imputing or estimating the missing data) or the endpoint data, and it creates efficient scoring systems that are either categorical, time-related ranks, or the observed levels. These were used to generate an empirical significance level with time point descriptive statistics.

One can estimate the size of the DVS treatment effect by comparing the observed DVS effect with the observed placebo treatment effect. In study 306, the reductions in mean HAMD-17 scores were -10.5, -9.6, and -10.5 points in the DVS 100 mg, 200 mg, and 400 mg/day groups, respectively. For the placebo group, the reduction in mean HAMD-17 score was -7.7. Thus, the estimated DVS treatment effects compared to placebo were -2.8, -1.9, and -2.8 points on the HAMD-17 Scale for the DVS 100 mg, 200 mg, and 400 mg/day group, respectively. These estimated DVS treatment effects are be modest. However, such effect sizes are similar to those observed in other antidepressant trials that have demonstrated efficacy.

Table 6.7.1.2 Fixed-dose Studies Estimated Size of Treatment Effects

DVS Treatment Effect Sizes in Fixed-dose Studies 306 and 308							
	Study 306				**Study 308**		
Efficacy Variable	PLA	DVS 100	DVS 200	DVS 400	PLA	DVS 200	DVS 400
Change in HAM-D_{17} score							
Final on-therapy evaluation: LOCF	-7.7	-10.5	-9.6	-10.5	-9.3	-12.6	-12.1
Observed-case analysis	-8.0	-11.7	-11.6	-13.4	-11.0	-16.4	-15.2

6.7.2 Efficacy Findings in Flexible-dose Studies

DVS treatment failed to demonstrate efficacy in all of the flexible-dose studies for the primary statistical analysis plan (ANCOVA using LOCF method. The p-values for studies 304, 309, 317, and 320 were 0.28, 0.38, 0.49, and 0.078, respectively. However, in study 317, venlafaxine treatment (150-225 mg/day) was statistically significantly superior to placebo treatment ($p = 0.005$). While there was no supportive evidence of efficacy based in the primary statistical analyses, there was some support for a claim of efficacy using alternative, pre-specified statistical analyses for studies 309 and 320.

DVS efficacy could be demonstrated in study 309, using the observed case, mixed-effects model, and the ETRANK method. (Please refer to the table below for the significance values). In study 320, the efficacy results are positive when the observed case and the ETRANK methods are used to interpret the efficacy results. Thus, there is some support for a claim that DVS treatment may have efficacious in some of the flexible-dose studies.

Table 6.7.2.1 Efficacy Results for Flexible-dose Studies

Efficacy Results for the Flexible-dose Studies

	Study 304	Study 309		Study 317		Study 320
Efficacy Variable & Statistical Analysis	DVS 100-200	DVS 200-400	Ven 75-150	DVS 200-400	Ven 150-225	DVS 200-400
Primary Variable: HAMD-17						
Final on-therapy evaluation- LOCF: primary analysis	0.277	0.38	0.17	0.488	**0.005**	0.078
Observed-case (week 8)	0.067	**<0.001**	**0.027**	0.173	**0.008**	**0.008**
Mixed-effect model	0.268	**0.011**	0.153	0.074	**<0.001**	0.012
ETRANKd	0.054	**0.028**	0.253	0.353	**<0.001**	**<0.001**
Key Secondary Variable: CGI-I						
Final on-therapy evaluation	0.259	0.40	0.107	0.604	**0.011**	**0.037**
Observed-case (week 8)	0.14	**<0.001**	**0.014**	0.141	**0.010**	**0.006**

Table 6.7.2.2 Estimated Size of Treatment Effects in Flexible-dose Studies

Treatment Effect Sizes in Flexible-Dose Studies 309, 317, and 320								
Efficacy Variable	**Study 309**			**Study 317**			**Study 320**	
	Plac	DVS	Ven	Plac	DVS	Ven	Plac	DVS
Change in $HAMD_{17}$								
Final on-therapy evaluation, LOCF	-12.5	-13.4	-13.8	-9.8	-10.5	-12.6	-7.5	-9.1
Observed-case analysis	-12.8	-16.4	-14.9	-10.7	-12.4	-13.8	-7.9	-10.7

In study 317, the estimated venlafaxine treatment effect size (compared to placebo) was a reduction of -2.8 points on the mean $HAMD_{17}$ score. In the same study, the estimated treatment effect size for DVS was -0.7 points on the $HAMD_{17}$ Scale.

6.8 Baseline Demographics and Characteristics for the Controlled Studies

In the intent-to-treat population for the combined seven placebo-controlled studies, there were 797, 1186, 797 and 242 subjects in the placebo, DVS, and venlafaxine ER groups, respectively. In the safety population, there were 1,211, 803, and 244 subjects, respectively. Generally, the demographic and baseline features were quite similar among the three treatment groups. The mean ages were 42, 42, and 44 years, respectively. The proportion of female subjects was similar among treatment groups (63, 59, and 71%, respectively). However, in Study 223, women of childbearing potential were excluded from the study. As a result, there was a lower proportion of women (31%) than men (69%) in this study.

The majority of subjects were White (81, 82, and 88%, respectively). Approximately 8% of subjects were Black, and approximately 6% were Hispanic. Other ethnicities (Arabic, Asian, Native American, and Other) comprised approximately 1% of the study population. These proportions were quite similar among treatment groups. Mean weight and height were very similar among treatment groups.

The baseline severity of the current major depressive episode, as measured by the HAMD-17, was very similar among treatment groups (24.2, 23.9, and 25.5, respectively). The duration of the current MDD episode differed somewhat among treatment groups (17.6, 17.9, and 11.8 months, respectively).

6.9 Pattern of Study Discontinuations

As expected, the proportion of discontinuations due to unsatisfactory response (efficacy) was higher in the placebo groups than in the DVS or venlafaxine groups ((range: 4-12%, 0-3% and 2%, respectively). The proportion of discontinuations due to adverse events was higher in the DVS groups than in the placebo or venlafaxine group (range: 9-21%, 1-6%, and 6-9%, respectively). For other discontinuation reasons, the proportions were quite similar among treatment groups.

In the DVS group, many of the discontinuations occurred within the first week. Approximately 44% of all DVS discontinuations occurred during the first week. These were mostly due to adverse events. In contrast, first-week discontinuations accounted for only 9% of the placebo discontinuations and 22% of the venlafaxine discontinuations.

Table 6.9 Discontinuation Reasons for the Controlled Studies Combined

Reason for DC	Placebo n = 803	DVS n = 1,211	VEN n = 244	Total n = 2,258
Total	138 (17)	313 (26)	41 (17)	492 (22)
Adverse event	29 (4)	82 (15)	17 (7)	228 (10)
Failed to return	35 (4)	63 (5)	7 (3)	105 (5)
Other event	12 (2)	17 (1)	5 (2)	34 (2)
Protocol violation	13 (2)	19 (2)	4 (2)	36 (2)
Subject request	11 (1)	16 (1)	3 (1)	30 (1)
Unsatisfactory response	38 (5)	!6 (1)	5 (2)	60 (3)

6.10 Concomitant Medications

In all studies, the use of concomitant medications did not affect the efficacy results. There was little use of concomitant psychotropic or psychoactive drugs. There was no apparent difference in the kind or pattern of concomitant medication use among treatment groups. The most frequently used concomitant medications were analgesics and antipyretics, nonsteroidal anti-inflammatory/antirheumatic products, and combination multivitamins.

7 Integrated Review of Safety

7.1 Safety Findings in the Placebo-Controlled Desvenlafaxine Trials

Short-term treatment with DVS appears to have been reasonably safe in the MDD population studied. Generally, the overall safety profile of DVS was similar to that of venlafaxine. Currently, the main safety concern is the risk of hypertension associated with DVS treatment. Similar blood pressure elevations occur with venlafaxine treatment. In fact, the Warnings section of labeling for venlafaxine identifies hypertension as a potential dose-related adverse event. Although DVS-related blood pressure elevation in the short-term trials did not appear to be associated with serious cardiovascular, cerebrovascular, renal, or other end-organ adverse events, it is possible that DVS-induced hypertension could lead to clinically significant consequences during longer term DVS treatment. In addition, there was a dose-related risk of hyperlipidemia in the short-term DVS trials. It will be important to assess the cardiovascular safety profile of DVS thoroughly, given these findings.

7.1.1. Deaths

Two (2) deaths occurred in the clinical program which was probably unrelated to DVS treatment. In the Phase 2 and Phase 3 studies, one (1) subject died. Subject 306-019-001105, a 40-year-old man, died from a completed suicide (by hanging) on study day 5. The subject was randomly assigned to treatment with 100 mg/day of DVS. Study medication was dispensed to him, but the investigative site was unable to determine if he had taken any study medication. The investigator and the Wyeth Research medical monitor considered the event to be unrelated to treatment but related to the subject's depression. From the available data, there is no indication that desvenlafaxine treatment may have contributed to suicidality in this case.

In addition, one (1) death was reported for a subject in a Phase 1 study. Subject 177-001-000128, a 40-year-old man, was found dead in his apartment 25 days after receiving the last dose of DVS. The medical examiner concluded that the cause of death was dilated cardiomyopathy with cocaine use as a contributory cause, based on autopsy and toxicology findings. The investigator and the Wyeth Research medical monitor considered the death to be unrelated to treatment.

7.1.2. Serious Adverse Events

There were relatively few serious adverse events (SAE) for a study population of this size. In the controlled trials there were 14, 8, and 1 SAE in the DVS, placebo, and venlafaxine groups, respectively. In the DVS groups, SAE probably or possibly related to treatment with DVS included abnormalities in liver function tests (two cases), dizziness, dystonia, tachycardia, and somnolence. All of these SAE led to discontinuation, and all of them resolved. The completed suicide (discussed above) was probably not related to treatment with DVS. Moreover, in a formal suicidality analysis, DVS was not associated with an increased risk of treatment-emergent suicidality. Since there were few SAE, it is not possible to determine whether they were dose-related.

Table 7.1.2 Serious Adverse Events in the Placebo-controlled DVS Trials

Serious Adverse Events in the DVS Controlled Trials Combined						
Serious Adverse Event	DVS	PLA	VEN	DVS DC	DVS related	DVS resolv
Suicide, completed	1	-	-	Yes	N	No
Suicide attempt	2	-	-	Yes	N x 2	Y
Overdose, intentional	2	3	-	Yes	N x 2	Y
Liver function tests abnl.	2	-	-	Yes	Y x 2	Y
Chest pain	1	1	1	Yes	N	Y
Dizziness	1	-	-	Yes	Prob.	Y
Cholecystitis	1	-	-	Yes	N	Y
Dystonia/accidental fall	1	-	-	Yes	Prob.	Y
Gastroenteritis	1	-	-	Yes	N	Y
Tachycardia	1	-	-	Yes	Poss.	Y
Somnolence	1	-	-	Yes	Poss.	Y
Depression	-	1	-			
Anemia	-	1	-			
Menstrual bleeding, abnl.	-	1	-			

7.1.3. Discontinuations Due to Adverse Events

A large proportion of DVS subjects discontinued due to adverse events. In the controlled trials, 16% of DVS subjects discontinued due to an AE (compared with 4% and 7% of the placebo and venlafaxine groups, respectively). Furthermore, the DVS discontinuations due to AE occurred early in the study (usually within the first week). The adverse events leading to discontinuation

in the DVS group were: nausea (6%); vomiting (3%); asthenia (2%), headache (2%), dizziness (2%), insomnia (2%), somnolence (2%); tremor (1%), sweating (1%), and impotence (1%). The pattern of venlafaxine discontinuations due to AE pattern was similar to that of the DVS group. In the placebo group, less than 1% of subjects discontinued for any of these reasons. There were several discontinuations due to hypertension in the DVS group (1.2%), compared to 2% and <1% in the venlafaxine ER and placebo groups, respectively.

Table 7.1.3 Discontinuations due to Adverse Events in the Controlled Trials

Discontinuations due to adverse events For ≥ 1% of DVS subjects			
AE leading to DC	DVS %	PLA %	VEN %
Total DCAE	15.5	3.9	7
Nausea	5.5	0.4	2.5
Vomiting	2.5	0.2	-
Dizziness	2.1	-	2
Insomnia	2	0.4	1.2
Headache	1.9	0.2	1.6
Asthenia	1.7	0.1	1.2
Somnolence	1.7	0.1	1.2
Sweating	1.4	0	0.4
Hypertension	1.2	<1	2
Tremor	1.2	-	-
Impotence	1	-	-

7.1.4. Common Drug-related Adverse Events

A number of commonly reported adverse events appeared to be related to DVS treatment. The following AE occurred in at least 5% of DVS subjects and were at least twice as commonly reported as in the placebo group: nausea (37%), dry mouth (23), insomnia (19), sweating (18), somnolence (16), dizziness (15), anorexia (12), constipation (12), asthenia (11), anorgasmia (10), impotence (9), vomiting (7), tremor (7), nervousness (6), abnormal vision (5), mydriasis (5), abnormal dreams (5), hypertension (4), vertigo (3). The gastrointestinal, central nervous system, and sexual adverse events were more common in the DVS group than in the venlafaxine group

In the fixed dose trials, the following events were reported at a higher incidence in the 400 mg group than either the 100 or 200 mg groups and appeared to show a dose-related trend: hypertension, asthenia, nausea, vomiting, anxiety, nervousness, tremor, dry mouth, sweating, abnormal ejaculation/orgasm, anorgasmia (men), impotence, and taste perversion.

Table 7.1.4 Commonly Reported Adverse Events in the Controlled DVS Trials

Adverse Event (Preferred term)	PLA n = 803 (%)	DVS 100 mg n = 118 (%)	DVS 200 mg n = 307 (%)	DVS 400 mg n = 317 (%)	DVS 100-400 n = 1211 (%)	VEN 75-225 mg n =244 (%)
Nausea	11	35	36	41	37	25
Dry Mouth	9	17	21	25	23	19
Insomnia	10	22	18	19	19	12
Sweating	4	10	19	21	18	14
Somnolence	6	20	16	16	16	14
Dizziness	8	17	16	16	15	9
Anorexia	1	12	11	11	12	10
Constipation	4	12	10	14	12	6
Asthenia	5	7	10	12	11	7
Ejaculation/orgasm abnl.	1	5	11	13	10	2
Impotence	2	7	8	11	9	9
Vomiting	2	5	6	8	7	3
Tremor	1	4	8	8	7	4
Nervousness	3	5	6	6	6	4
Anorgasmia (women)	0	4	0	3	6	3
Abnormal vision	< 1	5	5	4	5	3
Mydriasis	< 1	3	6	6	5	3
Abnormal Dreams	3	6	4	4	5	4
Hypertension	3	2	5	4	4	5
Vertigo	1	0	5	3	3	4

7.1.5. Less Common Drug-related Adverse Events

Less commonly reported adverse events that were probably or possibly related to DVS treatment include: tachycardia (3), vasodilatation (3), and libido decreased (3). The table below presents the adverse events that were reported for at least 2% of the DVS population and were reported less commonly for placebo. All of the adverse events appear to be possibly of probably related to DVS treatment.

Adverse Events in > 2% of DVS subjects and more common than in the placebo group				
	Percentage of Patients Reporting Event			
Body System Preferred Term	PLA n = 803	DVS 100 mg n = 118	DVS 200 mg n = 307	DVS 100- 400 n = 1211
Tachycardia	1	3	1	3
Vasodilatation	1	2	4	3
Anxiety	3	3	4	5
Libido Decreased	1	4	3	3
Memory Impairment	1	3	0	1
Thinking Abnormal	1	2	3	2
Trismus	1	3	1	2
Yawn	1	3	4	4
Eye Pain	1	3	<1	1

7.1.6. Adverse Events of Particular Interest: Cardiovascular and Cerebrovascular

The Division requested that the sponsor use a list of search terms to capture selected cardiovascular and cerebrovascular adverse events. The terms included: syncope, fainting, presyncope, lightheadedness, high blood pressure, low blood pressure, blood pressure increased or blood pressure elevated, hypertension, hypotension, low heart rate/pulse, decreased heart rate/pulse, tachycardia, bradycardia, stroke, TIA (transient ischemic attack), and cerebrovascular event.

After a review of the verbatim terms reported in the clinical safety database for all phase 2 and 3 studies, the following 25 COSTART terms were selected to include all of the adverse events that were relevant to the Division's request: arrhythmia, AV (atrioventricular) block first degree, bundle branch block, cerebral ischemia, cerebrovascular accident, chest pain, chest pain substernal, coronary artery disorder, dizziness, electrocardiogram abnormal, embolus, extrasystoles, hypertension, hypotension, myocardial infarct, myocardial ischemia, peripheral vascular disorder, postural hypotension, pulmonary embolus, ST depressed, subarachnoid hemorrhage, syncope, T inverted, tachycardia, vascular disorder.

The table below illustrates the results using the preferred terms to which the verbatim terms coded. There was an excess in the DVS group (compared to placebo) of hypertension, tachycardia, dizziness, and chest pain. The following adverse events were more common in the venlafaxine group than in the DVS group: hypertension and chest pain.

Table 7.1.6 Cardiovascular Adverse Events in the Controlled DVS Trials

Adverse event	DVS n = 1211	Placebo n = 803	VEN n = 244
Chest pain	27 (2.2)	14 (1.7)	9 (3.7)
Bundle branch block	1 (0.1)	0	0
Hypertension	46 (3.8)	20 (2.5)	11 (4.5)
Hypotension	2 (0.2)	1 (0.1)	0
Myocardial ischemia	0	1 (0.1)	0
Peripheral vascular disorder	4 (0.3)	1 (0.1)	0
Hypotension, postural	8 (0.7)	1 (0.1)	2 (0.8)
Syncope	1 (0.1)	1 (0.1)	0
Tachycardia	35 (2.9)	8 (1)	5 (2)
Dizziness	183 (15)	60 (8)	23 (9)

One of the adverse events listed in the table above was an SAE (tachycardia). None of the adverse events resulted in discontinuations. However, there were other subjects who discontinued due to abnormal vital signs and abnormal ECG. Discontinuations due to hypertension occurred for 1.2% of DVS subjects, 1% of placebo subjects, and 2% of venlafaxine subjects.

7.1.7. Vital Signs Findings

7.1.7.1. Blood Pressure Findings

7.1.7.1.1. Summary of Blood Pressure Findings

Blood pressure elevation was a consistent finding in the DVS trials. The following is a list of important points regarding blood pressure elevation associated with DVS treatment:

1. DVS raised mean BP by 3.5- 4.0 mm Hg for SBP and 2.0- 2.5 mm Hg for DBP (these are the placebo-subtracted changes in mean BP values).
2. The blood pressure effect was consistent across the seven (7) controlled trials.
3. The BP effect occurred early in the trials and persisted at a consistent magnitude.
4. The DVS BP effect appears very similar to the venlafaxine BP effect in terms of magnitude, time course, and duration of effect.
5. Dose relationship: there is not a clear dose relationship for the *magnitude* of the change in mean blood pressure. However, there is a dose relationship for the *duration* of blood pressure increases (sustained hypertension: elevated BP on two (2) or three (3) consecutive visits).
6. There were no reports of clinically significant adverse events related to BP elevation in the short-term controlled trials (cardiovascular, cerebrovascular, renal, etc.).
7. However, in the long-term studies, there were three (3) cases of cerebrovascular accidents (CVA) or transient ischemic attacks (TIA) in which DVS treatment might have been a factor in development of the adverse event.
8. The blood pressure effect could be clinically significant during long-term use of DVS.
9. Desvenlafaxine treatment also increased mean cholesterol and triglyceride levels, potentially increasing cardiovascular risk.
10. There were no deaths related to elevated blood pressure in the controlled trials.
11. There were no reported serious adverse events (SAE) related to elevated blood pressure elevation in the controlled trials.
12. There were discontinuations due to hypertension in the DVS group (1.2%) compared to 2% and < 1% in the venlafaxine and placebo groups, respectively.
13. 'Hypertension' was reported as an adverse event for 4% of the DVS group, 5% of the venlafaxine group, and 3% of the placebo group.

7.1.7.1.2 Cardiorenal Division Consult

Mehul Desai, M.D. (Medical Officer, Division of Cardiorenal Drug Products) performed a comprehensive set of analyses of the blood pressure data from the DVS program. His findings will be discussed below. Dr. Desai has filed a formal consult as well.

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7.1.7.1.2.1. DVS Treatment Increases Mean Systolic and Diastolic Blood Pressure

As the sponsor notes, DVS treatment was consistently associated with increases in mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP), compared with a decrease in mean SBP and DBP in the placebo group. The increase in mean blood pressure in the DVS group appears comparable to that observed in the venlafaxine group in the controlled studies. The DVS-related changes in SBP and DBP were quite consistent across studies, and the changes were consistent over time within studies. The magnitude of BP change for the DVS-related, population, mean, placebo-subtracted increase from baseline was approximately 3.5- 4.0 mm Hg for SBP and 2.0- 2.5 mm Hg for DBP. These DVS effects on blood pressure were very often statistically significant, compared to treatment with placebo.

