CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	1/21/2010
From	Ellis F. Unger, M.D., Deputy Director, ODE-I
Subject	Deputy Office Director Decisional Memo
NDA#	22-567
Applicant Name	PGx Health, LLC
Date of Submission	March 22, 2010
PDUFA Goal Date	January 22, 2011
Proprietary Name / Established (USAN) Name	Viibryd Vilazodone Hydrochloride
Dosage Forms / Strength	Oral tablets: 10 mg, 20 mg, and 40 mg
Indication	… for the treatment of major depressive disorder (MDD)
Action:	*Approval*

Material Reviewed/Consulted Action Package, including:	
Project Manager	William Bender
Medical Officer Clinical Review	Cheri Lindberg/Robert Levin (team leader)
Clinical Pharmacology Review	Bei Yu/Huixia Zhang/Jee Eun Lee/Jogarao Gobburu/Venkatesh Bhattaram/Yaning Wang/Issam Zineh
Statistical Review	Phillip Dinh/Peiling Yang (team leader)
Pharmacology Toxicology	Violetta Klimek/ Linda Fossom (team leader)
Chemistry Manufacturing and Controls	Pei-I Chu/ Chhagan Tele (team leader)
Statistical Review and Evaluation of Carcinogenicity Study	Mohamed Nagem/Karl Lin (team leader)
Environmental Assessment	Pei-I Chu/ Chhagan Tele (team leader)
Division of Scientific Investigations	Anthony Orencia/Purohit-Sheth, Tejashri
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology	Loretta Holmes/Kristina Tolliver (team leader)
Division of Risk Management, Office of Surveillance and Epidemiology	Shawna Hutchinson – REMS Robin Duer - Med Guide
Division of Drug Marketing, Advertising and Communications (DDMAC)	Jessica Cleck Derenick
Cross-Discipline Team Leader	Robert Levin/Mitchell Mathis
Proprietary Name Review	Loretta Holmes
Director, Division of Psychiatry Products	Thomas Laughren

Action:

The Division of Psychiatry Products is recommending approval of vilazodone hydrochloride, 10-, 20-, and 40-mg Tablets for oral administration for the treatment of major depressive disorder (MDD). I concur with their recommendation for approval.

Introduction:

Vilazodone is a small molecule, both a selective serotonin reuptake inhibitor (SSRI) and a partial 5-HT_{1A} receptor agonist, although the clinical significance of the latter is unknown. Vilazodone is not marketed anywhere.

Regulatory Background:

The IND for vilazodone for this indication was submitted on 11/21/1997 by Lipha Pharmaceuticals. Sponsorship of the IND was transferred numerous times, as summarized in Dr. Levin's CDTL review. The applicant had originally hoped to use genetic markers to direct clinical decision-making; however, those plans were ultimately abandoned. A pre-NDA meeting was scheduled for June, 2009; however, the applicant found the Division's preliminary comments sufficient to address their questions and the meeting was cancelled.

Chemistry Manufacturing and Controls (CMC):

Pursuant to their initial review, the CMC team sent an information request (IR) letter to the applicant on 10/15/2010, and the applicant's responses were deemed adequate. The ONDQA Biopharmaceutics review the found the proposed dissolution methodology and specifications to be acceptable. The Environmental Assessment review found no pending issues. Accordingly, the NDA was recommended for approval from a CMC perspective.

Pharmacology/Toxicology:

The review found the application approvable. Vilazodone binds with high affinity to the serotonin reuptake site (Ki = 0.1 nM), but not to the dopamine or norepinephrine reuptake sites. Vilazodone inhibits reuptake of serotonin (IC_{50} = 1.6 nM) and binds to 5-HT_{1A} receptors with an IC_{50} of 2.1 nM, where it functions as a partial agonist.

(b) (4)

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Serotonergic mechanisms in the central nervous system (CNS) are complex. Experimentally, vilazodone has been observed to exhibit both agonism and antagonism, depending on the experimental model and region of the brain studied. Moreover, 5-HT_{1A} receptors are present at both presynaptic and postsynaptic nerve terminals, and their various interactions are not fully understood. In short, the net effect of 5-HT_{1A} partial agonism on serotonergic transmission in the CNS has not been well-characterized, and the clinical significance of those effects, if any, is certainly unknown.

(b) (4)

Moreover, their proposed

proprietary name, “Viibryd,” (b) (4) Through much discussion and negotiation, the review team was able to reach agreement with the applicant on a description of vilazodone’s mechanism of action (section 12.1 of the label):

> “The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic 5-HT_{1A} receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone’s antidepressant effect are unknown.”

(b) (4) It is notable that the applicant has made no effort to show a benefit in comparison to other antidepressants; no comparators were included in the phase 3 program. Vilazodone has two major human metabolites, M10 and M17, each circulating at greater than 10% of total drug-related exposure. Neither is thought to have important serotonergic activity. Both have been assessed for toxicity; however, it is unclear if M17 has been adequately assessed for embryo-fetal toxicity because it was not found to be present in the plasma of either rats or rabbits. The applicant has agreed to explore this issue in a reproductive toxicity study, post-approval, in which M17 is administered by a route that will produce systemic exposure greater than or equal to the exposure in humans at the maximum recommended human dose (MRHD). Alternatively, they could show that the original rabbit study was adequate to assess the embryo-fetal toxicity of M17 by demonstrating that the rabbit’s systemic exposure to M17 in that study was greater than or equal to that in humans at the MRHD.

