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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name Vilazodone HCl
(Proposed) Trade Name Viibryd
Therapeutic Class Antidepressant
Applicant PGxHealth, LLC

Formulation(s) 10, 20, 40 mg tablet
Dosing Regimen Once daily – oral
Indication(s) Major Depressive Disorder
Intended Population(s) Adult

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, approval is recommended (with revisions to the proposed label) of NDA 022567 Viibryd (vilazodone) for the treatment of Major Depressive Disorder in adult patients.

1.2 Risk Benefit Assessment

The efficacy of vilazodone was demonstrated in two (2) of seven (7) controlled trials designed to evaluate vilazodone as a treatment for Major Depressive Disorder in adult outpatients. Review of the safety data submitted by the applicant reveals a safety profile that is similar to other serotonin reuptake inhibitors; with the exception of ophthalmologic abnormalities, there were no unexpected findings.

The efficacy of only one dose of vilazodone, 40 mg qd, was explored. It is the opinion of this reviewer that the dose-response relationship of vilazodone has not been adequately characterized. This should be explored as a post-marketing commitment with a fixed-dose design to provide a valid and rigorous examination of dose-response relationships for efficacy as well as safety and tolerability.

Post-marketing commitments will help elucidate tolerance and withdrawal effects of vilazodone and provide a more thorough understanding of the drug in patients with renal and hepatic impairment.

The labeling should include recommendations to [REDACTED] (b) (4) [REDACTED] Although in the placebo-controlled database, the mean change from baseline and outliers for heart rate and blood pressure were not significantly different for vilazodone compared with placebo; this reviewer concurs with recommendations of the QT-IRT to monitor blood pressure and pulse rate in patients with hypertension or pre-existing heart disease. Concurrence is based on the opinion that it is necessary to further characterize the pharmacokinetic profile of vilazodone with regard to drug-disease interactions and dose response. In the thorough QT study, at the 80 mg dose of vilazodone, 18% of patients met tachycardia outlier criteria as compared with 5% in the placebo group. Current data regarding food effect, dose-response, and drug-disease interaction (severe hepatic and severe renal impairment) indicate that it may be difficult to predict exposure.

Overall, in view of the potential clinical benefit, the risk-benefit assessment is favorable for vilazodone 40 mg/day for the treatment of Major Depressive Disorder in the adult population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In accordance with section 505-1(a) of FDCA, it has been determined that a REMS is necessary for antidepressant medications to ensure the benefits of the drug outweigh the increased risk of suicidality in children, adolescents, and young adults as observed in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. No specific risk was observed within this clinical development program; however, a Medication Guide REMS is required for all members of this therapeutic class.

The REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved.

1.4 Recommendations for Postmarket Requirements and Commitments

Because the efficacy of only one dose of vilazodone, 40 mg qd, was studied, the dose-response of this drug has not been adequately explored. Therefore, the applicant should conduct a clinical trial evaluating vilazodone compared with placebo in fixed doses of 10 mg/day, 20 mg/day, 30 mg/day, and 40 mg/day.

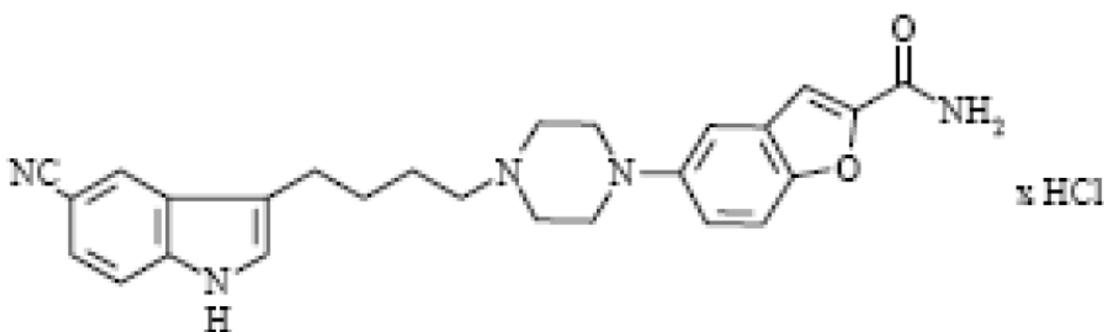
The applicant should also conduct a placebo-controlled, randomized withdrawal trial to assess the occurrence of withdrawal and rebound during taper and discontinuation.

The applicant should also adequately characterize vilazodone with regard to hepatic and renal impairment. The current trials have assessed a small number of patients with mild to moderate impairment of hepatic and renal impairment; no patients with severe impairment have been studied.

2 Introduction and Regulatory Background

2.1 Product Information

USAN: Vilazodone hydrochloride
Molecular Formula: C₂₆H₂₇N₅O₂HCl



Vilazodone hydrochloride is a new molecular entity with putative antidepressant activity as a serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist. Vilazodone has greater in vitro potency and selectivity for serotonin reuptake than fluoxetine. In vitro binding studies also indicate that vilazodone has a greater potency at the 5-HT_{1A} receptor than specific 5-HT_{1A} ligands such as buspirone, an accepted adjunctive treatment for Major Depressive Disorder.

Proposed Trade Name (established name): Viibryd is the proposed trade name and vilazodone HCl is the established name adopted by the United States Adopted Names (USAN) Council.

Chemical Class: New Molecular Entity – belongs to the structural chemical group of the indolalkylamines and is formulated at 10, 20, and 40 mg tablets for oral administration.

Pharmacologic Class: Selective Serotonin Reuptake Inhibitor (b) (4)

Proposed Indications: Treatment of Major Depressive Disorder

Proposed Age Group: Adults

Proposed Dosage and Administration: The recommended dose for vilazodone is 40 mg once daily. Vilazodone should be titrated to the 40 mg dose, starting with an initial dose of 10 mg once daily for 7 days followed by 20 mg once daily for an additional 7 days. Vilazodone should be taken with food.

2.2 Tables of Currently Available Treatments for Proposed Indications

A number of antidepressant medications are available for the treatment of Major Depressive Disorder, including:

Tricyclic Antidepressants	imipramine, desipramine, amitriptyline, nortriptyline, doxepin, amoxapine, trimipramine, protriptyline, maprotiline.
Monoamine Oxidase Inhibitors (MAOI)	phenylzine, tranylcypromine, isocarboxazid, maprotiline, selegiline patch
Selective Serotonin Reuptake Inhibitors (SSRI)	fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram
Serotonin and Norepinephrine Reuptake Inhibitors	venlafaxine, duloxetine, desvenlafaxine
Other Antidepressants	bupropion HCl, bupropion HBr, trazadone, nefazodone, mirtazapine

Electroconvulsive therapy is also available for the treatment of MDD.

2.3 Availability of Proposed Active Ingredient in the United States

This product is a new molecular entity under development for licensing by the applicant and is currently not marketed in the United States. The applicant indicates that the drug product would be readily available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Vilazodone is in the therapeutic class of serotonin specific reuptake inhibitors (SSRI). Although no specific safety issues related to the following items were identified in the vilazodone clinical development program SSRIs, as a class, have been associated with the following safety concerns:

- Suicidality
- Serotonin syndrome
- Seizures
- Abnormal bleeding
- Activation of mania or hypomania
- Hyponatremia

- Discontinuation syndrome

These issues are specifically addressed in Section 7, Review of Safety.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Type of Meeting/Correspondence (Meeting Date) [Correspondence Finalized]	FDA recommendations/comments
Initial IND 54613 (11/21/1997) [12/21/1997]	<ul style="list-style-type: none"> • Per telephone conversation of 12/21/1997, recommend ophthalmology monitoring because of corneal opacities in the six-month dog study. • Request verification of 26 week rat study mammary gland findings.
IND 54613 Type C Meeting (August 7, 2006) [August, 15 2006]	<ul style="list-style-type: none"> • Regarding adequacy of the Phase 1 studies: “the <i>adequacy of the studies will be a review</i> issue. It is suggested the sponsor consider exploring the relationship between vilazodone exposure (e.g. concentration, dose) and response (e.g. efficacy, safety).” • The sponsor should also refer to the Guidance on drug interaction studies on the FDA website.
IND 54613 Type B Meeting (May 11, 2009) [May 19, 2009]	<ul style="list-style-type: none"> • Discussion of pivotal trial CLDA-07-DP-02 • The sponsor agreed to send... the identifying data on the 2 phase II studies that have already been submitted. The information from three trials undertaken by GSK will be submitted, however, the sponsor reported that some appendices were unable to be located. We requested that the primary efficacy results including the Montgomery-Asberg Depression Rating Scale (MADRS) endpoint and the 17-item Hamilton Rating Scale for Depression (HAM-D17) endpoint be sent to us. The sponsor confirmed that all data will be submitted as part of the filing to the new drug application. • We consider Study CLDA-07-DP-02 the first pivotal

	trial to confirm the findings on (b) (4) genetic marker... findings need to be replicated before they could be considered in support of a labeling claim.
IND 54613 Type B Teleconference (June 17, 2009)	<ul style="list-style-type: none"> The data from the two pivotal studies will be presented separately and discussed in the clinical summary of efficacy. PGxHealth does not intend to pool the efficacy data from the two pivotal studies other than for the purposes of subgroup analyses. Data from the five Phase II studies conducted under the sponsorship of Merck and GSK are not considered supportive for the proposed dose and indication.
IND 54613 Email [July 31, 2009]	From PGxHealth, regulatory affairs "I wanted to clarify that we have removed the Pharmacogenetics data from the NDA planned for Q4 of 2009."

2.6 Other Relevant Background Information

The ownership of vilazodone has been transferred among several sponsors, as indicated below:

November 11, 1997 Initial IND 54613 Submission Lipha Pharmaceuticals, Inc (an Associate of Merck)
August 26, 1998 Transfer of ownership from Lipha Pharmaceuticals, NY to Merck KGaA, DE Authorization of PPD Pharmaco as US Agent for IND 54613
May 1, 2001 Transfer of Ownership from Merck to GSK
February 11, 2003 Transfer of ownership from GSK to Merck KGaA
November 7, 2003 Notice of establishment of EMD Pharmaceuticals, Inc. as IND Agent

October 25, 2004

Transfer of ownership of IND 54613 from EMD to Genaissance Pharmaceuticals (GNSC)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was appropriately organized to allow information to be reviewed in an acceptable manner. The responses of PGxHealth to all of FDA's requests were timely and well organized.

3.2 Compliance with Good Clinical Practices

According to statements included in the reports for the pivotal trials the applicant certified that the studies were conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

The Division of Scientific Investigation (DSI) inspected four clinical sites that participated in the pivotal Phase 3 trials and did not find any regulatory violations over the course of the audits of these sites. Audits of the applicant revealed no discrepancies or regulatory violations in terms of oversight and monitoring of the pivotal Phase 3 studies, test article accountability, qualifications of investigators or site monitors, transfer of obligations, adverse event reports, or handling of data.

During this inspection, records and documents included, but were not limited to: organization and personnel; conduct of regulatory responsibilities; appropriate transfer of regulatory responsibilities, contracts, work orders, and agreements; investigator selection; FDA 1572's; clinical investigator training; monitoring procedures; data verification; adverse event reporting procedures; primary efficacy process and verification; eligibility assessment; data collection and computerized systems and use of e-CRF's; test article accountability and reconciliation; and sponsor correspondence.

One Form FDA 483 was issued to Dr. Arifulla Khan, an investigator in Protocol CLDA-07-DP-02, one of the two phase 3 efficacy studies. The Form FDA 483 was issued because the investigation was not conducted in accordance with the investigational plan, and that the investigator did not maintain adequate histories or data pertinent to the research investigation. Dr. Khan responded adequately to the inspectional findings

in a letter dated July 13, 2010. The minor regulatory violations are not considered to have an impact on data integrity and patient safety. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

One Form FDA 483 was issued to Dr. Jerry C. Steiert, an investigator in Protocol CLDA-07-DP-02, one of the two phase 3 efficacy studies. The Form 483 was issued because the investigation was not conducted in accordance with the investigational plan. Specifically, there was lack of full documentation that the washout period for an herbal medication was completed. Dr. Steiert responded adequately to the findings.

The DSI inspection reports indicate that the applicant appears to have executed responsibilities appropriately, and no significant issues were noted. The studies appear to have been conducted adequately, and the data generated appear acceptable in support of the proposed indication.

3.3 Financial Disclosures

Form 3454 (version 10/09) was included in the submission. For the Phase 3 studies the applicant has adequately disclosed financial arrangements with the investigators; no specific issues that raise doubt about the integrity of the data are identified.

Vilazodone was licensed to two previous sponsors (Merck and GSK). Two of the five Phase 2 trials did not collect financial disclosures. PGxHealth obtained a letter from a previous sponsor regarding financial disclosures. The division's response indicated that this is acceptable only if the two Phase 2 trials without financial disclosure are not pivotal studies that support the labeling claims in the NDA. None of the Phase 2 trials are considered pivotal studies for this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry, manufacturing and controls data were reviewed by Dr. Pei-I Chu. The reviewer considered the NDA approvable from a CMC perspective pending satisfactory responses from the applicant regarding questions regarding the drug substance and drug product. At the time of this writing, the response had not been received.

There are no recommendations for post-marketing commitments, agreements, or risk management steps.

The Office of Compliance has determined that pre-approval inspections for the drug substance, drug product and packaging sites are not needed based on the drug profile.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology data was reviewed by Violetta Klimek, Ph.D. At the time of this writing, the review was not available. The review team held several status meetings during the course of this NDA and no significant issues were identified by the pharmacology/toxicology reviewer.

4.4 Clinical Pharmacology

The clinical pharmacology data were reviewed by Bei Yu, Ph. D. At the time this review was completed, the clinical pharmacology review was not available. The review team held many status meetings during the course of this NDA and no significant issues were identified by the clinical pharmacology reviewer.

4.4.1 Mechanism of Action

The applicant reports “vilazodone is a potent and selective inhibitor of serotonin reuptake and a potent and selective partial agonist at the 5HT-1A subtype of serotonin receptors.” It is thought to optimize the regulation of the 5-HT circuitry at both pre- and post-synaptic sites to augment 5-HT transmission, putatively producing antidepressant effect.

Reviewer comment: The in vivo 5-HT1A receptor binding study of vilazodone failed to provide compelling evidence of 5-HT1A binding activity. The meeting minutes from the End of Phase 2 Meeting on December 20, 2005 indicate: “The Office of Clinical Pharmacology noted that the PET study utilizing a 40 mg dose produced mean receptor occupancy of < 30%, whereas the common thought is that at least 80% occupancy may be needed for antidepressant efficacy.”

(b) (4)

4.4.2 Pharmacodynamics

The clinical study report indicates vilazodone binds in vitro with high affinity to the human 5-HT reuptake site (5-HT transporter) with a $K_i=0.1\text{nM}$ and shows lower affinity for the norepinephrine and dopamine reuptake sites. Vilazodone also potently binds to the rat 5-HT transporter and inhibits with high affinity both rat and human 5-HT reuptake. Functionally, vilazodone is a centrally-active 5-HT reuptake inhibitor.

The study report also indicates that vilazodone binds with high affinity to the rat and human 5-HT_{1A} receptor binding sites and is 60 times more potent than buspirone. In vivo studies provide a functional profile for vilazodone that is characteristic of a 5-HT_{1A} partial agonist.

In cardiovascular studies, vilazodone was not active in a human hERG (human ether-a-go-go related gene) channel assay, nor did it have activity indicative of potential proarrhythmogenic effects in guinea pig papillary muscles.

4.4.3 Pharmacokinetics

Absorption

Vilazodone is absorbed after oral administration with T_{max} occurring at 4 to 6 hours. Vilazodone has linear pharmacokinetics with single doses of 2.5 mg to 80 mg and with repeated doses of 20 mg to 80 mg. In the presence of a high fat breakfast the C_{max} values are approximately 150% higher and AUC values approximately 60-90% higher.

Distribution

Vilazodone is highly protein bound, ranging from 96-99% in human serum.

Metabolism

Vilazodone is extensively metabolized by the liver. CYP3A4 is the major enzyme responsible for vilazodone metabolism with minor contributions from CYP2C19 and CYP2D6. The use of vilazodone 10 mg with ketoconazole 200 mg resulted in a 50% increase in C_{max} and AUC. The use of vilazodone with inducers of CYP3A4 may reduce vilazodone concentrations.

Excretion

The elimination half-life is, on average, about 24 hours. The range in various studies is from 8.5 to 36 hours. The half-life for vilazodone following a single 40 mg dose in healthy young adults ranged from 13 – 30 hours. Shorter half-lives were seen in studies where drug concentrations were measured for only 24 hours post-dose. Some studies reported half-lives from approximately 24 – 29 hours with multiple dosing while another study reported a range of 28 – 37 hours. The majority of vilazodone is eliminated in the feces, presumably via secretion of the parent and metabolites into bile.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program of vilazodone for the treatment of MDD in adults included 24 Phase 1 studies, five Phase 2 studies, and three Phase 3 studies during which 2898 subjects received vilazodone.

Table 5.1 Phase 1 Clinical Trials in Healthy Subjects

Protocol	Study Design	Subjects M/F (ITT)	Treatment Arms	Duration/Applicant's Conclusions
EMD 68 843-007 Single dose Food Effect	Single-center OL, R, 2-way crossover of fed and fasting	16/0 Healthy Subjects	Vilazodone 20mg Oral	1 day in each of 2 periods Conclusion: <i>Clear demonstration of food effect – higher exposures with food.</i>
SB-659746/004 Single dose Bioavailability	Open-label, randomized, 3- period crossover	2/12 Healthy subjects 2/13 Healthy subjects 2/11 Healthy subjects	Vilazodone 10mg micronized tablet Vilazodone 10mg non-micronized tablet Vilazodone 10mg micronized capsule	1 day in each of 3 periods Conclusion: <i>Bioavailabilities were similar among the three formulations</i>
SB-659746/013 Single dose Bioequivalence	OL, R, 2 session crossover	18/10 Healthy subjects 19/10 Healthy subjects	Vilazodone 20mg phase II capsule Vilazodone 20mg Phase III capsule	1 day in each session 1 day in each of 3 sessions Conclusion: <i>Bioequivalence criteria met.</i>
SB 659746/047	OL, R, 3 session	17/9	Vilazodone 20mg Phase II capsule	1 day in each of 3 sessions

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Single dose Bioequivalence	crossover	16/12 17/13 Healthy subjects	Vilazodone 20mg Form IV capsule Vilazodone 20mg (b) (4)	Conclusion: (b) (4)
SB-659746/050 Single dose Bioequivalence	OL, R, 2 period crossover	13/17 12/16 Healthy subjects	Vilazodone 20mg tablet Vilazodone 20mg Phase III tablet	1 day in each of 2 periods Conclusion: <i>BE criteria met</i>
(b) (4) R06-1586 Single dose Bioequivalence	DB, R, 2-way crossover	50/23 50/26 Healthy subjects	Vilazodone 40mg (b) (4) tab Vilazodone 40mg (b) (4) tab	1 day in each of 2 periods Conclusion: <i>BE criteria met (high drop out rate d/t nausea and vomiting)</i>
PGX-08-P1-05 Single dose Food Effect Bioavailability	OL, R, 3 period crossover	11/9 Healthy subjects	Vilazodone 20mg tablet	1 day in each of 3 periods Conclusion: <i>Food increased oral bioavailability</i>
PGX-08-P1-08 Single dose Bioavailability	OL, R, 2 period crossover	7/5 7/5 Healthy subjects	Vilazodone 20mg tablet Vilazodone 5 mg IV formulation	1 day in each of 2 periods Conclusion: <i>BA of oral:IV was 72%:81% per dose normalized AUC</i>
PGX-08-P1-07 PK - ADME	OL	7/0 Healthy subjects	Vilazodone 20 mg solution (oral) μ Ci radiation	1 day Conclusion: <i>85% radioactivity recovered, 20% urine, 65% feces</i>

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GPP-007-CLN-CP1-2003-234 Multiple dose Drug interaction	Single center, OL, single sequence, 2 session	22/23 Healthy subjects	Vilazodone 20mg capsule Nifedipine 20 mg capsule CYP cocktail: Debrisoquine Mepheytoin Flurbiprofen Caffeine Oral	10 days: 3 day on CYP drugs only, wash-out followed by 7 days of vilazodone alone, then vilazodone plus CYP drugs Conclusion: <i>20 mg dose is not likely to cause clinically significant drug interactions with 1A2, 2C9, 2C19, 2D6, 3A4</i>
GPP-007-CLN-CP1-2003-240 Single dose Drug interaction	A: single center, R, DB, 2-part crossover B: single center, R, DB, PC	A: 8/7 B: 11/11 Healthy subjects	Vilazodone 5 mg Vilazodone 10mg Ketoconazole 200 mg Placebo oral	A: 1 day vilazodone; 13 days ketoconazole B: 13 days ketoconazole or 13 days placebo Conclusion: <i>A: systemic exposure increased by 45% B: systemic exposure increased 50% with ketoconazole at steady state</i>
PGX-08-P1-1 PK study renal impairment Single dose	Multicenter OL, SD	22/10 Subjects with mild/mod renal impairment and normal renal function	Vilazodone 20mg Oral tablet	1 day Conclusion: Mild or moderate renal impairment has little effect on pK after 20 mg dose
PGX-08-P1-02 PK Study Hepatic impairment	Multicenter, OL, SD	23/10 Subjects with mild/mod hepatic	Vilazodone 20mg Oral tablet	1 day Mild or moderate hepatic impairment has little or no effect on the

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Single dose		impairment and normal function		PK after a single oral dose of 20 mg
GPP-007-CLN-CP1-1998-230 PK MD	SC, DB, R, PC, multiple ascending dose	9/0 12/0 12/0 12/0 Healthy subjects	Placebo capsule Vilazodone 10mg Vilazodone 20mg Vilazodone 40mg Oral	11 days – single dose vilazodone or placebo followed by multiple oral doses vilazodone or placebo Conclusion: The 20 mg dose can be considered max tolerated dose in healthy males.
GPP-007-CLN-CP1-1996-231 PK SD	DB, PC, R, single ascending dose (SAD) in 2 parts	6/0 6/0 6/0 6/0 6/0 Healthy subjects	1: Placebo Vilazodone 2.5mg Vilazodone 5 mg Vilazodone 10mg Vilazodone 20mg 2: Planned but not performed Placebo Vilazodone 40 mg Vilazodone 80 mg Oral	1 day A dose dependent increase in number and intensity of AEs, mainly GI.
GPP-007-CLN-CP1-1997-232 PK SD	DB, PC, R, SAD	9/0 9/0 9/0 9/0 Healthy subjects	Placebo Vilazodone 20mg Vilazodone 40mg Vilazodone 80mg Oral	1 day Conclusion: This study indicates a longer $t^{1/2}$ 20-24 hours. Dose dependent increase in hGH was observed.
GPP-007-CLN-CP1-2003-237 PK SD MD Elderly	MC, SB,R, PC, parallel group, SAD, and MAD	5/6 1/3 2/3 5/3 5/2 3/5 Healthy	Placebo, elderly Placebo, young Vilazodone 5mg elderly Vilazodone 10mg elderly Vilazodone 20mg Elderly Vilazodone 20mg young	Session 1: 1 day of vilazodone or placebo Session 2: 7 days of vilazodone or placebo

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		subjects		
GPP-007-CLN-CPI-2001-255 PET Study Receptor occupancy	Single center, single dose 2 scan	2/0 4/0 Healthy subjects	Vilazodone 20mg Vilazodone 40mg	2 days (day 0 and day 7)
GPP-007-CLN-CP1-2001-241 Multiple dose REM suppression study	Single center, DB, PC, randomized, crossover	7/8 Healthy subjects	Placebo capsule Vilazodone 1 mg Vilazodone 5 mg Vilazodone 10mg oral	12 days of vilazodone, 3 days of placebo and 1 day of no dose for 4- 1week periods
PGX-08-P1-06 TQT – ECG	DB, R, PC, Moxifloxacin controlled, 3- arm, ascending dose parallel group	23/22-pbo 30/36-vil 22/23-mox Healthy subjects	Placebo Vilazodone 10mg Vilazodone 20mg Vilazodone 40mg Vilazodone 60mg Vilazodone 80mg Moxiflox. 400mg Oral	15 days of placebo or 4 days of moxifloxacin and 11 days of placebo or 15 days of vilazodone Conclusion: Vilazodone had no effect on HR, PR, QRS or cardiac morphology. up to 80 mg showed no increase in QTcl.
GPP-007-CLN-CP1-2003-238 Multiple dose effects on ejaculation latency	Multi-center, DB, R, PC, double- dummy parallel group	22/0 21/0 23/0 Healthy subjects	Placebo to match fluoxetine and vilazodone vilazodone 20mg fluoxetine 20 mg	28 days of fluoxetine, vilazodone or placebo
PGX-08-PI-04 Ethanol effect Bioavailability	Single center, OL 2-period crossover, multiple dose	27/10 Healthy subjects	Vilazodone 40mg Ethanol 30 mL Oral	2 days Vilazodone plus ethanol followed by a ten day washout, then vilazodone alone

PGX-08-P1-03 BA Effect of gastric pH	OL 2-period crossover, multiple dose	16/21 Healthy subjects	Placebo Vilazodone 20mg Oral	8 days (1 day vilazodone; 7 days pantoprazole; the last was vilazodone + pantoprazole)
GPP-007-CLP-CP1-2001-235 PD Sleep EEG	DB, R, PC, Crossover	10/0 Healthy subjects	Placebo Vilazodone 20 mg Oral	2 days Vilazodone or placebo on Days 8 and 15

5.2 Review Strategy

The applicant conducted two adequate and well-controlled trials, studies **GNSC-04-DP-02** and **CLDA-07-DP-02**, which were the focus of the efficacy review. Seven placebo-controlled trials (five phase 2 studies and two phase 3 studies) were the focus of the safety review. In addition, data from the 52-week, uncontrolled, long-term safety study, **CLDA-07-DP-04** and the 'all vilazodone exposure' safety data were reviewed.

