CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-992

MEDICAL REVIEW(S)

CDTL MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 5, 2008

FROM: Gwen L. Zornberg, M.D., Sc.D.
Acting Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for desvenlafaxine (DVS) extended release capsules) for the treatment of Major Depressive Disorder (MDD)
Wyeth Pharmaceuticals Inc.

TO: File NDA 21-992 (desvenlafaxine succinate) Sustained Release Oral Tablets (50 mg, 100 mg, 200 mg tablets) Response to Approvable Letter (submissions 27 June 2007 & 29 August 2007) SN 000 (new drug application dated August 29, 2007)

REVIEWERS: Chemistry, Thomas Oliver, Ph.D.; Biopharmaceutics, Dr. Kofi Kumi; Biostatistics, Dr. Yeh-Fong Chen, Ph.D. Clinical, Dr. Robert Levin; and Pharmacology/Toxicology, Dr. Linda Fossom. Office of Surveillance and Epidemiology, Sharon Mills, BSN, RN, CCRP.

1.0 BACKGROUND

Pristiq (desvenlafaxine succinate, i.e., DVS) tablets is an extended release formulation of the major active metabolite of the selective serotonin and norepinephrine reuptake inhibitor (SNRI) type antidepressant, venlafaxine, developed for the treatment of Major Depressive Disorder (MDD) in adults. This submission by Wyeth, which is a response to the approvable action (letter dated 22 January 2007) for the original NDA submission seeks a claim for the short-term use of Pristiq in the treatment of patients diagnosed with MDD in the range of 50 to 200 mg given daily. This submission, which is a response to the approvable action, is comprised primarily of safety and efficacy data from 2 more

recent fixed dose trials (studies 332 and 333) of identical design evaluating the lower dose of 50 mg/day as well as the 100 mg/day dose, in the acute treatment of MDD.

Pristiq was developed under IND 64,552 that was initially submitted as an NDA 21-992 on 22 December 2005 based on short-term studies of DVS administered as fixed and flexible dose groups of 100 mg, 200, and 400 mg/day. The findings suggested that DVS is efficacious and reasonably safe in the treatment of MDD at these dose levels, although a dose response to adverse drug reactions was observed. In clinical trials no additional benefit of effectiveness was demonstrated at doses greater than 100 mg daily in the original submission in this study population of largely moderately depressed patients. The long-term study of DVS (200 mg and 400 mg/day dose groups) had not been completed at the time of the original submission. The Division issued an Approvable action letter on January 22, 2007 with respect to the acute treatment of MDD. The agency noted that a relatively high proportion of patients discontinued due to adverse events early in the trials (weeks 1-2), most commonly nausea, vomiting, dizziness, and sweating.

This 29 August 2007 submission presenting new data from 2 identically designed trials including new data on the lower 50 mg/day dose in comparison to placebo and the 100 mg/day group to improve the risk/benefit profile of DVS in the treatment of MDD represents the complete response by Wyeth to the Approvable action letter. A maintenance study was also submitted (study 333) that evaluated maintenance treatment in 200 mg and 400 mg groups, not in the clinically relevant 50 mg and 100 mg/day groups. Consequently, this maintenance study was not found by Dr. Laughren to be germane to this response to the NDA approvable letter.

2.0 CHEMISTRY

The chemistry review has not been completed as of this date. Dr. Oliver stated that he expected that an approval action would be non-objectionable at this point based on the review of quality issues being finalized in keeping with guidelines.

Consequently, I am not aware of any CMC issues at present that would likely preclude an approval action for the claim of the acute treatment of MDD for this response to the approvable letter. Consequently, this recommendation is in part conditional on the final recommendations of the pending CMC review.

3.0 PHARMACOLOGY

Dr. Linda Fossom found the nonclinical carcinogenicity data submitted by Wyeth to be non-objectionable. In her review, she evaluated the combined fertility and embryo-fetal toxicity study in rats and found that it does not adequately assess the potential of desvenlafaxine succinate to cause embryo-fetal toxicity, including teratogenicity, due to a decreased number of fetuses available for analysis at the high dose of 300 mg/kg. Dr. Fossom posited that the data suggest that this appears to result from the effects of

desvenlafaxine succinate on fertility and pre-implantation loss, and would not be the case if dosing commenced only during the period of organogenesis.

Based on Dr. Fossom's review, I am not aware of any pharmacology/toxicology issues at this point that would preclude an approval action for this NDA and the response to the approvable letter.

4.0 BIOPHARMACEUTICS

Dr. Kumi reviewed the 3 new drug interaction studies (198, 401, and 900) that compared the effect of DVS 100 mg on CYP2D6 mediated desipramine metabolism and a study of the relative differences in pharmacokinetics between the CYP2D6 genotype subjects who are extensive metabolizers versus the poor metabolizers after a single dose administration of DVS or venlafaxine. A Pharmacogenomic consult was requested by OCP for the evaluation of the phenotype of the patients involved in the study. Dr. Kumi suggested that in labeling caution should be advised when DVS is co-administered with desipramine and overall thought that the findings in the response to the approvable letter to be non-objectionable.

Based on Dr. Kumi's review, I am not aware of any pharmacologic issue that would preclude a direct approval action.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application focused on 2 short-term (8-week), double-blind, randomized, fixed-dose, parallel group (50 mg/day and 100 mg/day DVS), placebo-controlled trials evaluating the treatment of MDD. The primary efficacy analysis was mean change form baseline to 8-week endpoint in the HAM-D-17 score at the final on-therapy evaluation. In every treatment group, as reasonable percentage ranging between 80 to 90% of patients completed the studies.

Dr. Yeh-Fong Chen, Ph.D. conducted the statistical review of studies 332 and 333. She excluded a subset of patients from the primary analysis for each of the studies because their assessments were collected outside the pre-specified window of greater or less than 3 days from the date of the scheduled visit. As a result of this analysis based on the analyses specified *a priori*, the comparison of the 50 mg/day dose groups in both studies 332 and 333 were significantly superior to placebo, $p = 0.02$ and $p = 0.004$, respectively. Though the primary efficacy analysis in the DVS 100 mg/day group was not significant in study 332 ($p= 0.09$) using this approach, the 100 mg dose group in study 332 was highly significantly superior to placebo in study 333 ($p < 0.001$). Sensitivity analyses using the MMRM method, which is an appropriate method to analyze these data,

supported the efficacy of both the DVS 50 mg and 100 mg daily dose groups, which were all significantly superior to placebo (all p-values for 50 and 100 mg from studies 332 and 333 were ≤ 0.006). In the 333 study, the CGI-I results based on the LOCF data were significantly superior to placebo, there was a trend toward superiority in the LOCF endpoint data of the332 study.

FDA Primary Efficacy Analyses – Mean Change from Baseline Endpoint on HAM-D-17 Scores*

Analysis		332			333		
		Placebo	DVS-50	DVS-100	Placebo	DVS-50	DVS-100
	N	150	150	147	161	164	158
	LSM	-9.6	-11.5	-11.0	-10.8	-13.2	-13.7
	P-value		0.02	0.09		p = 0.004	< 0.001
	N						
	LSM		-12.5	-11.7	-11.5	-14.3	-14.
	P-value		0.003	0.03		< 0.001	< 0.001

* Final On Therapy Analysis (LOCF)

There was no evidence supporting a dose-response for efficacy in the combined database. Lower doses such as DVS 25 mg/day have not been evaluated. The sponsor provided data pertaining to longer term efficacy for MDD, however, the DVS groups of 200 mg/day and 400 mg/day do not correspond the doses most clinically relevant in the acute studies (50 and 100 mg/day). The high doses evaluated in the maintenance study, higher than those recommended based on data from the acute treatment trial holds little clinical relevance.

5.1.2 Conclusions Regarding Efficacy Data

Based on my review of the data in addition to the review of Dr. Levin and Chen, the sponsor has provided sufficient evidence to support the claim of short-term efficacy of Pristiq in the treatment of MDD in the 50, 100 and 200 mg dose groups.

5.2 Safety Data

In the data combined from studies 332 and 333, the majority of common, drug-related adverse events largely involved the central nervous system, gastrointestinal symptoms, and/or sexual function. The pattern of drug-related adverse events is essentially the same as that observed in the earlier DVS studies. The most common drug-related CNS adverse events were insomnia, dizziness, asthenia, anxiety, and somnolence. The most common gastrointestinal system adverse events were nausea, vomiting, dry mouth, diarrhea, and constipation.

5.2.1 Clinical Data Sources for Safety Review

The safety data was reviewed by Dr. Levin. The safety profile was similar to DVS at 200mg and 400 mg, as well as venlafaxine, in terms of types of adverse drug reactions (ADRs). The risk of sustained hypertension increases with higher dose levels of DVS, as

does the risk of elevated serum cholesterol and triglyceride levels, sexual dysfunction and the common ADRs of nausea, hyperhidrosis skin reactions, insomnia, dry mouth, dizziness, and somnolence. There were no unexpected ADRs. The occurrence of ADRs was reduced at the 50 mg dose compared to the higher DVS fixed dose groups. Treatment of MDD with DVS at 50 mg daily provides enhanced safety and tolerability.

5.3 Clinical Sections of Labeling

Pristiq labeling is being finalized in Physician's Labeling Rule format and will be sent by the Division to Wyeth for by 8 February 2008.

6.0 FOREIGN REGULATORY ACTIONS

To the best of my knowledge, Pristiq is not approved anywhere at this time. The sponsor will be asked to provide a review of the status of all desvenlafaxine actions taken or pending before foreign regulatory agencies. Solvay needs to provide English translations of current approved foreign labeling not previously submitted.

7.0 WORLD LITERATURE

Wyeth conducted thorough literature searches to identify any changes in the safety profile. The references identified did not provide an y new meaningful safety information.

8.0 CONCLUSIONS AND RECOMMENDATIONS

Based on the data provided in the reviews and correspondence, I recommend that an approval action be taken on Wyeth's response to the approvable letter including the submission of new clinical data evaluating exposure to 50 mg daily in 2 randomized, placebo-controlled trials. Based on the reviews of Dr. Levin and Dr. Chen, I believe that Wyeth has submitted sufficient clinical data to support the conclusion that desvenlafaxine (Pristiq) 50 mg and 100 mg daily is effective and acceptably safe in the treatment of patients diagnosed with MDD. In the combined data from all trials, there is no evidence for a difference in effectiveness over the dose range studied, 50 mg to 400 mg/day. Wyeth did not study patients diagnosed with Treatment Resistant Major Depression leaving unanswered the question of the need for higher doses in these patients. Of concern is the support for a dose response for a number of adverse drug reactions. In particular, the risk of sustained hypertension increases with higher dose levels of DVS, as well as risk of elevated serum cholesterol and triglyceride levels in addition to sexual dysfunction and the common ADRs of nausea, hyperhidrosis skin reactions, insomnia, dry mouth, dizziness, somnolence. Consequently, the 50 mg dose affords no less effectiveness than the higher DVS dose levels studied coupled with superior safety and tolerability. Based on the data, it is possible that lower dosages, such as DVS 25 mg or 12.5 mg daily may offer improved efficacy combined greater safety and tolerability. If the DVS dosing range approved is restricted to 50 and 100 mg daily, there would be no need for language limiting the dose to 100 mg/day in labeling.

While it is clear that desvenlafaxine has a qualitatively negative effect on sexual function from the adverse events collected during the earlier trials, we do not have quantified, systematically collected sexual dysfunction data. Accordingly, we will recommend that Wyeth commit to conducting a controlled study to evaluate and quantify the impact of desvenlafaxine on sexual function. We will request that this study include a validated and reliable outcome measure to quantify specific domains of sexual function including sex drive, arousal, erection/lubrication, and ability to reach and satisfaction with orgasm. We request that Wyeth commit to conducting and submitting the results of this study no later than — years after the date of approval for this NDA.

The combined clinical data in the original application and the data in the Efficacy and Safety sections submitted in response to the approvable letter demonstrates effectiveness of DVS at the recommended doses (50-200 mg/day) as a treatment for Major Depressive Disorder over an interval of 6 weeks, however, the is not greater efficacy shown at doses greater than 50 mg daily. Moreover, the data in this submission do not provide information about the duration and conditions of treatment with DVS that are necessary to sustain its antidepressant effects over the full duration of an acute major depressive episode at these same recommended doses. It would be informative to identify a ~~doc~~ dose response curve for efficacy with the identification of reduced efficacy at least one lower dose. I would recommend, though not as a requirement, that the sponsor study the safety, efficacy and tolerability of lower doses of DVS.

While it is widely assumed that continued treatment of symptomatically remitted patients reduces their risk of relapse, which may be the reason why the proposed labeling for desvenlafaxine recommends that — we have no evidence that DVS has efficacy beyond the 8 weeks of short-term treatment evaluated. I recommend that as a phase ~~IV~~ commitment ~~that~~ Wyeth conduct and submit the results of a randomized withdrawal study to address longer-term efficacy of DVS. ~~We request that~~ They should ~~you~~ commit to conducting this study and submitting the results no later than — years after the date of approval for this NDA.

Research on the safety and efficacy of Pristiq in long-term treatment and in a pediatric population aged — to 17 years would be recommended to provide valuable clinical information in pediatric patients ages 7 to 17 (children and adolescents). Both children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these age strata. We will require that Wyeth commit to the conduct and submission of the results of these studies no later than — years after the date of approval for this NDA.

In addition, as a post-marketing commitment, the Division will require that Wyeth commit to conducting a standard embryo-fetal toxicity study (dosing after implantation) in rats and that you submit the results of this study no later than 3 years after the date of approval of this NDA.

The recommendation for an approval action is conditional on recommendation by CMC for approval, as well as agreement between FDA and Wyeth on acceptable language in Pristiq labeling, as well as the Medication Guide that will be required.

cc:
NDA 21-992
HFD-130
HFD-130/GZornberg/RLevin/MMathis/TLaughren /RGrewal/PDavid/SHardeman

DOC:Pristiq_MDD_Zornberg_AE_Memo_Addendum.doc

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/s/

Gwen Zornberg
2/5/2008 09:58:29 PM
MEDICAL OFFICER

NDA #21-992: Review of Complete Approvable Response

NDA #:	21-992
Sponsor:	Wyeth
Drug:	Pristiq (desvenlafaxine)
Type of submission:	Complete Approvable Response
Date of submission:	August 29, 2007
PDUFA date:	February 29, 2008
Formulation:	Oral tablets

1. Introduction

On December 22, 2005, the sponsor submitted the original NDA (#21-992) for desvenlafaxine (DVS) in the treatment of Major Depressive Disorder (MDD) in adults. In the original NDA studies, the sponsor conducted placebo-controlled, short-term studies of DVS administered as fixed and flexible doses of 100, 200, and 400 mg per day. The studies demonstrated that DVS was efficacious and reasonably safe in the treatment of MDD. Thus, the Division took an approvable action and issued an approvable letter on January 22, 2007. Subsequently, the sponsor submitted a complete response to the approvable action on August 29, 2007.

The sponsor's response consists primarily of new safety and efficacy data from two identically designed short-term, placebo-controlled trials (studies 332 and 333) using a lower fixed dose (50 mg per day) of DVS than had been used in previous trials. The sponsor chose to study the lower dose of 50 mg/day (compared to 100 mg/day and placebo), since a relatively high proportion of subjects in the initial trials had discontinued early (in Weeks 1 and 2) due to adverse events. These adverse events included nausea, vomiting, dizziness, and sweating. Furthermore, these discontinuations and associated adverse events occurred in a dose-related manner. Other safety findings that occurred in a dose-dependent manner included: blood pressure elevation, heart rate elevation, elevations of serum cholesterol and triglyceride, and proteinuria. Since the sponsor had not established a minimally effective dose, and the occurrence of many important safety findings were dose-related, the Division requested that the sponsor study lower doses of DVS in controlled trials, in order to identify a minimally effective dose.

Additional components of the approvable response include: 1) a safety update for the MDD trials, with a data cut-off date of February 28, 2007; 2) revised desvenlafaxine labeling in the new physician's labeling rule (PLR) format; 3) new data from Study 302, a placebo-controlled, randomized withdrawal maintenance study (using DVS doses of 200 and 400 mg/day); 4) a revised risk management plan; and 5) a worldwide literature update regarding desvenlafaxine.

2. Review of Controlled Trials 332 and 333

2.1 Title of Studies

The identically designed studies 3151A1-332-US (332) and 315A1-333-EU (333) were entitled:

"A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of 2 Fixed Doses (50 mg, 100 mg) of Desvenlafaxine Sustained-release Tablets in Adult Outpatients with Major Depressive Disorder."

2.2 Objective

The primary objective in studies 332 and 333 was to compare the antidepressant efficacy, safety, and tolerability of DVS in subjects with a diagnosis of Major Depressive Disorder treated with daily, fixed DVS doses of 50 mg, 100 mg, or placebo.

2.3 Subject Selection Criteria

The subject selection criteria were identical in studies 332 and 333. The inclusion and exclusion criteria were appropriate for an acute, controlled trial in subjects with Major Depressive Disorder. Furthermore, the subject selection criteria in these two new studies were identical to those in the previous desvenlafaxine studies in MDD.