Two-year carcinogenicity studies were conducted in B6C3F1 mice and Wistar rats, given oral vilazodone at approximately 16.5 and 36 times the MRHD, respectively. The studies were deemed to be acceptable. In mice, the incidence of hepatocellular carcinomas was increased in males at 16.5 times, but not 5.5 times, the MRHD. Mammary gland adenocarcinomas were increased in females at 5.5 and 16.5 times the MRHD (associated with increased prolactin levels – known to cause mammary tumors in rodents), but not at 1.8 times the MRHD. In rats, there were no biologically relevant drug-related increases in incidences of neoplasms at doses up to 36 times the MRHD.

Results of mutagenicity assays were mixed: vilazodone was clastogenic *in vitro* in assays for chromosomal aberrations using V79 CHO cells in the presence and in absence of S9 metabolic activation, and using human lymphocytes in the presence of S9 activation. Vilazodone was negative for mutagenicity in the Ames test and in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) assay. It was also negative in several *in vivo* studies that included: 1) a chromosomal aberration assay in the rat bone marrow cells; 2) a micronucleus test in rats; and 3) an unscheduled DNA synthesis (UDS) assay in rat hepatocytes.

Treatment of rats with vilazodone at 30 times, but not 6 times, the MRHD caused impairment of male fertility; there was no effect on female fertility.

Vilazodone caused developmental toxicity in rats (reduced fetal weight and delayed bone ossification) but was not teratogenic in either rats or rabbits.

Relevant to gastrointestinal adverse reactions observed in the phase 2 and 3 clinical trials, there were no notable effects on gastrointestinal transport or gastric emptying in rodents in the safety pharmacology studies.

Site Inspections:

Four U.S. investigators (2 in each of the phase 3 trials) were inspected in support of this NDA; the applicant was inspected as well. Because larger sites were selected for inspection, the Division of Scientific Investigations had access to records of 311 subjects at 6 centers during their inspections, or approximately 35% of subjects in the phase 3 trials.

Minor regulatory deficiencies were found in one of the studies, but they were isolated and thought to have minimal impact on either data integrity or protection of human subjects. Overall, the data were deemed reliable for the proposed indication, with general adherence to Good Clinical Practices (GCP) regulations governing the conduct of clinical investigations.

Pharmacokinetics:

Vilazodone exhibits dose-proportional pharmacokinetics over a dose range from 5 to 80 mg. Administration with a high-fat or light meal increases oral bioavailability, and when administered with food, vilazodone's absolute bioavailability is ~72%. The applicant proposes that vilazodone be taken with food, as it was in the phase 3 program, and the Division agrees with this recommendation. The median T_{max} is 4-5 hours, and terminal half-life is ~25 hours.

Vilazodone is widely distributed, with a volume of distribution of 600 L after a 5 mg infusion, and the drug is highly protein-bound (96-99%).

Vilazodone's accumulation is predictable from single-dose data (accumulation factor of about 1.8, and consistent across different doses), and steady state is achieved in ~3 days. The mean steady state C_{max} after daily 40 mg dosing under fed conditions is ~160 ng/mL.

Vilazodone is extensively metabolized through CYP and non-CYP pathways, with 1% and 2% of the unchanged drug recovered in urine and feces, respectively. Among the CYP pathways, CYP3A4/5 is principally responsible for vilazodone's metabolism, with only minor contributions from CYP2C19 and CYP2D6. *In vitro* studies show that vilazodone is unlikely to inhibit or induce the metabolism of other CYPs (except for CYP2C8). Strong CYP3A4 inhibitors can reduce vilazodone's metabolism and increase exposure modestly (coadministration with ketoconazole increases the AUC and C_{max} by 50%). The label includes a recommendation to reduce the vilazodone dose from 40 to 20 mg daily when administered with strong CYP3A4 inhibitors. Theoretically, CYP3A4 inducers (e.g., carbamazepine) might decrease vilazodone exposure, although this was not studied. The applicant has agreed to conduct a drug-drug interaction trial of vilazodone using carbamazepine in healthy subjects as a postmarketing commitment.

Vilazodone had minimal effects on other drugs, except that coadministration of vilazodone with a CYP2C8 substrate can lead to an increase in the concentration of the other drug.

Thorough QT Study:

As described by others, vilazodone was tested in a thorough QT study at doses up to 80 mg. The study demonstrated appropriate assay sensitivity, and the baseline-corrected QTc interval was <10 msec for vilazodone, below the threshold of clinical concern.

Phase 2 Dose-Finding Trials:

The Phase 2 program included 5 dose-finding studies. Three incorporated flexible-dose designs (244, 245, and 247) and 2 were fixed-dose designs (246 and 248). The studies were quite similar: all were 8-week, randomized, double-blind, placebo-controlled, parallel group studies in adult outpatients meeting DSM-IV criteria for MDD. Each study enrolled between 86 and 140 subjects per treatment group. The Hamilton Rating Scale for Depression (HAM-D) was the 1° efficacy endpoint, assessed as change from baseline to Week 8 on the sum the scores for the first 17 items (HAM-D-17). Studies 244, 245, and 246 included an active comparator to assess assay sensitivity. The dosing paradigms and active comparators are shown in Table 1:

Table 1: Phase 2 Dose-Finding Studies

Trial number	**Vilazodone Dosing**				**Active comparators (mg/day)**
	Flexible-dose studies	**Fixed-dose studies**			
		5 mg/d	**10 mg/d**	**20 mg/d**	
244	20-100 mg/d				fluoxetine 20
245	10-20; 40-60; 80-100 mg/d				fluoxetine 20
246	---		X	X	citalopram 20
247	5-20 mg/d				---
248	---	X	X	X	---

None of the 5 studies showed a statistically significant treatment effect of vilazodone on its 1° endpoint; in fact, none were even close. None of the 3 active comparator studies showed the comparator to be statistically distinguishable from placebo. It could be concluded, therefore, that the 2 studies lacking an active control group were “negative” trials (b) (4)