Review materials included the original data sets, individual study reports, integrated efficacy and safety summaries, patient narratives, and case report forms.

5.3 Discussion of Individual Studies/Clinical Trials

The efficacy of vilazodone as an antidepressant was evaluated in two Phase 3 clinical efficacy trials, GNSC-04-DP-02 and CLDA-07-DP-04, which are discussed in Section 6.

The individual study results for the 5 Phase 2 studies conducted by Merck and GSK are not considered supportive of efficacy claims because (b) (4)

However, these Phase 2 studies provided information with regard to dose selection and safety.

The efficacy results of the 5 Phase 2 studies are presented in the following table, reproduced from the Biostatistics Review.

Table 5.3.1 Biostatistics Review/Confirmation Table – HAM-D

Report Number (Protocol Number)	Dose/Size	Efficacy results Phase 2 Studies				
		N	baseline (standard deviation)	least square means; change from baseline (standard error)	Difference from placebo	Unadjusted P-value [§]
*244 (EMD 68 843-009)	Vilazodone (20-100 mg)	86	23.4 (2.9)	-8.9 (0.8) [†]	0.76 [†]	0.4938 [†]
	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 (EMD 68 843-010)	Vilazodone 10-20 mg	104	23.8 (3.0)	-9.7 (0.7) [†]	0.5 [†]	0.6479 [†]
	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 (SB 659746-003)	Vilazodone 10 mg	120	23.8 (3.1)	-10.8 (0.7)	-0.5	0.5852 [†]
	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 (SB 659746-014)	Vilazodone (5-20 mg)	109	23.3 (2.7)	-10.7 (0.7)	-1.0	0.2723
	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)		

GPP-007-CLN-CP2-2001-244

Study EMD 68 843 [vilazodone]-009

This was a randomized, double-blind, multicenter (13 U.S. sites) parallel group, phase 2 study comparing vilazodone, titrated over a two week period to a maximum tolerated dose of 20, 40, 60, 80, or 100 mg/day, to placebo and the active comparator, fluoxetine 20 mg/day, in adult patients meeting DSM-IV criteria for Major Depressive Disorder (single or recurrent episode). Patients completed a 3- to 7-day, single-blind, placebo period followed by a double-blind treatment period of approximately 8 weeks. All treatments were to be administered orally, once daily. The protocol instructed subjects to take the medication with food.

Patients were to have a Hamilton Depression Rating Scale-17 item (HAM-D-17) total score, of ≥ 20 at screening and baseline and could not have a decrease $>20\%$ in the HAM-D assessment from screening to baseline.

Patients were screened and if qualified, were enrolled in the study. All patients were to take part in each of the three study phases:

Phase 1

At the time of enrollment, patients started the first phase of the study; a 7 day, single-blind, washout in which they received an oral placebo dose once daily.

Phase 2

A two-week, double-blind, dose-titration period in which patients assigned to EMD 68 843 received 10 mg on Day 1. Thereafter, if the current dose was tolerated, the dose was to be increased from 20 mg to 100 mg once daily (over approximately 3 days per dose level). Patients assigned to fluoxetine or placebo received 20 mg of fluoxetine or placebo, respectively, once daily throughout the titration period.

Phase 3

The third phase consisted of a six-week, double-blind, dose-maintenance period. By Day 15, the investigator was to establish a maximum dose level for each patient based on tolerability. Patients in the vilazodone group treatment received doses ranging from

20 mg to 100 mg once daily, patients in the fluoxetine or placebo groups received 20 mg of fluoxetine or placebo until Visit 8 (Day 56).

Efficacy Variables

The efficacy measures included the Hamilton Rating Scale for Depression (HAM-D-17), the Montgomery-Asberg Depression Rating Scale (MADRS) total score, HAM-D Depressed Mood score (item 1 of HAM-D), Clinical Global Impression-Severity (CGI-S), and CGI-Improvement (CGI-I). The CGI comprises two one-item measures evaluating the severity of the illness (CGI-S) and improvement from initiation of treatment (CGI-I). CGI-S is measured as a 1-7 ranking of severity of illness where 1=normal, not ill at all and 7=among the most extremely ill. The CGI-I is measured as a 1-7 ranking of improvement from baseline, where 1=very much improved and 7=very much worse.

The primary efficacy variable was the HAM-D-17 total score, which can range from 0 to 50 (based on 0-4 or 0-2 scale for 17 items assessing depressive symptoms). A higher score indicates more severe depression. Secondary efficacy variables included the HAM-D-1 Depressed Mood score, MADRS (which can range from 0 to 60 based on ten items assessing depressive symptoms). A higher score indicates more severe depression. The review focused on the intent-to-treat (ITT) sample, defined in the protocol as all patients who were randomized and received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one follow-up time. This is technically, a modified ITT population.

The primary efficacy objective of this study was to reject the null hypothesis that EMD has equal efficacy to placebo in the ITT population using the HAM-D-17 total score change from baseline to endpoint, last observation carried forward (LOCF). The main effects analysis of variance (ANOVA) model with treatment and center was to be used and a full model, including the treatment by center interaction, was to be used for exploratory analysis of the interaction. If ANOVA assumptions were violated, additional and appropriate non-parametric statistical analysis was to be performed. The estimate of treatment effect was to be presented as a two-sided 95% confidence interval for the contrast comparing vilazodone with placebo.

Study Results

In total, 420 patients were enrolled, of whom 374 (89%) entered the single-blind placebo period and 289 (69%) were randomized. Of the randomized patients 99% were evaluable for safety, 93% participated in at least one efficacy evaluation and were classified as ITT. Although the number of patients randomized to the three treatment groups was similar, the number of patients in the per-protocol population was lower in the vilazodone group (n=34) than in the placebo group (n=58).

The demographic characteristics among the three treatment groups were similar, although the vilazodone group tended to be older than the placebo group. The mean baseline HAM-D-17 score for the safety population was approximately 24 for each of the three treatment groups. The use of pain relievers as concomitant medications was prevalent in all groups. Fewer subjects in the vilazodone group were considered to be compliant with dosing, specifically, 73% placebo, 71% fluoxetine, and 57% vilazodone.

Efficacy Findings

The applicant's report indicates that the mean improvement in the HAM-D-17 total score from baseline to endpoint was not different for the vilazodone treatment group compared with the placebo group. A large placebo effect was observed.

Table 5.3.2 Change from Baseline for Primary and Secondary Efficacy Measures EMD 68843 is vilazodone

Table 5.3.2: Efficacy score changes from Baseline to Endpoint (ITT population)

ASSESSMENT	Baseline and change from Baseline						EMD 68 843 vs. placebo p-value	EMD 68 843 vs. fluoxetine p-value
	Placebo N= 95		Fluoxetine N= 89		EMD 68 843 N= 86			
	Mean	(SD)	Mean	(SD)	Mean	(SD)		
HAM-D total								
Baseline	24.0	(3.1)	24.4	(3.2)	23.4	(2.9)		
Change at Endpoint	-9.3	(7.8)	-9.1	(7.4)	-8.9	(7.7)	0.4885	0.7042
HAM-D depressed mood								
Baseline	3.0	(0.5)	3.1	(0.6)	2.9	(0.6)		
Change at Endpoint	-1.2	(1.1)	-1.4	(1.1)	-1.3	(1.2)	0.7041	0.5241
MADRS								
Baseline	30.0	(3.8)	30.8	(4.2)	30.2	(4.0)		
Change at Endpoint	-10.4	(9.8)	-11.8	(10.1)	-12.7	(9.9)	0.1745	0.6052
CGI-Severity								
Baseline	4.3	(0.6)	4.4	(0.6)	4.3	(0.6)		
Change at Endpoint	-1.1	(1.4)	-1.2	(1.3)	-1.3	(1.2)	0.4184	0.9121
CGI - Improvement Endpoint	2.8	(1.3)	2.6	(1.2)	2.7	(1.2)	0.5754	0.8713
PGI - Improvement Endpoint	3.3	(1.4)	3.0	(1.4)	2.8	(1.3)	0.0251	0.3339
MEL								
Baseline	12.3	(2.9)	12.2	(3.1)	12.5	(2.6)		
Change at Endpoint	-3.4	(4.8)	-4.7	(4.6)	-5.0	(4.2)	0.0405	0.6970

Data from end-of-text [Table 9.2.7](#).

For HAM-D (total and mood), MADRS, CGI-S and MEL scores, more improvement from Baseline corresponds to a larger negative value. For CGI-I and PGI scores more improvement from Baseline corresponds to a smaller positive value.

Source: CSR EMD 68843-009

The applicant reports a dose-response comparison was not appropriate because during the dose-maintenance period, most (52/66, 78%) patients received 80-100 mg/day.

Discussion

This first phase II study was to establish the upper limit of the dose range of the compound in terms of tolerability, and if efficacy at such a dose was observed. The study was not designed to provide dose-response information; there is evidence of intolerable adverse events at the higher doses.

The impression is that this trial did not demonstrate a difference among the three treatment groups. The mean change in the primary efficacy variable was greater for placebo than for the active comparator and vilazodone. The active comparator group did not demonstrate statistical superiority to placebo; therefore, it appears that this study lacks the sensitivity to detect a drug effect and conclusions of effectiveness cannot be drawn from this study.

GPP-0070-CLN-CP2-2001-245

EMD 68 843-010

A Double-Blind, Randomized, Multicenter, Parallel Design Study to Evaluate the Efficacy and Safety of **Three Dose Ranges of EMD 68 843 [vilazodone] in Comparison with Placebo and Fluoxetine in Outpatients with Major Depressive Disorder (MDD)**

Principal Investigator: James Claghorn, MD
Claghorn-Lesem Research Clinic, Inc.
Bellaire, Texas, USA

The primary objective of this study was to evaluate the therapeutic efficacy and safety of EMD 68 843 (vilazodone), at three dose ranges compared to placebo and fluoxetine, 20 mg, in patients with MDD, as measured by the Hamilton Depression Rating Scale, first 17 items (HAM-D-17).

Trial EMD 68 843-010 was a phase 2, randomized, double-blind, multicenter, placebo- and active-controlled trial of 3 doses of vilazodone, conducted at 21 US sites. The study was conducted in male and female, adult outpatients 18-70 years of age who met DSM-IV criteria for major depressive disorder. Patients with serious co-occurring psychiatric and/or medical diagnoses were excluded. Baseline HAM-D-17 score of ≥ 20 and Montgomery Asberg Depression Rating Scale (MADRS) score ≥ 25 were required for randomization.

The trial consisted of a 7-day single-blind, placebo run-in period followed by an 8-week double-blind treatment period. Because of gastrointestinal tolerability issues, a 2-week titration period was required. The patients were screened and when enrolled began the

7-day placebo run-in. Patients were then randomized to low, medium, or high doses of vilazodone (10-20 mg/day, 40-60 mg/day, or 80-100 mg/day), fluoxetine 20 mg/day, or placebo. All treatments were administered orally, once daily, with food.

Because of gastro-intestinal (GI) tolerability, a 14-day titration period was employed:

- Low Dose – EMD 10-20 mg:
Received 10 mg/day for 14 days – if no improvement¹ at Day 14, the dose was increased to 20 mg/day on Day 15
- Medium Dose – EMD 40-60 mg:
Received 10 mg on Day 1, 20 mg/day on Days 2 and 3, 40 mg/day for Days 4-14; if no clinical improvement was seen at Day 14, the dose was to be increased to 60 mg/day on Day 15
- High Dose – EMD 80-100 mg:
Received 10 mg on Day 1, 20 mg/day on Days 2 and 3, 40 mg/day from Days 4-6 and 80 mg/day for Days 7-14; if no clinical improvement was seen at Day 14, the dose was to be increased to 100 mg/day on Day 15
- Fluoxetine – 20 mg
On Day 1 and all subsequent days the patients received a matching oral treatment of fluoxetine 20 mg
- Placebo
On Day 1 and all subsequent days the patients received a matching oral placebo treatment

Patients were evaluated at Screening (day -7 to -3), Baseline (Day 0), Days 7, 14, 21, 28, 42, and at the end of the double-blind treatment period on Day 56. A post-study safety assessment was to occur at Day 63.

The primary efficacy variable was the change from baseline to endpoint in the 17-item HAM-D-17 score for the low- and medium-dose vilazodone groups compared to placebo.

The secondary efficacy variables included the change from baseline to endpoint in HAM-D Depressed Mood score, MADRS total score, CGI-S, and CGI-I, among others. Secondary efficacy variables also included responders analyses for HAM-D total, MADRS, CGI-S, and remission analysis (HAM-D-17 total score ≤ 7).

The dose levels of EMD administered on Day 15 were maintained throughout the third phase of the study (Days 15-56) unless the tolerance level was unacceptable. If at any time the tolerability was not acceptable, patients could revert to the lowest dose within the respective range. The total study duration for each patient was a maximum of 10 weeks. Tolerability of the drug was based on subjective complaints and the clinical assessment of the investigator.

The primary endpoint was evaluated with the 2-sided analysis of variance (ANOVA) test on the modified intent-to-treat population (all subjects who were randomized and who received at least one dose of study agent in the treatment period). If a patient discontinued the study prematurely, the last available measurement under randomized treatment was to be carried forward to the endpoint analysis.

Study Results

In total, 960 patients were enrolled and started the 7-day placebo period. At Day 0 (Baseline visit) 517 (54%) were randomized. To qualify for randomization the HAM-D-17 total score at Day 0 was to be ≥ 20 and MADRS total score ≥ 25 . Of those randomized, 485 (94%) participated in at least one efficacy evaluation and were evaluated as the ITT (intent-to-treat) population. Similar numbers of patients were randomized among the five treatment groups. Higher numbers of patient withdrawals occurred in all vilazodone groups as compared to placebo and fluoxetine groups. Most of the withdrawals were due to adverse events.

The applicant did not provide a table of the demographic characteristics of the ITT population. In the safety population, the demographic characteristics were similar for all treatment groups, most of the patients were Caucasian (75-88%), female (55-70%) and between the ages of 31-60 years. The median baseline HAM-D-17 score was 23 for each treatment group, with the means ranging from 23.4 – 23.9. Medical histories, psychiatric histories and concomitant medications were similar for each group. Treatment compliance was approximately 80% for the placebo, fluoxetine, and low-dose groups and progressively declined in the medium and high dose groups.

Efficacy Findings

The mean improvement in the HAM-D total score from baseline to Endpoint was not different for the low and medium vilazodone treatment groups compared with the placebo treatment group. A large placebo effect was observed in the change from baseline to Endpoint (see table 5.2.1).

Protocol amendment 3 of June 11, 1999 states: “remove the 80 – 100 mg EMD 68843 dose group from the confirmatory statistical analysis, which made the confirmatory analysis be between the 10-20 mg and 40-60 mg dose groups and placebo only”.

According to the applicant, a large placebo effect was observed for most efficacy assessments. Fluoxetine, at a recommended dose, failed to show superiority compared with placebo.

Discussion

This is a 'failed study'.

(b) (4)

GPP-007-CLN-CP2-2003-246

SB-659746-A/003

**A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study
Evaluating the Efficacy and Safety of SB-659746-A (10 and 20 mg/day) and
Citalopram (20 mg/day) in patients with Major Depressive Disorder**

Sponsor: GlaxoSmithKline
Compound: SB-659746-A – vilazodone
Initiation 08Oct2001
Completion 01Nov2002

Primary Objective

To evaluate the antidepressant efficacy of vilazodone, 10 mg/day and 20 mg/day compared with placebo in outpatients with MDD. The primary efficacy measure was the change from baseline to week 8 in the HAM-D-17 total score.

Secondary Objectives

To assess the safety and tolerability of vilazodone
To provide preliminary data on the time to onset of therapeutic effect of vilazodone
To provide preliminary data on the anxiolytic effect of vilazodone

Subjects

Outpatients from 39 U. S. centers were eligible for enrollment in the trial. Randomization of 508 evaluable subjects was thought to be sufficient to provide 127 patients in each of the 4 treatment arms.

Key Inclusion Criteria

- Male or female outpatients between 18-65 years of age with MDD
- Major Depressive Episode (MDE) of less than one year's duration
- HAM-D-17 \geq 20 at screening and baseline
- Females of child bearing potential with negative pregnancy test and using double barrier contraceptive measures

Key Exclusion Criteria

- HAM-D-17 decreased by $\geq 25\%$ between screening and baseline
- Co-morbid Axis I diagnosis
- Actively suicidal or likely to require hospitalization during the trial
- ECT within six months of screening
- Patients requiring other psychotropic medications
- Patients with clinically significant cardiac, renal, neurologic, cerebrovascular, metabolic or pulmonary disease
- Pregnant or lactating females
- Patients previously unresponsive to SSRIs

Prohibited Medications

Insulin treatment was prohibited, although oral hypoglycemic agents were allowed. Migraine medications with a serotonergic mechanism of action were prohibited. Psychotropic medications were prohibited.

Study Design

This was an 8-week, 4-arm, parallel group, placebo and active comparator controlled, fixed dose study. The four treatment groups were: vilazodone 10 mg/day, vilazodone 20 mg/day, citalopram 20 mg/day, and placebo.

Screening – Visit 1

Screening assessments were performed and patients were provided with one bottle of single-blind placebo for the 7-day placebo washout/run-in period.

Baseline – Visit 2

Following the one week single-blind placebo phase, baseline evaluations were conducted to determine eligibility to enter the 8-week double-blind treatment phase. Those eligible were randomized to one of the 4 treatment arms (1:1:1:1).

The patients were instructed to take the study medication once daily, in the morning, with food.

Patients randomized to receive the 20 mg dose of vilazodone received 10 mg/day for the first 7 days of double-blind treatment period, after which the dose was increased to 20 mg/day.

Vilazodone (10 and 20 mg), citalopram (20 mg), and placebo were identical in appearance as chocolate brown capsules. The investigational plan does not specify the blinding procedure used for titration to vilazodone 20 mg.

Double-Blind Treatment – Visits 3-8 (Weeks 1-8)

Treatment phase visits were scheduled at the end of Weeks 1, 2, 4, 6, and 8. A mandatory follow up was scheduled for 14 days after the last dose of double-blind study medication. A 28-day follow up was scheduled if there were any ongoing adverse events at the 14-day follow up assessment. If a patient completed the 28 day follow-up visit, the maximum amount of time participated in the study was 13 weeks.

Efficacy Variables

Assessments included the HAM-D-17 as the primary efficacy variable. Several measures, including, Hospital Anxiety and Depression Scale (HAD), MADRS, CGI, Sheehan Disability Scale (SDS), were listed as secondary endpoints although none were evaluated with a rigorous statistical plan, and all are regarded as exploratory.

Study Results

Patients in the ITT dataset were between 18 and 64 years old, with a mean age of 38 years. Seventy-nine percent (79%) were Caucasian, 10% were African-American, 1% were classified as Oriental and 9% were classified as other. Sixty percent (60%) were female. The treatment groups were comparable at baseline on the demographic and symptom severity variables.

A total of 511 patients were randomized, 3 subjects at center 022 were excluded from the safety and efficacy tables on the recommendation of GSK Worldwide Regulatory Compliance. The remaining subjects were randomized, of which 68% completed the 8-week treatment phase. The ITT population consisted of 96% of those randomized.

Table 5.3.3 HAM-D-17 Total Score Change from Baseline

Group	Baseline	LOCF Wk 8 ¹	Difference	Difference ² (adjusted LSM)	P-value
Placebo N=128	23.3	13.1	10.2		
Vilazodone 10 N=119	23.8	13.0	10.8	-0.5	0.585
Vilazodone 20 N=121	23.7	12.6	11.1	-0.8	0.407
Citalopram 20 N=115	23.1	12.3	10.8	-0.7	0.511

¹primary analysis; ²difference in adjusted least squares means

Source: CSR SB659746-A003

Discussion

The improvement in the HAM-D-17 total score ranged from 10.2-11.1 points in all groups, including the active comparator and placebo. (b) (4)

GPP-007-CLN-CP2-2003-247

SB-659746-014

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Flexible-dose Study Evaluating the Efficacy and Safety of SB-659746-A in Patients with Major Depressive Disorder

Sponsor: GlaxoSmithKline
Compound: SB-659746-A – **vilazodone**
Initiation: 05-Nov-2001
Completion: 08-Nov-2002

Primary Objective

- To evaluate the antidepressant efficacy of flexible doses of vilazodone (5-20 mg/day) compared with placebo in outpatients with Major Depressive Disorder (MDD)

Secondary Objectives

- To assess the safety and tolerability of vilazodone
- To provide preliminary data on the anxiolytic effect of vilazodone

Subjects

Outpatients from 27 centers in the U. S. and Canada with a diagnosis of MDD were eligible for enrollment. The target for randomization was 216 subjects to yield 108 patients in each treatment group.

