CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date of review	January 5, 2011
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	22-567
Sponsor	PGx Health, LLC
Submission Date	March 22, 2010
Related IND	54-613
Proprietary / Established name	VIIBRYD Vilazodone Hydrochloride
Dosage forms / strength	10, 20, and 40 mg oral tablets
Proposed Indication	Major Depressive Disorder in Adults
Recommended:	Approval

1. Introduction to the Review

The sponsor has submitted NDA 22-567 for vilazodone hydrochloride oral tablets in the treatment of adults with major depressive disorder. Vilazodone is a new molecular entity that has selective serotonin reuptake inhibitor (SSRI) properties as well as 5-HT_{1A} partial agonist properties. The sponsor has evaluated vilazodone in 24 phase 1 studies, five phase 2 studies, and three phase 3 studies. The five phase 2 controlled studies were either negative (2) or failed (3). In these studies, the sponsor explored a dose range of 5-100 mg per day. There was no clear trend toward a beneficial treatment effect. Gastrointestinal adverse reactions (nausea, vomiting, and diarrhea) were dose-limiting toxicities associated with a significant proportion of discontinuations, especially at doses above 40 mg/day.

In the two pivotal phase 3 trials, the sponsor studied a single dose (40 mg/day). There were no active comparators in either study. In one study, subjects who did not tolerate 40 mg/day could continue treatment with 20 mg/day. This included a very small number of subjects. In the second study, subjects were discontinued if they could not tolerate 40 mg/day. In all other respects, the studies had the identical design. The review team agrees that, in both studies, the sponsor demonstrated the efficacy of vilazodone 40 mg/day in the treatment of adult subjects with major depressive disorder. The review team also agrees that treatment was reasonably safe and well tolerated in the studies. In general, the safety and tolerability profiles of vilazodone were highly similar to those of other SSRI antidepressants. There were no new or unexpected safety findings with vilazodone, compared to those observed with SSRIs. Currently, it is unclear whether the 5-HT_{1A}

partial agonist properties of vilazodone confer additional benefit or risk compared to SSRI antidepressants.

The review team's main concern about the vilazodone clinical program is whether the sponsor adequately explored a range of doses in the trials, given that the pivotal trials assessed only one dose (40 mg/day). Two of the phase 2 studies (246 and 248) used fixed doses of vilazodone (5, 10, and 20 mg/day). Study 246 included an active control, but Study 248 did not. While these studies were negative or failed on the primary efficacy endpoint (HAMD scores), there appeared to be a trend toward an effect on the secondary endpoint (MADRS scores). However, there are a number of problems in relying on the secondary efficacy analysis. Overall, it is uncertain whether the 20 mg dose might be effective. On the other hand, there are dose-related adverse reactions (nausea and vomiting) that were associated with discontinuation of treatment. Thus, the review team has concluded that the sponsor should be required to conduct a postmarketing placebo-controlled and active-controlled study using fixed doses of vilazodone (20 mg and 40 mg), in order to further explore the effective dose range of vilazodone.

2. Background/Regulatory History

The initial IND (54-613) for vilazodone in the treatment of major depressive disorder was submitted on November 21, 1997 by Lipha Pharmaceuticals, an associate of Merck. A number of sponsors have held the vilazodone IND during the clinical development program. Lipha transferred ownership to Merck on August 26, 1998. On May 1, 2001 Merck transferred ownership to GSK; and on February 11, 2003 GSK transferred ownership to Merck. On November 7, 2003 EMD Pharmaceuticals became the IND holder. On October 25, 2004 EMD transferred ownership to Genaissance Pharmaceuticals. Subsequently, the company name of Genaissance changed to Cogenics on January 8, 2007. The name then changed to PGxHealth on September 28, 2007.

The clinical program was discussed with the sponsor at an end of Phase 2 (EOP2) meeting on December 20, 2005. The Division and the Sponsor reached agreement on the design of the Phase 3 studies (GNSC-04-DP-02 and GNSC-07-02). There was agreement that the Montgomery-Asberg Depression Rating Scale (MADRS) was an acceptable primary endpoint for a study in major depressive disorder. The Division and the Sponsor also agreed that ophthalmologic exams would not be required for these 8-week studies. However, for longer term exposures, the Sponsor would be required to conduct baseline and repeat (every 6 months) slit lamp exams and dilated fundoscopy to assess for lenticular and retinal changes.

During the period, May 8, 2008 and June 10, 2009, the Division provided guidance and feedback to the sponsor during face-face meetings, teleconferences, letters, and email communications. The topics of discussion included pivotal clinical protocols, a thorough QT study protocol, proposed analyses regarding possible genetic markers of response to vilazodone. During a pre-NDA meeting (June 17, 2009), we discussed the content and format of the clinical section for the subsequent NDA submission. We agreed that the efficacy data from the two pivotal trials would be presented separately and would not be

pooled. In addition, we agreed that the 5 phase 2 studies would not be considered supportive of the indication. The sponsor would submit the individual study reports.

3. Chemistry Manufacture and Controls (CMC) Review

Pei-I Chu, Ph.D. from ONDQA DPA1 performed the CMC review for the Division of Psychiatry Products. Dr. Chu has concluded that the sponsor has provided adequate CMC data to support approval of the NDA. There are no outstanding CMC issues. I agree with her conclusions.

3.1 Drug Substance

Dr. Chu has concluded that the drug substance and stability data provided support approval of the NDA.

Vilazodone hydrochloride is a new chemical entity belonging to the structural chemical group of the indolalkylamines. The full chemical designation is 2-benzofuran-carboxamide, 5-[4-[4-(5- cyano- 1H-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1) indolalkylamines. The full chemical designation is 2-benzofurancarboxamide, 5-[4-[4-(5- cyano- 1H-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1). Vilazodone HCl drug substance is a white to cream-colored solid. It is achiral and slightly hygroscopic. Solid state form analysis demonstrates that it exists in multiple polymorphs (b) (4) (b) (4) form IV was chosen for development. The solubility in water is 0.32mg/mL. The partition coefficient between n-octanol and water is (b) (4) The pKa is 7.1. The melting point and decomposition starts at ~270ºC.

3.2 Drug Product

Dr. Chu has concluded that the drug product and stability data provided support approval of the NDA.

In her review, Dr. Chu notes that Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are immediate-release, oval, film-coated, tablets, manufactured from a (b) (4) with total tablet weights of 103 mg, 206 mg and 412 mg, respectively. The 10 mg tablets are pink; the 20 mg, orange; and the 40 mg, blue. The tablets are debossed with the strength on one side and plain on the other. The tablets are packaged in appropriately-sized, 30-count, 90-count and 500-count high-density polyethylene (HDPE) bottles, and in film/aluminum foil blisters.