Although these studies were unsuccessful on their 1° endpoints, the 2 fixed-dose trials (246 and 248) showed dose-responses on a 2° endpoint, the Montgomery-Asberg Depression Rating Scale (MADRS), suggestive of a treatment effect for the 20 mg/day vilazodone groups (the nominal unadjusted *p*-values were 0.06 in both studies). The 2° endpoint data for the MADRS total score are summarized in Table 2:

Table 2: Efficacy Results for Fixed-Dose Phase 2 Trials on the 2° MADRS Endpoint

study	dose (mg/d)	ℵMADRS (vilazodone minus placebo)	p-value
246	10	-2.3	0.12
	20	-2.8	0.06
248	5	-0.4	0.72
	10	-1.9	0.16
	20	-2.5	0.06

Evidence of Effectiveness:

The applicant submitted two phase 3 trials to establish the evidence of effectiveness for vilazodone for the sought indication "treatment of MDD." Results of one of the two phase 3 trials has been published: Rickels K, et al. *J Clin Psychiatry* 2009;70:326-33.

These were identified by the applicant as studies GNSC-04-DP-02 and CLDA-07-DP-02, and are referred to as Studies 4 and 7, respectively, in this memorandum.

Design: Both were multicenter, randomized, double-blind, placebo-controlled studies of vilazodone in adults meeting DSM-IV-TR criteria for MDD, with a single or recurrent episode. Both were short-term studies, 8 weeks in length – the same length as the failed phase 2 studies.

Both phase 3 studies randomized subjects 1:1 to vilazodone or placebo, and the vilazodone dose was ultimately fixed at 40 mg/d; however, the dose was gradually "ramped" to decrease side effects: 10 mg/d during Week 1, 20 mg/d in Week 2, and finally 40 mg/d during the last 6 weeks (Weeks 3 to 8). In Study 4 (only), patients who could not tolerate the 40 mg daily dose could be maintained on 20 mg/d. Vilazodone was to be taken with food to enhance bioavailability.

Dose Selection: Selection of dose was based on the phase 2 findings, wherein the 20 mg/d dose trended towards showing a treatment effect, as well as a positron emission tomography (PET) study showing that 40 mg/day is required to achieve significant occupancy of 5-HT_{1A} receptors. Adverse events such as dizziness and abnormal dreams were dose-dependent, leading to higher drop-outs at doses of 60 mg/d. Of note, a 40 mg/d fixed-dose had not been evaluated in phase 2.

For both studies, subjects were required to have a total HAM-D-17 of >22 and a HAM-D depressed mood score (item 1 of HAM-D) of >2 at both screening and baseline visits.

Endpoints: Not surprisingly, in light of the phase 2 results, the 1° efficacy endpoint was the MADRS total score (and not the more commonly used HAM-D), assessed as change from Baseline to Week 8. The analytic approach was an analysis of covariance (last observation carried forward, LOCF), and the intent-to-treat (ITT) population was the population of interest, defined as subjects who received ≥1 dose of their assigned treatment and who had ≥1 post-baseline efficacy assessment. There were numerous 2° efficacy endpoints, including: MADRS response, MADRS remission, Δ HAM-A total score, Δ HAM-D, HAM-D response, HAM-D

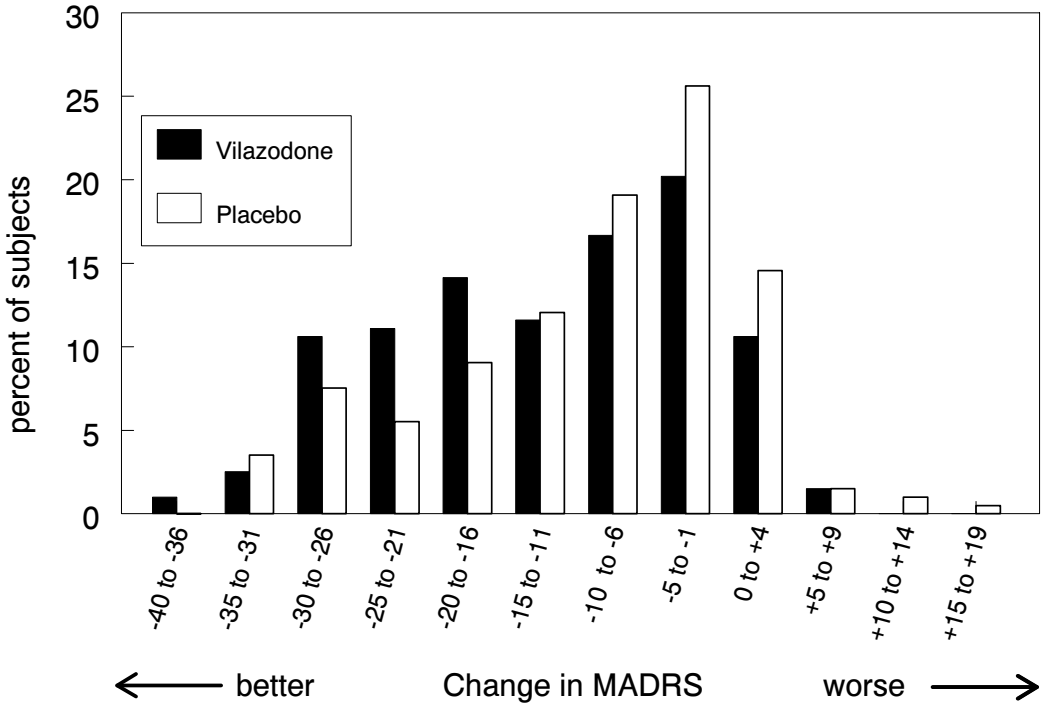
remission, HAM-A total score, Δ Clinical Global Impressions-Severity (CGI-S), Clinical Global Impressions-Improvement (CGI-I), and CGI-I response. Because there was no prospective plan to control Type-I error for the plethora of 2° endpoints, they should be considered exploratory in nature.

