significant decreases in supine diastolic BP occurred after combined desipramine and DVS SR treatment. Supine diastolic BP significantly increased from 2 to 8 hours after test article administration with a maximum mean increase of 7.63 mm Hg 4 hours after test article administration. Supine diastolic BP significantly decreased from 72 to 96 hours postdose, with a maximum decrease of 4.67 mm Hg occurring 96 hours after test article administration. These mean changes were significantly different between the groups from 2 to 8 hours after test article administration.

Summary and Conclusion: Desvenlafaxine elimination occurs primarily through glucuronidation and renal excretion of desvenlafaxine and the glucuronide conjugate of desvenlafaxine. CYP3A4 metabolism of desvenlafaxine to N,O didesmethylvenlafaxine (NODV) is a minor elimination pathway (<5%). Desvenlafaxine is a weak inhibitor of CYP2D6 activity but has no inhibitory effects on other cytochrome P450s (CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4) and does not induce CYP3A4 expression. Desipramine is a secondary amine tricyclic used in the treatment of depression. Desipramine is primarily eliminated through CYP2D6-mediated metabolism to 2-hydroxydesipramine and is commonly used as a probe substrate for testing CYP2D6 activity. In the presence of CYP2D6 inhibitors, concentrations of desipramine are expected to increase while those of the primary metabolite, 2-hydroxydesipramine, would decrease. In the current study, desipramine exposure, as measured by C_{max} and AUC, increased by 50% and 83%, respectively, during coadministration of desipramine and DVS SR. The C_{max} of 2-hydroxydesipramine decreased by 19% and AUC for the metabolite increased by 24% in the desipramine with DVS SR treatment. Although Cl/F for desipramine decreased by approximately 54%, desipramine renal clearance remained unchanged by coadministration of desipramine with DVS SR. An approximately 21% decrease was seen in the renal clearance of 2-hydroxydesipramine.

Reviewer comments: *The reviewer agrees with the sponsor conclusions that DVS is likely to have inhibited the CYP2D6 mediated metabolism of desipramine to 2-hydroxydesipramine. Co-administration of desipramine and DVS should be avoided or the dosage of desipramine should be reduced.*

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ST 7-1. LISTING OF DEMOGRAPHIC AND BASELINE DATA
 CLINICAL INVESTIGATION OF DVS-223 PROTOCOL 3151A1-183

SAFETY POPULATION

INVESTIGATOR: 001-USA

| SUBJECT | TREATMENT SEQUENCE | RAND. CODE | SEX | DATE OF BIRTH | AGE (YEARS) | ETHNIC ORIGIN | BASELINE HEIGHT (CM) | BASELINE WEIGHT (KG) | BMI (kg/m ²) | PRIMARY DIAGNOSIS | INFORMED CONSENT DATE |
|---------|-----------------------|---------------|------|------------------|----------------|---------------------------------|----------------------------|----------------------------|-----------------------------|----------------------|-----------------------------|
| 000001 | DESIP/DESIP+DVS | 1 | Male | | 36 | Black or African American | 175 | 84.4 | 27.6 | Healthy Subject | 17JAN2005 |
| 000002 | DESIP/DESIP+DVS | 2 | Male | | 27 | Black or African American | 183 | 74.6 | 22.3 | Healthy Subject | 17JAN2005 |
| 000003 | DESIP/DESIP+DVS | 3 | Male | | 31 | Black or African American | 179 | 85 | 26.5 | Healthy Subject | 18JAN2005 |
| 000004 | DESIP/DESIP+DVS | 4 | Male | | 32 | White | 182 | 85 | 25.7 | Healthy Subject | 18JAN2005 |
| 000005 | DESIP/DESIP+DVS | 5 | Male | | 32 | Asian | 162 | 65.4 | 24.9 | Healthy Subject | 18JAN2005 |
| 000006 | DESIP/DESIP+DVS | 6 | Male | | 23 | White | 177 | 72.2 | 23.0 | Healthy Subject | 18JAN2005 |
| 000007 | DESIP/DESIP+DVS | 7 | Male | | 33 | Black or African American | 169 | 66.6 | 23.3 | Healthy Subject | 18JAN2005 |
| 000008 | DESIP/DESIP+DVS | 8 | Male | | 22 | Black or African American | 180 | 91 | 23.1 | Healthy Subject | 18JAN2005 |
| 000009 | DESIP/DESIP+DVS | 9 | Male | | 40 | White | 183 | 94.6 | 28.2 | Healthy Subject | 18JAN2005 |
| 000010 | DESIP/DESIP+DVS | 10 | Male | | 42 | Black or African American | 166 | 71 | 25.8 | Healthy Subject | 19JAN2005 |
| 000011 | DESIP/DESIP+DVS | 11 | Male | | 29 | Black or African American | 174 | 87.6 | 28.9 | Healthy Subject | 19JAN2005 |
| 000012 | DESIP/DESIP+DVS | 12 | Male | | 25 | Black or African American | 183 | 90.6 | 24.1 | Healthy Subject | 19JAN2005 |
| 000013 | DESIP/DESIP+DVS | 13 | Male | | 23 | Black or African American | 159 | 76 | 30.1 | Healthy Subject | 19JAN2005 |
| 000014 | DESIP/DESIP+DVS | 14 | Male | | 32 | Black or African American | 189 | 95.3 | 26.6 | Healthy Subject | 19JAN2005 |
| 000015 | DESIP/DESIP+DVS | 15 | Male | | 40 | White | 169 | 75 | 26.3 | Healthy Subject | 19JAN2005 |
| 000016 | DESIP/DESIP+DVS | 16 | Male | | 34 | Black or African American | 184 | 89.3 | 26.5 | Healthy Subject | 07FEB2005 |
| 000017 | DESIP/DESIP+DVS | 17 | Male | | 23 | Black or African American | 173 | 84.6 | 26.4 | Healthy Subject | 07FEB2005 |

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**ST 8-5: PHARMACOKINETIC PROFILE OF DESIPRAMINE IN SUBJECTS RECEIVING DESIPRAMINE 50 MG WITHOUT AND WITH
COADMINISTRATION of DVS SR**

| Treatment: 50 mg Desipramine | | | | | | | | | | |
|------------------------------|-------------------|-------------------|----------------------|-----------------------|---------------------|-------------------------|------------------|----------------|---------------------|-------------------|
| Subject | $t_{1/2}$ (hr) | t_{max} (hr) | C_{max} (ng/mL) | AUC_0 (ng*hr/mL) | AUC (ng*hr/mL) | AUC Extrapolated % | Cl/F (L/hr) | V_d/F (L) | Cl/F (L/hr/kg) | V_d/F (L/kg) |
| 1 | 23.30 | 8.00 | 11.00 | 512 | 531 | 3.00 | 94.11 | 3172 | 1.12 | 37.58 |
| 2 | 19.11 | 8.00 | 20.30 | 539 | 548 | 1.00 | 91.30 | 2518 | 1.22 | 33.75 |
| 3 | 14.74 | 8.00 | 10.10 | 229 | 233 | 4.44 | 214.45 | 4501 | 2.52 | 53.06 |
| 4 | 27.09 | 8.03 | 28.50 | 884 | 923 | 4.32 | 54.14 | 2116 | 0.84 | 24.00 |
| 5 | 16.80 | 8.00 | 19.50 | 458 | 462 | 1.06 | 108.13 | 2621 | 1.65 | 40.08 |
| 6 | 23.18 | 6.00 | 28.30 | 834 | 860 | 3.00 | 58.16 | 1945 | 0.81 | 26.94 |
| 7 | 50.42 | 8.00 | 30.30 | 1339 | 1682 | 20.41 | 29.72 | 2162 | 0.45 | 32.46 |
| 8 | 23.08 | 8.00 | 14.00 | 387 | 399 | 3.11 | 125.30 | 4172 | 1.38 | 45.84 |
| 9 | 13.45 | 6.00 | 13.10 | 241 | 244 | 2.06 | 205.07 | 3979 | 2.17 | 42.06 |
| 10 | 15.20 | 6.00 | 18.90 | 401 | 463 | 1.29 | 107.91 | 2366 | 1.52 | 33.32 |
| 11 | 20.25 | 4.00 | 19.20 | 425 | 434 | 2.08 | 115.31 | 3389 | 1.32 | 38.46 |
| 12 | 32.03 | 6.00 | 20.40 | 908 | 994 | 8.65 | 50.31 | 2325 | 0.62 | 28.04 |
| 13 | 26.89 | 8.00 | 34.10 | 1121 | 1177 | 4.81 | 42.47 | 1648 | 0.56 | 21.68 |
| 14 | 26.65 | 12.03 | 21.80 | 1047 | 1111 | 5.84 | 44.98 | 1729 | 0.47 | 18.05 |
| 15 | 17.19 | 8.00 | 15.80 | 451 | 456 | 2.38 | 109.55 | 2716 | 1.40 | 36.22 |
| 16 | 154.31 | 6.00 | 31.20 | 2439 | 5823 | 58.12 | 8.59 | 1912 | 0.10 | 21.29 |
| 17 | 18.59 | 3.00 | 28.00 | 483 | 489 | 2.48 | 106.62 | 2880 | 1.26 | 33.81 |
| 18 | 20.72 | 3.00 | 32.50 | 594 | 605 | 1.91 | 92.60 | 2469 | 0.96 | 28.71 |
| 19 | 83.36 | 12.00 | 30.40 | 2575 | 4078 | 36.88 | 12.28 | 1474 | 0.13 | 15.29 |
| 20 | 20.62 | 6.00 | 15.20 | 433 | 441 | 1.85 | 113.32 | 3370 | 1.81 | 53.64 |
| 21 | 19.63 | 6.07 | 22.70 | 504 | 512 | 1.53 | 97.72 | 2768 | 1.09 | 30.96 |
| 22 | 21.50 | 6.00 | 20.00 | 629 | 644 | 2.27 | 77.66 | 2409 | 0.86 | 26.59 |
| 23 | 10.84 | 6.00 | 7.88 | 134 | 135 | 5.34 | 399.67 | 5781 | 5.91 | 92.34 |
| 24 | 16.96 | 6.00 | 15.00 | 327 | 331 | 2.12 | 151.22 | 3701 | 1.98 | 48.44 |
| 25 | 24.40 | 8.00 | 16.30 | 592 | 613 | 3.43 | 91.53 | 2870 | 1.25 | 44.15 |
| 26 | 21.24 | 6.00 | 28.10 | 670 | 684 | 2.02 | 73.08 | 2239 | 1.13 | 34.66 |
| 27 | 21.10 | 6.00 | 26.20 | 717 | 729 | 1.66 | 68.58 | 2087 | 1.06 | 32.11 |
| 28 | 20.77 | 6.00 | 20.40 | 746 | 764 | 2.32 | 66.44 | 1961 | 0.83 | 24.75 |
| 29 | 16.59 | 6.03 | 13.00 | 304 | 308 | 2.69 | 162.38 | 3866 | 1.85 | 44.38 |