The drug product will be manufactured by Patheon Puerto Rico, Inc. (Manati, Puerto Rico). Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are manufactured from a (b) (4) process using standard techniques, equipment and controls. Manufacturing consists of (b) (4) Excipients used in the formulation include lactose, microcrystalline cellulose, colloidal silicone dioxide, magnesium stearate and (b) (4) film coating. The film coat is comprised of:

(b) (4) The batch formula for a commercial scale batch is (b) (4) for the 10mg, 20mg and 40mg tablets, which would results in (b) (4) 10mg tablets, (b) (4) 20mg tablets or (b) (4) 40mg tablets. Vilazodone HCl tablets may be stored in bulk prior to packaging to accommodate for packaging schedule. The HDPE bottles are sized to accommodate 30, 90, or 500 tablets/bottle. Each bottle also contains a 1-g desiccant canister. The applicant has submitted 18 month stability data for 6 batches using drug substance manufactured by Merck (three each of 10mg and 40mg tablets) and 12 month stability data of drug product manufactured with API from Scino Pharm. Based on real time and accelerated stability data at the ICH conditions, the 10mg and 40mg tablets are considered stable under proposed storage container closure systems. Tablets manufactured with API from SPT have the same stability as those manufactured with API from Merck based on comparison of 12-month stability data for SPT-API tablets and Merck-API tablets. The data support the proposed shelf life of 24 months when stored at room temperature.

3.3 Pre-approval Inspection of Facilities and Quality Issues Observed

The facilities inspection has been completed. The Office of Compliance has determined that the drug substance, drug product, and packaging facilities are adequate. Pre-approval inspections for the drug substance, drug product, and packaging sites are not needed based on the drug profile.

3.4 Unresolved CMC Issues

There are no unresolved CMC approvable issues. The sponsor has committed to meeting the following requests: 1) they will provide a revised (b) (4) validation report to demonstrate the limit of quantitation for Form IV (b) (4), and 2) they will include an updated dissolution method validation report using a stability indicating analytical method. Dr. Chu does not recommend any phase 4 commitments.

4. Nonclinical Pharmacology/Toxicology

Violetta Klimek, Ph.D. performed the pharmacology/toxicology review. Dr. Klimek and the team leader, Linda Fossom, Ph.D. have concluded that the sponsor has provided adequate pharmacology/toxicology data for approval of the NDA. Dr. Klimek and Dr. Fossom have concluded that there are no unresolved pharmacology/toxicology issues. I agree with their conclusions. The pharm/tox team has made a number of recommendations for labeling that we have incorporated.

5. Clinical Pharmacology/Biopharmaceutics

Bei Yu, Ph.D. performed the Clinical Pharmacology/Biopharmaceutics review. Dr. Yu and the OCP team have concluded that the sponsor has provided adequate clinical pharmacology and biopharmaceutics information to support approval of the NDA. There are no outstanding issues. I agree with Dr. Yu's conclusions.

5.1 Pharmacokinetics Findings

5.1.1 Absorption and Food Effect

Dr. Yu notes that vilazodone exhibits dose-proportional pharmacokinetics over the dose range of 5-80 mg after single-dose and multiple-dose administration. The absolute bioavailability of vilazodone is approximately 72% when administered with food. Administration of vilazodone 20 mg/day with food (a high fat/high calorie or a light meal/low calorie) increased exposures. The C_{max} increased by 150-160%; and the AUC increased by approximately 85%. The sponsor has proposed in labeling that vilazodone should be taken with food, based on the higher systemic exposure under fed conditions. The Division agrees with this recommendation.

The median T_{max} is 4-5 hours. The $T_{1/2}$ is approximately 25 hours. The accumulation ratio for vilazodone is approximately 1.5 to 1.8

5.1.2 Distribution

Vilazodone is highly protein-bound (96-99%). Vilazodone is widely distributed, with a volume of distribution of 605 L after a 5 mg infusion.

5.1.3 Metabolism

Vilazodone is extensively metabolized. It appears that there are no active metabolites. CYP450 pathways account for approximately 60% of vilazodone metabolism. Approximately 40% of vilazodone is possibly metabolized by carboxyl esterase. CYP3A4/5 is the major isoenzyme involved in the metabolism of vilazodone. Coadministration with ketoconazole increases the vilazodone AUC and Cmax by 50%. Presumably, coadministration with potent inducers of CYP3A4 (e.g., carbamazepine) would decrease vilazodone exposures; however, the sponsor has not conducted a study with a CYP3A4 inducer. OCP requests that the sponsor conduct an in vivo study of vilazodone used concomitantly with an inducer of CYP3A4, such as carbamazepine. I agree with this recommendation.

The CYP2C19 and CYP2D6 isoenzymes make minor contributions to the metabolism of vilazodone. CYP2C19 and 2D6 genotypes are not associated with different drug response. CYP1A2, CYP2A6, CYP2C9, and CYP2E1 have minimal contribution to the metabolism of vilazodone.

5.1.4 Elimination

Fecal excretion is the major route of elimination of vilazodone. A mass balance study demonstrated that 85% of radioactivity was recovered overall. Approximately 65% was recovered in feces, and 20% was recovered in urine. Approximately 3% of the dose was recovered as unchanged drug (2% in feces and 1% in urine).

5.1.5 Specific Populations

Dr. Yu has concluded that the PK profiles were comparable among: 1) healthy subjects, 2) patients with moderate and mild hepatic impairment, and 3) patients with mild and moderate renal impairment. Patients with severe hepatic or renal impairment were not studied. There were no significant differences in the pharmacokinetics of vilazodone between subjects $\geq$ 65 years of age and subjects < 65. Generally, lower body weights correlated with higher exposures. Systemic exposures were higher in females than males; however, female subjects had lower body weights than males, overall.

5.3 OCP Labeling Recommendations

The Office of Clinical Pharmacology review team has recommended labeling language for a number of sections in labeling. I agree with all of the recommendations. The Division has incorporated the recommendations in a separate labeling document in the following sections: Highlights, Dosing and Administration, Drug Interactions, Use in Specific Populations, and Clinical Pharmacology.

5.4 Recommended Postmarketing Commitments

Dr. Yu and the OCP review team recommend that the sponsor conduct the following studies as postmarketing commitments:

1. A controlled, fixed-dose study assessing the efficacy and safety of vilazodone 20 mg and 40 mg, compared to placebo in the treatment of subjects with major depressive disorder.
2. An in vivo study of a CYP3A4 inducer. OCP recommends a randomized, two-way crossover study in healthy subjects treated with vilazodone 20 mg under basal conditions and after pre-treatment with carbamazepine 400 mg/day for 7-14 days.
3. A clinical study of vilazodone treatment in patients with severe hepatic impairment.
4. An in vitro study of the effect of PgP on the pharmacokinetics of vilazodone and the effect of vilazodone on PgP.

I agree with Dr. Yu's recommendations for postmarketing commitments. The Division has conveyed these commitments to the sponsor.

6. Thorough QT Study

The Cardiorenal QT Interdisciplinary Review Team reviewed the data from the sponsor's thorough QT study. The team has concluded that treatment with vilazodone did not prolong the QTc interval. I agree with this conclusion.

The largest upper bounds of the 2-sided 90% CI for the mean difference between vilazodone (doses 10 mg – 80 mg) and placebo were below 10 ms. The largest lower

bound of the two-sided 90% CI for the ΔΔQtcI for moxifloxacin was greater than 5 ms at Day 6, and the moxifloxacin profile over time is adequately demonstrated in Figure 4 (Day 6), indicating that assay sensitivity was established.