Results – Study 4:
Study 4 was conducted from February, 2006 to May, 2007. The statistical analysis plan was finalized 2/27/2007, with amendments 5/17/2007 and 7/13/2007.

Study 4 was conducted at 18 sites in the US. A total of 561 patients were screened to enroll 205 subjects per treatment group, with 1/6 of screened patients failing to meet entrance criteria. Approximately 25% of subjects discontinued in both treatment groups. Twice as many subjects discontinued because of an adverse event in the vilazodone group relative to the placebo group, whereas approximately half as many discontinued for lack of efficacy, and one-third as many withdrew consent. The ITT population included 97% of the enrolled subjects in both groups.

Demographic and baseline disease-related variables were reasonably matched between treatment groups. Mean age was 40 years; subjects were 63% female and 14% black. The mean baseline MADRS total score was 31. The least square mean changes for MADRS (Baseline to Week 8) were -9.7 in the placebo group and -12.9 in the vilazodone group. The difference between groups was -3.2 (standard error [SE] = 0.99; 95% CI = -5.1, -1.2; p = 0.001). A mixed-effects model for repeated measures (MMRM) analysis supported the 1° efficacy analysis.

Figure 1 shows the distribution of changes in MADRS for the 2 treatment groups (a more readily interpretable variation on the cumulative distribution function curves, generated by Dr. Dinh for this study, and typically shown for Alzheimer's Disease drugs), with each "bin" representing a 5-point ΔMADRS. The figure was generated from the data in the SAS transport file 0000\m5\datasets\gnsc-04-dp-02\analysis\a-madr.xpt, using LOCF to impute missing data.



The effect on ΔMADRS is modestly shifted to the left ("better") in vilazodone-treated subjects.

An analysis of covariance on the change from Baseline to Week 8 in the HAM-D-17 total score using the ITT population with missing values imputed by LOCF, the metric typically used to show evidence of efficacy for antidepressant drugs, supported the primary efficacy results.

Of note, 41 subjects were maintained on the 20 mg/d dose (or equivalent in the placebo group) because of poor tolerability. There were 28 such subjects in the vilazodone group and 13 in the placebo group. Thirteen of these patients completed the study, i.e., 6 on vilazodone and 5 on placebo, and in this selected population, the difference in least squares mean change from baseline on the MADRS total score was -4.3 (95% CI -11.6, 2.9; p = 0.23). This trend suggests that the 20-mg daily dose might have efficacy in this patient population.

Results – Study 7:

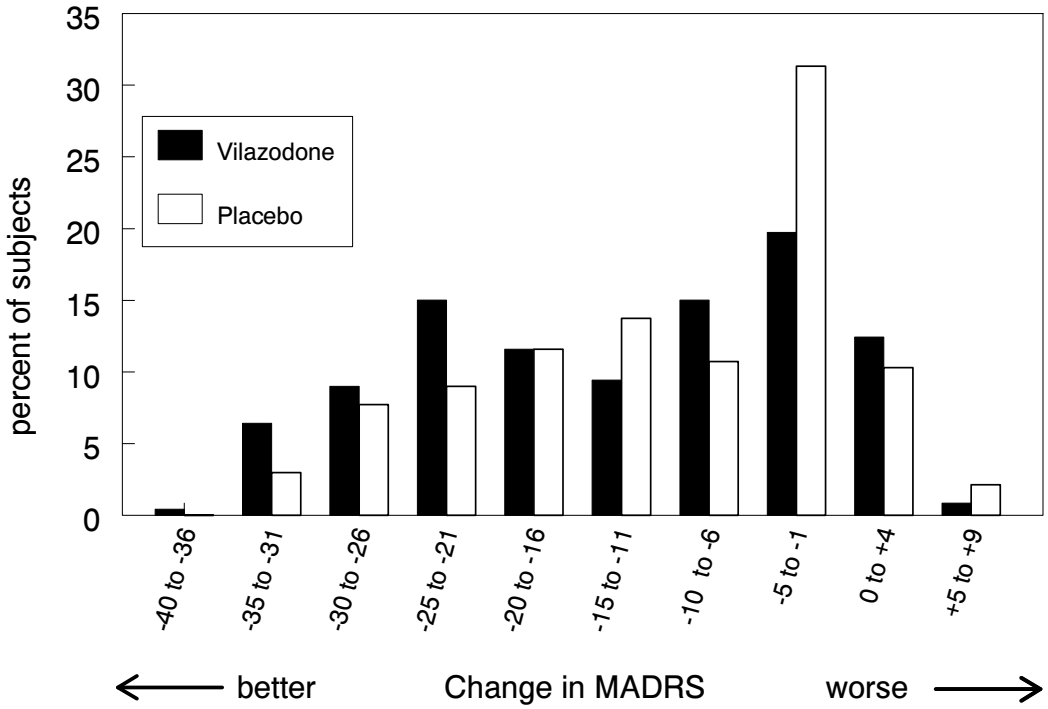
Study 7 was conducted from March 31, 2008 to February 10, 2009. The statistical analysis plan was finalized February 3, 2009, with an amendment on May 13, 2009.

Study 7 enrolled subjects at 15 US sites. A total of 659 patients were screened to enroll ~240 subjects per treatment group, with 13% of screening failures related to inability to meet entrance criteria. Nineteen percent (19%) of subjects discontinued in each treatment group. The leading causes were "lost to follow-up" (7% in both groups), and withdrawal of consent (5% in both groups). The placebo group had a slightly higher rate of discontinuation for lack of efficacy (3%, versus 1% for vilazodone) and a lower rate for adverse events (2%, versus 5% for vilazodone).