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ST 8-5: Pharmacokinetic Profile of Desipramine in Subjects Receiving Desipramine 50 mg Without and With Coadministration of DVS SR

| Treatment: 50 mg Desipramine +DVS SR | | | | | | | | | | |
|--------------------------------------|-------------------|-------------------|----------------------|-------------------------------|-----------------------------|-----------------------|----------------|----------------|-------------------|-------------------|
| Subject | $t_{1/2}$ (hr) | t_{max} (hr) | C_{max} (ng/mL) | AUC_0 (ng \cdot hr/mL) | AUC (ng \cdot hr/mL) | AUC Extrapolated % | CL/F (L/hr) | V_d/F (L) | CL/F (L/hr/kg) | V_d/F (L/kg) |
| 2 | 29.43 | 3.02 | 46.10 | 1235 | 1300 | 5.03 | 38.46 | 1633 | 0.52 | 21.89 |
| 4 | 32.26 | 3.00 | 47.20 | 1497 | 1626 | 7.93 | 30.75 | 1431 | 0.36 | 16.83 |
| 5 | 23.35 | 8.00 | 32.70 | 1052 | 1087 | 3.19 | 45.99 | 1549 | 0.70 | 23.69 |
| 6 | 26.55 | 8.00 | 33.60 | 1027 | 1069 | 3.90 | 46.76 | 1791 | 0.65 | 24.81 |
| 7 | 54.01 | 6.05 | 45.70 | 2177 | 2785 | 21.82 | 17.95 | 1399 | 0.27 | 21.00 |
| 8 | 28.60 | 3.00 | 24.50 | 761 | 806 | 5.58 | 62.07 | 2561 | 0.68 | 28.14 |
| 9 | 20.03 | 4.00 | 20.60 | 541 | 549 | 1.53 | 91.00 | 2630 | 0.96 | 27.80 |
| 11 | 22.07 | 8.00 | 23.30 | 774 | 798 | 2.92 | 62.68 | 1906 | 0.72 | 22.78 |
| 12 | 36.12 | 8.00 | 30.00 | 1214 | 1361 | 10.79 | 36.73 | 1914 | 0.46 | 23.75 |
| 14 | 37.55 | 8.00 | 27.70 | 1360 | 1527 | 11.00 | 32.73 | 1773 | 0.34 | 18.51 |
| 15 | 25.73 | 8.00 | 32.00 | 1096 | 1146 | 4.18 | 43.64 | 1620 | 0.58 | 21.60 |
| 16 | 165.04 | 8.00 | 48.80 | 3445 | 3255 | 59.27 | 6.06 | 1442 | 0.07 | 16.66 |
| 17 | 18.54 | 3.00 | 33.40 | 807 | 816 | 1.13 | 61.26 | 1639 | 0.72 | 19.37 |
| 18 | 29.12 | 6.00 | 36.40 | 1348 | 1438 | 6.31 | 34.76 | 1460 | 0.40 | 16.98 |
| 20 | 26.21 | 6.00 | 26.40 | 866 | 929 | 4.64 | 53.80 | 2034 | 0.86 | 32.49 |
| 21 | 27.80 | 3.00 | 24.30 | 939 | 997 | 5.83 | 50.16 | 2012 | 0.56 | 22.50 |
| 22 | 30.89 | 6.00 | 31.40 | 1115 | 1205 | 7.50 | 41.48 | 1848 | 0.46 | 20.40 |
| 23 | 13.32 | 6.00 | 20.70 | 391 | 395 | 2.77 | 126.52 | 2431 | 2.02 | 38.84 |
| 26 | 30.29 | 6.00 | 35.80 | 1243 | 1340 | 7.16 | 37.33 | 1631 | 0.58 | 25.25 |
| 27 | 26.10 | 8.00 | 31.30 | 1017 | 1063 | 4.36 | 47.03 | 1771 | 0.72 | 27.25 |
| 28 | 29.54 | 8.00 | 36.90 | 1439 | 1557 | 7.58 | 32.11 | 1369 | 0.41 | 17.28 |
| 29 | 25.23 | 12.00 | 18.20 | 790 | 819 | 3.49 | 61.99 | 2224 | 0.70 | 25.39 |

ST 8-6: DESCRIPTIVE STATISTICS OF DESIPRAMINE PHARMACOKINETIC PARAMETERS IN SUBJECTS RECEIVING DESIPRAMINE 50 MC WITHOUT AND WITH COADMINISTRATION OF DVS SR

| | $t_{0.5}$ (hr) | t_{max} (hr) | C_{max} (ng/mL) | AUC (ng*hr/mL) | CL/F (L/hr) | CL/F (L/hr/kg) | V_d/F (L/kg) | 0-120h (%) | λ_z (mg) | CL_e (L/h) |
|---------------------------------------|-------------------|-------------------|----------------------|-------------------|----------------|-------------------|-------------------|---------------|---------------------|-----------------|
| Treatment = 50 mg Desipramine | | | | | | | | | | |
| N ^a | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 27 | 27 | 27 |
| Mean | 21.718 | 8.649 | 20.796 | 642 | 105.049 | 1.377 | 30.893 | 1.172 | 0.587 | 0.887 |
| SD | 7.299 | 1.793 | 7.244 | 350 | 88.193 | 1.032 | 14.259 | 1.428 | 0.714 | 0.490 |
| SE | 1.379 | 0.339 | 1.369 | 66.205 | 13.076 | 0.195 | 2.695 | 0.275 | 0.137 | 0.094 |
| Min | 10.84 | 3.00 | 7.86 | 135 | 29.72 | 0.46 | 18.05 | 0.17 | 0.08 | 0.35 |
| Median | 20.75 | 6.00 | 20.15 | 539 | 82.71 | 1.18 | 33.78 | 0.82 | 0.41 | 0.79 |
| Max | 50.42 | 12.03 | 34.10 | 1682 | 369.67 | 5.91 | 92.34 | 7.92 | 3.96 | 2.96 |
| CV% | 33.6 | 27.0 | 34.8 | 54.5 | 85.9 | 75.0 | 39.8 | 121.8 | 121.7 | 55.2 |
| Geometric Mean | 20.783 | 8.399 | 19.502 | 558 | 89.647 | 1.162 | 34.853 | 0.864 | 0.431 | 0.805 |
| Treatment = 50 mg Desipramine +DVS SR | | | | | | | | | | |
| N ^a | 23 | 23 | 23 | 23 | 23 | 23 | 23 | 20 | 20 | 20 |
| Mean | 28.174 | 6.612 | 31.204 | 1176 | 48.578 | 0.645 | 23.831 | 1.954 | 0.977 | 0.948 |
| SD | 7.855 | 2.250 | 8.256 | 477 | 22.599 | 0.344 | 5.314 | 0.685 | 0.331 | 0.222 |
| SE | 1.638 | 0.469 | 1.721 | 98.512 | 4.712 | 0.072 | 1.108 | 0.149 | 0.074 | 0.050 |
| Min | 13.32 | 3.00 | 18.20 | 385 | 17.95 | 0.27 | 10.83 | 0.56 | 0.28 | 0.53 |
| Median | 27.80 | 6.00 | 31.40 | 1087 | 45.99 | 0.58 | 22.78 | 1.89 | 0.95 | 1.00 |
| Max | 54.01 | 12.00 | 47.20 | 2785 | 128.52 | 2.02 | 38.84 | 3.11 | 1.55 | 1.28 |
| CV% | 27.9 | 34.0 | 26.5 | 40.6 | 45.6 | 53.4 | 22.5 | 34.0 | 33.9 | 23.4 |
| Geometric Mean | 27.207 | 6.184 | 30.186 | 1093 | 45.762 | 0.589 | 23.108 | 1.823 | 0.911 | 0.920 |

a: Subjects 16, 19 were excluded from descriptive statistics because of high Extrapolated AUC(%) values.

b: Subject 12 was excluded from descriptive statistics because missing urine data.

c: Subjects 3, 10, 13, 24, 25 were excluded from descriptive statistics because of early discharge.

d: Subjects 1, 7, 16, 22 was excluded from descriptive statistics because missing urine data.

ST 8-8: DESCRIPTIVE STATISTICS OF 1-HYDROXYDESIPTAMINE PLASMA CONCENTRATIONS (NG/ML) IN SUBJECTS RECEIVING DESIPTAMINE 50 MG WITHOUT AND WITH COADMINISTRATION OF DVS SR

| Time (hr) | 0 | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 24 | 48 | 72 | 96 | 120 |
|---------------------------------------|-------|-------|-------|--------|--------|--------|--------|--------|--------|-------|-------|-------|-------|-------|
| Treatment = 50 mg Desipramine | | | | | | | | | | | | | | |
| N ^a | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Mean | 0.013 | 0.230 | 2.699 | 9.590 | 11.359 | 11.035 | 11.190 | 10.041 | 8.655 | 4.602 | 2.204 | 1.040 | 0.486 | 0.226 |
| SD | 0.067 | 0.291 | 2.092 | 5.565 | 4.796 | 3.584 | 3.417 | 2.501 | 2.604 | 1.188 | 0.917 | 0.592 | 0.400 | 0.265 |
| SE | 0.013 | 0.055 | 0.395 | 1.052 | 0.906 | 0.677 | 0.646 | 0.473 | 0.492 | 0.224 | 0.173 | 0.112 | 0.076 | 0.050 |
| Min | 0.000 | 0.000 | 0.000 | 3.050 | 4.240 | 4.680 | 5.540 | 6.330 | 4.610 | 2.360 | 0.554 | 0.000 | 0.000 | 0.000 |
| Median | 0.000 | 0.000 | 2.240 | 7.930 | 10.600 | 11.500 | 10.850 | 9.785 | 7.845 | 4.610 | 1.995 | 0.850 | 0.430 | 0.128 |
| Max | 0.352 | 0.909 | 8.570 | 26.200 | 21.400 | 19.200 | 20.100 | 16.400 | 16.100 | 7.230 | 4.030 | 2.250 | 1.300 | 0.602 |
| CV% | 529.2 | 126.4 | 77.5 | 58.0 | 42.2 | 32.5 | 30.5 | 24.9 | 32.3 | 24.7 | 41.6 | 57.0 | 82.3 | 117.5 |
| Geometric Mean | NC | NC | NC | 3.269 | 10.446 | 10.441 | 10.686 | 9.751 | 7.699 | 4.653 | 2.014 | NC | NC | NC |
| Treatment = 50 mg Desipramine +DVS SR | | | | | | | | | | | | | | |
| N ^a | 23 | 23 | 23 | 23 | 23 | 23 | 23 | 22 | 23 | 23 | 23 | 23 | 23 | 23 |
| Mean | 0.026 | 0.336 | 2.587 | 7.021 | 9.474 | 9.811 | 9.774 | 9.477 | 7.639 | 5.606 | 3.197 | 1.815 | 1.037 | 0.611 |
| SD | 0.123 | 0.331 | 1.843 | 2.703 | 4.010 | 3.632 | 2.878 | 2.971 | 2.537 | 1.398 | 0.956 | 0.719 | 0.478 | 0.368 |
| SE | 0.026 | 0.069 | 0.384 | 0.564 | 0.336 | 0.757 | 0.600 | 0.643 | 0.529 | 0.289 | 0.199 | 0.150 | 0.100 | 0.077 |
| Min | 0.000 | 0.000 | 0.291 | 1.910 | 3.290 | 3.380 | 4.040 | 3.620 | 3.260 | 2.670 | 1.640 | 0.611 | 0.590 | 0.000 |
| Median | 0.000 | 0.381 | 2.100 | 7.320 | 8.980 | 9.050 | 9.870 | 9.060 | 7.440 | 5.520 | 3.090 | 1.770 | 1.120 | 0.593 |
| Max | 0.589 | 1.000 | 7.590 | 11.100 | 21.600 | 19.700 | 18.100 | 15.400 | 13.300 | 8.950 | 5.330 | 3.630 | 2.010 | 1.300 |
| CV% | 479.6 | 98.5 | 71.2 | 38.5 | 42.3 | 37.0 | 29.4 | 31.4 | 33.0 | 24.8 | 29.9 | 39.6 | 46.1 | 60.2 |
| Geometric Mean | NC | NC | 1.966 | 6.412 | 3.724 | 9.185 | 9.369 | 9.011 | 7.236 | 5.426 | 3.061 | 1.631 | NC | NC |

Concentration Units: ng/mL.

NC - Not Calculated.

a: Subjects 16, 19 were excluded from descriptive statistics because of high Extrapolated AUC(%) values.

n: Subjects 3, 19, 13, 24, 25 were excluded from descriptive statistics because of early discharge.