Study PGX-08-P1-06 was phase 1, single-center, randomized, double-blind, placebo-controlled and active-controlled (moxifloxacin 400 mg), 3-arm, parallel-group, thorough QT study in 157 healthy male and female subjects. The administration of moxifloxacin was not administered in a double-blind manner. The primary objective was to determine the time-matched change from baseline QTc, based on an individual correction (QtcI) method. This method provides an optimization of QT correction for heart rate, in contrast to fixed exponent approaches such as Bazett (QTcB) or Fridericia (QTcF) methods. The secondary objective was to evaluate the safety and tolerability of vilazodone (up to 80 mg/d) compared to placebo or moxifloxacin. The table below illustrates the summary of findings from the QT study.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound of QtcI for Vilazodone and the Largest Lower Bound for Moxifloxacin

Treatment	Time (h)	ΔΔQTcI (ms)	90% CI (ms)
Vilazodone 20 mg (Day 6)	10	6.0	(2.9, 9.2)
Moxifloxacin 400 mg (Day 6)	4	12.4	(8.3, 16.5)
Vilazodone 40 mg (Day 9)	10	5.1	(1.2, 8.9)
Moxifloxacin 400 mg (Day 9)	4	11.0	(7.2, 14.8)
Vilazodone 60 mg (Day 12)	10	1.6	(-2.0, 5.2)
Moxifloxacin 400 mg (Day 12)	4	8.3	(4.4, 12.2)
Vilazodone 80 mg (Day 15)	2	1.9	(-2.1, 5.9)
Moxifloxacin 400 mg (Day 15)	4	9.2	(4.9, 13.4)

Multiple endpoint adjustment was not applied. The largest lower bounds after Bonferroni adjustment for 4 time points are 6.8 ms, 5.8 ms, 2.9 ms, and 3.4 ms, respectively, for Day 6, 9, 12 and 15, respectively.

The QTIRT notes that the supratherapeutic dose of vilazodone (80 mg) produces mean Cmax and AUC values 2.0-fold higher than the observed Cmax for the dose studied (40 mg) in the clinical trials. This increase in exposures is expected to be greater than the increase in exposure due to drug-drug interaction with ketoconazole (1.5-fold increase).

There were no sudden deaths or significant ventricular arrhythmias in this study. One subject experienced convulsive syncope while having her blood drawn. This was reported as convulsive syncope of vasovagal etiology. ECG taken soon after the episode was reportedly normal. However this event also had temporal association to study drug and may be due to non-arrhythmogenic mechanisms. There were 3 other episodes of syncope in the vilazodone group reported as vasovagal. No narratives are available for these events. There were no sudden deaths, and there were no significant ventricular arrhythmias in the study.

The QTIRT has recommended deletion of the sponsor's proposed language regarding (b) (4) in section 6. They recommend including the description of the QT study results in Section 12.2 as follows:

Generally, I agree with the proposed labeling. We have incorporated a slightly modified version in the Clinical Pharmacology section of labeling.

7. Ophthalmology Consult

We have requested an ophthalmology consult due to the finding of cataract development during controlled trials of vilazodone. Currently, the ophthalmology consult is not available.

Under the vilazodone IND (54-613), Merck conducted clinical ophthalmological testing in two phase 2, eight-week, placebo- and active-controlled studies (studies 009 and 010), due to the findings in dogs of reduced tear production and streak-like corneal opacities.

7.1 Previous FDA Ophthalmology Consult Findings

In previous consults (2001 and 2005) regarding cataract development in the phase 2, 8-week, controlled studies, Wiley Chambers, M.D. expressed concern about the development of cataracts. In the May, 2001 consult, Dr. Chambers discussed the following observations and conclusions regarding studies 009 and 010:

1. It is not clear how the data has been reported in this table. Corneal abnormalities should include all events in the stroma, endothelium and epithelium. Anterior chamber should include cell and flare. Lens should include all types of cataracts. The data should be verified before final conclusions are drawn.

2. The rate of reporting for cataract formation is very high for an eight week study. Cataract formation appears to be occurring at an unacceptable rate. This needs to be explained.

3. The retina abnormalities should be explained.

4. The reduction in tear production as measured by Schirmer demonstrated a dose dependent response.

5. Ocular testing has detected abnormalities in tear production, cataract formation, and retinal abnormalities. Conclusions on the cornea cannot be made because of

inconsistent data. In the absence of negative ocular findings, ocular testing should be continued. Ocular testing should continue during the development of this drug product.

On December 20, 2005 the Division met with Genaissance Pharmaceuticals to discuss the design of the pivotal phase 3 studies. The sponsor requested that the Division not require ophthalmological examinations in these studies. In his December 19, 2005 consult, Dr. Chambers stated the following in response to the sponsor's questions:

1. The determinations of Vilazodone's potential to cause cataract and retinal lesions will need to be evaluated in longer term studies.

2. Ocular testing has detected abnormalities in tear production, cataract formation and retinal abnormalities, but there have been methodological problems in the monitoring. The ocular dryness and corneal opacities appear to be a related problem, i.e., ocular dryness, if left untreated can lead to corneal opacities particularly in dogs. Vilazodone appears to cause ocular dryness within the first two weeks of treatment. This is similar to many other drug products and could be labeled and treated with Over-the-Counter demulcents. It is unlikely that significant additional information will be learned from ocular monitoring for dry eye in the proposed eight week study.

3. Lens opacities and the development of retinal lesions can only be evaluated in studies extending for 18-24 months in the case of lens opacities and 12-24 months in the case of retinal lesions. The likelihood of detecting significant changes in the lens or retina in 8 week studies is very low.

4. **Recommended Regulatory Action**: Ocular testing is not necessary in the currently proposed study. Ocular testing should be conducted in longer term (18-24 month) studies during the development of this drug product. Monitoring should occur at 6 month intervals in the longer term studies.

7.2 Discussion with Dr. Chambers

During a discussion on December 9, 2010, Dr. Chambers stated that the rate of cataract formation in the phase 2 controlled studies was higher than expected. In addition, Dr. Chambers stated that the rate of cataract formation and progression in the phase 3, long-term, open-label vilazodone study was higher than expected. However, Dr. Chambers stated that he could not conclude from these studies whether treatment with vilazodone was causally related to the development of cataracts. For a definitive assessment of cataract formation, he would recommend that the sponsor conduct an 18-24 month controlled study. When asked about whether to consider a warning for cataracts in labeling, Dr. Chambers stated that part of the reason for not pushing for a warning for cataracts is that cataracts are not life-threatening and can be corrected with surgery. He also said that one could consider including a warning for cataracts and encourage the sponsor to conduct a definitive, controlled, long-term study assessing for cataracts. With

the available data, Dr. Chambers emphasized that he could not conclude that vilazodone treatment did or did not lead to cataract development.

7.3 Sponsor's Analysis of the Ophthalmologic Findings

The sponsor consulted an independent ophthalmologist to review the data from the ophthalmology and adverse events assessments performed in the phase 2 studies (009 and 010). In March, 2005, (b) (4) noted that the ophthalmological examinations and the data collection methods were not optimal. There was no requirement for serial evaluations to be performed by the same examiner, which complicated the interpretation of the results. (b) (4) concluded that vilazodone was associated with ocular drying in humans but was not associated with cataracts or retinal abnormalities.