2.3.1 Inclusion Criteria

1. Outpatient men and women at least 18 years of age
2. Primary diagnosis of Major Depressive Disorder based on DSM-IV criteria, single or recurrent episode, without psychotic features
3. Depressive symptoms were present for at least 30 days before the screening visit.
4. HAMD-17 score was at least 20 at screening and baseline.
5. Item 1 (depressed mood) score on HAMD-17 was at least 2.
6. CGI-S score of at least 4 at screening and baseline
7. Sexually active individuals (except for women of non-childbearing potential) must have agreed to use a medically acceptable method of contraception during the study and for at least 15 days after the last dose of study medication. Medically acceptable forms of contraception included oral contraceptives, injectable or implantable methods, intrauterine devices, or properly used double-barrier contraception (eg, condom plus diaphragm).

2.3.2 Exclusion Criteria

1. Treatment with desvenlafaxine at any time in the past
2. Known hypersensitivity to venlafaxine
3. Significant risk of suicide, based on clinical judgement. Frequent suicidal thoughts and suicide being considered as a possible solution, even without specific plans or intention.
4. Women who were pregnant, breastfeeding, or planning to become pregnant during the study.
5. Current (within 12 months of baseline) psychoactive substance abuse or dependence (including alcohol), manic episode, Posttraumatic Stress Disorder, Obsessive Compulsive Disorder, or a lifetime diagnosis of Bipolar or Psychotic Disorder as assessed by the modified MINI and confirmed by the investigator. Current (within 12 months of baseline) Generalized Anxiety

Disorder, Panic Disorder, or Social Anxiety Disorder, as assessed by the modified MINI and considered by the investigator to be primary, causing a higher degree of distress or impairment than Major Depressive Disorder. Presence (within 12 months before baseline) of a clinically important personality disorder such as antisocial, schizotypal, histrionic, borderline, or narcissistic personality disorder, as assessed during the psychiatric evaluations.

6. A Covi Anxiety Scale total score greater than the Raskin Depression Scale total score at screening or at baseline.
7. A Covi Anxiety Scale item score greater than 3 on any single item or a total score greater than 9 at screening or at baseline.
8. Depression due to a general medical condition or a neurological disorder.
9. History of a seizure disorder other than a single childhood febrile seizure.
10. Any unstable hepatic, renal, pulmonary, cardiovascular (including uncontrolled hypertension), ophthalmologic, neurologic, or any other medical condition that might confound the study or put the subject at greater risk during study participation.
11. History or current evidence of gastrointestinal disease known to interfere with the absorption or excretion of drugs; or, history of surgery known to interfere with the absorption or excretion of drugs.
12. History of neoplastic disorder (within 2 years), with the exception of basal cell or squamous cell carcinoma of the skin.
13. Presence of increased intraocular pressure or history of narrow-angle glaucoma.
14. Major acute illness during the 90 days before screening.
15. Myocardial infarction within 180 days before screening.
16. Clinically important abnormalities (as determined by the investigator) on screening, physical examination, ECG, laboratory tests, or urine drug screen.
17. Use of prohibited treatments (specified in the protocol).

2.4 Design of Studies 332 and 333

2.4.1 Study Design and Schedule of Assessments

The designs of studies 332 and 333 were identical, and they were analogous to the earlier short-term, controlled DVS studies. Studies 332 and 333 were appropriately and well-designed to address the primary objective. Studies 332 and 333 were Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group, 8-week studies of two fixed-doses of desvenlafaxine (50 mg and 100 mg per day) in adult outpatients with Major Depressive Disorder. Subjects randomized to treatment with desvenlafaxine began with 50 mg/day for 7 days. On Day 8, subjects randomized to DVS 100 mg/day had their dose increased to 100mg/day for the remainder of the study. Subjects in all three treatment groups continued the assigned fixed-dose of study drug through Day 56. A seven-day taper period was recommended; however, the taper may have been omitted, shortened, or lengthened at the discretion of the investigator. There was a 7-day follow-up period after discontinuation of study drug.

The study flowchart below illustrates the schedule of assessments and procedures during the screening, study treatment, tapering, and follow-up phases. Clinic visits were scheduled at screening, baseline (day −1), and on days 1, 7, 14, 21, 28, 42, 56, 63, and 70. There were telephone contacts on days 59 and 66.

Table 2.1 Study Flowchart for Studies 332 and 333

Procedure/ Study Day	Screen (10 +/- 4 days)	Base-line (-1)	Double-blind Treatment Period (days 1-56 +/– 3 days)							Taper period		Post-study follow-up	
			1	7	14	21	28	42	56	59	63	66	70
Informed consent													
Eligibility	x	x											
Medical history	x												
Psychiatric history	x												
Modified MINI	x												
randomization		x											
Dispense drug		x	x	x	x	x	x	x					
Begin drug			x										
Telephone cont.										x		x	
Concomit. meds	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical exam	x								x				
Height	x												
Weight	x	x	x	x	x	x	x	x	x		x		x
Blood pressure	x	x		x	x	x	x	x	x		x		x
Pulse	x	x		x	x	x	x	x	x		x		x
Clinical labs	x								x				
ECG	x	x							x				
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x
DESS checklist									x		x		x
HAMD-17	x	x		x	x	x	x	x	x				
MADRS		x		x	x	x	x	x	x				
CGI-S	x	x		x	x	x	x	x	x				
CGI-I				x	x	x	x	x					

2.4.2 Dosing and Administration of Study Drug

At baseline (Day –1), subjects were randomly assigned to one of two fixed desvenlafaxine doses (50 or 100 mg/day) or placebo. Subjects received the assigned medication in individual blister packs. Each blister pack contained two tablets for each day. Subjects were instructed to take 2 tablets each day and to take both tablets at the same time. Subjects could take the study drug at any time of the day, with or without food, but they were instructed to take the study tablets at the same time each day throughout the study. If a subject could not tolerate 2 tablets per day, he or she was discontinued from the study.

Table 2.4.2 Study Drug Regimens

Study Drug Group	Tablet A	Tablet B	Daily DVS dose
DVS 50 mg/day			
Days 1-56	DVS 50 mg	Placebo	DVS 50 mg
Taper days 1-7	Placebo	Placebo	0
DVS 100 mg/day			
Days 1-7	DVS 50 mg	Placebo	DVS 50 mg
Days 8-56	DVS 50 mg	DVS 50 mg	DVS 100 mg
Taper days 1-7	DVS 50 mg	Placebo	DVS 50 mg
Placebo			
Days 1-56	Placebo	Placebo	0
Taper days 1-7	Placebo	Placebo	0

2.4.3 Efficacy Variables

2.4.3.1 Primary Efficacy Variable

The pre-specified primary efficacy variable was the Hamilton Depression Rating Scale-17 item (HAMD-17) score, as it was in the previous desvenlafaxine MDD trials. The HAMD-17 is an appropriate outcome measure, as it is well-validated, reliable, and widely accepted for use in clinical trials of Major Depressive Disorder.

2.4.3.2 Key Secondary Efficacy Variable

The pre-specified key secondary efficacy variable was the Clinical Global Impression-Improvement Rating Scale (CGI-I), which was also used in the earlier short-term, controlled trials. This is an appropriate and acceptable secondary efficacy variable, which is validated, reliable, and widely accepted.

Other exploratory secondary efficacy measures included the following:

- Montgomery-Asberg Depression Rating Scale (MADRS) score
- Clinical Global Impression Rating Scale (CGI-S) score
- Remission rate (percentage of subjects with HAMD-17 scores of ≤ 7)
- Response rates as measured by: HAMD-17, MADRS, and CGI-I
- Visual Analog Scale-Pain Intensity (VAS-PI) score
- HAMD-6 (Bech version: HAMD items 1, 2, 7, 8, 10, and 13) total score
- Covi Anxiety Scale score

2.4.4 Concomitant Medication

Non-psychopharmacologic drugs with psychotropic effects were permitted if the subject had been using a stable dose of the drug for at least 90 days before study Day 1 and was expected to continue taking the drug without dose changes throughout the study. The use of common cold preparations was permitted. The use of zaleplon or zolpidem for sleep was permitted up to 10 mg at bedtime, 3 times per week for the first 14 days of treatment. Subjects were instructed not to take cold preparations, zaleplon, or zolpidem within 24 hours before and study visit. Supportive non-behavioral psychotherapy was permitted, if there had been no change in intensity or frequency within 180 days before study Day 1 and no change had occurred for the duration of the study. Other treatments were permitted if not specifically prohibited.

Prohibited medications are listed in the table below. All treatments prohibited before study day 1 were also prohibited during the trial. In addition, MAOIs could not have been taken within the 7 days after discontinuing use of study drug. For some subjects, it may have been necessary to prescribe an antidepressant medication (other than an MAOI) after the last dose of study medication (at Day 56 or at early discontinuation), but before study drug had been completely discontinued.

Table 2.4.4 Prohibited Medications

Prohibited Treatments	Days before Study Day 1					Post Rx
	7	14	30	90	180	7
Sedative-hypnotics (except zaleplon or zolpidem)	x					
Herbal drugs for anxiety, insomnia, depression	x					
Other psychotropic drugs or substances	x					
Nonpsychopharm drugs w/ psychotropic effects	x					
Antidepressants (except fluoxetine & venlafaxine		x				
Monoamine oxidase inhibitors		x				x
Anxiolytics (benzodiazepine & nonbenzodiazepine)		x				
Triptans		x				
Investigational drugs or procedures			x			
Antipsychotics			x			
Fluoxetine			x			
Venlafaxine				x		
Electroconvulsive therapy					x	
Formal psychotherapy					x	

2.4.5 Efficacy Analysis

2.4.5.1 Primary Efficacy Analysis

The primary analysis was the mean change from baseline for the HAM-D-17 score at the final on-therapy evaluation. This was analyzed using an analysis of covariance (ANCOVA) with treatment and site as factors and baseline HAMD-17 scores as covariate. The assumptions of the ANCOVA models were evaluated at the final on-therapy evaluation based on the primary efficacy variable. The test of homoscedasticity was performed with the Levene test. If the assumption of homoscedasticity was not met, a non-parametric ANCOVA based on ranked data was performed. An interaction term using the covariate and treatment was added to the primary model to test parallelism. If the assumption of parallelism was violated, the covariate was removed from the model, and an ANOVA with treatment and site as factors was performed. The sponsor notes that in studies with large sample sizes, ANCOVA is robust even when normality is violated. Thus, normality was not tested.

Closed testing procedures were performed to compare the primary efficacy results of the two doses of desvenlafaxine (50 and 100 mg) with placebo, as measured by the change in mean HAMD-17 scores from baseline. A general linear model with multiple contrast statements was used to calculate F-statistics for the global null hypothesis and all intersection hypotheses. The closure principle was used to determine which hypothesis should be retained or rejects at $\acute{\alpha} = 0.05$.

If a significant treatment effect was detected for one or both dose of desvenlafaxine, then a sequential testing method was applied to the dose(s) as follows: for one or both DVS dose group(s), if a significant from placebo on the primary efficacy variable was noted using the closed testing procedure, the key secondary efficacy variable was tested at the 0.05 level, in order to compare the DVS dose(s) with placebo.

The HAMD-17 mean score change from baseline was also analyzed using a mixed effects model, with treatment, time, and the interaction of treatment and time as fixed effects, baseline HAMD-17 score as covariate, and site as a random effect. An auto-regression of the first order (AR (1)) covariance matrix was used to model the within-subject errors. In addition, the sponsor also used the ETRANK method to analyze the HAMD-17 results. The ETRANK method corrects for missing data patterns.

2.4.5.2 Key Secondary Efficacy Variable Analysis

The sponsor pre-specified the CGI-I score as the key secondary efficacy variable. Sequential testing was applied to the CGI-I. The order of testing was to first test the HAMD-17. If a desvenlafaxine treatment group (DVS dose) was significantly different from placebo on the HAMD-17 primary analysis, then the CGI-I findings were analyzed. The CGI-I score was analyzed as a categorical variable using the Cochran-Mantel-Haenszel test, with treatment as the factor, controlling for site. The ridit scoring scheme was used, which yields a non-parametric analysis. Mean CGI-I scores were also analyzed by ANOVA, with treatment and site as factors.

2.4.5.3 Other Secondary Efficacy Analyses

Changes in mean scores on the HAMD-6, MADRS, Covi Anxiety Scale, CGI-S, and VAS-PI were evaluated using ANOVA, with treatment and site as factors and the baseline values as the covariate.

Remission, defined as a HAMD-17 score of ≤ 7 was analyzed using a logistic regression model, with treatment and site as factors and the baseline HAMD-17 score as the covariate. Response was defined as a decrease of $\geq 50\%$ on the HAMD-17. The response rate was analyzed with the logistic regression model, with treatment and site as factors and baseline HAMD-17 score as a covariate.

Subjects who had a CGI-I score of 1 or 2 were also classified as responders. The CGI-I data were analyzed with the logistic regression model, with treatment and site as factors. A second model with treatment-by-site interaction as an additional factor was performed to explore the possibility of a treatment-by-site interaction.

Response, as measured by the MADRS, was defined as a decrease of $\geq 50\%$ on the MADRS from baseline. The response rate on the MADRS was analyzed with the logistic regression model, with treatment and site as factors and baseline MADRS score as a covariate.

Efficacy analyses for the secondary variables were conducted at each time point using the LOCF technique and observed-cases data. The sponsor did not adjust for multiplicity for any of the secondary efficacy variables.

2.5 Disposition of Subjects

2.5.1 Disposition in Studies 332 and 333

In Study 332, 16%, 23%, and 21% of subjects discontinued from the placebo, DVS 50 mg, and DVS 100 mg groups, respectively. In Study 333, 8%, 10%, and 13% of subjects discontinued from the placebo, DVS 50 mg, and 100 mg groups, respectively. These proportions are relatively low for an acute, controlled trial in Major Depressive Disorder. Furthermore, the proportions of discontinuations due to adverse events were low (3-7%); however, discontinuations due to adverse events were more common in the DVS 100 mg groups (7%) than in the placebo or DVS 50 mg groups (3-5%).

Table 2.5 Disposition and Reasons for Discontinuation in Studies 332 and 333

	Study 332			Study 333		
Reason for discontinuation	Placebo (n =152)	DVS 50 (n = 151)	DVS 100 (n = 148)	Placebo (n = 161)	DVS 50 (n = 166)	DVS 100 (n = 158)
Total Discontinuations	25 (16)	34 (23)	31 (21)	13 (8)	17 (10)	20 (13)
Adverse event	4 (3)	5 (3)	11 (7)	5 (3)	8 (5)	11 (7)
Failed to return	6 (4)	15 (10)	11 (7)	0	0	2 (1)
Investigator request	0	1 (1)	0	0	0	2 (1)
Other event	3 (2)	2 (1)	3 (2)	1 (1)	0	0
Protocol violation	1 (1)	2 (1)	0	1 (1)	4 (2)	0
Subject request unrelated to study	6 (4)	9 (6)	5 (3)	1 (1)	3 (2)	4 (3)
Lack of Efficacy	5 (3)	0	1 (1)	5 (3)	2 (1)	1 (1)

2.6 Efficacy Results for Studies 332 and 333

2.6.1 Sponsor's Efficacy Results

The table below summarizes the results of the sponsor's efficacy analyses. In the sponsor's primary LOCF analyses, the overall comparison for DVS (the 50 mg and 100 mg dose groups combined) versus placebo is statistically significant, favoring treatment with DVS ($p= 0.046$ and $p< 0.001$ in studies 332 and 333, respectively).

In Study 332, the apparent treatment effect for the 50 mg group (-11.5 points on the HAMD) compared to placebo (-9.53) was statistically significant ($p= 0.018$). The estimated size of the treatment effect (-1.97 points on the HAMD) was modest. However, for the 100 mg group, the modest estimated size of the treatment effect compared to placebo (-1.47 points) was not statistically significant ($p= 0.065$).

In Study 333, the treatment effects in both DVS dose groups were statistically significant. The estimated treatment effects, while modest, were larger than those in Study 332. For the 50 mg group, the treatment effect was -2.5 points on the HAMD ($p= 0.002$). For the 100 mg group, the treatment effect was -3.0 points on the HAMD ($p< 0.001$).

Table 2.6.1.1 Summary of Sponsor's Efficacy Analysis Results for the Primary Endpoint, Change from Baseline in HAM-D_{17} Score

Analysis		Study 332			Study 333		
		Placebo	DVS SR 50 mg	DVS SR 100 mg	Placebo	DVS SR 50 mg	DVS SR 100 mg
Final On-Therapy Evaluation (LOCF)	N	150	150	147	161	164	158
	LSM[1]	-9.53	-11.5	-11.0	-10.7	-13.2	-13.7
	P-Value[2]		0.018	0.065		0.002	<0.001
	P-Value[3]	0.046			<0.001		
OC Analysis	N	115	104	102	138	145	126
	LSM[1]	-10.0	-12.1	-11.9	-11.6	-14.7	-15.2
	P-Value[2]		0.026	0.047		<0.001	<0.001
	P-Value[3]	0.049			<0.001		
MMRM Analysis	N	115	104	102	138	145	126
	LSM[1]	-9.86	-12.40	-11.88	-11.49	-14.37	-14.91
	P-Value[2]		<0.001	0.006		<0.001	<0.001
	P-Value[3]	Not Available			Not Available		

[1] LSM stands for least square mean
[2] These P-Values are for the comparisons with placebo
[3] This P-Value is for the overall comparison

As illustrated in the table above, studies 332 and 333 were also positive in the pre-specified, non-primary observed case (OC) analysis and mixed models-repeated measures (MMRM) analysis for DVS overall as well as for the 50 mg and 100 mg dose groups. In the OC analysis for Study 332, the effect size was −2.1 (p= 0.026) for the 50 mg dose group and −1.9 (p= 0.047 for the 100 mg dose group. In the OC analysis for Study 333, the effect size was 3.1 (p< 0.001) and −3.6 (p< 0.001) for the 50 mg and 100 mg dose groups, respectively. In the MMRM analysis for Study 332, the effect sizes were −2.54 (p< 0.001) and −2.02 (p= 0.006) in the 50 mg and 100 mg groups, respectively. For the MMRM analysis in Study 333, the effect sizes were −2.88 (p< 0.001) and 3.42 (p< 0.001) in the 50 mg and 100 mg dose groups, respectively.