Demographic and baseline disease-related variables were similar in the two treatment groups. Mean age was 42 years: subjects were 56% female and 14% black. The mean baseline MADRS total score was 32. The least square mean changes for MADRS (Baseline to Week 8) were -10.8 in the placebo group and -13.3 in the vilazodone group, with a difference between

groups of -2.5 (SE=0.96; 95% CI = -4.4, -0.6; *p* = 0.009). A MMRM analysis supported the 1° efficacy analysis.

Figure 2 shows the distribution of changes in MADRS for the 2 treatment groups, with each "bin" representing a 5-point ΔMADRS. The figure was generated from the SAS transport file 0000\m5\datasets\clda-07-dp-02\analysis\dmadrl.xpt, using LOCF for missing assessments.



The effect on ΔMADRS is modestly shifted to the left ("better") in vilazodone-treated subjects. The most apparent shift is from the minimally better category (-5 to -1) to the 3 categories ranging from -21 to -35 (approximately 12% of subjects).

An analysis of covariance on the change from Baseline to Week 8 in the HAM-D-17 total score (ITT population; missing values imputed LOCF) supported the primary efficacy results.

Onset of Effect: The FDA biostatistician conducted MMRM analyses for Trials 7 and 4 as sensitivity analyses, showing results as a function of time (Table 3):

Table 3: ΔMADRS by Visit for Trials 7 and 4 (adapted from FDA Office of Biostatistics Review)

	Trial 7		Trial 4	
Visit Week	Difference	P-Value	Difference	P-Value
1	-0.4	P=0.347	-1.7	P=0.0001
2	-1.0	P=0.087	-1.7	P=0.0063
4	-1.6	P=0.050	-2.9	P=0.0005
6	-2.3	P=0.017	-4.1	P<0.0001
8	-2.9	P=0.006	-3.6	P=0.0007

The efficacy results as a function of time are somewhat surprising, in that a treatment effect is observed as early as 1 week after initiation of treatment (in Trial 4). Not only does this suggest a rapid onset of effect, but, perhaps even more surprising, the effect is observed at the starting vilazodone dose – only 10 mg/d – which is a mere quarter of the final, fixed 40-mg dose.

The observation should be considered in perspective, however: the finding is present in only 1 of 2 studies, and analyses of the 1° endpoint at multiple time points was not subjected to a rigorous, prospectively-designed statistical approach intended to consider multiplicity and Type-I error.

(b) (4)

Subgroup Analyses: In Trials 4 and 7, effects were generally consistent across subgroups of gender, age, baseline disease severity, and race (although there were too few non-Caucasian subjects to draw meaningful conclusions regarding specific non-Caucasian subgroups). In both trials, the effect size tended to be more pronounced in subjects older than 40 years and subjects with more severe baseline disease.

Efficacy Conclusions: I agree with Drs. Dinh, Lindberg, Levin, and Laughren that the dossier submitted by the applicant demonstrates efficacy for vilazodone, at a dose of 40 mg/d, for the treatment of MDD. The magnitude of the treatment effect is, at best, only modest, but the results are statistically persuasive, and appear robust to sensitivity analyses. (b) (4)

Safety:

Adequacy of Exposure: The principal support of safety came from the five phase 2 studies and two phase 3 studies. All were 8 weeks in length, and they included 1578 patients with MDD exposed to vilazodone. In addition, the applicant submitted a long-term open-label study, designed to meet the 1994 ICH E1 guidelines for drugs intended for long-term treatment of non-life-threatening conditions (which it barely did). The long-term study included 599 subjects overall (exposed to vilazodone), of whom 314 were exposed for 6 months (ICH E1: *N* should be 300 to 600) and 118 were exposed for 1 year (ICH E1; *N* should be >100). Exposure in all studies, including the shorter phase 1 studies, totaled 2898 adult subjects exposed to one or more doses of vilazodone. The phase 2 and 3 studies included 309 subjects over 55 years old, and 37 subjects over 65 years old. There was no pediatric exposure in this program.

Deaths: There were 3 deaths, but none of these subjects had received vilazodone at any time.

Serious Adverse Events: Approximately ~100 serious adverse events (SAEs) were reported in 81 subjects in the vilazodone development program. Many were psychiatric in nature, and probably represented worsening of the underlying condition – events typical and expected in psychiatric drug development programs.

The applicant's accounting of the SAEs did not reveal any patterns suggestive of vilazodone-related toxicity. Overall, the proportions of subjects with SAEs were similar in the vilazodone (1.8%) and placebo groups (2.3%). Dr. Lindberg, the primary clinical reviewer, carefully considered the narrative of each SAE, and found none of particular concern (except serotonin syndrome, see below). Most were relatively common types of background events, typically reported in clinical trials, with no patterns suggesting that any particular events, or cluster of related events, were more common in subjects exposed to vilazodone. Specifically, there were few adverse events that occurred in more than one subject in the vilazodone (or placebo) group.