Key Inclusion Criteria

- Male or female outpatients, 18-65 years of age with MDD
- MDD of less than one year's duration
- HAM-D-17 ≥ 20 at screening and baseline
- Females of child bearing potential with negative pregnancy test and using double barrier contraceptive measures

Key Exclusion Criteria

- HAM-D-17 decreased by $\geq 25\%$ between screening and baseline
- Co-morbid Axis I diagnosis
- Actively suicidal or likely to require hospitalization during the trial

- ECT within 6 months of Screening
- Patients requiring other psychotropic medications
- Patients with clinically significant cardiac, renal, neurologic, cerebrovascular, metabolic or pulmonary disease
- Pregnant or lactating females
- Patients previously unresponsive to SSRIs

Prohibited Medications

Insulin treatment was prohibited, although oral agents for the treatment of diabetes were allowed. Migraine medications with serotonergic mechanism of action were prohibited, as were psychotropic medications.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of flexible doses of vilazodone (5 to 20 mg/day).

Screening – Visit 1

Approximately 7 days prior to the baseline visit, informed consent was obtained and screening assessments were performed to determine eligibility to be enrolled in the study. If eligible, patients were provided with one bottle of single-blind placebo for the 7-day placebo washout/run-in period.

Baseline – Visit 2

Following the one-week single-blind placebo phase, baseline evaluations were conducted to determine eligibility to enter the 8-week double-blind treatment phase. The subjects meeting all inclusion and no exclusion criteria were randomized 1:1 to either vilazodone or placebo.

The patients were instructed to take the study medication once daily, in the morning, with food.

Double-Blind Treatment – Visits 3-8 (Weeks 1-8)

All patients in the vilazodone arm received 5 mg for the first week of the treatment phase. The dose could then be increased to 10 mg followed by 20 mg at the discretion of the investigator, based on clinical response and tolerability. Dose levels could only be increased by one level at 7 day intervals.

A dose level reduction during the treatment phase was permitted in the event of an intolerable adverse event (AE); however, this was permitted only once during the course of the study.

Treatment phase visits were scheduled at the end of Weeks 1, 2, 3, 4, 6, and 8. A 14-Day follow-up visit occurred at the end of Week 8 or upon early termination. A 28-Day follow-up visit was scheduled if there were ongoing AEs.

If a patient completed the 28-Day follow-up visit, the maximum amount of time in study was 13 weeks.

Efficacy Variables

The primary efficacy variable was the change from baseline to Week 8, LOCF, in the HAM-D-17 total score, comparing vilazodone to placebo. Several secondary efficacy variables were employed, although none were assessed with an appropriate statistical plan. As such, all are regarded as exploratory. The secondary efficacy variables were: HAM-D-1, HAM-D anxiety item scores, CGI-S and CGI-I, SDS, and MADRS.

Study Results

Patients in the intent to treat (ITT) dataset were between 18 and 64 years old, with a mean age of 34 years. Eighty-four (84) percent were Caucasian, 8% were African-American, 2% were classified as Oriental and 7% were classified as other. Sixty-two (62) percent were female. The treatment groups were comparable at baseline on the demographic and key variables of symptom severity.

A total of 228 patients were randomized, 113 to the vilazodone group and 115 to the placebo group. Of the randomized population, 161 (71%) subjects completed the 8-week treatment phase and 67 (29%) patients withdrew early. The ITT population consisted of 96% of those randomized. The number of patients in the ITT population was evenly distributed between the two treatment groups. The following table taken from the applicant's submission indicates study completers in the ITT population.

Table 5.3.4 Study Completers - 659746-014

Reason for Study Conclusion	Treatment Group n (%)		
	Vilazodone (N = 109)	Placebo (N = 111)	Total (N = 220)
Completed Study ¹	75 (68.8)	86 (77.5)	161 (73.2)
Total Number of Withdrawals	34 (31.2)	25 (22.5)	59 (26.8)
Adverse Event ²	10 (9.2)	2 (1.8)	12 (5.5)
Insufficient Therapeutic Effect	5 (4.6)	9 (8.1)	14 (6.4)
Protocol Deviation (Incl. Non-Compliance)	3 (2.8)	2 (1.8)	5 (2.3)
Lost to Follow-up	9 (8.3)	5 (4.5)	14 (6.4)
Other ³	7 (6.4)	7 (6.3)	14 (6.4)

Data Source: [Table 12.7, Section 12](#)

1. A subject was considered to have completed if they remained in the study up to and including Visit 8 (week 8).
2. Including death as an outcome
3. Including unknown and non-study-related personal reasons

Source: CSR 659746-014

As illustrated in the following table, the HAM-D-17 total score at week 8 is not significantly different from placebo.

Table 5.3.5 HAM-D-17 Total Score Study 659746-014

Group	Baseline	LOCF Wk 8 ¹	Difference	Difference ² (adjusted LSM)	P-value
Placebo N=110	23.5	13.7	9.7		
Vilazodone 10 N=107	23.3	12.8	10.7	-1.0	0.27

¹primary analysis; ²difference in adjusted least squares means

Source: CSR 659746-014 Table 13.3

Discussion

[REDACTED]

(b) (4)

The adjusted mean difference between vilazodone and placebo HAM-D-17 at Week 8 LOCF was -1.0 point (p=0.3). There was no statistically significant evidence indicating a difference in the change from baseline to Week 8 LOCF endpoint in HAM-D total score between placebo and vilazodone.”

There was not statistically significant evidence of a change from baseline in HAM-D anxiety items total score between vilazodone and placebo.

Of note, the study was not designed to provide dose-response information and the statistical information in this clinical study report did not provide a summary analysis on the basis of vilazodone dose.

GPP-007-CLN-CP2-2003-248

SB-659746-A/002

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating Efficacy and Safety of Three Doses of Vilazodone (5 mg, 10 mg, and 20 mg) in Patients with Major Depressive Disorder

Sponsor: GlaxoSmithKline
Compound: SB-659746-A – **vilazodone**
Initiation: 24-Sep-2001
Completion: 30-Aug-2002

Primary Objective

- To evaluate the antidepressant efficacy of three doses of vilazodone compared to placebo in outpatients with Major Depressive Disorder (MDD)

Secondary Objectives

- To assess the safety and tolerability of vilazodone
- To provide preliminary data on the time to onset of therapeutic effect
- To provide preliminary data on the anxiolytic effect of vilazodone

Subjects

A target of 552 outpatients with a diagnosis of MDD from 39 centers in the United States was proposed to yield 138 patients in each treatment group.

Key Inclusion Criteria

- Male or female outpatients, 18-65 years of age with MDD
- MDD of less than one year's duration
- HAM-D-17 ≥ 20 at screening and baseline

- HAM-D-1 (depressed mood) ≥ 2 at screening and baseline

Key Exclusion Criteria

- HAM-D-17 decreased by $\geq 25\%$ between screening and baseline
- Co-morbid Axis I diagnosis
- Actively suicidal or likely to require hospitalization during the trial
- ECT within 6 months of screening
- Patients requiring other psychotropic medications
- Patients with clinically significant cardiac, renal, neurologic, cerebrovascular, metabolic or pulmonary disease
- Pregnant or lactating females (females of childbearing potential must have negative pregnancy test and use acceptable contraception)
- Patients previously unresponsive to SSRIs

Prohibited Medications

- Insulin (oral agents acceptable)
- Migraine medication with serotonergic mechanism of action
- Psychotropic medications

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of three doses of vilazodone (5, 10, and 20 mg/day) compared with placebo.

Screening – Visit 1

One week prior to the baseline visit, informed consent was documented and screening assessments were performed to determine eligibility for the one week, single-blind placebo run-in phase. If eligible, the patient was registered, the placebo was dispensed, and the baseline visit was scheduled for one week later.

Baseline – Visit 2

Baseline evaluations were conducted to determine eligibility to enter the 8-week, double-blind treatment phase. The subjects meeting all inclusion and no exclusion criteria were randomized to one of 4 treatment arms: vilazodone 5 mg, 10 mg, 20 mg, or placebo. They were instructed to take the study medication once daily in the morning with food. During the run-in phase and throughout the treatment phase no other psychotropic medications were allowed.

Double-Blind Treatment – Visits 3-8 (Weeks 1-8)

Patients randomized to the 20 mg dose received 10 mg/day for the first 7 days of the double-blind treatment and then had the dose increased to 20 mg/day, for other

treatment arms, the starting dose was the final dose. Treatment phase visits were scheduled at the end of Week 1, 2, 3, 4, 6, and 8. A mandatory 14-day (a 1-7 ranking of severity of illness where 1=normal, not ill at all and 7=among the most extremely ill).follow-up visit occurred 2 weeks after the last dose of study medication at the end of Week 8 or early termination. A 28-day follow-up Visit was also scheduled if there were any ongoing adverse events at the 14-Day follow-up Visit.

If a patient completed the 28 day follow-up Visit, the maximum amount of time participated in the study was 13 weeks.

Efficacy Variables

The primary efficacy variable was the change from baseline to Week 8, LOCF, in the HAM-D-17 total score. The primary comparisons of interest were vilazodone 5, 10, and 20 mg/day compared to placebo.

Secondary efficacy variables included comparisons of each dose of vilazodone to placebo at Week 8 OC and LOCF for several variables, none of which were considered to be 'key secondary efficacy variables'. The list of variables included the following, among others: HAM-D-1 (depressed mood), HAM-D anxiety items, MADRS, CGI-I and CGI-S and response and remission assessments.

Study Results

Patients in the intent to treat (ITT) dataset were between 18 and 64 years old, with a mean age of 34 years. Eighty-four (84) percent were Caucasian, 8% were African-American, 2% were as Oriental and 7% were classified as "other." Sixty-two percent (62%) were female. The treatment groups were comparable at baseline on the demographic and key efficacy variables.

Table 5.3.6 Study Completers - 659746 A002

Table 3 Number (%) of Subjects Who Completed the Study or were Withdrawn by Reason for Withdrawal (ITT Population)

Reason for Study Conclusion	n (%)				Total (N = 533)
	SB659746-A 20 mg (N = 132)	SB659746-A 10 mg (N = 133)	SB659746-A 5 mg (N = 140)	Placebo (N = 128)	
Completed Study ¹	90 (68.2)	105 (78.9)	112 (80.0)	97 (75.8)	404 (75.8)
Total Number of Withdrawals	42 (31.8)	28 (21.1)	28 (20.0)	31 (24.2)	129 (24.2)
Adverse Event	4 (3.0)	4 (3.0)	5 (3.6)	2 (1.6)	15 (2.8)
Insufficient Therapeutic Effect	7 (5.3)	2 (1.5)	7 (5.0)	11 (8.6)	27 (5.1)
Protocol Deviation (Incl. Non-Compliance)	8 (6.1)	5 (3.8)	4 (2.9)	1 (0.8)	18 (3.4)
Lost to Follow-up	12 (9.1)	11 (8.3)	9 (6.4)	8 (6.3)	40 (7.5)
Other ²	11 (8.3)	6 (4.5)	3 (2.1)	9 (7.0)	29 (5.4)

Data Source: [Table 12.7, Section 12](#)

1. A subject was considered to have completed if they remained in the study up to and including Visit 8 (week 8).
2. Including unknown and non-study-related personal reasons.

Source: CSR 659746 A002

A total of 555 patients were randomized, six (6) patients at center 013 were excluded from the safety and efficacy analyses upon recommendation of GSK Worldwide Regulatory Compliance. Of the remaining 549 patients in the randomized population, 404 (74%) patients completed the 8-week treatment phase and 145 (26%) patients withdrew early from the treatment phase. The ITT population consisted of 97% of those randomized. The number of patients in the ITT population was evenly distributed among the four treatment groups.

Table 5.3.7 HAM-D-17 Total Score- Study 659746 A002

Group	Baseline	LOCF Wk 8 ¹	Difference	Difference ² (adjusted LSM)	P-value
Vilazodone 5 mg n=140	24.0	13.0	-11.0	0.5	0.56
Vilazodone 10 mg n=133	24.5	11.7	-12.8	-1.2	0.18
Vilazodone 20 mg n=132	24.3	12.6	-11.7	-0.2	0.80
Placebo n=128	23.7	12.2	-11.5		

¹primary analysis; ²difference in adjusted least squares means

Source: Table 5.3.1 Biostatistics Review Confirmation

Discussion

This is a negative study,

(b) (4)

6 Review of Efficacy

Efficacy Summary

The Division met with the Applicant on June 17, 2009 when it was agreed that data from the five phase 2 studies conducted under the sponsorship of Merck and GSK and submitted previously to FDA to IND 54613 would not be considered supportive for the proposed dose and indication. The Division agreed that the clinical summary of efficacy should include a brief summary of the primary results for these (phase 2) studies and the results are not required in the side-by-side efficacy evaluations.

The efficacy data relevant to the indication of MDD arise from 2 randomized, double-blind, placebo-controlled phase 3 studies: GNSC-04-DP-02 and CLDA-07-DP-02 denoted "04" and "07," respectively, in this review. Studies 04 and 07 were conducted by PGxHealth at the proposed dose of 40 mg daily, were adequate, well-controlled, and had acceptable endpoints. This clinical review will summarize the study designs and efficacy findings from both of these studies.

Vilazodone at 40 mg taken once daily with food demonstrated efficacy for the treatment of MDD, based on the change from baseline at Week 8, LOCF. Treatment margins (difference of vilazodone – placebo) for LSM change from baseline to Week 8, LOCF were -3.2 and -2.5 for the primary efficacy endpoint in Studies 04 and 07, respectively. In both trials, vilazodone demonstrated statistically significant improvements compared to the placebo group.

6.1 Indication – Major Depressive Disorder

Pivotal Study #1 **GNSC-04-DP-02**

6.1.1 Methods

GNSC-04-DP-02 was a multicenter, 8-week, randomized, double-blind, placebo-controlled, flexible dose study in adults aged 18-65 years with a DSM-IV-TR diagnosis of MDD. This clinical trial took place at 18 sites, all within the United States. The first patient was enrolled February 22, 2006 and the last patient completed the final evaluation on May 23, 2007.

Primary Objective

The primary objective was to assess the efficacy of vilazodone compared with placebo in the treatment of MDD as measured by the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) after 8 weeks of treatment. The MADRS is accepted by the Agency as a standard measure for antidepressant clinical trials.

Secondary Objectives

The applicant identified three secondary objectives:

- To assess the safety profile of vilazodone compared with placebo
- To assess the efficacy of vilazodone compared with placebo by using secondary measures of depression, anxiety, and overall clinical impression
- To discover genetic markers associated with treatment response and/or AEs in patients taking vilazodone.

The Arizona Sexual Experiences Scale (ASEX) was employed to evaluate sexual function, because of the known sexual side effects associated with SSRIs.

The Hamilton Rating Scale for Anxiety (HAM-A) was used to measure the severity of anxiety symptoms. The primary analysis of HAM-A was a change from baseline to Week 8 analyses (ANCOVA, LOCF) performed using only the patients with a HAM-A total score ≥ 18 at baseline, suggesting a co-occurring condition of 'clinical anxiety'.

Study Design

This was a randomized, double-blind, placebo-controlled, flexible-dose, multicenter study of treatment with vilazodone in adults with MDD. Before undergoing any study procedures, written, informed consent was obtained from each patient. A washout period of 2 to 12 weeks (depending on the drug being washed out) occurred if the patient was taking another antidepressant or excluded medication. After the washout, screening assessments were performed and the subjects were evaluated according to inclusion and exclusion criteria.

Both vilazodone and matching placebo tablets were available in 10 mg and 20 mg strength. The tablets were packaged such that patients took 2 tablets per day during the titration and the fixed-dose phases of treatment. If a dosage reduction was required, one 20 mg tablet/day was taken.

At baseline, the subjects were randomly assigned (1:1 ratio) to receive either vilazodone or matching placebo. The initial dose of vilazodone or matching placebo was 10 mg/day for the first 7 days (Days 1-7), 20 mg/day for the next 7 days (Days 8-14), and 40 mg/day for the remaining 42 days (Days 15-56) of the trial. Two flexible dose options were available to the investigator if the subject experienced an intolerable AE:

- If the AE occurred during the dose titration period at the 20 mg/day dose, the patient could remain at 20 mg/day until Week 8 (Visit 5) with the option of increasing the dose to 40 mg/day if the AE/s resolved
- If the subject had intolerable AE/s during or after starting the 40 mg/day dose at Day 15, the dose could be reduced to 20 mg/day at any time. If placed on the lower dose, the subject remained on that dose throughout the study

During the 8-week (including the 2-week titration period) treatment period, the subjects received a maximum dosage of 40 mg/day vilazodone or matching placebo in oral tablet form. The assigned treatment was taken with food each morning. The double-blind treatment period was 8 weeks, during which the subjects returned to the study site for efficacy and safety assessments at the end of Weeks 1, 2, 4, 6, and 8.

Table 6.1.1 Study Schedule of Visits

Phase	Pre-Randomized		Double-Blind Treatment				
	Screen	Baseline	Titration Phase		Treatment Phase		
Treatment		randomization ^a	10 mg	20 mg	40 mg	40 mg	40 mg
Visit	1	2	3	4	5	6	7
Week	-1	0	1	2	4	6	8 or ES ^b
Day ±	-1	0	7	14	28	42	56

^a Randomization occurred at Day 0 if patients continued to meet eligibility criteria.

^b End of Study Visit

Key Inclusion Criteria:

- Male or female 18-65 years of age
- MDD single or recurrent (DSM-IV-TR)
- HAM-D ≥22 on the first 17 items

Key Exclusion Criteria:

- Serious psychiatric co-morbidity; although generalized anxiety disorder (GAD), social phobia, simple phobia were permitted
- History of inadequate response to 2 consecutive antidepressants
- Serious medical co-morbidity
- Pregnant, lactating or planning to become pregnant females

The inclusion and exclusion criteria were appropriate for this study. Overall, the population is reasonable to demonstrate the proposed objectives. Those patients who have failed two antidepressant trials have been excluded and this is acceptable given the study is not designed for an indication of treatment resistant depression.

Primary endpoint

The primary endpoint was the mean change in MADRS total score from baseline to Week 8 with missing data imputed by the last observation carried forward (LOCF) method. This accepted and well established endpoint is a standard measure for antidepressant clinical trials and was agreed upon a priori as indicated in the End of Phase 2 meeting minutes of December 20, 2005. The endpoint is expected to provide a clinically meaningful measure of improvement in the symptoms of depression.

The mean change in MADRS total score from baseline to week 8 was analyzed using an analysis of covariance model, with terms for treatment and center, and adjusting for baseline MADRS score. The intent-to-treat (ITT) population was used for this analysis. The ITT population in this study is defined as all randomized patients who took at least one dose of study medication and had at least one post-baseline efficacy measurement within 7 days of the last dose of study medication with data collected on or before Day 71. This is not a typical definition of the ITT population; however, it does not appear that this issue had a significant affect on the efficacy results.

The secondary endpoints are exploratory as none were specified as key secondary measures or agreed on a priori. Of note, this information was communicated to the sponsor in an email on May 11, 2007.

Statistical Plans

The three populations analyzed in this study report are defined by the applicant as:

1. **Intent to treat (ITT)** – all randomized patients that received at least one dose of study medication and had at least one post-baseline efficacy measurement within 7 days of the last dose of study medication with data collected on or before Day 71.
2. **Modified intent to treat (mITT)** – all patients in the ITT population who completed the MADRS (primary efficacy measure) at Week 8.
3. **Safety population** – all randomized patients who took at least one dose of study medication and had at least one safety measurement. This population was used for all safety analyses and all demographic and baseline characteristic analyses.

It should be noted, that the ITT population, as defined by the applicant, is actually a 'modified ITT' population. As a general rule, ITT is an 'as randomized' population.

The ITT population was used for all efficacy analyses; the mITT was used, in addition to ITT, for efficacy analyses of the primary efficacy endpoint and analyses of key secondary endpoints.

Table 6.1.2 Study Populations

Population	Number (%) of Patients by Treatment Group	
	Vilazodone	Placebo

All randomized patients	205 (100)	205 (100)
ITT population	198 (96.6)	199 (97.1)
mITT population	152 (74.1)	154 (75.1)
Safety population	205 (100)	204 (99.5)

Source: CSR: GNSC-04-DP-02 Table 11-1 p.56

Three patients (2 vilazodone and 1 placebo) received at least one dose of study medication and had at least one post-baseline efficacy assessment, but were not included in the ITT analyses because each of the three had only one efficacy assessment and that assessment was outside of the predefined treatment window.

Analysis of the primary efficacy endpoint, change in MADRS total score from baseline to Week 8 was a single comparison and therefore there was no multiplicity issue. The main secondary efficacy variables for inferential analyses were MADRS response, MADRS remission, and HAM-A total score. The analyses for these main secondary variables were performed on both the ITT and the mITT populations.

Analysis of HAM-A results included evaluation of a subgroup of clinical anxiety patients; clinical anxiety patients were defined as those patients with a baseline HAM-A total score ≥ 18 . This is useful for exploratory purposes only, as this could be another manifestation of the primary diagnosis, MDD.

Results

6.1.2 Subject Disposition

Of 561 patients screened, 151 patients failed the screening process. The remaining 410 patients were randomized 1:1 to vilazodone or placebo, resulting in 205 patients in each group. Of the 205 patients randomized, 152 in the vilazodone group completed all visits through Week 8 (Visit 7) and 154 on placebo completed all visits.