Thus, these results provide supportive evidence for the efficacy of 50 mg and 100 mg DVS fixed-dose treatment. As in the primary analysis, the estimated sizes of the DVS treatment effects were modest in OC and MMRM analyses. However, these estimated effect sizes are similar to those in controlled trials of antidepressants in Major Depressive Disorder.

The tables below illustrates the changes over time in adjusted mean HAMD-17 scores for the DVS 50 mg, DVS 100 mg, and placebo groups. The analysis did not adjust for multiplicity. Table 2.6.2 illustrates that changes in mean HAMD score were statistically significant for the 50 mg dose group at Weeks 4, 6, 8 and at the final on-therapy visit. However, the results of the overall DVS (combined dose groups) analysis were positive only for Weeks 6 and 8 as well as for the final on-therapy analysis. For the 100 mg dose group in Study 332, the changes in mean HAMD scores compared to the placebo group were not statistically significant at any time point. In Study 333, (as illustrated in table 2.6.3), the treatment effect for the 50 mg dose group was statistically significant for

Weeks 6, 8, and at the final on-therapy endpoint. For the 100 mg dose group, the treatment effect was statistically significant at Weeks 4, 6, 8, and for the final on-therapy visit.

Table 2.6.1.2 Study 332: Sponsor's results for changes in HAMD-17 score over time for the (ANCOVA) LOCF Analysis

Week of Therapy	Therapy Group	n	Raw Mean Score	Adj Change From Baseline	Std Error	Adj Means (95% CI)	Diff Adj Mean (95% CI) vs Pbo.	Overall p-Value	p-Value vs DVS SR 50 mg	p-Val vs DVS 100 r
Baseline	Placebo	150	23.0			23.2 (23.2, 23.2)				
	DVS SR 50 mg	150	23.4			23.2 (23.2, 23.2)				
	DVS SR 100 mg	147	23.4			23.2 (23.2, 23.2)				
Week 1	Placebo	147	19.2	-3.81	0.37	19.4 (18.7, 20.2)		0.416	0.331	0.767
	DVS SR 50 mg	147	19.1	-4.31	0.37	18.9 (18.2, 19.7)	0.5 (-0.5, 1.5)			0.206
	DVS SR 100 mg	143	19.7	-3.65	0.38	19.6 (18.9, 20.3)	-0.2 (-1.2, 0.9)			
Week 2	Placebo	149	17.6	-5.45	0.43	17.8 (17.0, 18.6)		0.368	0.205	0.240
	DVS SR 50 mg	150	17.2	-6.20	0.42	17.0 (16.2, 17.9)	0.8 (-0.4, 1.9)			0.931
	DVS SR 100 mg	146	17.2	-6.15	0.43	17.1 (16.3, 17.9)	0.7 (-0.5, 1.9)			
Week 3	Placebo	149	15.9	-7.08	0.48	16.2 (15.2, 17.1)		0.344	0.147	0.387
	DVS SR 50 mg	150	15.3	-8.06	0.48	15.2 (14.2, 16.1)	1.0 (-0.3, 2.3)			0.559
	DVS SR 100 mg	147	15.7	-7.66	0.48	15.6 (14.6, 16.5)	0.6 (-0.7, 1.9)			
Week 4	Placebo	150	15.5	-7.61	0.50	15.6 (14.7, 16.6)		0.065	0.019	0.269
	DVS SR 50 mg	150	14.1	-9.25	0.50	14.0 (13.0, 15.0)	1.6 (0.3, 3.0)			0.219
	DVS SR 100 mg	147	15.0	-8.39	0.50	14.9 (13.9, 15.8)	0.8 (-0.6, 2.2)			
Week 6	Placebo	150	14.3	-8.86	0.53	14.4 (13.4, 15.4)		0.039	0.013	0.080
	DVS SR 50 mg	150	12.7	-10.7	0.53	12.5 (11.5, 13.6)	1.8 (0.4, 3.3)			0.469
	DVS SR 100 mg	147	13.2	-10.2	0.54	13.1 (12.0, 14.1)	1.3 (-0.2, 2.8)			
Week 8	Placebo	150	13.9	-9.34	0.58	13.9 (12.8, 15.0)		0.020	0.006	0.053
	DVS SR 50 mg	150	11.9	-11.5	0.58	11.7 (10.6, 12.8)	2.2 (0.6, 3.8)			0.430
	DVS SR 100 mg	147	12.6	-10.9	0.58	12.3 (11.2, 13.5)	1.6 (-0.0, 3.2)			
Final	Placebo	150	13.7	-9.53	0.58	13.7 (12.6, 14.9)		0.046	0.018	0.065
	DVS SR 50 mg	150	12.0	-11.5	0.58	11.8 (10.6, 12.9)	1.9 (0.3, 3.5)			0.604
	DVS SR 100 mg	147	12.4	-11.0	0.59	12.2 (11.1, 13.4)	1.5 (-0.1, 3.1)			

Table 2.6.1.3 Study 333: Sponsor's results for changes in HAMD-17 score over time for the (ANCOVA) LOCF Analysis

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) Vs Placebo.	Overall p-Value	p-Value Vs DVS SR 50 mg	p-Value Vs DVS SR 100 mg
LOCF	Baseline	Placebo	161	24.3			24.3 (24.3, 24.3)				
		DVS SR 50 mg	164	24.3			24.3 (24.3, 24.3)				
		DVS SR 100 mg	158	24.4			24.3 (24.3, 24.3)				
	Week 1	Placebo	156	21.6	-2.64	0.29	21.7 (21.1, 22.3)		0.788	0.977	0.542
		DVS SR 50 mg	162	21.6	-2.63	0.29	21.7 (21.1, 22.3)	-0.0 (-0.8, 0.8)			0.557
		DVS SR 100 mg	156	22.0	-2.40	0.29	21.9 (21.4, 22.5)	-0.2 (-1.0, 0.5)			
	Week 2	Placebo	161	18.8	-5.53	0.42	18.8 (18.0, 19.6)		0.629	0.386	0.942
		DVS SR 50 mg	164	18.2	-6.03	0.42	18.3 (17.5, 19.1)	0.5 (-0.6, 1.6)			0.429
		DVS SR 100 mg	158	18.8	-5.57	0.42	18.8 (17.9, 19.6)	0.0 (-1.1, 1.2)			
	Week 3	Placebo	161	16.3	-7.93	0.47	16.4 (15.5, 17.3)		0.252	0.168	0.136
		DVS SR 50 mg	164	15.4	-8.81	0.47	15.5 (14.6, 16.4)	0.9 (-0.4, 2.1)			0.898
		DVS SR 100 mg	158	15.4	-8.89	0.48	15.4 (14.5, 16.4)	1.0 (-0.3, 2.2)			
	Week 4	Placebo	161	14.9	-9.17	0.52	15.2 (14.1, 16.2)		0.043	0.103	0.014
		DVS SR 50 mg	164	13.8	-10.3	0.51	14.0 (13.0, 15.0)	1.1 (-0.2, 2.5)			0.389
		DVS SR 100 mg	158	13.3	-10.9	0.52	13.4 (12.4, 14.4)	1.7 (0.4, 3.1)			
	Week 6	Placebo	161	14.1	-10.0	0.57	14.3 (13.2, 15.4)		0.002	0.002	0.002
		DVS SR 50 mg	164	11.7	-12.4	0.56	11.9 (10.8, 13.0)	2.3 (0.8, 3.8)			0.937
		DVS SR 100 mg	158	11.8	-12.4	0.57	11.9 (10.8, 13.0)	2.4 (0.9, 3.9)			
	Week 8	Placebo	161	13.3	-10.7	0.60	13.7 (12.5, 14.8)		<0.001	0.003	<0.001
		DVS SR 50 mg	164	10.9	-13.1	0.60	11.2 (10.0, 12.4)	2.4 (0.9, 4.0)			0.511
		DVS SR 100 mg	158	10.5	-13.7	0.61	10.7 (9.5, 11.9)	3.0 (1.4, 4.6)			
Final on-therapy	Final	Placebo	161	13.3	-10.7	0.61	13.7 (12.5, 14.8)		<0.001	0.002	<0.001
		DVS SR 50 mg	164	10.9	-13.2	0.60	11.2 (10.0, 12.3)	2.5 (0.9, 4.1)			0.498
		DVS SR 100 mg	158	10.4	-13.7	0.61	10.6 (9.4, 11.8)	3.0 (1.4, 4.7)			

The table below summarizes the statistical reviewer's efficacy results for studies 332 and 333. The source of the analysis and the table is the statistical review by Yeh-Fong-Chen, Ph.D.

2.6.2 FDA Statistics Reviewer's Efficacy Results

Yeh-Fong Chen, Ph.D conducted the statistical review of studies 332 and 333. Dr. Chen's results differ somewhat from the sponsor's, since she excluded a subset of subjects from the primary analysis for each of the studies. Dr. Chen noted that some subjects had efficacy data collected during unscheduled visits that occurred at time points outside of the pre-specified allowable window of +/− 3 days from the date of a scheduled visit. Visits were scheduled for Weeks 2, 4, 6, and 8. However, some subjects had visits at Week 5 and/or Week 7, instead of at Weeks 6 and 8. In Study 332, 9% of subjects had Week 5 assessments, and 7% of subjects had Week 7 assessments. In Study 333, between 5% and 10% of subjects had assessments at Week 5 and/or Week 7 instead of Week 6 and/or Week 9. Dr. Chen excluded data for these subjects from the analysis and then performed the primary and non-primary efficacy analyses using the data from the remaining subjects.

As illustrated in Dr. Chen's results table below, Study 332 was no longer positive ($p= 0.54$) for the overall DVS primary analysis (ANCOVA/LOCF). Thus, by the pre-specified closed testing plan, the individual doses could not be analyzed formally. There was a modest difference between the DVS 50 mg and placebo groups (−1.92 points on the HAMD). Similarly, there was a moderate difference between the 100 mg and placebo groups (−1.39).

In Dr. Chen's MMRM re-analysis (with unstructured covariance) of Study 332, the results remain positive; although, the degree of statistical significance is smaller than in the sponsor's MMRM analysis. The overall comparison between the DVS and placebo groups yields a statistically significant result ($p= 0.02$), favoring treatment with DVS. The treatment effect for DVS 50 mg compared to placebo (−2.65) was statistically significant ($p= 0.003$). The treatment effect for DVS 100 mg compared to placebo (−1.92) was also statistically significant ($p= 0.03$). Thus, Dr. Chen's MMRM analysis provides supportive evidence for the efficacy of DVS 50 mg and 100 mg in Study 332.

In her analysis of Study 333, Dr. Chen concluded that Study 333 remained positive overall ($p= 0.001$), as well as for the 50 mg and 100 mg dose groups individually ($p= 0.004$ and $p< 0.001$, respectively) in the primary LOCF analysis. The treatment effects for the 50 mg and 100 mg groups compared to placebo were -2.38 and -2.87 points, respectively. These effect sizes are modest; however, they are larger than those in Study 332. In the MMRM re-analysis, the treatment effect for the overall DVS group was statistically significant ($p= 0.006$). Furthermore, the treatment effects for the 50 mg and 100 mg groups were statistically significant (-2.78; $p< 0.001$; and -3.43; $p< 0.001$, respectively. Thus, the results of Dr. Chen's analyses provides evidence for the efficacy of DVS

Table 2.6.2.1 Summary of Reviewer's Analysis Results for the Primary Endpoint, Change from Baseline in HAM-D_{17} Score

Analysis		Study 332			Study 333		
		Placebo	DVS SR 50 mg	DVS SR 100 mg	Placebo	DVS SR 50 mg	DVS SR 100 mg
Final On-Therapy Evaluation	N	150	150	147	161	164	158
	LSM[1]	-9.57	-11.49	-10.96	-10.78	-13.16	-13.65
	P-Value[2]		0.02	0.09		0.004	<0.001
	P-Value[3]	0.054			0.001		
MMRM Analysis	N	115	104	102	138	145	126
	LSM[1]	-9.81	-12.46	-11.73	-11.47	-14.25	-14.90
	P-Value[2]		0.003	0.03		<0.001	<0.001
	P-Value[3]	0.02			0.006		

[1] LSM stands for least square mean
[2] These P-Values are for the comparisons with placebo
[3] This P-Value is for the overall comparison

2.6.3 Secondary Efficacy Analyses Results

2.6.3.1 Key Secondary Efficacy Results

For both studies, the key secondary endpoint was the change in CGI-I score at the final on-therapy visit. CGI-I scores are rated from 1 (very much improved) to 7 (very much worse). In Study 332, the change in mean CGI-I score (compared to the placebo group) was not statistically significant for either the 50 mg or the 100 mg dose groups (p= 0.079 and 0.057, respectively). In contrast, for Study 333, the changes in the final on-therapy CGI-I scores differed statistically significantly for the DVS 50-mg group (p= 0.002) and the 100-mg (p<0.001) groups, compared with the placebo group. At the final on-therapy evaluation, the proportion of subjects with CGI-I scores of 1 (very much improved) or 2 (much improved) was 73% in the DVS 50-mg and DVS 100-mg groups compared with 53% in the placebo group.

Table 2.6.3.1.1 Sponsor's Analysis Results for Secondary Endpoint CGI-I based on the LOCF data for Study 332

Week of Therapy	Therapy Group	n	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	p-value vs. placebo
Week 8	Placebo	150	31 (20.7)	37 (24.7)	42 (28.0)	38 (25.3)	2 (1.3)	–
	DVS SR 50 mg	150	48 (32.0)	36 (24.0)	39 (26.0)	22 (14.7)	5 (3.3)	0.033
	DVS SR 100 mg	147	42 (28.6)	39 (26.5)	38 (25.9)	27 (18.4)	1 (0.7)	0.038
Final	Placebo	150	33 (22.0)	37 (24.7)	41 (27.3)	37 (24.7)	2 (1.3)	–
	DVS SR 50 mg	150	48 (32.0)	35 (23.3)	39 (26.0)	23 (15.3)	5 (3.3)	0.079
	DVS SR 100 mg	147	45 (30.6)	37 (25.2)	36 (24.5)	27 (18.4)	2 (1.4)	0.057

Source: Sponsor's Table 9-3 of CSR

Table 2.6.3.1.2 Sponsor's Analysis Results for Secondary Endpoint CGI-I based on the LOCF data for Study 333

Week of Therapy	Therapy Group	n	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	p-value vs. placebo
Week 8	Placebo	161	56 (34.8)	31 (19.3)	40 (24.8)	24 (14.9)	5 (3.1)	5 (3.1)	–
	DVS SR 50 mg	164	78 (47.6)	41 (25.9)	22 (13.4)	14 (8.5)	6 (3.7)	3 (1.8)	0.003
	DVS SR 100 mg	158	82 (51.9)	34 (21.5)	22 (13.9)	17 (10.8)	3 (1.9)		<0.001
Final	Placebo	161	56 (34.8)	30 (18.6)	40 (24.8)	25 (15.5)	5 (3.1)	5 (3.1)	–
	DVS SR 50 mg	164	79 (48.2)	40 (24.4)	21 (12.8)	15 (9.1)	6 (3.7)	3 (1.8)	0.002
	DVS SR 100 mg	158	82 (51.9)	34 (21.5)	22 (13.9)	17 (10.8)	3 (1.9)		<0.001

Source: Sponsor's Table 9-3 of CSR

3. Safety Analysis for Studies 332 and 333

3.1 Summary of Safety Findings in Studies 332 and 333

In studies 332 and 333, desvenlafaxine doses of 50 mg and 100 mg per day were safe and well tolerated. Compared to previous DVS studies using doses of 100, 200, and 400 mg, there were no new or unexpected safety findings in studies 332 and 333. In fact, the safety profile of DVS 50 mg per day was more favorable than that of higher doses of DVS. As indicated in previous studies, the occurrence of adverse events and safety concerns associated with DVS exposure are generally dose-related. Compared to DVS doses of 100-400 mg/day, treatment with 50 mg/day was associated with a lower risk of the following toxicities: elevated blood pressure, tachycardia, nausea, vomiting, anorexia, hyperlipidemia, proteinuria, asthenia, anxiety, insomnia, dizziness, sweating, blurred vision, mydriasis, and sexual dysfunction. Furthermore, a significantly smaller proportion of subjects treated with DVS 50 mg discontinued due to these adverse events, compared to subjects treated with DVS 100-400 mg/day.

3.2 Exposure Data from Studies 332 and 333

In Study 332, a total of 199 subjects were exposed to desvenlafaxine (151 were exposed to 50 mg/day, and 148 were exposed to 100 mg/day). In Study 333, a total of 324 subjects were exposed to desvenlafaxine (161 were exposed to 50 mg/day, and 158 were exposed to 100 mg/day). Thus, in the two studies combined, 317 subjects were exposed to 50 mg/day, and 306 subjects were exposed to 100 mg/day. Overall, the exposure to DVS 50 mg/day was 48.62 patient-years, and the exposure to DVS 100 mg/day was 47.01 patient-years. The total DVS exposure in the studies combined was 95.62 patient-years.