I inspected the SAEs in this submission in the adverse event dataset (SAS transport file \0000\m5\datasets\iss \analysis\d-ae.xpt), blinded to treatment group, and coded each event as shown (Table 4):

Table 4: My Coding and Summary of SAEs in the Phase 2 and 3 Trials (number of events, %)

	vilazodone	placebo
N	2177	997
infection	8 (0.4)	1 (0.1)
suicidal ideation, attempt, suicide	7 (0.3)	7 (0.7)
pregnancy, positive pregnancy test	6 (0.3)	5 (0.5)
pneumonia	4 (0.2)	1 (0.1)
chest pain (not angina or unknown)	3 (0.1)	0 (0)
diarrhea, colitis, enteritis, proctitis, gastroenteritis	3 (0.1)	0 (0)
cholelithiasis, cholecystitis, gall bladder disorder	3 (0.1)	0 (0)
overdose	3 (0.1)	1 (0.1)
transient ischemic attack	2 (0.1)	0 (0)
depression	2 (0.1)	3 (0.3)
fever	1 (0)	0 (0)
abscess, boil, furuncle	1 (0)	0 (0)
cancer (non-squamous cell)	1 (0)	0 (0)
all neoplasia	1 (0)	0 (0)
angina	1 (0)	0 (0)
arteriosclerosis, vascular disease	1 (0)	0 (0)
deep venous thrombosis	1 (0)	0 (0)
thrombophlebitis, thrombosis, thrombus, clot, embolism	1 (0)	0 (0)
hypertension	1 (0)	0 (0)
dehydration, volume depletion	1 (0)	0 (0)
arrhythmia	1 (0)	0 (0)
supraventricular arrhythmia	1 (0)	0 (0)
atrial fibrillation	1 (0)	0 (0)
hypokalemia	1 (0)	0 (0)
hyponatremia	1 (0)	0 (0)
tremor, shakiness, trembling	1 (0)	0 (0)
psychosis, hallucinations	1 (0)	0 (0)
anxiety, nervousness, panic attacks	1 (0)	0 (0)
headache	1 (0)	0 (0)
migraine	1 (0)	0 (0)
blood urea nitrogen or creatinine elevated, acute/chronic renal failure	1 (0)	0 (0)
bleeding	1 (0)	0 (0)
apnea, respiratory failure, cyanosis	1 (0)	0 (0)
COPD, COPD exacerbation	1 (0)	0 (0)
pulmonary embolism	1 (0)	0 (0)
weight gain	1 (0)	0 (0)
serotonin syndrome	1 (0)	0 (0)
bronchitis, tracheitis, bronchiectasis	1 (0)	1 (0.1)
fracture	1 (0)	2 (0.2)
urinary stone	0 (0)	1 (0.1)
hernia	0 (0)	1 (0.1)
wheeze, bronchospasm, asthma	0 (0)	2 (0.2)

In this classification/accounting system, various SAEs are classified under more than one heading, and various headings include more than one SAE. For example, I classify a single SAE of “atrial fibrillation” not only as “atrial fibrillation,” but also as an “arrhythmia,” and a “supraventricular arrhythmia.” Conversely, the heading “infection” includes “pneumonia,” “cholecystitis,” “abscess,” “bronchitis,” etc. Some isolated events that are uncommon and

seemingly unlikely to be drug-related were not included, i.e., duodenal stricture, endometriosis, bronchoscopy, etc.

Using this classification scheme, I found no patterns of concern here. None of the SAEs stand out as being more common in the vilazodone group, with the exception of pneumonia. Given this "signal," one can consider the frequencies of infections in the common adverse events, and there was no difference between treatment groups (~19% for both vilazodone and placebo in the all-placebo-controlled safety database). This, in light of the lack of a reasonably plausible mechanistic explanation for infections, the small numbers of these SAEs, the multiplicity of events considered, and the lack of a "signal" for infections in the common adverse events, this single "signal" for pneumonia most likely represents play of chance and should be dismissed as such.

Common Adverse Events:

The common (non-serious) adverse events have been summarized by others. Excesses in gastrointestinal (GI) side effects (diarrhea, nausea, vomiting) predominate, and sleep disorders are also more common in the vilazodone group (Table 5):

Table 5: Common and Drug-Related Adverse Events

Adverse Event Term	Vilazodone 40 mg	Placebo
Diarrhea	28%	9%
Nausea	23%	5%
Vomiting	5%	1%
Insomnia	6%	2%

Gastrointestinal side effects: Gastrointestinal side effects were dose-limiting in phase 1 studies, and largely based on that experience, they are thought to be dose-related. *It is remarkable that 54% of subjects in the placebo-controlled phase 3 safety database experienced a gastrointestinal adverse event (source: applicant's integrated summary of safety (ISS) [5.3.5.3.2], Table 31, page 107).* Fortunately, there were relatively few discontinuations for GI side effects, and very few SAEs.

The onset of GI side effects tended to occur in the first week or two of vilazodone treatment. This is well-illustrated in the applicant's plots of time-to-first-event of nausea (Figure 3) and diarrhea (Figure 4):

Figure 3: Time to Onset of Nausea (source: ISS appendix 2, Figure 1.3, page 17)