The sponsor stated that in the phase 3, uncontrolled, long-term study, visual acuity scores remained stable for 98% of the subjects, and few subjects had abnormal findings on slit-lamp biomicroscopy, corneal evaluations, or dilated fundoscopy. In summary, the sponsor concluded that the results of detailed ophthalmologic exams did not demonstrate clinically significant eye changes, except for a mild drying effect. The sponsor stated that there is no indication of any clinically important ophthalmologic effects of vilazodone.

7.4 Conclusions and Recommendations Regarding the Risk of Cataract Development

Currently, the ophthalmology consult is pending. At this point, it is difficult for the Division to interpret the data. However, in previous consults and in recent discussions, Dr. Chambers has stated that the rate of cataract formation was higher than expected in two controlled phase 2 studies and in the phase 3, open-label, long-term study. The sponsor did not conduct ophthalmological assessments in the phase 3 studies. My impression is that there is a signal for cataract formation associated with vilazodone treatment that the sponsor should explore in the type of definitive study that Dr. Chambers has described. None of the sponsors of the vilazodone IND have conducted such a study.

I recommend that the Division consider requiring the sponsor to conduct a long-term (18-24 month), active-controlled (antidepressant) study to prospectively assess for ophthalmologic toxicity. I also recommend that the Division consider specific labeling regarding cataracts, including the possibility of a warning for cataracts. While the relationship between cataract development and treatment with vilazodone is unclear, cataracts can be a serious medical condition. It could be useful to inform clinicians and patients about this potential risk.

8. Clinical

8.1 Efficacy

Cheri Lindberg, M.D. performed the clinical review. Dr. Lindberg has concluded that, in two adequate and well controlled studies, the sponsor demonstrated the efficacy of vilazodone in the treatment of adult subjects with a diagnosis of major depressive disorder. I agree with Dr. Lindberg's conclusions.

8.1.1 Study GNSC-04-DP-02

Study GNSC-04-DP-02 was an 8-week, phase 3, multicenter (18 U.S. sites), randomized, placebo-controlled, fixed-dose study of vilazodone 40 mg in the treatment of adults (18-70 years-old) with a diagnosis of major depressive disorder. The study included 407 subjects. There were 198 subjects treated with vilazodone and 199 treated with placebo. The study was conducted from February 22, 2006 to May 23, 2007.

Subjects initiated treatment with vilazodone 10 mg/day for 7 days, followed by 20 mg/day for 7 days. Subjects were then treated with the target dose of 40 mg/day for up to 6 weeks. Vilazodone was administered with food, because bioavailability is increased considerably (by approximately 85%) in the presence of food. If subjects could not tolerate the 40 mg dose, they could continue in the study while treated with 20 mg/day.

The primary objective was to assess the efficacy of vilazodone, compared to placebo, in the treatment of MDD as measured by the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) score after 8 weeks of treatment. A secondary endpoint was the change from baseline to week 8 in the Clinical Global Impression-Severity (CGI-S) Scale score. The sponsor did not prospectively designate the CGI-S as a key secondary endpoint.

As illustrated in the sponsor's table below from the Clinical Summary of Efficacy, the least square mean (SE) changes in MADRS score were -12.9 (0.77) and -9.6 (0.76) for the vilazodone and placebo groups, respectively. The LS Mean treatment difference (-3.2) was statistically significant (p= 0.0010), in favor of vilazodone treatment.

Table 2: Change from Baseline in MADRS Total Score at Week 8/EOT (LOCF) (ITT Population) (GNSC-04-DP-02)

Statistic	Vilazodone N = 198	Placebo N = 199	*P*-value[a]
LS Mean (SE)	-12.9 (0.77)	-9.6 (0.76)	
95% CI (LS Mean)	-14.4, -11.4	-11.1, -8.1	
LS Mean Treatment Difference		-3.2	0.0010
95% CI (LS Mean Treatment Difference)		-5.2, -1.3	

KEY: ANCOVA = analysis of covariance; CI = confidence interval; EOT = end of treatment; ITT = intent-to-treat; LOCF = last observation carried forward; LS Mean = least squares mean; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error.

[a] *P*-value for treatment difference between vilazodone and placebo groups was calculated using ANCOVA including treatment, center, and baseline MADRS total score in the model.

Source: GNSC-04-DP-02, Section 14, Table 10.1.

The results are supported by the secondary efficacy results of the CGI-S analysis as illustrated below. The least square mean (SE) changes in CGI-S score were -1.4 (0.010) and -1 (0.09) for the vilazodone and placebo groups, respectively. The LS Mean treatment difference (-0.4) was statistically significant (p= 0.0010), in favor of vilazodone treatment.

Table 3: CGI-S and CGI-I at Week 8/EOT (LOCF) (ITT Population) (GNSC-04-DP-02)

Assessment Statistic	Vilazodone N = 198	Placebo N = 199	*P*-value
CGI-S Score (Change from Baseline to Week 8/EOT)			
LS Mean (SE)	-1.4 (0.10)	-1.0 (0.09)	
95% CI (LS Mean)	-1.6, -1.2	-1.2, -0.8	
LS Mean Treatment Difference		-0.4[a]	0.0010
95% CI (LS Mean Treatment Difference)		-0.2, -0.7[a]	
CGI-I Score at Week 8/EOT			
LS Mean (SE)	2.6 (0.09)	3.0 (0.09)	
95% CI (LS Mean)	2.4, 2.8	2.8, 3.1	
LS Mean Treatment Difference		-0.4	0.0006
95% CI (LS Mean Treatment Difference)		-0.6, -0.2	

8.1.2 Study 2 (CLDA-07-DP-02)

Essentially, Study CLDA-07-DP-02 had an identical design to that of Study GNSC-04-DP-02, except that subjects who could not tolerate 40 mg/day could not continue in the study on 20 mg/day. This was an 8-week, phase 3, multicenter (15 U.S. sites), randomized, placebo-controlled, fixed-dose (40 mg/day) study of vilazodone in adult subjects with a diagnosis of major depressive disorder. The study was conducted from

March 31, 2008 to February 10, 2009. The study included 470 subjects. In the ITT population, there were 231 subjects treated with vilazodone and 232 treated with placebo. Subjects initiated treatment with vilazodone 10 mg/day for 7 days, followed by 20 mg/day for 7 days. Subjects were then treated with the target dose of 40 mg/day for up to 6 weeks. Vilazodone was administered with food. Subjects who did not tolerate vilazodone 40 mg/day were discontinued from the study.

As in Study GNSC-04-DP-02, the primary efficacy endpoint was the change from baseline in MADRS total score at Week 8. As illustrated in the sponsor's table 4 below from the Clinical Summary of Efficacy, the least square mean (SE) changes in MADRS score were -13.3 (0.090) and -10.8 (0.090) for the vilazodone and placebo groups, respectively. The LS Mean treatment difference (-2.5) was statistically significant (p= 0.0093), in favor of vilazodone treatment.

Table 4: Change from Baseline in MADRS Total Score at Week 8/EOT (LOCF) (ITT Population) (CLDA-07-DP-02)

Statistic	Vilazodone N = 231	Placebo N = 232	*P*-value[a]
n	231	231	
LS Mean (SE)	-13.3 (0.90)	-10.8 (0.90)	
95% CI (LS Mean)	-15.1, -11.5	-12.6, -9.1	
LS Mean Treatment Difference		-2.5	0.0093
95% CI (LS Mean Treatment Difference)		-4.4, -0.6	

KEY: ANCOVA = analysis of covariance; CI = confidence interval; EOT = end of treatment; ITT = intent-to-treat; LOCF = last observation carried forward; LS Mean = least squares mean; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error.