DVS exposure in patient-years for studies 332 & 333 (treatment and taper periods)								
	DVS 50 mg/d				DVS 100 mg/d			
Study	Double-blind		Taper		Double-blind		Taper	
	n	Pt-years	n	Pt-years	n	Pt-years	n	Pt-years
332	151	20.35	108	2.00	148	19.99	110	2.08
333	166	23.51	145	2.72	158	22.31	138	2.58

DVS exposure in patient-years for studies 332 and 333 combined (treatment and taper periods						
Study	DVS 50 mg/d		DVS 100 mg/d			
	n	Pt-years	n	Pt-years	n	Pt-years
332 + 333	317	48.62	306	47.01	623	95.62

3.3 Deaths in Studies 332 and 333

There were no deaths in any treatment group in either study.

3.4 Serious Adverse Events in Studies 332 and 333

There very were few serious adverse events in the studies. Furthermore, most of the serious adverse events were not related to treatment with desvenlafaxine. In the desvenlafaxine group, 9 (1.4%) subjects had a total of 11 serious adverse events. In the placebo group, two (0.6%) subjects had a serious adverse event. There were no new or unexpected serious adverse events reported with exposure to desvenlafaxine.

In the desvenlafaxine 50 mg group, the SAE were: thrombosis (lower limb), migraine, depression (2), and suicidal ideation. In the desvenlafaxine 100 mg group, the SAE were: intentional overdose (2), suicide attempt, elevated serum transaminase, hypotension, and lumbar disk herniation. The SAE probably related to desvenlafaxine exposure included elevated serum transaminase, hypotension, and migraine. The SAE in the placebo group were intestinal obstruction and womb infection (the narrative was extremely limited; it was essentially a line listing that stated "womb infection").

3.5 Discontinuations Due to Adverse Events in Studies 332 and 333

The proportion of subjects who discontinued due to an adverse event was relatively small. Approximately 4% of the DVS group and 3% of the placebo group discontinued due to adverse events. A higher proportion of the DVS 100 mg group (7%) discontinued due to an adverse event, compared to the DVS 50 mg group (4%). The most common adverse events leading to discontinuation in the desvenlafaxine group were nausea (1.4%), anxiety (0.8%), insomnia (0.6%), headache (0.6%), vomiting (0.5%), sweating (0.5%), and depression (0.5%). As illustrated in the table below, the remaining adverse events associated with discontinuation in the DVS group were reported for $\leq$ 0.3% of subjects. The adverse events probably related to treatment with DVS include the following: nausea, anxiety, insomnia, headache, vomiting, sweating, asthenia, dizziness, orgasm abnormality (for men and women), vertigo, and paresthesia. There were no new or unexpected adverse events associated with discontinuation from the study.

Table 3.4.1 Discontinuations due to AE for 332 and 333 combined

Body system/ DC-Adverse event	Placebo N = 313	DVS 50 mg N = 317	DVS 100 mg N = 306	DVS total N = 623
Any DC-adverse event	9 (2.9)	13 (4.1)	22 (7.2)	25 (4)
Nausea	2 (0.6)	2 (0.6)	7 (2.3)	9 (1.4)
Anxiety	0	1 (0.3)	4 (1.3)	5 (0.8)
Insomnia	0	2 (0.6)	2 (0.7)	4 (0.6%)
Headache	1 (0.3)	1 (0.3)	3 (1)	4 (0.6%)
Vomiting	0	2 (0.6)	1 (0.3)	3 (0.5)
Sweating	0	2 (0.6)	1 (0.3)	3 (0.5)
Depression	0	2 (0.6)	1 (0.3)	3 (0.5)
Suicidal ideation	0	2 (0.6)	0	2 (0.3)
Somnolence	0	2 (0.6)	0	2 (0.3)
Abdominal pain	2 (0.6)	1 (0.3)	1 (0.3)	2 (0.3)
Asthenia	0	0	2 (0.7)	2 (0.3)
Dizziness	0	1 (0.3)	1 (0.3)	2 (0.3)
Orgasm abnormality	0	0	2 (0.7)	2 (0.3)
Suicide attempt	0	0	1 (0.3)	1 (0.2)
Intentional overdose	0	0	1 (0.3)	1 (0.2)
Hypertension	2 (0.6)	0	1 (0.3)	1 (0.2)
Bradycardia	0	1 (0.3)	0	1 (0.2)
Anorexia	0	1 (0.3)	0	1 (0.2)
Constipation	1 (0.3)	1 (0.3)	0	1 (0.2)
Diarrhea	0	1 (0.3)	0	1 (0.2)
Gastritis	0	1 (0.3)	0	1 (0.2)
Depersonalization	0	0	1 (0.3)	1 (0.2)
Vertigo	0	0	1	1 (0.2)
Hostility	1 (0.3)	1 (0.3)	0	1 (0.2)
Apathy	0	0	1 (0.3)	1 (0.2)
Paresthesia	0	0	1 (0.3)	1 (0.2)
Libido decreased	0	0	1 (0.3)	1 (0.2)

3.6 Common Adverse Events in Studies 332 and 333 Combined

The table below illustrates the most common adverse events reported in studies 332 and 333. The majority of common, drug-related adverse events consisted of central nervous system, gastrointestinal symptom, and sexual function adverse events. The pattern of drug-related adverse events are essentially the same as that in the earlier DVS studies. The most common drug-related CNS adverse events were insomnia, dizziness, asthenia, anxiety, and somnolence. The most common gastrointestinal system adverse events were nausea, vomiting, dry mouth, diarrhea, and constipation.

Table 3.6.1 Common Adverse Events ≥ 2% Studies 332 and 333 combined from Safety Update

	Placebo N = 313	DVS 50 mg N = 317	DVS 100 mg N = 306	DVS total N = 623
Cardiovascular				
Hypertension	4 (1)	8 (3)	8 (3)	16 (3)
Palpitation	4 (1)	3 (1)	7 (2)	10 (2)
Gastrointestinal				
Nausea	33 (11)	69 (22)	71 (23)	140 (22)
Dry mouth	21 (7)	37 (12)	50 (16)	87 (14)
Diarrhea	29 (9)	35 (11)	18 (6)	53 (9)
Constipation	12 (4)	27 (9)	24 (8)	51 (8)
Anorexia	9 (3)	18 (6)	24 (8)	42 (7)
Abdominal pain	21 (7)	24 (8)	21 (7)	45 (7)
Dyspepsia	9 (3)	10 (3)	9 (3)	19 (3)
Vomiting	11 (4)	9 (3)	9 (3)	18 (3)
Nervous system				
Insomnia	14 (5)	37 (12)	34 (11)	71 (11)
Dizziness	12 (4)	42 (13)	21 (7)	63 (10)
Headache	53 (17)	62 (20)	67 (22)	129 (21)
Asthenia	13 (4)	26 (8)	26 (9)	52 (8)
Somnolence	15 (5)	19 (6)	27 (9)	46 (7)
Anxiety	6 (2)	9 (3)	20 (7)	29 (5)
Nervousness	4 (1)	6 (2)	10 (3)	16 (3)
Abnormal dreams	9 (3)	12 (4)	10 (3)	22 (4)
Libido decreased	2 (1)	7 (2)	9 (3)	16 (3)
Vertigo	1 (0.3)	7 (2)	5 (2)	12 (2)
Hostility	5 (2)	7 (2)	8 (3)	15 (2)
Tremor	5 (2)	6 (2)	8 (3)	14 (2)
Paresthesia	5 (2)	6 (2)	8 (3)	14 (2)
Other Systems				
Sweating	15 (5)	30 (10)	35 (11)	65 (10)
Abnormal vision (mydriasis/blurred)	4 (1)	10 (3)	9 (3)	19 (3)
Abnormal ejaculation/orgasm	0	4 (1)	9 (3)	13 (2)
Impotence (men)	0	3 (3)	6 (5)	9 (1)

3.7 Vital Signs Findings in Studies 332 and 333

In studies 332 and 333, treatment with 50 mg and 100 mg per day was associated with only a small number of subjects who had blood pressure and pulse rate elevations that were in the potentially clinically significant range. There were no serious adverse events associated with elevations of blood pressure and heart rate. In both studies for both dose levels, there were modest increases in mean systolic and diastolic blood pressure. For the 50 mg dose group, the maximum increase in mean systolic blood pressure (compared to placebo) was 3.3 mm Hg. The maximum increase in mean diastolic blood pressure was 2.1 mm Hg. In the 100 mg group, the maximum increase in mean systolic blood pressure was 3.7 mm Hg, and the maximum increase in mean diastolic blood pressure was 2.0 mm Hg. In the DVS studies overall, the increases in blood pressure were clearly dose-related.

Treatment with 50 mg was associated with the smallest increases in blood pressure compared with higher DVS doses.

3.8 ECG Findings in Studies 332 and 333

In studies 332 and 333, there were no important ECG findings. There were no individual ECG findings that were clinically significant. Furthermore, there were no mean ECG findings in the DVS group that were significantly different from those in the placebo group.

3.9 Clinical Laboratory Findings in Studies 332 and 333

There were few subjects in studies 332 and 333 who had clinical laboratory findings that were in the range considered potentially clinically significant. Consistent with laboratory findings in previous DVS studies, some subjects had such elevations of serum AST, ALT, cholesterol, and triglyceride concentrations. In addition, a number of subjects had proteinuria. As in previous DVS studies, there were also increases in mean transaminase, cholesterol, and triglyceride concentrations.

3.9.1 Liver Function Test Findings

Potentially clinically significant serum AST elevations ($\geq$ 3 times the upper limit of normal) occurred in 0.6%, 0.4%, and 0 subjects in the placebo, DVS 50 mg, and DVS 100 mg groups, respectively. Serum ALT elevations occurred in 0.4%, 1.5%, and 0.3% of the placebo, DVS 50 mg, and DVS 100 mg groups, respectively. Elevation of serum total bilirubin concentration occurred in 1.1%, 0, and 0.3% of the placebo, DVS 50 mg, and DVS 100 mg groups, respectively. There were no cases of abnormal liver function test abnormalities meeting criteria of Hy's rule. There were no serious adverse events associated with abnormalities of liver function tests.

In studies 332 and 333, treatment with DVS was associated with small increases in mean serum transaminase levels (AST and ALT); however, the increases (< 5%) were not clinically significant. The mean bilirubin concentrations decreased in the DVS groups.

3.9.2 Cholesterol and Triglyceride

Potentially clinically significant elevations of serum total cholesterol concentration occurred in 2.2%, 3.3%, and 3.8% of the placebo, DVS 50 mg, and DVS 100 mg groups, respectively. Potentially clinically significant elevations of serum LDL concentrations occurred in 0, 0.9%, and 0 of the placebo, DVS 50 mg, and DVS 100 mg groups, respectively. Potentially clinically significant elevations of serum triglyceride occurred in 2.8%, 2.1%, and 0.9% of the placebo, DVS 50 mg, and DVS 100 mg groups, respectively.

Generally, the changes in mean serum cholesterol and triglyceride concentrations were minimal in studies 332 and 333. For the placebo group, the mean serum total cholesterol decreased by 2.7%. In contrast the mean total cholesterol increased by 1.3% and 0.2% in the DVS 50 mg and DVS 100 mg groups, respectively. The mean serum LDL concentration changed by −4.3%, +0.6%, and −0.4% in the placebo, DVS 50 mg, and DVS 100 mg groups, respectively. The mean serum triglyceride concentration changed by +1%, +5%, and −1.6% in the placebo, DVS 50 mg, and DVS 100 mg groups, respectively. Thus, the changes in mean serum lipid concentrations were not clinically significant.

3.9.3 Proteinuria

As in previous studies DVS studies, treatment with DVS in studies 332 and 333 was associated with proteinuria in a dose-related manner. In the placebo group, 3.5% of subjects had proteinuria. In the DVS 50 mg and 100 mg groups, 6.4% and 7.7% of subjects had proteinuria, respectively.

4.0 Review of the Safety Update

4.1 Primary Components of the Safety Update

The central components of the safety update include the following:

1. Safety data from studies 332 and 333
2. Integrated summaries and tables combining data from the new fixed dose studies with safety data from previous fixed dose studies
3. Additional exposure and safety data from: 1) maintenance study 302, a placebo-controlled, randomized withdrawal study of 200 mg/day and 400mg/day versus placebo; and 2) data from Study 303, a 10-month, open-label study.
4. Integrated updates by study type (controlled fixed and flexible-dose vs. open-label vs. randomized withdrawal) and dose-level (50, 100, 200, and 400 mg/day fixed and flexible doses). This includes updates for study drug exposure and all safety parameters (deaths, serious adverse events, AE leading to discontinuations, common and less common AE and drug-related AE, vital signs, ECG, and clinical laboratory findings).

4.2 Updated Cumulative Desvenlafaxine Exposures

Overall in the desvenlafaxine MDD studies, a total of 3,292 subjects were exposed to DVS for a total of 1,289.4 person-years. In the placebo-controlled trials combined, there were 1,834 subjects exposed to desvenlafaxine for a total of 252.9 person-years. In the 50 mg fixed-dose group, a total of 317 subjects were exposed to DVS for a total of 43.9 person-years. In the 100 mg fixed-dose group, there were 424 subjects exposed to DVS for a total of 57.3 person-years. In the 200 mg group, there were 307 subjects with a total exposure of 38.5 person-years. A total of 317 subjects were exposed to fixed-doses of 400 mg for a total of 39.4 person-years.

The DVS exposures for the long-term extension studies and the randomized withdrawal maintenance trial are described below:

1. Exposures in the long-term extension studies:

    - DVS followed by DVS: 1,437 subjects for 660.71 subjects-years
    - Placebo followed by DVS: 525 subjects for 263.19 subject-years
    - Venlafaxine followed by DVS: 183 subjects for 112.45 subject-years

2. Maintenance study (302)

    - Open-label phase: 594 subjects for 108.82 subject-years
    - Double-blind treatment and taper periods: 190 subjects for 74.82 subject-years

4.3 Summary of Findings from the Safety Update

Information from the safety update did not reveal any new or unexpected findings with desvenlafaxine treatment. The new data consisted primarily of the safety data from studies 332 and 333. Generally, exposure to fixed doses of DVS 50 mg was safer and better tolerated than treatment with fixed doses of DVS 100 mg. Furthermore, the cumulative data for DVS fixed-doses (50, 100, 200, and 400 mg/day) indicate that virtually all of the drug-related toxicities of DVS occur in a dose-related manner. Thus, treatment with DVS 50 mg/day provides a more favorable safety and tolerability profile compared to higher fixed doses, on average.

5 Sponsor's Literature Review

The sponsor provided a list of references along with some of the full text articles. The references are listed in the appendix. The sponsor did not perform a literature review, a summary of the literature, or any safety analyses regarding the literature. I have read the references that were provided as either full-text articles or as abstracts. Essentially, the references not provide any new meaningful safety information.

The sponsor performed a literature search for published articles regarding desvenlafaxine in the treatment of Major Depressive Disorder and Vasomotor Symptoms associated with menopause for the period ending September 30, 2005. The citations listed focus on references in which DVS-233, WY-45233, or O-desmethylvenlafaxine (ODV) was directly studied, but does not include references that describe activities of DVS-233, WY-45233, or O-desmethylvenlafaxine in the presence of or resulting from the administration of venlafaxine.

The sponsor conducted a search of five major biomedical and pharmaceutical databases (MEDLINE, BIOSIS, Current Contents, Derwent Drug File, and EMBASE) through OVID, in addition to the Wyeth Product and Publications Database.

These databases provide complementary information resources and, at Wyeth, cover the time periods from 1996 to week 04 of September 2005 (MEDLINE); 1985 to week 43 of 2005 (BIOSIS); 1996 to week 43 of 2005 (Current Contents); 1964 to week 37 of 2005 (Derwent Drug File); 1988 to week 41 of 2005 (EMBASE); and week 01 of March 2003 to week 01 of October 2005 (Wyeth Product and Publications).

Identification and Credentials of Researcher Helen Kellar-Wood, PhD Senior Information Scientist II Research Information Management

Search Methodology The search criteria for Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-indexed Citations, BIOSIS Previews, Current Contents/Science Edition, Derwent Drug File, EMBASE, and Wyeth Products and Publications databases are listed below:

6. Conclusions and Recommendations

I recommend that the division take an approval action for NDA #21-992. The indication is desvenlafaxine for the treatment of Major Depressive Disorder in adults.

Results from studies 332 and 333 demonstrate that treatment with desvenlafaxine fixed-doses of 50 mg and 100 mg was efficacious and reasonably safe and well tolerated. In fact, treatment with desvenlafaxine 50 mg/day generally provided a significantly more favorable safety and tolerability profile, compared to treatment with desvenlafaxine doses of 100, 200, and 400 mg per day. Virtually all of the important drug-related adverse events associated with desvenlafaxine are dose-dependent. Results of studies 332 and 333 did not reveal any new or unexpected safety findings, compared to safety results of previous desvenlafaxine studies. Similarly, new data from the safety update did not reveal any new or unexpected findings.

The sponsor has submitted a complete response to the division's approvable action, and the components of the response are generally acceptable. There are a number of items in the sponsor's proposed labeling that will require modification. These items primarily consist of adverse events descriptions and summary tables. A detailed labeling review will be conducted and will be presented in a separate document.

8 Appendix

Literature References

Bibliographic Listings by Category the relevant publications are listed below by category.