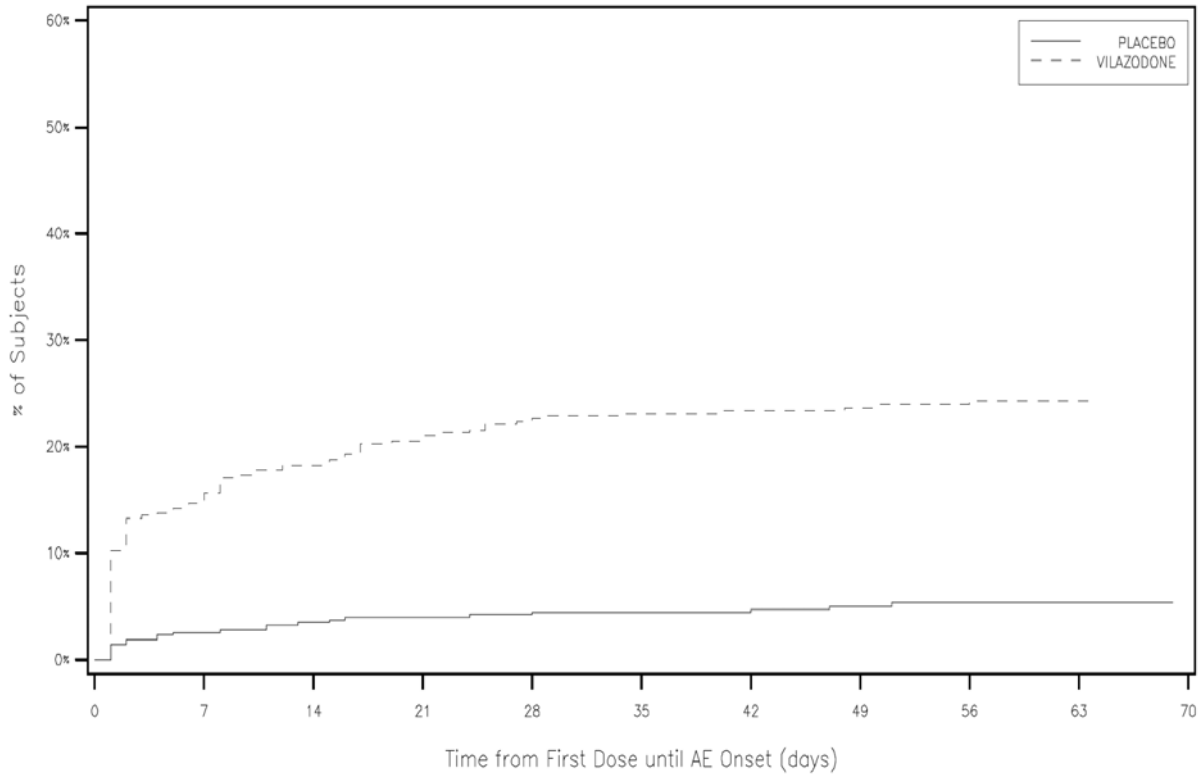
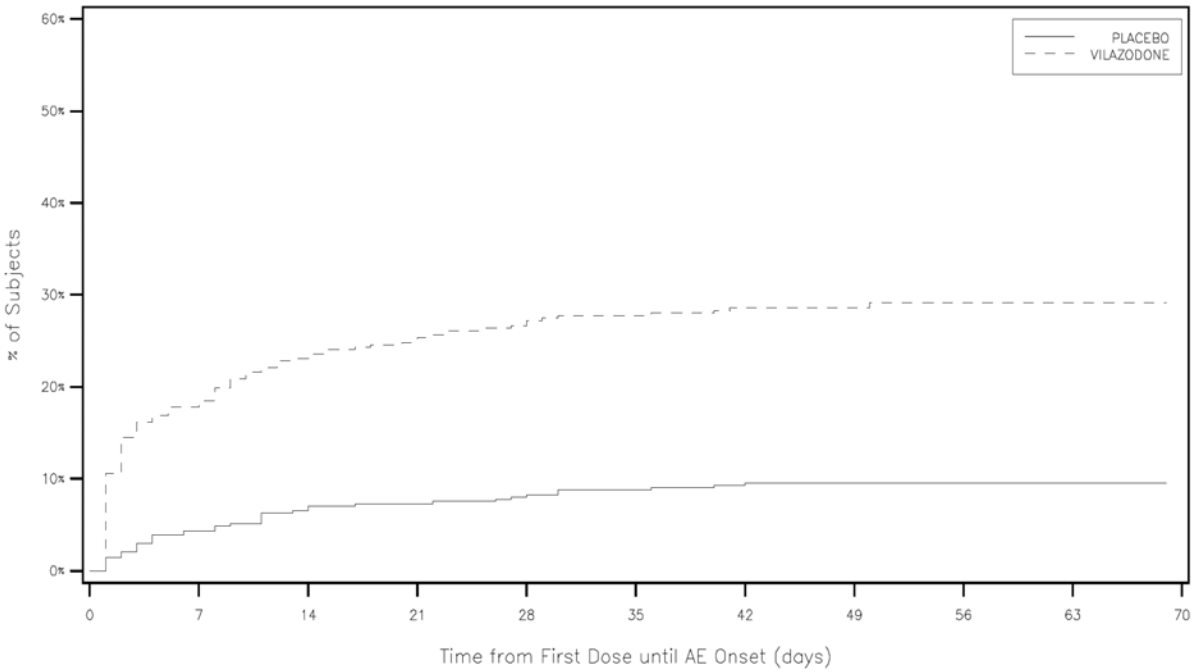


Figure 4: Time to Onset of Diarrhea (source: ISS appendix 2, Figure 1.1, page 15)



Sleep-related Adverse Events: Sleep disturbances were also of note, and were twice as common in subjects who received vilazodone as those who received placebo. In the all placebo-controlled safety database, sleep-related adverse events can be summarized as follows (Table 6):

Table 6: Sleep-related Adverse Events in the All Placebo-controlled Safety Database, n (%)

	vilazodone	placebo
N	**1578**	**997**
insomnia	137 (8.7)	43 (4.3)
abnormal dreams	71 (4.5)	22 (2.2)
nightmares	30 (1.9)	8 (0.8)

SSRI Reactions: Dr. Lindberg searched the safety database for cases suggestive of SSRI reactions, and found two subjects with probable serotonin toxicity. One occurred in a patient who had intentionally overdosed on vilazodone, and the other occurred in a patient during rapid titration of vilazodone.

Ophthalmological Findings: There was concern regarding potential ophthalmological toxicity, based on an observation of transient corneal opacities (not lenticular opacities, i.e., cataracts) in a canine study. Longer-term animal studies did not confirm these findings, and found no evidence of cataract formation. Based on the initial animal findings, the phase 2 studies and longer-term phase 3 study included various types of ophthalmologic monitoring: slit lamp exams, fundoscopy, monitoring of intraocular pressure and visual acuity, and Schirmer's test (lacrimation).