Table 7.1.7.1.2.1 Changes in Mean Systolic and Diastolic Blood Pressure

Supine mean systolic/diastolic BP changes (mm Hg) from baseline			
	Placebo	DVS 100-400 mg	Venlafaxine 75-225mg
Week 1 (Visit 3)	-1.44/-1.09	2.35/1.03*	2.20/0.64*
Week 8 (Visit 8)	-1.71/-0.75	2.19/2.15*	2.20/1.16*
Week 1 (placebo subtracted)		3.79/2.12	3.64/1.73
Week 8 (placebo subtracted)		3.9/2.9	3.91/1.91

*DVS and Venlafaxine changes in SBP and SBP were statistically significant ($p < 0.05$), compared to placebo

7.1.7.1.2.2. Potential Clinical Significance of Blood Pressure Changes

Dr. Desai notes that it is somewhat difficult to determine the extent to which the B.P. elevations might be clinically significant. The placebo-controlled had a relatively short duration (8 weeks). Furthermore, there were few serious adverse events or significant cardiovascular or other end-organ events that might have been related to DVS treatment or blood pressure elevation. There are data from longer-term DVS studies in MDD; however, these studies are not placebo-controlled. On the other hand, there is some suggestion that DVS-related elevations in blood pressure could be clinically significant, based on two cases of cerebrovascular accidents (CVA) in the *long-term* studies.

In one case, a 45 year-old white female, with a history of hypertension and smoking, was hospitalized for a stroke on [redacted] She had completed placebo-controlled DVS Study 308 and then enrolled in Study 303, a long-term, open-label, safety and efficacy extension study ([redacted]. The CVA occurred 110 days after beginning DVS

treatment in the short-term, controlled trial. Dr. Desai concluded that, from the information available, it seems possible that the CVA could be partly related to DVS treatment; however, it is also possible that treatment with DVS had no relation to the CVA.

In the second CVA case, a 76 year-old white female with a history of MDD enrolled in study 307, a long-term, open-label, safety and efficacy study in elderly subjects. The subject experienced dizziness, nausea, and blurred vision in the setting of high blood pressure on ——— . These adverse events led to hospitalization. The subject began receiving study drug DVS 100/day on ——— The dose was increased to 200 mg daily one week later. Evaluation in hospital included an MRI scan which showed evidence of a small left frontal and posteroparietal subarachnoid hemorrhage. This subject did not have a prior history of hypertension; although, it was noted in the narrative that the subject did have "mild hypertension" prior to treatment with study drug.

Strokes and subarachnoid hemorrhages do occur in older patients or patients with underlying vascular disease, hypertension, and/or smoking histories. While, it is difficult to sustain an argument that these AE's are solely drug-related, it also cannot be concluded that DVS played no role in these AE's. A long-term, controlled clinical trial evaluating cardiovascular outcomes would be needed to answer the question being asked.

Dr. Desai discussed the potential for long-term risks associated with DVS treatment.
The magnitude of the mean, placebo-subtracted blood pressure increases associated with DVS treatment was approximately 3.5- 4.0 mm Hg for SBP and 2.0- 2.5 mm Hg for DBP. Such changes could be clinically significant. Epidemiologic studies suggest that higher blood pressures lead to an increased risk for adverse clinical outcomes (e.g. heart failure, angina, myocardial infarction, stroke, peripheral vascular disease, renal insufficiency, left ventricular hypertrophy) compared to lower blood pressures. Any of the listed adverse outcomes (and possibly others) could result from treatment with a drug that leads to a sustained increase in blood pressure.

Furthermore, the authors of The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JCN7) suggest that systolic blood pressure reductions of as little as 2 mm Hg in the general population could lead to a 6% reduction in the risk of stroke and a 4% reduction in the risk of coronary heart disease. Thus, a 2 mm Hg increase in the mean systolic pressure in the general population should theoretically lead to a quantifiable increase in risk of stroke and/or coronary heart disease, assuming all other cardiovascular risk factors remain unchanged. However, one complicating factor is that DVS treatment has been associated with decreases in weight, which could improve cardiovascular outcomes. On the other hand, DVS treatment leads to increases in total cholesterol levels, which could increase the risk for cardiovascular disease. Dr. Desai concludes that, in the absence of a randomized, placebo-controlled clinical trial of sufficient patient-years of drug exposure, the net clinical benefit (or harm) cannot be adequately characterized.

7.1.7.1.2.3 Comparison of Blood Pressure Effects between DVS and Venlafaxine

Dr. Desai compared the DVS-related increase in blood pressure with the venlafaxine-related increase in blood pressure in the controlled studies. Essentially, the treatment effects of DVS and venlafaxine on blood pressure appear to be very similar.

The figure below illustrates the distribution of supine systolic BP changes from baseline after one week of study drug treatment in the placebo arm (top), DVS arm (middle), and venlafaxine arm (bottom). The analyses at other assessment times yielded approximately the same results throughout the studies. The data represented in the figure below were pooled from the seven short-term, placebo-controlled fixed and flexible dose studies of DVS. The doses of DVS used were 100 mg, 200 mg, or 400 mg daily. The doses of venlafaxine used ranged from 75– 225 mg daily. A total of 820, 1244, and 249 pooled placebo, DVS, and venlafaxine study subjects were randomized into the seven studies.

As illustrated in the figures, the distribution of blood pressures in the DVS and venlafaxine arms is shifted slightly to the right, compared to placebo. In addition, there are more outliers (systolic BP change from baseline > 20 mm Hg) in both the DVS and Venlafaxine groups.

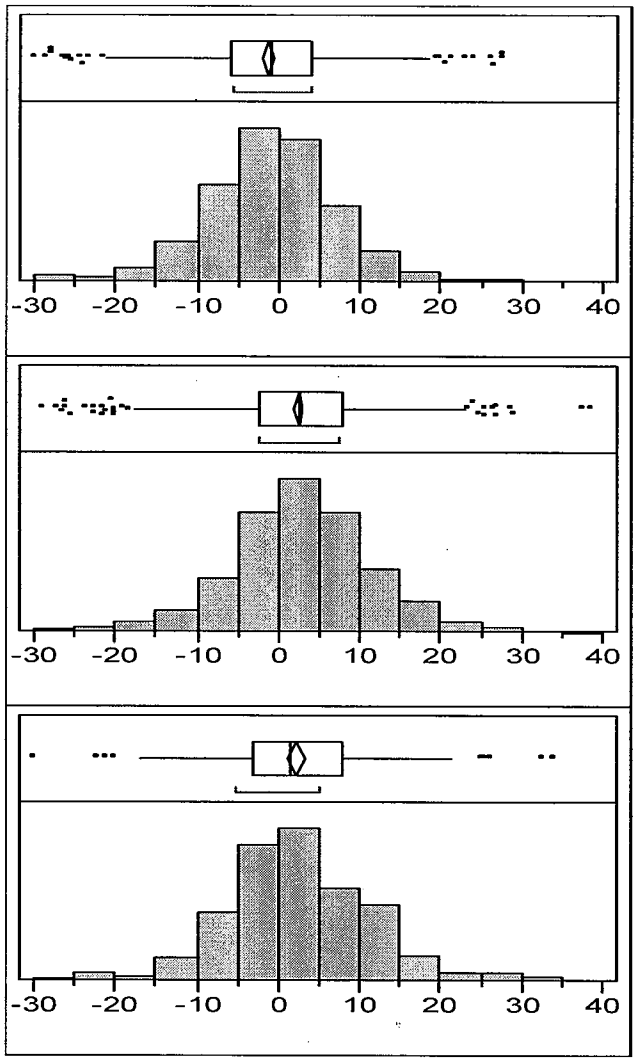


Figure 1: Supine systolic BP changes from baseline for placebo (top), DVS (middle), venlafaxine (bottom) during Visit 3.

[Source of data analyses and tables: Mehul Desai, M.D., Division of Cardiorenal Drug Products]

7.1.7.1.2.4. Potential Relationship between DVS Dose and Blood Pressure Changes

Dr. Desai has addressed the question of whether the DVS blood pressure effects are dose-related. Essentially, the magnitude of the increase in mean blood pressure does not appear to be dose-related. The figure below summarizes the pooled, supine BP results from the three (3) fixed-dose studies (studies 223, 306, and 308), in which subjects were treated with either 100 mg, 200 mg, or 400 mg of DVS or placebo. The top two panels show the mean change from baseline in the supine diastolic BP. The bottom two panels show the mean change from baseline

in the supine systolic BP. The left two panels show the results at Visit 3 (one week post study drug initiation) while the right two panels show the results at Visit 8 (8 weeks post study drug initiation).

Dr. Desai did not perform a formal statistical analysis to calculate p-values for the analysis below for each DVS dose compared to placebo. However, the sponsor's analyses indicated that each dose of DVS was statistically significantly different from placebo. In most cases, the p-values were considerably smaller than $p = 0.05$). Thus, treatment with all fixed DVS doses (100, 200, and 400 mg) was associated with statistically significant increases in mean blood pressure, compared to placebo treatment.

On the other hand, there does appear to be a relationship between DVS dose and the risk of developing "sustained hypertension." The definition of "sustained hypertension" includes criteria for *duration* of blood pressure elevation (BP abnormalities on two or three consecutive visits) in addition to criteria for *magnitude* of BP change. (Dr. Wang performed analyses of blood pressure data that account for duration of blood pressure abnormalities in specific subjects. This will be discussed in a subsequent section).

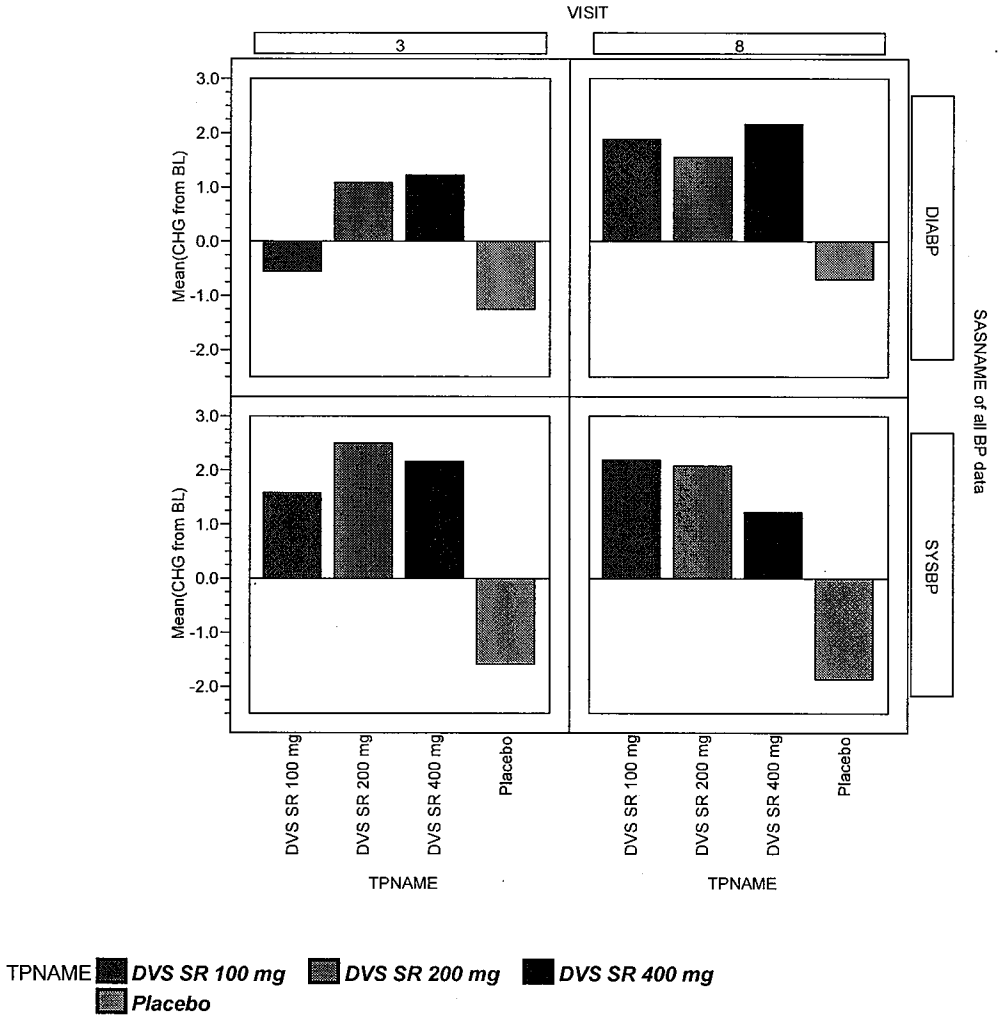


Figure 2: Mean changes from baseline in supine diastolic BP (top panels) and supine systolic BP (bottom panels) at Visit 3 (left 2 panels) and Visit 8 (right 2 panels).

[Source: analyses performed by Mehul Desai, M.D.

7.1.7.1.2.5. Potential Labeling of the Desvenlafaxine Blood Pressure Effect

Finally, we asked Dr. Desai how we might describe in labeling the elevations in blood pressure and the risk of hypertension associated with DVS treatment. Dr. Desai recommends that, if DVS is considered approvable, the labeling of hypertension adverse events and high blood pressure should be similar to that of venlafaxine, and it should be no less restrictive. *[Reviewer's note: 'sustained hypertension' is labeled in the WARNINGS section for venlafaxine products].*

7.1.7.1.3. Sustained Hypertension

Yaning Wang, Ph.D., Pharmacometrics Reviewer, Office of Pharmacology. Dr. Wang has been instrumental in analyzing the blood pressure data from the DVS controlled trials.

7.1.7.1.3.1. Venlafaxine and Sustained Hypertension (from previous venlafaxine trials)

Data from a number of previous randomized, double-blind, placebo-controlled trials of venlafaxine (the parent drug of DVS) indicate that venlafaxine treatment is associated with a dose-related risk of developing sustained hypertension. Sustained hypertension was defined as treatment-emergent supine *diastolic* blood pressure (SDBP) $\geq$ 90 mm Hg **and** at least 10 mm Hg above baseline for at least *three* (3) consecutive visits. Summary data are presented in the table below. These results are also described in venlafaxine product labeling in the Warnings section

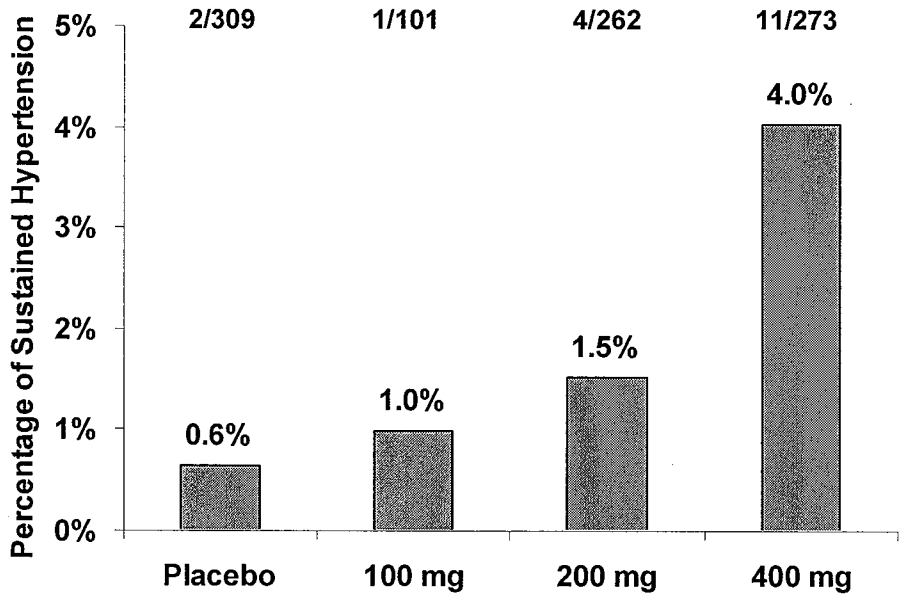
Table 7.1.7.1.3.1 Venlafaxine and Sustained Hypertension

Venlafaxine Treatment Group	Sustained HTN (elevated SDBP)
Venlafaxine < 100 mg/day	3%
Venlafaxine 100- 200 mg/day	5%
Venlafaxine 201- 300 mg/day	7%
Venlafaxine > 300 mg/day	13%
Placebo	2%

7.1.7.1.3.2. Desvenlafaxine and 'Sustained Hypertension'

The biostatistics reviewer (Yaning Wang, Ph.D.) and this reviewer planned analyses to explore the relationship between desvenlafaxine and sustained hypertension, using the same definition that was used for venlafaxine: supine **diastolic** blood pressure (SDBP) $\geq$ 90 mm Hg **and** $\geq$ 10 mm Hg above baseline, for three (3) consecutive on-therapy visits. The results are presented in the figures below. (Fixed doses).

Figure 7.1.7.1.3.2. Dose-dependent Sustained Hypertension



Logistic Modeling Results for Sustained Hypertension

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

Source of data, table and analysis: Yaning Wang, Ph.D.,

Pharmacometrics Reviewer, Office of Clinical Pharmacology

In the fixed-dose studies, treatment with higher DVS doses was associated with an increased risk of developing sustained hypertension (as defined above). The proportions of subjects who developed sustained hypertension were 4%, 1.5%, 1% and 0.6% for the DVS 400 mg, DVS 200 mg, DVS 100 mg, and the placebo groups, respectively.

Additional blood pressure data analyses support the conclusion that DVS treatment was associated with significant elevations in blood pressure. For these additional analyses, systolic B.P. data was included, in addition to DBP, because elevation of systolic pressure may be a more important risk factor than elevation of diastolic blood pressure for developing cardiovascular adverse outcomes. In separate analyses, we defined sustained hypertension in two different ways, based on the duration of blood pressure elevation:

1) Systolic BP $\geq$ 140 mm Hg **OR** a diastolic BP $\geq$ 90 mm Hg measured on *two* (2) consecutive visits
2) Systolic BP $\geq$ 140 mm Hg **OR** a diastolic B.P $\geq$ 90 mm Hg measured on *three* (3) consecutive visits

The table below illustrates the results for the DVS dose groups combined (all fixed and flexible dose groups) compared to placebo). The analysis was performed for subjects with normal BP at baseline versus those with abnormal BP at baseline. DVS treatment, compared to placebo, increased the risk of developing 'sustained hypertension' as defined by elevations on two or three consecutive visits. In the second table, the same analyses have been performed for the DVS group in the flexible-dose studies, compared to the placebo and venlafaxine groups. The results are similar; although, in the three-consecutive-visit analysis, the risk of developing sustained hypertension appeared greater, compared to DVS treatment.

Table 7.1.7.1.3.2.1 Sustained Hypertension in DVS Controlled Trials Combined

DVS and Sustained Hypertension *(on 2 consecutive visits)*		
Treatment Group	↑ SBP **OR** ↑DBP on two (2) consecutive visits	
	Normal baseline BP	Elevated baseline BP
DVS 100- 400 mg/d Placebo	13.7% (83/607) 5.2% (14/267)	72% (60/83) 45% (21/47)
DVS and Sustained Hypertension *(on 3 consecutive visits)*		
Treatment Group	↑ SBP **OR** ↑DBP on three (3) consecutive visits	
	Normal baseline BP	Elevated baseline BP
DVS 100- 400 mg/d Placebo	8.2% (46/562) 1.1% (3/262)	61% (45/74) 38% (18/47)

The tables below illustrate results from a similar set of analyses for the flexible-dose studies including venlafaxine.

Table 7.1.7.1.3.2.2 Sustained Hypertension in DVS Flexible-dose Trials

DVS and Sustained Hypertension *(on 2 consecutive visits)*		
Treatment Group	↑ SBP **OR** ↑DBP on two (2) consecutive visits	
	Normal baseline BP	Elevated baseline BP
DVS 100- 400 mg/d Ven ER 75-225 mg/d Placebo	8% (32/407) 11% (22/200) 5% (19/425)	77% (27/35) 74% (28/38) 60% (30/50)
DVS and Sustained Hypertension *(on 3 consecutive visits)*		
Treatment Group	↑ SBP **OR** ↑DBP on three (3) consecutive visits	
	Normal baseline BP	Elevated baseline BP
DVS 100- 400 mg/d Ven ER 75-225 mg/d Placebo	5% (17/380) 5% (1/194) 2% (9/413)	55% 18/33) 56% (21/37) 39% (19/49)

Blood Pressure Outliers: sustained hypertension (Sponsor's Analysis)

The tables below illustrate the results of the blood pressure analyses that the Division requested of the sponsor. The results are similar to the Division's results.