1.3.1 Placebo-Controlled, Double-Blind Trials

Citations 1 to 3 refer to the same poster/abstract:

1. Parks V, Patat A, Behrle J, Parker V, Decours J. Safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ascending single doses of desvenlafaxine (DVS-233 SR) in healthy subjects. Clinical Pharmacol Ther. 2005;77(2, Suppl):P28.

2. Parks V, Patat A, Behrle JA, Troy SM, Decours JH. Safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ascending single oral doses of sustained-release desvenlafaxine succinate (DVS-SR) in healthy subjects. Clinical Pharmacol Ther. 2005;77(2, Suppl):P44.

3. Parks V, Patat A, Behrle J, Troy S, Decours JP. Safety, pharmacokinetcs (PK) and pharmacodynamics (PD) of ascending single oral doses of sustained release desvenlafaxine succinate (DVS-SR) in healthy subjects. Abstract and Poster presented at: American Society for Clinical Pharmacology and Therapeutics (ASCPT); Mar 2-5, 2005; Orlando, FL, USA.

Citations 5 and 6 refer to the same poster/abstract: 4. Richards LS, Behrle JA, Nichols AI, Fruncillo R, Paul J. An ascending multiple-dose study of the safety and pharmacokinetics of desvenlafaxine SR in healthy subjects. Abstract and Poster presented at: American Society for Clinical Pharmacology and Therapeutics (ASCPT); Mar 2-5, 2005; Orlando, FL, USA.

5. Richards LS, Behrle JA, Nichols AI, Fruncillo R, Paul J. An ascending multiple-dose study of the safety and pharmacokinetics of desvenlafaxine SR in healthy subjects. Clinical Pharmacol Ther. 2005;77(2, Suppl. S):P84.

1.3.2 Nonplacebo-Controlled, Double-Blind Trials No citations were found for non-placebo-controlled, double-blind trials.

1.3.3 Open-Label Trials

Citations 1 and 2 refer to the same poster/abstract: 1. Behrle JA, Nichols AI, McGrory S, Raible D. An open label, randomized, single dose, dose-proportionality study of oral doses of desvenlafaxine SR in healthy subjects. Abstract and Poster presented at: American Society for Clinical Pharmacology and Therapeutics (ASCPT); Mar 2-5, 2005; Orlando, FL, USA.

2. Behrle JA, Nichols AI, McGrory S, Raible D. An open label, randomized, single dose, dose-proportionality study of oral doses of desvenlafaxine SR in healthy subjects. Clinical Pharmacol Ther. 2005;77:P82.

Citations 3 and 4 refer to the same poster/abstract: 3. Nichols AI, Patat A, Baird-Bellaire S, Behrle JA, Chretien P. An open-label, randomized, cross-over study of the relative bioavailability of desvenlafaxine following oral administration of venlafaxine ER and sustained release desvenlafaxine in healthy subjects. Abstract and Poster presented at: American Society for Clinical Pharmacology and Therapeutics (ASCPT); Mar 2-5, 2005; Orlando, FL, USA.

4. Nichols AI, Patat A, Baird-Bellaire S, Behrle JA, Chretien P. An open-label, randomized, crossover study of the relative bioavailability of desvenlafaxine after oral administration of extended-release venlafaxine and sustained-release desvenlafaxine succinate in healthy subjects. Clinical Pharmacol Ther. 2005;77(2, Suppl):P86.

Citations 5 and 6 refer to the same poster/abstract: 5. Parker VD, Richards LS, Nichols AI, Behrle JA, Fruncillo R. The absolute bioavailability of an oral formulation of desvenlafaxine SR in healthy subjects. Abstract and Poster presented at: American Society for Clinical Pharmacology and Therapeutics (ASCPT); Mar 2-5, 2005; Orlando, FL, USA.

6. Parker VD, Richards LS, Nichols AI, Behrle JA, Fruncillo R. The absolute bioavailability of an oral formulation of desvenlafaxine SR in healthy subjects. Clinical Pharmacol Ther. 2005;77(2, Suppl):P47.

1.3.4 Review Articles

1. Bayes M, Rabasseda X, Prous JR. Gateways to clinical trials. Methods Find Exp Clin Pharmacol. 2005;27(5):331-72.

2. Dey M, Constantine GD. Wyeth: The leader in women's health - Yesterday, today, and tomorrow. Sexuality, Reproduction & Menopause. 2004;2(3):181-184.

3. Honebrink A. Treatment of menopausal symptoms post-Women's Health Initiative: Refinement of existing treatments and development of new therapies. Expert Opin Emerg Drugs. 2005;10(3):619-641.

4. Mealy NE, Bas M. Desvenlafaxine Succinate. Drugs Future. 2004:29(9):939.

5. Mealy NE, Bas M. Desvenlafaxine Succinate. Drugs Future. 2004:29(11):1137.

6. Mandavilli A. Mood swings. Nature Med. 2004;10(10):1010-1012.

7. Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. Human cytochromes and some newer antidepressants: kinetics, metabolism, and drug interactions. J Clin Psychopharmacol. 1999;19(5 Suppl 1):23S-35S.

8. Cohen LJ, De Vane CL. Clinical implications of antidepressant pharmacokinetics and pharmacogenetics. Ann Pharmacother. 1996;30(12):1471-1480.

9. Moller HJ, Volz HP. Drug treatment of depression in the 1990s. An overview of achievements and future possibilities. Drugs. 1996;52(5):625-638.

1.3.5 Case Reports No citations were found for case reports.

1.3.6 Summaries of Case Reports No citations were found for summaries of case reports.

1.3.7 Nonclinical Studies

Citations 1 and 2 refer to the same poster/abstract: 1. Deecher D, Leventhal L, Numan S, Sipe K, Cosmi S, Merchenthaler I, Winneker R. Desvenlafaxine alleviates vasomotor instability in two rodent models of hot flush. Abstract and Poster presented at: 34th Annual Meeting for the Society for Neuroscience Conference; Oct 23-27, 2004; San Diego, CA, USA.

2. Deecher DC, Leventhal L, Numan S, Sipe K, Cosmi S, Merchenthaler I, Winneker R. Desvenlafaxine alleviates vasomotor instability in two rodent models of hot flush. Abstract in 34th Annual Meeting for the Society of Neuroscience. 2004;890.2.

3. Deecher D, Leventhal L, Cosmi S, Johnston G, Merchenthaler I, Winneker R. Desvenlafaxine restores thermoregulatory function in two preclinical models of temperature regulation. Poster presented at: 87th Annual Meeting of the Endocrine Society; Jun 4, 2005; San Diego, CA, USA.

4. Muth EA, Moyer JA, Haskins JT, Andree TH. Biochemical, neurophysiological and behavioral effects of WY-45,233 and other identified metabolites of the antidepressant venlafaxine. Abstract in Psychopharmacology (Berl). 1988;96(Suppl):284.

5. Muth EA, Moyer JA, Haskins JT, Andree TH, Husbands GEM. Biochemical, neurophysiological, and behavioral effects of WY-45,233 and other identified metabolites of the antidepressant venlafaxine. Drug Dev Res. 1991;23(2):191-199.

6. Muth EA, Moyer JA, Andree TH. A pharmacological profile of WY-45,233, the major metabolite in humans of the novel bicyclic antidepressant candidate, WY-45,030. Abstract 130.4 in Abstr Soc Neurosci. 1986;12(1):473.

7. Weiss J, Dormann SMG, Martin FM, Kerpen CJ, Ketabi KN, Haefeli WE. Inhibition of P-glycoprotein by newer antidepressants. J Pharmacol Exp Ther. 2003;305(1):197-204.

8. Couture L, Elie R, Lavoie PA. Effect of antidepressants on ATP-dependent calcium uptake by neuronal endoplasmic reticulum. Can J Physiol Pharmacol. 2001;79(11):946- 952.

9. Hesse LM, Venkatakrishnan K, Court MH, von Moltke LL, Duan SX, Shader RI, Greenblatt DJ. CYP2B6 mediates the in vitro hydroxylation of bupropion: potential drug interactions with other antidepressants. Drug Metab Dispos. 2000;28(10):1176-1183.

10. von Moltke LL, Greenblatt DJ, Duan SX, Schmider J, Kudchadker L, Fogelman SM, Harmatz JS, Shader RI. Phenacetin 0-deethylation by human liver microsomes in vitro: inhibition by chemical probes, SSRI antidepressants, nefazodone and venlafaxine. Psychopharmacology. 1996;128(4):398-407.

11. Owens MJ, Morgan WN, Plott SJ, Nemeroff CB. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. J Pharmacol Exp TAer. 1997;283(3):1305-1322.

Robert L. Levin, M.D., January 21, 2008
Medical Reviewer,
FDA CDER ODE1 DNDP HFD 130

cc: HFD 130
T Laughren
M Mathis
G Zornberg
R Levin
R Grewal
Y Chen
P Yang

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Levin
1/22/2008 07:31:18 PM
MEDICAL OFFICER

Gwen Zornberg
1/29/2008 10:41:17 AM
MEDICAL OFFICER
Based on the findings in the 50 mg group and conclusions in the reviews of Dr. Levin, as well as Drs. Kumi and Chen, I recommend that the division take an approval action for NDA 21-992. The indication for Prisitiq is Major Depressive Disorder in adults.

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 16, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for desvenlafaxine sustained release (DVS-SR) tablets for major depressive disorder (MDD) (short-term efficacy only)

TO: File NDA 21-992
[Note: This overview should be filed with the 12-22-05 original submission of this NDA.]

1.0 BACKGROUND

DVS-SR is an extended release formulation of desvenlafaxine, an SNRI-type antidepressant. It is the major active metabolite of venlafaxine and has essentially the same pharmacological profile as venlafaxine XR which is approved for the treatment of MDD, GAD, Social Anxiety Disorder, and Panic Disorder. This NDA seeks a claim for the short-term treatment of MDD, in a dose range of 100 to 200 mg/day.

DVS-SR was developed under IND 64,552. We held a number of meetings with the sponsor of this IND during the development of DVS-SR, and had planned on taking it to the PDAC. However, as we neared the end of the review cycle, we decided that there were no critical review issues that needed input from the PDAC.

2.0 CHEMISTRY

There are no CMC issues that would preclude an approvable action for this NDA. However, there is a recommendation from the Office of Compliance that we withhold approval due to GMP concerns. In particular, the drug product manufacturing facility in Guayama, PR was found unacceptable due to an outstanding Warning Letter resulting from a recent CGMP inspection. This site needs to be re-inspected before a final action can be taken. In addition, there are several other CMC issues that need to be addressed prior to final approval, and these will be detailed in the approvable letter. The CMC recommendation is actually for a non-

approvable action. However, it is my impression that the deficiencies can likely be addressed, therefore, I am recommending an approvable action.

3.0 PHARMACOLOGY

There are no pharmacology/toxicology issues at this point that would preclude an approvable action for this NDA. The pharm/tox group has made a number of changes to labeling. They have no recommendations for phase 4 commitments.

4.0 BIOPHARMACEUTICS

DVS-SR is an extended release formulation of desvenlafaxine. It can be given once-a-day, and has a t1/2 of about 9-12 hours. Steady-state is reached in about 4-5 days. Cmax is achieved at about 6-10 hours, and there is a minimal food effect. About 50% of DVS is eliminated unchanged in the urine. Metabolism is primarily by conjugation, with only a minor role for oxidative metabolism. None of the metabolites of DVS is active. We will recommend limiting the dose in renally impaired patients (50 mg/day), hepatically impaired patients (100 mg/day),

OCP recommends approval of this NDA if agreement is reached on dissolution specifications and labeling. They have some minor recommendations for labeling, including a recommendation that DVS-SR not be used in patients with moderate, severe, and ESRD until a 50 mg strength is developed. They have proposed a dissolution method and specification for the approvable letter. They have no recommendations for phase 4 commitments.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were seven phase 3 double-blind, randomized, parallel-group, placebo-controlled, short-term (8-week) efficacy and safety trials in this program. These studies evaluated DVS-SR doses in adult outpatients with MDD in a range of 100 to 400 mg/day. The primary endpoint was change from baseline to endpoint in HAMD-17 total score. Two of these studies (304 and 223) were clearly negative, and were not further reviewed. The 5 remaining studies were the focus of our review: 2 fixed dose studies (306 and 308) and 3 flexible-dose studies (309, 317, and 320). Two of these 5 studies (the 2 fixed-dose studies, 306 and 308) were positive on the protocol-specified analysis (LOCF) for the primary endpoint. The 3 flexible-dose studies were not nominally positive, however, 2 (309 and 320) were positive on alternative analyses (OC, MMRM, and ETRANK) that seemed more appropriate given the dropout patterns in these trials.

Thus, I agree with the statistical reviewer that these 2 trials can be considered strongly supportive. Had a more rational SAP been in place from the beginning, these would be 2 additional positive trials.

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 3 doses in study 306, 2 doses were statistically superior to placebo (100 and 400 mg/day), but not the 200 mg/day dose (at least not in the protocol-specified analysis, but was highly statistically significant on the OC analysis). Both doses in study 308 (200 and 400 mg/day) were statistically superior to placebo. There was no indication of a numerical advantage for higher doses compared to lower doses in these studies. Thus, the sponsor has recommended 100 mg/day as the target dose, . This seems reasonable, however, labeling will need to be clear that no advantage of doses higher than 100 mg/day was demonstrated. The sponsor should be asked to commit to a fixed dose study at the lower end of the dose response curve to better establish efficacy at the lower end. In fact, it is my impression that the sponsor has studies ongoing that are exploring the efficacy of a 50 mg/day dose.

Secondary Efficacy Variables

CGI-I was the designated key secondary endpoint for these studies. Both the 200 and 400 mg/day doses were statistically superior to placebo for this endpoint for study 308. Dr. Kong felt that the procedure specified for protecting the overall family-wise error rate for study 306 may not have been adequate for the secondary endpoint. Nevertheless, the nominal p-values for the 100 and 400 mg/day vs placebo comparisons were quite small, and he concluded that these data are certainly supportive of a positive outcome. I agree, and feel this is sufficient to support inclusion of the key secondary findings in labeling.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of gender, because there were not sufficient data to explore differences based on age or race. There was no indication of any difference in effectiveness based on gender.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive depression trials.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy in this NDA. The sponsor has already conducted a maintenance study of DVS-SR in MDD, although the results have not yet been submitted. We will request that they submit the results of this study as a phase 4 commitment.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of DVS-SR in the treatment of MDD.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for MDD for this NDA were derived from a total of n=2667 patients with MDD exposed to DVS-SR across the clinical trials comprising the phase 2-3 DVS-SR program. Of these 2667 DVS-SR exposed MDD patients, 1211 were exposed in placebo-controlled 8-week trials involving doses in a range of 100-400 mg/day. This phase 2-3 DVS-SR exposure represents about 1137 patient-years of exposure. Of these patients, 928 were exposed for at least 6 months and 274 for at least 1 year. In addition to the phase 2-3 data, there were 643 subjects exposed to DVS-SR in phase 1 studies.

5.2.2 Common Adverse Event Profile for DVS-SR in MDD

The profile of common and drug-related adverse events (incidence at least 5% and at least twice the placebo rate) was very similar to that seen for venlafaxine XR, and included: abnormal ejaculation/orgasm (men); abnormal vision; anorexia; anorgasmia (men); asthenia; constipation; dry mouth; impotence; mydriasis; nausea; nervousness; somnolence; sweating; tremor; and vomiting. It was of interest that the frequency of many of these adverse events appeared to be somewhat higher for DVS-SR compared to venlafaxine XR (which was a comparator in several of these studies), particularly nausea and vomiting. The common and drug-related adverse events associated with discontinuation (incidence at least 1% and at least twice the placebo rate) included: nausea (6%); vomiting (3%); asthenia, headache, dizziness, insomnia, somnolence (2%); tremor, sweating, and impotence (1%), compared with <1% for each event in the placebo group. There is no apparent QTc effect for DVS-SR.

5.2.3 Adverse Events of Particular Interest

5.2.3.1 Hypertension

Overall, for the placebo-controlled phase 3 trials there was a placebo-subtracted increase for the combined drug group of about 2-4 mmHg for blood pressure. Using criteria for sustained

hypertension there was a clear dose-response for this effect, with about 4% of 400 mg/day patients meeting this standard, compared to 0.6% of placebo-treated patients. We will alert prescribers to this concern in a Warnings statement, and advise routine monitoring of blood pressure. The effect seen with DVS-SR is virtually identical to that seen with venlafaxine.

5.2.3.2 Tachycardia

There was a mean increase in pulse rate of about 2 bpm for the combined DVS-SR drug groups, compared to a slight decrease for placebo. Heart rate determined from ECG data revealed a larger effect, with placebo-subtracted HR of 1.1, 4.1, and 6.9 bpm for the 100, 200, and 400 mg/day groups, respectively. This, again, was similar to what is seen for venlafaxine.

5.2.3.3 Weight Decrease

There was a mean decrease in weight of about 1 kg for the combined DVS-SR drug groups, compared to essentially no change for placebo. This, again, was similar to what is seen for venlafaxine.

5.2.3.4 Lipid Increases

As was seen for venlafaxine, DVS-SR is associated with dose-related increases in total cholesterol, LDL cholesterol, and triglyceride. The changes are potentially important and will be mentioned prominently in Precautions, along with advice to consider monitoring these parameters during chronic treatment.

5.2.3.5 Liver Enzyme Increases

There is a slight but probably not clinically important effect on transaminases associated with DVS-SR use.