ST 8-11: PHARMACOKINETIC PROFILE OF 2-HYDROXYDESI-PRAMINE IN SUBJECTS RECEIVING DESI-PRAMINE 50 MG WITHOUT AND WITH COADMINISTRATION OF DVS SR

| Treatment: 50 mg Desipramine | | | | | | | | | |
|------------------------------|-------------------|-------------------|----------------------|-----------------------|---------------------|-------------------------|-----------------|------------------|------------------|
| Subject | $t_{1/2}$ (hr) | t_{max} (hr) | C_{max} (ng/mL) | AUC_0 (ng·hr/mL) | AUC (ng·hr/mL) | AUC Extrapolated % | AUC Ratio* | CL/F (L/hr/kg) | Vz/F (L/kg) |
| 1 | 25.87 | 3.00 | 10.10 | 314 | 327 | 4.14 | 0.82 | 1.81 | 87.04 |
| 2 | 18.78 | 3.00 | 13.90 | 338 | 347 | 5.22 | 0.83 | 1.93 | 46.88 |
| 3 | 13.81 | 2.03 | 13.90 | 278 | 281 | 3.20 | 1.21 | 2.09 | 41.67 |
| 4 | 26.20 | 8.03 | 13.60 | 470 | 487 | 3.38 | 0.53 | 1.21 | 45.68 |
| 5 | 14.75 | 2.00 | 18.00 | 324 | 329 | 3.50 | 0.71 | 2.32 | 49.40 |
| 6 | 24.18 | 6.00 | 9.90 | 328 | 340 | 3.38 | 0.39 | 2.04 | 71.14 |
| 7 | 42.39 | 8.00 | 6.33 | 280 | 329 | 14.91 | 0.20 | 2.28 | 139.54 |
| 8 | 21.77 | 3.00 | 8.20 | 214 | 220 | 4.77 | 0.55 | 2.49 | 78.28 |
| 9 | 12.87 | 2.00 | 20.30 | 314 | 317 | 2.10 | 1.30 | 1.67 | 31.23 |
| 10 | 15.11 | 3.00 | 18.70 | 309 | 314 | 3.85 | 0.68 | 2.24 | 48.90 |
| 11 | 18.58 | 4.00 | 14.30 | 260 | 264 | 2.95 | 0.81 | 2.16 | 57.84 |
| 12 | 30.48 | 6.00 | 7.07 | 318 | 343 | 7.30 | 0.35 | 1.81 | 79.54 |
| 13 | 27.06 | 8.00 | 8.89 | 295 | 310 | 4.93 | 0.26 | 2.12 | 82.80 |
| 14 | 31.23 | 4.00 | 8.04 | 404 | 440 | 8.21 | 0.40 | 1.19 | 53.45 |
| 15 | 16.37 | 3.00 | 15.40 | 349 | 352 | 1.75 | 0.77 | 1.90 | 44.78 |
| 16 | 72.59 | 96.00 | 0.33 | 15 | 63 | 44.19 | 0.01 | 8.90 | 932.04 |
| 17 | 7.63 | 3.00 | 16.40 | 240 | 246 | 4.78 | 0.52 | 2.40 | 61.12 |
| 18 | 24.35 | 3.00 | 14.30 | 278 | 287 | 3.13 | 0.47 | 2.02 | 71.04 |
| 19 | 108.33 | 12.00 | 0.57 | 50 | 97 | 47.85 | 0.02 | 5.38 | 839.41 |
| 20 | 23.84 | 6.00 | 13.80 | 325 | 334 | 2.74 | 0.76 | 2.39 | 82.24 |
| 21 | 21.19 | 4.00 | 9.11 | 232 | 238 | 4.15 | 0.47 | 2.35 | 71.87 |
| 22 | 21.82 | 6.00 | 10.90 | 243 | 250 | 4.57 | 0.39 | 2.21 | 69.45 |
| 23 | 10.62 | 3.00 | 20.00 | 217 | 219 | 3.87 | 1.82 | 3.65 | 55.80 |
| 24 | 19.21 | 6.00 | 15.20 | 295 | 300 | 2.79 | 0.91 | 2.18 | 60.48 |
| 25 | 23.55 | 4.03 | 12.10 | 393 | 404 | 2.85 | 0.66 | 1.50 | 64.63 |
| 26 | 20.84 | 6.00 | 15.40 | 404 | 412 | 1.92 | 0.60 | 1.22 | 56.52 |
| 27 | 23.25 | 2.00 | 28.20 | 587 | 601 | 2.32 | 0.82 | 1.29 | 42.08 |
| 28 | 23.14 | 6.00 | 11.10 | 406 | 419 | 3.08 | 0.55 | 1.51 | 50.32 |
| 29 | 17.32 | 6.03 | 12.40 | 285 | 289 | 2.56 | 0.94 | 1.98 | 49.41 |
| 30 | 29.89 | 6.00 | 9.31 | 422 | 451 | 6.61 | 0.37 | 1.80 | 77.04 |

ST-8-11. Pharmacokinetic Profile of 2-Hydroxydesipramine in Subjects Receiving Desipramine 50 mg Without and With Coadministration of DVS SR

| Treatment: 50 mg Desipramine +DVS SR | | | | | | | | | |
|--------------------------------------|-------------------|-------------------|----------------------|-----------------------|---------------------|-------------------------|-----------------|------------------|------------------|
| Subject | $t_{1/2}$ (hr) | t_{max} (hr) | C_{max} (ng/mL) | AUC_t (ng*hr/mL) | AUC (ng*hr/mL) | AUC Extrapolated % | AUC Ratio* | CL/F (L/hr/kg) | Vz/F (L/kg) |
| 1 | 31.22 | 3.00 | 8.29 | 376 | 404 | 8.93 | 0.42 | 1.47 | 66.06 |
| 2 | 28.69 | 4.00 | 10.60 | 374 | 393 | 4.89 | 0.30 | 1.70 | 70.54 |
| 4 | 36.92 | 3.00 | 11.20 | 463 | 522 | 11.32 | 0.32 | 1.13 | 59.99 |
| 5 | 21.49 | 4.00 | 13.20 | 431 | 442 | 2.40 | 0.41 | 1.73 | 53.60 |
| 6 | 27.42 | 3.00 | 8.98 | 340 | 356 | 4.53 | 0.33 | 1.94 | 78.88 |
| 7 | 70.76 | 6.05 | 4.04 | 245 | 355 | 31.03 | 0.13 | 2.11 | 215.70 |
| 8 | 27.99 | 3.00 | 9.59 | 281 | 296 | 5.22 | 0.37 | 1.85 | 74.85 |
| 9 | 21.67 | 4.00 | 16.00 | 397 | 407 | 4.28 | 0.74 | 1.30 | 40.55 |
| 11 | 23.25 | 6.00 | 11.00 | 358 | 370 | 3.17 | 0.46 | 1.54 | 51.77 |
| 12 | 35.10 | 6.00 | 7.64 | 351 | 389 | 9.91 | 0.29 | 1.59 | 60.70 |
| 14 | 42.32 | 6.00 | 8.91 | 464 | 543 | 14.61 | 0.36 | 0.96 | 56.66 |
| 15 | 26.58 | 6.00 | 13.30 | 463 | 486 | 4.68 | 0.42 | 1.37 | 52.58 |
| 16 | 560.06 | 4.00 | 0.58 | 56 | 375 | 85.03 | 0.05 | 1.48 | 1198.60 |
| 17 | 19.66 | 3.00 | 13.40 | 315 | 321 | 3.41 | 0.39 | 1.84 | 52.24 |
| 18 | 31.27 | 6.00 | 7.77 | 360 | 390 | 7.57 | 0.27 | 1.49 | 67.26 |
| 20 | 30.31 | 4.00 | 11.40 | 388 | 414 | 6.24 | 0.45 | 1.93 | 84.38 |
| 21 | 28.79 | 6.00 | 7.95 | 282 | 311 | 5.99 | 0.31 | 1.80 | 74.75 |
| 22 | 34.40 | 6.00 | 5.87 | 230 | 253 | 9.22 | 0.21 | 2.16 | 108.26 |
| 23 | 15.54 | 3.02 | 21.60 | 369 | 375 | 3.65 | 0.95 | 2.13 | 47.75 |
| 26 | 30.47 | 6.00 | 11.70 | 484 | 521 | 7.26 | 0.39 | 1.48 | 65.28 |
| 27 | 31.07 | 6.00 | 15.40 | 650 | 700 | 7.17 | 0.66 | 1.10 | 49.25 |
| 28 | 34.07 | 6.00 | 10.30 | 482 | 536 | 9.91 | 0.34 | 1.18 | 57.94 |
| 29 | 30.63 | 6.00 | 8.48 | 388 | 414 | 6.36 | 0.51 | 1.38 | 60.92 |
| 30 | 29.34 | 8.02 | 10.40 | 420 | 454 | 7.84 | 0.31 | 1.79 | 75.63 |

* $AUC\ Ratio = AUC_{2-hydroxy\ desipramine} / AUC_{desipramine}$

**ST 8-12: DESCRIPTIVE STATISTICS OF 2-HYDROXYDESIPRAMINE PHARMACOKINETIC PARAMETERS IN SUBJECTS RECEIVING
DESIPRAMINE 50 MG
WITHOUT AND WITH COADMINISTRATION OF DVS SR**

| | $t_{1/2}$ (hr) | $t_{1/2\alpha}$ (hr) | C_{max} (ng/mL) | AUC (ng*hr/mL) | AUC Ratio ^a | CL/P (L/hr/kg) | V_d/F (L/kg) | 0-120h (%) | Δc (mg) | CL_R (L/h) |
|---------------------------------------|-------------------|-------------------------|----------------------|-------------------|---------------------------|-------------------|-------------------|---------------|--------------------|-----------------|
| Treatment = 50 mg Desipramine | | | | | | | | | | |
| N ^{a, b} | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 27 | 27 | 27 |
| Mean | 21.922 | 4.505 | 13.373 | 338 | 0.853 | 2.029 | 62.533 | 34.812 | 17.455 | 56.143 |
| SD | 6.687 | 1.935 | 4.833 | 87 | 0.318 | 0.473 | 20.461 | 5.211 | 2.604 | 16.059 |
| SE | 1.264 | 0.366 | 0.876 | 16.361 | 0.080 | 0.089 | 3.867 | 1.003 | 0.501 | 3.091 |
| Min | 10.62 | 2.00 | 6.33 | 219 | 0.20 | 1.19 | 31.23 | 25.59 | 12.80 | 28.47 |
| Median | 21.90 | 4.00 | 13.70 | 328 | 0.81 | 2.03 | 59.16 | 34.50 | 17.25 | 53.72 |
| Max | 42.39 | 9.03 | 26.20 | 601 | 1.62 | 3.65 | 139.54 | 45.39 | 22.69 | 85.87 |
| CV% | 30.5 | 43.0 | 34.8 | 25.8 | 48.7 | 23.3 | 32.7 | 14.9 | 14.9 | 28.6 |
| Geometric Mean | 20.986 | 4.100 | 12.832 | 328 | 0.588 | 1.977 | 59.864 | 34.534 | 17.267 | 53.983 |
| Treatment = 50 mg Desipramine +DVS SR | | | | | | | | | | |
| N ^{a, c, d} | 23 | 23 | 23 | 23 | 23 | 23 | 23 | 20 | 20 | 20 |
| Mean | 30.824 | 5.308 | 10.783 | 420 | 0.406 | 1.609 | 71.545 | 34.695 | 17.347 | 44.720 |
| SD | 10.534 | 1.894 | 3.885 | 99 | 0.177 | 0.346 | 34.773 | 5.148 | 2.573 | 11.694 |
| SE | 2.197 | 0.395 | 0.768 | 20.593 | 0.037 | 0.072 | 7.251 | 1.151 | 0.575 | 2.615 |
| Min | 15.54 | 3.00 | 4.04 | 253 | 0.13 | 0.96 | 40.55 | 24.89 | 12.44 | 27.28 |
| Median | 30.31 | 6.00 | 10.40 | 404 | 0.37 | 1.59 | 65.26 | 35.61 | 17.51 | 42.89 |
| Max | 70.76 | 9.02 | 21.69 | 700 | 0.95 | 2.18 | 215.70 | 45.65 | 22.82 | 74.17 |
| CV% | 34.2 | 35.7 | 34.2 | 23.5 | 43.5 | 21.5 | 48.6 | 14.8 | 14.8 | 26.1 |
| Geometric Mean | 29.497 | 4.971 | 10.201 | 409 | 0.375 | 1.571 | 68.870 | 34.317 | 17.156 | 43.340 |

a: Subjects 16, 19 were excluded from descriptive statistics because of high Extrapolated AUC(%) values.

b: Subject 22 was excluded from descriptive statistics because missing urine data.

c: Subjects 8, 10, 13, 24, 25 were excluded from descriptive statistics because of early discharge.

d: Subjects 1, 7, 16, 22 was excluded from descriptive statistics because missing urine data.

^a AUC Ratio = $AUC_{2\text{-hydroxy desipramine}}/AUC_{\text{desipramine}}$

ST 8-14: DESCRIPTIVE STATISTICS OF DESVENLAFAXINE PLASMA CONCENTRATIONS ON DAYS 12, 13, AND 14

| Day | 12 | 13 | 14 |
|----------------|---------|---------|---------|
| N* | 24 | 24 | 24 |
| Mean | 575.136 | 610.831 | 644.784 |
| SD | 171.710 | 178.753 | 159.788 |
| SE | 35.060 | 36.488 | 32.612 |
| Min | 178.91 | 140.61 | 208.07 |
| Median | 618.33 | 669.56 | 691.77 |
| Max | 856.95 | 841.43 | 901.49 |
| CV% | 29.9 | 29.3 | 24.8 |
| Geometric Mean | 543.081 | 573.597 | 619.988 |

* Data for Subject 3, 10, 13 were excluded from the descriptive statistics because one or more DVS-SR concentration for each of the 3 subjects was not available.