All short-term controlled trials (all ages)			
Blood pressure criteria	PLAC	DVS 100-400 mg	VEN 75-225 mg
SBP ≥ 140 mm Hg for 2 consecutive visits	6%	10%	12%
SBP ≥ 140 mm Hg for 3 consecutive visits	3%	6%	7%
DBP ≥ 90 mm Hg for 2 consecutive visits	7%	12%	11%
DBP ≥ 90 mm Hg for 3 consecutive visits	3%	6%	7%

All short-term controlled trials (age ≥ 50 years)			
Blood pressure criteria	Placebo	DVS 100-400 mg	VEN 75-225 mg
SBP ≥ 140 mm Hg for 2 consecutive visits	13%	18%	15%

SBP ≥ 140 mm Hg for 3 consecutive visits	8%	12%	8%
DBP ≥ 90 mm Hg for 2 consecutive visits	13%	12%	14%
DBP ≥ 90 mm Hg for 3 consecutive visits	5%	6%	4%

All short-term controlled trials (age ≥ 65 years)			
Blood pressure criteria	Placebo	DVS 100-400 mg	Venlafaxine 75-225
SBP ≥ 140 mm Hg for 2 consecutive visits	29%	39%	42%
SBP ≥ 140 mm Hg for 3 consecutive visits	29%	26%	33%
DBP ≥ 90 mm Hg for 2 consecutive visits	10%	13%	17%
DBP ≥ 90 mm Hg for 3 consecutive visits	0%	3%	8%

Fixed-dose studies (all ages)				
Blood pressure criteria	Placebo	DVS 100 mg/day	DVS 200 mg/day	DVS 400 mg/day
SBP ≥ 140 mm Hg for 2 consecutive visits	5%	6%	12%	13%
SBP ≥ 140 mm Hg for 3 consecutive visits	3%	5%	7%	9%
DBP ≥ 90 mm Hg for 2 consecutive visits	8%	6%	14%	13%
DBP ≥ 90 mm Hg for 3 consecutive visits	4%	5%	7%	7%

Fixed-dose studies (age ≥ 50 years)				
Blood pressure criteria	Placebo	DVS 100 mg/day	DVS 200 mg/day	DVS 400 mg/day
SBP ≥ 140 mm Hg for 2 consecutive visits	9%	12%	24%	21%
SBP ≥ 140 mm Hg for 3 consecutive visits	5%	12%	13%	17%
DBP ≥ 90 mm Hg for 2 consecutive visits	12%	4%	18%	13%
DBP ≥ 90 mm Hg for 3 consecutive visits	4%	4%	7%	7%

Long-term Studies: Sustained Hypertension (Sponsor's Analysis)

All long-term studies (all ages)	
Blood pressure criteria	N = 2134
SBP ≥ 140 mm Hg for 2 consecutive visits	17%
SBP ≥ 140 mm Hg for 3 consecutive visits	12%
DBP ≥ 90 mm Hg for 2 consecutive visits	18%
DBP ≥ 90 mm Hg for 3 consecutive visits	11%

All long-term studies (age ≥ 50 years)	
Blood pressure criteria	
SBP ≥ 140 mm Hg for 2 consecutive visits	28%
SBP ≥ 140 mm Hg for 3 consecutive visits	21%
DBP ≥ 90 mm Hg for 2 consecutive visits	22%
DBP ≥ 90 mm Hg for 3 consecutive visits	13%

All long-term studies (age ≥ 65 years)	
Blood pressure criteria	
SBP ≥ 140 mm Hg for 2 consecutive visits	30%
SBP ≥ 140 mm Hg for 3 consecutive visits	22%
DBP ≥ 90 mm Hg for 2 consecutive visits	17%
DBP ≥ 90 mm Hg for 3 consecutive visits	10%

7.1.7.1.4 Analysis of Concomitant Antihypertensive Medication Use during the DVS Trials

In the original NDA submission, the sponsor did not include an analysis of potential concomitant antihypertensive medication use. We requested relevant data and analyses in order to further examine the relationship between treatment with desvenlafaxine and the development or exacerbation of hypertension. The sponsor provided appropriate data from the placebo-controlled trials as well as from the long-term, open-labels studies. The analyses included descriptions and quantification of antihypertensive use in general, as well as analyses for particular classes of antihypertensive medications. Antihypertensive medication use was analyzed according to: 1) total number of subjects in each group treated with antihypertensive drugs at any point in the studies; and 2) total number of subjects in each group for whom antihypertensive treatment was initiated only after beginning treatment with study drug. The four tables below illustrate the findings.

Generally, there were no clear differences among the placebo, desvenlafaxine, and venlafaxine groups in the number of subjects treated with antihypertensive medication, regardless of whether antihypertensive treatment was initiated before or after beginning study drug treatment. At baseline, there did not appear to be significant differences among the three groups in the number of subjects who were treated with antihypertensive drugs. Also, there did not appear to be a difference among groups at baseline in the number of subjects who had a diagnosis of hypertension.

The reason for the lack of a difference among treatment groups in antihypertensive use is unclear.
The finding is not consistent with the finding of blood pressure elevation in the desvenlafaxine and venlafaxine groups. One explanation could be that there was a relatively high threshold for

treating subjects with antihypertensive medications, despite the occurrence of elevated blood pressure. Alternatively, subjects requiring antihypertensive treatment may have been discontinued from the studies and referred for treatment of hypertension.

Table 7.1.7.1.4.1 Combined controlled trials

Combined placebo-controlled trials: antihypertensive medication use during treatment phase			
	Placebo N = 803	DVS N = 1211	VEN N = 244
Any antihypertensive use during trial	10%	10%	9%
Initiated antihypertensive use During trial	1%	1%	0.4%

Table 7.1.7.1.4.2 Fixed-dose trials

Fixed-dose studies: antihypertensive medication use during treatment phase				
	Placebo N =323	DVS 100 mg n = 118	DVS 200 mg N = 307	DVS 400 mg N = 317
Any antihypertensive use during trial	10%	9%	16%	8%
Initiated antihypertensive use During trial	1%	0	1%	1%

Table 7.1.7.1.4.3 all flexible-dose trials

All Flexible-dose studies			
	Placebo N = 480	DVS N = 469	VEN N = 244
Any antihypertensive use during trial	9%	9%	9%
Initiated antihypertensive use During trial	1%	1%	0.4%

Table 7.1.7.1.4.4 Flexible-dose trials using venlafaxine

Flexible-dose studies using Venlafaxine			
	Placebo N = 245	DVS N = 231	VEN N = 244
Any antihypertensive use during trial	10%	12%	9%
Initiated antihypertensive use During trial	1%	2%	0.4%

7.1.6.2. Heart Rate Findings

Desvenlafaxine treatment was associated with dose-related increases in heart rate. Two subjects had increases in heart rate that were considered potentially clinically significant. This was reported as a serious adverse event for approximately 1% of the DVS group. Tachycardia was reported as an adverse event for one subject in the DVS group.

ECG analysis indicates that desvenlafaxine treatment results in an increase of mean heart rate by approximately 5 beats per minute (placebo-subtracted). Furthermore, the increase in mean heart rate was dose-related. In the fixed-dose studies, the increase in heart rate (compared to placebo) was approximately 1.1, 4.1, and 6.9 beats per minute for the DVS 100, 200, and 400 mg/day groups, respectively. The clinical significance of this increase in heart rate is currently unclear.

7.1.6.3. Body Weight Findings

Decreases from baseline in mean body weight occurred with DVS treatment during the short term, 8-week studies. In the DVS group, mean body weight decreased by 1.0 kg. In the placebo group, mean weight decreased by 0.1 kg. There was no indication of a dose-response relationship. It is unlikely that the magnitude of the mean weight loss is clinically significant. No subject in any of the treatment groups discontinued from the study due to weight loss.

7.1.7. Electrocardiogram Findings

7.1.7.1. QT Interval Outliers

There were few outliers as defined by the QT parameters below. There is no significant difference among treatment groups in the proportion of subjects who were QT outliers.

Table 7.1.7.2 ECG Outliers in Placebo-controlled Trials

ECG Outliers in the Placebo-controlled Trials			
Parameter	PLA N = 707	DVS N = 964	VEN N = 220
QT interval ≥ 480 ms	< 1	< 1%	0
QTcB (women) > 470 or ↑ ≥ 60 ms	1%	1%	1%
QTcB (men) > 450 or ↑ ≥ 60 ms	3%	3%	0
QTcB > 500 ms	< 1%	< 1%	0
QTcF (women) > 470 or ↑ ≥ 60 ms	< 1%	1%	0
QTcF (men) > 450 or ↑ ≥ 60 ms	1%	1%	0
QTcF > 500 ms	0	< 1%	0
QTcN (women) > 470 or ↑ ≥ 60 ms	< 1%	< 1%	0
QTcN (men) > 450 or ↑ ≥ 60 ms	1%	1%	0
QTcN > 500 ms	0	< 1%	0

7.1.7.2. Mean QT Interval Changes

The table below illustrates the changes in mean QT parameters for the desvenlafaxine and venlafaxine groups compared to the placebo group. There were some statistically significant changes in placebo-subtracted mean QT changes from baseline. There were modest, statistically significant decreases in mean uncorrected QT interval values for the DVS group. In addition, there were small, statistically significant increases in mean QTcB for the placebo group. Finally, there were smaller, non-statistically significant increases in mean QTcF and QTcN parameters for the DVS group. For the venlafaxine group, the increases in mean QTcB were somewhat smaller compared to the DVS group. Furthermore, there were decreases in mean QTcF and QTcN in the venlafaxine group compared to the DVS and placebo groups. It is unlikely that these changes in QT interval parameters are clinically significant; especially since the QTcF analysis is probably the most useful correction in this case (due to increases in heart rate associated with DVS treatment), and the changes in mean QTcF are small.

Table 7.1.7.2.1: Mean Change in QT Parameters (placebo-subtracted) for Controlled Trials *Combined*

QT parameter (placebo-subtracted	PLA N= 557-707	DVS N= 775-964	VEN N= 180-220
QT interval week 8 (ms) QT interval final on-Rx	-	- 8.5 ms* - 8.6 ms*	- 8.9 ms * - 9.0 ms*
QTcB week 8 QTcB final on-Rx	-	+ 4.9 ms* + 5.0 ms*	+ 2.1 ms + 2.0 ms
QTcF week 8 QTcF final on-Rx	-	+ 0.7 ms + 0.6 ms	- 1.7 ms - 0.8 ms
QTcN week 8 QTcN final on-Rx	-	+ 1.3 ms + 0.8 ms	- 1.2 ms - 2.2 ms

*Statistically significant difference compared to placebo

Dose-relationship (not a clear relationship): QT results in fixed-dose studies
There does not appear to be a dose-relationship for changes in mean QT parameters.

Table 7.1.7.2.2: Mean Change in QT Parameters (placebo-subtracted) for *Fixed-dose Trials*

QT parameter (placebo-subtracted	DVS 100 mg N= 86/95	DVS 200 mg N = 194/238	DVS 400 mg N = 191/257
QT interval week 8 (ms) QT interval final on-Rx	+ 1.9 ms + 2.6 ms	- 6.3 ms - 6.6 ms	- 12.9 ms - 14.3 ms
QTcB week 8 QTcB final on-Rx	+ 4.9 ms + 4.7 ms	+ 5.8 ms + 4.8 ms	+ 6.4 ms + 6.8 ms
QTcF week 8 QTcF final on-Rx	+ 3.8 ms + 4.5 ms	+ 1.6 ms + 0.1 ms	- 0.3 ms - 0.4 ms
QTcN week 8 QTcN final on-Rx	+ 4.0 ms + 4.2 ms	+ 2.3 ms + 0.1	+0.8 ms - 0.6 ms

*Statistically significant difference compared to placebo

There was no signal suggesting that DVS leads to prolongation of the QT interval. There were no clinically significant differences between DVS-treated and placebo-treated subjects for QT, QTcF, QTcN, PR, and QRS intervals. However, there were mean increases in QTcB. DVS treatment was also associated with mean increases in heart rate and mean decreases in both PR and QT intervals.

Two subjects in the DVS group discontinued due to an abnormal ECG. There was one case of QT interval prolongation (with no associated clinically significant event). In the second case, a subject had ST depression and T wave inversion on ECG. These changes were not attributed to DVS treatment. There were no discontinuations due to ECG abnormalities in the venlafaxine or placebo group.

A dedicated QTc study was designed to assess the potential effect of single doses of 200 mg and 600 mg of desvenlafaxine on QT interval prolongation. The study was a single-dose, double-blind, randomized, placebo- and active controlled (moxifloxacin 400 mg) crossover study in 68 healthy women aged 18-54 years. The 600 mg dose of DVS was chosen because this dose yields plasma concentrations higher (3 times a 200mg dose) than those expected in patients at the maximum recommended dose. Women were chosen since they are generally more susceptible to QT prolongation. Moxifloxacin was used as a positive control group to establish assay sensitivity.

The sponsor's Table 2.2.4.1.1.2.1-1 from the Integrated Summary of Safety summarizes the effect on mean corrected QT interval (QTc) with Fridericia's and linear population correction methods at 8 hours post dose. Table 2.2.4.1.1.2.1-1: Estimate and 90% CI for QTc changes from time-matched baseline relative to placebo at 8 hour post-dose with different heart rate corrections

Table 7.1.7.3.3 Estimate and 90% CI for QTc changes from time-matched baseline relative to placebo at 8 hour post-dose with different heart rate corrections

Drug Dose	Fridericia's QT Correction (msec)*	Population QT Correction (msec)*
Desvenlafaxine 200 mg	1.50 (-0.88, 3.88)	3.18 (0.87, 5.50
Desvenlafaxine 600 mg	-2.43 (-4.90, 0.04)	0.98 (-1.42, 3.38)
Moxifloxacin 400 mg	10.80 (8.44, 13.16)	10.92 (8.62, 13.22)

Based on the primary and secondary endpoints of Fridericia's correction of QT (QTcF) and the population correction of QT (QTcN), the study appears to be negative for a DVS effect on QTc. Ninety-percent (90%) confidence intervals were constructed to compare the change from baseline of QTc for each dose of DVS to change from baseline of QTc for placebo. All CI are exclusive of and less than 10msec. The definition of a negative study (based upon the 12 May 2005 Step 4 ICH guidance) is one in which the upper bound of the two-sided 90% CI for the time-matched mean effect of drug compared to placebo on the QTc interval excludes 10 msec. Moxifloxacin produced a statistically significant increase over placebo in QTcF and QTcN at the Tmax of this study. The CI for both corrections is inclusive of and exceeds 10 msec; therefore,

the study is positive for moxifloxacin effect on QTc, as expected. This negative thorough QTc interval study supports the conclusion that DVS demonstrates little potential to cause clinically relevant QT interval prolongation.

7.1.8 Clinical Laboratory Test Findings

7.1.8.1. Outliers for Clinical Laboratory Parameters

In all treatment groups, only a small number of subjects had clinical laboratory test abnormalities that were potentially clinically significant. For most laboratory parameters, there was not an excess of abnormalities in the DVS group. However, there was an excess of subjects with elevations in lipid concentrations, compared to the placebo venlafaxine groups. For the total cholesterol concentration, potentially clinically important elevations occurred in 6%, 2%, and 4% in DVS, placebo, and venlafaxine groups, respectively. Clinically significant elevations in LDL concentrations occurred in 1.6%, 0.2%, and 0.6% in the DVS, placebo, and venlafaxine groups, respectively. Triglyceride concentrations were significantly elevated in 4.5%, 2.6%, and 3.5% of the DVS, placebo, and venlafaxine groups, respectively. In the fixed-dose studies, there appeared to be a dose-related increased risk of developing significant elevations of total cholesterol and triglycerides. Lipid elevations are known to occur with venlafaxine treatment.

DVS treatment was also associated with an excess of subjects (compared to the placebo and venlafaxine groups) who developed significant elevations in liver enzyme concentrations (ALT/SPGT). Significant serum ALT elevations were reported for 0.6%, 0.1%, and 0 in the DVS, placebo, and venlafaxine groups, respectively.

A small number of subjects discontinued due to abnormal clinical laboratory results. In the DVS group, the most common such abnormality was elevated liver enzymes. In two (2) cases, investigators judged that the liver function test abnormalities were due to DVS treatment. In both cases, the abnormalities resolved upon discontinuing the drug. Neither case included elevation in bilirubin concentration, and neither case met criteria for Hy's law.

7.1.8.2 Discontinuations Due to Abnormal Clinical Laboratory Findings

The table below lists the discontinuations due to abnormal clinical laboratory test findings. There were relatively few such discontinuations. Generally, less that 1% of the study population discontinued for any particular laboratory abnormality. The exceptions included subjects discontinuing due to elevation of liver enzymes (1%, 1%, and < 1% in the DVS, placebo, and venlafaxine groups, respectively.

Table 7.1.8.2: Discontinuations due to Clinical Laboratory Abnormalities

Discontinuations Due to Abnormal Clinical Laboratory Findings			
Laboratory abnormality	DVS n = 1211	PLA n = 803	VEN n = 244
Liver enzymes elevated	13 (1)	7 (1)	1 (< 1)

Cholesterol elevated	2 (< 1)	1 (< 1)	1 (< 1)
Triglyceride elevated	6 (< 1)	1 (< 1)	-
Leukocytopenia	1 (< 1)	-	-
Neutropenia	-	-	1 (< 1)
Hyperglycemia	-	2 (< 1)	1 (< 1)
Thyroxine decreased	-	-	1 (< 1)
Prolactin elevation	1 (< 1)	-	-
Testosterone elevated	-	1 (< 1)	-

7.1.8.3 Potentially Clinically Significant Laboratory Abnormalities

The sponsor's criteria for determining laboratory test results that were potentially clinically significant are outlined in Appendix 10.6. For liver enzymes (ALT, AST, and alkaline phosphatase), three (3) times the upper limit of normal was considered potentially clinically significant. For bilirubin, 1.5 times the upper limit of normal was considered potentially clinically significant. The proportions of subjects in each treatment group selected results of potential clinical significance are listed in the table below. It appears that no subjects had abnormal thyroid function test results that were considered potentially clinically significant.

Table 7.1.8.3: Subjects with Potentially Clinically Significant Laboratory Abnormalities

Parameter	Placebo (n = 691)	DVS (n = 952)	Ven (n = 209)
Liver enzymes	1.6%	1.6%	0
Bilirubin	1.2%	0.4%	0
Cholesterol, total	2%	6%	4%
LDL	0.2%	1.6%	0.6%
HDL	1.9%	1.3%	1.8%
Triglyceride	2.6%	4.5%	3.5%
Thyroxine, free			
T4 total			

7.1.8.4 Changes in Mean Clinical Laboratory Parameters

Desvenlafaxine treatment was associated with a number of statistically significant changes in mean clinical laboratory parameters. Furthermore, many of these mean changes were dose-related. The parameters affected included liver enzymes, cholesterol, triglycerides, and thyroid hormones. The specific changes are listed in the table below. As illustrated, the largest changes occurred for GGT (+ 26.8%) , bilirubin (– 17.4%), alkaline phosphatase (+ 10.1%), ALT (+ 9.4%), AST (+ 7.6%), total T4 (– 9.2%), and free T4 (– 8.3%). The clinical significance of these mean changes is unclear. There were very few potentially clinically significant changes for individual subjects for these laboratory parameters.

Laboratory parameter	Percentage change	Statistically significant	Dose-related change
AST	+ 7.6%	Yes	Yes
ALT	+ 9.4%	Yes	Yes
GGT	+ 26.8%	Yes	Yes
Bilirubin	− 17.4%	Yes	Yes
Alkaline phosphatase	+ 10.1%	Yes	Yes
Total cholesterol	+ 3.1%	Yes	Yes
LDL cholesterol	+ 3.4%	Yes	no
HDL cholesterol	+ 2.8%	Yes	Yes
Triglycerides	+ 4.5%	Yes	no
Total thyroxine (T4)	− 9.2%	Yes	no
Free thyroxine index	− 8.3%	Yes	no
T3 uptake	+ 1%	Yes	no
Creatinine	− 0.4%	no	no

In order to determine whether the abnormalities in serum liver enzyme concentrations might have been clinically significant, the sponsor analyzed the data to see if any relevant subject had laboratory results that met criteria for Hy's law. Criteria for Hy's law include: 1) AST or ALT concentrations > three (3) times the upper limit of normal; 2) total bilirubin levels > 34 μmol/L; and 3) alkaline phosphatase concentration within normal limits. There were no subjects identified who met these criteria.

Since the mean total bilirubin concentrations were significantly decreased in the DVS group, the sponsor examined whether the decreases were true decreases or caused by assay interference that might mask a potentially medically important increase in total bilirubin concentration. The sponsor conducted a spiking study. There was no indication that DVS interfered with the total bilirubin assay over the tested range of 10 to 1000 ng/mL of DVS in either normal human serum or Level 2 serum control with high total bilirubin concentrations.

7.1.8.5 Urinalysis Findings: Proteinuria and Hematuria

In the short-term, placebo-controlled trials, desvenlafaxine treatment was associated with a dose-related increase in the risk of developing proteinuria and hematuria. Proteinuria occurred in 5.5% of the DVS group, compared to 3.1% of the placebo group and 3.4% of the venlafaxine group. In the placebo, 100 mg. 200 mg, and 400 mg groups, proteinuria occurred in 1.9%, 3.2%, 4.9%, and 6.9%, respectively. Hematuria was reported for 10.2% of the DVS group, compared to 9.4% of the placebo group and 11.7% of the venlafaxine group. As would be expected, a higher proportion of female subjects in the DVS group had hematuria (15.4%) compared to male subjects (2.9%). The finding of hematuria was not dose-related.

Dr. Desai (Cardiorenal Division) also analyzed the urinalysis data. He determined that there was an excess of cases of proteinuria and hematuria in the DVS group, compared to the venlafaxine and placebo groups. We wanted to determine if this might be potentially clinically significant and if the urinary abnormalities might be associated with elevated blood pressure in individual subjects. Of note, there was no significant difference in serum creatinine or BUN findings across treatment groups. Results of Dr. Desai's analysis are presented and discussed below.