The following table is copied from the applicant's submission (CSR/21 December 2007 p. 54) and is a concise representation of subject disposition:

Table 6.1.3 Patient Disposition

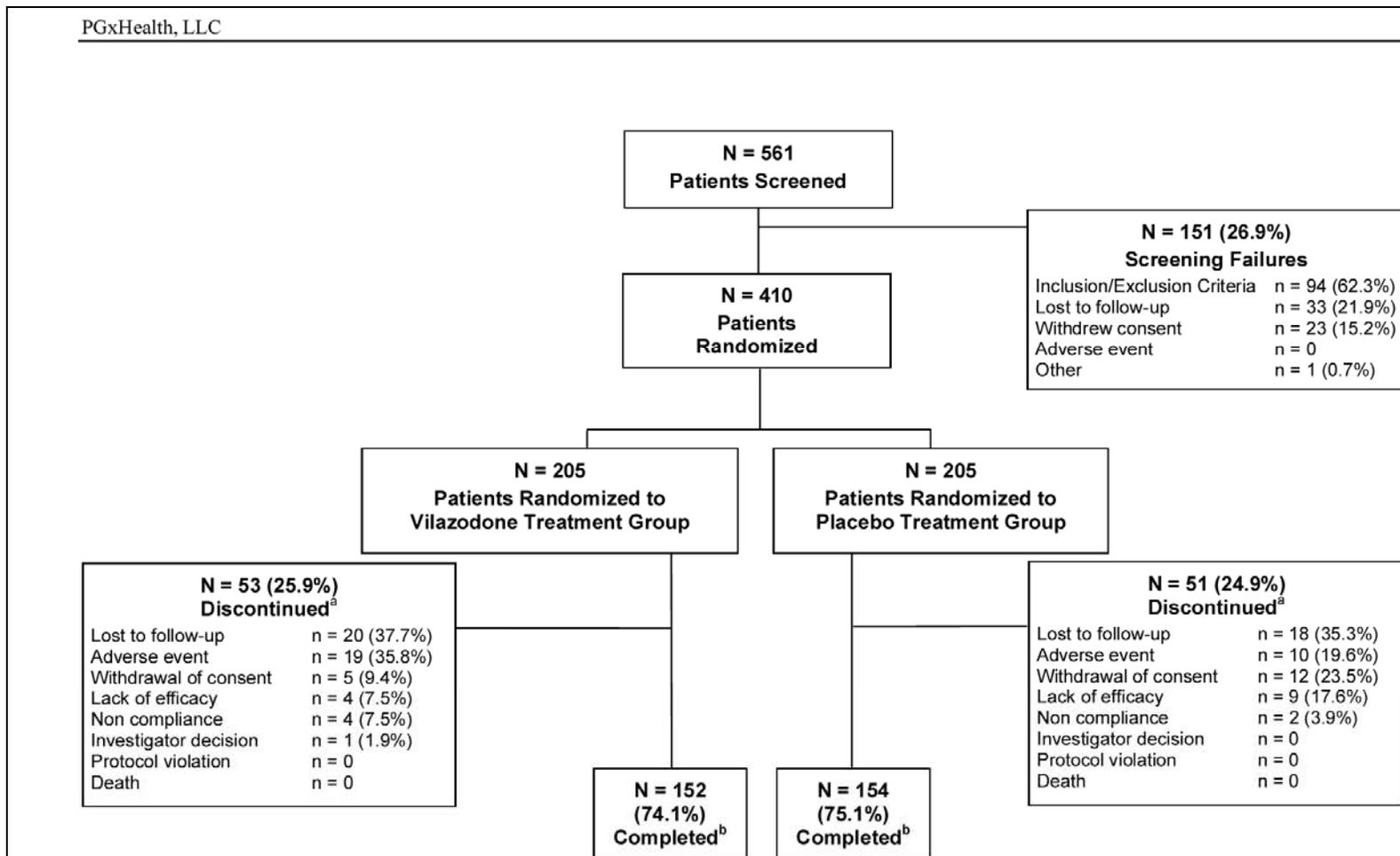


Figure 10-1 Patient Disposition

Source: Section 14.3.6.1, Table 1, Section 14.3.6.3, Table 3, and Section 14.3.6.20, Figure 1

- a. for each reason for discontinuation, percent (%) values in this figure were calculated using a denominator of the total number (N) of patients discontinued in each treatment group
- b. a patient was considered to have completed the study when he/she completed all visits through Week 8 (Visit 7)

Source: CSR: GNSC-04-DP-02 p.54

Of the randomized patients, the numbers of patients who completed the study through Week 8 were similar for the vilazodone and placebo groups; approximately 25% of patients in each treatment group discontinued prior to Week 8. The most common reason for discontinuation was ‘lost to follow-up’ in both treatment groups. It should be noted that 20 patients were lost to follow up in the vilazodone group compared with 18 patients in the placebo group.

More patients in the vilazodone group discontinued due to an AE, 19 (9%) for vilazodone and 10 (5%) for placebo. More patients in the placebo group discontinued due to withdrawal of consent, 5 (2%) vilazodone and 12 (6%) for placebo; and lack of efficacy 4 (2%) for vilazodone and 9 (4%) for placebo.

The most common adverse events leading to dropout included diarrhea, headache, depression, suicidal ideation, and heart palpitations.

Overall, 561 patients were screened for entry into the study, 410 patients were randomized to either vilazodone or placebo. All patients began the study with a two-week titration; the doses for the final 6 weeks of the study were as follows:

Table 6.1.4 Dose Titration Pattern-Study Completers

Dose at Visit 2/3/4/5/6	Vilazodone N=152 (%)	Placebo N=154 (%)	Total N=360 (%)
10/20/40/40/40	139 (91.4)	149 (96.8)	288 (94.1)
10/20/20/20/20	5 (3.3)	1 (0.6)	6 (2.0)
10/20/20/40/40	3 (2.0)	2 (1.3)	5 (1.6)
10/20/40/20/20	3 (2.0)	1 (0.6)	4 (0.3)
10/20/40/40/20	1 (0.7)	0 (0.0)	1 (0.3)
10/20/40/40/missing	1 (0.7)	1 (0.6)	2 (0.7)

Source: CSR GNSC-04-DP-02 Table 14.3.6.22 p.609

Comment: As noted in the dose titration pattern table above, thirteen patients in the vilazodone group and 5 patients in the placebo group were not able to tolerate the 40 mg dose and were maintained at 20 mg for the 6 week post titration, double-blind treatment period.

6.1.2 Demographics

The majority of patients in this study were Caucasian females, with a mean age of 40 years. In both groups, the second most frequent race was Black/African American; however, the percentage of Black patients in the vilazodone group was approximately half that of the placebo group. It is doubtful that this difference would bias the results in favor of vilazodone. Overall, the patient population in this trial is representative of the target patient population of patients treated for MDD.

Table 6.1.5 Demographics

Demographic		Treatment Group		Total n=409 (%)
Category	Variable	Vilazodone n=204 (%)	Placebo n=204 (%)	
Gender n (%)	Female	127 (62.0)	130 (63.7)	257 (62.8)

	Male	78 (38.0)	74 (36.3)	152 (37.2)
Race n (%)	White	181 (88.3)	157 (76.9)	338 (82.6)
	Black/African American	20 (9.8)	36 (17.6)	56 (13.7)
	Asian	2 (1.0)	2 (1.0)	4 (1.0)
	American Indian/ Alaskan Native and White	1 (0.5)	3 (1.5)	4 (1.0)
	Native Hawaiian/ Pacific Islander	0	3 (1.5)	3 (0.7)
	Other	1 (0.5)	2 (1.0)	3 (0.7)
Ethnicity n (%)	Hispanic or Latino	17 (8.3)	13 (6.4)	30 (7.3)
	Not Hispanic or Latino	188 (91.7)	191 (93.6)	379 (92.7)
Age (years)	Mean	40.0	39.8	39.9
	Standard Deviation	12.1	12.7	12.4
	Median	40.0	39.0	40.0
	Range	18-63	18-65	18-65

Source: CSR: GNSC-04-DP-02 p.59

Baseline Characteristics

The baseline height and weight were similar between the two groups. The mean patient height was 169.3 cm (SD \pm 9.40) for the vilazodone group and 168.8 cm (SD \pm 10.31) for the placebo group. Mean body weight at the screening visit was 85.1 kg (SD \pm 22.18) for the vilazodone group and 84.0 kg (SD \pm 22.0) for the placebo group.

The medical and surgical histories revealed no significant differences that would be likely to have an effect on the outcome of the study.

The psychiatric histories of all patients in the safety population revealed similar characteristics for both the vilazodone and placebo groups. As indicated in the table below, the mean ages of the first episode of depression were similar: approximately 33 years for the vilazodone group and 32 years for the placebo group. The duration of depressive symptoms was similar between the vilazodone and placebo groups; this was

the first MDE in approximately one-third of the subjects in both groups. Severity of symptoms was similar in both groups: 100 percent of the patients in both groups had symptom severity of either moderate or severe, and 28% had symptom severity of severe.

Table 6.1.6 Baseline Psychiatric History

Major Depressive Episode (MDE)	Vilazodone N=205 (%)	Placebo N=204 (%)
Duration of MDE:		
1-6 months	107 (52.2)	110 (53.9)
6-12 months	68 (33.2)	78 (38.2)
>12 months	30 (14.6)	16 (7.8)
1 st Lifetime MDE:		
Yes	72 (35.1)	76 (37.3)
No	133 (64.9)	128 (62.7)
Age (years) of 1 st MDE:		
Mean		
SD	33.4	31.9
Min	13.4	13.8
Max	6	5
	63	64
Current MDE severity:		
Mild	0	0
Moderate	147 (71.7)	147 (72.1)
Severe	58 (28.3)	57 (27.9)

Source: CSR: GNSC-04-DP-02 Section 14.3.6.4 p. 464

Prior and Concomitant Medications

Concomitant medications were used by 79% of the vilazodone group and 78% of the placebo group. The majority of the medications used during the trial were over the counter pain relievers, anti-hypertensive medications, and antacids.

The number of patients on prior psychiatric medication was similar between the two groups (vilazodone 14% and placebo 12%); adequate time for washout of prior medications appeared to be adhered to. It seems unlikely that the use of the concomitant medications would have significantly biased the results based on the pharmacology of the medications and roughly equal distributions between the two groups. These prior and concomitant medications are likely to be used in the population for which this drug is intended.

Protocol Deviations

Review of the data indicates that protocol deviations occurred due to concomitant medications, inclusion/exclusion criteria, study drug dosing, study medication details,

study procedures, visit schedule interval, and medication therapy. None of these deviations was considered to be major and patients with protocol deviations were not excluded from the efficacy or safety analyses.

Efficacy Findings

For efficacy results, missing values were imputed using the last observation carried forward (LOCF) approach. Only assessments done after dosing were used in the LOCF procedure. Primary and Secondary endpoint analyses included only those measurements obtained while patients were receiving active treatment with either vilazodone or placebo.

Table 6.1.7 Least Squares Mean Change in MADRS Total Score

Least Square Mean Change in MADRS total score: Treatment Group Difference by Study Visit						
	ITT Population			mITT Population		
Study Week	Value	P-value	95%CI	Value	P-Value	95% CI
1	-1.7	0.0002	-2.5, -0.8	-1.7	0.0005	-2.7, -0.8
2	-1.5	0.0127	-2.7, -0.3	-1.4	0.0395	-2.8, -0.1
4	-2.6	0.0011	-4.1, -1.0	-2.5	0.0049	-4.2, -0.8
6	-3.6	0.0001	-5.3, -1.8	-3.7	0.0002	-5.6, -1.8
8	-3.2	0.0010	-5.2, -1.3	-3.3	0.0027	-5.4, -1.1

Source: CSR GNSC-04-DP-02 Table 11-9 p.71

6.1.4 Analysis of Primary Endpoint(s)

The results from the primary analysis indicate that patients treated with vilazodone demonstrate improvement on the total MADRS score when compared to the patients treated with placebo. The mean change from baseline in the MADRS total score at Week 8 was analyzed using ANCOVA with terms for treatment, center, and baseline MADRS total score. The ITT population (LOCF), mean change from baseline was -12.9 for the vilazodone group and -9.7 for the placebo group, to yield a difference between groups (vilazodone-placebo) of -3.2. The following table extracted from the Biometrics review of Dr. Dinh illustrates these findings.

Table 6.1.8 Change from Baseline to Week 8 LOCF – MADRS

Table 10. 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		
<i>Mean (Standard deviation)</i>	30.7 (3.9)	30.8 (3.9)
<i>Median (Min – Max)</i>	31 (20 – 41)	31 (21 – 43)
Change from baseline		
<i>LS Means</i>	-9.7	-12.9
<i>Difference from placebo (SE)</i>		-3.2 (0.99)
<i>(95% confidence interval)</i>		(-5.1, -1.2)
<i>P-value</i>		0.001

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

The difference was similar between treatment groups when mITT population was analyzed. The mean change from baseline for the mITT population was a difference between groups of -3.3, (-15.6 vilazodone and -12.3 placebo).

The Applicant reports a statistically and clinically significant difference between treatment groups for both ITT (p=0.001) and mITT (p=0.003) populations. The improvement in vilazodone-treated patients relative to placebo was observed as early as the first week of treatment with greatest relative response at Weeks 6 and 8. The change from baseline in the MADRS total score at week 8 was -2.9 for females and -3.4 for males, indicating improvement in both genders. The majority of the patients in this study (83%) were white. While significant improvement in depressive symptoms was seen in white patients, the treatment effect was not apparent for other races. Presumably because of the low numbers of other races that were enrolled in the study.

The blind was not broken during this study. Only the independent biostatistician at (b) (4) had access to the randomization codes for each patient. The blinding for this study was acceptable and controlled as well as possible. There is the possibility that the high rate of GI adverse events could lead an investigator to infer the treatment arm; however, blinding for this study was acceptable and well-controlled.

6.1.5 Analysis of Secondary Endpoints(s)

The main secondary efficacy variables for inferential analyses were MADRS response, MADRS remission, and HAM-A total score in a subset of patients with HAM-A total score ≥18. The analyses for these variables were performed on both the ITT and mITT

populations. Response and remission rates, based on pre-defined criteria, were determined using MADRS and HAM-D results. Response rates were also determined using CGI-I data.

MADRS Response

There were more MADRS responders in the vilazodone group. In the ITT population LOCF analyses, 80 (40.4%) patients in the vilazodone groups and 56 (28.1%) patients in the placebo group met MADRS response criteria ($\geq 50\%$ reduction in total score from baseline at Week 8).

The results of MADRS Response were insignificant for the ITT population; however, notable in that the adjusted p value for the treatment group difference was 0.0464 for the mITT population. The mITT includes all ITT patients who completed the MADRS at Week 8. For the mITT population vilazodone n=152 and placebo n=154.

MADRS Remission

Remission on the MADRS was defined as a total score of < 10 at Week 8. There were more MADRS remitters in the vilazodone group than in the placebo group; however, the difference between treatment groups in remission rate was not statistically significant (raw p=0.0506, adjusted p=0.1012). Similar estimates of remission were found in the mITT population.

HAM-A total score

The mean change in HAM-A total score from baseline to Week 8 was greater in the vilazodone group. However, the mean treatment group difference was not statistically significant for either the ITT or the mITT.

Conclusions

The 40 mg/day dose of vilazodone is superior to placebo based on the primary efficacy analysis at the 8-week endpoint. The treatment group difference for the ITT, as defined by the applicant, was -3.2 with a p value of 0.001. Based on other antidepressants, this effect size is likely to be clinically meaningful. Sensitivity analysis confirmed by the statistical review is supportive of the primary efficacy analysis.

The primary analysis of HAM-A was the change from baseline to Week 8 using a subgroup of patients with a HAM-A total score > 19 at baseline. The results of the ITT population demonstrated that the mean treatment group difference of -1.2 was not statistically significant.

Pivotal Study #2 **CLDA-07-DP-02**

6.1.1 Methods

Study **CLDA-07-DP-02** is a multicenter, randomized, double-blind, placebo-controlled, fixed titration, 8-week clinical trial designed to assess the efficacy and safety of vilazodone in the treatment of adults (18-70 years of age, inclusive) diagnosed with MDD according to DSM-IV-TR criteria. This study was conducted at fifteen sites in the United States under the sponsorship of PGxHealth.

Primary Objective

To compare the efficacy of vilazodone in the treatment of MDD as measured by the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at Week 8 or End of Treatment Visits. The MADRS is accepted by the Agency as a standard measure for antidepressant trials.

Secondary Objectives

The applicant identified three secondary objectives:

- To assess the safety profile of vilazodone
- To analyze a pre-specified genetic biomarker, referred to as (b) (4), associated with treatment response to vilazodone and to conduct further exploratory analyses of genetic biomarkers related to vilazodone
- Secondary efficacy and safety analyses using the MADRS, HAM-D and subscales, Hamilton Anxiety Scale (HAM-A), Clinical Global Impressions (CGI), Changes in Sexual Functioning Questionnaire (CSFQ), and Columbia-Suicide Severity Rating Scale (C-SSRS)

Study Design

CLDA-07-DP-02 enrolled approximately 470 patients randomly assigned to vilazodone or placebo, 40 mg, taken orally, once daily with food each morning. The study was divided into three periods: a washout period, a screening period, and an 8-week-double-blind treatment period. The washout period permitted the time for discontinuation of current antidepressants or any additional medications that were prohibited by the protocol. At Visit 2 (Week 0), baseline assessments were performed, the patients were randomized, and study drug was dispensed. After the baseline visit, safety and efficacy measurements were obtained at post-treatment weeks 1, 2, 4, 6, and end of treatment or week 8.

Patients were randomized to received vilazodone tablets or matching placebo tablets. All patients took 2 tablets each day during the titration and fixed-dosage phases of treatment. Patients randomized to vilazodone took 1 placebo and 1 active tablet for one week, then 2-10 mg tablets for one week and then 2-20 mg tablets for the remainder of the study.

Key Inclusion Criteria

- Male or female (of child-bearing potential using adequate and reliable methods of birth control) patients 18-70 years of age, inclusive
- MDD per DSM-IV-TR with current MDE of at least 4 weeks but no more than 2 years duration
- MDD diagnosis confirmed at baseline by the Mini International Neuropsychiatric Interview (MINI)_MINI
- HAM-D score ≥ 22 on the first 17 items of the 21-item HAM-D at screening and baseline

Key Exclusion Criteria

- Current Axis I disorder of post-traumatic stress disorder (PTSD), eating disorder, obsessive compulsive disorder (generalized anxiety disorder, social phobia, or simple phobia permitted)
- Patients with history of schizophrenia, schizoaffective disorder or bipolar I or II disorder (with a history of hypomanic or manic episodes)
- Patients who met DSM-IV-TR criteria for substance abuse (alcohol or drugs) within 3 months prior to screening or substance dependence within 6 months prior to screening
- Patients who met criteria for any of the following DSM-IV specifiers: catatonic features, postpartum onset, seasonal pattern, psychotic features
- Electroconvulsive therapy (ECT) within the past 6 months
- Psychotherapy within the past 6 months
- Patients with inadequate response to at least 2 consecutive antidepressants from different classes, given at adequate doses for an adequate duration within the same episode
- Patients with a history of clinically significant cardiac, renal, neurologic, cerebrovascular, hepatic, hematologic, metabolic or pulmonary disorders
- Pregnant (or intending to become pregnant) or lactating females

Prohibited Medications

- Monoamine oxidase inhibitors (MAOIs), fluoxetine
- All other antidepressants, sedative, hypnotics, beta adrenergic blockers, benzodiazepines or other psychoactive medications, including herbal preparations
- Triptans and ergot derivatives
- CYP450 3A4 inhibitors such as grapefruit juice, ketaconazole, diltiazem, and macrolide antibiotics
- Singulair (montelukast)
- Previous vilazodone treatment

Primary Endpoint

The primary efficacy measure was the change from baseline to week 8 in the MADRS total score.

The main secondary efficacy variable included MADRS response, MADRS remission, and change in HAM-A total score from baseline to week 8.

Statistical Plans

The three populations analyzed in this study report are defined by the applicant as:

1. **Intent to treat (ITT)** – all randomized patients that received at least one dose of study medication and had at least one post-baseline efficacy measurement.
2. **Modified intent to treat (mITT)** – all patients in the ITT population who completed the MADRS (primary efficacy measure) at Week 8.
3. **Safety population** – all randomized patients who took at least one dose of study medication and had at least one safety measurement. This population was used for all safety analyses and all demographic and baseline characteristic analyses.

The primary efficacy endpoint was the change from baseline in MADRS total score at Week 8. The intent-to-treat (ITT) population was used for the primary efficacy analysis using LOCF methods. The model was an analysis of covariance (ANCOVA), with terms for treatment and center, adjusting for baseline MADRS.

A mixed-effects model repeated measures (MMRM) analysis was performed. 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 value and baseline-by-visit interaction. The treatment group comparisons were based on evaluating the difference in LS means between groups at each post-baseline visit. If patients discontinued early and between visits, the last observation was carried forward to the next scheduled visit for the analysis.

All analyses were performed on the ITT and the modified ITT populations. The ITT population consisted of patients who were randomized, took at least one dose of study drug, and had at least one post-baseline efficacy endpoint measurement. The mITT population consisted of the subset of the ITT population who completed their Week 8 MADRS assessment.

The secondary efficacy endpoints included the 17-item HAM-D, 21-item HAM-D, and HAM-A total scores, CGI-S and CGI-I scores, MADRS and 17-item HAM-D response and remission rates.

There were three protocol amendments to the study that primarily involved the genetic biomarker section of the protocol; although minor changes were also made in the exclusion criteria and descriptive text.

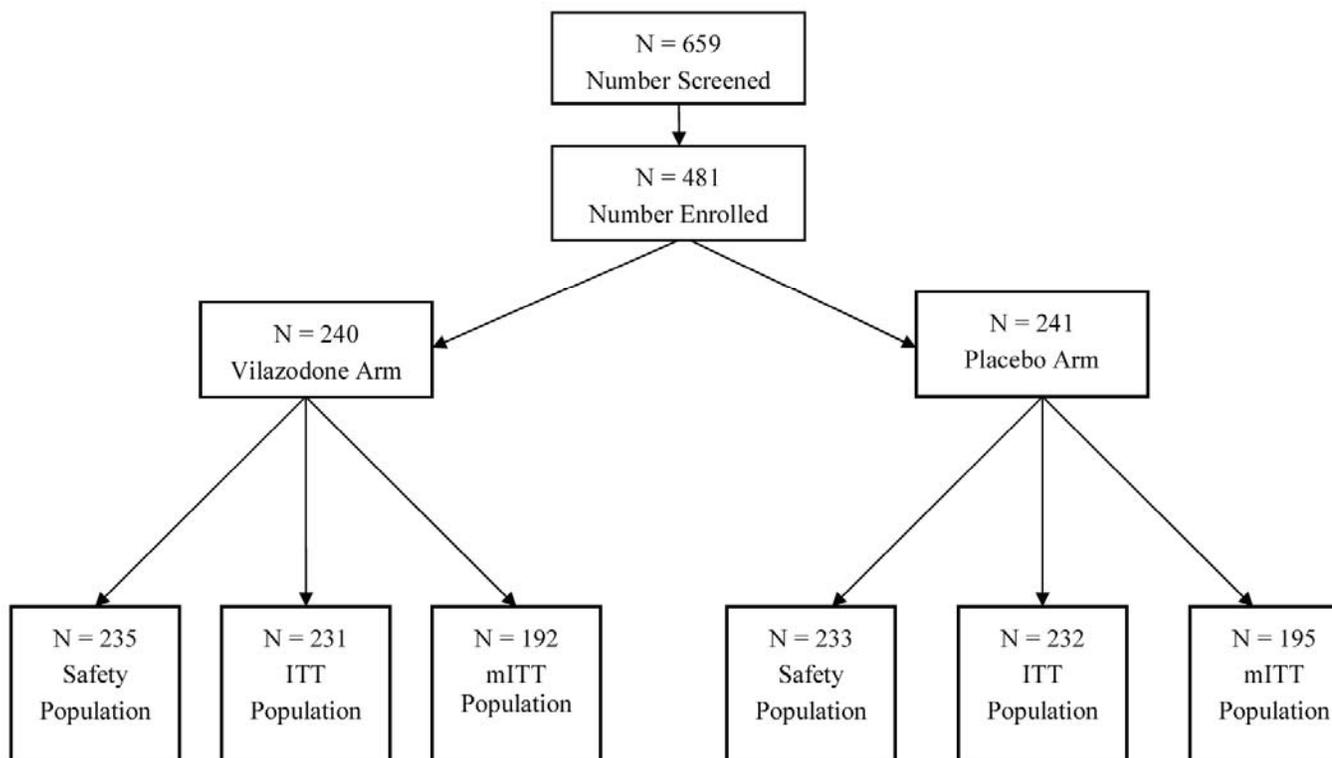
The blind was not broken during this study. Only the independent biostatistician at (b) (4) had access to the randomization codes for each patient. The blinding for this study was acceptable and controlled as well as possible. There is the possibility that the high rate of GI adverse events could lead an investigator to infer the treatment arm; however, blinding for this study was acceptable and well-controlled.