The only finding from the phase 2 studies was a slight decrease in tear production, which may have accounted for some of the reports of blurred vision and the few reports of corneal abnormalities.

In the controlled phase 3 studies, no treatment-emergent cataracts were reported in the listing of adverse events. Of 110 patients with a cataract at baseline in the 1-year open-label safety study, overall cataract severity was determined to have worsened for 14 patients (12.7%). There were also 4 patients in the 1-year study (3.6%) with apparently normal lenses at baseline, in whom new lens changes were reported. Other ophthalmologic adverse events in the open-label study included dry eye (4.7%), blurred vision (4.0%), and lacrimation increased (1.2%). All of these rates are difficult to interpret in the absence of a control group.

Dr. Wiley Chambers, the ophthalmology consultant, noted in his final consultation (dated January 7, 2011) that the applicant has adequately assessed the ophthalmological safety profile of vilazodone. He concluded that dry eyes are likely an effect of vilazodone. He notes a somewhat high rate of cataract progression in the year-long study, but acknowledges the difficulty in interpreting this in the absence of a concurrent control group. He notes that a controlled clinical trial, two or more years in length, would be needed to determine whether or not cataract induction and/or progression is associated with vilazodone use, but stops short of suggesting that we require this post-approval. He further opines that the ophthalmological risks can be managed through labeling. Dr. Robert Levin, the clinical team leader, has recommended that the risk of cataracts be elevated to a warning/precaution in labeling, and that we require an 18-month active-controlled trial to assess cataract induction and/or progression. Dr. Laughren opines that that the two findings of concern, i.e., dry eyes and possible cataract

formation, should be noted in the adverse reactions section of labeling, and not described in warnings and precautions. After discussion, Dr. Levin has expressed agreement that neither a warning/precaution nor a phase 4 study is needed to address the cataract issue. There is agreement, therefore, that the term "cataract" can be added to the terms "dry eye" and "blurred vision" in the "Other adverse reactions observed in clinical studies" table, under Adverse Reactions.

Sexual Dysfunction: SSRIs are known to cause sexual dysfunction, and there were excess sexual adverse reactions in the development program. These will be presented in labeling in a table.

(b) (4)

Drug Abuse and Dependence: Vilazodone is not a controlled substance. Animal studies did not show abuse or dependence potential; however, vilazodone's abuse potential was not systematically evaluated in humans. A January 5, 2011, memorandum from the Controlled Substances Staff concurs with the Division's view that vilazodone has a low potential for abuse.

Important Issues:

Adequacy of Dose Exploration:

The inadequacy of dose exploration is clearly the "Achilles heel" of this application. Vilazodone has dose-related side effects, and there are hints from both the phase 2 and phase 3 studies that a lower dose could be efficacious. With respect to the phase 2 studies, exploratory analyses of MADRS, a 2° endpoint, showed a positive trend at 20 mg/d. For the phase 3 studies, there was an apparent response on MADRS in one of two studies on 10 and 20 mg/d (Weeks 1 and 2), as well as a suggestion of a response in subjects who took 20 mg because they could not tolerate 40 mg.

One could argue, on the basis of the applicant's PET study, that there was little evidence for 5-HT_{1A} receptor occupancy following a 20-mg vilazodone dose, whereas occupancy was 15-35% with the 40 mg dose. It is important to consider, however, that the study was conducted with only single doses of vilazodone, and a multiple-dose study might have been more relevant and showed greater receptor occupancy. Moreover, the relationship between 5-HT_{1A} receptor occupancy and clinical effect is unknown.

In any case, the applicant has agreed to conduct, as a postmarketing commitment, a study to evaluate fixed doses of 20 and 40 mg, to include both an active control and placebo.

Maintenance Study: Although the applicant has demonstrated vilazodone's effectiveness as an antidepressant in 8-week studies, they provided no longer-term data to assess maintenance efficacy. The applicant has agreed to conduct a maintenance study post-approval as a postmarketing commitment.

Advisory Committee: This application was not referred to the Psychopharmacological Drugs Advisory Committee, because Vilazodone is one of now many antidepressants with predominantly SSRI activity, and efficacy and safety profiles seemed similar to others in the class. Absent other critical review issues, the Division decided, and the Office concurred, that not taking the application to an advisory committee was reasonable and justified.

Pediatric Assessments: Pediatric assessments will be handled as postmarketing requirements (PMRs), see approval letter for details.

Risk Evaluation and Mitigation Strategy (REMS):

Section 505-1 of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). As noted by the review team, there is concern regarding suicidality, as well as other risks.

In accordance with section 505-1 of FDCA and under 21 CFR 208, the review team has opined that a Medication Guide is required for vilazodone, because vilazodone poses a serious and significant public health concern. The Medication Guide is necessary because: 1) patient labeling could help prevent serious adverse effects; and 2) there are serious risks that patients should be made aware of, because information concerning the risks could affect patients' decisions to use, or continue to use vilazodone.

The review team, including pertinent staff from OSE, agrees that the elements of the REMS will be a Medication Guide and a timetable for the submission of assessments of the REMS.

Postmarketing Requirements and Commitments:

The review team has recommended post-marketing requirements and commitments enumerated in the approval letter.

Conclusions:

For the reasons stated above, I am today approving the NDA for vilazodone for the treatment of MDD. Postmarketing requirements and commitments are delineated in the approval letter, and approved labeling is attached. The labeling includes a class boxed warning for suicidality.

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

/s/

ELLIS F UNGER
01/21/2011