The table below demonstrates the results of urine protein and urine hemoglobin collected in the three (3) fixed dose studies at baseline and Visit 8 (day 56). The table displays the number of subjects with an abnormal urinalysis (UA) as defined as trace, +, ++, or +++ protein or hemoglobin.

With respect to proteinuria, the results suggest that subjects treated with DVS are at a somewhat higher risk of an abnormal urinalysis compared to subjects taking placebo control. Although not shown in the table below, it is reassuring is that most subjects with an abnormal UA had only trace or + urine protein. It is also reassuring that renal function, as assessed by mean serum creatinine level change from baseline, did not worsen with DVS treatment relative to placebo. With respect to hemoglobinuria, the results do not suggest any evidence of a difference between DVS and placebo. Only a small number of subjects had a combination of an abnormal UA (with both proteinuria and hematuria), along with an increased total cholesterol and hypertension.

Table 7.1.8.5 Urinalysis Findings in Short-term Controlled Trials

	Placebo	100 mg DVS	200 mg DVS	400 mg DVS
Visit 1 (pre study drug baseline)	N = 325	N = 120	N = 316	N = 321
# of subjects with trace, +, ++, or +++ protein on UA	8	2	8	13
# of subjects with trace, +, ++, or +++ hemoglobin on UA	26	12	26	31
Visit 8 (end of study)	N = 268	N = 94	N = 226	N = 249
# of subjects with trace, +, ++, or +++ protein on UA	6	3	11	17
# of subjects with trace, +, ++, or +++ hemoglobin on UA	26	10	21	29

Source: Analysis by Mehul Desai, M.D. (Cardiorenal Division)

As the sponsor notes, the urinalysis data suggest that treatment with desvenlafaxine may be associated with increased urinary excretion. The mechanism of the increased protein excretion is not clear, but it may be related to noradrenergic stimulation. Generally, the protein excretion is mild, and it is not associated with increased serum creatinine or increased BUN concentration. Furthermore, cases of proteinuria generally did not co-occur in subjects who had hypertension. Currently, the clinical significance of this finding is not clear. The sponsor proposes to include

'proteinuria' in the "Other Adverse Events" section of labeling (categorized as 'frequent,' i.e., occurring on one (1) or more occasions in at least 1/100 subjects.

7.1.9. Withdrawal or Discontinuation Symptoms

Subjects in the controlled DVS studies had their DVS dose tapered (as opposed to discontinued abruptly), in order to reduce the risk of discontinuation-emergent adverse events. The taper period included two (2) weeks of dose tapering and a follow-up visit three (3) weeks after discontinuation of treatment. The investigator could change the taper schedule as needed. The taper schedule for DVS and venlafaxine in the short-term, placebo-controlled studies is presented in the table below.

Table 7.1.9.1 Schedule for Drug Taper and Discontinuation

Final on-therapy daily dose	Week 1 post study daily dose	Week 2 post study daily dose	Week 3 post study daily dose
Desvenlafaxine 100 mg	0	0	0
Desvenlafaxine 200 mg	100 mg	0	0
Desvenlafaxine 400 mg	200 mg	100 mg	0
Venlafaxine ER 75 mg	0	0	0
Venlafaxine ER 150 mg	75 mg	0	0
Venlafaxine ER 225 mg	150 mg	75 mg	0

Taper and post-discontinuation-emergent adverse events were defined as adverse events that were not present during the seven (7) days before the tapering period or events that were present and had become more severe during the taper and post-discontinuation period.
Discontinuation symptoms were evaluated by: 1) recording adverse events that emerged during the taper and discontinuation periods; and 2) by using the specific Discontinuation-Emergent Signs and Symptoms (DESS) checklist to assess discontinuation-emergent symptoms. The DESS is the most useful and specific assessment tool for evaluating the presence of discontinuation symptoms related to SSRI and other antidepressant tapering and discontinuation. The purpose of the DESS checklist is to assess in a directed manner discontinuation-emergent symptoms resulting from discontinuation of study drug. The DESS checklist consists of specific questions regarding emergence or changes in severity of 43 particular symptoms. Subjects could report that a symptom was unchanged, not present, improved, worsened, or new. A score of 0 was applied to symptoms that were unchanged, not present, or improved; a score of 1 was applied to symptoms that were new or worsened. The maximum score is 43. The DESS checklist was administered by a clinician at baseline and on study days 56, 63, 70, and 77. The clinician asked the subject: "During the past seven (7) days, have you experienced any changes in the following symptoms?" The reference assessment for analysis was the last day of treatment (day 56). Specific DESS items are listed in the table below.

Table 7.1.9.2 Discontinuation-Emergent Signs and Symptoms Checklist Items

Discontinuation-Emergent Signs and Symptoms Checklist		
1. Nervousness or anxiety	16. Shaking, trembling	31.Shortnes of breath, gasping for air
2. Elevated mood, feeling high	17. Muscle tension or Stiffness	32. Chills
3. Irritability	18. Muscle aches or pains	33. Fever
4. Sudden worsening of mood	19. Restless feeling in legs	34. Vomiting
5. Sudden outbursts of anger or anger attacks	20. Muscle cramps, spasms or twitching	35. Nausea
6. Sudden panic attacks or anxiety attacks	21. Fatigue, tiredness	36. Diarrhea
7. Bouts of crying or tearfulness	22. Unsteady gait or incoordination	37. Stomach cramps
8. Agitation	23. Blurred vision	38. Stomach bloating
9. Feeling unreal or detached	24. Sore eyes	39. Unusual visual sensations (lights, colors, geometric shapes)
10. Confusion or trouble concentrating	25. Uncontrolled mouth, tongue movements	40. Burning, numbness, tingling sensations
11. Forgetfulness or problems with memory	26. Problems with speech or speaking clearly	41. Unusual sensitivity to sound
12. Mood swings	27. Headache	42. Ringing or noises in ears
13. Trouble sleeping, insomnia	28. Increased saliva in mouth	43. Unusual tastes or smells
14. Increasing dreaming or nightmares	29. Dizziness, lightheadedness, sensation of spinning, dizziness	
15. Sweating more than usual	30. Nose running	

For the seven (7) controlled studies combined, discontinuation symptoms were reported by 25% of subjects treated with placebo, 32% of subjects treated with DVS, and 25% of subjects treated with venlafaxine. In the fixed-dose studies, discontinuation symptoms were reported by 24% of subjects treated with placebo, 27%subjects treated with DVS 100 mg, 32% of subjects treated with DVS 200 mg, and 38% of subjects treated with DVS 400 mg. In the flexible-dose studies with venlafaxine, discontinuation symptoms were reported by 25% subjects treated with placebo, 26%subjects treated with DVS, and 25% subjects treated with venlafaxine.

The most common (> 5% and at least 2 times greater with DVS than with placebo) discontinuation symptoms reported are shown in the tables below. The most common were nausea, dizziness, and headache. In the fixed-dose studies, there was a dose-response relationship for nausea.

Table 7.1.9.3 Discontinuation-emergent symptoms in controlled trials combined

Discontinuation-emergent symptoms in controlled trials combined (≥ 5% of DVS group and twice the rate of placebo)			
Adverse event	placebo n - 270	DVS 100-400 mg	Venlafaxine ER N = 61
Nausea	2%	5%	5%
Dizziness	1%	7%	3%

Table 7.1.9.4 Discontinuation-emergent symptoms in fixed-dose trials

Discontinuation-emergent symptoms in fixed-dose trials (≥ 5% of DVS group and twice the rate of placebo)				
Adverse event	placebo n = 148	DVS 100 mg n = 34	DVS 200 mg n = 153	DVS 400 mg n = 164
Infection	0	6%	3%	2%
Diarrhea	1%	9%	1%	1%
Nausea	1	3%	4%	9%
Abnormal dreams	0	6%	2%	2%
Dizziness	0	6%	8%	8%

Table 7.1.9.5 Discontinuation-emergent symptoms in flexible-dose trials

Discontinuation-emergent symptoms in flexible-dose trials including venlafaxine ER (≥ 5% of DVS group and twice the rate of placebo)			
Adverse event	placebo n = 56	DVS 200-400 mg n = 81	VEN 75-225 mg n = 61
Headache	4%	7%	3%
Emotional lability	0	6%	5%

There were relatively few subjects in the DESS analysis, because a large proportion of subjects continued DVS treatment in the long-term study 30; therefore, they did not taper and discontinue their doses after the short-term studies.

The method of statistical analysis was determined a priori and was accepted by the Division. The DESS scores were grouped by treatment group and by time of assessment. In the analysis, t-tests were used to determine statistical differences in DESS scores between the DVS and placebo group. To address the potential problem of multiplicity, adjusted p-values based on the false discovery rate were computed.

There were no statistically significant differences in mean DESS scores between any DVS dose group and placebo at any time point. Furthermore, discontinuation-emergent adverse events were not commonly reported in the controlled studies. However, there were numerical trends for a higher proportion of DVS-treated subjects (compared to placebo-treated subjects to report the following discontinuation symptoms: dizziness, nausea, headache, abnormal dreams, emotional lability, and diarrhea. These types of discontinuation-emergent symptoms are characteristic of those reported after discontinuation of other SNRI and SSRIs. There were no new or unexpected findings upon tapering and discontinuation of desvenlafaxine.

7.1.10. Human Reproduction and Pregnancy Data

Eighteen (18) pregnancies were reported during or shortly after the short-term controlled studies. There were 15 in the DVS group, two (2) in the placebo group, and one (1) in the venlafaxine group. Four (4) additional pregnancies were reported for the long-term studies. The outcomes of the pregnancies included eight (8) elective terminations, five (5) healthy babies, one (1) spontaneous abortion, one (1) salpingectomy for an ectopic pregnancy, and five (5) pregnancies with an unknown outcome. Further details about these pregnancies and outcomes are not currently available. Other human reproductive data are not available.

7.1.11. Overdose Experience with Desvenlafaxine in Controlled Trials

There were a number of intentional and unintentional overdoses in the short-term controlled trials. Only two overdoses with large amounts of DVS SR (1800 mg and 5200 mg) occurred, both as multi-drug overdoses. These subjects recovered, and did not have unexpected toxicities as a result of the DVS exposure.

Accidental and intentional overdoses of greater than 600 mg/day were evaluated with regard to adverse events reported within five (5) days of the overdose date. This included new episodes of an adverse event or exacerbation of an ongoing adverse event, defined as an increase in severity. Accidental and intentional overdoses greater than 600 mg/day were reported for 34 subjects. Of the 34 subjects who reported overdoses greater than 600 mg/day, 16 reported adverse events within 5 days of the overdose. There were no deaths associated with DVS overdose. All subjects who had a DVS overdose recovered. The adverse events that were reported within five days after an overdose were: headache (5), nausea (2), infection (2), tachycardia (1), flu syndrome (1), pharyngitis (1), fever (1), vomiting (2), constipation (1), eructation (1), back pain (1), agitation (1), dry mouth (1), and insomnia (1). None of these individual adverse events was considered a serious adverse event. In one case, a subject ingested and overdose of 1,800 mg of DVS, 1,050 mg of Wellbutrin XR, and 14 Lortabs. The subject was brought to the emergency room, and she was treated with gastric lavage and activated charcoal. She was reported as stable in the emergency room for 12 hours, except for mild tachycardia. Her heart rate ranged from 100 to 115 beats per minute, with normal sinus rhythm. The subject was admitted to the intensive care unit overnight. She recovered on the following day, and was transferred to the Behavioral Medicine facility for further psychiatric care.

In another case, a subject took an overdose consisting of 5,200 mg of DVS and 120 mg of clonazepam. After the overdose, he experienced amnesia for 3 days. He experienced vomiting and somnolence for approximately for 24 hours. He recovered completely.

7.1.12. Experience with Venlafaxine Overdose

Gregory Dubitsky, M.D. (Medical Officer in the Division of Psychiatry Products) has completed two reviews regarding the toxicity of venlafaxine in overdose. The first review was completed on July 4, 2006. It is entitled "Review and Evaluation of Clinical Data: Toxicity of Venlafaxine in Overdosage." The review was prompted by the release of the United Kingdom's Medicines and

Healthcare products Regulatory Agency (MHRA) review of the safety and efficacy of selective serotonin reuptake inhibitors (SSRI's) and venlafaxine in late 2004. This examination identified a number of safety issues pertaining to venlafaxine. Among the concerns was the toxicity of venlafaxine in overdosage.

Venlafaxine overdose has been associated with an increased fatality rate in the U.K. and an increased rate of admission to the ICU/CCU in the U.S., relative to overdoses with SSRIs. Dr. Dubitsky notes that it is theoretically possible that venlafaxine-treated patients carry an increased risk of suicidal behavior and, to some unknown extent, such a factor could contribute to the increased occurrence of fatal outcomes with venlafaxine overdoses. However, there is no clear evidence to date that venlafaxine induces suicidal behavior in adult populations. Also, systematic evaluations of overdose sequelae suggest an elevated risk of seizures and serotonin toxicity with venlafaxine overdosage.

Spontaneous reporting data are consistent with these findings. Almost all fatalities with venlafaxine alone appear to occur after ingestions over 2.5 grams, with the lowest fatal overdose following an ingestion of 2.25 grams. Seizures associated with fatal overdosage of venlafaxine alone tend to occur after large ingestions. Although there are no clear signals of cardiotoxicity associated with overdosage with venlafaxine alone, such risk cannot be completely ruled out based on available data.

Dr. Dubitsky recommended that labeling revisions reflect: 1) the potential risks of increased mortality and other serious sequelae, such as seizures and serotonin syndrome, with venlafaxine overdosage; 2) the uncertainty surrounding those risks, and 3)

On August 10, 2006, the Division issued a letter to Wyeth, requesting that specific language be added in the labeling in order to provide adequate information for the safe and effective use of venlafaxine.

The company responded with additional relevant information as well as proposed revisions to the Division's requested labeling. The company submitted the labeling supplement on September 7, 2006 (NDA 20-699/SLR-072). Dr. Dubitsky reviewed the material, and he completed the second review on October 12, 2006.

In the review, Dr. Dubitsky stated: "the sponsor has presented substantive new data regarding the risk of suicide in patients treated with venlafaxine based on experience at Kaiser Permanente (KP) in Northern California. This study was funded by Wyeth." The objective of this investigation was to determine whether venlafaxine treatment increases the risk of suicide-related fatality, suicide attempt, or fatal outcome (from overdose and all attempts) compared to fluoxetine, citalopram, or paroxetine. Across the four antidepressant drugs, there were no large differences in gender distribution, age, or diagnostic indication (depression versus anxiety).

"However [per Dr. Dubitsky], suicide risk factors (prior suicide attempts, prior psychiatric hospitalizations, and previous antidepressant drug treatment) were somewhat more prevalent in patients treated with venlafaxine. Additionally, higher percentages of venlafaxine-treated patients had important comorbid conditions (i.e., a prior diagnosis of bipolar disorder, psychotic disorder, personality disorder, or substance abuse) compared to the SSRI-treated patients. This pattern also generally held true when the subset of antidepressant-naïve patients (i.e., with no antidepressant use in the previous year) was analyzed."

In the Reviewer's Comments section, Dr. Dubitsky stated: "This study does suggest that, in the U.S., venlafaxine-treated patients carry a slightly higher burden of suicide risk factors compared to those treated with three commonly used SSRIs, citalopram, fluoxetine, and paroxetine. It also suggests that venlafaxine-treated patients may be more likely to attempt suicide than those treated with the other three agents but the increased risk is likely to be small and may be biased by residual confounding. Due to lack of information on overdose ingestions, no conclusions can be drawn directly pertaining to the toxicity of venlafaxine in overdosage."

Wyeth also presented updated cumulative data from the Wyeth Safety Surveillance System (S3) as of 5-5-06 for medically confirmed reports of venlafaxine overdose. This revealed 2,854 individual reports, which were evaluated to determine the frequency of adverse experiences relative to the total number of reports. The most commonly reported events (by MedDRA preferred term) were tachycardia (24.9% of all reports), sedation (19.4%), mydriasis (8.4%), convulsion (7.5%), and vomiting (5.0%). Serotonin syndrome was reported in approximately 1.3% of medically-confirmed venlafaxine overdose reports.

Of the 2,854 overdose reports, 1,735 documented venlafaxine ingestions over 225mg. Of these, 1,687 were non-fatal, and 48 were fatal. Dr. Dubitsky performed an analysis based on a range of ingested doses of venlafaxine. Dose ranges were selected to represent 14-day supplies of 75mg, 150mg, and 225mg daily venlafaxine dosages. Wyeth emphasizes the point that a small number of fatal overdoses did involve ingestions of relatively small amounts of venlafaxine: 7 multi-drug and one single-drug overdose were in the lowest dose range (>225 to 1,050mg). Thus, they argue that our recommendation

Based on the new information provided by the sponsor, Dr. Dubitsky has concluded that Wyeth's counterproposal for describing information pertaining to overdosage with venlafaxine in labeling appears to be reasonable. He has recommended that this supplement be approved.

Below is the new labeling language for venlafaxine that is recommended for approval:

OVERDOSAGE/ Human Experience:

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma),

mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

7.1.13. Suicidality Analyses of Clinical Trial Data

The sponsor performed a formal analysis of suicidality that occurred during the short-term controlled trials. This was conducted by the standardized method that has been developed by FDA. In order to identify adverse events of potential relevance for the suicidality analysis, the sponsor used the following text strings in searches of all pertinent preferred terms and verbatim terms:

"accident-," "attempt," "burn," "cut," "drown," "gas," "gun," "hang," "hung," "immolat," "injur-," "jump," "monoxide," "mutilat-," "overdos-," "self damag-," "self harm," "self inflict," "self injur" "shoot," "slash," "suic-," "poison," "asphyxiation," "suffocation," "firearm"

An examination of all verbatim terms was performed, and any events that had, at face value, no relationship to volitional acts were eliminated (eg, mosquito bites, sprained ankles). Any event in which intent may have been present, or which were ambiguous, were retained (eg, laceration). After cases were identified, narratives for each case were prepared.

The blinded narrative summaries were reviewed by two (2) independent physician for "possibly suicide-related" adverse events, and categorized using the FDA classification of events. The categories used for the classification of events are shown in the table below.

Categorization of Suicidality Events	
Category code	Description
1	Completed suicide
2	Suicide attempt
3	Preparatory acts towards imminent behavior
4	Suicidal ideation

5	Self-injurious behavior, intent unknown
6	Not enough information (fatal)
7	Self-injurious behavior, no suicidal intent
8	Other: accidental, psychiatric, medical
9	Not enough information (non-fatal)

After the individual reviewer categorized each case, results were compared and a consensus was reached about a classification for each case. The 2 individual reviewers had the same assessment for 21 of the 23 cases; the remaining 2 cases were then reconciled. After the classifications were completed, the narratives were unblinded and assessed.

Sixteen (16) subjects were identified as having had possible adverse events consistent with suicidality. The cases were classified by blinded reviewers. One completed suicide occurred in a subject who was randomly assigned to receive 100 mg of DVS; but, it was unclear if the subject was actually taking the study drug. There were two (2) subjects in the DVS group who had suicide attempts. One (1) subject in the placebo group had a suicide attempt. Three (3) subjects in the DVS group experienced suicidal ideation; two (2) subjects in the venlafaxine group had suicidal ideation; and three (3) subjects in the placebo group had suicidal ideation. One (1) subject in the DVS group and one (1) subject in the venlafaxine group had self-injurious behavior. Two (2) subjects in the placebo group had events classified as 'not enough information available (code 9). The types of events are listed in the table below.

Suicidality Events Reported in the Controlled Trials			
Suicidality category	Placebo N = 803	DVS N = 1,211	Venlafaxine N = 224
Completed suicide (code 1)	-	1	-
Suicide attempt (code 2)	1	2	-
Suicidal ideation (code 4)	3	3	2
Self-injurious behavior Code 7)	-	1	1
Not enough information (code 9)	2	-	-

A statistical analysis was performed using the FDA categories described. These analyses were performed using SAS version 8.2 and Comprehensive Meta Analysis–Biostat, and they were conducted by the Biostatistics and Clinical Technology section of Wyeth. To address the potential problem of trial similarity, the seven placebo-controlled DVS trials were pooled using "trial" as the unit of investigation. Because individual trials were not sufficiently powered to detect signals of rare events, meta-analytic methods were used for the analysis. A weighted average of treatment effect for various codes was calculated by pooling studies with identical codes. Results of both the fixed- and random-effects analyses are presented. The Mantel-Haenszel method was used to compute the pooled odds ratios. To correct for continuity for trials with zero cells, 0.50 was added to each of the 4 cells before the odds ratio and 95% confidence intervals were computed. The results of the analysis of suicidality data using the FDA criteria are presented in the table below.