*Appears This Way
On Original*

ST 8-15. CYP2D6 GENOTYPE AND PREDICTED CYP2D6 PHENOTYPE

| Subject | Final Genotype | Predicted CYP2D6 Phenotype |
|---------|----------------|----------------------------|
| 1 | | Extensive metabolizer |
| 2 | | Extensive metabolizer |
| 3 | | Extensive metabolizer |
| 4 | | Extensive metabolizer |
| 5 | | Extensive metabolizer |
| 6 | | Extensive metabolizer |
| 7 | | Intermediate metabolizer |
| 8 | | Extensive metabolizer |
| 9 | | Extensive metabolizer |
| 10 | | Extensive metabolizer |
| 11 | | Extensive metabolizer |
| 12 | | Intermediate metabolizer |
| 13 | | Intermediate metabolizer |
| 14 | | Extensive metabolizer |
| 15 | | Extensive metabolizer |
| 16 | | Poor metabolizer |
| 17 | | Extensive metabolizer |
| 18 | | Extensive metabolizer |
| 19 | | Poor metabolizer |
| 20 | | Extensive metabolizer |
| 21 | | Extensive metabolizer |
| 22 | | Extensive metabolizer |
| 23 | | Ultra-rapid metabolizer |
| 24 | | Extensive metabolizer |
| 25 | | Extensive metabolizer |
| 26 | | Extensive metabolizer |
| 27 | | Extensive metabolizer |
| 28 | | Extensive metabolizer |
| 29 | | Extensive metabolizer |
| 30 | | Extensive metabolizer |

Study Title (0600D3-186-US, CSR 48798): An Open-Label, 4-Period, Randomized Crossover Study Of The Pharmacokinetic Profile And Tolerability Of 3 New Dosage Strengths Of DVS-233 SR In Healthy Adults.

Objectives: The primary objective of this study was to evaluate the pharmacokinetic profile of single oral doses of 3 new dosage formulations (50 mg, 100 mg, and 200 mg) of desvenlafaxine succinate monohydrate sustained release (DVS-233 SR, DVS-SR) compared with the 75-mg SR formulation of DVS. The secondary objective was to compare the safety and tolerability of single oral doses of 3 new dosage formulations of DVS SR with those of the 75-mg SR formulation of DVS.

Study Design: This was an open-label, randomized, inpatient, single-dose, 4-period, crossover study performed to evaluate the pharmacokinetic profile and tolerability of 3 new dosage formulations of desvenlafaxine SR. Twenty healthy male subjects from 18 to 45 (mean \pm SD = 37 \pm 6.2 years) years of age, inclusive, with no clinically important medical history and no important findings on physical examination, 12-lead electrocardiograph (ECG), or clinical laboratory evaluations were enrolled. The mean \pm SD height and weight were 174.4 \pm 5.5 cm and 77.4 \pm 6.8 kg, respectively. Each subject participated in the study for approximately 3 weeks which included 4 single-dose treatment periods separated by washout intervals of at least 5 days and also a screening phase within 2 weeks before the initial administration of DVS SR. DVS SR 50-mg, 100-mg, and 200-mg oral tablets; doses of 100 mg and 200 mg, were administered after an overnight fast of approximately 10 hours. Batch numbers were 2002B0105, 2002B0109, and 2002B0107 for the 50-, 100- and 200-mg tablets, respectively. DVS-233 SR 75-mg oral tablets; dose of 150 mg, was administered after an overnight fast of approximately 10 hours. Batch number was 2002B0050. Each dose was administered with 240 mL of room-temperature tap water while the subject was in an upright position. The following table provides the treatment sequence.

Treatment Sequence for DVS-233 SR Formulations

| Sequence Group | Period 1 | Period 2 | Period 3 | Period 4 |
|----------------|------------|------------|------------|------------|
| A | 2 x 75 mg | 2 x 50 mg | 1 x 100 mg | 1 x 200 mg |
| B | 2 x 50 mg | 1 x 200 mg | 2 x 75 mg | 1 x 100 mg |
| C | 1 x 100 mg | 2 x 75 mg | 1 x 200 mg | 2 x 50 mg |
| D | 1 x 200 mg | 1 x 100 mg | 2 x 50 mg | 2 x 75 mg |

Blood samples (5 mL each) for the desvenlafaxine assays were collected at scheduled time points (0, 0.5, 1, 2, 4, 6, 8, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours post dose). A total of 15 pharmacokinetic samples were collected for each subject in each treatment period.

Analytical Method: Plasma was assayed for desvenlafaxine levels using a validated high-performance liquid chromatography method with fluorescence detection. Based on a 1.0-mL plasma sample, the method has a minimum quantifiable concentration of 5.0 ng/mL for desvenlafaxine. The performance of the desvenlafaxine assays during the analysis of the plasma samples from this study is summarized in the following table.

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

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

Table 6.5.2-2. Analytical Summary of Desvenlafaxine Assays

| Analyte | HIGH QC (300.0 NG/ML) | | | MEDIUM QC (60.0 NG/ML) | | | LOW QC (15.0 NG/ML) | | |
|----------------|--------------------------|------|--------|---------------------------|------|--------|---------------------|------|--------|
| | Conc. | CV% | Bias % | Conc. | CV% | Bias % | Conc. | CV% | Bias % |
| Desvenlafaxine | 297.3 | 7.26 | -0.90 | 58.88 | 5.90 | -1.86 | 14.97 | 5.54 | -0.21 |

Abbreviations: QC = quality control.

Data Analysis: The plasma concentrations of desvenlafaxine were analyzed by using model-independent pharmacokinetic methods. Pharmacodynamic assessments were made by using a 100-mm visual analogue scale (VAS) for nausea. The desvenlafaxine plasma concentrations at each sampling time, the desvenlafaxine pharmacokinetic parameters, and the VAS nausea scores were compared among the 4 treatments by using an analysis of variance for a 4-period crossover design. Assessments of the magnitude of differences between the 3 new dosage formulations and the 75-mg tablet were made using the 2-sided bioequivalence test procedure applied to dose normalized log-transformed data. Safety and tolerability were evaluated from results of spontaneously reported signs and symptoms, scheduled physical examinations, nausea VAS, blood pressure and pulse rate measurements, ECGs, and clinical laboratory evaluations. All adverse events were monitored throughout the study and were assessed by the investigator as they occurred.

Results: Mean plasma concentration time profile is provided in the Attachments. The statistical comparisons among the treatments, including the geometric mean relative bioavailability and 90% confidence limits area provided in the following tables. The mean desvenlafaxine plasma concentrations for each treatment, are provided in the Attachments. Dose-normalized C_{max} and AUC, respectively, for each treatment are provided in the Attachments. Summary of the mean \pm SD and geometric mean of estimates of the desvenlafaxine pharmacokinetic parameter values for the 4 treatments as well as the statistical comparisons among the treatments are provided in the following table.

Desvenlafaxine Pharmacokinetic Parameters

| Treatment | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | AUC _T (ng•h/mL) | AUC (ng•h/mL) |
|--|------------------------------|-------------------------|-------------------------|-------------------------------|---------------------|
| DVS-233 SR 2x75 mg | 272 ± 49 ^a 267 | 7.6 ± 4.3 6.7 | 9.7 ± 1.8 9.5 | 6765 ± 1576 6524 | 6908 ± 1603 6667 |
| DVS-233 SR 2x50 mg | 165 ± 33 161 | 6.6 ± 3.3 6.0 | 9.5 ± 1.7 9.4 | 3825 ± 1167 3633 | 3946 ± 1174 3758 |
| DVS-233 SR 1x100 mg | 182 ± 40 178 | 7.4 ± 3.6 6.8 | 9.4 ± 1.4 9.3 | 4426 ± 1342 4218 | 4542 ± 1342 4342 |
| DVS-233 SR 1x200 mg | 354 ± 67 348 | 9.1 ± 6.2 7.7 | 9.7 ± 1.5 9.6 | 9038 ± 2126 8807 | 9215 ± 2156 8984 |
| <i>4-Period Crossover Analysis of Variance of Log-Transformed Data^{a,c}</i> | | | | | |
| Sequence | 0.53 | 0.35 | 0.57 | 0.20 | 0.21 |
| Subject (sequence) | 0.003** | 0.02* | 0.001** | 0.001** | 0.001** |
| Treatment | 0.20 | 0.34 | 0.84 | 0.04* | 0.05 |
| Period | 0.81 | 0.35 | 0.61 | 0.01* | 0.01* |
| <i>Least Squares Geometric Mean Ratio^d (Relative Bioavailability) and 90% Confidence Limits^b</i> | | | | | |
| DVS-233 SR 2x50 mg | 90% | — | — | 84% | 85% |
| | 85-96% | | | 74-95% | 75-96% |
| DVS-233 SR 1x100 mg | 100% | — | — | 97% | 98% |
| | 91-110% | | | 86-109% | 87-109% |
| DVS-233 SR 1x200 mg | 98% | — | — | 101% | 101% |
| | 88-108% | | | 93-110% | 93-109% |

a: Mean ± SD and geometric mean.

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

b: Prior to statistical calculations, C_{max}, AUC_T, and AUC were normalized to the 100-mg dose.

c: *p < 0.05, **p < 0.01.

d: DVS-233 SR 2 x 75-mg treatment is the reference treatment.

Following administration of DVS-233 SR 2 x 75-mg treatment, the mean t_{max} and the mean half-life (t_{1/2}) were similar for all treatments ranging from 7 to 9 hours and 9.4 to 9.7 hours, respectively. Following administration of the 100-mg doses of DVS-233 SR (2 x 50-mg and 1 x 100-mg treatments), the mean C_{max} differed by approximately 10% (~165 ng/mL and ~182 ng/mL, respectively) and the mean AUC differed by approximately 15%.

The 50-mg, 100-mg, and 200-mg DVS-233 SR tablets all met the bioequivalence criteria for dose-normalized C_{max} compared with the reference 75-mg tablets. Additionally, both the 100-mg and the 200-mg tablets met the bioequivalence criteria for dose-normalized AUC. Only the 2 x 50-mg treatment missed the bioequivalence criteria for AUC. The dose-normalized AUC geometric mean was 85%, and the 90% confidence interval was 75% to 96%.

The mean nausea ratings versus time profiles for all 4 treatments are presented in the Attachments. There were no statistical differences among the 4 formulations in the mean VAS

E_{max}, tE_{max}, or AURC. Only 1 subject (18601-003) reported a VAS \geq 10 mm (score was 15 mm) at 2 hours postdose with DVS-233 SR 1 x 200-mg.

Safety Summary: No serious adverse events, withdrawals or deaths occurred in the study. The most common Treatment Emergent Adverse Event (TEAEs) was nausea, reported at 2 x 50 mg (15%), 1 x 200 mg (10%) and 2 x 75 mg (5%) doses. Statistically significant adjusted mean changes in systolic and diastolic blood pressures were noted after administration of desvenlafaxine SR 1 x 200 mg, 2 x 50 mg, and 2 x 75 mg in at least 1 reporting time period. Adjusted mean changes in pulse rate were statistically significant in at least 1 reporting time period for all doses. None of these changes were found to be clinically important by the sponsor's (WR) medical monitor. Two (2) subjects had QTc intervals that met the criteria for potential clinical importance. Subject 18601-007 had screening and baseline QTc intervals of 404 ms and 410 ms, respectively; 72 hours after receiving 2 x 75 mg of desvenlafaxine SR, the QTc interval was 465 ms. This normalized to 407 ms by the next day and to 389 ms by the end of the study. Subject 18601-017 had screening and baseline QTc intervals of 400 ms and 417 ms, respectively. Seventy-two (72) hours after receiving 1 x 200 mg of desvenlafaxine SR, he had a QTc interval of 451 ms. Again, this normalized to 433 ms by the next day and to 384 ms by the end of the study. These 2 observations were isolated, occurring in only 1 ECG recording for each subject. The medical monitor judged that these were spurious changes and were not clinically important.

Conclusion: Both C_{max} and AUC of the 100-mg and 200-mg formulations met the dose normalized bioequivalence criteria compared with the 75-mg formulation. However, the 50-mg formulation did not meet the bioequivalence criteria.