Results

The first patient was randomized March 31, 2008, the last patient completed the study February 10, 2009; the final clinical study report was dated November 3, 2009.

Table 6.1.9 Patient Disposition-Study CLDA-07-DP-02

Figure 1: Patient Disposition



Note: The data for Patient IDs of 2080-058 and 2020-173 were excluded.
 Patient IDs 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient enrolled at 2 different clinical sites and the patient participated consecutively. Patient IDs 2020-173 (placebo) and 2080-074 (vilazodone) were the same patient and the patient participation was overlapping at 2 clinical sites.

Source: Figure 14.1 (in Section 14.1.2.1)

Table reproduced from the Applicant’s submission CSR CLDA-07-DP-02 p. 50

6.1.2 Demographics

There were more females (56.2%) than males (43.8%). The percentage of females was slightly higher in the vilazodone group. The mean age of 41.7 years was similar in the vilazodone and placebo groups. The majority, 79.7%, of enrolled patients were white in both the vilazodone and placebo groups. Ethnicity was identified as ‘Not Hispanic or Latino’ for more than 90% of patients in both groups.

Table 6.1.10 Demographics CLDA 07-DP-02

Table 9: Demographic and Baseline Characteristics (Safety Population): Sex, Race, and Ethnicity

	Vilazodone N=235	Placebo N=233	Total N=468
Parameter	n (%)	n (%)	n (%)
Sex			
Male	96 (40.9)	109 (46.8)	205 (43.8)
Female	139 (59.1)	124 (53.2)	263 (56.2)
Race			
American Indian or Alaskan Native	7 (3.0)	0	7 (1.5)
Asian	8 (3.4)	8 (3.4)	16 (3.4)
Black or African American	35 (14.9)	31 (13.3)	66 (14.1)
Native Hawaiian or other Pacific Islander	2 (0.9)	1 (0.4)	3 (0.6)
White	182 (77.4)	191 (82.0)	373 (79.7)
American Indian or Alaskan Native, Asian, White	1 (0.4)	0	1 (0.2)
American Indian or Alaskan Native, White	0	2 (0.9)	2 (0.4)
Ethnicity			
Hispanic or Latino	14 (6.0)	16 (6.9)	30 (6.4)
Not Hispanic or Latino	221 (94.0)	217 (93.1)	438 (93.6)

Note: The data for Patient IDs of 2080-058 and 2020-173 were excluded from analysis. Patient IDs 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient and the patient participation was consecutive. Patient IDs 2020-173 (placebo) and 2080-074 (vilazodone) were the same patient and the patient participation was overlapping.
Source: [Table 14.1.4.1](#)
Cross-reference: [Listing 16.2.4.1](#)

Source: CSR CLDA-07-DP-02 p54

Baseline Characteristics

The baseline height and weight were similar between the two groups. The mean patient height was 168 cm for the vilazodone group and 170 cm for the placebo group. Mean body weight at the Screening Visit was 192 pounds for the vilazodone group and 195 pounds for the placebo group.

The medical and surgical histories revealed no significant differences that would be likely to have an effect on the outcome of the study.

The psychiatric histories of all patients in the safety population revealed similar characteristics for both the vilazodone and placebo groups. As indicated in the table

below, the mean age of the first MDE was approximately 32 years for the vilazodone group and 33 years for the placebo group. The duration of depressive symptoms was similar between the two groups; this was the first MDE in approximately 66.5% of the subjects in both groups. Severity of symptoms was similar in both groups and 100 percent of the patients in both groups had symptom severity of either moderate or severe.

Table 6.1.11 Baseline Characteristics

Baseline Psychiatric History			
Major Depressive Episode (MDE)	Vilazodone N=235(%)	Placebo N=233(%)	Total N=468(%)
Duration of MDE			
1-6 months	110 (46.8)	120 (51.5)	230 (49.1)
6-12 months	61 (26.0)	59 (25.3)	120 (25.6)
>12 months	63 (26.8)	54 (23.2)	117 (25.0)
1st Lifetime MDE			
Yes	66 (28.1)	67 (28.8)	133 (28.4)
No	169 (71.9)	166 (71.2)	335 (71.6)
Age of 1st MDE			
N	235	233	468
Mean	32.0	33.2	32.6
SD	13.4	14.1	13.8
Min	6	8	6
Max	64	70	70
Current MDE			
Mild	0	0	0
Moderate	175 (74.5)	165 (70.8)	340 (72.6)
Severe	60 (25.5)	68 (29.2)	128 (27.4)

Source: CSR CLDA-07-DP-02 Table 14.1.5 p.126

Prior and Concomitant Medications

Psychotropic medications, including antidepressants (other than study drug), mood stabilizers, benzodiazepines, and antipsychotics could not be used during the study. Eligible patients were instructed by the investigator to discontinue their current antidepressant medication for the specified and appropriate washout period.

Other medications initiated before the double-blind period were permitted at the discretion of the investigator, but were to remain at a stable dose throughout the study. The list of medications was reviewed and it seems unlikely that the use of concomitant medications would have significantly biased the results based on the roughly equal

distributions between the two groups. These prior and concomitant medications are likely to be used in the population for which the drug is intended.

Treatment Compliance

Treatment compliance was defined as 80-120% of prescribed drug taken during any evaluation period. For both treatment groups more than 90% of patients were compliant at each time point. Treatment compliance was similar between vilazodone and placebo groups at each visit. Over, 88% of vilazodone and 94% of placebo patients were compliant.

6.1.3 Subject Disposition

Overall, 659 patients were screened for entry into the study, 481 were randomized to either vilazodone treatment (n=240) or placebo (n=241). Of the total 659 patients, 178 (27%) were screen failures. Nearly half (n=87, 48.9%) did not meet the inclusion/exclusion criteria, 37 patients (20.8%) withdrew consent, 25 patients (14.0%) were lost to follow up and "other" was listed as the reason for screen failure of 29 (16.3%) patients.

Of the 481 randomized patients, 388 (80.7%) completed the study. The number of completers was similar in both the vilazodone and placebo groups.

For the 93 (19%) of patients who discontinued, the most frequent reasons were lost to follow up (36% vilazodone and 37% placebo) and withdrawal of consent (23% vilazodone and 24% placebo). Of those patients who discontinued due to an adverse event, 12 (26%) were in the vilazodone group and 4 (9%) were in the placebo group. Three patients (6%) in the vilazodone group effect and 7 (15%) patients in the placebo group discontinued due to patient-reported lack of therapeutic effect.

The most common adverse events leading to discontinuation in the vilazodone group included two patients with nausea and 1 of each of the following: palpitations, delirium, angina, pneumonia, dyspepsia, vomiting, feeling abnormal, feeling jittery, dizziness, and migraine. Discontinuation due to AEs in the placebo group included 1 of each: irritability, anxiety, tension, and skin reaction.

Protocol Deviations

No patient was discontinued from this trial for a protocol deviation. The most frequent protocol deviations were study medication non-compliance (57 patients) and study visit outside of visit window (43 patients). Subjects with protocol deviations were not excluded from the efficacy or safety analyses.

It should be noted that Patient 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient and the patient participation was consecutive. Patient 2020-0173

(placebo) and 2080-074 (vilazodone) were the same patient and the patient participation was overlapping. The data for Patient 2080-058 and 2020-173 were excluded from efficacy and safety analyses.

MADRS response was defined as a decrease in total score by at least 50% from the baseline at endpoint. MADRS remission was defined as final MADRS total of <10. The 17-item HAM-D response was defined as a decrease in the 17-item HAM-D total score by at least 50% from baseline. HAM-D remission was defined as a final 17-item HAM-D total of <7. Cochran-Mantel-Haenszel tests were used for these analyses comparing response and remission rates for the treatment groups, stratifying by center.

The 17-item HAMD-D, 21-item HAM-D, and HAM-A total scores, as well as the CGI-S score were analyzed using the same models as MADRS total score. As a subgroup, the change from baseline to endpoint between treatment groups in HAM-A total was assessed in patients with baseline HAM-A scores ≥ 18 .

6.1.4 Analysis of Primary Endpoint

The results from the primary analysis indicate that patients treated with vilazodone demonstrate improvement on the total MADRS score when compared to the patients treated with placebo. The ITT population (LOCF), mean change from baseline was -13.3 for the vilazodone group and -10.8 for the placebo group, to yield a difference between groups (vilazodone-placebo) of -2.5. This difference resulted in statistically significant finding with a p-value of 0.009.

Table 6.1.12 Change from Baseline to Week 8 LOCF – MADRS

Table 3. 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		
<i>Mean (Standard deviation)</i>	32.0 (3.6)	31.9 (3.5)
<i>Median (Min – Max)</i>	32 (24 – 42)	32 (22 – 42)
Change from baseline		
<i>LS Means</i>	-10.8	-13.3
<i>Difference from placebo (SE)</i>		-2.5 (0.96)
<i>(95% confidence interval)</i>		(-4.4, -0.6)
<i>P-value</i>		0.009

The data for Patient IDs of 2080-058, 2020-173, and 2080-074 were excluded from analysis. Patient IDs 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient enrolled at 2 different clinical sites and participation was consecutive. Patient IDs 2020-173 (placebo) and 2080-074 (vilazodone) were the same patient and participation was overlapping at 2 different clinical sites.

(Source: CLDA-07-DP-02 Study Report; Table 11, page 57)

Conclusion

The 40 mg/day dose of vilazodone is superior to placebo in the LOCF primary efficacy analysis at the 8-week endpoint. The effect size, as measured by difference between drug and placebo on change from baseline, is modest but still could be clinically meaningful. Overall, it is considered to be a positive study.

6.1.5 Analysis of Secondary Endpoints

The main secondary efficacy variables for inferential analyses were MADRS response, MADRS remission, and HAM-A total score. The analyses for these variables were performed on the ITT population. Response and remission rates, based on pre-defined criteria, were determined using MADRS total scores.

MADRS Response

There were more MADRS responders in the vilazodone group. In the ITT population LOCF analyses, 100 (43.7%) patients in the vilazodone group and 70 (30.3%) patients in the placebo group met response criteria (defined as $\geq 50\%$ reduction in MADRS total

score from baseline at Week 8). The difference between the two treatment groups was statistically significant, $p=0.0024$.

MADRS Remission

There were more MADRS remitters in the vilazodone group. In the ITT population LOCF analyses, 63 (27.3%) patients in the vilazodone group and 47 (20.3%) patients in the placebo group met remission criteria (defined as MADRS total score at Week 8 <10). The difference between the two groups was not statistically significant, $p=0.0662$.

HAM-A total score

The HAM-A total score least-squares mean change from baseline at Week 8, ITT population, LOCF, was -7.0 for the vilazodone group and -5.7 for the placebo group. The difference of -1.2 between the groups was statistically significant, $p=0.04$. The HAM-A total score change from baseline at Week 8 are presented in the following table.

Although the HAM-A results from this study are statistically significant, this is not considered to be clinically meaningful. To claim an indication for the treatment of anxiety would be required to meet diagnostic criteria for a primary diagnosis of anxiety. Also, a formal hypothesis with division approval would be required. In this study, the primary diagnosis is MDD. Anxiety is a specific component of MDD that tends to improve as the depression is treated.

Table 6.1.13 HAM-A Change from Baseline to Week 8

Table 15: Hamilton Anxiety Scale Total Score Change at Week 8 (Intent-to-Treat Population; Last Observation Carried Forward)			
Statistic	Vilazodone N=231	Placebo N=232	P-value
Model A ^a			
n	231	231	
LS-Mean (SE)	-7.0 (0.55)	-5.7 (0.55)	
95% CI (LS-Mean)	-8.0, -5.9	-6.8, -4.7	
LS-Mean Treatment Difference		-1.2	0.0371
95% CI (LS-Mean Treatment Difference)		-2.4, -0.1	
Treatment Effect			0.0371
Center Effect			0.2173
Baseline HAM-A Effect			<0.0001
Model B ^b			
Treatment Effect			0.0035
Center Effect			0.1986
Treatment*Center Interaction			0.1014
Baseline HAM-A Effect			<0.0001

^a Analysis of covariance (ANCOVA) test including treatment, center and baseline Hamilton Anxiety Scale (HAM-A) total score in the model.
^b ANCOVA test including treatment, center, treatment-by-center interaction and baseline HAM-A total score in the model.

Note: The data for Patient IDs of 2080-058, 2020-173, and 2080-074 were excluded from analysis. Patient IDs 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient enrolled at 2 different clinical sites and the patient participation was consecutive. Patient IDs 2020-173 (placebo) and 2080-074 (vilazodone) were the same patient and the patient participation was overlapping at 2 different clinical sites.

CI = confidence interval; LS = least squares; SE = standard error.
Source: Table 14.2.4.1
Cross-reference: Listing 16.2.6.3

Source: CSR CLDA-07-DP-02 p.66

6.1.6 Analysis of Other Endpoints

In an analysis of a **subset of patients with baseline HAM-A scores ≥ 18** (ITT) the HAM-A total score least-squares mean change from baseline at Week 8 LOCF was -9.5 for the vilazodone group and -8.7 for the placebo group. The difference between the treatment groups of -0.8 was not statistically significant, $p=0.40$. Using the same population of patients (ITT), a repeated measures analysis demonstrated that differences between treatment groups were not statistically significant at any time point.

Crosscutting Issues

6.1.7 Subpopulations

GNSC-04-DP-02

The subgroup analysis for gender indicated numerical improvements in the change from baseline MADRS scores for both males and females, with a slightly greater difference from placebo in the male population (-3.4 males and -2.9 females). The subgroup analysis for race indicated a numerical improvement for white patients; whereas the treatment effect is null for non-whites. The subgroup analysis for age, ≤ 40 years or > 40 years, indicated numerical improvements in both groups with a greater difference from placebo in the older group.

CLDA-07-DP-02

The subgroup analysis for gender indicated a greater change from baseline for females. In this study, only 1% of the subjects were over the age of 65 years. When stratified as ≤ 40 years or > 40 years, the greater improvement was seen in the older age group. Subgroup analysis for race was analyzed as white and non-white. There was a more favorable response in the white group. Overall, it appears that a greater sample size yields a more favorable vilazodone outcome.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In the pivotal trials, the applicant evaluated the efficacy of only one dose of vilazodone, 40 mg qd. The dose-response of this drug has not been adequately explored as previous studies were not designed to provide reliable dose-response information. Neither of the pivotal trials was designed to investigate the effectiveness of the 20 mg qd dose; doses higher than 40 mg qd have been associated with significant GI and psychiatric adverse events. There is also a significant food effect with this medication which could lead to variable exposures if labeling recommendations are not followed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The two pivotal studies, 04 and 07, were of 8 week's duration and in the opinion of this reviewer, were not designed to assess the persistence of efficacy and/or tolerance effects.

Study **CLDA-07-DP-04**, a 52-week uncontrolled study was conducted to assess the long-term safety of vilazodone in patients with MDD. This study included male or female patients, 18 to 70 years of age with HAM-D-17 \geq 18.

A secondary objective of this study was to assess the effectiveness of vilazodone during longer-term treatment. The efficacy variables were the change in MADRS total score from baseline to Week 8, change in CGI-S score from baseline to Week 8 and the change in the two scores over time.

The 'Effectiveness Population' consisted of enrolled subjects who took study drug and had a post-baseline effectiveness measurement. This population was used for the effectiveness analyses. The mean response at each assessment visit was computed using observed case values only. Two-sided 95% CIs were computed for the mean.

The mean MADRS total scores decreased (change from baseline at Week 52 was -22.8) over time. Because this was an uncontrolled study, it is not prudent to make an assessment. The persistence of efficacy and or tolerance effects has not been adequately evaluated for vilazodone.

6.2.0 Efficacy Conclusions

The applicant submitted two adequate and well-controlled phase 3 studies to demonstrate the efficacy and safety of vilazodone 40 mg/day, in the treatment of MDD. There were no obvious irregularities in the conduct of the trials. The impression is that the 40 mg/day dose of vilazodone is superior to placebo in the LOCF primary efficacy analyses at the 8-week endpoint. The effect size, as measured by difference between drug and placebo on change from baseline is likely to be clinically meaningful.

7 Review of Safety

Safety Summary

Overarching Summary

This safety summary focuses primarily on findings of the Phase 2/3 studies, though Phase 1 studies were also reviewed and are included in the body of the review. The Phase 2/3 placebo controlled studies pooled data provide placebo comparisons. This data includes the 2 pivotal trials (CLDA-07-DP-02 and GNSC-04-DP02) and 5 Phase 2 studies that were done by Merck and GSK that were not included in the efficacy assessment due to issues that were discussed earlier in this review. These 5 clinical trials also provide placebo comparisons.

A total of 2898 subjects were exposed to vilazodone in the clinical development program for the treatment of Major Depressive Disorder. In the phase 1 trials, 721 subjects were exposed to vilazodone. In the controlled, short-term trials 1578 patients were exposed to vilazodone. In the long-term, open-label study, 599 subjects were exposed to vilazodone. The total vilazodone exposure in clinical studies was 551 subject-years. The vilazodone exposure was 203 subject-years in the short-term, controlled trials, and the exposure was 348 subject years in the long-term study.

Early pre-clinical findings indicated corneal opacities in dogs. This finding resulted in the inclusion of extensive investigation of ocular concerns in the 5 phase 2 studies and the long-term uncontrolled study. Overall, ocular concerns are detailed in section 7.3.5.1

Examining the dose-relatedness of adverse events, the GI adverse events appeared to be relatively consistent across the dose ranges, although a very slight increase was noted as the dose reached 40 mg/day and higher. The psychiatric and nervous system AEs (dizziness, somnolence, tremor, insomnia, abnormal dreams, anxiety, and nightmares) more than doubled with doses exceeding 40 mg/day.

Short-term treatment with vilazodone appears to have been reasonably safe in the MDD population studied. Generally, the types of adverse events related to vilazodone treatment are similar to those seen with other SSRIs.

7.1 Methods

The safety evaluation of vilazodone consisted of a review of the deaths, serious adverse events, adverse events that led to early discontinuation, common adverse events, clinical laboratory results, vitals, ECG findings, and safety findings specifically related to antidepressants from 24 Phase 1 studies, 5 Phase 2 studies, and 3 Phase 3 studies. Consultations were requested to assess ocular findings, abuse potential, and the thorough QT study.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Per agreement with the applicant, the ISS included data from the phase 2 and phase 3 studies; data from the phase 1 studies were presented in the individual clinical study reports.

7.1.2 Categorization of Adverse Events

The ISS indicates that each verbatim AE term was coded at the study level to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 11.1.

To ensure consistency in reporting adverse events across studies, re-coding of AEs from legacy studies was performed by (b) (4) using MedDRA version 11.1. General conventions were consistent with ICH-endorsed guidelines for choosing MedDRA terms. PGxHealth reviewed and approved all terms that were split.

The JMP file for adverse events was reviewed with an emphasis on verbatim to the preferred term coding. It appeared that most verbatim terms were appropriately coded to preferred terms.

Concomitant medications were coded using the September 2008 version of the World Health Organization Drug Dictionary (WHODD).

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

As per prior agreement with the applicant, four safety subsets were generated from an integrated database of all Phase 2 and Phase 3 studies. The 4 subsets include:

Placebo-controlled Phase 3 Database (GNSC-04-DP-02 and CLDA-07-DP-02)

Each subject receiving vilazodone in the Phase 3 pivotal studies was titrated to 40 mg/day of vilazodone. In study GNSC-04-DP-02, subjects could be down-titrated or maintained at 20 mg/day according to the discretion of the investigator (this was not an option in study CLDA-07-DP-02). All subjects were considered part of the 40 mg/day group. Statistical tests comparing placebo with vilazodone treatment were conducted for this database only.

All Placebo controlled Database (all Phase 2 studies and the two pivotal studies)

The groups were divided according to study drug and dose. Subjects in the Placebo-controlled Phase 3 database who did not titrate to vilazodone 40 mg/day were assigned to the vilazodone <40 mg/day group.

Uncontrolled, Long-term Safety Database (CLDA-07-DP-04)

This group consisted of one arm, vilazodone 40 mg/day.

All Vilazodone Exposure Database (vilazodone subjects from all Phase 2 and 3 studies)

This database consists of all subjects receiving vilazodone from all Phase 2 studies, the two pivotal studies and the uncontrolled long term study. Only demographics,

disposition, exposure, AEs, SAEs, and AEs leading to discontinuation were summarized for the All Vilazodone Exposures database. Active comparator treatment groups are not included in any summaries.

The general approach was for this review focused on the 'All Placebo-controlled Database', consisting of the five phase 2 studies and the two pivotal studies. The seven studies in the 'All Placebo-controlled Database' were of similar duration and appropriate to pool into a single database for review. The long-term uncontrolled database was the primary database for the investigation of lenticular opacities and cataracts.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In general, the overall exposure is considered to be adequate based on the number of subjects exposed to vilazodone at the proposed dose of 40 mg/day. However, the demographics indicate that most of the exposure was in white females, younger than 55 years of age, this is representative of the target population for treatment. The subpopulations were adequately represented based on the demographic pattern of other antidepressant studies.

In the Phase 1 clinical development program, 721 male and female subjects were exposed to doses of vilazodone ranging from 1 to 80 mg in single and repeat dose studies. Most subjects were healthy volunteers, although a small number of subjects with mild to moderate hepatic and renal impairment were also evaluated.

Table 7.2.1 Vilazodone Exposure All Placebo-Controlled Phase 2 and 3 Studies

	Placebo N= 997	Vilazodone <40 mg/day N=903	Vilazodone 40 mg/day N=441	Vilazodone >40 mg/day N=227	Vilazodone All doses N=1578
Subject-years exposure ¹	136.1	113.8	60.9	28.8	203.5
Duration of exposure (days)					
n	994	903	441	227	1571
Mean	50.0	46.0	50.4	46.4	47.3
SD	14.51	18.38	14.92	16.76	17.34
Median	56.0	56.0	56.0	56.0	56.0
Min	1	1	4	7	1
Max	77	76	90	70	90
Duration of exposure (%)					
N	994	903	441	227	1571
>0 days	994(100)	903 (100)	441 (100)	227 (100)	1571 (100)
≥7 days	985 (99)	868 (96)	432 (98)	227 (100)	1527 (97)
≥14 days	952 (96)	799 (89)	419 (95)	215 (95)	1433 (91)
≥28 days	876 (88)	717 (79)	392 (89)	179 (78)	1288 (82)
≥42 days	818 (82)	671 (74)	375 (85)	165 (73)	1211 (77)
≥56 days	615 (62)	468 (52)	282 (64)	114 (50)	864 (55)
Unknown/Missing	3	0	0	0	7
¹ calculated by summing days of exposure over all subjects and dividing by 365.25					

Exposure in the open-label, long-term safety database is illustrated in the following table. As indicated in the following table, by six months nearly half of the subjects had dropped out of vilazodone treatment and by the one year mark, only 20% of the subjects remained in the study. This rate of discontinuation resulted in barely meeting the ICH E1 exposure requirements of 300 subjects for six months and 100 subjects for one year.