[a] The ANCOVA test included treatment, center, and baseline MADRS total score in the model.

Source: CLDA-07-DP-02, Table 14.2.1.1.

The results were supported by the secondary efficacy results of the CGI-S analysis illustrated below. The least square mean (SE) changes in CGI-S score were -1.4 (0.012) and -1.1 (0.12) for the vilazodone and placebo groups, respectively. The LS Mean treatment difference (-0.4) was statistically significant (p= 0.0035), in favor of vilazodone treatment.

8.2 Pediatric Use/PREA Waivers and Deferrals

The use of vilazodone has not been studied in pediatric patients. In accordance with the Pediatric Research Equity Act, the sponsor submitted a request for (b) (4)

A PeRC meeting was held on December 1, 2010. The PeRC agreed with the Division's request for a waiver for children younger than 7 years-old and a deferral for studies in children and adolescents between the ages of 7 and 17. PeRC requested (as PMR) that the sponsor conduct one PK, safety and tolerability study and two placebo and active-controlled (fluoxetine) efficacy and safety studies. And, they requested that the sponsor conduct a juvenile animal study as a postmarketing requirement.

8.3 Safety Review

Cheri Lindberg, M.D conducted the safety review. Dr. Lindberg has concluded that treatment with vilazodone was reasonably safe and well tolerated in the pivotal studies. Dr. Lindberg has also concluded that the safety profile of vilazodone is very similar to those of SSRI antidepressants. There were no new or unexpected adverse reactions, compared to what one would expect with an SSRI. I agree with Dr. Lindberg's conclusions regarding the safety analysis.

8.3.1 General Safety Considerations

Dr. Lindberg has concluded that the sponsor conducted adequate safety assessments and submitted adequate safety data for assessing the safety profile of treatment with vilazodone. I agree with her conclusion. The types and frequency of safety assessments were adequate for a short-term trial in subjects with major depressive disorder. The safety assessments included the following: adverse events monitoring, vital signs monitoring, ECG, pregnancy testing, systematic monitoring of extrapyramidal symptoms, clinical laboratory testing, urine drug screen, and alcohol screening.

8.3.2 Exposure

The vilazodone exposure was adequate to support the application. Overall, 2898 subjects were exposed to vilazodone in the clinical development program for a total vilazodone exposure of 551 subject-years. In the 7 short-term, controlled studies, there were 1578 subjects exposed to vilazodone for a total exposure of 203 subject-years. In the two pivotal phase 3 studies, there were 436 subjects exposed to vilazodone for a total exposure of 60.9 subject-years. In the long-term, open-label study, there were 599 subjects exposed to vilazodone for a total exposure of 348 subject-years.

8.3.3 Major Safety Findings

There were 3 deaths in the clinical development program. None of the deaths were related to treatment with vilazodone; none of these subjects were treated with vilazodone. One subject in the QT study died as a result of homicide. One subject completed suicide prior to randomization in a controlled study, and one subject completed suicide during treatment with placebo. In the short-term, controlled studies, there were no serious adverse events that appeared to be related to treatment with vilazodone. Dr. Lindberg concluded that three serious adverse events were possibly related to treatment with vilazodone: depression with psychotic features, angina, and atypical chest pain. However,

as Dr. Lindberg notes, there was not sufficient information available from these cases to establish causality. Adverse reactions leading to discontinuation included vomiting, nausea, diarrhea, and palpitations.

Dr. Lindberg searched the safety database for cases of SSRI class adverse reactions of particular concern. There were two cases of probable serotonin toxicity. One case occurred after an intentional overdose of vilazodone. The other case occurred during rapid titration of vilazodone. Dr. Lindberg identified one case of seizure that was possibly related to treatment with vilazodone. Dr. Lindberg also identified 5 cases of mania or hypomania that were probably related to treatment with vilazodone. There were no cases of hyponatremia in the database. There were 2 cases of bleeding events (hemorrhagic diarrhea and epistaxis) that were possibly drug-related.

As illustrated in the table below, the most common adverse reactions were diarrhea, nausea, vomiting, dry mouth, dizziness, insomnia, abnormal dreams, and decreased libido. Other significant adverse reactions included akathisia, restlessness, anorgasmia, and abnormal orgasm.

Adverse Reactions Occurring in ≥2% of VIIBRYD-treated Patients and > Placebo-treated Subjects

System Organ Class **Preferred Term**	**VIIBRYD** **40 mg/day** **N = 436**	**Placebo** **N = 433**
Gastrointestinal disorders		
Diarrhea	28	9
Nausea	23	5
Dry mouth	8	5
Vomiting	5	1
Dyspepsia	3	2
Flatulence	3	2
Gastroenteritis	3	<1
Nervous system disorders		
Dizziness	9	5
Somnolence	3	2
Paresthesia	3	1
Tremor	2	0
Psychiatric disorders		
Insomnia	6	2
Abnormal dreams	4	1
Libido decreased	4	<1
Restlessness *	3	<1

Orgasm abnormal**	3	0
General disorders		
Fatigue	4	3
Feeling jittery	2	<1
Cardiac disorders		
Palpitations	2	<1
Musculoskeletal and connective tissue disorders		
Arthralgia	3	2
Reproductive system and breast disorders		
Delayed ejaculation***	2	0
Erectile dysfunction***	2	1
Metabolism and nutrition disorders		
Increased appetite	2	1

*Includes restlessness, akathisia, and restless legs syndrome

**Includes orgasm abnormal and anorgasmia

***Male patients only (Placebo n=182; VIIBRYD n=170)

Dose-related adverse reactions in the phase 2 and phase 3 short-term, controlled studies included nausea, vomiting, diarrhea, and dizziness.

As Dr. Lindberg has noted, treatment with vilazodone did not have any significant effects on blood pressure, heart rate, or body weight. There were no significant effects on ECG parameters in the controlled studies. Similarly, there were no significant effects on the QTc interval or other parameters in the dedicated QT study. Treatment with vilazodone was not associated with any abnormalities in clinical laboratory parameters.

There is no foreign experience with vilazodone. The sponsor did not submit a safety update, because there were no ongoing studies of vilazodone.

9. Statistical Analysis

Phillip Dinh, Ph.D. performed the statistical review. Dr. Dinh confirmed the sponsor's efficacy findings, and he concluded that both pivotal studies demonstrated the efficacy of vilazodone 40 mg/day in the treatment of adult subjects with a diagnosis of major depressive disorder. I agree with Dr. Dinh's conclusions. Dr. Dinh did not formally analyze the efficacy data from the five phase 2 studies that were either negative (2) or failed (3) studies.

For both studies, the primary efficacy endpoint was the change in the Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to week 8. Dr. Dinh confirmed the sponsor's analysis results for the primary efficacy outcome in both studies.

The sponsor did not pre-specify a key secondary endpoint. The following secondary endpoints are considered exploratory: the changes from baseline in CGI-I, CGI-S, and HAM-A scores.

9.1 Analysis of Study CLDA-07-DP-02

The primary efficacy measure was the change from baseline to week 8 in the MADRS score. Missing values were imputed by the Last Observation Carried Forward (LOCF) method. The primary analysis was an ANCOVA model with terms for treatment and center, and baseline MADRS score as a covariate. Centers were pooled as necessary for the analysis.