5.2.3.6 Thyroxine Decreases

There is a slight but probably not clinically important effect on thyroxine associated with DVS-SR use. This is probably a result of induction.

5.2.3.7 Proteinuria

There is what appears to be a dose-dependent increase in proteinuria associated with DVS-SR use. There was no relationship between this finding and increases in blood pressure, or in other measures of renal function (BUN or creatinine). The effect at what is likely to be the most commonly used dose of 100 mg/day is probably not clinically important. However, this effect bears watching.

5.2.4 Conclusions Regarding Safety of DVS-SR in the Treatment of MDD

I agree with Dr. Levin that the adverse event profile for DVS-SR is quite similar to that seen for venlafaxine XR, and can be adequately characterized in labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided literature references that were reviewed by Dr. Levin. He has indicated that they provide no new information that would change his conclusions about the approvability of this application.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, DVS-SR is not approved anywhere at this time for the treatment of MDD.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 4 sites, and data from 3 of these sites were deemed to be acceptable. DSI has not yet reached a conclusion about the 4th site. In any case, data from this site are not critical to the positive outcome from the study that was conducted at that site (306), i.e., the results are positive with or without the data from that site.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included an extensively modified version of labeling with the approvable letter.

10.2 Foreign Labeling

DVS-SR is not approved anywhere at this time for the treatment of MDD.

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for phase 4 commitments.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Wyeth has submitted sufficient data to support the conclusion that DVS-SR is effective and acceptably safe in the treatment of MDD. However, before we can take an approval action, the sponsor needs to respond to various requests we have made, including re-inspection of the PR site, and we need to reach agreement on labeling. Thus, I recommend that we issue the attached approvable letter along with our proposal for labeling, in anticipation of final approval.

cc:
Orig NDA 21-992
ODE-I/RTemple
HFD-130
HFD-130/TLaughren/MMathis/NKhin/RLevin/RGrewal

DOC: Desvenlafaxine_Laughren_AE_Memo.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
1/16/2007 03:46:40 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 7, 2006

FROM: Mitchell V. Mathis, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21-992 (This overview should be filed with the 12-22-2005 original submission.)

SUBJECT: Recommendation of Approvable Action for Desvenlafaxine Succinate (DVS) Tablets for the Treatment of Major Depressive Disorder (MDD)

1. BACKGROUND

DVS is an extended-release tablet for oral administration that contains desvenlafaxine succinate. Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of the structurally novel antidepressant, venlafaxine.

The desvenlafaxine IND (64,552) was submitted to the FDA Division of Neuropharmacological Drug Products on April 12, 2002 to support the DVS clinical development program for Major Depressive Disorder (MDD). On February 4, 2003, a pre-Phase 3 meeting was held to discuss whether Wyeth's proposed Phase 3 clinical development plan provided adequate evaluations of the safety and efficacy of DVS tablets to support an MDD indication (see minutes issued on February 28, 2003). On September 8, 2005, a pre-NDA meeting was held to discuss Wyeth's proposed content and format of the NDA submission (see minutes issued on September 30, 2005). For more detail on the early regulatory history of DVS, please refer to Appendix 10.1 of Dr. Levin's Clinical Review.

The sponsor submitted the above referenced NDA on December 22, 2005 with a PDUFA goal date of January 22, 2007 (this goal date was extended due to sponsor's submission of a major amendment dated 7/31/2006).

This NDA has been reviewed by Fanhui Kong, Ph.D., from the Office of Biostatistics (review dated 08/3/2006), Robert Levin, M.D., Medical Officer, DPP (review dated 10/16/2006), and Kofi Kumi, Ph.D., Office of Clinical Pharmacology and Biopharmaceutics (review dated 10/26/2006). The Division of Cardio-Renal Drug Products was consulted regarding the issue of sustained hypertension (see Dr. Desai's review dated 8/1/2006). At the time of completion of this memo, the Chemistry and Pharmacology/Toxicology reviews are not finalized.

2.0 CHEMISTRY

Thomas Oliver, Ph.D., Chemistry Team Leader, has identified several CMC concerns that need to be addressed prior to taking an approval action. Primary among these is a recommendation from the Office of Compliance for an overall withhold on this application due to GMP concerns.

3.0 PHARMACOLOGY

Although the final review is pending, I am not aware of any pharmacology/toxicology issues that would preclude an approvable action for this NDA.

4.0 CLINICAL PHARMACOLOGY

OCPB supports a recommendation of approval of this NDA provided agreement is reached on labeling and specifications for the *in vitro* release test. They also recommended the following:

Patients with moderate, severe, and end-stage renal disease should not be administered DVS until a 50 mg strength is commercially available and the dose should not be escalated in patients with renal impairment.

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

Language indicating

No Phase 4 commitments were identified from OCPB.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Review of efficacy was based on the results of seven placebo-controlled trials is the acute treatment of Major Depressive Disorder (single or recurrent episode, without psychotic features) in adults.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

The efficacy of DVS in the treatment of MDD was demonstrated in two of seven controlled trials (see Dr. Levin's Clinical Review for details of efficacy 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 (HAMD-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 studies 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 (CGI-I)).

In addition, the results of three 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 efficacy 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 are designed specifically to manage missing data.

Fixed-dose Study Efficacy Results

Efficacy Results in Fixed-dose Studies							
	Study 223		Study 306			Study 308	
Efficacy Variable & Statistical Analysis	DVS 200 mg	DVS 400 mg	DVS 100 mg	DVS 200 mg	DVS 400 mg	DVS 200 mg	DVS 400 mg
Primary Variable: HAMD-17							
Final on-therapy evaluation- LOCF (primary analysis)	0.59	0.52	**0.004**	0.076	**0.002**	**0.002**	**0.008**
Observed-case (week 8)	0.21	0.71	**0.001**	**0.002**	**<0.001**	**<0.001**	**<0.001**
Mixed-effect model	0.67	0.61	**<0.001**	**0.004**	**<0.001**	**<0.001**	**<0.001**
ETRANKd	0.28	0.93	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Key Secondary Variable: CGI-I							
Final on-therapy evaluation (primary analysis)	0.51	0.28	**0.001**	**0.046**	**0.013**	**0.004**	**0.028**
Observed-case (week 8)	0.28	0.38	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

5.1.3 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses presented by the Sponsor and reviewed by Drs. Levin and Kong support the efficacy claim of DVS in the treatment of MDD.

6.0 Safety Data

6.1 Safety Findings in the Placebo-Controlled DVS Trials

The safety profile of DVS is similar to that of venlafaxine. As with venlafaxine, there is a concern for hypertension associated with DVS treatment. Similar blood pressure elevations occur with both drugs. 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 sustained hypertension could lead

to clinically significant consequences during longer term treatment. In addition, there is a dose-related risk of tachycardia and hyperlipidemia.

Two deaths were reported during the clinical development program, but they do not appear to be related to DVS treatment.

6.1.2 Safety Findings and Issues of Particular Interest

6.1.2.1 Common and Drug-Related Adverse Events

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.

6.1.2.2 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 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 or three 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. In the long-term studies, there were three cases of cerebrovascular accident (CVA) or transient ischemic attack (TIA) in which DVS treatment might have been a factor in development of the adverse event.
8. Desvenlafaxine treatment also increased mean cholesterol and triglyceride levels, potentially increasing overall cardiovascular risk.
9. There were no deaths related to elevated blood pressure in the controlled trials.
10. There were no reported serious adverse events (SAE) related to elevated blood pressure in the controlled trials.
11. There were discontinuations due to hypertension in the DVS group (1.2%) compared to 2% and < 1% in the venlafaxine and placebo groups, respectively.
12. 'Hypertension' was reported as an adverse event for 4% of the DVS group, 5% of the venlafaxine group, and 3% of the placebo group.

Reviewer comment: From Dr. Levin's Clinical Review and Dr. Desai's (Cardio-renal Division, CDER) consultation it is clear that DVS increases blood pressure in clinical trials similar to its parent compound venlafaxine, but it is not clear what the clinical significance of this effect is over

the long term. Labeling should be clear about changes seen in blood pressure in patients taking DVS.

6.1.2.3 Heart Rate and ECG Data

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.

ECG analysis indicates that desvenlafaxine treatment results in an increase in 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 not clear.

There was no signal suggesting that DVS leads to prolongation of the QT interval. The Sponsor presented a negative thorough QTc study (see page 56 of Dr. Levin's review). There were no clinically significant differences between DVS-treated and placebo-treated subjects for QT, QTcF, QTcN, PR, and QRS intervals. DVS treatment was also associated with mean increases in heart rate and mean decreases in both PR and QT intervals.

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)

6.1.2.4 Laboratory Tests

Desvenlafaxine treatment was associated with a number of statistically significant changes in mean clinical laboratory parameters for liver-associated enzymes, cholesterol, tryglycerides, and thyroid hormones. Furthermore, many of these mean changes were dose-related. See Dr. Levin's review for specific discussions; 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. No subjects were identified as meeting the criteria for Hy's law.

In addition, DVS subjects had a statistically significant increase in proteinuria. Generally, the cases of proteinuria did not occur in the same subjects who had hypertension. There was not a statistically significant excess of cases of glucosuria, increased serum creatinine or BUN, or other renal or urinary abnormalities. The clinical significance of the proteinuria observed in the trials is currently unclear.

6.1.2.5 Body Weight

DVS cause a decrease in mean body weight (mean decrease 1.0 kg for DVS versus 0.1Kg for placebo) occurred during the 8-week studies. There was no indication of a dose-response relationship. No subject in any of the treatment groups discontinued from the study due to weight loss, and it is unlikely that this magnitude of weight loss is clinically significant.

6.2 Conclusion Regarding Safety

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.

Several statistically significant laboratory abnormalities were seen in DVS treated subjects. Abnormalities in liver function, thyroid function, lipid profiles, and urine protein have been described from the placebo-controlled trial data. The clinical significance of these abnormalities, if any, is not known.

7.0 FOREIGN REGULATORY ACTION

To my knowledge, DVS is not approved for any indication in any country at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was not presented to the PDAC.

9.0 DSI INSPECTIONS

A request for DSI Audit of Clinical Study Sites has been submitted and the results of that audit are not available at the time of this memo.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified and relevant language from the approved labeling for venlafaxine has been incorporated into DVS labeling where appropriate. Our proposed labeling should be included in the action letter.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that DVS is effective and reasonably safe in the treatment of MDD. I recommend that we issue an approvable action letter. The primary safety concern is hypertension (as it is with venlafaxine), which will be addressed in labeling. Labeling will also address relevant information about venlafaxine, the parent compound, in addition to the

DVS-specific concerns of: drug-related adverse events as well as statistically significant changes in serum lipids, liver enzymes, thyroid function tests, and proteinuria. We may consider approval of this NDA provided the sponsor responds adequately to the CMC and Office of Compliance concerns, and upon receipt of an agreement between the sponsor and the Agency regarding labeling language.

No Phase 4 commitments have been identified by the team at this time.

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/s/

Mitchell Mathis
11/8/2006 12:38:30 PM
MEDICAL OFFICER
Approvable

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-992
Submission Code	N- (000)
Letter Date	12-22-05
Stamp Date	12-22-05
PDUFA Goal Date	1-22-07
Reviewer Name	Robert Levin, M.D.
Review Completion Date	10-24-06
Established Name	Desvenlafaxine
(Proposed) Trade Name	(pending)
Therapeutic Class	2020100
Applicant	Wyeth
Priority Designation	S
Formulation	Oral, extended-release tablets 100 mg and 200 mg tablets
Dosing Regimen	100 mg once daily, orally
Indication	Major Depressive Disorder
Intended Population	Major Depressive d/o (Adults)

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1 EXECUTIVE SUMMARY

1.1 Recommendations 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 diagnosis of Major Depressive Disorder (MDD), single or recurrent episode, without psychotic features. Desvenlafaxine treatment was reasonably safe in the controlled trials. The safety profile of DVS treatment appears to be quite similar to that of venlafaxine, the parent drug of desvenlafaxine. In the short-term, controlled trials that included a venlafaxine treatment arm, there were no important differences in the safety profiles of desvenlafaxine and venlafaxine. There were no unexpected adverse events related to treatment with desvenlafaxine.

1.2 Recommendations on Postmarketing Actions

1.2.1 Risk Management Activities

In order to formulate specific recommendations for potential risk management activities, the Division will conduct internal discussions and consult with the Office of Surveillance and Epidemiology. Safety issues to consider will include: 1) toxicity in overdose with desvenlafaxine; 2) cardiovascular risks (hypertension and hyperlipidemia); 3) hepatic abnormalities (elevation in serum liver enzyme concentrations); and 4) urinary abnormalities (proteinuria and hematuria).

1.2.2 Required Phase 4 Commitments

Currently, the Division does not request any Phase 4 commitments. The sponsor has already conducted a controlled study of desvenlafaxine in the maintenance treatment of Major Depressive Disorder.

1.3 Summary of Clinical Findings

1.3.1. Overview of the DVS Clinical Program

Desvenlafaxine (DVS) is the major active metabolite of venlafaxine (EFFEXOR®). DVS is a combination serotonin and norepinephrine reuptake inhibitor (SNRI) that has pharmacological properties consistent with antidepressant activity.

The sponsor has conducted seven (7) multicenter, randomized, double blind, placebo-controlled,

short-term (8-week) trials to evaluate the efficacy and safety of DVS in the treatment of Major Depressive Disorder (MDD) in adults. Three (3) studies (223, 306, and 308) used fixed-dosing of DVS (100 mg, 200 mg, or 400 mg per day). Four (4) studies (304, 309, 317, and 320) used flexible dosing of DVS (100-400 mg/day). Studies 309 and 317 also included venlafaxine ER as an active comparator. The flexible venlafaxine ER doses ranged from 75 to 225 mg per day.

In the short-term, controlled trials, 1,211 subjects were treated with DVS; 803 were treated with placebo; and 244 were treated with venlafaxine. Subjects included male and female adult (18 to 74years of age) outpatients with a primary diagnosis of Major Depressive Disorder, single or recurrent episode, without psychotic features. The trials were conducted in the U.S., Europe, South Africa, and Taiwan. The mean age was 44. Approximately 63% of subjects were female, and 37% were male. Most subjects were White (83%). Approximately 8% of subjects were Black, and 6% were Hispanic. Other ethnicities (Arabic, Asian, Native American, and Other) comprised approximately 1% of the study population.

1.3.2 Efficacy

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 (HAMD-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 (CGI-I) 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 probably 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 (a non-parametric method). The latter two analyses handle missing data differently. These are discussed in more detail in Dr. Fanhui 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 positive antidepressant trials.

All four DVS flexible-dose studies failed on the primary ANCOVA LOCF analysis (304, 309, 317, and 320). 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) was a reduction of -2.8 points on the mean HAMD-17 Scale score. In the same study, the estimated size of the DVS treatment effect was -0.7 points on the HAMD-17 Scale.

1.3.3 Safety

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.

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 (the proportion of the DVS group versus the proportion of the venlafaxine group): 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. The deaths were 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, seven (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 (2) 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 common 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 following commonly reported adverse events occurred in at least 5% of DVS subjects and were reported at least twice as commonly 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 appeared to be related to DVS treatment. In the fixed dose trials, the following adverse events were reported for a higher proportion of the 400 mg group than in the 100 mg or 200 mg groups: asthenia, chills, nausea, dry mouth, vomiting, sweating, abnormal ejaculation/orgasm, anorgasmia, and impotence.

Currently, the main safety concern with desvenlafaxine treatment is the risk of developing hypertension. Blood pressure elevation is known to occur with treatment with the parent drug, venlafaxine as well. In fact, the Warnings section of labeling for venlafaxine discusses sustained hypertension as a dose-related adverse event. 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 after 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 (BP) 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 BP 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. There is not a clear dose relationship for the *magnitude* of the BP change. However, there does appear to be a dose relationship for the *duration* of the BP elevation (sustained hypertension: BP elevation for 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 the adverse event.
8. The desvenlafaxine BP 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 BP elevation in the controlled trials.
11. There were no serious adverse events (SAE) related to elevated BP in the controlled trials.
12. 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.
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.

DVS treatment was also associated with dose-related increases in heart rate. The increase in mean heart rate was approximately five (5) beats per minute in the placebo-controlled trials. Two subjects had increases in heart rate that were considered potentially clinically significant. Tachycardia was reported as a serious adverse event for approximately 1% of 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 is not a signal for QT interval prolongation associated with desvenlafaxine treatment. 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. Statistically significant increases in mean QTcB were observed. However, there were no statistically significant differences in mean QTcF or QTcN in the controlled trials. 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.

Several abnormalities in clinical laboratory results were related to DVS treatment. An excess of subjects in the DVS group had 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% of 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 DVS treatment.

Significant changes occurred 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%, mean ALT increased by 9.4%, and mean 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 concentrations, the decreases varied inversely with DVS dose. For all other laboratory parameters, no apparent dose relationship observed. Currently, the clinical significance of these mean changes is unclear.

In addition, a statistically significant excess of DVS subjects had proteinuria. Generally, the cases of proteinuria did not occur in the same subjects who had hypertension. There was not a statistically significant excess of cases of glucosuria, increased serum creatinine or BUN, or other renal or urinary abnormalities. The clinical significance of the proteinuria observed in the trials is currently unclear.

1.3.4 Dosing and Administration

For the treatment of Major Depressive Disorder, the sponsor recommends a desvenlafaxine starting dose of 100 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 100 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/day of desvenlafaxine. The daily dose should not exceed more than 50 mg/day 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 per day. Similarly, for elderly patients, the Biopharmaceutics team recommends that the daily desvenlafaxine dose not exceed 100 mg per day. 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.