Table 7.2.2 Vilazodone exposure open-label long-term study

	Vilazodone 40 mg/day N=599
Subject-years of exposure [†]	348.2
Duration of exposure (days)	
N	599
Mean	212.3
SD	146.95
Median	214.0
Min	1
Max	392
Duration of exposure, n (%)	599
> 0 days	599 (100)
≥ 7 days	594 (99)
≥14 days	576 (96)
≥28 days	529 (88)
≥42 days	498 (83)
≥56 days	464 (83)
≥3 months	389 (65)
≥6 months	314 (52)
≥9 months	277 (46)
≥10 months	265 (44)
≥11 months	261 (44)
≥12 months	118 (20)
[†] subject-years calculated by summing days of exposure and dividing by 365.25	

7.2.2 Explorations for Dose Response

Vilazodone was investigated in the Phase 1 studies across doses of 1 mg to 80 mg. Throughout the clinical development program, more AEs were reported with higher doses of vilazodone. In a repeat dose study with placebo or vilazodone at doses of 20, 40, and 80 mg/day for 10 days, a dose-dependent increase in the number of TEAEs was observed, most commonly, GI TEAEs. Regardless of the dose of vilazodone, nausea, diarrhea, vomiting, headache, and dizziness were reported as TEAEs. As the dose of vilazodone exceeded 40 mg/day were there more AEs leading to discontinuation.

Both pivotal trials were designed to study only one dose of vilazodone, 40 mg/day. Study GNSC-04-DP-02 (pivotal trial) included an option for the investigator to maintain a dose of 10 or 20 mg/day if an ‘unacceptable adverse event’ precluded titration to 40 mg/day. As a result, 13 of 152 patients in the vilazodone arm and 5 of 154 patients in the placebo arm were not titrated to the 40 mg/day target.

7.2.3 Special Animal and/or In Vitro Testing

Clinical trials included specific laboratory testing to determine whether vilazodone exerted any demonstrable effect on thyroid function. This special analysis was designed in response to the observation in a single carcinogenicity study of thyroid adenomas and follicular hyperplasia associated in mice. Overall conclusions regarding thyroid function included the fact that changes in laboratory test results suggesting possible treatment-emergent hypothyroidism or hyperthyroidism occurred no more frequently in subjects who received vilazodone than subjects who received placebo.

Protocols for mouse and rat carcinogenicity studies were presented to the Executive CAC in July 1998 and at a second meeting in April 2000.

Executive CAC recommendations and conclusions:

Mouse Carcinogenicity Study – The committee concurred that the increased incidences of mammary adenocarcinomas and adenoacanthomas in females at the high dose and hepatocellular neoplasms in male mice at the high dose were drug related.

Rat Carcinogenicity Study – No biologically relevant, drug-related increases in neoplasm incidence were observed in rats administered vilazodone.

Further interpretation of this matter will be addressed in the Pharmacology/Toxicology reviews. The Pharmacology Toxicology review was not available at the time of this writing.

Corneal opacities were observed in dogs during the first few weeks of dosing with vilazodone. However, the opacities resolved and cataracts were not observed for up to 52 weeks of dosing dogs and were never seen in other species.

7.2.4 Routine Clinical Testing

The clinical trials program included routine clinical testing at screening, baseline, at various timepoints during the studies. There was no scheduled follow-up to assess clinical testing after the Week 8 visit for the two pivotal studies. Clinical assessments included:

Hematology: WBC with differential, RBC with indices, hemoglobin, hematocrit, platelet

Chemistry: ALT, AST, albumin, ALP, bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, GGT, glucose, magnesium, phosphorus, potassium, total protein, sodium, thyroid function tests, and uric acid

Urinalysis: color, appearance, specific gravity, pH, protein, urobilinogen, nitrite, glucose, ketones, bilirubin, occult blood, microscopic examination, and leukocyte esterase

Urine drug screen: amphetamines, barbiturates, cocaine, marijuana, methadone, opiates, phencyclidine, benzodiazepines, and propoxyphene

Pregnancy tests: Screening serum pregnancy tests were analyzed by the central laboratory. Urine pregnancy tests were done at baseline, Week 2, and Week 8 (Visit 7 or early termination) by the study staff.

Ophthalmologic evaluations: slit lamp biomicroscopy, dilated funduscopy, tests of visual acuity, intraocular pressure, and Schirmer's test for decreased lacrimation. The ocular monitoring was conducted in the five Phase 2 studies and the uncontrolled, long-term Phase 3 study.

Electrocardiograms: 12 lead ECGs were assessed periodically and in a 'Thorough QT Study' PGX-08-P1-06.

Vital signs: systolic blood pressure, diastolic blood pressure, pulse, respiratory rate.

Overall, appropriate clinical measurements were assessed at appropriate intervals. Whether the 80 mg dose is adequate to represent the high clinical scenario is unknown.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the comprehensive review by Biopharmaceutics.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Serotonin Reuptake Inhibitors, as a class, are contraindicated in patients taking monoamine oxidase inhibitors. Warnings and precautions for the use of SSRIs include clinical worsening, suicide risk, anxiety, insomnia, discontinuation symptoms, activation of mania or hypomania, hyponatremia, seizures, and abnormal bleeding.

Potential Serotonin Toxicity

Because Serotonin Syndrome is a known complication of treatment with SSRIs, the AEs in the Phase 2 and Phase 3 studies were searched for preferred terms that might indicate serotonin syndrome. When the terms were identified, Hunter's serotonin toxicity criteria were applied to identify patients with possible serotonin toxicity. The JMP line listings were reviewed to confirm the applicant's assessment. Two subjects were identified with probable vilazodone related serotonin toxicity and are described in the following narratives.

CLDA-07-SP-04-4040-0001

A 24-year-old African American female in the 52-week, long-term, open-label study, received vilazodone 10 mg/day x 1 week; vilazodone 20 mg/day x 1 week, and vilazodone 40 mg/day for the next 262 days. On the last day of study medication she experienced anxiety, visual hallucinations, and became combative. Vitals: blood pressure 152/79 mmHg, heart rate 155, and temperature 98.4°. She reportedly had missed 'a couple of days of medication and took 5-6 pills to 'catch up'. This patient took an overdose and experienced signs and symptoms consistent with serotonin toxicity.

GPP-007-CLN-CP2-2001-245/EMD-68843-010/0038-1358

A 42-year-old white male in an 8-week, Phase 2 study received vilazodone 10 mg/day x one day, 20 mg/day x 2 days, 40 mg/day x 3 days, and 80 mg/day x 6 days. He experienced middle insomnia throughout the dosing period. On Day 12 (the final dose), he experienced derealization, flushed feeling, hypnogogic hallucinations, olfactory hallucinations, and myoclonic jerks. It is likely that the patient was experiencing serotonin toxicity due to the rapid dose titration.

Seizures

Review of the entire vilazodone exposure database indicates one seizure which is described in Section 7.3.2, Nonfatal SAEs.

Hyponatremia

Review of the JMP line listing for sodium values revealed only one result lower than 130 mmol/L, this was a screening result of 129 mmol/L. Despite the known concern regarding hyponatremia/SIAH with this drug class, there was no evidence of hyponatremia in the all Phase 2 and Phase 3 database.

Activation of Mania or Hypomania

Activation of mania or hypomania is a known complication of antidepressant use. The applicant identified ten subjects from a search that included at least one of 3 or more of the following TEAEs: affect lability, aggression, agitation, anger, delusions, euphoria, flight of ideas, grandiosity, hallucinations, irritability, and hostility, among others. Using these criteria, 7 (0.3%) subjects receiving vilazodone and 1 (0.2%) subject receiving placebo were identified as possible substance induced mania from the database search of all vilazodone exposure which includes the 7 placebo controlled studies and the long-term uncontrolled study.

Review of the JMP line listing of AEs and narrative reports supports the applicant's assessment that the incidence of activation of manic/hypomanic symptoms associated with vilazodone use during treatment of MDD are within or below the expectations observed with other antidepressants.

Abnormal Bleeding

The TEAEs related to bleeding occurred in <1% of subjects in the Phase 2 and 3 database. For the all placebo-controlled database, 2.8% of those in placebo group and 2.8% of those in the vilazodone group experienced a TEAE in various SOCs related to bleeding. From a clinical perspective, the bleeding events in the subjects taking vilazodone appear to be minor and not necessarily attributable to the drug.

7.3 Major Safety Results

7.3.1 Deaths

Phase 1

One subject in study PGX-08-P1-06 died during the study due to a fatal stab wound. The narrative report indicates this 29-year-old white (Hispanic or Latino) female received a fatal stab wound. She was randomized to the moxifloxacin treatment arm (never received vilazodone) and completed treatment on (b) (6). On (b) (6) 25 days after completing the study drug, she was fatally stabbed in her home during a domestic dispute.

Phase 2/3

Two deaths occurred in GPP-007-CLN-CP2-2001-245; however, neither patient was receiving active treatment with vilazodone. **Both of the deaths were suicides.** One patient died during the pre-treatment phase and one patient was receiving placebo.

1. 026-1231 – Suicide by Gun Shot

This patient was a 54-year-old Caucasian male. He was randomized to receive placebo and was scheduled for his first dose on Aug. 6, 1998. On (b) (6) he died from a self-inflicted **gun shot to the head**. The patient's medical history included anxiety, major depressive disorder, alcohol abuse, renal lithiasis, and surgery for herniated disk. This death is not related to the study medication.

2. 027-G01 – Suicide by Carbon Monoxide

This patient was a 47-year-old male who had not been randomized to a study medication when his death occurred. The patient had signed informed consent, but no procedures were performed because he failed to attend the screening visit. On (b) (6) it was reported that the patient had attempted **suicide by carbon monoxide** inhalation. He was hospitalized for three weeks and died on (b) (6) as a result of CO poisoning. The death is not related to the study medication.

7.3.2 Nonfatal Serious Adverse Events

In the double-blind, pivotal trials, 2.4% and 2.1% of the vilazodone-treated and placebo-treated patients had at least one SAE (see Table below). Of these SAEs, the

percentage of patients who experienced a particular SAE was similar with the exception of infections. It is likely that enterocolitis and gastroenteritis would map to gastrointestinal AEs rather than infection (there is no documentation of actual infection). The SAE of pneumonia occurred four times more frequently in the vilazodone-treated patients than the placebo-treated patients. However, due to the limited number of patients exposed no definitive conclusion can be made regarding the association of vilazodone exposure and infections.

Table 7.3.1 Subjects with Serious Adverse Events
All Phase 2 and Phase 3 Studies by System Organ Class and Preferred Term

System Organ Class Preferred Term	Vilazodone N=2177 (%)	Placebo N=997 (%)
Number of subjects with at least 1 SAE	53 (2.4)	21 (2.1)
Total number of SAEs	70	27
Psychiatric Disorders		
Suicidal ideation	10 (0.5)	9 (0.9)
Suicide attempt	3 (0.1)	5 (0.5)
Depression	3 (0.1)	1 (0.1)
Intentional self-injury	2 (0.1)	3 (0.3)
Major depression	1 (0)	0
Panic attack	1 (0)	0
Completed suicide	0	1 (0.1)
Infections and Infestations		
Pneumonia	8 (0.4)	1 (0.1)
Abdominal wall abscess	4 (0.2)	1 (0.1)
Bronchitis	1 (0)	0
Cervicitis	1 (0)	1 (0.1)
Enterocolitis infectious	1 (0)	0
Gastroenteritis	1 (0)	0
Nervous System Disorder		
Transient ischemic attack	7 (0.3)	0
Carotid arteriosclerosis	2 (0.1)	0
Migraine	1 (0)	0
Serotonin syndrome	1 (0)	0
Syncope	1 (0)	0
Tremor	1 (0)	0
Injury, Poisoning and Procedural Complications		
Overdose	6 (0.3)	3 (0.3)
Concussion	3 (0.1)	3 (0.3)
Fracture	1 (0.1)	0
Skin laceration	1 (0.1)	3 (0.3)
Pneumothorax	1 (0.1)	0
	0	1 (0.1)

General Disorders and Administration Site Conditions	4 (0.2)	0	
Chest pain	2 (0.1)	0	
Chest discomfort	1 (0)	0	
Pyrexia	1 (0)	0	
Pregnancy, Puerperium and Perinatal Conditions	4 (0.2)	2 (0.2)	
Pregnancy	4 (0.2)	2 (0.2)	
Respiratory, Thoracic and Mediastinal Disorders	4 (0.2)	2 (0.2)	
Acute Respiratory failure	1 (0)	0	
Asthma	0	2 (0.2)	
Chronic Obstructive Pulmonary Disease	1 (0)	0	
Pulmonary embolism	1 (0)	0	
Sleep apnea syndrome	1 (0)	0	
Hepatobiliary Disorders	3 (0.1)	0	
Gallbladder disorders	3 (0.1)	0	
Investigations	3 (0.1)	3 (0.1)	
Pregnancy test positive	2 (0.1)	3 (0.3)	
Bronchoscopy	1 (0)	0	
Reproductive System and Breast Disorders	3 (0.1)	0	
Ectropion of Cervix	1 (0)	0	
Endometriosis	1 (0)	0	
Menometrorrhagia	1 (0)	0	
Cardiac Disorders	2 (0.1)	0	
Angina pectoris	1 (0)	0	
Atrial fibrillation	1 (0)	0	
Gastrointestinal Disorders	2 (0.1)	1 (0.1)	
Diarrhea	1 (0)	0	
Duodenal stenosis	1 (0)	0	
Abdominal hernia	0	1 (0.1)	
Metabolism and Nutrition Disorders	2 (0.1)	0	
Dehydration	1 (0)	0	
Hypokalemia	1 (0)	0	
Hyponatremia	1 (0)	0	
Obesity	1 (0)	0	
Vascular Disorders	2 (0.1)	0	
Deep vein thrombosis	1 (0)	0	
Hypertension	1 (0)	0	
Neoplasms Benign, Malignant and Unspecified	1 (0)	0	
Prostate Cancer	1 (0)	0	
Renal and Urinary Disorders	1 (0)	1 (0.1)	
Renal failure	1 (0)	0	
Nephrolithiasis	0	1 (0.1)	

Phase 1

In the Phase 1 studies 5 serious adverse events (SAEs) were reported. Narrative reports follow the table for each of the events. One patient experienced a “paranoid reaction” 5 days after he completed the 8-week double blind arm of vilazodone. There is insufficient evidence to assume causality. Subject 230-202 experienced many AEs that appear to be associated with the study medication, vilazodone 40 mg/day.

Table 7.3.2 Phase 1 Serious Adverse Events

ID	Drug	Serious Adverse Event	Intervention	Outcome	D/C from Study	Related to Study Drug
238-140	Vilazodone	Mandibular Fracture (trauma)	Corrective Surgery	Recovered	No	Not Likely
238-018	Vilazodone 20 mg/day	“Paranoid Reaction”	Psychiatric Assessment	Recovered	No	Possibly
230-202	Vilazodone 40 mg/day	Labile Mood Delusional Thought Content	Psychiatric Hospitalization	Recovered	Yes	Yes
0601-183	Vilazodone 40 mg	Syncope (seizure)	Neurology Consult	Recovered	Yes	Possibly
0601-106	Moxifloxacin	Convulsion (history of Seizures)	Medical Evaluation	Resolved	No	No

Study GPP-007-CLN-CP1-2003-238

- Subject 0140 experienced a fractured mandible as a result of trauma; he required corrective surgery. This is considered to be unrelated to the study drug.
- Subject 00018 experienced a ‘paranoid reaction’ five days after the last dose of study medication (unblinding revealed vilazodone treatment from Aug 30 – Sep 27). Although the patient was not hospitalized, psychiatric follow up was required and this was considered an SAE. This is considered to be possibly related to the study drug. The psychiatrist assessed improved insight, did not diagnose mania or depression and reported full recovery without the need for treatment.

Study GPP-007-CLN-CP1-1998-230

- Subject 202, a 40-year-old male, experienced 54 AEs of increasing intensity during the course of treatment. Ultimately emotional lability, aggressive behavior, and delusional content of thought resulted in prolonged hospitalization of this 'healthy volunteer'. The narrative indicates that on April 21, 1997 (Day 16) the medication was stopped due to a combination of AEs. The volunteer reported restless legs after every dose of medication but the severity was increasing during the course of treatment. From Day 12 he reported parasthesia/heavy sensations on his back. He was emotionally unstable. He reported vivid, colorful dreams during the night. On Day 15 he reported hyperesthesia (sounds 10 times stronger than normal). The parasthesia in his extremities and back were increasing in intensity. This was an inpatient study, these events required extended hospitalization, and psychiatric treatment was not indicated in the narrative report. The subject reported resolution of all AEs as of May 17, 1997.

Study PGX-08-P1-06 (Thorough QT Study)

- One subject (0601-183) in the vilazodone group experienced syncope on Day 9. This 36-year-old white female (Hispanic or Latino) experienced convulsive syncope and was discontinued from the study. She was randomized to the vilazodone treatment arm and received the first dose of vilazodone 10 mg on Nov 23, 2008. About 3 hours after the dose of vilazodone 40 mg on [REDACTED]^{(b) (6)}, while having her blood drawn, the subject experienced an apparent seizure. After further investigation, this was assessed to be convulsive syncope secondary to a vasovagal episode. This is considered to be possibly related to the study drug.
- One subject (0601-106) in the moxifloxacin group experienced convulsion on Day 7. The event lasted one minute and was assessed as not related to the study drug.

Phase 2

In the Phase 2 studies, 44 serious adverse events were reported by 41 patients. Table 7.3.2 illustrates the SAEs; narrative reports for pertinent events follow the table. Of the 44 serious adverse events, 23 were reported in the vilazodone treatment groups, 13 in the placebo groups, 5 in the active comparator groups, and 3 were reported prior to study medication randomization.

Table 7.3.3 Phase 2 Placebo-controlled Studies – Serious Adverse Events

ID	Drug	Serious Adverse Event	Intervention	Outcome	D/C From Study	Related To Study Drug
001-1075	(b) (6)	Suicidal Ideation	Hospitalized	Recovered	Yes	Possibly
022-1017		Overdose	Hospitalized	Recovered	Yes	Possibly
025-1376		Diarrhea	Hospitalized	Recovered	Yes	Possibly
033-1260		Depression	Hospitalized	Recovered	Yes	Unlikely
035-1466		Overdose (insomnia)	Emergency Room	Recovered	Yes	Yes
035-1470		HTN	Hospitalized	Recovered	Yes	Yes
042-1598		Pregnancy	Elective Termination	Resolved	Yes	No
001-03565		Pregnancy	Elective Termination	Resolved	No	No
013-02429		Pregnancy	None	Ongoing	Yes	Possibly
002-02046		Pregnancy	None	Ongoing	No	No
017-02545		Tremors	Emergency Room	Resolved	Yes	Possibly
023-02759		Migraine	Unknown	Resolved	Yes	Possibly
021-02713		TIA	Hospitalized	Resolved	Yes	Possibly
026-02866		Fractured R foot	Hospitalized MV accident	Resolved	No	Unlikely
001-04006		Atrial Fibrillation	ECG – med follow-up	Resolved	No	Possibly
006-04187		Self mutilation	Hospitalized	Recovered	Yes	Unlikely
023-04417		Cervicitis	Hospitalized	Recovered	Yes	Unlikely
005-01334		Suicidal Ideation	Hospitalized	Resolved	Yes	Possibly
036-01704		Pneumonia	Hospitalized	Resolved	Yes	No
008-00245		Pregnancy	None	Resolved	No	No
018-00588	Medication Missing	None	Resolved	No	No	
005-1099	Suicide Attempt	Hospitalized	Alive with sequelae	Yes	No	

006-1219	(b) (6)	Facial fracture	Hospitalized	Recovered	Yes	No
		Pneumo-thorax				
008-1284		Asthma	Hospitalized	Recovered	Yes	No
		Pneumonia	Hospitalized	Recovered		
013-1397		Pregnancy	None	Ongoing	No	No
021-1104		Suicidal Ideation	Hospitalized	Unknown	Yes	No
022-1028		Overdose	Hospitalized	Recovered	Yes	No
031-1544		Pregnancy	None	Unknown	No	No
014-02449		Depression	Hospitalized for psychosis	Resolved	Yes	No
016-02534		Pregnancy	Elective Termination	Resolved	Yes	No
021-03532		Suicidal Ideation	Hospitalized	Resolved	Yes	No
042-03424		Renal Calculus	Hospitalized	Resolved	No	No
024-00793		Pregnancy	Elective Termination	Resolved	No	No
024-00795		Abdominal Hernia	Hospitalized	Resolved	No	No
003-1166		Arrhythmia	Hospitalized CABG Pacemaker Implant	Recovered	Yes	No
		Unstable Angina				
006-1217		Pneumonia	Hospitalized	Recovered	Yes	No
033-1152		Stomach Cramps	Hospitalized	Recovered	Yes	Unlikely
011-02347		Overdose Intentional	Emergency Room	Resolved	Yes	Possibly
027-471		Hernia	Surgery	Recovered	Yes	No
029-285	Pregnancy	Unknown	Unknown	Yes	No	
001-0085	UTI	Unknown	Recovered	Yes	No	

GPP-007-CLN-CP2-2001-244 (EMD 68843-009)

Patient ID **001-1075** was a 20-year-old Caucasian female who was randomized to vilazodone; she received the first dose of study medication on July 24, 1998. On August

10, 1998 she reported suicidal ideation (the dose was 60 mg at the time). She took her last dose of vilazodone on August 15, 1998; she was hospitalized for suicidal ideation on [REDACTED] (b) (6) and was discontinued from the study.

GPP-007-CLN-SP2-2001-245 (EMD 68843-010)

Patient ID **022-1017** was a 19-year-old Caucasian female who was randomized to the medium dose vilazodone treatment arm; she received the first dose on September 29, 1998. On [REDACTED] (b) (6) she attempted suicide by overdose. She consumed 8 Unisom tablets with an undisclosed amount of Tylenol and liquor. She was treated in the emergency room and admitted to the psychiatric unit on [REDACTED] (b) (6). Her medical history includes a previous suicide attempt in 1992. The patient was withdrawn from the study on November 19, 1998.

Patient ID **022-1028** was a 36-year-old Caucasian male who was randomized to the placebo treatment group. On [REDACTED] (b) (6), as a suicide attempt, he ingested a 90-day supply of Zoloft 50 mg, Darvocet N-100 (n=17), flurazepam 15 mg (n=17) and Soma (n=28). The patient was intubated in the emergency room and admitted for treatment and observation. On Day 2 of hospitalization a psychiatric consultation was obtained. The subject was assessed as recovered on [REDACTED] (b) (6). He was discontinued from the study.

Patient ID **033-1260** was a 35-year-old Caucasian female who was randomized to the high dose vilazodone treatment group; she received her first dose of study medication on September 30, 1998. On [REDACTED] (b) (6) she reported worsening of depression for which she was hospitalized. She was in the hospital for one week and was discharged on [REDACTED] (b) (6) when the SAE was considered to be resolved. Her medical history included recurrent depression, fibromyalgia, and IBS. Medication history includes: paroxetine in 1993 and Soma since 1997. While hospitalized she was prescribed Seroquel 150 mg, Effexor, and Buspar. The last dose of study medication was taken on November 2, 1998 and she was withdrawn from the study on December 29, 1998.