Sensitivity analyses on the primary efficacy variable included an ANCOVA model, as above, with the treatment-by-center interaction and a mixed-effects model for repeated measures (MMRM). For the MMRM analysis, the model included fixed categorical effect terms for treatment, center, visit, and treatment-by-visit interaction, as well as continuous fixed covariates for baseline MADRS and baseline-by-visit interaction.

Table 1 from Dr. Dinh's review illustrates the primary efficacy results. The difference in least square mean from placebo was -2.5 points on the MADRS. The result was statistically significant (p= .009) in favor of vilazodone treatment. This effect size is modest, and it falls within the range of effect sizes typically observed with antidepressant treatment.

Table 1. Study CLDA-07-DP-02: Sponsor's primary efficacy results: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	231	232
Baseline MADRS total score		
Mean (Standard deviation)	32.0 (3.6)	31.9 (3.5)
Median (Min – Max)	32 (24 – 42)	32 (22 – 42)
Change from baseline		
LS Means	-10.8	-13.3
Difference from placebo		-2.5
(95% confidence interval)		(-4.4, -0.6)
P-value		0.009

Table 2 from Dr. Dinh's review illustrates the CGI-Improvement scale results, which were not pre-specified as a key secondary endpoint. However, the CGI-I is a meaningful secondary efficacy endpoint. Dr. Dinh performed an analysis of covariance on the CGI-I at week 8 with missing values imputed by the LOCF method. The results suggest that vilazodone treatment was efficacious.

Table 2. Study CLDA-07-DP-02: Sponsor's efficacy results: CGI-I at week 8 (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	231	231
LS Means	2.8	2.5
Difference from placebo		-0.3
(95% confidence interval)		(-0.5, -0.1)
Unadjusted p-value		0.004

(Source: CLDA-07-DP-02 Study Report; Table 19, page 71)

Dr. Dinh performed a sensitivity analysis on the primary efficacy variable (MADRS scores). Table 3 summarizes an MMRM analysis of the treatment effects of vilazodone over the duration of the study. The model included baseline MADRS score as a fixed covariate, a baseline-by-visit interaction, treatment group and visit as fixed factors, and treatment-by-visit interaction. Subjects were treated as a random effect. An unstructured covariance matrix was used. Dr. Dinh notes that these results are slightly different from the sponsor's results reported on page 62 of the CLDA-07-DP-02 Study Report. However, the conclusion is the same and is supportive of the primary efficacy analysis.

Table 3. Study CLDA-07-DP-02: Reviewer's efficacy analysis: change from baseline in the MADRS total score (MMRM analysis) over time in the ITT sample

	Placebo		Vilazodone		Vilazodone - Placebo	
visit	N	Mean	N	Mean	Diff	P-value*
Week 1	231	-3.3	232	-3.7	-0.4	0.347
Week 2	223	-5.7	224	-6.7	-1.0	0.087
Week 4	216	-9.2	213	-10.8	-1.6	0.050
Week 6	207	-11.4	203	-13.7	-2.3	0.017
Week 8	196	-11.9	194	-14.8	-2.9	0.006

(Source: Statistical reviewer's results).
Subjects 2080-058, 2020-173, and 2080-047 were excluded from this analysis.
*P-values are not adjusted for multiplicity

9.2 Analysis of Study GNSC-04-DP-02

The primary efficacy endpoint was the change from baseline to week 8 in the MADRS score, with dropout values imputed by the last observation carried forward (LOCF) method. The primary analysis model was ANCOVA with treatment and center factors, and baseline MADRS score as a covariate. The primary efficacy measure was assessed at baseline, weeks 1, 2, 4, 6, and 8 or at early termination. Dr. Dinh confirmed the sponsor's primary efficacy results. Vilazodone was statistically superior to placebo on the change from baseline to week 8 in the MADRS score.

Table 4. Study GNSC-04-DP-02: Sponsor's primary analysis: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	199	198
Baseline MADRS total score		
Mean (Standard deviation)	30.7 (3.9)	30.8 (3.9)
Median (Min – Max)	31 (20 – 41)	31 (21 – 43)
Change from baseline		
LS Means	-9.7	-12.9
Difference from placebo (SE)		-3.2 (0.99)
(95% confidence interval)		(-5.1, -1.2)
P-value		0.001

(Source: GNSC-04-DP-02 Study Report; Tables 11-6 & 11-7, page 66)

Dr. Dinh also confirmed the sponsor's secondary CGI-I efficacy results, as illustrated in the table below.

Table 5. Study GNSC-04-DP-02: Sponsor's secondary efficacy results: CGI-I at week 8 (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	199	198
LS Means	3.0	2.6
Difference from placebo		-0.4
(95% confidence interval)		(-0.6, -0.2)
Unadjusted p-value		0.001

(Source: GNSC-04-DP-02 Study Report; Table 11-26, page 85)

Dr. Dinh also performed a sensitivity analysis on the primary efficacy variable (MADRS score). Table 6 summarizes an MMRM analysis of the treatment effects of vilazodone over the duration of the study. The model included baseline MADRS total score as a fixed covariate, treatment group and visit as fixed factors, and treatment-by-visit interaction. Subjects were treated as a random effect. An unstructured covariance matrix was used. Dr. Dinh notes that these results are slightly different from the sponsor's results reported on pages 160-162 of the GNSC-04-DP-02 Study Report. However, the results are supportive of the primary efficacy analysis.

Table 6. Study GNSC-04-DP-02: Reviewer's efficacy analysis: change from baseline in the MADRS total score (MMRM analysis) over time in the ITT sample

	Placebo		Vilazodone		Vilazodone - Placebo	
visit	N	Mean	N	Mean	Diff	P-value*
Week 1	194	-2.3	192	-4.0	-1.7	0.0001
Week 2	190	-4.8	179	-6.6	-1.7	0.0063
Week 4	178	-7.6	163	-10.4	-2.9	0.0005
Week 6	162	-9.3	160	-13.3	-4.1	<0.0001
Week 8	154	-10.8	152	-14.4	-3.6	0.0007

(Source: Statistical reviewer's results).

*P-values are not adjusted for multiplicity

9.3 Efficacy Findings in Subgroups

Dr. Dinh performed efficacy analyses for subgroups stratified by gender, race, and age. In study CLDA-DP-02, the treatment effect appeared numerically greater for female subjects compared to male subjects. However, there were numerical improvements for both subgroups. In the primary analysis stratified by race (White and Others), there were numerical treatment effects in both subgroups. Only 1% of the subjects were over the age of 65 years. Dr. Dinh dichotomized subjects into 2 groups (≤ 40 years and > 40 years). There were numerical improvements in both age groups. The numerical effect was higher for subjects > 40 years-old. Due to small sample sizes, race was dichotomized into white versus non-white. There was numerical improvement for the White group; however, there was no apparent treatment effect for other races. The majority if subjects in the study were white. There were numerical treatment effects in both age subgroups (≤ 40 years and > 40 years-old. There was a larger effect in the older age group.