Reviewer's comment: *The reviewer agrees that with the sponsor's conclusions. Nausea was the most frequent adverse event. Incidences of changes in blood pressure were noted.*

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Attachments

ST 8-2. STATISTICAL COMPARISONS OF DESVENLAFAXINE CONCENTRATIONS IN HEALTHY SUBJECTS RECEIVING A SINGLE ORAL DOSE
OF DVS-233 SR

SUPPORTIVE TABLE ST 8-2 - Statistical Comparisons of Desvenlafaxine Concentrations
In Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR

Protocol 060003-106-US

16:51 Friday
February 21, 2003

| | | (UNIT = NG/ML) | | | | | | | | | | | | | | |
|--|------|-------------------------|-------|--------|--------|--------|--------|--------|--------|--------|--------|-------|-------|--------|--------|----|
| | | TIME AFTER DOSE (HOURS) | | | | | | | | | | | | | | |
| | | 0 | 0.5 | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 16 | 24 | 36 | 48 | 60 | 72 |
| DVS-233 SR 2x75-mg | | | | | | | | | | | | | | | | |
| MEAN | 0.00 | 21.31 | 59.63 | 126.37 | 225.93 | 246.25 | 238.07 | 224.18 | 214.78 | 197.84 | 158.63 | 73.38 | 30.28 | 11.78 | 3.73 | |
| S.D. | 0.00 | 11.15 | 25.07 | 44.71 | 60.53 | 54.82 | 49.96 | 51.68 | 56.31 | 59.34 | 58.19 | 29.36 | 13.04 | 7.28 | 4.73 | |
| % CV | . | 52.33 | 42.04 | 35.38 | 26.67 | 22.26 | 20.61 | 23.06 | 26.17 | 29.36 | 36.64 | 39.60 | 43.05 | 61.77 | 127.11 | |
| DVS-233 SR 2x50-mg | | | | | | | | | | | | | | | | |
| MEAN | 0.00 | 17.25 | 48.87 | 92.88 | 142.77 | 185.39 | 150.56 | 139.45 | 128.18 | 109.89 | 78.80 | 38.48 | 17.35 | 5.37 | 1.08 | |
| S.D. | 0.00 | 10.38 | 30.45 | 36.46 | 32.66 | 36.85 | 35.59 | 31.33 | 32.42 | 36.47 | 36.04 | 20.24 | 11.07 | 6.10 | 2.71 | |
| % CV | . | 60.18 | 61.84 | 39.58 | 22.88 | 23.71 | 23.64 | 22.46 | 25.10 | 33.19 | 45.74 | 52.58 | 63.81 | 103.84 | 248.94 | |
| DVS-233 SR 1x100-mg | | | | | | | | | | | | | | | | |
| MEAN | 0.00 | 14.63 | 46.71 | 93.58 | 153.86 | 173.21 | 162.55 | 147.49 | 144.10 | 129.79 | 98.36 | 46.44 | 19.38 | 7.28 | 1.77 | |
| S.D. | 0.00 | 9.04 | 17.56 | 29.25 | 44.95 | 46.79 | 38.77 | 32.87 | 35.13 | 37.25 | 38.58 | 24.23 | 11.15 | 5.75 | 3.37 | |
| % CV | . | 61.79 | 37.60 | 31.26 | 29.32 | 27.01 | 23.85 | 22.29 | 24.38 | 28.70 | 39.83 | 52.28 | 57.41 | 79.31 | 194.43 | |
| DVS-233 SR 1x200-mg | | | | | | | | | | | | | | | | |
| MEAN | 0.00 | 34.37 | 88.43 | 184.21 | 303.85 | 321.23 | 304.50 | 254.44 | 277.14 | 269.32 | 223.37 | 91.71 | 45.03 | 15.43 | 5.73 | |
| S.D. | 0.00 | 22.16 | 41.77 | 64.22 | 66.12 | 65.32 | 48.15 | 36.57 | 44.60 | 56.11 | 100.08 | 36.89 | 19.70 | 10.69 | 6.25 | |
| % CV | . | 64.47 | 47.23 | 34.86 | 21.91 | 20.34 | 15.81 | 14.42 | 15.98 | 20.84 | 44.80 | 40.22 | 43.23 | 69.27 | 109.10 | |
| P-VALUES FROM ANALYSIS OF VARIANCE FOR A FOUR-PERIOD CROSS-OVER DESIGN # | | | | | | | | | | | | | | | | |
| SOURCE OF VARIATION | | | | | | | | | | | | | | | | |
| SEQUENCE | - | .75 | .74 | .45 | .72 | .68 | .66 | .32 | .22 | .35 | .40 | .52 | .51 | .46 | .56 | |
| SUBSEQUENCE | - | .001 | .001 | .001 | .001 | .001 | .002 | .008 | .04 | .005 | .001 | .001 | .001 | .001 | .001 | |
| TREATMENT | - | .38 | .03 | .16 | .66 | .31 | .51 | .51 | .35 | .03 | .61 | .89 | .52 | .31 | .04 | |
| PERIOD | - | .98 | .07 | .02 | .46 | .10 | .63 | .29 | .26 | .02 | .885 | .001 | .002 | .885 | .001 | |

PRIOR TO STATISTICAL COMPARISONS, ALL DESVENLAFAXINE PLASMA CONCENTRATIONS WERE NORMALIZED TO THE 100-MG DOSE.

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**ST 8-3. PHARMACOKINETIC PARAMETERS OF DESVENLAFAXINE IN HEALTHY SUBJECTS RECEIVING A SINGLE ORAL DOSE OF
DVS-233 SR**

SUPPORTIVE TABLE ST 8-3 - Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR
Protocol 0600D3-186-US

16:51 Friday
February 21, 2003

| TREATMENT: Desvenlafaxine SR 2x75-mg Tablets | | | | | | | | |
|--|-----------------------------|-------------------------|------------------------------|-------------------------|---------------------------------|------|------------------|-----------------------------|
| SUBJECT | C _{MAX} (ng/mL) | T _{MAX} (h) | L _{AG} RDA (1/h) | t _{1/2} (h) | AUC _{0-∞} (ng·h/mL) | MIC | CL/F (L/h/kg) | V _d /F (L/kg) |
| 1 | 258.1 | 6.0 | 0.089 | 7.74 | 2855 | 2832 | 0.49 | 5.52 |
| 2 | 252.9 | 6.0 | 0.091 | 7.61 | 8420 | 6489 | 0.26 | 2.91 |
| 3 | 340.6 | 6.0 | 0.072 | 9.69 | 7774 | 7550 | 0.28 | 2.44 |
| 4 | 318.9 | 12.0 | 0.085 | 8.17 | 7810 | 7913 | 0.27 | 2.17 |
| 5 | 240.1 | 8.0 | 0.058 | 11.91 | 5915 | 7081 | 0.27 | 4.60 |
| 6 | 345.8 | 6.0 | 0.060 | 11.48 | 3902 | 9052 | 0.26 | 4.26 |
| 7 | 322.9 | 12.0 | 0.081 | 8.53 | 7171 | 7284 | 0.25 | 3.13 |
| 8 | 190.5 | 4.0 | 0.083 | 8.34 | 2355 | 2483 | 0.23 | 9.69 |
| 9 | 318.5 | 16.0 | 0.095 | 7.29 | 8888 | 9225 | 0.20 | 2.14 |
| 10 | 294.2 | 4.0 | 0.082 | 8.43 | 5705 | 5777 | 0.39 | 4.63 |
| 11 | 266.9 | 6.0 | 0.058 | 12.03 | 6681 | 6810 | 0.38 | 5.20 |
| 12 | 293.4 | 4.0 | 0.071 | 9.72 | 8125 | 8235 | 0.22 | 2.16 |
| 13 | 254.6 | 4.0 | 0.072 | 9.61 | 6603 | 6762 | 0.27 | 2.72 |
| 14 | 240.0 | 6.0 | 0.060 | 11.48 | 7256 | 7420 | 0.25 | 4.07 |
| 15 | 207.6 | 4.0 | 0.059 | 11.74 | 6906 | 7066 | 0.31 | 5.21 |
| 16 | 259.0 | 6.0 | 0.059 | 11.76 | 7123 | 7310 | 0.25 | 4.26 |
| 17 | 349.1 | 4.0 | 0.079 | 8.82 | 7168 | 7287 | 0.26 | 3.37 |
| 18 | 200.8 | 16.0 | 0.097 | 7.17 | 5522 | 5580 | 0.29 | 2.98 |
| 19 | 232.0 | 16.0 | 0.070 | 9.81 | 8185 | 8327 | 0.24 | 2.43 |
| 20 | 243.7 | 6.0 | 0.059 | 11.71 | 5940 | 6173 | 0.33 | 5.54 |
| MEAN | 271.5 | 7.6 | 0.074 | 9.65 | 6765 | 6808 | 0.31 | 4.22 |
| S.D. | 48.8 | 4.3 | 0.014 | 2.75 | 1576 | 1603 | 0.14 | 1.60 |
| % CV | 18.0 | 56.4 | 18.2 | 18.1 | 23.3 | 23.2 | 44.27 | 37.98 |
| GEOMETRIC MEAN | 267.4 | 6.7 | 0.073 | 9.50 | 6524 | 6667 | 0.29 | 4.00 |
| MIN | 190.5 | 4.0 | 0.058 | 7.17 | 2355 | 2483 | 0.20 | 2.14 |
| MAX | 349.1 | 16.0 | 0.097 | 12.03 | 8902 | 9225 | 0.33 | 9.69 |

. DATA NOT AVAILABLE.

+ SUBJECT WAS NOT USED IN SUMMARY STATISTICS CALCULATIONS

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SUPPORTIVE TABLE ST 8-3 - Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving a Single Oral Dose of DVS-133 SR

Protocol 050603-186-US

15:51 Friday
February 21, 2003

TREATMENT: Desvenlafaxine SR 2x50-mg tablets

| SUBJECT | C _{MAX} (ng/mL) | T _{MAX} (h) | L _{IN} SDA (1/h) | t _{1/2} (h) | AUC _t -- (ng*h/mL) -- | AUC | CL/F (L/h/kg) | V _d /F (L/kg) | C _{max} Ratio* (%) | AUC Ratio* (%) |
|-------------------|-----------------------------|-------------------------|------------------------------|-------------------------|-------------------------------------|------|------------------|-----------------------------|--------------------------------|-------------------|
| 1 | 162.2 | 12.0 | 0.076 | 9.08 | 3723 | 3886 | 0.33 | 4.36 | 94.3 | 148.3 |
| 2 | 146.3 | 6.0 | 0.078 | 9.88 | 2888 | 2653 | 0.43 | 5.52 | 86.2 | 61.3 |
| 3 | 192.6 | 6.0 | 0.074 | 9.38 | 3594 | 3732 | 0.38 | 4.73 | 84.9 | 70.4 |
| 4 | 210.7 | 8.0 | 0.091 | 7.64 | 3659 | 3744 | 0.38 | 4.18 | 98.1 | 71.0 |
| 5 | 184.3 | 6.0 | 0.061 | 11.42 | 4426 | 4602 | 0.27 | 4.53 | 115.2 | 97.5 |
| 6 | 189.4 | 4.0 | 0.055 | 12.58 | 4883 | 4747 | 0.31 | 5.92 | 82.2 | 78.7 |
| 7 | 173.4 | 6.0 | 0.056 | 10.48 | 4445 | 4645 | 0.27 | 4.03 | 80.5 | 85.7 |
| 8 | 122.0 | 4.0 | 0.087 | 7.94 | 2099 | 2225 | 0.61 | 7.04 | 96.8 | 134.4 |
| 9 | 159.4 | 16.0 | 0.112 | 6.18 | 5096 | 5165 | 0.24 | 2.16 | 75.1 | 84.0 |
| 10 | 186.6 | 12.0 | 0.082 | 9.45 | 4925 | 5002 | 0.39 | 3.57 | 95.1 | 129.9 |
| 11 | 131.8 | 6.0 | 0.063 | 11.26 | 3265 | 3394 | 0.48 | 6.51 | 74.1 | 74.8 |
| 12 | 217.4 | 6.0 | 0.062 | 11.10 | 6110 | 6236 | 0.20 | 3.20 | 111.2 | 113.6 |
| 13 | 128.0 | 4.0 | 0.072 | 9.67 | 4415 | 4566 | 0.26 | 3.69 | 75.4 | 101.3 |
| 14 | 178.6 | 6.0 | 0.073 | 8.88 | 4107 | 4203 | 0.28 | 4.04 | 111.6 | 84.9 |
| 15 | 131.0 | 2.0 | 0.060 | 11.48 | 1806 | 1912 | 0.76 | 12.54 | 96.1 | 40.6 |
| 16 | 198.4 | 6.0 | 0.065 | 10.62 | 4813 | 4896 | 0.25 | 3.83 | 114.9 | 100.5 |
| 17 | 191.5 | 4.0 | 0.065 | 10.59 | 4812 | 4963 | 0.26 | 3.96 | 82.3 | 102.2 |
| 18 | 101.5 | 6.0 | 0.096 | 7.25 | 1877 | 1972 | 0.54 | 5.69 | 75.8 | 53.0 |
| 19 | 158.2 | 6.0 | 0.086 | 9.08 | 3332 | 3494 | 0.38 | 4.45 | 100.2 | 62.9 |
| 20 | 129.0 | 6.0 | 0.086 | 8.06 | 2809 | 2894 | 0.47 | 5.43 | 78.8 | 70.3 |
| MEAN | 164.5 | 6.6 | 0.075 | 9.30 | 3825 | 3946 | 0.37 | 4.97 | 91.4 | 98.8 |
| S.D. | 32.7 | 3.3 | 0.034 | 1.69 | 1167 | 1174 | 0.14 | 2.12 | 14.0 | 28.0 |
| % CV | 19.9 | 49.3 | 19.1 | 17.8 | 30.5 | 29.7 | 38.20 | 42.85 | 15.2 | 31.5 |
| GEOMETRIC MEAN | 161.3 | 6.0 | 0.074 | 8.35 | 2633 | 2752 | 0.34 | 4.65 | 90.1 | 84.8 |
| MIN | 101.5 | 2.0 | 0.055 | 6.18 | 1806 | 1912 | 0.20 | 2.16 | 74.1 | 40.6 |
| MAX | 217.4 | 16.0 | 0.112 | 12.58 | 6110 | 6236 | 0.76 | 12.54 | 115.2 | 148.3 |