Patient ID **035-1466** was a 31-year-old Hispanic male who was randomized to the low dose vilazodone treatment arm; he received the first dose of study medication on October 2, 1998. On [REDACTED] (b) (6) he overdosed. The report indicates that he became frustrated because he was unable to sleep and he took 250 mg chloral hydrate. He still was unable to go to sleep so he took 8000 mg chloral hydrate after which he became concerned and presented to the emergency room. He was evaluated at the emergency room by a crisis worker and released to return home. He was not discontinued from the study at that time and the serious adverse event was considered to be resolved. Within 72 hours of the overdose, the patient presented with profound depression and suicidal ideation which led to discontinuation from the study. His last dose of study medication was on October 23, 1998, he was withdrawn from the study

on November 3, 1998. He was subsequently treated with another antidepressant (Remeron). The event of insomnia is considered to be related to the study medication and the suicidal ideation as possibly related.

Patient ID **035-1470** was a 68-year-old Caucasian female who was randomized to the high dose vilazodone treatment arm; she received the first dose of study medication on November 17, 1998. On [REDACTED] (b) (6) the patient was hospitalized for treatment of hypertension. The report indicates that on December 9, 1998 she complained of a migraine headache with musical hallucinations and poorly formed visual hallucinations. On [REDACTED] (b) (6) her BP was 160/100, repeat BP was 182/100 and she reported palpitations and a 'heavy feeling' in her chest. She was given two doses of clonidine with good results and she was discharged from the hospital on [REDACTED] (b) (6). Medication history included (but not limited to): amitriptyline, Prozac, Celexa, and Synthroid. This SAE is considered likely to be related to the study medication.

GPP-007-CLN-CP2-2003-246 (SB-659746-A)

Patient ID **021-02713** was a 64-year-old female who was randomized to vilazodone treatment; 41 days after the first dose of study medication she developed confusion, agitation, dizziness, stiff neck, and disorientation. ECG was within normal limits and she seemed to improve; however, when she returned home she became more confused and disoriented. She was admitted to the hospital for observation. The following day she did not remember the event. She was alert and oriented and was subsequently diagnosed with a transient ischemic attack (TIA). The study medication was discontinued and the event resolved. She was withdrawn from the study. This is possibly related to the study medication.

Patient ID **017-02545**-The following narrative is copied from the clinical study report: This report refers to a 28-year-old female (patient identification number 003.017.02545). The patient's current medical history included intermittent insomnia. Concomitant medication use included acetylsalicylic acid/caffeine/paracetamol (Excedrin)-last dose 21-Nov-2001.

On 13-Nov-2001, the patient was randomized to study medication. On [REDACTED] (b) (4), the patient was withdrawn from the study due to lack of efficacy and received the last dose of study medication. On [REDACTED] (b) (4), 10 days post the last dose of study medication, the patient was taken to the emergency room due to body tremors. The patient reported a sudden onset of body tremors Wednesday evening, which were "violent" in nature. The patient was treated with intravenous diazepam (Valium), and the tremors subsided "to some degree". The patient was diagnosed with stress. The patient presented on [REDACTED] (b) (6) for further evaluation. Diagnosis of "we don't know what this is" was made. The patient was prescribed alprazolam (Xanax) .05 mg TID and was sent home. CT (computed tomography) scan and complete laboratory work-up reported no findings.

On [REDACTED] (b) (6), the patient came into the clinic for follow-up. The patient's tremors were at her head, neck, torso, arms, and down to her knees. The tremors were described as coarse tremors, three to five beats/second. Due to the tremors, the patient had bruising on her head from hitting it on the floor. The tremors were significant enough that she was unable to drive or perform many of her ADLs (activities of daily living). There appeared to be no obvious cognitive deficits. The patient was sent to a local healthcare facility for a medical and neurological work-up. The patient had been randomized to double-blind oral vilazodone (659746) 20 mg. The investigator reported that the patient had never before been treated for depression. The investigator felt the need to break the blind to appropriately evaluate and treat the patient. The event resolved on 24-Dec-2001.

GPP-007-CLN-SP2-2001-247 (SB-659746-A)

Patient **ID 001-04006** was a 64-year-old male who was randomized to the vilazodone treatment group. Approximately 8 weeks after beginning the study medication, and on the day of the final dose, the subject had an ECG which revealed bradycardia and normal sinus rhythm. The following day, he had a physical examination and his pulse was noted to be irregular. Another ECG was done which revealed atrial fibrillation. He was referred for internal medicine evaluation – outcome unknown. At the 14-day follow-up visit and ECG revealed normal sinus rhythm.

Patient **ID 006-04187** was a 24-year-old male who was randomized to the vilazodone treatment group; he received the first dose of study medication on August 17, 2002. On [REDACTED] (b) (6) weeks after the first dose of the study medication he experienced self-inflicted lacerations to the forearm after a night of heavy drinking. He was taken to the emergency room where it was determined that his blood alcohol level was elevated. The lacerations were sutured; he was treated with IV fluids and tetanus update. The study medication was stopped and he was discontinued from the trial. His psychiatric history was significant for depression and 'cutting'.

GPP-007-CLN-CP2-2001-248 (SB-659746-A)

Patient **ID 005-1334** was a 53-year-old male who was randomized to the vilazodone (20 mg) treatment arm. Approximately 7 weeks after the study medication was initiated, the subject was hospitalized for suicidal ideation. The trial medication was discontinued and the event resolved after 24 days of hospitalization. His medical history includes diabetes, for which he was prescribed metformin.

Phase 3 Placebo Controlled (non-fatal SAEs)

In the two placebo-controlled Phase 3 studies 11 SAEs in 9 patients were reported in the vilazodone group and 9 SAEs in 7 patients were reported in the placebo group. For

the vilazodone group the 11 SAEs included two malignancies (possibly three, although it is listed as pleural effusion), one concussion (related to alcohol consumption), one suicide attempt, one psychotic episode, one angina (pre-existing cardiovascular disease). Of those, three are considered by this reviewer as possibly related to vilazodone: depression with psychotic features, angina and atypical chest pain. Sufficient information is not available to establish causality. The SAEs in the placebo group are significant in that the suicidal ideation is likely related to not being in an active treatment arm.

Table 7.3.4 Phase 3 Placebo Controlled SAEs

ID	Drug	Serious Adverse Event	Intervention	Outcome	D/C From Study	Related to Study Drug
0404-004	Vilazodone	Prostate Cancer	Hospitalized	Unknown	Yes	No
0404-012	Vilazodone	Concussion	Hospitalized	Recovered	No	Not Likely
0800-033	Vilazodone	Suicide Attempt (OD Tylenol)	Hospitalized	Recovered	Yes	Not likely
0800-037	Vilazodone	Lymphoma	Hospitalized	Unknown	Yes	No
0800-083	Vilazodone	Depression w/psychotic features	Hospitalized	Resolved at time of hospital discharge	Yes	Possibly
		Psychosis	Hospitalized	Recurrent Psychosis	Yes	Possibly
0400-016	Placebo	Suicidal Ideation	Hospitalized	Recovered	Yes	No
0404-003	Placebo	Depression	Unknown	Recovered	Yes	No
0500-012	Placebo	Pregnancy	None follow-up HCG Negative	Recovered	No	No
0800-022	Placebo	Depression Suicidal Ideation	Hospitalized	Ongoing Suicidality Depressed mood	Yes	No
0800-057	Placebo	Suicidal Ideation	Hospitalized	Recovered	Yes	No
2010-014	Vilazodone	Angina	Hospitalized	Resolved	Yes	Possibly
		AS Carotid	Hospitalized	Chronic	Yes	No

		Disease	carotid end-arterectomy			
2020-061	Vilazodone	Pleural Effusion	Hospitalized	Unknown	Yes	Not likely
2020-168	Vilazodone	Chest Pain Atypical	Hospitalized	Resolved	No	Possibly
2070-009	Vilazodone	Cholecystitis	Hospitalized	Recovered	No	Not likely
2050-084	Placebo	Asthma	Hospitalized	Recovered		Not likely
		Asthma	Hospitalized	Recovered		Not likely
2080-019	Placebo	Ankle Fracture	Hospitalized	Not Recovered		Not likely

Study GNSC-04-DP-02

In this study 6 SAEs were reported in 5 patients in the vilazodone group and 6 SAEs were reported in 5 patients in the placebo group. Narrative reports of SAEs were reviewed, those of interest include:

Subject **0404-012** was a 27-year-old white male with a history of nephrectomy, splenectomy, hypertension, and hyperlipidemia. Concomitant medications included ibuprofen, Atacand, rosuvastatin, and Ziac. The patient was randomized to vilazodone and received his first dose of 10 mg on Nov 22, 2006 and was titrated per protocol to 40 mg on Dec 6, 2006. On [REDACTED] (b) (6), the patient suffered a head concussion. The patient was intoxicated and fell, hitting his head on the pavement and losing consciousness. The patient was hospitalized, lacerations required sutures. No action was taken with the study drug in response to the SAE and he completed the study on Jan 16, 2007.

Subject **0800-033** was a 20-year-old white female with a history of IBS, headache, and breast augmentation. Concomitant medications included orthotricyclen and Phenergan. The patient was randomized to vilazodone and received her first dose of 10 mg on Jul 21, 2006 and was titrated per protocol to 40 mg on Aug 4, 2006. On [REDACTED] (b) (4) the patient took an overdose of acetaminophen. Psychiatry consultation revealed a break up with her boyfriend and a history of self injurious behavior (cutting). It was recommended that the patient not be started on psychiatric medications immediately because of the recovering status of her liver. The patient was discharged to home and recovered without sequelae. The patient received her last dose of study medication on [REDACTED] (b) (6), one week prior to the onset of the SAE. At the early termination visit on

Sep 21, 2006 there were no notable abnormalities. It is unlikely that this event was related to the study drug.

Subject **0800-083** was a 60-year-old Caucasian female with a history of chronic pain, cardiac murmur and hyperlipidemia. The patient was randomized to the vilazodone treatment group and received the first dose of 10 mg on March 16, 2007. After one week the dose was increased to 20 mg and by March 30, 2007 the dose was increased, per protocol, to 40 mg/day. On April 27, the patient reported 'worsening depression'. Treatment with vilazodone was discontinued by the patient because of depression. She received the last dose of study medication on April 29, 2007. She also received Ambien, lorazepam, aripiprazole, and bupropion for the reported symptoms of 'worsening depression'. On [REDACTED] (b) (6) she was hospitalized for depression with psychotic features. She presented at the emergency room in a confused, guarded, and paranoid state with disorganized thoughts. Urine toxicology was negative, thyroid function tests were within normal limits, and CT scan was unremarkable. Axis I diagnoses included: Psychotic Disorder, NOS; r/o MDD, recurrent, with psychotic features. She was prescribed but refused to take aripiprazole intermittently throughout her hospitalization. Her mood stabilized and affect brightened and on [REDACTED] (b) (6) she was discharged with plans for outpatient follow-up. At the time of her discharge from the hospital she denied hallucinations, delusions, suicidal, or homicidal ideation. The patient was considered recovered without sequelae from the SAE at the time of discharge. Discharge medications included aripiprazole, lorazepam, simvastatin, and medroxyprogesterone acetate.

Subject **0800-057** was a 46-year-old American Indian/Alaskan Native female with a history of cerebral palsy, gestational diabetes, bursitis, headache, rheumatoid arthritis and hypertension. Concomitant medications included Aleve, loratidine, and sertraline (discontinued 10/31/2006). The patient was randomized to placebo (the narrative states vilazodone in the heading and placebo in the text-the dataset indicates placebo) on Nov 21, 2006. On [REDACTED] (b) (6) she experienced SI and presented to the emergency room with suicidal ideation and thoughts of self harm. She was hospitalized for the event. On [REDACTED] (b) (6) she was discharge to home. She received her last dose of the study drug on Jan 3, 2007. The event was attributed to the disease under study, not related to vilazodone.

Study CLDA-07-DP-02

In this study 5 SAEs were reported in 4 patients in the vilazodone group and 2 SAEs were reported in 2 patients in the placebo group. Narrative reports of SAEs were reviewed, those of interest include:

Subject **2010-014** was a 69 year-old White female with multiple medical problems, including hyperlipidemia, II/IV systolic murmur, GERD, tinnitus, insomnia, and sinus congestion. She was randomized to vilazodone and received 10 mg/day beginning July 22, 2008, the dose was titrated to 40 mg/day by September 3, 2008. Angina was first

recorded on August 20, 2008 (at a primary care visit) and on the office visit of (b) (6) she complained of chest tightness and pressure. She appeared diaphoretic and pale, BP 134/66, HR 67 bpm, RR 20 bpm. She was given 0.4 mg SL nitroglycerin and sent to hospital by EMS. On (b) (6) she underwent cardiac catheterization which revealed single vessel disease (LAD). She was discontinued from the study on (b) (6). The patient had underlying cardiac disease; however, the event of angina, though unlikely is possibly related to the study drug (reviewer's opinion).

Subject **2020-168** was a 53-year-old Native Hawaiian/Pacific Islander female with hypertension, GERD, steatohepatitis, and headache. She was randomized to vilazodone treatment and received the first dose of 10 mg/day on October 29, 2008. Her dose was increased to 20 mg/day from November 5 to November 11 with treatment interrupted from (b) (6) due to hospitalization (details were not provided in the narrative). The dose was increased to 40 mg from November 12 through December 23. She reported chest pain beginning November 4, 2008. On (b) (6) she presented to the emergency room with a (b) (6) history of chest discomfort. She also reported migraine symptoms. Her blood pressure was 172/108 mmHg, heart rate 67 bpm. It was noted that she had discontinued Cozaar (which she had taken since 2002) against medical advice on August 28, 2008. Pre-existing hypertension was cited as the reason. It is unlikely that this event was related to vilazodone, although it is a possible contributing factor (reviewer's opinion).

Phase 3 Uncontrolled, Long-term Study CLDA-07-DP-04 (Non-fatal SAEs)

There were 33 SAEs that occurred in 23 (4%) patients. The SAE of pneumonia occurred in 2 patients, and all other SAEs occurred in 1 patient each. The most frequent system organ classes consisted of: Infections and Infestations – 5 patients, Respiratory; Thoracic and Mediastinal – 4 patients; Nervous System Disorders – 3 patients; Psychiatric Disorders – 3 patients; and General Disorders ad Administration Site Conditions – 3 patients. There was one episode of syncope.

Narrative provided for an episode of syncope:

Patient **4290-040** was a 70 year old white female. Past medical/surgical history included former smoker, facelift, stress test, and benign ovarian tumors removed. Concomitant medical conditions included syncope, hypertension, hiatal hernia, pelvic cystic mass, arthritis, insomnia, hypothyroidism, generalized fatigue, hypercholesterolemia, irregular heartbeat, lipoma on left shoulder, acid reflux, gastroesophageal reflux disease, recurrent urinary tract infections, post menopausal, bursitis, degenerative joint disease, hip pain, trochanteric lumbar spine problem, severe headaches, sleep apnea, and sleep disorder. Her first lifetime episode of MDD occurred at age 56 years and the duration of the current MDD episode (considered severe in severity) was more than 12 months.

She received treatment with vilazodone at 10 mg from 28 March to 02 April 2008, at 20 mg from 03 to 07 April 2008, and 40 mg from 08 to 12 April 2008. On [REDACTED]^{(b) (6)}, the patient was hospitalized for a syncopal episode which led to study drug discontinuation. The stop date of the syncopal episode was 12 April 2008; she took her last dose of study drug on 12 April 2008. The patient was discharged from the hospital on [REDACTED]^{(b) (6)} and she was recovered with sequelae (no details provided).

Concomitant medications reported at the onset of this SAE included aspirin, atenolol, Lasix (furosemide), and Synthroid (levothyroxine); the atenolol was stopped immediately after the syncopal episode.

The investigator considered the syncopal episode to be serious due to hospitalization. The event was considered severe in intensity and unlikely related to study drug; however, no alternate causality was reported.

7.3.3 Dropouts and/or Discontinuations

In the Phase 1 development program for vilazodone, 721 male and female subjects were exposed to doses of vilazodone ranging from 1 to 80 mg in single and repeat dose studies. Most subjects were healthy volunteers, although subjects with mild to moderate hepatic and renal impairment were also evaluated.

The treatment emergent adverse events leading to discontinuation were predominantly within the gastrointestinal and nervous systems. During Phase 1 development, the applicant reports that 88 subjects (12%) discontinued due to an AE, of whom 24 (3% overall) discontinued for vomiting.

In the 'All Placebo-controlled Database', 292 (19%) of patients in the vilazodone group and 41 (4%) in the placebo group experienced at least 1 adverse event leading to discontinuation. The most common AEs leading to discontinuation were GI events, specifically, nausea, diarrhea, and vomiting. Psychiatric events of insomnia and abnormal dreams occurred at the same rate as vomiting and resulted in discontinuation.

In the Phase 3 placebo-controlled trials, 31(7%) patients in the vilazodone group discontinued due to an adverse event compared with 14 (3%) in the placebo group. The most common adverse events leading to discontinuation in the phase 3 studies were gastrointestinal complaints (2.3% versus 0.2% in placebo), and the most concerning adverse events leading to discontinuation were cardiac disorders (1.1% versus 0% in placebo), predominantly palpitations: 4 patients on vilazodone and zero patients on placebo discontinued due to palpitations. One event of pneumonia was reported, however, review of the narrative indicates the patient had a pleural effusion and liver mass.

Table 7.3.5 AEs Leading to Discontinuation – Phase 3 Placebo-Controlled

System Organ Class Preferred Term	Vilazodone 40 mg/day N=436	Placebo N=433
Gastrointestinal disorders	10 (2.3)	1 (0.2)
Diarrhea	4 (0.9)	0
Nausea	2 (0.5)	1 (0.2)
Abdominal discomfort	1 (0.2)	0
Abdominal pain	1 (0.2)	0
Dyspepsia	1 (0.2)	0
Vomiting	1 (0.2)	0
General disorders	6 (1.4)	1 (0.2)
Fatigue	2 (0.5)	0
Asthenia	1 (0.2)	0
Chest pain	1 (0.2)	0
Feeling abnormal	1 (0.2)	0
Feeling jittery	1 (0.2)	0
Irritability	0	1 (0.2)
Cardiac disorders	5 (1.1)	0
Palpitations	4 (0.9)	0
Angina pectoris	1 (0.2)	0
Ventricular extrasystoles	1 (0.2)	0
Psychiatric disorders	4 (0.9)	6 (1.4)
Depression	2 (0.5)	1 (0.2)
Confusional state	1 (0.2)	0
Panic attack	1 (0.2)	0
Anxiety	0	1 (0.2)
Suicidal ideation	0	3 (0.7)
Tension	0	1 (0.2)
Nervous system disorders	2 (0.5)	4 (0.9)
Dizziness	1 (0.2)	0
Migraine	1 (0.2)	0
Headache	0	3 (0.7)
Tension headache	0	1 (0.2)
Blood and lymphatic system disorders	1 (0.2)	0
Lymphadenopathy	1 (0.2)	0
Infections and infestations	1 (0.2)	0
Pneumonia *(actually pleural effusion)	1 (0.2)	0
Neoplasm, benign, malignant and unspecified	1 (0.2)	0
Prostate cancer	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0
Dyspnea	1 (0.2)	0
Musculoskeletal and connective tissue disorders	0	1 (0.2)
Muscular weakness	0	1 (0.2)
Skin and subcutaneous disorders	0	1 (0.2)
Skin reaction	0	1 (0.2)

During the phase 3 uncontrolled study there were 124 patients (21%) who had a TEAE that led to discontinuation. The applicant provided a summary table of discontinuations

with incidence of >1%. The most frequent TEAEs leading to discontinuation were as expected, nausea 8 (1.3%) and diarrhea 7 (1.2%), followed by anxiety 6 (1%) and insomnia 5 (1%). Interestingly, after insomnia, palpitations was the next most frequent with 4 (1%). The narratives for these AEs were perused, it is difficult to interpret the association as these patients had multiple medical conditions and were taking numerous concomitant medications.

Four patients had a positive pregnancy test during the treatment period. All 4 had negative pregnancy tests at screening and baseline, during the treatment period had a positive test and was discontinued prematurely due to pregnancy. A fifth patient had a ruptured ectopic pregnancy. Follow up on these pregnancies can be found in Section 7.6.2 of this review.

7.3.5.1 Ocular Findings

Background

During the development of vilazodone, questions have been raised concerning four potential ocular problems: lens opacities, retinal lesions, corneal opacities, and ocular dryness. The Division of Anti-Infective and Ophthalmology has been consulted to review this data. At the time of this writing the consult has not been completed.

Systematic ophthalmologic evaluation of patients in the clinical studies began when dose-dependent occurrence of corneal opacities was demonstrated in dogs ^{(b) (4)}

At that time, Dr. Wiley Chambers concluded that ocular testing had detected abnormalities in tear production, cataract formation and retinal abnormalities. The results from the corneal studies were deemed inconclusive due to inconsistent data. Dr Chambers recommended that ocular testing continue.

Two ophthalmology consults have been completed for IND 54613. The first consultation, dated May 6, 2001 included the review of a 52-week toxicology study (which confirmed transient corneal opacities in dogs), and the review of slit lamp and funduscopy findings from studies EMD 68843-009 and -010.

The Reviewer's comments were as follows:

1. It is not clear how the data has been reported and this 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.
3. The retina abnormalities should be explained.
4. Reduction in tear production demonstrated a dose dependent effect.

The second ophthalmology consult is, dated December 19, 2005, regarding the End of Phase 2 Meeting states:

- The potential of vilazodone to cause cataract and retinal lesions needs to be evaluated in longer term studies.
- 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 following text is taken from minutes of the End of Phase 2 meeting on December 20, 2005:

Does the agency concur that detailed ophthalmologic examinations are not needed in this trial? Does the agency concur that detailed ophthalmologic examinations are no longer necessary in the development program for vilazodone?

Comment: *We agreed that detailed ophthalmologic examinations are not needed in this trial because it would be too short in any case to detect lenticular or retinal changes. However, we did inform them that for longer term exposures they will need to include baseline and every 6 months slit lamp exams and dilated funduscopy to assess for possible lenticular or retinal changes.*

Applicant response

The applicant engaged an independent 'expert' to review data from the visual assessments performed in the five 8-week Phase 2 clinical studies and TEAE data from the Phase 2 clinical program. The applicant's independent expert noted that data collection methods in the Phase 2 studies for cataracts and funduscopy were not optimal in that there was no requirement for the evaluations to be performed by the same examiner, which complicated the interpretation of the results. Nevertheless, the expert concluded that the data collected provided sufficient support that vilazodone did not cause cataracts or deleterious funduscopy findings over the 8-week treatment period in Phase 2.

The applicant indicates that in the uncontrolled long-term study, visual acuity scores remained stable at End of Treatment for 98% of the subjects and 'few subjects' had abnormal findings on slit-lamp biomicroscopy, corneal evaluations, or dilated funduscopy.

The applicant asserts that the results of detailed ophthalmologic exams did not demonstrate clinically significant eye changes and except for a mild drying effect on the eye, there are no indications of any clinically important ophthalmologic effects of vilazodone.

Reviewer assessment

The data presented in the five Phase 2 studies and the long-term, open-label study are difficult to interpret. Slit lamp and fundoscopic evaluations collected for each eye were

assessed as normal or abnormal within each region and sub-region. Treatment-emergent abnormalities were enumerated and summarized with frequencies and percentages at the end of study visit. An end of study assessment of abnormal for a region or sub-region was considered treatment emergent only if the baseline assessment was present and normal. The denominator for percentages is the number of subjects with a normal baseline assessment and a post-baseline assessment. If a region of a particular eye is marked normal but one or more of its sub-regions are marked abnormal, then the region of that eye will be considered abnormal. This reviewer found it very difficult to confirm the data reported by the applicant.