Results of Suicidality Analysis (odds ratios, CI, p-values)			
Study Number	Odds ratio	Confidence interval	p-value
FDA Outcome (code 1 and code 2)			
Pooled analysis: (studies 306, 308, 309)			
Fixed-effect	0.984	(0.159, 6.066)	p = 0.986
Random-effect	0.984	(0.159, 6.066)	p = 0.986
Code 1 (completed suicide)			
Study 306	1.03	(0.042, 25.56)	
Code 2 (suicide attempt)			
Pooled analysis: (studies 306, 308, 309)			
Fixed-effect	0.812	(0.162, 4.069)	p = 0.800
Random-effect	0.812	(0.127, 5.125)	p = 0.825
Code 4 (suicidal ideation)			
Pooled analysis: (studies 223, 306, 308, 320)			
Fixed-effect	0.556	(0.135, 2.282)	p = 0.414
Random-effect	0.574	(0.130, 2.536)	p = 0.464
Code 7 (self-injurious behavior, no suicidal intent)			
Study 306	1.009	(0.041, 24.92)	p = 0.996
Code 8 (other: accidental, psychiatric, medical)			
Pooled analysis: (studies 304, 306, 308, 317)			
Fixed-effect	1.246	(0.317, 4.903)	p = 0.753
Random-effect	1.142	(0.276, 4.727)	p = 0.855
Code 9 (not enough information; not fatal)			
Pooled analysis: (studies 223, 306, 308, 320)			
Fixed-effect	0.173	(0.018, 1.673)	p = 0.130
Random-effect	0.173	(0.18, 1.672)	p = 0.130

A second set of analyses based on HAM-D17 item 3 (suicide) was conducted by the sponsor. The definitions used were the same as those used by the FDA in their draft guidance:

"Emergence of suicidality" is defined as follows: a subject is assigned a value of "1" if there is a change in rating of the HAM-D17 item 3 ("suicide") from 0 at baseline or from 1 at baseline to 2 or more at any time during the controlled phase of the trial. Analyses based on odds ratios and corresponding 95% confidence interval were computed with a chi-square p-value for each study, dose level (if applicable), and pooled doses within each study, for = 2 weeks, = 4 weeks, and overall (at any time during the controlled portion of the trial).

"Worsening of suicidality" is defined as follows: at any time during the controlled phase of the trial, a subject has an increase of 1 point or more on the HAM-D17 item 3, regardless of any subsequent change. Analyses based on odds ratios and corresponding 95% confidence interval were computed with a chi-square p-value for each study, dose level (if applicable), and pooled doses within each study, for =2 weeks, =4 weeks, and overall (at any time during the controlled portion of the trial). The results are presented in Supportive Table ST 2-34.

The odds of the emergence or worsening of suicidality did not differ significantly between DVS and placebo in most evaluation periods for each study. Significant differences compared with

placebo in favor of DVS SR (i.e., p=0.05 and odds ratios less than 1.0) were observed at some doses and time points for emergence of suicidality in studies 306 and 320 and for worsening of suicidality in studies 306, 308, and 320.

Analysis of the HAM-D-17 Item 3 data indicated that there were no significantly higher odds of emergence or worsening of suicidality in DVS-treated than with placebo-treated subjects at any evaluation period. In fact, there was evidence of reduction of suicidality for DVS-treated subjects compared with placebo, as seen by the significant p-values and odds ratios less than 1.0 in studies 306, 308, and 320.

Overall, the suicidality analyses revealed that there is no pattern suggesting that treatment with DVS induces or exacerbates suicidality. The events in the analysis were generally evenly distributed across the DVS, venlafaxine ER, and placebo treatment groups, suggesting that suicidality that occurred in the controlled trials is probably related to their underlying depressive illness.

7.1.14. Postmarketing Experience

There has been no postmarketing experience with desvenlafaxine in any country.

7.1.1.15. Review of Long-term, Open-label Safety Data & 4-Month Safety Update

The Four-Month Safety Update consisted primarily of safety and exposure from ongoing long-term, open label studies 303, 307, and 318. In addition, the sponsor provided additional data and analysis regarding the laboratory findings (from the controlled trials) of proteinuria, hemoglobinuria, and elevations is serum liver enzyme concentrations.

7.1.1.15.1. Table of long-term studies (302, 303, 307, and 318)

Study	Design	Subjects	DVS dose
302	Relapse prevention trial: 6-month, open-label DVS stabilization phase, followed by 12-month, double-blind, placebo-controlled, randomized withdrawal phase.	MDD subjects from 18 to 75 years of age (N = 593)	DVS 200-400 mg/day Flexible dosing
303	10-month, open-label long-term safety study as an extension to 8-week, placebo-controlled short-term efficacy trials (304, 306, 308, 309, 317, and 320)	MDD subjects from 8 to 75 years of age (N = 1,394)	DVS 200-400 mg/day Flexible dosing
307	6-month, open-label study of DVS in MDD subjects	MDD elderly subjects age 65 or older (N = 52)	DVS 100-200 mg/day Flexible dosing
318	12-month, open-label study in MDD subjects	MDD subjects from 18 to 75 years of age (N = 104)	DVS 200-400 mg/day Flexible dosing

7.1.1.15.2. Description of Long-term Studies (302, 303, 307, 318)

Study 302
Study 302 was a long-term relapse prevention trial male and female subjects (age 18-75) with a diagnosis of MDD. Subjects were initially treated with DVS (200-400 mg/day) in an open-label manner for up to 6 months. Responders who continued treatment entered a double-blind, placebo-controlled phase lasting up to 12 months. A total of 593 subjects enrolled in the open-label treatment phase. Of these, 416 completed, and 177 discontinued treatment during the open-label phase.

Study 303
Study 303 was a long-term, 10-month, open-label, continuation safety study of DVS (flexible-dose 200-400 mg/day) in 1,394 subjects (male and female subjects (age 18-75) with Major Depressive Disorder who had been treated with DVS, placebo, or venlafaxine ER in one of the short-term, placebo-controlled studies of DVS in MDD. (Feeder studies included fixed-dose studies 304, 306, and 308; flexible-dose studies included 309, 317, and 320. (439 completed, and 682 discontinued). Subjects were not required to have had a therapeutic response during the double-blind, placebo-controlled period of DVS treatment.

Study 307
Study 307 was a long-term (6-month) open-label study of DVS (flexible-dose 100-200 mg/day) in 52 elderly subjects (age 65 or older) with a diagnosis of MDD.

Study 318
Study 318 was a long-term, 12-month, open-label study of DVS flexible-dose 200-400 mg/day in 104 subjects (male and female subjects (age 18-75) with a diagnosis of MDD.

7.1.1.15.3. Total Desvenlafaxine Exposure in Long-term Studies (subject-years)

For long-term studies 302, 303, 307, and 318, the total desvenlafaxine exposure was 985.15 subject-years. For the subset of subjects treated with desvenlafaxine for at least six (6) months, the total desvenlafaxine exposure was 8.78 subject-years.

7.1.1.15.4. Discontinuations- Reasons for Discontinuation

In the long-term studies combined, 45% of subjects discontinued. The most common reason for discontinuation was adverse event (21%). These findings are not unexpected.

Reason for discontinuation	DVS 100-200 mg/day (N = 2143)
Total discontinuations	45%
Adverse event	21%
Failed to return	8%
Unsatisfactory response	5%
Subject request unrelated to study	5%
Other event	3%
Protocol violation	3%

7.1.1.15.5. Deaths and Serious Adverse Events

There were no deaths in the long-term desvenlafaxine studies. There were relatively few serious adverse events in a group of studies with such a large number of subjects. Approximately 1.8% of subjects had serious adverse events reported. The SAE that were probably related to treatment with desvenlafaxine include: cerebrovascular accident (1), hypertension (2), seizure, and mania. SAE that were possibly related to treatment with desvenlafaxine include: cerebrovascular accident (2), myocardial infarction, chest pain, syncope, Pancreatitis, Rhabdomyolysis, bowel obstruction, ataxia, blurred vision, and panic attack.

SERIOUS ADVERSE EVENTS	DVS 100-400 mg/d n = 2143
Total SAE possibly or probably related to DVS	39 (1.8)
Suicidal ideation	6 (< 1)
Suicide attempt	2 (< 1)
Intentional overdose	4 (< 1)
Cerebrovascular accident	3 (< 1)
Hypertension	2 (< 1)
Myocardial infarction	1 (< 1)
Chest pain	3 (< 1)
Syncope	1 (< 1)
Seizure	3 (< 1)
Pancreatitis	1 (< 1)
Rhabdomyolysis	1 (< 1)
Homicidal ideation	1 (< 1)
Bowel obstruction	1 (< 1)
Mania	2 (< 1)
Ataxia	1 (< 1)
Blurred vision	1 (< 1)
Panic attack	1 (< 1)

7.1.1.15.6. Discontinuations due to adverse events

In the long-term studies, 21% of subjects discontinued due to adverse events. These adverse events associated with discontinuation are quite similar to those associated with discontinuation in the placebo-controlled, short-term trials. There were no new or unexpected adverse events for AE reported for > 1% of the long-term study population.

Adverse event	DVS 100-400 mg/d (N = 2143)
Any adverse event	21%
Cardiovascular	
Hypertension	2%
Nervous system	

Dizziness	3%
Asthenia	2%
Somnolence	2%
Insomnia	2%
Headache	1%
Anxiety	1%
Thinking abnormal	1%
Digestive system	
Nausea	5%
Vomiting	1%
Abdominal pain	1%
Diarrhea	1%
Dry mouth	1%
Other	
Abnormal vision	1%
Sweating	1%

7.1.1.15.7. Common Adverse Events in Long-term Studies

The most commonly reported adverse events in the long-term studies are listed in the table below. The types and pattern of common adverse events are quite similar to those reported in the short-term, placebo-controlled trials. There were no new or unexpected commonly reported adverse events in the long-term studies. The most common were: nausea (38%), headache (29%), dry mouth (25%), insomnia (22%), sweating (22%), dizziness (21%), somnolence (17%), asthenia (16%), constipation (15%), and anorexia (13%). Hypertension was reported as an adverse event for 8% of subjects in the long-term studies.

Adverse event	DVS 100-400 mg/d N = 2143
Nervous system	
Headache	29%
Insomnia	22%
Dizziness	21%
Somnolence	17%
Asthenia	16%
Nervousness	7%
Tremor	7%
Abnormal dreams	6%
Anxiety	5%
Libido decreased	4%
Trismus	3%
Vertigo	3%
Paresthesia	3%
Cardiovascular	
Hypertension	8%
Vasodilatation	4%
Tachycardia	3%
Palpitation	3%

Digestive system	
Nausea	38%
Dry mouth	25%
Constipation	15%
Anorexia	13%
Diarrhea	9%
Vomiting	7%
Other	
Abnormal vision	5%
Mydriasis	5%
Weight gain	4%
Sweating	22%
Abnormal ejacultation/orgasm	5%
Anorgasmia	3%
Impotence	4%

7.1.1.15.8. Concomitant Antihypertensive Medication Use

In the long-term, open-label studies (excluding the controlled, relapse prevention trial), 14% of subjects were treated with antihypertensive medication at some point during the study, regardless of whether antihypertensive medication treatment had been initiated before or during the study. After beginning the study, 4% of subjects in the long-term studies initiated treatment with antihypertensive medication.

Long-term studies (303, 307, 318)	**DVS N = 1550**
Any antihypertensive use during trial	14%
Initiated antihypertensive use during the study	4%

7.1.1.15.9. Vital Signs

In the long-term studies, 2% of subjects discontinued from the studies due to hypertension. Few subjects discontinued due to hypotension, elevated heart rate, or weight gain (< 1% for each).

Discontinuations due to abnormal vital signs	
Parameter	**N = 2143**
Hypertension	43 (2)
Hypotension	8 (< 1)
Pulse elevation	5 (< 1)
Weight gain	6 (< 1)

7.1.1.15.10. ECG: (outliers, mean)

Discontinuations due to abnormal ECG	
Parameter	N = 2143
QT prolongation	1 (< 1)
Abnormal ECG	1 (< 1)

ECG Outliers: potentially clinically significant Long-term studies	
QT ≥ 480 msec	2%
QTcB (women) > 470 or ↑ ≥ 60	3%
QTcB (men) > 450 or ↑ ≥ 60	5%
QTcB > 500 msec	< 1%
QTcF (women) > 470 or ↑ ≥ 60	< 1%
QTcF (men) > 450 or ↑ ≥ 60	1%
QTcF > 500 msec	< 1%

7.1.1.15.11. Clinical laboratory: discontinuations

There were relatively few subjects who discontinued due to abnormal clinical laboratory results. Approximately 1% of subjects in the long-term open-label had serum liver enzyme elevations that led to discontinuation. None of these cases met criteria for Hy's law. None of these cases were considered serious adverse events. As illustrated in the table below, all other abnormal laboratory results that led to discontinuation occurred in less than 1% of subjects in the long-term studies.

Discontinuations due to laboratory abnormalities	
Laboratory parameter	**N = 2134**
↑Liver enzyme	26 (1)
↑Triglyceride	9 (< 1)
↑Cholesterol	2 (< 1)
↑Glucose	1 (< 1)
↓Thyroxine decrease	1 (< 1)
↑Prolactin	1 (< 1)
Neutropenia	1 (< 1)
Leukopenia	1 (< 1)

7.1.1.15. Laboratory Outliers- potentially clinically significant results

The most common potentially clinically significant laboratory results were hemoglobinuria (16%), proteinuria (8%), cholesterol elevation (9%), triglyceride elevation (7%), and liver enzyme elevation. These findings are consistent with the findings in the short-term controlled trials. However, a considerably higher proportion of subjects in the long-term studies had hemoglobinuria and proteinuria compared to subjects in the controlled trials. Currently, the clinical significance of the urinary abnormalities is unclear. These cases were not associated with elevations in serum creatinine or BUN. Furthermore, the cases of hematuria did not occur in excess in female subjects, compared to male subjects.

Laboratory abnormalities that were potentially clinically significant	
Laboratory parameter	N = 2134
+ urine hemoglobin	16%
+ urine protein	8%
↑ total cholesterol	9%
↑ LDL	2%
↑ HDL	2%
↑ Triglycerides	7%
↑ ALT	2%
↑ AST	1%
↑ bilirubin	1%
↑ glucose	1%
+ urine glucose	2%
↑ creatinine	< 1%
↓ WBC	1%

7.2 Adequacy of Patient Exposure and Safety Assessment

7.2.1. Exposure: Populations Exposed and Extent of Exposure

In the desvenlafaxine clinical program for Major Depressive Disorder, 3007 subjects were exposed to study drug. Of these, 2667 were exposed to desvenlafaxine, 244 were exposed to venlafaxine, and 803 were exposed to placebo. In the controlled, short-term trials, 1211 subjects were exposed to desvenlafaxine. In open-label long-term studies, 2143 subjects were exposed to desvenlafaxine. The total desvenlafaxine exposure in the clinical studies was 1137 subject-years. The desvenlafaxine exposure was 152 subject-years in the short-term, controlled trials, and the exposure was 985 subject-years in the long-term studies.

Table 7.2.1.1 Exposure to Study Drug

Study drug	N	Exposure (subject-years)
Total DVS	2667	1,137.2 SY
Short-term DVS	1211	152.0 SY
Long-term DVS	2143	985.2 SY
Venlafaxine	244	33.2 SY

Placebo	803	112.8 SY

The mean DVS dose in the short-term controlled trials ranged from 233 to 250 mg/day, depending on the duration of treatment. Approximately 14%, 45%, and 41% of DVS subjects were treated with 100 mg, >100-200 mg, and >200 mg/day, respectively. In the venlafaxine group, the mean daily dose ranged from 126 to 130 mg/day. Approximately 28% and 72% were treated with venlafaxine dose ranges of 0-100 mg and >100-200 mg/day, respectively.

Table 7.2.1.2 Exposure to Study Drug in Short-term Controlled Trials

Total Exposure to DVS, Venlafaxine ER, and Placebo in controlled trials					
Placebo		DVS 100-400 mg		Venlafaxine 75-225 mg	
n	Subject-years	n	Subject-years	n	Subject-years
803	112.8	1211	152.0	244	33.2

Table 7.2.1.3 Exposure to Study Drug in Fixed-dose Trials

Fixed-dose studies: total exposure to DVS by Dose and Placebo							
Placebo		DVS 100 mg		DVS 200 mg		DVS 400 mg	
n	Subject-years	n	Subject-years	n	Subject-years	n	Subject-years
323	44.4	118	15.0	307	38.6	317	39.4

Table 7.2.1.4 Exposure to Study Drug in Flexible-dose Trials

Flexible-dose studies: total exposure to DVS, Venlafaxine, and Placebo					
Placebo		DVS 100-400 mg		Venlafaxine 75-225 mg	
n	Subject-years	n	Subject-years	n	Subject-years
480	68.4	469	59.1	244	33.2

7.2.2. Adequacy of Overall Clinical Experience

The studies were designed and conducted adequately for reasonably assessing the safety profile of desvenlafaxine in the treatment of adult patients with a diagnosis of Major Depressive Disorder.

7.2.3. Adequacy of Routine Clinical Testing

The routine clinical safety testing was adequate for reasonably assessing the safety profile of desvenlafaxine in the treatment of adult patients with a diagnosis of Major Depressive Disorder.

7.2.4. Adequacy of Metabolic, Clearance, and Drug Interaction Evaluation

The clinical program was adequate for assessing pharmacokinetic, biopharmaceutic, and drug interaction parameters.

7.2.5. Adequacy of Evaluation for Potential Adverse Events

The program was adequate for assessing potential adverse events during the clinical trials. In particular, the use of patient diaries for recording adverse events was extremely useful.

7.2.6. Assessment of Quality and Completeness of Data

The data submitted were of good quality, and they were complete for the purposes of the safety review.

7.3 Safety Conclusions

Short-term treatment with DVS appears to have been reasonably safe in the MDD population studied. Generally, the types of adverse events related to DSV treatment were quite similar to those related to venlafaxine treatment. There were no unexpected adverse events. However, many of the common, drug-related adverse events were reported more frequently in the DVS group than in the venlafaxine group. These common adverse events included: nausea (37% vs. 25%), insomnia (19% vs. 12%), sweating (18% vs.14%), dizziness (15% vs. 9%), and constipation (12% vs. 6%), asthenia (11% vs. 7%), anorgasmia/abnormal ejaculation (10% vs. 2%), vomiting (7% vs. 3%), and tremor (7% vs. 4%).

Two (2) deaths occurred in the DVS clinical program that was probably unrelated to DVS treatment. One MDD subject completed suicide by hanging. One healthy volunteer died several days after completing a Phase 1 study. Based on autopsy and toxicology findings, the death was thought to be related to dilated cardiomyopathy, with cocaine use as a contributory cause.

There were relatively few serious adverse events (SAE) for a study population of this size. There were 14 SAE in the DVS group, 7 in the placebo group, and one (1) in the venlafaxine ER group. The SAEs that were probably related to DVS treatment included: liver function test abnormalities (2), dizziness (1), and dystonia (1). Two SAE were possibly related to DVS treatment: tachycardia and somnolence. In the DVS group, one (1) subject completed suicide, and four (4) subjects had non-lethal suicide attempts or intentional overdoses. These adverse events do not appear to have been related to DVS treatment. Moreover, in a formal suicidality analysis, DVS was not associated with an increased risk of treatment-emergent suicidality.

Discontinuations due to adverse events accounted for a large proportion of DVS subjects (16%). In comparison, 4% of the placebo group and 7% venlafaxine groups discontinued due to adverse events. Furthermore, the DVS discontinuations due to AE occurred early (usually within the first

week of the study). The types of AE leading to discontinuation were similar in the DVS and venlafaxine groups. However, nausea and vomiting were more common in the DVS group
The AE leading to discontinuation in the DVS group were: nausea (6%), vomiting (3%), asthenia (2%), headache (2%), dizziness (2%), insomnia (2%), somnolence (2%), tremor (1%), sweating (1%), and impotence (1%).

The following commonly reported adverse events occurred in at least 5% of DVS subjects and were at least twice as commonly reported in the DVS group as in the placebo group: nausea (37%), dry mouth (23), insomnia (19), sweating (18), somnolence (16), dizziness (15), anorexia (12), constipation (12), asthenia (11), anorgasmia (10), impotence (9), vomiting (7), tremor (7), nervousness (6), abnormal vision (5), mydriasis (5), abnormal dreams (5), hypertension (4), vertigo (3). The gastrointestinal, central nervous system, and sexual adverse events were more common in the DVS group than in the venlafaxine group Less commonly reported adverse events that were probably related to DVS treatment included: tachycardia (3), vasodilatation (3), and libido decreased (3).