9.4 Exploration of Dose-Response Relationships in Study GNSC-04-DP-02

In this study, subjects who could not tolerate the target dose of 40 mg/day were permitted to continue in the study while treated with 20 mg/day. Dr. Dinh performed an efficacy analysis on the small number of subjects who were treated with 20 mg/day. The results are illustrated in Dr. Dinh's table 16 below. Only 28 subjects continued treatment with 20 mg/day. The LS Mean change in MADRS scores were -4.6 and -8.9 for the placebo and vilazodone groups, respectively. The difference between the placebo and vilazodone group was -4.3. The difference was not statistically significant (p= 0.2323). Dr. Dinh notes that it is difficult to interpret the results of this subgroup analysis, due to the small number of subjects in the subgroup.

Table 16. Study GNSC-04-DP-02: Reviewer's analysis: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample for subjects who did not achieve and stay at the target dose of 40 mg/day

	Placebo	Vilazodone
Sample size	13	28
Change from baseline		
LS Means	-4.6	-8.9
Difference from placebo		-4.3
(95% confidence interval)		(-11.6, 2.9)
P-value		0.2323

(Source: Statistical reviewer's results)

9.5 Summary of Primary Efficacy Results from the Phase 2 Studies

Dr. Dinh has summarized the efficacy findings from the five controlled phase 2 studies. The dosages in these five studies ranged from 5 mg/day to 100 mg/day. Three of these studies included an active control for assay sensitivity. The primary efficacy measure for these studies was the change from baseline to the end visit in the HAM-D-17 total score.

The primary efficacy results of these five studies are summarized in Dr. Dinh's Table 7 below. The three studies that had an active control were considered failed, [redacted](b) (4). The remaining two studies were negative.

Table 7. Summary of results on the primary efficacy variables of the phase 2 studies (HAMD)

Report Number (Protocol Number)	Dose/Size	Efficacy results				
		N	Baseline (SD)	LS Means Change from baseline (SE)	Diff from placebo	Unadjusted P-value§
*244	Vilazodone (20-100 mg)	86	23.4 (2.9)	-8.9 (0.8)†	0.76†	0.4938†
(EMD 68 843-009)	Fluoxetine 20 mg	89	24.4 (3.2)	-9.5 (0.8)†	0.15†	0.8924†
	Placebo	95	24.0 (3.1)	-9.6 (0.8)†		
*245	Vilazodone 10-20 mg	104	23.8 (3.0)	-9.7 (0.7)†	0.5†	0.6479†
(EMD 68 843-010)	Vilazodone 40-60 mg	97	23.9 (3.1)	-10.5 (0.8)†	-0.3†	0.7527†
	Vilazodone 80-100 mg	93	23.5 (3.0)	-8.6 (0.8)†	1.6†	0.1310†
	Fluoxetine 20 mg	92	23.5 (2.3)	-11.1 (0.8)†	-0.9†	0.3866†
	Placebo	99	23.4 (2.8)	-10.2 (0.8)†		
*246	Vilazodone 10 mg	120	23.8 (3.1)	-10.8 (0.7)	-0.5	0.5852†
(SB 659746-003)	Vilazodone 20 mg	123	23.7 (3.1)	-11.1 (0.7)	-0.8	0.4069†
	Citalopram 20 mg	117	23.1 (2.6)	-10.9 (0.7)	-0.7	0.5111†
	Placebo	129	23.3 (2.8)	-10.2 (0.7)		
*247	Vilazodone (5-20 mg)	109	23.3 (2.7)	-10.7 (0.7)	-1.0	0.2723
(SB 659746-014)	Placebo	111	23.5 (2.5)	-9.7 (0.7)		
*248	Vilazodone 5mg	140	24.0 (3.0)	-11.0 (0.6)	0.5	0.5654
(SB 659746-002)	Vilazodone 10mg	133	24.5 (3.3)	-12.8 (0.6)	-1.2	0.1770
	Vilazodone 20mg	132	24.3 (3.0)	-11.7 (0.6)	-0.2	0.8019
	Placebo	128	23.7 (2.9)	-11.5 (0.7)		

*All reports begin with GPP-007-CLN-CP2-2003-xxx.
§ P-values are based on respective ANCOVA analyses.
† Reviewer's results. These results are for informational purposes only because they do not strictly conform to the statistical analysis plan. For example, the active controls were not part of the primary contrast so they were not included in the primary analysis model. In study 245, the high dose group was excluded from the primary confirmatory hypotheses. There was also lack of details in term of how centers were pooled. Thus, the results presented in this table are only approximate and are different from the sponsor's results reported in the study reports. However, the results do not change the conclusions of the studies.
(Sources: Study 244: pages 142-143/1543; Study 245: pages 160-161/3600; Study 246: pages 75, 85/1724; Study 247: pages 71, 81/1234; Study 248: pages 73, 84/1624)

9.6 Summary of Secondary Efficacy Results (MADRS) from the Two Phase 2, Fixed-Dose Studies

Two of the phase 2 studies had a fixed-dose design (studies 246 and 248. As noted above, Study 246 was a failed study, and Study 248 was a negative study, based on the primary efficacy analyses in which the HAMD was the primary efficacy measure. In both of these studies, the secondary efficacy measure was the MADRS. As illustrated in the sponsor's

table below, in Study 246 there was a trend toward a positive treatment effect for vilazodone 20 mg/day in the LOCF analysis. The estimated treatment effect was -2.8 points on the MADRS, and the p value was 0.059. The analysis did not adjust for multiplicity.

Study 246 Secondary MADRS Results:

Table 27 Summary of Analysis for Change from Baseline in MADRS Total Score – Adjusted for Centre and Baseline MADRS Total Score (ITT Population)

Change from Baseline to:	Treatment Comparison	Difference[1]	95% CI	P-Value
Week 8 OC	Vilazodone 20 mg vs. Placebo	-3.1	[-6.1, -0.2]	0.035
	Vilazodone 10 mg vs. Placebo	-2.1	[-5.0, 0.9]	0.165
	Citalopram 20 mg vs. Placebo	-2.3	[-5.4, 0.7]	0.136
Week 8 LOCF	Vilazodone 20 mg vs. Placebo	-2.8	[-5.7, 0.1]	0.059
	Vilazodone 10 mg vs. Placebo	-2.3	[-5.2, 0.6]	0.123
	Citalopram 20 mg vs. Placebo	-3.5	[-6.6, -0.5]	0.022

Data Source: Table 13.44, Section 13

1. Difference in adjusted least square means shown (vilazodone or citalopram minus placebo).

In Study 248, there appeared to be a trend toward a positive treatment effect for vilazodone 20 mg/day in the LOCF analysis. The estimated treatment effect was -2.5 MADRS points, and the unadjusted p value was 0.062.

Study 248 Secondary MADRS Results:

Table 27 Summary of Analysis for Change from Baseline in MADRS Total Score – Adjusted for Centre and Baseline MADRS Total Score (ITT Population)

Change from Baseline to:	Treatment Comparison	Difference[1]	95% CI	P-Value
Week 8 OC	SB659746-A 20 mg vs. Placebo	-2.2	[-4.9, 0.5]	0.105
	SB659746-A 10 mg vs. Placebo	-0.8	[-3.3, 1.8]	0.563
	SB659746-A 5 mg vs. Placebo	-0.2	[-2.7, 2.4]	0.900
Week 8 LOCF	SB659746-A 20 mg vs. Placebo	-2.5	[-5.2, 0.1]	0.062
	SB659746-A 10 mg vs. Placebo	-1.9	[-4.5, 0.7]	0.158
	SB659746-A 5 mg vs. Placebo	-0.4	[-2.9, 2.1]	0.725

Data Source: Table 13.44, Section 13

1. Difference in adjusted least square means shown (SB659746-A minus placebo).

10. Advisory Committee Meeting

We did not convene an advisory committee meeting, because the review issues were clear. There were no controversial aspects of the submission.