1.3.5 Drug-Drug Interactions

1.3.5.1. 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.

1.3.5.2. 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.

1.3.5.3. Potential for other drugs to affect desvenlafaxine

Inhibitors of CYP3A4

Reportedly, CYP3A4 is minimally involved in desvenlafaxine elimination. However, concomitant use of desvenlafaxine with potent inhibitors of CYP3A4 could possibly result in higher concentrations of desvenlafaxine.

Inhibitors of other CYP enzymes

Based on in vitro data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of desvenlafaxine.

1.3.5.4. 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 metabolized by these CYP isozymes.

1.3.6. Special Populations

1.3.6.1. 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 is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from exposure to desvenlafaxine, 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.

1.3.6.2. 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. Thus, 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.

1.3.6.3. 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. The Biopharmaceutics reviewer recommends that the daily DVS dose not exceed 100 mg in patients with hepatic impairment.

1.3.6.4. 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. The sponsor recommends a DVS starting dose of — mg —day in patients with severe renal impairment and end-stage renal disease (ESRD). However, the Biopharmaceutics reviewers (Kofi Kumi, Ph.D. and Yaning Wang, Ph.D.) recommend a starting dose of 50 mg per day in patients with moderate and severe renal impairment and in patients with end-stage renal disease (ESRD). Due to the significantly decreased clearance of DVS and the significantly increased DVS exposures in this population, I agree with the recommendation to begin DVS treatment with 50 mg per day in patients with this degree of renal function impairment.

Renal excretion is the predominant route of elimination of desvenlafaxine. 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 of DVS 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.

1.3.6.5. Elderly Patients

The recommended starting dose in patients older than 75 years of age is 100 mg per day. Generally, I agree with this 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 decreases renal function.

1.3.6.6. Pediatric Use

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

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Desvenlafaxine succinate (DVS) is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) under development for the treatment of Major Depressive Disorder (MDD). Desvenlafaxine (also known as O-desmethylvenlafaxine) is the major active metabolite of venlafaxine (Effexor). DVS is chemically unrelated to tricyclic, tetracyclic, or other available antidepressants. It does not have monoamine oxidase (MAO) inhibitory activity, and it has virtually no affinity for muscarinic, cholinergic, H1-histaminergic, or a1-adrenergic receptors. DVS lacks significant affinity for various ion channels including calcium, chloride, potassium, and sodium. DVS has activity in a number of neurochemical, electrophysiologic, and behavioral assays used to predict antidepressant efficacy.

2.2 Currently Available Treatment for the Indication, Major Depressive Disorder

For the acute treatment of Major Depressive Disorder, a number of antidepressant medications are available:

1. Tricyclic antidepressants include: imipramine, desipramine, amitryptiline, nortryptiline, doxepin, amoxapine, trimipramine, protryptiline, and maprotiline. Clomipramine is used to treat depression; however, it is not formally approved for the treatment of MDD.
2. Monoamine oxidase inhibitors (MAOI) include: phenylzine, tranylcypromine, isocarboxazid, maprotiline, and selegiline patch.
3. Selective serotonin reuptake inhibitors (SSRI) include: fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram.
4. Serotonin and norepinephrine reuptake inhibitors: venlafaxine and duloxetine.
5. Other antidepressants: bupropion, Trazadone, Nefazodone, and mirtazapine.
6. Electroconvulsive therapy (ECT) is available for the treatment of MDD.

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient of desvenlafaxine would be readily available in the U.S.

2.4 Important Safety Issues with Pharmacologically Related Products (SNRI antidepressants: venlafaxine and duloxetine)

2.4.1. Venlafaxine

Venlafaxine (the parent drug of desvenlafaxine) is contraindicated in patients who have hypersensitivity to venlafaxine. It is also contraindicated for patients taking monoamine oxidase inhibitors (MAOI). Warnings for venlafaxine use include clinical worsening and suicide risk and sustained hypertension. Precautions include anxiety and insomnia, discontinuation symptoms, changes in body weight, changes in appetite, activation of mania or hypomania, hyponatremia, mydriasis, seizures, abnormal bleeding, serum cholesterol elevation, and use in patients with concomitant illness (cardiovascular disease, renal impairment, and hepatic impairment).

2.4.2. Duloxetine

Important concerns with duloxetine treatment include hypersensitivity to duloxetine, toxicity when used concomitantly with monoamine oxidase inhibitors (MAOIs), and use in patients who have narrow angle glaucoma. Precautions with duloxetine treatment include hepatotoxicity, blood pressure elevation, induction of mania and hypomania, seizures, narrow angle glaucoma, and discontinuation symptoms.

2.5 Presubmission Regulatory Activity

The desvenlafaxine IND (64,552) was submitted to the FDA Division of Neuropharmacological Drug Products on April 12, 2002 to support the DVS SR clinical development program for Major

Depressive Disorder (MDD). On February 4, 2003, a pre-Phase 3 meeting was held to discuss whether Wyeth's proposed Phase 3 clinical development plan provided adequate evaluations of the safety and efficacy of DVS SR tablets to support the MDD indication. FDA issued minutes on February 28, 2003. On September 8, 2005, a pre-NDA meeting was held to discuss Wyeth's proposed content and format of the NDA submission. FDA issued minutes on September 30, 2005. (For details, please refer to Appendix 10.1).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Statistics Consult Findings

The Biostatistics reviewer, Fanhui Kong, Ph.D. replicated the sponsor's efficacy analyses and results for five (5) of the seven (7) controlled trials that he reviewed (306, 308, 309, 317, and 320). Dr. Kong did not perform a formal statistical analysis for studies 223 and 304, since they clearly failed using the primary and other pre-specified statistical analysis plans.

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3.1.1 Efficacy Results for Fixed-Dose Studies

Dr. Kong agrees that the efficacy of DVS was demonstrated in two of three fixed-dose trials (306 and 308), as determined by the primary efficacy analysis plan. The primary efficacy analyses used a last observation carried forward (LOCF) method conducted on the change from baseline in mean $HAMD_{17}$ scale scores using analysis of covariance (ANCOVA). Due to the potential problems associated with multiplicity, (multiple DVS dose groups), the results were adjusted by Dunnett's method. The key secondary efficacy variable was the Clinical Global Impression-Improvement scale (CGI-I) score. Closed testing procedures were used to compare the dose groups of DVS with placebo based on the primary efficacy variable in order to control the overall type I error rate.

In study 306, DVS dose groups of 100 mg and 400 mg met the significance criterion (p= 0.004 and 0.002, respectively). However, the DVS 200 mg dose group did not meet significance (p= 0.076). In study 308, both DVS dose groups (200 mg and 400 mg) met the significance criterion (p= 0.002 and p= 0.008, respectively). (The results are illustrated in the table below). The significance results were supported by nonparametric methods as well as other pre-specified analyses: 1) analysis of covariance on observed case (OC); 2) a mixed-effect model with repeated measurement procedure (MMRM); and 3) ETRANK, a nonparametric procedure analyzing repeated measurements data including data from subjects who discontinued from the study. Furthermore, in both 306 and 308, the key secondary analyses of the CGI-I results were positive for all DVS dose groups.

Table 3.1. Statistical Results for Primary and Key Secondary Efficacy Variables in Fixed-dose studies 306 and 308 a

Efficacy Variable	Study 306			Study 308	
	DVS 100 mg	DVS 200 mg	DVS 400 mg	DVS 200 mg	DVS 400 mg
Primary Variable: $HAMD_{17}$ score					
Primary statistical analysis- LOCF Final on-therapy evaluation	**0.004**	0.076	**0.002**	**0.002**	**0.008**
Non-primary statistical analyses					
Observed-case analysis	0.001	0.002	< 0.001	< 0.001	< 0.001
Mixed-effect model*	< 0.001	0.004	< 0.001	< 0.001	< 0.001
ETRANK **	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Key Secondary Variable: CGI-I					
Final on-therapy evaluation (LOCF analysis)	0.001	0.046	0.013	0.004	0.028
Observed-case analysis	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Significant differences between active treatment and placebo are shown in bold.
P-values are the adjusted p-values using Dunnett's procedure (adjusting for multiplicity).
CGI-I=Clinical Global Impressions Scale-Improvement; $HAM\text{-}D_{17}$=Hamilton Rating Scale for Depression, 17-item; Ven ER= venlafaxine extended-release formulation.

* Mixed-effect model with AR (1) covariance structure.
**ETRANK analysis: full data analysis with Entsuah score empirical significance levels (p-values).

In Study 223, both dose groups (200 mg and 400 mg) failed to demonstrate efficacy (p = 0.59 and 0.52, respectively) in the primary statistical analysis (LOCF). Similarly, both dose groups failed in the other pre-specified analyses (OC, MMRM, and ETRANK).

3.1.2 Efficacy Results for Flexible-dose Studies

The primary efficacy analysis using LOCF data in all of the flexible-dose studies (304, 309, 317 and 320) did not demonstrate the efficacy of DVS in the treatment of MDD. The lack of significance could be the result of unbalanced early dropouts due to adverse events. Removing these patients from the analysis resulted in significance of LOCF analyses in studies 309 and 320. In addition, the OC, MMRM and ETRANK analyses for studies 309 and 320 supports the conclusion that DVS was efficacious in the treatment of MDD. In study 317 (but not 309), the primary analysis demonstrated that venlafaxine ER was efficacious in the treatment of MDD.

Table 3.2. Statistical Results for Primary & Key Secondary Efficacy Variables in Flexible-Dose Studies 309, 317, and 320

Efficacy Variable	Study 309[a]		Study 317[a]		Study 320[a] DVS
	DVS	Ven Er[g]	DVS	VEN	
Primary Variable: $HAMD_{17}$ score					

Primary Statistical Analysis Final on-Rx evaluation: LOCF	0.381	0.171	0.488	**0.005**	0.078
Observed-case analysis	< 0.001	0.027	0.173	0.008	0.008
Mixed-effect model[c]	0.011	0.153	0.074	< 0.001	0.012
ETRANK[d]	0.028	0.253	0.353	< 0.001	< 0.001
Key Secondary Variable: CGI-I score					
Final on-therapy evaluation (LOCF analysis)	0.404	0.107	0.604	0.011	0.037
Observed-case analysis	< 0.001	0.014	0.141	0.010	0.006

a: Significant differences between active treatment and placebo are shown in bold.
b: DVS doses in Studies 309, 317, and 320 were 200 to 400 mg/day. Ven ER doses in Study 309 were 75 to 150 mg/day and in Study 317 were 150 to 225 mg/day.
c: Mixed-effect model with AR (1) covariance structure.
d: ETRANK analysis: full data analysis with Entsuah score empirical significance levels (p-values).

Study 304 failed in the primary analysis (LOCF), as well as in the other pre-specified analyses (OC, MMRM, and ETRANK). The p-values were 0.28, 0.067, 0.27, and 0.054, respectively.

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3.2 Cardiorenal Consult Findings

Mehul Desai, M.D., (Medical Officer, Division of Cardiorenal Drug Products) has expertly performed a thorough analysis of the blood pressure data from the DVS program. Dr. Desai's consult findings will be discussed in the vital signs section in the safety review below.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submission that was reviewed included raw data sets, summary data tables, safety and efficacy summaries, individual study reports, relevant narratives and case report forms, correspondence. All of these materials were reviewed in detail. Other material reviewed included reviews performed by important FDA consultants. These included: Mehul Desai, M.D., Medical Officer in the Division of Cardiorenal Drug Products; Fanhui Kong, Ph.D., from the Biostatistics Division; and Yaning Wang, Ph.D., Pharmacometrics Reviewer, Office of Clinical Pharmacology.

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4.2 Tables of Clinical Studies Reviewed

4.2.1 Table of Short-term, Placebo-controlled Desvenlafaxine Trials

The table below outlines the seven (7) short-term, placebo-controlled trials of desvenlafaxine in the treatment of Major Depressive Disorder. The designs are illustrated along with the efficacy results.

Pivotal Placebo-controlled Trials in the Desvenlafaxine Clinical Program				
Study number	Study Design	Treatment regimens	Subjects ITT Pop.	Efficacy Results
Flexible-dose Studies				
223-FR/PL/US/ZA 9-02 to 3-03	Randomized, double-blind, placebo-controlled, fixed-dose, 8-week study in adult outpatients with Major Depressive Disorder	Total DVS 200 mg/d DVS 400 mg/d Placebo	n = 213 n = 63 n = 72 n = 78	 p = 0.59 p = 0.52
306-US 11-03 to 11-04	Randomized, double-blind, placebo-controlled, fixed-dose, 8-week study in adult outpatients with	Total DVS 100 mg/d DVS 200 mg/d	n = 461 n = 114	 **p = 0.004*** p = 0.076

	Major Depressive Disorder	DVS 400 mg/d Placebo	n = 116 n = 113 n = 118	**p = 0.002***
308-EU/WW 11-03 to 9-04	Randomized, double-blind, placebo-controlled, fixed-dose 8-week study in adult outpatients with Major Depressive Disorder	DVS 200 mg/d DVS 400 mg/d Placebo	n = 369 n = 121 n = 124 n = 124	**p = 0.002*** **p = 0.008***
Flexible-dose Studies				
304-US 6-03 to 5-04	Randomized, double-blind, placebo-controlled, flexible-dose, 8-week study in adult outpatients with Major Depressive Disorder	Total DVS 100 or 200 mg/d Placebo	n = 234 n = 120 n = 114	p = 0.28)
309-EU 4-04 to 3-05	Randomized, double-blind, placebo-controlled and active-controlled (venlafaxine), flexible-dose, 8-week study in adult outpatients with Major Depressive Disorder.	Total DVS 200 or 400 mg/d Ven 75 or 150 mg/d Placebo	n = 364 n = 117 n = 127 n = 120	p = 0.38 p = 0.17
317-US 3-04 to 5-05	Randomized, double-blind, placebo-controlled and active-controlled (venlafaxine) flexible-dose, 8-week study in adult outpatients with Major Depressive Disorder	Total DVS 200 or 400 mg/d Ven 150 or 225 mg/d Placebo	n = 350 n = 110 n = 115 n = 125	p = 0.49 **p = 0.005***
320-US 7-04 to 5-05	Randomized, double-blind, placebo-controlled, flexible-dose, 8-week study in adult outpatients with Major Depressive Disorder	Total DVS 200 or 400 mg/d Placebo	n = 235 n = 117 n = 118	p = 0.078
* = statistically significant treatment effect compared to placebo				

4.2.2 Long-term, Open-label Desvenlafaxine Studies

The table below outlines the long-term, open-label studies that have been reviewed.

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 18 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

4.3 Review Strategy

All of the available efficacy and safety data were reviewed. The seven placebo-controlled trials were reviewed in equal detail. In addition, safety data from the long-term, open-label studies and the placebo-controlled relapse prevention trial were reviewed. Review materials included the original data sets, individual study reports, integrated efficacy and safety summaries, patient narratives, case report forms, and patient safety profiles.

4.4 Data Quality and Integrity

The data provided were of good quality and integrity. The type of data and the manner of organization and presentation were good.

4.5 Compliance with Ethical Standards and Good Clinical Practices

The DVS clinical studies appear to have been performed in accordance with applicable laws, regulations, and guidelines. These include: 1) the US Food and Drug Administration (FDA) Code of Federal Regulations (21 CFR, Part 50); 2) formal regulatory guidance of the International Conference on Harmonisation (ICH); 3) principles of Good Clinical Practice guidance; and 4) guidance of the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects and European guidances.

The protocols received independent ethics committee (IEC) or institutional review board (IRB) approval before the studies began. The protocol amendments received approval while the studies were in progress and before unblinding the data.

Written informed consent was obtained from all subjects before their enrollment. Subjects provided signed and witnessed assent. The identity of the subjects was kept confidential. Each subject was assigned a subject number, which was used on the case report forms (CRFs) instead of the name of the subject.

4.6 Financial Disclosures

The sponsor provided the required financial disclosures. It did not appear that investigators had any significant conflict of interest.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetic profile of DVS has been investigated in 19 Phase 1 studies enrolling 564 healthy subjects, 36 patients with hepatic impairment, and 43 subjects with renal impairment.

The PK profile has been assessed after single doses (50 to 900 mg) and multiple doses (100 mg to 450 mg/day for up to 14 doses). In three pivotal efficacy and safety studies, sparse sampling was conducted to permit population PK modeling. In addition, DVS PK data from 399 Phase 1 subjects have been pooled to examine the potential effects of the intrinsic factors of age, gender, body weight, and ethnicity on DVS pharmacokinetics. (Please refer to the table below, which illustrates the PK profile of DVS).

Table 5.1 DVS Pharmacokinetic Profile

Desvenlafaxine Pharmacokinetic Profile		
Parameter	**Single-dose**	**Steady-state**
Cmax (ng/mL)	205	284
Tmax (h)	7	6
AUC (ng*h/mL	5044	---
AUC 0-24h (ng*h/mL)	4795	5121
t1/2 (h)	11	11
Cl (L/h)	23	20
Cl (L/h/kg}	0.3	0.26
CLr (L/h)	10	---
CLr (mL/min)	168	---
Ae (%-dose)	61	---

5.1.1 Absorption

DVS SR is well absorbed and has an absolute oral bioavailability of approximately 80%. After single-dose administration, DVS is slowly absorbed; the mean tmax occurs between 5 and 11 hours after dose administration. The pharmacokinetics of DVS are approximately linear over the dose range of 100 to 600 mg, and the single-dose pharmacokinetics appear to adequately predict the multiple-dose pharmacokinetics. Administration of DVS with food had a minimal effect on drug absorption, resulting in an approximate 1-hour delay before Cmax occurred. Small (~15%) increases in Cmax were observed when DVS was administered after a high-fat meal. These increases were not considered clinically significant.