A number of commonly reported adverse events were probably related to DVS treatment. In the fixed dose trials, the following events were reported at a higher incidence in the 400 mg group than in either the 100 mg or 200 mg groups and appeared to show a dose-related trend: asthenia, chills, nausea, dry mouth, vomiting, sweating, abnormal ejaculation/orgasm, anorgasmia, and impotence.
Currently, the main safety concern is the risk of hypertension associated with DVS treatment. Such blood pressure elevations occur with venlafaxine treatment as well. In fact, the product label for venlafaxine discusses sustained hypertension as an adverse event in the Warnings section. Although DVS-related blood pressure elevations in these short-term trials did not appear to be related to clinically significant cardiovascular, cerebrovascular, renal, or other end-organ adverse events, it is possible that DVS-induced hypertension could have clinically significant consequences during longer term exposure. In addition, there was a dose-related risk of hyperlipidemia in the short-term DVS trials. It will be important to assess the cardiovascular safety profile of DVS thoroughly, given these findings.
Blood pressure elevation was a consistent finding in the DVS trials. The following is a list of important points regarding blood pressure elevation associated with DVS treatment:

1. DVS raised mean BP by 3.5- 4.0 mm Hg for SBP and 2.0- 2.5 mm Hg for DBP (these represent the placebo-subtracted changes in mean BP values).
2. The blood pressure effect was consistent across the seven (7) controlled trials...
3. The BP effect occurred early in the trials and persisted at a consistent magnitude.
4. The DVS BP effect appears to be quite similar to the venlafaxine BP effect in terms of magnitude, time course, and duration of effect.
5. There were relatively few cases in which antihypertensive drug treatment was initiated during the studies.
6. Dose relationship: there is not a clear dose relationship for the *magnitude* of BP change. However, there is a dose relationship for the *duration* of the blood pressure effect (sustained hypertension: elevations of BP for two (2) or three (3) consecutive visits).

7. There were no reports of clinically significant adverse events related to BP elevation in the short-term controlled trials (cardiovascular, cerebrovascular, renal, etc.).
8. However, in the long-term studies, there were three (3) cases of cerebrovascular accidents (CVA) or transient ischemic attack (TIA) in which DVS treatment might have been a factor in the adverse event.
9. The desvenlafaxine blood pressure effect could be clinically significant during long-term use of DVS.
10. DVS also increases mean cholesterol and triglyceride levels, potentially increasing cardiovascular risk.
11. There were no deaths related to elevated blood pressure in the controlled trials.
12. There were no serious adverse events (SAE) related to elevated blood pressure in the controlled trials.
13. There were some discontinuations due to hypertension in the DVS group (1.2%) compared to 2% and < 1% in the venlafaxine and placebo groups, respectively.
14. Hypertension was reported as an adverse event for 4% of the DVS group, 5% of the venlafaxine group, and 3% of the placebo group.

DVS treatment was also associated with dose-related increases in heart rate. Two subjects had increases in heart rate that were considered potentially clinically significant. This was reported as a serious adverse event for approximately 1% of the DVS group. Tachycardia was reported as an adverse event for one subject in the DVS group.

Decreases from baseline in mean body weight occurred with DVS treatment during the short-term, 8-week studies. In the DVS group, mean body weight decreased by 1.0 kg. In the placebo group, mean weight decreased by 0.1 kg. There was no indication of a dose-response relationship. It is unlikely that the magnitude of the mean weight loss is clinically significant. No subject in any of the treatment groups discontinued from the study due to weight loss.

Results from the controlled trials and the dedicated QT study demonstrated that there was no signal suggesting that DVS leads to prolongation of the QT interval. There were no clinically significant differences between DVS-treated and placebo-treated subjects in mean QT, QTc, PR, and QRS intervals. DVS treatment was associated with mean increases in heart rate and mean decreases in both PR and QT intervals on ECG. Mean increases in QTcB, but not QTcF or QTcN, were also observed. There were no changes in mean QRS intervals after DVS treatment. Two subjects in the DVS group discontinued due to an abnormal ECG. There was one case of QT interval prolongation (with no associated clinically significant event). In the second case, a subject had ST depression and T wave inversion on ECG. These changes were not attributed to DVS treatment. There were no discontinuations due to ECG abnormalities in the venlafaxine or placebo group.

There were abnormalities in clinical laboratory results related to DVS treatment. There was an excess of subjects in the DVS group with elevations in lipid concentrations, compared to the placebo and venlafaxine groups. For total cholesterol concentration, clinically important elevations occurred in 6%, 2%, and 4% in DVS, placebo, and venlafaxine groups, respectively. Clinically significant elevations in LDL concentrations occurred in 1.6%, 0.2%, and 0.6% in the

DVS, placebo, and venlafaxine groups, respectively. Triglyceride concentrations were significantly elevated in 4.5%, 2.6%, and 3.5% of the DVS, placebo, and venlafaxine groups, respectively. In the fixed-dose studies, there appeared to be a dose-related increased risk of developing significant elevations of total cholesterol and triglycerides. Lipid elevations are known to occur with venlafaxine treatment.

DVS treatment was also associated with a higher proportion of subjects (compared to the placebo and venlafaxine groups) who developed significant elevations in serum liver enzyme (ALT/SPGT) concentration. Significant serum ALT elevations were reported for 0.6%, 0.1%, and 0 in the DVS, placebo, and venlafaxine groups, respectively. A small number of subjects discontinued due to abnormal clinical laboratory findings. In the DVS group, the most common such abnormality was elevated liver enzymes. In two (2) cases, investigators judged that the liver function test abnormalities were due to DVS treatment. In both cases, the abnormalities resolved upon discontinuing the drug.

There were significant changes in mean laboratory parameters as well. In the DVS treatment group, (compared to placebo), there were statistically significant changes from baseline in the mean values for serum lipids, liver enzymes, and thyroid hormone. Mean total cholesterol increased by 3.1%, LDL increased by 3.4%, and HDL increased by 2.9%. Mean serum AST increased by 7.6%, ALT increased by 9.4%, and mean serum GGT increased by 27%. Mean serum free thyroxine decreased by 8.5%, and mean T4 decreased by 9.2%.

For the increases in mean lipid concentrations, GGT, free thyroxine, and T4, the magnitude of the mean change was dose-related. For the mean free thyroxine and T4, the decreases varied inversely with DVS dose. For all other laboratory parameters, there was no apparent dose relationship observed. Currently, the clinical significance of these mean changes is unclear.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing and Administration

For Major Depressive Disorder, the sponsor recommends a desvenlafaxine starting dose of [redacted] mg once daily orally, with or without food. The sponsor acknowledges that there was no clear evidence in the controlled trials suggesting that doses greater than [redacted] mg/day confer additional benefit. However, safety findings indicate that there is a dose-related risk for developing certain toxicities associated with DVS treatment. The sponsor states [redacted] I agree with the sponsor's recommendations for initial dosing and administration in patients without significant impairment of renal function.

For patients with moderate renal impairment, severe renal impairment, and end-stage renal disease (ESRD), the Biopharmaceutics team and I recommend that one initiate treatment with 50 mg [redacted] of desvenlafaxine. We recommend that the dose not exceed 50 mg [redacted] of DVS in these patients. The DVS exposures in patients with this degree of renal function impairment are

considerably higher than the DVS exposures in patients with normal or mildly impaired renal function.

For patients with hepatic impairment, the Biopharmaceutics team recommends that the daily desvenlafaxine dose not exceed 100 mg. Similarly, for elderly patients, the Biopharmaceutics team recommends that the daily desvenlafaxine dose not exceed 100 mg. I agree that the Division should consider making these recommendations to the sponsor.

The sponsor states that although acute episodes of Major Depression often require several months or longer of sustained antidepressant therapy, there is insufficient evidence available to inform clinicians and patients about whether desvenlafaxine should be used in maintenance treatment. The sponsor states that patients should be reassessed periodically to determine the need for maintenance treatment and the appropriate dose for such treatment. I agree with these recommendations about continuation or maintenance therapy with desvenlafaxine.

When discontinuing treatment with desvenlafaxine, it is advisable to reduce the dose gradually, rather than discontinuing medication abruptly, whenever possible, in order to prevent or reduce the risk of developing discontinuation-emergent symptoms. Such symptom include nausea, dizziness and headache; however, there are a number of other discontinuation-emergent symptoms that have been reported in association with tapering and discontinuing desvenlafaxine, venlafaxine, other SNRI antidepressants, and SSRI antidepressants. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, the clinician may consider resuming the previously prescribed dose. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

8.2 Drug-Drug Interactions

8.2.1. Switching Patients To or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with desvenlafaxine. In addition, at least seven (7 days) should be allowed after stopping desvenlafaxine before starting an MAOI.

8.2.3. Central Nervous System (CNS)-Active Agents

The risk of using desvenlafaxine in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when desvenlafaxine is taken in combination with other CNS-active drugs.

Based on the known mechanism of desvenlafaxine and the potential for serotonin syndrome, caution is advised when desvenlafaxine is co-administered with other agents that may affect the serotonergic neurotransmitter system (such as triptans, serotonin reuptake inhibitors, sibutramine, St. John's Wort (Hypericum perforatum) and/or lithium).

Ethanol
A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking desvenlafaxine.

8.2.4. Potential for other drugs to affect desvenlafaxine

Inhibitors of CYP3A4
Reportedly, CYP3A4 is minimally involved in desvenlafaxine elimination. Concomitant use of desvenlafaxine with potent inhibitors of CYP3A4 may result in higher concentrations of desvenlafaxine. Therefore, medications that inhibit CYP3A4 (e.g., amiodarone, diltiazem, verapamil, HIV protease inhibitors, ketoconazole, erythromycin) may increase desvenlafaxine exposure when used concomitantly with desvenlafaxine.

8.2.5. Potential for desvenlafaxine to affect other drugs

Drugs metabolized by CYP2D6
In vitro studies demonstrated that desvenlafaxine had a weak inhibitory effect on the CYP2D6. When desvenlafaxine succinate was administered (at a dose of 400 mg daily) in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased approximately 83%. Thus, concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 may result in higher concentrations of that drug.

Drugs metabolized by CYP3A4
In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. However, in a clinical study, when desvenlafaxine 400 mg was administered in conjunction with a single 4 mg dose of midazolam, a CYP3A4 substrate, the AUC of midazolam decreased by approximately 31%. Thus, the clinician should be aware of the potential of desvenlafaxine to inhibit CYP3A4 and increase the exposure of concomitantly administered medications that are metabolized significantly by CYP3A4.

Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19
In vitro, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes. Based on these data, desvenlafaxine would not be expected to affect the pharmacokinetics of drugs that are

However, oxidative metabolism via isoenzyme CYP3A4 represents only a minor metabolic pathway and the potential for clinically relevant elevations of desvenlafaxine levels due to this drug Cytochrome CYP-450 isoenzyme CYP2D6 Clinical data shows desvenlafaxine to be a weak inhibitor of cytochrome CYP-450 isoenzyme CYP2D6. Coadministration of a CYP2D6 substrate (e.g., desipramine, codeine, dextromethorphan, fluoxetine, metoprolol, paroxetine, risperidone) with desvenlafaxine succinate may result in higher concentration of the CYP2D6 substrate. Appropriate information is provided in the product labeling and postmarketing pharmacovigilance will be used to assess the potential for clinically relevant drug interactions with desvenlafaxine and CYP2D6 substrates.

8.3 Special Populations

8.3.1. Women who are Pregnant, Breastfeeding, or in Labor

There are no adequate and well-controlled studies in pregnant women; therefore, desvenlafaxine should be used during pregnancy only if the potential benefits justify the potential risks. The effect of desvenlafaxine on labor and delivery in humans is unknown. Desvenlafaxine O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from TRADENAME, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3.2. Treatment of Pregnant Women during the Third Trimester

Neonates exposed to SNRIs or SSRIs late in the third trimester can develop complications requiring prolonged hospitalization, respiratory support, and tube feeding. Symptoms may be consistent with SNRI/SSRI toxicity or SNRI/SSRI discontinuation symptoms. When treating pregnant women with desvenlafaxine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering desvenlafaxine in the third trimester.

8.3.3. Patients with Hepatic Impairment

The sponsor states that no dosage adjustment is necessary for patients with hepatic impairment. However, clinicians should use caution when using desvenlafaxine in a patient with hepatic impairment, since desvenlafaxine is metabolized significantly in the liver. I agree with the recommendation from our biopharmaceutics reviewers that the DVS dose in patients with moderate to severe hepatic impairment should not exceed 100 mg per day.

8.3.4. Patients with Renal Impairment

The sponsor notes that care should be taken when treating patients with desvenlafaxine with severe renal insufficiency and with end-stage renal. While the sponsor recommends a DVS starting dose of [redacted] mg [redacted] day in patients with severe renal impairment and end-stage renal disease (ESRD), the biopharmaceutics reviewers recommend a starting dose of 50 mg per day in patients with severe renal impairment. Due to the significantly different PK profile of desvenlafaxine in this population, I agree with the recommendation to begin DVS treatment with 50 mg per day in patients with severe renal impairment. In these patients, we recommend that the DVS dose not exceed 50 mg per day.

Renal excretion is the predominant route of elimination of desvenlafaxine. The creatinine clearance is the major determinant of variability in desvenlafaxine clearance, and DVS total body clearance was significantly reduced in subjects with impaired renal function (by 38% in mild; 42% in moderate; 55% in severe renal impairment; and 59% in ESRD) compared to subjects with normal renal function. The reduced clearance resulted in significant increases in exposure (AUC): 29% in mild, 60% in moderate, 91% in severe and 112% in ESRD subjects. The mean terminal half-life was prolonged from 11 hours in the control subjects to approximately 14, 16, 18, and 23 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively. Less than 5% of the drug in the body was cleared during a standard 4-hour hemodialysis procedure.

8.3.5. Elderly Patients

The recommended dose in patients older than 75 years of age is 100 mg. Generally, I agree with the recommendation, unless the patient has significant renal or hepatic disease, or if they are taking specific medications that could have significant interaction with desvenlafaxine. It should be noted that there was an age-dependent decrease in desvenlafaxine clearance, resulting in a 25% increase in C_{max} and a 54% increase in AUC in subjects older than 75 years of age, compared to subjects 18- 45 years of age. A significant portion of the decreased desvenlafaxine clearance in the elderly could be related to decreased renal function.

8.4 Pediatric Use

The safety and effectiveness of desvenlafaxine in the pediatric population have not been studies. When considering desvenlafaxine treatment in a child or adolescent, the clinician must balance the potential risks with the potential benefits and clinical need.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.1.1. Efficacy Conclusions

The efficacy of DVS in the treatment of MDD was demonstrated in two (2) of the seven (7) controlled trials. Fixed-dose studies 306 and 308 were positive, as measured by the primary efficacy endpoint (change from baseline in mean Hamilton Depression Rating Scale-17 score at the end of Week 8. The primary statistical analysis of the HAMD-17 endpoint was an analysis of covariance (ANCOVA) using a last observation carried forward (LOCF) method.

For both 306 and 308, DVS treatment was statistically significantly superior to treatment with placebo. Study 306 was positive for the fixed doses of 100 and 400 mg per day ($p = 0.004$ and 0.002, respectively). However, for the 200 mg/day group, there was not a statistically significant treatment effect. Study 308 was positive for the 200 mg/day and 400 mg/day treatment groups ($p= 0.002$ and 0.008, respectively). For all dose groups in the two positive fixed-dose studies, the key secondary endpoint was also positive (change in mean Clinical Global Impression-Improvement Scale).

In addition, the results of three (3) pre-specified, non-primary statistical analyses support the conclusion that DVS was efficacious in the treatment of MDD. These alternative statistical methods may have advantages over the LOCF method for interpreting these particular trial results, since a high proportion of the DVS group discontinued early in treatment (within the first week) due to adverse events. The analyses included an observed case analysis (OC), a mixed-effect model (MMRM), and the ETRANK method. The latter two analyses handle missing data differently. These are discussed in more detail in Dr. Kong's Biostatistics review.

One can estimate the size of the DVS treatment effect by comparing the observed DVS effect with the observed placebo treatment effect. In study 306, the reductions in mean HAMD-17 Scale scores were -10.5, -9.6, and -10.5 points in the DVS 100 mg, 200 mg, and 400 mg/day groups, respectively. For the placebo group, the reduction in mean HAMD-17 score was -7.7. Thus, the differential DVS treatment effects compared to placebo were -2.8, -1.9, and -2.8 points on the HAMD-17 Scale for the DVS 100 mg, 200 mg, and 400 mg/day groups, respectively. The estimated size of the DVS treatment effect appears to be modest. However, such effect sizes are similar to those observed in other antidepressant trials.

All four (4) flexible-dose studies failed on the primary ANCOVA LOCF analysis (304, 309, 317, and 320) in the DVS groups. The p-values were 0.28, 0.38, 0.49, and 0.078, respectively. However, in study 317, venlafaxine ER treatment (150-225 mg/day) was statistically significantly superior to placebo treatment ($p = 0.005$). For venlafaxine ER, the estimated size of the treatment effect (compared to the placebo treatment effect) was a reduction of -2.8 points on the mean HAMD-17 Scale score. In the same study, the estimated treatment effect size for DVS was -0.7 points on the HAMD-17 Scale.

9.1.2. Safety Conclusions

Short-term treatment with DVS appears to have been reasonably safe in the MDD population studied. Generally, the types of adverse events related to DSV treatment were quite similar to those related to venlafaxine treatment. There were no unexpected adverse events. However, many of the common, drug-related adverse events were reported more frequently in the DVS group than in the venlafaxine group. These common adverse events included: nausea (37% vs. 25%), insomnia (19% vs. 12%), sweating (18% vs.14%), dizziness (15% vs. 9%), and constipation (12% vs. 6%), asthenia (11% vs. 7%), anorgasmia/abnormal ejaculation (10% vs. 2%), vomiting (7% vs. 3%), and tremor (7% vs. 4%).

Two (2) deaths occurred in the DVS clinical program that was probably unrelated to DVS treatment. One MDD subject completed suicide by hanging. One healthy volunteer died several days after completing a Phase 1 study. Based on autopsy and toxicology findings, the death was thought to be related to dilated cardiomyopathy, with cocaine use as a contributory cause.

There were relatively few serious adverse events (SAE) for a study population of this size. There were 14 SAE in the DVS group, 7 in the placebo group, and one (1) in the venlafaxine ER group. The SAEs that were probably related to DVS treatment included: liver function test abnormalities (2), dizziness (1), and dystonia (1). Two SAE were possibly related to DVS treatment: tachycardia and somnolence. In the DVS group, one (1) subject completed suicide, and four (4) subjects had non-lethal suicide attempts or intentional overdoses. These adverse events do not appear to have been related to DVS treatment. Moreover, in a formal suicidality analysis, DVS was not associated with an increased risk of treatment-emergent suicidality.

Discontinuations due to adverse events accounted for a large proportion of DVS subjects (16%). In comparison, 4% of the placebo group and 7% venlafaxine groups discontinued due to adverse events. Furthermore, the DVS discontinuations due to AE occurred early (usually within the first week of the study). The types of AE leading to discontinuation were similar in the DVS and venlafaxine groups. However, nausea and vomiting were more common in the DVS group The AE leading to discontinuation in the DVS group were: nausea (6%), vomiting (3%), asthenia (2%), headache (2%), dizziness (2%), insomnia (2%), somnolence (2%), tremor (1%), sweating (1%), and impotence (1%).

The following commonly reported adverse events occurred in at least 5% of DVS subjects and were at least twice as commonly reported in the DVS group as in the placebo group: nausea (37%), dry mouth (23), insomnia (19), sweating (18), somnolence (16), dizziness (15), anorexia (12), constipation (12), asthenia (11), anorgasmia (10), impotence (9), vomiting (7), tremor (7), nervousness (6), abnormal vision (5), mydriasis (5), abnormal dreams (5), hypertension (4), vertigo (3). The gastrointestinal, central nervous system, and sexual adverse events were more common in the DVS group than in the venlafaxine group Less commonly reported adverse events that were probably related to DVS treatment included: tachycardia (3), vasodilatation (3), and libido decreased (3).

A number of commonly reported adverse events were probably related to DVS treatment. In the fixed dose trials, the following events were reported at a higher incidence in the 400 mg group than in either the 100 mg or 200 mg groups and appeared to show a dose-related trend: asthenia, chills, nausea, dry mouth, vomiting, sweating, abnormal ejaculation/orgasm, anorgasmia, and impotence.
Currently, the main safety concern is the risk of hypertension associated with DVS treatment. Such blood pressure elevations occur with venlafaxine treatment as well. In fact, the product label for venlafaxine discusses sustained hypertension as an adverse event in the Warnings section. Although DVS-related blood pressure elevations in these short-term trials did not appear to be related to clinically significant cardiovascular, cerebrovascular, renal, or other end-organ adverse events, it is possible that DVS-induced hypertension could have clinically significant consequences during longer term exposure. In addition, there was a dose-related risk of hyperlipidemia in the short-term DVS trials. It will be important to assess the cardiovascular safety profile of DVS thoroughly, given these findings.

Blood pressure elevation was a consistent finding in the DVS trials. The following is a list of important points regarding blood pressure elevation associated with DVS treatment:

1. DVS raised mean B.P. by 3.5- 4.0 mm Hg for SBP and 2.0- 2.5 mm Hg for DBP (these are the placebo-subtracted changes in mean BP values).
2. The blood pressure effect was consistent across the seven (7) controlled trials...
3. The B.P. effect occurred early in the trials and persisted at a consistent magnitude.
4. The DVS B.P. effect appears very similar to the venlafaxine B.P. effect in terms of magnitude, time course, and duration of effect.
5. Dose relationship: there is not a clear dose relationship for the magnitude of B.P. change. However, there does appear to be a dose relationship for the duration of the blood pressure effect (sustained hypertension: BP elevation on two (2) or three (3) consecutive visits).
6. There were no reports of clinically significant adverse events related to B.P. elevation in the short-term controlled trials (cardiovascular, cerebrovascular, renal, etc.).
7. However, in the long-term studies, there were three (3) cases of cerebrovascular accidents or transient ischemic attacks in which DVS treatment might have been a factor in the development of the adverse events.
8. The blood pressure effect could be clinically significant during long-term use of DVS.
9. DVS also increases mean cholesterol and triglyceride levels, potentially increasing cardiovascular risk.
10. There were no deaths related to elevated blood pressure in the controlled trials.
11. There were no serious adverse events (SAE) related to elevated blood pressure in the controlled trials.
12. There were discontinuations due to hypertension in the DVS group (1.2%) compared to 2% and < 1% in the venlafaxine and placebo groups, respectively.
13. 'Hypertension' was reported as an adverse event for 4% of the DVS group, 5% of the venlafaxine ER group, and 3% of the placebo group.