11. Financial Disclosure

There are no unresolved issues regarding financial disclosures. The sponsor included in the NDA submission Form 3454 (version 10/09) "Certification: Financial Interests and Arrangements of Clinical Investigators." The sponsor indicated that they had not entered

into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR54.2(a).

12. Labeling

We have conducted a labeling review and have begun to discuss labeling with the sponsor.

13. DSI Inspections

Anthony Orencia, M.D. conducted the DSI review for a total of 4 sites from the two pivotal studies. There were no sites of particular concern. We selected two sites for each study that enrolled a large number of subjects enrolled.

13.1 Study CLDA-07-DP-02: Arifulla Khan, M.D.

Arifulla Khan, M.D. was the principal investigator at Site #2020: Northwest Clinical Research Center, 1951 152nd Place NE, Suite 200, Bellevue, WA 98007. At this site, 217 subjects were screened; 162 subjects were randomized to treatment; and 125 subjects completed the study. Dr. Orencia concluded that there was no underreporting of adverse events. There were several observations, and a Form FDA 483 was issued. Dr. Khan responded adequately to the inspectional findings listed in a letter. Dr. Orencia concluded the minor regulatory violations did not have an impact on data integrity and subjects' safety. The study appeared to have been conducted adequately at this site, and the data generated by this site may be used in support of the NDA.

13.2 Study CLDA-07-DP-02: Jerry C. Steiert, M.D.

Jerry C. Steiert, M.D. was the principal investigator at Site #2080: Summit Research Network, Seattle, WA 98104. At this site, 84 subjects were screened; 65 subjects were enrolled and randomized; and 55 subjects completed the study. Dr. Orencia concluded that there was no underreporting of adverse events. There were several observations, and a Form FDA 483 was issued. Dr. Steiert responded adequately to the inspectional findings listed in a letter. Dr. Orencia concluded the minor regulatory violations did not have an impact on data integrity and subjects' safety. The study appeared to have been conducted adequately at this site, and the data generated by this site may be used in support of the NDA.

13.3 Study GNSC-04-DP-02: Nader Oskooilar, M.D., Ph.D.

Nader Oskooilar, M.D., Ph.D. was the principal investigator at Site #2030: Pharmacology Research Institute, 1601 Dove Street Suite 290, Newport Beach, CA 92660. At this site, 62 subjects were screened and enrolled, and 44 subjects completed the study. Dr. Orencia concluded that the conduct of the study of this site was in compliance with Good Clinical Practices. A Form FDA 483 was not issued. The data in support of the NDA are acceptable.

13.4 Study GNSC-04-DP-02: Karl Rickels, M.D.

Karl Rickels, M.D. was the principal investigator at Site #0400: University Department of Psychiatry, Mood and Anxiety Disorders Section, 3535 Market Street, Suite 670Philadelphia, PA 19104-3309. Dr. Orencia concluded that the conduct of the study of this site was in compliance with Good Clinical Practices. A Form FDA 483 was not issued. The data in support of the NDA are acceptable.

13.5 Inspection of PGx Health

Dr. Orencia noted that there were no significant issues in the adherence to sponsor responsibilities in the conduct of the pivotal clinical trials. The sponsor appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was not issued. The data in support of clinical efficacy and safety at this Sponsor site appeared acceptable for this specific indication.

14. Conclusions and Recommendations

14.1 Recommended Regulatory Action

I recommend an approval action. In two adequate and well controlled studies, the sponsor has demonstrated the efficacy of vilazodone 40 mg/day in the treatment of subjects with major depressive disorder. Treatment with vilazodone was reasonably safe and well tolerated in these studies. Generally, the safety profile of vilazodone was extremely similar to those of other SSRI antidepressants. There were no new or unexpected safety findings with vilazodone compared to those observed with SSRIs.

I recommend the following postmarketing requirements that the Division has proposed:

1. I recommend that the Division require the sponsor to conduct pediatric studies in major depressive disorder. We will waive the pediatric study requirement for ages 0 to 6 years-old in the treatment of major depressive disorder, because studies are highly impractical due to the low prevalence of this disorder in this age range. We will defer the requirement for pediatric studies for ages 7 to 17 years-old in the treatment of major depressive disorder. The Division will require the sponsor to obtain pharmacokinetic, safety, and tolerability data in pediatric subjects, in order to provide information about dosing of vilazodone in pivotal studies in MDD. The Division will require the sponsor to conduct two placebo-controlled and active-controlled (fluoxetine) efficacy and safety studies of vilazodone in pediatric subjects (7 to 17 years-old) with a diagnosis of major depressive disorder. At least one of these must be a fixed-dose study.

   To support the use of vilazodone in children younger than 13 years of age, the Division will require the sponsor to conduct a study to assess the safety of vilazodone in juvenile rats. This study must include evaluation of neurological and behavioral development as well as reproductive development.

I recommend the following postmarketing commitments that the Division has proposed:

1. A controlled maintenance study to evaluate the longer-term efficacy of vilazodone in the treatment of adults with major depressive disorder. This study must be placebo-controlled, utilize a randomized withdrawal design, and include an adequate period of stabilization with open-label treatment of vilazodone prior to double-blind randomization.

2. The Division will request that the sponsor conduct a study to further explore the effective dose range of vilazodone in the treatment of major depressive disorder. It is not clear that the lowest effective dose of vilazodone has been identified, because only one dose (40 mg/day) was studied. However, there are suggestions that 20 mg/day may be effective at least in some subjects. In one study, subjects who did not tolerate 40 mg/day could continue in the study on a dose of 20 mg/day; some may have had a significant treatment effect. In addition, data from the phase 2 fixed-dose studies suggest that 20 mg/day may have been effective, as measured by the secondary efficacy measure (MADRS). Moreover, some important adverse reactions are dose-related. Thus, the Division will request that the sponsor further assess the efficacy and safety of vilazodone in the treatment of adults with MDD using fixed doses of vilazodone (20 mg and 40 mg), an active control (for assay sensitivity), and placebo in an adequate and well controlled trial.

3. The Division will request that the sponsor conduct a drug-drug interaction study of vilazodone and a CYP3A4 inducer (carbamazepine) in healthy subjects. Vilazodone is primarily metabolized by CYP3A4. The sponsor has not studied the effect of CYP3A4 induction on vilazodone exposure.

4. The Division will request that the sponsor conduct a study to evaluate the pharmacokinetics of vilazodone in patients with severe hepatic impairment. Vilazodone undergoes extensive hepatic metabolism. The sponsor has not studied the pharmacokinetics of vilazodone in patients with severe hepatic impairment.

5. The Division will request that the sponsor conduct an in vitro study to evaluate whether vilazodone is a substrate or inhibitor of PgP.

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/s/

ROBERT L LEVIN
01/05/2011