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SUPPORTIVE TABLE ST 8-3 - Pharmacokinetic Parameters of Desvenlafaxine
In Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR

Protocol S600D1-186-US

14151 Pri
February 21, 2

TREATMENT: Desvenlafaxine SR 1x100-mg tablet

| SUBJECT | C _{MAX} (ng/mL) | T _{MAX} (h) | LAMSDA (1/h) | t _{1/2} (h) | AUC _t -- (ng*h/mL) -- | AUC | CL/F (L/h/kg) | V _Z /F (L/kg) | C _{max} Ratio* (%) | AUC Ratio* (%) |
|-------------------|-----------------------------|-------------------------|-----------------|-------------------------|-------------------------------------|------|------------------|-----------------------------|--------------------------------|-------------------|
| 1 | 157.5 | 4.0 | 0.080 | 8.62 | 3122 | 2276 | 0.57 | 7.07 | 91.6 | 86.6 |
| 2 | 139.1 | 6.0 | 0.086 | 8.03 | 3127 | 2233 | 0.51 | 5.89 | 77.1 | 82.1 |
| 3 | 138.7 | 8.0 | 0.077 | 9.04 | 3721 | 2817 | 0.46 | 6.03 | 61.1 | 82.2 |
| 4 | 157.3 | 6.0 | 0.081 | 8.28 | 4785 | 4886 | 0.29 | 3.59 | 88.1 | 92.6 |
| 5 | 194.5 | 6.0 | 0.063 | 11.05 | 4323 | 4362 | 0.29 | 4.62 | 121.6 | 92.4 |
| 6 | 271.9 | 6.0 | 0.063 | 11.15 | 6198 | 6311 | 0.25 | 3.83 | 117.9 | 104.6 |
| 7 | 206.8 | 6.0 | 0.071 | 9.70 | 4376 | 4513 | 0.27 | 3.83 | 93.3 | 92.8 |
| 8 | 159.1 | 6.0 | 0.085 | 8.14 | 4028 | 4171 | 0.33 | 3.85 | 125.2 | 852.0 |
| 9 | 177.3 | 16.0 | 0.101 | 6.88 | 6024 | 6118 | 0.20 | 2.03 | 82.5 | 89.5 |
| 10 | 161.0 | 6.0 | 0.086 | 8.02 | 3390 | 3483 | 0.43 | 4.87 | 82.1 | 90.4 |
| 11 | 173.2 | 4.0 | 0.064 | 10.86 | 4093 | 4233 | 0.32 | 5.03 | 87.3 | 92.3 |
| 12 | 202.5 | 4.0 | 0.075 | 9.29 | 4912 | 5040 | 0.25 | 3.29 | 103.6 | 91.8 |
| 13 | 212.5 | 6.0 | 0.076 | 9.07 | 4698 | 4782 | 0.25 | 3.31 | 125.3 | 106.1 |
| 14 | 161.0 | 6.0 | 0.053 | 11.09 | 5059 | 5165 | 0.24 | 3.75 | 105.6 | 104.4 |
| 15 | 260.8 | 6.0 | 0.059 | 11.81 | 7494 | 7670 | 0.19 | 3.22 | 188.5 | 162.8 |
| 16 | 214.6 | 6.0 | 0.058 | 15.18 | 4568 | 4569 | 0.26 | 3.84 | 124.3 | 92.8 |
| 17 | 193.0 | 12.0 | 0.077 | 9.00 | 4173 | 4661 | 0.28 | 3.58 | 82.9 | 90.9 |
| 18 | 119.8 | 16.0 | 0.090 | 7.70 | 3126 | 3248 | 0.32 | 3.67 | 88.8 | 87.3 |
| 19 | 189.4 | 12.0 | 0.070 | 9.94 | 5695 | 5775 | 0.23 | 3.31 | 128.4 | 104.0 |
| 20 | 140.7 | 6.0 | 0.066 | 10.57 | 4313 | 4402 | 0.31 | 4.67 | 85.9 | 107.0 |
| MEAN | 182.3 | 7.4 | 0.075 | 9.43 | 4426 | 4542 | 0.31 | 4.17 | 103.1 | 102.3 |
| S.D. | 39.5 | 3.6 | 0.011 | 1.36 | 1342 | 1342 | 0.15 | 1.16 | 27.4 | 41.3 |
| % CV | 21.7 | 48.9 | 14.8 | 14.4 | 29.3 | 29.5 | 32.65 | 27.88 | 26.6 | 39.9 |
| GEOMETRIC MEAN | 178.4 | 6.8 | 0.074 | 9.34 | 4218 | 4342 | 0.30 | 4.02 | 100.1 | 97.7 |
| MIN | 119.8 | 4.0 | 0.059 | 6.88 | 2122 | 2253 | 0.19 | 2.03 | 61.1 | 52.1 |
| MAX | 271.9 | 16.0 | 0.101 | 11.81 | 7494 | 7670 | 0.27 | 7.07 | 188.5 | 252.0 |

* DATA NOT AVAILABLE.

* PRIOR TO THE RATIO CALCULATION, C_{max} AND AUC WERE NORMALIZED TO THE 100-MG DOSE. THE REFERENCE TREATMENT IS 2x75 MG.

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SUPPORTIVE TABLE ST 3-3 - Pharmacokinetic Parameters of Desvenlafaxine
in Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR

Protocol 050003-186-03

15:31 Friday
February 21, 2003

TREATMENT: Desvenlafaxine SR 1x200-mg tablet

| SUBJECT | C _{MAX} (ng/mL) | T _{MAX} (h) | LAMSDA (1/h) | CL/F (L/h) | AUC _t -- (ng•h/mL) -- | AUC -- (L•h/kg) -- | CL/F (L/h/kg) | V _Z /F (L/kg) | C _{max} Ratio* (%) | AUC Ratio* (%) |
|-------------------|-----------------------------|-------------------------|-----------------|---------------|-------------------------------------|-----------------------|------------------|-----------------------------|--------------------------------|-------------------|
| 1 | 361.3 | 6.0 | 0.086 | 9.08 | 5248 | 5368 | 0.48 | 5.62 | 105.2 | 102.4 |
| 2 | 393.1 | 6.0 | 0.074 | 9.45 | 9342 | 9437 | 0.24 | 3.39 | 104.7 | 109.1 |
| 3 | 407.1 | 6.0 | 0.081 | 8.58 | 9252 | 9190 | 0.28 | 3.51 | 89.7 | 86.7 |
| 4 | 387.4 | 10.0 | 0.070 | 9.84 | 7755 | 7942 | 0.36 | 5.87 | 72.3 | 75.3 |
| 5 | 331.6 | 4.0 | 0.073 | 9.52 | 7928 | 8018 | 0.32 | 4.23 | 103.6 | 84.9 |
| 6 | 399.7 | 6.0 | 0.043 | 11.07 | 18501 | 13678 | 0.29 | 4.64 | 84.7 | 88.5 |
| 7 | 374.8 | 12.0 | 0.090 | 8.70 | 9946 | 10016 | 0.25 | 3.10 | 87.0 | 103.1 |
| 8 | 283.6 | 8.0 | 0.084 | 9.26 | 7458 | 7566 | 0.36 | 4.20 | 111.6 | 228.5 |
| 9 | 241.2 | 16.0 | 0.063 | 10.98 | 7651 | 8488 | 0.30 | 4.68 | 56.8 | 68.8 |
| 10 | 417.7 | 4.0 | 0.082 | 9.58 | 9490 | 9632 | 0.30 | 3.73 | 106.5 | 125.0 |
| 11 | 320.1 | 4.0 | 0.089 | 10.05 | 8150 | 8248 | 0.33 | 4.78 | 89.9 | 90.8 |
| 12 | 366.6 | 8.0 | 0.066 | 10.43 | 11308 | 11463 | 0.22 | 3.25 | 92.7 | 104.4 |
| 13 | 283.9 | 16.0 | 0.076 | 9.14 | 8753 | 8848 | 0.27 | 3.60 | 83.7 | 99.1 |
| 14 | 285.2 | 6.0 | 0.068 | 10.26 | 6788 | 6956 | 0.38 | 5.17 | 89.1 | 78.3 |
| 15 | 374.7 | 24.0 | 0.058 | 12.04 | 14117 | 14542 | 0.25 | 3.46 | 132.4 | 154.3 |
| 16 | 428.0 | 6.0 | 0.054 | 12.95 | 8319 | 9532 | 0.26 | 4.79 | 123.1 | 97.8 |
| 17 | 328.8 | 6.0 | 0.073 | 9.43 | 9680 | 9776 | 0.26 | 3.28 | 70.6 | 100.6 |
| 18 | 343.6 | 6.0 | 0.097 | 7.16 | 6235 | 6352 | 0.34 | 3.49 | 128.3 | 85.4 |
| 19 | 548.4 | 24.0 | 0.043 | 10.97 | 14011 | 13204 | 0.20 | 3.20 | 177.3 | 118.9 |
| 20 | 326.2 | 4.0 | 0.084 | 8.22 | 8994 | 9065 | 0.30 | 3.53 | 99.6 | 110.1 |
| MEAN | 353.5 | 9.1 | 0.073 | 9.68 | 9038 | 9215 | 0.30 | 4.06 | 105.6 | 105.2 |
| S.D. | 86.8 | 6.2 | 0.011 | 1.45 | 2126 | 2156 | 0.07 | 0.77 | 26.5 | 35.1 |
| % CV | 18.9 | 68.2 | 14.6 | 14.9 | 23.5 | 23.4 | 22.26 | 19.23 | 26.3 | 33.4 |
| GEOMETRIC MEAN | 348.0 | 7.7 | 0.072 | 9.58 | 8807 | 8984 | 0.28 | 3.99 | 97.6 | 101.1 |
| MIN | 241.2 | 4.0 | 0.054 | 7.16 | 5248 | 5368 | 0.20 | 3.10 | 56.8 | 68.8 |
| MAX | 548.4 | 24.0 | 0.097 | 12.95 | 14117 | 14542 | 0.48 | 5.62 | 177.3 | 228.5 |

. DATA NOT AVAILABLE.

* PRIOR TO THE RATIO CALCULATION, C_{max} AND AUC WERE NORMALIZED TO THE 100-MG DOSE. THE REFERENCE TREATMENT IS 2x75 MG.