DVS treatment was also associated with dose-related increases in heart rate. Two subjects had increases in heart rate that were considered potentially clinically significant. This was reported as a serious adverse event for approximately 1% of the DVS group. Tachycardia was reported as an adverse event for one subject in the DVS group.

Decreases from baseline in mean body weight occurred with DVS treatment during the short-term, 8-week studies. In the DVS group, mean body weight decreased by 1.0 kg. In the placebo group, mean weight decreased by 0.1 kg. There was no indication of a dose-response relationship. It is unlikely that the magnitude of the mean weight loss is clinically significant. No subject in any of the treatment groups discontinued from the study due to weight loss.

Results from the controlled trials and the dedicated QT study demonstrated that there was no signal suggesting that DVS leads to prolongation of the QT interval. There were no clinically significant differences between DVS-treated and placebo-treated subjects in mean QT, QTc, PR, and QRS intervals. DVS treatment was associated with mean increases in heart rate and mean decreases in both PR and QT intervals on ECG. Mean increases in QTcB, but not QTcF or

QTcN, were also observed. There were no changes in mean QRS intervals after DVS treatment. Two subjects in the DVS group discontinued due to an abnormal ECG. There was one case of QT interval prolongation (with no associated clinically significant event). In the second case, a subject had ST depression and T wave inversion on ECG. These changes were not attributed to DVS treatment. There were no discontinuations due to ECG abnormalities in the venlafaxine or placebo group.

There were abnormalities in clinical laboratory results related to DVS treatment. There was an excess of subjects in the DVS group with elevations in lipid concentrations, compared to the placebo and venlafaxine groups. For total cholesterol concentration, clinically important elevations occurred in 6%, 2%, and 4% in DVS, placebo, and venlafaxine groups, respectively. Clinically significant elevations in LDL concentrations occurred in 1.6%, 0.2%, and 0.6% in the DVS, placebo, and venlafaxine groups, respectively. Triglyceride concentrations were significantly elevated in 4.5%, 2.6%, and 3.5% of the DVS, placebo, and venlafaxine groups, respectively. In the fixed-dose studies, there appeared to be a dose-related increased risk of developing significant elevations of total cholesterol and triglycerides. Lipid elevations are known to occur with venlafaxine treatment.

DVS treatment was also associated with a higher proportion of subjects (compared to the placebo and venlafaxine groups) who developed significant elevations in serum liver enzyme (ALT/SPGT) concentration. Significant serum ALT elevations were reported for 0.6%, 0.1%, and 0 in the DVS, placebo, and venlafaxine groups, respectively. A small number of subjects discontinued due to abnormal clinical laboratory findings. In the DVS group, the most common such abnormality was elevated liver enzymes. In two (2) cases, investigators judged that the liver function test abnormalities were due to DVS treatment. In both cases, the abnormalities resolved upon discontinuing the drug.

There were significant changes in mean laboratory parameters as well. In the DVS treatment group, (compared to placebo), there were statistically significant changes from baseline in the mean values for serum lipids, liver enzymes, and thyroid hormone. Mean total cholesterol increased by 3.1%, LDL increased by 3.4%, and HDL increased by 2.9%. Mean serum AST increased by 7.6%, ALT increased by 9.4%, and mean serum GGT increased by 27%. Mean serum free thyroxine decreased by 8.5%, and mean T4 decreased by 9.2%.

For the increases in mean lipid concentrations, GGT, free thyroxine, and T4, the magnitude of the mean change was dose-related. For the mean free thyroxine and T4, the decreases varied inversely with DVS dose. For all other laboratory parameters, there was no apparent dose relationship observed. Currently, the clinical significance of these mean changes is unclear.

9.2 Recommendation on Regulatory Action

I recommend that the Division take an approvable action for NDA 21,992: desvenlafaxine in the treatment of Major Depressive Disorder in adults. In two (2) out of seven (7) adequate, well-controlled trials, the sponsor demonstrated the efficacy of desvenlafaxine (DVS) in the treatment of adult outpatients with a primary psychiatric diagnosis of Major Depressive Disorder (MDD), single or recurrent episode, without psychotic features. Desvenlafaxine treatment was reasonably safe in all of the controlled trials. The safety profile DVS treatment is quite similar to that of venlafaxine, the parent drug of desvenlafaxine. Based on the data from the short-term, controlled trials, there were no important differences in the safety profiles of desvenlafaxine and venlafaxine.

9.3 Recommendations on Postmarketing

9.3.1 Risk Management Activity

In order to formulate specific recommendations for risk management activities, the Division will conduct internal discussions and consult with other FDA divisions (Cardiorenal Drug Products and the Office of Surveillance and Epidemiology. Safety issues to consider include: overdose with desvenlafaxine, treatment-emergent suicidality, cardiovascular risks (hypertension and hyperlipidemia), hepatic abnormalities, and potential product name confusion due to two different proprietary names for desvenlafaxine.

9.3.2 Required Phase 4 Commitments

Currently, the Division does not request any specific Phase 4 commitments. The sponsor has already conducted a study of desvenlafaxine in the long-term, maintenance treatment of patients with Major Depressive Disorder.

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1

Appendix 10.2: Division Communications with the Sponsor Regarding the Desvenlafaxine Clinical Program

Table 1.3.1-1: Select Sponsor Agency Communications on Clinical Development

Date *Meeting/Communication* Main Recommendations	Wyeth Action(s)/FDA response
04 Feb 2003 *Pre-Phase 3 Meeting*	
• FDA requested that a venlafaxine treatment arm be included in a larger DVS SR trial. FDA indicated that the trial did not need to be powered to detect differences between DVS SR and venlafaxine.	• Two (2) phase 3, flexible-dose studies (3151A1-309-EU and 3151A1-317-US) included a venlafaxine arm. Venlafaxine ER doses were 75 to 150 mg/day and 150 to 225 mg/day in studies 309 and 317, respectively.
• FDA recommended that Wyeth attempt to determine the lowest effective dose because tachycardia and hypertension are dose-dependent.	• Trials were conducted on a wide dose range (100 to 400 mg/day). A dose of 100 mg/day was shown to be effective. Doses of 200 and 400 mg/day were also shown to be effective.
• The proposed overall clinical development plan was accepted.	• None needed.
• The proposed inclusion and exclusion criteria for the pivotal trials were deemed acceptable.	• None needed.
• FDA indicated that they would be willing to accept the HAM-D_6 scale as the primary efficacy endpoint provided that the sponsor could demonstrate that the scale is adequately validated.	• Wyeth modified the phase 3 protocols to use the HAM-D_{17}, instead of the HAM-D_6, scale as the primary efficacy parameter.
• FDA disagreed with Wyeth's proposed list of key secondary outcome measures and indicated that most could not be used in product labeling. FDA noted that they would accept 1 measure of the Clinical Global Impressions Scale as a key secondary endpoint.	• The protocols were modified to use the CGI-I scale as the key secondary efficacy parameter for all phase 3 trials.
• FDA indicated that multiplicity should be addressed in the statistical analysis plans, including different outcomes (primary and secondary) and different doses.	• Sequential testing was the method of adjustment used for different outcomes. Dunnett's was used to adjust for multiple comparisons testing across doses in study 3151A1-306-US. The methods of adjustment were declared a priori in all protocols and statistical analysis plans.
• FDA accepted Wyeth's proposal not to conduct a mass balance study, provided that linear pharmacokinetics were demonstrated within the intended therapeutic dose range.	• Linear pharmacokinetics were demonstrated (5.3.3.1; CSR-49864, study 0600D3-172-US) across a wide range of doses that encompass the therapeutic range. No further action was needed.

1 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 2

Appendix 10.3: Subject Selection Criteria

Inclusion Criteria:

1. Outpatients with a primary diagnosis of Major Depressive Disorder, single or recurrent episode, without psychotic features (based on DSM-IV criteria).

2. Presence of depressive symptoms for at least one month before entry into the study.

3. Men and **(for Study 223 only):** postmenopausal or surgically sterile women aged 18 to 65 years, inclusive. Postmenopusal women had t have 12 months of spontaneous amenorrhea. Surgically sterile women were defined as having hysterectomy, bilateral oophorectomy, or bilateral tubal ligation.

   The other studies included women of childbearing potential who agreed to use a medically acceptable method of contraception during the study and for at least 15 days after the last dose of test article. Medically acceptable forms of contraception included oral contraceptives, injectable or implantable methods, intrauterine devices, or properly used double-barrier contraception, eg, condom plus diaphragm. It was important that subjects not become pregnant or impregnate others while they were in this study.

4. Minimum prestudy and Day -1 score of 24 on the MADRS, and no more than a 20% decrease in the MADRS total score between the prestudy screening and study Day -1.

5. Minimum study Day -1 score of 2 on item 1 (depressed mood) of the HAM-D scale.

6. (306; Minimum screening and baseline score of 4 on the CGI-S)

Exclusion Criteria:

1. Treatment with venlafaxine (IR or ER) or desvenlafaxine within 3 months of Study Day 1

2. History of hypersensitivity to venlafaxine (IR or ER)

3. Significant risk of suicide at study entry or during the study based on clinical judgment; and/or a score ≥ 5 on the suicidality item of the MADRS scale.

4. Current (within 12 months of baseline) DSM-IV-defined: a) psychoactive substance abuse or dependence (including alcohol); b) a manic episode or a lifetime diagnosis of bipolar; c) obsessive-compulsive, or psychotic disorder. Subjects whose clinical picture was dominated by an anxiety disorder as defined by DSM-IV. Personality disorder (such as antisocial, schizotypal disorder, histrionic, borderline, narcissistic) severe enough to compromise the investigator's ability to evaluate the efficacy and safety of the test article.

5. Current DSM-IV-defined anxiety disorder that was considered by the investigator as being primary, causing a higher degree of distress or impairment than MDD.

   (306; 308; 309: a Covi Anxiety Scale total score greater than the Raskin Depression total score at screening or baseline. A Covi Anxiety Scale item score greater that 3 on any single item or a total score greater than 9 at screening or baseline.

6. Depression associated with the presence of an organic mental disorder because of a general medical condition or a neurologic disorder.

7. History of a seizure disorder other than a single childhood febrile seizure.

8. Onset of depression 6 months after a stroke.

9. Myocardial infarction within 6 months before the start of double-blind treatment.

10. History or presence of clinically important hepatic or renal disease or other medical disease that might compromise the study or be detrimental to the subject (eg, clinically important cardiac arrhythmia, uncontrolled diabetes, uncontrolled hypertension).

11. Major acute illness during the 3 months before screening.

12. History of neoplastic disorder (within 2 years), with the exception of treated basal or squamous cell carcinoma of the skin.

13. Known presence of raised intraocular pressure or history of narrow-angle glaucoma.

14. Clinically important abnormalities on prestudy physical examination, ECG, laboratory tests, or urine drug screen (UDS).

15. History or current evidence of gastrointestinal disease known to interfere with the absorption or excretion of drugs.

16. Lactating women or women of childbearing potential. A woman of childbearing potential was defined as one who was biologically capable of becoming pregnant. This included women who were using contraceptives or whose sexual partners were either sterile or using contraceptives.

17. Use of any investigational drugs or procedures, or antipsychotic drugs within 30 days; fluoxetine (Prozac) within 21 days; regular use of sumatriptan (Imitrex), naratriptan (Amerge), zolmitriptan (Zomig), or drugs with a similar mechanism of action indicated for the treatment of migraine within 14 days; use of any MAO inhibitor, sertraline (Zoloft), or paroxetine (Paxil) within 14 days; or use of any other antidepressant, anxiolytic, or sedative-hypnotic drug (except zaleplon [Sonata] or zolpidem [Ambien] up to 10 mg at bedtime during the first 2 weeks of treatment, with use limited to no more than 3 times per week) or any other psychotropic drug or substance (eg, lithium, stimulants) within 7 days of the start of the double-blind treatment period. Also, subjects were instructed not to take zaleplon or zolpidem 24 hours before any visit. Use of ß- adrenergic receptor blockers was prohibited during the study.

18. Electroconvulsive therapy (ECT) within 6 months of study day 1.

19. Use of any nonpsychopharmacologic drug with psychotropic effects within 7 days of the start of the double-blind treatment period, unless a stable dose of the drug had been maintained for at least 3 months before the start of the double-blind treatment period.

20. Formal psychotherapy within 6 months of study day 1. However, supportive nonbehavioral psychotherapy was permitted if there had been no change in intensity or frequency within the last 6 months and no change was anticipated for the duration of the study.

21. Presence of raised intraocular pressure or history of narrow-angle glaucoma.

Appendix 10.4: Schedule of Efficacy and Safety Assessments in the DVS Trials

Schedule of Assessments in the Controlled DVS Trials

Assessment	Screen	Base-line	Day 7	D 14	Day 21	D 28	Day 2	Day 56	Post-study
HAM-21		X	X	X	X	X	X	X	
MADRS	X	X	X	X	X	X	X	X	
CGI-I	X	X	X	X	X	X	X	X	
Plasma drug level				X				X	
Vital signs	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	
ECG	X							X	
Clinical laboratory	X			X		X		X	
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X

Appendix 10.5: Protocol for Blood Pressure Measurement

Vital signs (supine and standing pulse and supine and standing BP) at screening, baseline, on study days 7, 14, 21, 28, 42, 56 or early withdrawal, 63, 70 and follow-up (Day 77). The procedure for measuring BP will be as follows: Subjects should be instructed not to smoke or consume beverages containing caffeine for at least 2 hours before the BP measurement. A mercury or digital sphygmomanometer with a BP cuff appropriate for the subject's arm girth should be used on the same arm and be performed by the same site personnel throughout the study. Subjects should be at rest for at least 2 minutes before the BP reading at each visit. Two (2) consecutive supine BP measurements are taken 2 minutes apart. The supine pulse is taken after the first supine BP measurement and before the second supine BP so that it is taken within the 2-minute time frame. Following the second supine BP measurement, the subject rises to a standing position. After 1 minute, two consecutive standing BP measurements are taken 2 minutes apart. The standing pulse is taken after the first standing BP and before the second standing BP, so that it is taken within the 2-minute time frame. Diastolic BP will be effort will be made to obtain vital sign measurements at the same time at each visit. Furthermore, the same person should obtain the vital sign measurements. The time vital sign measurements are obtained will be recorded on the CRF.

Appendix 10.6

Sponsor's Criteria for Laboratory Test Results of Potential Clinical Significance

Table 3.1.1-1: Criteria for Determining Laboratory Test Results of Potential Clinical Importance in Phase 2 and 3 Studies

Test	Criteria[a]
Hematology	
Hemoglobin[a]	<95 g/L or >165 g/L (women) or <115 g/L or >185 g/L (men)
Hematocrit[a]	<0.32 L/L or >0.50 L/L (women) or <0.37 L/L or >0.55 L/L (men)
WBC count[a]	$<2.8 \times 10^9$/L or $>16 \times 10^9$/L
Platelet count[a]	$<75 \times 10^9$/L or $>700 \times 10^9$/L
Blood Chemistry	
Sodium[a]	<126 mmol/L or >156 mmol/L
Potassium[a]	<2.5 mmol/L or >6.5 mmol/L
Calcium[a]	<2.046 mmol/L or >2.994 mmol/L
Chloride[a]	<90 mmol/L or >118 mmol/L
Glucose[a,b]	<2.22 mmol/L or ≥11.10 mmol/L
Uric acid[a]	>0.4758 mmol/L (women) or >0.5948 mmol/L (men)
Albumin[a]	<25 g/L
Total bilirubin[c]	≥1.5 x ULN
ALT/SGPT[c]	≥3 x ULN
AST/SGOT[c]	≥3 x ULN
Alkaline phosphatase[c]	≥3 x ULN
BUN[c]	≥1.5 x ULN
Creatinine[c]	≥1.5 x ULN
Bicarbonate[c]	Increase ≥4 mmol/L and ONR or decrease ≥4 mmol/L and ONR
Lipid Profile	
Total cholesterol[b,c]	Increase ≥1.29 mmol/L and value ≥6.75 mmol/L
Total cholesterol[a,b]	≥7.758 mmol/L
HDL cholesterol[b,c]	Decrease >0.21 mmol/L and value <0.91 mmol/L
LDL cholesterol[b,c]	Increase ≥1.29 mmol/L and value ≥4.91 mmol/L
Triglycerides[a,b]	≥3.7 mmol/L
Urinalysis	
Specific gravity[a]	<1.001 or >1.035
pH[a]	≤4 or ≥9
Protein/albumin[a]	Positive value
Sugar/glucose[a]	Positive value
Blood/hemoglobin[a]	Positive value
Ketones/acetone[a]	Positive value

Table 3.1.1-1: Criteria for Determining Laboratory Test Results of Potential Clinical Importance in Phase 2 and 3 Studies

Test	Criteria[a]

ALT/SGPT=alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT=aspartate aminotransferase/serum glutamic oxaloacetic transaminase; GGT=gamma-glutamyltransferase; HDL=high-density lipoprotein; LDL=low-density lipoprotein; ONR=outside normal range; ULN=upper limit of normal range; WBC=white blood cell.

a. Criteria were defined by the US Food and Drug Administration.
b. Tests were to be performed in fasting subjects. Data for nonfasting subjects are presented in supportive tables only.
c. Criteria were defined by Wyeth.

Appendix 10.7: Mean Laboratory Results in the Controlled, Short-term Trials

Table 3.2.1-1: Selected Mean Laboratory Results for Group A1 (Short-Term, All Studies), On-Therapy Period

Variable (Unit) Time Period	Placebo N	Placebo Baseline Mean	Placebo Mean Change From Baseline	DVS SR 100-400mg N	DVS SR 100-400mg Baseline Mean	DVS SR 100-400mg Mean Change From Baseline	Venlafaxine ER 75-225mg[a] N	Venlafaxine ER 75-225mg[a] Baseline Mean	Venlafaxine ER 75-225mg[a] Mean Change From Baseline	Between Group p-Value[b]
Creatinine (µmol/L)										
Week 8	553	70.647	1.110**	765	71.785	-0.319	165	70.418	-0.334	0.018A
Final on-therapy	680	71.275	0.791*	945	71.900	-0.119	204	70.161	0.198	
AST/SGOT (mU/mL)										
Week 8	538	22.4	0.2	745	22.5	1.7***	162	21.4	0.4	0.010A 0.029C
Final on-therapy	665	22.5	0.1	926	22.4	1.6***	199	21.4	0.5	0.003A 0.038C
ALT/SGPT (mU/mL)										
Week 8	544	23.9	0.2	759	24.4	2.3***	163	22.9	0.1	<0.001A 0.009C
Final on-therapy	673	23.7	0.1	940	24.2	2.6***	201	23.0	0.3	<0.001A 0.009C
GGT (mU/mL)										
Week 8	551	24.2	-0.5	764	28.0	7.5***	164	25.9	1.4	<0.001A <0.001C
Final on-therapy	679	24.1	-0.5	944	27.7	7.7***	203	25.6	1.2	<0.001A <0.001C
Total bilirubin (µmol/L)										
Week 8	551	9.374	-0.636***	764	9.204	-1.578***	164	8.880	-1.520***	<0.001A <0.001B
Final on-therapy	679	9.429	-0.619***	944	9.298	-1.657***	202	8.951	-1.437***	<0.001A <0.001B
Alkaline phosphatase (mU/mL)										
Week 8	551	73.1	-0.8	764	73.3	7.4***	164	70.9	3.4***	<0.001A <0.001B <0.001C
Final on-therapy	679	73.0	-0.8*	944	73.0	6.8***	203	69.2	3.5***	<0.001A <0.001B <0.001C
Total cholesterol, fasting (mmol/L)[c]										
Week 8	488	5.32909	-0.11610***	673	5.42605	0.17030***	134	5.40014	0.10414	<0.001A <0.001B
Final on-therapy	579	5.30846	-0.10734***	805	5.44702	0.14623***	157	5.39339	0.07998	<0.001A <0.001B
HDL cholesterol, fasting (mmol/L)[c]										
Week 8	485	1.36191	-0.01431	671	1.36428	0.03761***	132	1.34301	0.06177**	<0.001A <0.001B
Final on-therapy	576	1.36605	-0.01547	803	1.36967	0.03602***	155	1.35709	0.05480**	<0.001A <0.001B
LDL cholesterol, fasting (mmol/L)[c]										
Week 8	473	3.27327	-0.08726***	648	3.33920	0.11339***	130	3.35230	0.06515	<0.001A 0.004B
Final on-therapy	563	3.25723	-0.07619**	774	3.35266	0.09309***	153	3.36667	0.03293	<0.001A 0.015B

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On Original

Table 3.2.1-1: Selected Mean Laboratory Results for Group A1 (Short-Term, All Studies), On-Therapy Period

Variable (Unit) Time Period	Placebo N	Placebo Baseline Mean	Placebo Mean Change From Baseline	DVS SR 100-400mg N	DVS SR 100-400mg Baseline Mean	DVS SR 100-400mg Mean Change From Baseline	Venlafaxine ER 75-225mg[a] N	Venlafaxine ER 75-225mg[a] Baseline Mean	Venlafaxine ER 75-225mg[a] Mean Change From Baseline	Between Group p-Value[b]
Triglycerides, fasting (mmol/L)[c]										
Week 8	488	1.52003	-0.02309	672	1.57073	0.07141*	134	1.47293	-0.02916	0.041A
Final on-therapy	579	1.50831	-0.03110	804	1.57475	0.06179	157	1.40686	-0.00113	0.019A
Bicarbonate (mmol/L)										
Week 8	550	25.10	-0.10	761	25.16	0.47***	165	24.68	0.88***	<0.001A <0.001B
Final on-therapy	678	25.05	-0.09	941	25.16	0.41***	203	24.68	0.84***	<0.001A <0.001B
Calcium (mmol/L)										
Week 8	553	2.43730	-0.01171**	765	2.42695	-0.01429***	165	2.43074	-0.01717*	
Final on-therapy	680	2.43322	-0.01054**	945	2.42651	-0.01237***	204	2.42525	-0.01467*	
Chloride (mmol/L)										
Week 8	553	104.4	-0.0	765	104.5	-0.9***	165	103.6	-0.2	<0.001A 0.006B
Final on-therapy	680	104.4	0.0	945	104.4	-0.8***	204	103.7	-0.3	<0.001A <0.001B
Free thyroxine index (unit)										
Week 8	500	2.63	0.03*	670	2.66	-0.22***	164	2.65	-0.19***	<0.001A <0.001B
Final on-therapy	605	2.64	0.03	819	2.67	-0.20***	201	2.65	-0.17***	<0.001A <0.001B
T3 uptake (AU)										
Week 8	501	33.20	0.32**	670	33.40	0.32**	164	33.41	0.20	
Final on-therapy	606	33.51	0.27**	819	33.36	0.42***	202	33.35	0.15	
Total T4 (nmol/L)										
Week 8	500	103.84	0.39	670	104.40	-9.57***	164	104.27	-7.96***	<0.001A <0.001B
Final on-therapy	605	103.15	0.38	819	105.11	-8.91***	201	104.28	-7.06***	<0.001A <0.001B

Table 3.2.1-1: Selected Mean Laboratory Results for Group A1 (Short-Term, All Studies), On-Therapy Period

ALT/SGPT=alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT=aspartate aminotransferase/serum glutamic oxaloacetic transaminase; AU=arbitrary units; GGT=gamma-glutamyltransferase; HDL=high-density lipoprotein; LDL=low-density lipoprotein; mU=milliunits; T3=triiodothyronine; T4=thyroxine.