5.1.2 Distribution

The plasma protein-binding of desvenlafaxine was relatively low (30% ± 12%), and it is independent of drug concentration. The DVS volume of distribution at steady-state after intravenous administration was 3.4 L/kg, indicating modest distribution into nonvascular compartments.

5.1.3 Metabolism

In vitro studies with DVS indicate that glucuronidation and N-demethylation in the liver are the primary metabolic pathways. Approximately 50% of desvenlafaxine is excreted unchanged

in urine. Desvenlafaxine is primarily metabolized in the liver by conjugation (mediated by UGT isoforms, including UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17) and to a minor extent through oxidative metabolism.1 Approximately 25% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O didesmethyl-venlafaxine) in urine. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. DVS does not inhibit or induce the activity of CYP3A4. However, it can weakly inhibit the activity of CYP2A6. DVS does not significantly inhibit the activity of CYP1A2, CYP2C8, CYP2C9, or CYP2C19, and it did not induce the activity of CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A5. DVS was not a substrate or inhibitor of P-glycoprotein (P-gp).

5.1.4 Elimination

DVS is eliminated primarily through renal excretion after oral administration of desvenlafaxine. The excretion profile of DVS was assessed following administration of [14C]-venlafaxine. After oral administration of single doses of [14C]-venlafaxine, 92% of the dose was excreted in the urine, and 2% was excreted in the feces over a 120-hour period. Of the dose excreted in the urine, 72% was excreted as products of O-demethylation (DVS or its metabolites: NODV, the glucuronide of DVS, or the glucuronide of NODV). Less than 1% of the dose was excreted in urine as unknown metabolites that could potentially be metabolites of venlafaxine. The only molecules that would be expected to be present after oral administration of venlafaxine that would not be present after oral administration of DVS are venlafaxine and NDV. All metabolites of DVS were accounted for in plasma and urine, and they are inactive.

5.1.5 Pharmacokinetics of Desvenlafaxine Enantiomers

DVS is composed of the succinate salt of (R)- and (S)-enantiomers of desvenlafaxine, in approximately equal proportions. DVS is reportedly not subject to sterioselective metabolism and/or elimination.

5.1.6 Drug Interactions

5.1.6.1. 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.

5.1.6.2. 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.

5.1.6.3. 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.

Inhibitors of other CYP enzymes
Based on in vitro data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of desvenlafaxine.

5.1.6.4. 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 metabolized by these CYP isozymes.

5.1.7 Population Pharmacokinetics

Population PK analyses were conducted in subjects with Major Depressive Disorder. The sponsor concludes that no dose adjustments are needed for MDD patients treated with DVS. There were no reported effects on DVS pharmacokinetics when the PK profile was evaluated based on demographic characteristics (body weight, age, gender, and race) and concomitant medication use. Renal function (creatinine clearance) was the major determinant of total clearance of DVS.

5.1.8 Special Populations and Demographic Factors

5.1.8.1. Effect of Age, Gender, and Race

There was an age-dependent decrease in DVS clearance, resulting in a 25% increase in C_{max} and a 54% increase in AUC in subjects greater than75 years of age, compared to subjects 18 - 45 years of age. Women had higher DVS exposures (18-37% increase in C_{max} and a 6-17 % increase in AUC) than age-matched men. No differences were seen when the pharmacokinetic profile of desvenlafaxine was analyzed by race. The sponsor does not recommend a change in the starting dose of DVS (100 mg/day) for subjects older than 75 years of age or for women.

5.1.8.2. Renal Impairment. Renal excretion is the predominant route of elimination of DVS. Thus, glomerular filtration rate, as measured by creatinine clearance, is the major determinant of variability in DVS clearance. Changes in the pharmacokinetics of DVS with increasing age are largely due to decreasing renal function. The pharmacokinetics of DVS were studies in subjects with mild (n = 9), moderate (n = 8), severe (n = 7) and end-stage renal disease (ESRD) (n = 9) requiring dialysis, as well as in healthy, age-matched control subjects (n = 8). Elimination was significantly correlated with creatinine clearance. 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 normal subjects. This reduced clearance resulted in significant increases in 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.

5.1.8.3. Hepatic Impairment

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The pharmacokinetic profile of DVS was studied in subjects with mild (Child-Pugh A, n = 8), moderate (Child-Pugh B, n = 8), and severe (Child-Pugh C, n = 8) hepatic impairment and to healthy subjects (n = 12). Generally, DVS exposure increased with increasing degrees of hepatic impairment: AUC was increased by approximately 41% and 45% in patients with moderate and severe hepatic impairment, respectively, compared to healthy subjects. Average AUC values were comparable in subjects with mild hepatic impairment and healthy subjects (<5% difference). Systemic clearance (CL/F) was decreased by approximately 12% and 25% in patients with moderate and severe hepatic impairment, respectively, compared to healthy subjects. The CL/F values were comparable in mild hepatic impairment and healthy subjects (< 5% difference). The average $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively.

5.2 Pharmacodynamic Profile

Dose-related effects in the Phase 1 studies included nausea, vomiting, supine blood pressure elevation, and orthostatic hypotension. The occurrences of these adverse events were used to determine the DVS maximum tolerated dose (MTD).

The pharmacodynamic effects of DVS were assessed using the spectral analysis of daytime EEGs, sleep EEG, pupillometry, and peripheral biomarkers (whole blood serotonin, plasma serotonin, and plasma norepinephrine). DVS produced central effects as measured by polysomnography (PSG). The effects were similar to those observed for venlafaxine and other antidepressants; they were characterized by increases in REM sleep latency and decreases in REM sleep duration. The pupillary effects observed after daily doses of DVS >150 mg were consistent with the blockade of noradrenergic reuptake and the potentiation of the pharmacologic effects of endogenous noradrenaline. The observed decreases in serotonin concentrations in whole blood after DVS administration indicate that DVS also inhibits serotonin reuptake. DVS appeared to have a pharmacologic profile similar to that of venlafaxine, as demonstrated by central and peripheral markers of serotonergic and noradrenergic reuptake inhibition.

5.3 Exposure-response Model

Dr. Yaning Wang notes that the sponsor developed a pharmacokinetic/pharmacodynamic relationship between desvenlafaxine plasma exposure and the change from baseline on the HAM-D_{17} score. The small proportion of variability in HAM-D_{17} score explained by the DVS exposure suggested that other unidentified factors also contribute to the variability in HAM-D_{17} score, and the studied exposure range may be located around the plateau region on the exposure-response curve.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication sought in each of the seven placebo-controlled trials is the acute treatment of Major Depressive Disorder (single or recurrent episode, without psychotic features) in adults.

6.2 Methods of Review

In reviewing the efficacy of the trials, this reviewer used all efficacy data provided by the sponsor (efficacy summaries, individual study reports, and efficacy data tables). In addition, this reviewer consulted with the statistics reviewer (Fanhui Kong, Ph.D.) and incorporated Dr. Kong's formal statistical review of efficacy into the clinical review. Each trial was reviewed independently and fully. Dr. Kong used the sponsor's raw efficacy data sets in an effort to replicate the sponsor's analyses of efficacy.

6.3 Efficacy Endpoints

In each of the seven controlled efficacy trials, the sponsor used the Hamilton Depression Rating Scale-17 Items (HAMD-17) as the primary efficacy measure. The HAMD-17 is an appropriate, standard, well-validated, and well-accepted scale for measuring a potential treatment effect in a trial in acute Major Depressive Disorder. The scale is clinically meaningful and it is sensitive for detecting treatment effects. The sponsor's proposed primary efficacy endpoint in all seven trials was the comparison between treatment groups in the change in mean HAMD-17 scores between baseline and the end of the study. This is a well-accepted, appropriate primary efficacy endpoint in a trial in Major Depressive Disorder.

The key secondary efficacy measure in all studies was the Clinical Global Impression-Improvement (CGI-I) scale. Investigators rate a subject's total improvement on a weighted scale ranging from 0 (not assessed) to 7 (very much worse). The CGI-I is a well-accepted, appropriate, validated scale for use in trials in Major Depressive Disorder. The secondary endpoint was a comparison between treatment groups in the change in mean CGI-I scores from baseline to the end of the study. This is an acceptable secondary endpoint
for the indication.

6.4 Subject Selection Criteria

The subject selection criteria were nearly identical among the seven controlled studies. Subjects were adult outpatients with a primary diagnosis of Major Depressive Disorder (MDD), single or recurrent episode, without psychotic features. The diagnosis of MDD was made based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). If other allowable psychiatric diagnoses were present, MDD had to be the predominant psychiatric disorder. Subjects had to have depressive symptoms for at least 30 days before the screening visit.

In five of the studies, the age range of subjects was 18 to 75 years old. However, in studies 223 and 320, the age ranges were 18-65 and ≥ 18, respectively. In Study 223, female subjects had to be of non-childbearing potential (surgically sterile or postmenopausal). The other studies included women of childbearing potential. Female subjects must have agreed to use a medically acceptable form of contraception during the study and for at least 15 days after the last dose of study drug.

In study 223, subjects had to have prestudy and study day -1 scores of ≥ 24 the Montgomery and Asberg Depression Rating Scale (MADRS) and no more than a 20% decrease in the MADRS score between screening and study day -1. They also had to have study day -1 scores of at least 2 on item 1 (depressed mood) of the 17-item Hamilton Rating Scale for Depression (HAM-D17) and scores of ≥ 4 on the Clinical Global Impressions-Severity of Illness (CGI-S) scale at the prestudy visit and on study day -1 (baseline). In the Phase 3 studies, screening and baseline HAMD-17 scores had to be ≥ 20 (studies 304, 306, 308, and 320) or ≥ 22 (studies 309 and 317). In all studies, the score on item 1 (depressed mood) of the HAMD-17 had to be ≥2, and the CGI-Severity scale score had to be ≥ 4 on the CGI-S.

In addition, the sponsor specified appropriate exclusion criteria regarding psychiatric comorbid illness, medical illness, and concomitant psychotropic medications. (Please refer to the complete list of subject selection criteria in Appendix).

6.5 Study Design

The seven studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group, 8-week trials of desvenlafaxine in the acute treatment of Major Depressive Disorder (MDD). Subjects were treated with desvenlafaxine doses ranging from 100 to 400 mg/day (or they were treated with matching placebo). Three of the trials were fixed-dose studies (223, 306, and 308), and four of the trials were flexible-dose studies (304, 309, 317, and 320). Studies 309 and 317 also included venlafaxine ER as an active control.

In the fixed-dose studies, subjects were randomly assigned to treatment with placebo or one of two or three doses of desvenlafaxine. The fixed doses were 200 mg/day and 400 mg/day in studies 223 and 308; they were 100, 200, and 400 mg/day in study 306. In the flexible-dose studies, subjects were randomly assigned to treatment with either: 1) placebo or desvenlafaxine in studies 304 and 320; or 2) placebo, desvenlafaxine, or venlafaxine ER in studies 309 and 317. The desvenlafaxine dose range was 100 or 200 mg/day in study 304. The DVS dose range was 200 or 400 mg/day in studies 309, 317, and 320. The venlafaxine ER dose range was 75 to 150 mg/day in study 309, and it was 150 mg/day or 225 mg/day in study 317.

The screening evaluation consisted of a medical and psychiatric history and a general physical examination. Laboratory studies included hematology, blood chemistry, free thyroxine index (FTI), a urine drug screen, and urinalysis. Other assessments included measurement of vital

signs and a standard 12-lead electrocardiogram (ECG). Demographic information was collected. The medical history included obtaining information about current and past illnesses, any history of hypertension, and current and prior medications. The psychiatric history included any previous psychiatric illnesses, a description of all previous treatments for depression, the date of an initial MDD diagnosis and the start date of the current MDD episode. For the psychiatric assessment, subjects were evaluated for the presence of a primary diagnosis of MDD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), criteria.

At the screening visit all subsequent visits, diary cards were dispensed to subjects for recording adverse events, concomitant medications, and study drug compliance. Study personnel reviewed the diary cards at each visit and recorded pertinent information on the case report forms. When the results of the screening safety evaluations had been received, subjects meeting the screening criteria returned for a baseline visit. The baseline (study day –1) evaluations included the HAM-D-21, MADRS, CGI-S, and CGI-I scales. Weight and vital signs (including supine pulse, and supine and standing BP) were also measured at baseline. In addition, the subject's diary card was reviewed for any adverse events and concomitant medications. The presence of all required inclusion criteria and the absence of all required exclusion criteria were documented on the case report form. The sponsor appropriately specified a number of psychoactive drugs as either prohibited or permitted as concomitant medications (refer to Appendix)

6.6 Treatment Regimens

6.6.1. Treatment regimens in fixed-dose studies

In studies 223, 306, and 308, dose groups included 200 mg/day, 400 mg. and matching placebo. Study 306 also included a group treated with 100 mg/day. The titration schedules were as follows:

Fixed-dose study drug schedules			
DVS 100 mg/d group	100 mg/day for days 1- 56 (study 306 only)		
DVS 200 mg/d group	100 mg/d days 1- 3	200 mg/d days 4- 56	
DVS 400 mg/d group	100 mg/d days 1- 3	200 mg/d days 4- 7	400 mg/day days 8- 56
Placebo group	Matching placebo	Matching placebo	Matching placebo

6.6.2 Treatment regimens in flexible-dose studies

Flexible-dose studies with Venlafaxine			
Study 309		**Study 317**	
DVS 200 or 400 mg Days 1-28 200 mg Days 29-56 200 or 400 mg	Venlafaxine 75 or 150 mg Days 1-28 75 mg Days 29-56 75 or 150 mg	DVS 200 or 400 mg Days 1-4 100 mg Days 5-28 200 mg Days 29-56 200 or 400 mg	VEN ER 150 or 225 mg Days 1-4 75 mg Days 5-28 150 mg Days 29-56 150 or 225 mg

Flexible-dose studies without Venlafaxine	
Study 304	**Study 320**
DVS 100 or 200 mg Days 1-14 100 mg Days 15-56 100 or 200 mg	DVS 200 or 400 mg Days 1-7 200 or 100 mg Days 8-14 200 mg Days 15-56 200 or 400 mg

6.7 Efficacy Assessments

The HAMD-21 and CGI-I were performed at baseline and at the end of weeks 1, 2, 3, 4, 6, and 8.

6.6 Safety Assessments

1. Vital signs, including weight, were measured at screening, baseline, and the end of weeks 1, 2, 3, 4, 6, and 8, and at the post-study visit.
2. Adverse events and concomitant medications were evaluated as above.
3. ECG was performed at screening and the end of week 8.
4. Clinical laboratory tests were performed at screening and at the end of weeks 2, 4, and 8.

At the end of the study, up to 2 weeks were allowed for tapering the dose of study drug. In study 223, a follow-up visit was scheduled 4 to 10 days after completion of the study or discontinuation of study drug. In the other six studies, subjects who discontinued early or did not enter the 10-month long-term study (open-label study 303), had their dose tapered, and they returned for a follow-up visit 4 to 10 days after treatment ended. Subjects who completed the double-blind period could enter study 303. Upon completion of treatment or early discontinuation, their dose was to be tapered, and a follow-up visit was scheduled for approximately seven days after discontinuation of treatment.

6.7 Efficacy Findings

6.7.1 Efficacy findings in Fixed-dose studies

The efficacy of DVS in the treatment of MDD was demonstrated in two (2) of 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 (HAMD-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).

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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 efficacy 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 are designed specifically to manage missing data.

Table 6.7.1.1 Fixed-dose Study Efficacy Results

Efficacy Results in Fixed-dose Studies							
	Study 223		Study 306			Study 308	
Efficacy Variable & Statistical Analysis	DVS 200 mg	DVS 400 mg	DVS 100 mg	DVS 200 mg	DVS 400 mg	DVS 200 mg	DVS 400 mg
Primary Variable: HAMD-17							
Final on-therapy evaluation- LOCF (primary analysis)	0.59	0.52	**0.004**	0.076	**0.002**	**0.002**	**0.008**
Observed-case (week 8)	0.21	0.71	**0.001**	**0.002**	**<0.001**	**<0.001**	**<0.001**
Mixed-effect model	0.67	0.61	**<0.001**	**0.004**	**<0.001**	**<0.001**	**<0.001**
ETRANKd	0.28	0.93	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Key Secondary Variable: CGI-I							
Final on-therapy evaluation (primary analysis)	0.51	0.28	**0.001**	**0.046**	**0.013**	**0.004**	**0.028**
Observed-case (week 8)	0.28	0.38	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

The mixed effect model allows analysis all available data, taking into account the correlation between observations. For the mixed effect model, an autoregressive first order covariance structure was used to model the within-subject correlation. The change from baseline on the HAM-D17 was analyzed as the response, with treatment, week, baseline scores, and a term for interaction between treatment and week of therapy as explanatory variables. Site was modeled as a random effect.

The ETRANK method was developed as a modification of Gould ranking methods. It addresses the criticisms of Gould made by Pledger and Hall by building time-related ranks. ETRANK uses a randomization technique to analyze incomplete repeated measures data when the pattern of withdrawal is treatment-related. The method uses either the observed full data set (without