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

| SUPPORTIVE TABLE ST 8-4 - Statistical Comparisons of Desvenlafaxine Pharmacokinetic Parameters In Healthy Subjects Receiving a Single Oral Dose of DVS-233 SR | | | | | | | | | |
|--|-----------|-----------------------------|-------------------------|-----------------|-------------------------|------------------------------------|--------------------------|------------------|-----------------------------|
| Protocol 060002-186-US | | | | | | 16:51 | Friday February 21, 2003 | | |
| TREATMENT | | C _{MAX} (ng/mL) | T _{MAX} (h) | LAMBDA (1/h) | t _{1/2} (h) | AUC ₀₋₁₆ * (ng•h/mL) | AUC * (ng•h/mL) | CL/F (L/h/kg) | V _Z /F (L/kg) |
| Desvenlafaxine SR 2x75-mg tablets | | | | | | | | | |
| | MEAN | 271.6 | 7.6 | 0.074 | 9.65 | 6765 | 6909 | 0.31 | 4.22 |
| | S.D. | 48.8 | 4.3 | 0.014 | 1.75 | 1576 | 1603 | 0.14 | 1.60 |
| | % CV | 18.0 | 55.4 | 18.2 | 18.1 | 23.3 | 23.2 | 44.3 | 38.0 |
| | GEO. MEAN | 267.4 | 6.7 | 0.073 | 9.50 | 6524 | 6667 | 0.29 | 4.00 |
| Desvenlafaxine SR 2x50-mg tablets | | | | | | | | | |
| | MEAN | 164.5 | 6.6 | 0.075 | 9.50 | 3825 | 3946 | 0.37 | 4.97 |
| | S.D. | 32.7 | 3.3 | 0.014 | 1.69 | 1167 | 1174 | 0.14 | 2.13 |
| | % CV | 19.9 | 49.3 | 19.1 | 17.8 | 30.5 | 29.7 | 38.3 | 42.9 |
| | GEO. MEAN | 161.3 | 6.0 | 0.074 | 9.35 | 3633 | 3759 | 0.34 | 4.65 |
| Desvenlafaxine SR 1x100-mg tablet | | | | | | | | | |
| | MEAN | 182.3 | 7.4 | 0.075 | 9.43 | 4426 | 4542 | 0.31 | 4.17 |
| | S.D. | 39.5 | 3.6 | 0.011 | 1.35 | 1342 | 1342 | 0.10 | 1.16 |
| | % CV | 21.7 | 48.9 | 14.8 | 14.4 | 30.3 | 29.5 | 32.7 | 27.9 |
| | GEO. MEAN | 178.4 | 6.8 | 0.074 | 9.24 | 4219 | 4342 | 0.30 | 4.02 |
| Desvenlafaxine SR 1x200-mg tablet | | | | | | | | | |
| | MEAN | 253.5 | 9.1 | 0.075 | 9.68 | 9039 | 9215 | 0.30 | 4.06 |
| | S.D. | 66.8 | 6.2 | 0.011 | 1.45 | 2126 | 2156 | 0.07 | 0.77 |
| | % CV | 26.8 | 68.2 | 14.6 | 14.9 | 23.5 | 23.4 | 22.3 | 19.0 |
| | GEO. MEAN | 248.0 | 7.7 | 0.072 | 9.58 | 8807 | 8984 | 0.29 | 3.95 |
| F-VALUES FROM LOG-TRANSFORMED ANALYSIS OF VARIANCE FOR A FOUR-PERIOD CROSS-OVER DESIGN : | | | | | | | | | |
| SOURCE OF VARIATION | | | | | | | | | |
| SEQUENCE | | .13 | .39 | .57 | .57 | .30 | .21 | .02 | .02 |
| SUB(SEQUENCE) | | .003 | .02 | .001 | .001 | .001 | .001 | .01 | .06 |
| TREATMENT | | .20 | .34 | .84 | .94 | .04 | .05 | .05 | .13 |
| PERIOD | | .81 | .38 | .61 | .61 | .01 | .01 | .01 | .06 |
| Ratio and 90% Confidence Interval of Least Squares Geometric Means(%) : Reference DVS-233 SR 2x75-mg Tablets : | | | | | | | | | |
| Desvenlafaxine SR 2x50-mg tablets | 90 | - | - | - | - | 84 | 85 | - | - |
| | 95- 96 | - | - | - | - | 74- 85 | 75- 96 | - | - |
| Desvenlafaxine SR 1x100-mg tablet | 100 | - | - | - | - | 97 | 98 | - | - |
| | 91-110 | - | - | - | - | 86-109 | 87-109 | - | - |
| Desvenlafaxine SR 1x200-mg tablet | 98 | - | - | - | - | 101 | 101 | - | - |
| | 88-108 | - | - | - | - | 93-110 | 93-109 | - | - |
| # PRIOR TO STATISTICAL COMPARISONS, DOSE-DEPENDENT PARAMETERS (C _{max} , AUC ₀₋₁₆ , AUC) WERE NORMALIZED TO THE 100-MG DOSE. | | | | | | | | | |

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ST 9-7. DESCRIPTIVE STATISTICS AND ANALYSIS WITHIN TREATMENT GROUPS FOR VITAL SIGNS AND PHYSICAL CHARACTERISTICS

24APR03 13:45

CHEMICAL INVESTIGATION OF DESVENLAFAXINE PROTOCOL 050003-195

Page 1

REPORT 6-3V-1 DESCRIPTIVE STATISTICS AND ANALYSIS WITHIN TREATMENT GROUPS FOR VITAL SIGNS AND PHYSICAL CHARACTERISTICS
TEST: SYSTOLIC BP (Supine) (mm Hg) / WITHIN TREATMENT GROUPS

| TREATMENT | N | OBSERVED | | | | | | BASELINE | | | | | | CHANGE |
|-------------------------|----|----------|--------|--------|-------|-------|--------|----------|--------|-------|-------|--------|--|--------|
| PK IDENTIFIER | | MIN | MAX | MEAN | STDEV | STDER | MIN | MAX | MEAN | STDEV | STDER | MIN | | |
| DESVENLAFAXINE 1X100 mg | | | | | | | | | | | | | | |
| Day 1, hr -0.5 | 20 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | 0.00 | | |
| Day 1, hr 2 | 20 | 98.00 | 152.00 | 109.80 | 12.51 | 2.98 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | -20.00 | | |
| Day 1, hr 4 | 20 | 100.00 | 150.00 | 109.50 | 11.57 | 2.59 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | -18.00 | | |
| Day 1, hr 8 | 20 | 100.00 | 128.00 | 107.10 | 6.73 | 1.50 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | -20.00 | | |
| Day 1, hr 12 | 20 | 98.00 | 136.00 | 107.20 | 6.29 | 1.55 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | -18.00 | | |
| Day 1, hr 24 | 20 | 98.00 | 122.00 | 108.50 | 7.34 | 1.64 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | -18.00 | | |
| Day 1, hr 48 | 20 | 100.00 | 122.00 | 108.80 | 7.49 | 1.68 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | -18.00 | | |
| Day 1, hr 72 | 20 | 100.00 | 130.00 | 109.00 | 7.50 | 1.68 | 96.00 | 140.00 | 109.80 | 10.82 | 2.42 | -18.00 | | |
| DESVENLAFAXINE 1X200 mg | | | | | | | | | | | | | | |
| Day 1, hr -0.5 | 20 | 98.00 | 140.00 | 108.80 | 9.86 | 2.21 | 98.00 | 140.00 | 108.00 | 9.86 | 2.21 | 0.00 | | |
| Day 1, hr 2 | 20 | 100.00 | 150.00 | 109.80 | 11.14 | 2.49 | 98.00 | 140.00 | 108.00 | 9.86 | 2.21 | -8.00 | | |
| Day 1, hr 4 | 20 | 100.00 | 130.00 | 108.20 | 8.08 | 1.81 | 98.00 | 140.00 | 108.00 | 9.86 | 2.21 | -20.00 | | |
| Day 1, hr 8 | 20 | 96.00 | 128.00 | 107.10 | 6.79 | 1.52 | 98.00 | 140.00 | 108.00 | 9.86 | 2.21 | -30.00 | | |
| Day 1, hr 12 | 20 | 94.00 | 120.00 | 107.10 | 6.44 | 1.44 | 98.00 | 140.00 | 108.00 | 9.86 | 2.21 | -30.00 | | |
| Day 1, hr 24 | 20 | 100.00 | 122.00 | 111.50 | 5.80 | 1.30 | 98.00 | 140.00 | 108.00 | 9.86 | 2.21 | -18.00 | | |
| Day 1, hr 48 | 20 | 100.00 | 126.00 | 110.80 | 7.83 | 1.71 | 98.00 | 140.00 | 108.00 | 9.86 | 2.21 | -16.00 | | |
| Day 1, hr 72 | 20 | 100.00 | 129.00 | 110.45 | 7.11 | 1.59 | 98.00 | 140.00 | 108.00 | 9.86 | 2.21 | -11.00 | | |
| DESVENLAFAXINE 2X50 mg | | | | | | | | | | | | | | |
| Day 1, hr -0.5 | 20 | 96.00 | 127.00 | 105.40 | 6.56 | 1.47 | 96.00 | 122.00 | 105.40 | 6.56 | 1.47 | 0.00 | | |
| Day 1, hr 2 | 20 | 98.00 | 128.00 | 109.10 | 6.50 | 1.90 | 96.00 | 122.00 | 105.40 | 6.56 | 1.47 | -10.00 | | |
| Day 1, hr 4 | 20 | 100.00 | 130.00 | 109.40 | 6.56 | 1.91 | 96.00 | 122.00 | 105.40 | 6.56 | 1.47 | -10.00 | | |
| Day 1, hr 8 | 20 | 98.00 | 128.00 | 110.00 | 7.17 | 1.60 | 96.00 | 122.00 | 105.40 | 6.56 | 1.47 | -4.00 | | |
| Day 1, hr 12 | 20 | 98.00 | 126.00 | 107.90 | 7.21 | 1.81 | 96.00 | 122.00 | 105.40 | 6.56 | 1.47 | -12.00 | | |
| Day 1, hr 24 | 20 | 98.00 | 130.00 | 110.30 | 6.83 | 2.15 | 96.00 | 122.00 | 105.40 | 6.56 | 1.47 | -8.00 | | |
| Day 1, hr 48 | 20 | 98.00 | 128.00 | 110.50 | 6.75 | 1.96 | 96.00 | 122.00 | 105.40 | 6.56 | 1.47 | -8.00 | | |
| Day 1, hr 72 | 20 | 98.00 | 129.00 | 109.80 | 6.09 | 1.81 | 96.00 | 122.00 | 105.40 | 6.56 | 1.47 | -12.00 | | |
| DESVENLAFAXINE 2X75 mg | | | | | | | | | | | | | | |
| Day 1, hr -0.5 | 20 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | 0.00 | | |
| Day 1, hr 2 | 20 | 96.00 | 140.00 | 107.10 | 10.39 | 2.32 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | -14.00 | | |
| Day 1, hr 4 | 20 | 100.00 | 150.00 | 112.60 | 13.33 | 2.98 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | -18.00 | | |
| Day 1, hr 8 | 20 | 95.00 | 130.00 | 106.60 | 7.87 | 1.76 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | -18.00 | | |
| Day 1, hr 12 | 20 | 92.00 | 130.00 | 109.00 | 9.12 | 2.04 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | -18.00 | | |
| Day 1, hr 24 | 20 | 98.00 | 126.00 | 109.50 | 6.82 | 1.53 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | -12.00 | | |
| Day 1, hr 48 | 20 | 100.00 | 130.00 | 110.00 | 7.76 | 1.74 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | -10.00 | | |
| Day 1, hr 72 | 20 | 100.00 | 140.00 | 109.30 | 10.97 | 2.30 | 100.00 | 124.00 | 106.80 | 7.44 | 1.66 | -16.00 | | |

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

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**ST 2-6. STATISTICAL COMPARISONS OF NAUSEA VAS RAW SCORES AND PHARMACODYNAMIC PARAMETERS IN HEALTHY SUBJECTS
AFTER RECEIVING A SINGLE ORAL DOSE OF DVS-233 SR**

SUPPORTIVE TABLE ST 2-6 - Statistical Comparisons of Nausea VAS Raw Scores and Pharmacodynamic Parameters
In Healthy Subjects After Receiving a Single Oral Dose of DVS-233 SR