All statistics are evaluated using data with nonmissing baseline values. N: the number of matched nonmissing pairs. A paired t-test was used to test for significant mean changes from baseline within treatment groups. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

a: Studies 309 and 317 only.

b: Comparison based on adjusted mean changes from baseline using analysis of covariance with baseline as covariate. Only significant ($p \leq 0.05$) differences between groups shown: A=placebo vs DVS SR 100-400 mg; B=placebo vs venlafaxine ER 75-225 mg; C=DVS SR 100-400 mg vs venlafaxine ER 75-225 mg.

c: Results for lipids presented only for fasting subjects.

CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3151A1/SCS2005/A1/LAB3 27OCT05 16:16

Robert Levin, M.D., October 24, 2006
Medical Reviewer,
FDA CDER ODE1 DNDP HFD 130

cc: NDA
HFD 130
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/s/

Robert Levin
10/24/2006 12:56:57 PM
MEDICAL OFFICER

Mitchell Mathis
11/6/2006 05:24:05 PM
MEDICAL OFFICER

Division of Cardio-Renal Drug Products

Memorandum

Date: 1-August-2006

From: Mehul Desai, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

Through: Norman Stockbridge M.D., Ph.D., Division Director
Division of Cardio-Renal Drug Products, HFD-110

To: Robert Levin, M.D., Medical Officer
Division of Psychiatry Products, HFD-130

Subject: N21,992

Name of Drug: Desvenlafaxine Succinate (DVS) Extended Release 100 mg and 200 mg

Formulation: tablets (extended release)

Related Applications: None

Approved Indications: None

Sponsor: Wyeth Pharmaceuticals, Inc.

Documents Used for Review:

1. Electronic NDA application – Submission 0000 on 'cdsesub1\evsprod\n21992'

Date Consult assigned: 21-June-2006

Date Consult completed: 1-August-2006

Reason for Consult/Background Information:

Comments:

Part A (Specific questions regarding hypertension and increases in blood pressure)

Question 1: To what extent are the elevations in blood pressure clinically significant?

The effects of DVS on blood pressure (BP) are statistically significantly higher compared to placebo based on short-term, controlled clinical trials. The extent to which the BP elevations seen with DVS are clinically significant is more difficult to characterize. The 7 fixed and flexible dose studies which all include placebo-control groups (and some which include venlafaxine as an active control) were relatively short in duration (8 weeks). Other studies in the DVS development program, although longer in

duration, were uncontrolled. There are some hints based on the adverse event narratives that the BP elevations might be clinically significant.

There was a case of a 45 year old white female, with a past history of hypertension and smoking, hospitalized for stroke on [redacted] She was enrolled into study 308 (a fixed-dose, placebo-controlled study) on [redacted] She completed this study and enrolled into study 303, a long-term, open-label, safety and efficacy extension study on 2-February-2004.

There was also a case of a 76 year old white female with a past history of major depression enrolled into study 307, a long-term, open-label, safety and efficacy study in elderly subjects that experienced symptoms of dizziness, nausea, and blurred vision in the setting of high blood pressure on [redacted] leading to hospitalization. The subject began receiving study drug DVS 100 mg daily on [redacted] The dose was increased to 200 mg daily one week later. Evaluation in hospital included an MRI scan which showed evidence of a small left frontal and posteroparietal subarachnoid hemorrhage. This subject did not have a prior history of hypertension although it was noted in the narrative that the subject did have "mild hypertension" prior to dosing study drug for which no action was indicated.

Question 2: What might be the expected longer term risks of such changes?

The magnitude of the population, mean, placebo-subtracted systolic/diastolic blood pressure increase from baseline observed with DVS (approximately 3.5-4.0/2.0 -2.5 mm Hg) could be clinically significant. Epidemiologic studies suggest that higher blood pressures lead to an increased risk for adverse clinical outcomes (e.g. heart failure, angina, myocardial infarction, stroke, peripheral vascular disease, renal insufficiency, left ventricular hypertrophy) compared to lower blood pressures. Any of the listed adverse outcomes (and possibly others) could result from a drug that leads to a sustained increase in blood pressure.

JNC 7 suggests that systolic blood pressure reductions of as little as 2 mm Hg in the general population could lead to a 6% reduction in the risk of stroke and a 4% reduction in the risk of coronary heart disease. On this basis, a mean 2 mm Hg ***increase*** in the systolic pressure in the general population should theoretically lead to a quantifiable increase in risk of stroke and/or coronary heart disease assuming all other cardiovascular risk factors remain unchanged. The complication factor is that DVS has been shown to decrease weight, which could improve cardiovascular outcomes, and raises total cholesterol levels, which could worsen cardiovascular outcomes. In the absence of a randomized, placebo-controlled clinical trial of sufficient patient-years of drug exposure, the net clinical benefit (or harm) can not be adequately characterized.

Question 3: How do the effects on blood pressure seem to compare to the effects of the parent drug, venlafaxine on blood pressure?

The figure below shows the distribution of supine systolic BP changes from baseline during Visit 3 (1 week after starting study drug) in the placebo arm (top), DVS arm (middle), and Venlafaxine arm (bottom). Visit 3 was arbitrarily chosen – other post study drug initiation Visits produced roughly similar distributions.

The data in the figure below were pooled from 7 short-term, placebo-controlled fixed and flexible dose studies of DVS conducted as part of Phase 2/3 development. Each of the 7 randomized, placebo-controlled studies was conducted in a double-blind manner and was 8 weeks in duration. Some of the studies included a Venlafaxine arm. The doses of DVS used were 100 mg, 200 mg, or 400 mg daily. The doses of Venlafaxine used ranged from 75 mg – 225 mg daily. A total of 820, 1244, and 249 pooled placebo, DVS, and Venlafaxine study subjects were randomized into the 7 studies. It is worth noting that the protocol did not specify a fixed time point during the day during which BP was to be assessed.

A quick glance at the data below does not show a striking difference in the profile of the 3 distributions below. However, a more careful look shows that the distribution in the DVS and Venlafaxine arms is shifted slightly to the right compared to placebo. In addition, there are more outliers (systolic BP change from baseline > 20 mm Hg) in both the DVS and Venlafaxine groups.

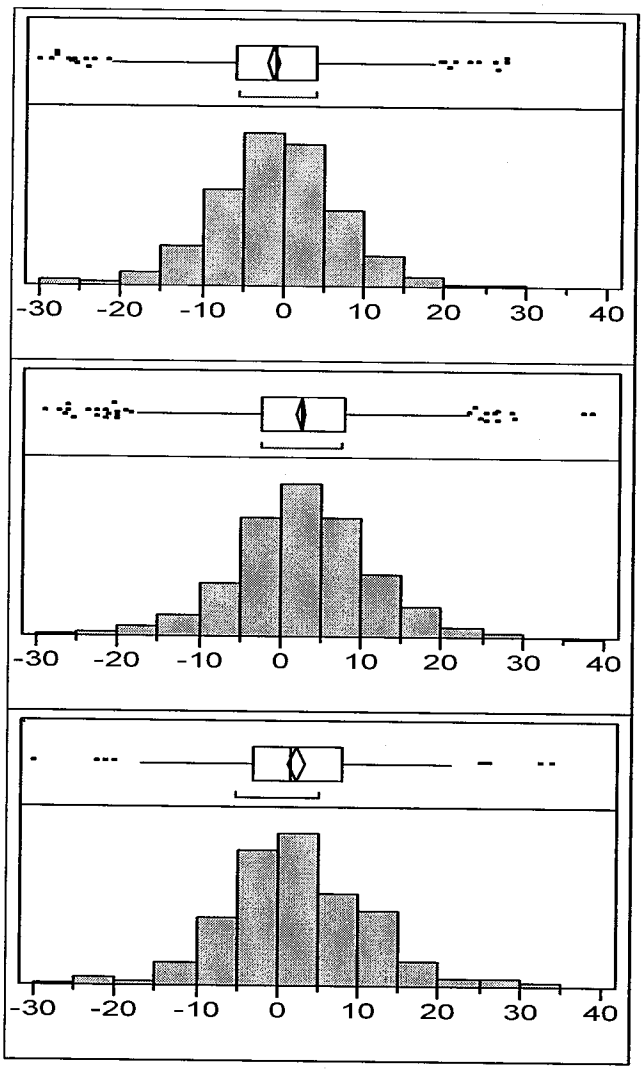

Figure 1: Supine systolic BP changes from baseline on placebo (top), DVS (middle), venlafaxine (bottom) during Visit 3.
Source: Analysis by Mehul Desai

The following table shows mean BP changes from baseline pooling all 7 studies described briefly above. The placebo subtracted BP changes from baseline in the DVS and Venlafaxine arms are approximately similar although the supine diastolic BP (placebo-subtracted) appears to be nominally higher on DVS. There does not appear to be any time dependence with respect to effects on BP. The BP effects are evident within 1 week of study drug initiation and persist at about the same level for the 8 week study duration.

Table 1: Supine systolic/diastolic BP changes (mm Hg) from baseline

	Placebo	DVS (100-400 mg)	Venlafaxine (75-225mg)
Week 1 (Visit 3)	-1.44/-1.09	2.35/1.03*	2.20/0.64*
Week 8 (Visit 8)	-1.71/-0.75	2.19/2.15*	2.20/1.16*
Week 1 (placebo subtracted)		3.79/2.12	3.64/1.73
Week 8 (placebo subtracted)		3.9/2.9	3.91/1.91

Source: Table 4.1.2.1-2 in Section 2.7 Clinical Summary (Sponsor's analysis)

* = Values for systolic BP and diastolic BP were statistically significant different compared to placebo with p-values of < 0.05 or lower for both DVS and Venlafaxine

Question 4: What type of further vital sign analyses might we request from the sponsor and perform ourselves?

The sponsor has provided various analyses in their submission to characterize the effects of DVS on BP that include analyses of mean BP effects and also categorical BP analyses. The sponsor's current analyses show that DVS has effects on BP that are statistically significantly different from placebo and that are similar to Venlafaxine. Additional BP analyses likely will not alter this conclusion.

Question 5: How might we label the AE of hypertension and increased blood pressure?

If DVS is considered approvable, the labeling of hypertension adverse events (AE's) and high blood pressure should be similar to that of Venlafaxine but no less restrictive.

Question 6: Do the effects on blood pressure appear to be dose-related?

The relationship between dose of DVS administered and BP appears to be weak if, in fact, there is a relationship. The figure below summarizes the pooled, supine BP results from the 3 fixed-dose studies (studies 223, 306, and 308). The studies involved 8 weeks of double-blind treatment with either 100, 200, or 400 mg daily (Note: the 100 mg dose was evaluated in only 1 of the 3 studies). The pooled population included 1084 subjects of which 327 received placebo, 120 received 100 mg DVS, 316 received 200 mg DVS, and 321 received 400 mg DVS. The study protocols did not specify a specific time of day (or time relative to dosing) when BP's were to be assessed. In the figure below, the top 2 panels show the mean change from baseline in the supine diastolic BP. The bottom 2 panels show the mean change from baseline in the supine systolic BP. The left 2 panels show the results at Visit 3 (one week post study drug initiation) while the right 2 panels show the results at Visit 8 (8 weeks post study drug initiation). The number of subjects included in the Visit 3 analysis are 315, 106, 275, and 289 for placebo, 100 mg, 200 mg, and 400 mg DVS respectively. The number of subjects included in the Visit 8 analysis are 304, 107, 285, and 293 subjects in placebo, 100 mg, 200 mg, and 400 mg DVS respectively.

Please note that the results shown in the figure below were similar though not identical to the sponsor's analysis. The reasons for the disparity are not completely clear. The overall conclusion does not change regardless of whichever analysis is used. I have not performed a statistical analysis to calculate p-values for the analysis below for each DVS dose compared to placebo. However, the sponsor's analyses of the data showed that each dose of DVS was statistically significantly different from placebo with a p-value 0.05 or less (in most cases much less than 0.05). If warranted, your Division should consider a more formal analysis by an FDA statistician.

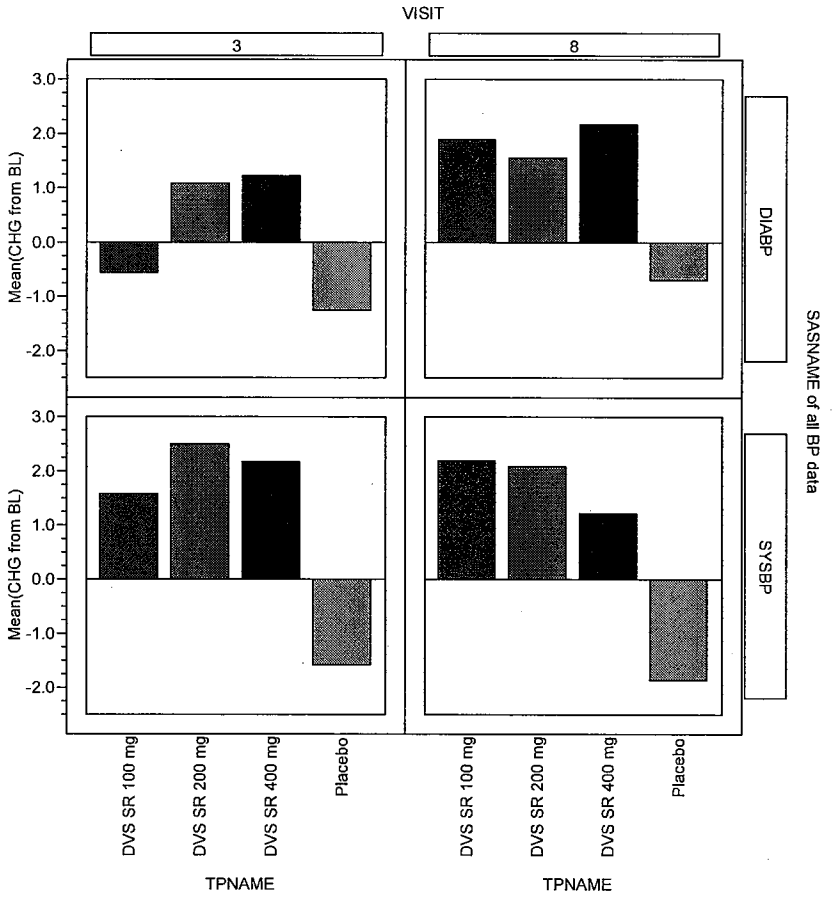

Figure 2: Mean changes from baseline in supine diastolic BP (top panels) and supine systolic BP (bottom panels) at Visit 3 (left 2 panels) and Visit 8 (right 2 panels).
Source: Analysis by Mehul Desai

Question 7: What would be a meaningful definition of sustained hypertension?

After a review of the literature, I'm unable to find a generally accepted definition of "sustained" drug-induced hypertension. In clinical practice, in a patient with suspected essential hypertension, it is not uncommon for a clinician to measure BP at least twice during two separate occasions (a couple weeks to several weeks apart) before deciding on a management approach. Intuitively, the greater the number of BP measurements collected on separate occasions, the greater the likelihood of a stable estimate of a patient's true blood pressure.

Question 8: To what extent could the cardiovascular adverse events reported in the trials be related to hypertension or significant elevations in blood pressure?

Please see the response to Question 1. Strokes and subarachnoid hemorrhages do occur in older patients or patients with underlying vascular disease, hypertension, and/or smoking histories. While, it is difficult to sustain an argument that these AE's are solely drug related, it also can not be concluded that

DVS played no role in these AE's. A long-term, controlled clinical trial evaluating cardiovascular outcomes would be needed to answer the question being asked.

Part B (Questions about proteinuria, hematuria, and hyperlipidemia)

Question 1: To what extent could these laboratory abnormalities be clinically significant?

The following table shows the results of urine protein and urine hemoglobin collected in the 3 fixed dose studies at Visit 1 (baseline) and Visit 8 (day 56). The results below reflect only on study drug data (post study drug discontinuation urine protein and hemoglobin results are not included in the table). In the table are shown the number of subjects with an abnormal urinalysis (UA) as defined as trace, +, ++, or +++ protein or hemoglobin.

With respect to proteinuria, the results below suggest that subjects receiving DVS are at a somewhat higher risk of an abnormal urinalysis compared to subjects taking placebo control. Although not shown in the table below, it is reassuring is that most subjects with an abnormal UA had trace or + urine protein. It is also reassuring that renal function, as assessed by mean serum creatinine level change from baseline, did not worsen on DVS relative to placebo.

With respect to hemoglobinuria, the results do not suggest any evidence of a difference between DVS and placebo.

	Placebo	100 mg DVS	200 mg DVS	400 mg DVS
Visit 1 (**pre study drug baseline**)	N = 325	N = 120	N = 316	N = 321
# of subjects with trace, +, ++, or +++ protein on UA	8	2	8	13
# of subjects with trace, +, ++, or +++ hemoglobin on UA	26	12	26	31
Visit 8 (**end of study**)	N = 268	N = 94	N = 226	N = 249
# of subjects with trace, +, ++, or +++ protein on UA	6	3	11	17
# of subjects with trace, +, ++, or +++ hemoglobin on UA	26	10	21	29

Source: Analysis by Mehul Desai

An analysis of cholesterol levels in the 3 fixed dose studies show that there is a dose-dependent increase in total cholesterol mean change from baseline in the 3 dose groups. The mean change from baseline in total cholesterol was -0.12, -0.05; 0.11, and 0.15 in the placebo, 100 mg DVS, 200 mg DVS, and 400 mg DVS groups respectively. Similar to effects of DVS on blood pressure, the effects of DVS on total cholesterol are difficult to quantify in term of clinical significance because the placebo-controlled studies were of relatively limited patient-year duration of exposure.

There were only a very few number of subjects that had a combination of an abnormal UA (with both proteinuria and hematuria), along with an increased total cholesterol and hypertension.

Question 2: How might these be labeled?

A brief description of the total cholesterol and urine protein changes should be included in labeling.

Recommendation/Conclusions:

Please see the responses to the individual questions.

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/s/

Mehul Desai
8/1/2006 11:55:04 AM
MEDICAL OFFICER

Norman Stockbridge
8/3/2006 07:35:34 AM
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