Protocol 0600D2-186-US

16:52 Friday
February 21, 2003

| TREATMENT | (UNIT = nm) | | | | | | | | | | | | Emax (nm) | tEmax (h) | AUPC (nm·h) |
|--|-------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------------|--------------|----------------|
| | 0 | 0.5 | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 24 | 48 | 72 | | | |
| Desvenlafaxine SR 2x75-mg tablets | | | | | | | | | | | | | | | |
| MEAN | 0.3 | 0.1 | 0.4 | 0.9 | 0.1 | 0.1 | 0.2 | 0.1 | 0.0 | 0.1 | 0.0 | 0.0 | 1.0 | 1.2 | 3.3 |
| S.D. | 0.7 | 0.3 | 0.9 | 2.1 | 0.3 | 0.3 | 0.4 | 0.2 | 0.0 | 0.2 | 0.0 | 0.0 | 2.1 | 1.0 | 7.9 |
| % CV | 219.0 | 307.8 | 366.7 | 248.2 | 307.8 | 447.2 | 244.2 | 447.2 | . | 447.2 | . | . | 225.2 | 84.3 | 341.0 |
| Desvenlafaxine SR 2x50-mg tablets | | | | | | | | | | | | | | | |
| MEAN | 0.1 | 0.3 | 0.6 | 0.9 | 0.2 | 0.2 | 0.2 | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | 1.3 | 2.0 | 7.7 |
| S.D. | 0.3 | 1.1 | 2.1 | 1.4 | 0.5 | 0.7 | 0.5 | 0.7 | 0.2 | 0.4 | 0.2 | 0.2 | 2.3 | 2.8 | 17.9 |
| % CV | 367.8 | 376.2 | 347.9 | 279.1 | 261.6 | 347.9 | 326.2 | 347.9 | 447.2 | 244.2 | 447.2 | 447.2 | 192.3 | 139.2 | 230.3 |
| Desvenlafaxine SR 1x100-mg tablet | | | | | | | | | | | | | | | |
| MEAN | 0.2 | 0.1 | 0.1 | 0.0 | 0.1 | 0.0 | 0.1 | 0.1 | 0.0 | 0.0 | 0.0 | 0.1 | 0.4 | 15.2 | 1.7 |
| S.D. | 0.7 | 0.3 | 0.2 | 0.0 | 0.4 | 0.0 | 0.2 | 0.2 | 0.0 | 0.0 | 0.0 | 0.3 | 0.8 | 31.7 | 4.4 |
| % CV | 347.9 | 307.8 | 447.2 | . | 447.2 | . | 447.2 | 447.2 | . | . | . | 307.9 | 205.2 | 207.5 | 256.0 |
| Desvenlafaxine SR 1x200-mg tablet | | | | | | | | | | | | | | | |
| MEAN | 0.1 | 0.3 | 0.7 | 0.9 | 0.2 | 0.1 | 0.1 | 0.1 | 0.0 | 0.0 | 0.1 | 0.0 | 1.4 | 2.7 | 3.9 |
| S.D. | 0.4 | 0.8 | 1.8 | 3.3 | 0.5 | 0.3 | 0.3 | 0.2 | 0.0 | 0.0 | 0.2 | 0.0 | 3.6 | 2.3 | 10.4 |
| % CV | 447.2 | 307.8 | 274.5 | 393.5 | 326.2 | 307.8 | 307.8 | 447.2 | . | . | 447.2 | . | 258.5 | 84.3 | 264.2 |
| P-VALUES FROM ANALYSIS OF VARIANCE FOR A FOUR-PERIOD CROSS-OVER DESIGN | | | | | | | | | | | | | | | |
| SOURCE OF VARIATION | | | | | | | | | | | | | | | |
| seq | .79 | .67 | .59 | .41 | .35 | .39 | .10 | .52 | .42 | .29 | .58 | .80 | .31 | .06 | .23 |
| sub(seq) | .48 | .42 | .34 | .29 | .09 | .55 | .22 | .45 | .47 | .63 | .43 | .45 | .36 | .99 | .54 |
| trt | .52 | .64 | .46 | .46 | .84 | .41 | .76 | .50 | .49 | .99 | .55 | .39 | .44 | .66 | .23 |
| period | .001 | .001 | .001 | .001 | .05 | .05 | .57 | .008 | .49 | .09 | .11 | .29 | .001 | .92 | .001 |

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REPORT 6-IV-1 DESCRIPTIVE STATISTICS AND ANALYSIS WITHIN TREATMENT GROUPS FOR VITAL SIGNS AND PHYSICAL CHARACTERISTICS

TEST: SYSTOLIC BP (Supine) (mm Hg) / WITHIN TREATMENT GROUPS

| TREATMENT | | | CHANGE | | | | ADJUSTED | |
|-------------------------|--|----|--------|--------|-------|-------|----------|--------|
| PK IDENTIFIER | | N | MAX | MEAN | STDEV | STERR | MEAN | STDEPR |
| DESVENLAFAXINE 1X100 mg | | | | | | | | |
| Day 1, hr -0.5 | | 26 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | |
| Day 1, hr 2 | | 20 | 14.00 | -0.90 | 9.53 | 3.15 | -0.31 | 1.85 |
| Day 1, hr 4 | | 20 | 14.00 | -0.30 | 8.64 | 1.93 | 0.64 | 2.10 |
| Day 1, hr 8 | | 20 | 16.00 | -2.70 | 9.32 | 2.08 | -1.13 | 1.49 |
| Day 1, hr 12 | | 20 | 14.00 | -2.60 | 8.16 | 1.82 | -1.11 | 1.63 |
| Day 1, hr 24 | | 20 | 10.00 | -1.30 | 8.14 | 1.82 | 0.12 | 1.53 |
| Day 1, hr 48 | | 20 | 16.00 | -1.00 | 8.98 | 2.01 | 0.33 | 1.59 |
| Day 1, hr 72 | | 20 | 16.00 | -0.80 | 9.95 | 2.23 | 0.54 | 1.69 |
| DESVENLAFAXINE 1X200 mg | | | | | | | | |
| Day 1, hr -0.5 | | 26 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | |
| Day 1, hr 2 | | 20 | 10.00 | 1.00 | 5.60 | 1.25 | 1.11 | 1.84 |
| Day 1, hr 4 | | 20 | 10.00 | 0.20 | 6.21 | 1.63 | 0.40 | 2.08 |
| Day 1, hr 8 | | 20 | 18.00 | -0.90 | 9.81 | 2.19 | -0.56 | 1.48 |
| Day 1, hr 12 | | 20 | 12.00 | -0.90 | 9.23 | 2.06 | -0.56 | 1.62 |
| Day 1, hr 24 | | 20 | 20.00 | 3.50 | 8.94 | 2.09 | 1.81* | 1.52 |
| Day 1, hr 48 | | 20 | 24.00 | 2.90 | 9.93 | 2.22 | 2.29 | 1.57 |
| Day 1, hr 72 | | 20 | 24.00 | 2.45 | 8.49 | 1.90 | 2.74 | 1.68 |
| DESVENLAFAXINE 2X50 mg | | | | | | | | |
| Day 1, hr -0.5 | | 26 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | |
| Day 1, hr 2 | | 20 | 16.00 | 3.70* | 6.84 | 1.53 | 3.26 | 1.81 |
| Day 1, hr 4 | | 20 | 18.00 | 4.00* | 7.65 | 1.71 | 3.14 | 2.09 |
| Day 1, hr 8 | | 20 | 22.00 | 4.60** | 5.77 | 1.28 | 3.17* | 1.49 |
| Day 1, hr 12 | | 20 | 20.00 | 2.50 | 6.98 | 1.56 | 1.14 | 1.63 |
| Day 1, hr 24 | | 20 | 30.00 | 4.90* | 9.21 | 2.06 | 2.60* | 1.53 |
| Day 1, hr 48 | | 20 | 26.00 | 5.10** | 7.43 | 1.87 | 3.89* | 1.59 |
| Day 1, hr 72 | | 20 | 16.00 | 3.40 | 7.49 | 1.57 | 2.18 | 1.69 |
| DESVENLAFAXINE 2X75 mg | | | | | | | | |
| Day 1, hr -0.5 | | 26 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | |
| Day 1, hr 2 | | 20 | 18.00 | 0.30 | 10.45 | 2.34 | 0.15 | 1.94 |
| Day 1, hr 4 | | 20 | 38.00 | 5.80 | 13.85 | 3.10 | 5.51** | 2.08 |
| Day 1, hr 8 | | 20 | 30.00 | *0.20 | 10.09 | 2.26 | -0.68 | 1.48 |
| Day 1, hr 12 | | 20 | 30.00 | 2.20 | 11.71 | 2.52 | 1.75 | 1.62 |
| Day 1, hr 24 | | 20 | 18.00 | 2.70 | 8.37 | 1.87 | 2.27 | 1.52 |
| Day 1, hr 48 | | 20 | 18.00 | 3.20 | 8.04 | 1.80 | 2.80 | 1.57 |
| Day 1, hr 72 | | 20 | 22.00 | 2.40 | 10.04 | 2.25 | 1.99 | 1.68 |

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

Appears This Way
On Original

REPORT 6-3V-1 DESCRIPTIVE STATISTICS AND ANALYSIS WITHIN TREATMENT GROUPS FOR VITAL SIGNS AND PHYSICAL CHARACTERISTICS

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

| TREATMENT PK IDENTIFIER | N | MIN | MAX | MEAN | STDEV | STDERR | MIN | MAX | MEAN | STDEV | STDERR | CHANGE MIN |
|----------------------------|----|-------|-------|-------|-------|--------|-------|-------|-------|-------|--------|---------------|
| DESVENLAFAXINE 1X100 mg | | | | | | | | | | | | |
| Day 1, hr -0.5 | 20 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | 0.00 |
| Day 1, hr 2 | 20 | 60.00 | 86.00 | 67.60 | 6.66 | 1.46 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | -16.00 |
| Day 1, hr 4 | 20 | 62.00 | 80.00 | 70.70 | 3.51 | 0.79 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | -8.00 |
| Day 1, hr 8 | 20 | 62.00 | 78.00 | 69.00 | 3.97 | 0.89 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | -10.00 |
| Day 1, hr 12 | 20 | 60.00 | 80.00 | 69.30 | 4.32 | 0.97 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | -12.00 |
| Day 1, hr 24 | 20 | 60.00 | 80.00 | 70.60 | 5.61 | 1.30 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | -12.00 |
| Day 1, hr 48 | 20 | 62.00 | 80.00 | 69.80 | 4.67 | 1.05 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | -10.00 |
| Day 1, hr 72 | 20 | 60.00 | 78.00 | 68.30 | 4.91 | 1.10 | 62.00 | 80.00 | 71.00 | 3.76 | 0.84 | -10.00 |
| DESVENLAFAXINE 1X200 mg | | | | | | | | | | | | |
| Day 1, hr -0.5 | 20 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | 0.00 |
| Day 1, hr 2 | 20 | 58.00 | 80.00 | 67.90 | 5.25 | 1.17 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | -16.00 |
| Day 1, hr 4 | 20 | 62.00 | 78.00 | 69.80 | 3.37 | 0.75 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | -10.00 |
| Day 1, hr 8 | 20 | 56.00 | 74.00 | 67.00 | 5.45 | 1.22 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | -20.00 |
| Day 1, hr 12 | 20 | 56.00 | 80.00 | 68.00 | 6.09 | 1.36 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | -14.00 |
| Day 1, hr 24 | 20 | 60.00 | 84.00 | 72.40 | 5.13 | 1.15 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | -6.00 |
| Day 1, hr 48 | 20 | 62.00 | 80.00 | 70.60 | 4.82 | 1.08 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | -16.00 |
| Day 1, hr 72 | 20 | 60.00 | 78.00 | 69.80 | 4.94 | 1.10 | 62.00 | 80.00 | 70.80 | 4.47 | 1.00 | -14.00 |
| DESVENLAFAXINE 1X50 mg | | | | | | | | | | | | |
| Day 1, hr -0.5 | 20 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | 0.00 |
| Day 1, hr 2 | 20 | 60.00 | 86.00 | 68.70 | 5.92 | 1.32 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | -10.00 |
| Day 1, hr 4 | 20 | 60.00 | 78.00 | 67.90 | 4.33 | 0.97 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | -10.00 |
| Day 1, hr 8 | 20 | 60.00 | 80.00 | 70.10 | 5.52 | 1.24 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | -12.00 |
| Day 1, hr 12 | 20 | 50.00 | 80.00 | 68.70 | 7.15 | 1.60 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | -20.00 |
| Day 1, hr 24 | 20 | 60.00 | 80.00 | 69.20 | 5.96 | 1.33 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | -10.00 |
| Day 1, hr 48 | 20 | 60.00 | 80.00 | 69.70 | 5.99 | 1.34 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | -10.00 |
| Day 1, hr 72 | 20 | 60.00 | 78.00 | 67.70 | 6.27 | 1.40 | 62.00 | 78.00 | 69.20 | 3.33 | 0.75 | -12.00 |
| DESVENLAFAXINE 2X75 mg | | | | | | | | | | | | |
| Day 1, hr -0.5 | 20 | 60.00 | 78.00 | 69.20 | 4.27 | 0.95 | 60.00 | 78.00 | 69.30 | 4.27 | 0.95 | 0.00 |
| Day 1, hr 2 | 20 | 58.00 | 80.00 | 68.00 | 5.62 | 1.26 | 60.00 | 78.00 | 69.30 | 4.27 | 0.95 | -12.00 |
| Day 1, hr 4 | 20 | 62.00 | 80.00 | 70.40 | 4.38 | 0.98 | 60.00 | 78.00 | 69.30 | 4.27 | 0.95 | -16.00 |
| Day 1, hr 8 | 20 | 60.00 | 78.00 | 70.30 | 4.35 | 1.02 | 60.00 | 78.00 | 69.30 | 4.27 | 0.95 | -10.00 |
| Day 1, hr 12 | 20 | 54.00 | 80.00 | 70.30 | 6.50 | 1.45 | 60.00 | 78.00 | 69.30 | 4.27 | 0.95 | -16.00 |
| Day 1, hr 24 | 20 | 60.00 | 80.00 | 70.50 | 5.10 | 1.14 | 60.00 | 78.00 | 69.30 | 4.27 | 0.95 | -10.00 |
| Day 1, hr 48 | 20 | 60.00 | 78.00 | 69.20 | 5.29 | 1.18 | 60.00 | 78.00 | 69.30 | 4.27 | 0.95 | -12.00 |
| Day 1, hr 72 | 20 | 60.00 | 80.00 | 68.70 | 6.66 | 1.49 | 60.00 | 78.00 | 69.30 | 4.27 | 0.95 | -14.00 |

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

Appears This Way
On Original