Because of the serious implications of ocular pathology, the division has requested ophthalmology consultation to assist with interpretation.

At the time of this writing, Dr. Chamber's consult was not available. However, during the status meeting of November 30, 2010 he informed the review team of his opinion. This reviewer interprets his comments as:

1. A definitive answer regarding the development of cataracts in association with vilazodone cannot be provided because a placebo controlled trial of one year's duration would be necessary to provide an answer. This is not a reason for a Post Marketing Requirement. The information regarding the possible association with cataract development should be provided in adverse reactions section of labeling.
2. The finding of retinal lesions is negative – retinal lesions did not occur more frequently in the vilazodone group than in the placebo group.
3. Vilazodone is associated with dry eye and should be labeled to indicate this finding.

Vilazodone Overdose

Overall, none of the overdoses related to vilazodone were lethal, the exposure to vilazodone was low and there were few episodes.

To confirm the applicant's report, JMP table line listings of all SAEs were referenced to identify reports of overdose, ingestion, toxicity, and suicide attempts. Narrative reports pertaining to overdoses of vilazodone are provided in the following text. Narrative reports regarding the overdose of other substances are provided in Section 7.3.2 Nonfatal SAEs.

Phase 1

There were no reports of overdose in the Phase 1 studies.

Phase 2 and Phase 3

According to the Integrated Summary of Safety, overdose of study medication occurred in 8 subjects and the child of one subject. Five of the eight ingested vilazodone study drug product and four subjects ingested a substance other than the study drug. One subject was not reported as an overdose, but the TEAE was reported as ‘serotonin syndrome’. In some cases, an irregularity in drug accountability was reported as an overdose.

Subject CLDA-07-DP-**04-4040-0001** (long-term, open-label study) – A 24-year-old African American female presented in a mute and combative state with symptoms of agitation and visual hallucinations. Vitals were reported as: blood pressure 152/79 mmHg, HR 155 bpm, and temperature 98.4°. The history indicates that she had “missed a couple of days and took 5 or 6 pills to catch up” the night prior to the event. She was given the following medications: haldol, lorazepam, midazolam, charcoal, famotidine, magnesium sulfate, and potassium. She was medically stabilized and discharged home in less than 48 hours. She was subsequently discharged from the study.

Subject **0010-1094** (EMD68843-009) – A 25-year-old Caucasian female inadvertently took a double-dose of study medication after approximately one month on study drug. The same day as the ingestion she reported two episodes of disorientation and restlessness. No action was taken and the subject recovered without event.

Subject **0035-1161** (SB 659746-002) – A 51-year-old Caucasian male, “experienced a mild overdose” while taking vilazodone 10 mg/day. The narrative does not indicate the amount of drug taken. No action was taken and he “recovered the same day.”

Subject **0018-0588** (SB 659746-002) – A 49-year-old Caucasian female “experienced a mild overdose (verbatim term=potential study drug overdose) after 32 days of taking vilazodone 5 mg/day.” The narrative does not indicate the amount of drug taken. The event was repeated a few days later. For both events, no action was taken and the subject fully recovered.

Subject CLDA-07-DP-**04-4180-004** (long-term, open-label study) – A 21-year-old Caucasian female, discovered that her 21-month-old son had obtained her study medication bottle (vilazodone 40 mg). She found him chewing on a “couple of pills” and she was able to remove 1 tablet from his mouth. She estimated that he had ingested 5 to 7 pills. The child was taken to the emergency room, given activated charcoal and subsequently had several episodes of emesis. The record indicates that after about 45 minutes he was noted to be very sleepy and lethargic. No seizure activity was noted. The subject was a Caucasian male, 35 inches tall and 26.4 pounds at the time of the event. Hematology and chemistry (including LFTs) lab values were within normal limits. He was admitted to a local children’s hospital with temperature 98.6, HR 132 bpm, RR 36 breaths per minute and blood pressure 130/69 mmHg. Within a few hours of arrival he was noted to be back to his usual baseline and taking appropriate hydration. At

admission and the following day, ECG revealed normal sinus rhythm. He was discharged home on the day following the incident.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase 1

Phase 1 consisted of 24 studies with short-term exposure in healthy subjects and subjects with hepatic or renal impairment. There were 721 subjects who received vilazodone at any dose during the Phase 1 studies. The applicant did not pool data from the Phase 1 studies in any safety database. The JMP tables for the Phase 1 studies were reviewed to assess the incidence of adverse events. As expected, the most frequent AEs were nausea, headache, diarrhea, dizziness, and vomiting.

Table 7.4.1 AEs Reported in ≥5% of Vilazodone Subjects – Phase 1

Adverse Event	N	% n=459
Nausea	240	52
Headache	199	43
Diarrhea	157	34
Dizziness	128	28
Vomiting	112	24
Fatigue	65	14
Abdominal pain or discomfort	34	7
Somnolence	29	6
Hyperhidrosis	26	6
Feeling hot	22	5

Phase 2/3 Studies

The safety population for the phase 2 and 3 placebo controlled studies consisted of 433 patients in the placebo groups and 436 patients in the vilazodone groups. A number of commonly reported adverse events appeared to be related to vilazodone treatment. The following AEs occurred in at least 5% of vilazodone subjects and were reported at least twice as commonly in the placebo group: diarrhea 28%, nausea 23%, vomiting 5%, sexual dysfunction 9%, and abnormal dreams 5%. Insomnia was reported more than two times as frequently in the vilazodone treated patients.

The most significant finding when reviewing the two pivotal studies is the high rate of gastrointestinal adverse events. The design for the two pivotal studies allowed for a dose titration phase and specified the drug to be taken with food. However, titration did not completely eliminate the adverse GI effects associated with vilazodone. More than

half of the patients exposed to vilazodone experienced a gastrointestinal adverse event. Sexual dysfunction was captured in the spontaneous adverse event reporting at approximately 10% and is addressed later in the safety review.

Table 7.4.2 AEs Reported in ≥2% of Vilazodone Treated Subjects Phase 3 Placebo-Controlled Database

	Vilazodone n=436 n (%)	Placebo n=433 n (%)
Gastrointestinal disorders	234 (54)	102 (24)
Diarrhea	122 (28)	40 (9)
Nausea	102 (23)	22 (5)
Vomiting	20 (5)	5 (1)
Gastroenteritis ¹	16 (4)	4 (1)
Nervous system disorders	218 (50)	101 (23)
Headache	66 (15)	62 (14)
Dizziness	37 (8)	20 (5)
Somnolence or sedation	21 (5)	12 (3)
Restlessness or akathisia ³	15 (3)	1 (0)
Tremor	7 (2)	0
Infections and infestations ²	74 (17)	77 (18)
Upper respiratory infection	15 (3)	32 (7)
Common cold	10 (2)	12 (3)
Psychiatric disorders	87 (20)	36 (8)
Insomnia	31 (7)	12 (3)
Anxiety (anxiety or panic)	7 (2)	6 (1)
Abnormal dreams	22 (5)	7 (2)
Sexual (abnormal orgasm or libido)	28 (6)	2 (0)
Musculoskeletal and connective tissue disorders	37 (8)	36 (8)
Pain	24 (6)	30 (7)
General disorders and administration site conditions	40 (9)	34 (8)
Fatigue	16 (4)	13 (3)
Skin and subcutaneous tissue disorders	18 (4)	13 (3)
Rash	5 (1)	5 (1)
Diaphoresis/sweating	10 (2)	3 (1)
Respiratory, thoracic and mediastinal disorders	15 (3)	10 (2)
Nasal congestion/inflammation	6 (1)	2 (0)
Sore throat	4 (1)	4 (1)
Injury, poisoning and procedural complications	18 (4)	18 (4)
Investigations ⁴	15 (3)	13 (3)
Abnormal lab results	5 (1)	2 (0)
Abnormal ECG or blood pressure	2 (0)	5 (1)
Weight gain	4 (1)	4 (1)
Metabolism and nutrition disorders	17 (4)	10 (2)
Increased appetite	10 (2)	4 (1)
Reproductive system and breast disorders	18 (4)	10 (2)
Erectile dysfunction	12 (3)	2 (0)
Cardiac disorders	12 (3)	1 (0)
Palpitations	8 (2)	1 (0)

¹ There were sixteen cases of “gastroenteritis” coded as infections and infestation, it is the opinion of this reviewer they should be coded as GI AEs.

² The 16 cases of gastroenteritis in vilazodone groups and 4 cases in placebo groups were subtracted from infections and infestations (90-16=74 and 81-4=77).

³ 'Restlessness' was coded as psychiatric, nervous system disorders, and 'restless legs', in this table all are combined with akathisia and coded as restlessness.

⁴ Reports are reviewed and discussed in specific areas of the Safety Review.

The following table illustrates the applicant's analysis of TEAEs by SOC and PT for the all placebo-controlled database. The same patterns of adverse events seem to persist across all dose levels. The gastrointestinal AEs appear to be more consistent across the dose range whereas the nervous system and psychiatric AEs show a significant dose-related increase. The rate of diarrhea and vomiting remained stable across the dose ranges; a small dose related increase was seen with nausea and dry mouth. The incidence of insomnia tripled from 6% to 18% from the 40 mg dose to >40 mg. There was also a substantial increase in the incidence of anxiety when the dose increased to >40 mg. Abnormal dreams and nightmares are also dose-related.

Table 7.4.3 Incidence of TEAEs Reported by ≥5% of Subjects by Daily Vilazodone Dose: All Placebo-Controlled Database

System Organ Class ^{a,b} Preferred Term ^{a,b}	Placebo N=997 n (%)	Vilazodone <40 mg/day N=903 n (%)	Vilazodone 40 mg/day N=441 n (%)	Vilazodone >40 mg/day N=227 n (%)	Vilazodone All Doses N=1578 n (%)
All Subjects^a					
Number of subjects with at least 1 TEAE	732 (73.4)	734 (81.3)	368 (83.4)	210 (92.5)	1318 (83.5)
Total Number of TEAEs	2218	2761	1199	1109	5087
Gastrointestinal Disorders	310 (31.1)	445 (49.3)	247 (56.0)	135 (59.5)	830 (52.6)
Diarrhoea	98 (9.8)	195 (21.6)	130 (29.5)	61 (26.9)	387 (24.5)
Nausea	84 (8.4)	146 (16.2)	112 (25.4)	67 (29.5)	328 (20.8)
Dry mouth	62 (6.2)	80 (8.9)	38 (8.6)	28 (12.3)	146 (9.3)
Dyspepsia	36 (3.6)	52 (5.8)	14 (3.2)	10 (4.4)	76 (4.8)
Vomiting	21 (2.1)	27 (3.0)	27 (6.1)	15 (6.6)	71 (4.5)
Nervous System Disorders	298 (29.9)	294 (32.6)	153 (34.7)	128 (56.4)	577 (36.6)
Headache	182 (18.3)	170 (18.8)	66 (15.0)	49 (21.6)	285 (18.1)
Dizziness	45 (4.5)	54 (6.0)	37 (8.4)	43 (18.9)	135 (8.6)
Somnolence	30 (3.0)	33 (3.7)	14 (3.2)	23 (10.1)	71 (4.5)
Tremor	5 (0.5)	10 (1.1)	7 (1.6)	13 (5.7)	30 (1.9)
Psychiatric Disorders	141 (14.1)	186 (20.6)	96 (21.8)	114 (50.2)	400 (25.3)
Insomnia	43 (4.3)	68 (7.5)	27 (6.1)	40 (17.6)	137 (8.7)
Abnormal dreams	22 (2.2)	26 (2.9)	20 (4.5)	25 (11.0)	71 (4.5)
Anxiety	25 (2.5)	32 (3.5)	5 (1.1)	18 (7.9)	55 (3.5)
Nightmare	8 (0.8)	11 (1.2)	5 (1.1)	14 (6.2)	30 (1.9)
Infections and Infestations	190 (19.1)	176 (19.5)	85 (19.3)	50 (22.0)	311 (19.7)
Nasopharyngitis	57 (5.7)	47 (5.2)	21 (4.8)	11 (4.8)	79 (5.0)
Upper respiratory tract infection	56 (5.6)	34 (3.8)	20 (4.5)	12 (5.3)	66 (4.2)
General Disorders and Administration Site Conditions	95 (9.5)	114 (12.6)	43 (9.8)	42 (18.5)	199 (12.6)
Fatigue	34 (3.4)	39 (4.3)	15 (3.4)	15 (6.6)	69 (4.4)

Table 7.4.3 – continued

System Organ Class ^{a,b} Preferred Term ^{a,b}	Placebo N=997 n (%)	Vilazodone <40 mg/day N=903 n (%)	Vilazodone 40 mg/day N=441 n (%)	Vilazodone >40 mg/day N=227 n (%)	Vilazodone All Doses N=1578 n (%)
Musculoskeletal and Connective Tissue Disorders	125 (12.5)	83 (9.2)	42 (9.5)	32 (14.1)	158 (10.0)
Eye Disorders	76 (7.6)	97 (10.7)	12 (2.7)	29 (12.8)	139 (8.8)
Skin and Subcutaneous Tissue Disorders	59 (5.9)	72 (8.0)	20 (4.5)	47 (20.7)	140 (8.9)
Hyperhidrosis	10 (1.0)	21 (2.3)	5 (1.1)	14 (6.2)	41 (2.6)
Pruritus	5 (0.5)	6 (0.7)	4 (0.9)	12 (5.3)	22 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	63 (6.3)	63 (7.0)	14 (3.2)	18 (7.9)	95 (6.0)
Metabolism and Nutrition Disorders	26 (2.6)	51 (5.6)	19 (4.3)	9 (4.0)	79 (5.0)
Investigations	81 (8.1)	100 (11.1)	22 (5.0)	31 (13.7)	154 (9.8)
Reproductive System and Breast Disorders	34 (3.4)	31 (3.4)	19 (4.3)	16 (7.0)	66 (4.2)
Injury, Poisoning and Procedural Complications	37 (3.7)	36 (4.0)	15 (3.4)	13 (5.7)	65 (4.1)
Renal and Urinary Disorders	16 (1.6)	26 (2.9)	9 (2.0)	13 (5.7)	48 (3.0)

a MedDRA version 11.1. Subjects were counted once at each level of summarization (overall, system organ class, and preferred term).

b All SOC and preferred terms with incidence $\geq 5.0\%$ in any treatment group are displayed.

KEY: SOC=system, organ class; TEAE=treatment-emergent adverse event.

Source: [Appendix 2, Table 5.1.1.](#)

7.4.2 Laboratory Findings

Mean Change from Baseline

a. Clinical Chemistry

Phase 1

No values of clinical concern were reported by the applicant for the Phase 1 studies.

Phase 2 and 3

1. Mean Change from Baseline

The applicant provided several tables to illustrate the findings from the phase 2 and 3 studies which were reviewed along with the JMP line listings. Overall, based on review of the data as submitted, it does not appear that there is a clinically significant difference between vilazodone and placebo in the mean change from baseline chemistry parameters.

Table 7.4.5 Chemistry: Mean Change from Baseline to LOCF Endpoint – All Placebo Controlled (Phase 2 and 3 Studies)*

	All doses vilazodone	<40 mg/day	40 mg/day	>40 mg/day	Placebo
ALT (alanine amino transferase) (U/L) N Change (SD)	1412 0.34 (10.7)	787 0.01 (10.5)	401 1.36 (11.4)	220 -0.32 (9.7)	897 0.12 (9.7)
AST (aspartate amino transferase) (U/L) N Change (SD)	1412 0.49 (7.4)	787 0.15 (7.6)	401 1.51 (7.9)	220 -0.15 (5.7)	897 0.17 (6.9)
ALP (alkaline phosphatase) (U/L) N Change (SD)	1412 0.50 (10.8)	787 0.21 (10.5)	401 0.63 (12.0)	220 1.33 (8.9)	898 -0.41 (9.1)
ALB (albumin) (U/L) N Change (SD)	1048 -0.56 (2.4)	681 -0.58 (2.2)	367 -0.52 (2.7)	N/A	713 -0.61
GGT (gamma glutamyl transferase) (U/L) N Change (SD)	750 -0.26 (13.7)	126 0.36 (10.5)	401 -0.62 (14.8)	219 0.08 (13.2)	569 -0.57 (13.6)
Bicarbonate mmol/l N Change (SD)	388 -0.23 (2.9)	20 -1.34 (2.9)	368 -0.17 (2.9)	N/A	384 -0.35 (3.1)
Bilirubin µmol/l N Change (SD)	1410 -0.23 (3.8)	787 -0.18 (4.0)	400 -0.40 (3.3)	219 -0.09 (3.9)	896 -0.09 (3.5)
BUN (blood urea nitrogen) mmol/l	1412	787	401	220	898

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N Change (SD)	0.09 (1.4)	0.07 (1.2)	0.13 (1.1)	0.06 (1.2)	0.8 (1.2)
Calcium mmol/l N Change (SD)	1412 -0.02 (0.1)	787 -0.02 (0.1)	401 -0.021 (0.1)	220 -0.02 (0.1)	898 -0.02 (0.1)
CK (creatine phosphokinase) (IU/L) N Change (SD)	364 12.9 (81)	106 5.38 (61.9)	34 40.6 (76.6)	220 12.8 (89)	185 -3.84 (100)
Chloride mmol/L N Change (SD)	1049 0.35 (2.7)	681 0.30 (2.6)	368 0.45 (2.9)	N/A	713 0.25 (2.5)
Creatinine µmol/l N Change (SD)	1412 3.1 (11.9)	787 2.0 (11.7)	401 4.08 (11.9)	220 5.42 (12.3)	898 1.03 (11.6)
Glucose mmol/l N Change (SD)	744 0.15 (1.4)	126 0.40 (1.2)	394 0.04 (1.4)	220 0.2 (1.3)	558 0.18 (1.2)
K+(potassium) mmol/l N Change (SD)	1404 -0.04 (0.5)	786 0.06 (0.4)	395 -0.13 (0.7)	219 0.01 (0.4)	887 -0.6 (0.4)
Phosphate mmol/l N Change (SD)	1041 0.00 (0.09)	681 0.01 (0.1)	360 -0.01 (0.1)	N/A	702 -0.01 (0.1)
PRL (prolactin) ng/ml N Change (SD)	362 1.3 (5.5)	105 0.66 (4.7)	34 1.62 (5.8)	219 1.45 (5.8)	185 0.9 (7.2)
Na+ (sodium) mmol/l N Change (SD)	1413 0.16 (2.6)	787 0.02 (2.5)	402 0.48 (2.9)	220 0.08 (2.5)	898 0.01 (2.5)

*Source: Appendix 2 Table 16.1 Integrated Summary of Safety

Review of the individual patient results revealed a number of elevated serum cholesterol and triglyceride results. In the all Placebo-controlled Database of vilazodone all doses, of 361 patients exposed, 5 (1.4%) had PCS results compared with 185 exposed in the placebo group where 0 had PCS results. Serum cholesterol and triglycerides were monitored in 2 phase 2 studies (EMD 68843-009 and -010). These were not listed in the table as there was no indication that the patients were fasting at the time of specimen collection, most of the patients with elevated results had abnormal values at screening, and there was no discernable pattern as the values tended to fluctuate throughout the study period. A review of the JMP line listing for abnormal cholesterol results indicated nearly equal percentages for the vilazodone and the placebo groups. Based on the data available from the two studies, there is no compelling reason to require further testing.

2. Outliers

The JMP line listings and CSR laboratory results were assessed for Hy's Law; no cases were reported or discovered to meet Hy's Law criteria. There were some cases of elevated liver enzymes, but many were high at Screening and there did not appear to be a pattern related to vilazodone use.

Table 7.4.6 Chemistry: Incidence of Potentially Clinically Significant Abnormalities – All Placebo Controlled Database, Safety Population

Parameter and Potentially Clinically Significant Criteria	Treatment Groups				
	Vilazodone				PBO
	All doses	<40 mg/d	40 mg/d	>40 mg/d	Placebo
	N PCS (%)	N PCS (%)	N PCS (%)	N PCS (%)	N PCS (%)
ALT (alanine amino transferase) (>3xULN)	1417 1 (0.1)	792 1 (0.1)	401 0 (0)	220 0 (0)	899 0 (0)
AST (aspartate amino transferase) (>3xULN)	1417 1 (0.1)	792 0 (0.1)	401 1 (0.2)	220 0 (0)	899 0 (0)
ALP (alkaline phosphatase) (2xULN)	1417 0 (0)	792 0 (0)	401 1 (0)	220 0 (0)	899 0 (0)
GGT (gamma glutamyl transferase) (3xULN)	746 4 (0.5)	126 1 (0.8)	398 2 (0.5)	218 1 (0.5)	569 1 (0.2)
Bilirubin (1.5xULN)	1411 8 (0.6)	790 3 (0.4)	398 1 (0.3)	219 4 (1.8)	897 4 (0.4)
BUN (blood urea nitrogen) (>30 mg/dl)	1412 0 (0)	792 0 (0)	396 0 (0)	220 0 (0)	899 2 (0.2)
Creatinine (>2.0 mg/dl)	1417 1 (0.1)	792 0 (0)	401 1 (0.2)	220 0 (0)	900 1 (0.1)
Cholesterol (>1.6xULN)	361 5 (1.4)	105 1 (1.0)	33 0 (0)	219 4 (1.8)	185 0 (0)
Calcium (<0.9xLLN) (<1.1xULN)	1417 1 (0.1) 1417 2 (0.1)	792 0 (0) 792 1 (0.1)	401 1 (0.2) 401 1 (0.2)	220 0 (0) 220 0 (0)	899 1 (0.1) 900 0 (0)
Phosphate (<0.8xLLN) (>1.2xULN)	1045 0 (0) 1046 5 (0.5)	684 0 (0) 685 3 (0.4)	361 0 (0) 361 2 (0.6)	0 0	703 2 (0.3) 703 2 (0.3)

Free T ₄ (<4.5µg/dl)	410 1 (0.2)	45 0 (0)	365 1 (0.3)	0	399 0 (0)
(>12.5µg/dl)	410 1 (0.2)	45 0 (0)	365 1 (0.3)	0	399 0 (0)
TSH (thyroid stimulating hormone)					
(<0.35mIU/L)	411 2 (0.5)	45 0 (0)	365 2 (0.5)	1 0 (0)	400 2 (0.5)
(>5.50mIU/L)	412 1 (0.2)	46 0 (0)	365 1 (0.3)	1 0 (0)	398 1 (0.3)
Sodium					
(<128 mmol/L)	1418 0 (0)	792 0 (0)	402 0 (0)	220 0 (0)	900 0 (0)
(>155 mmol/L)	1418 0 (0)	792 0 (0)	402 0 (0)	220 0 (0)	900 0 (0)
Potassium					
(<3.2 mmol/L)	1410 0 (0)	791 0 (0)	396 0 (0)	219 0 (0)	889 0 (0)
(>5.8 mmol/L)	1406 5 (0.4)	790 1 (0.1)	393 4 (1.0)	219 0 (0)	887 0 (0)

Source: ISS Appendix 2 Table 13.1

Uncontrolled, Long-term Safety Database

The ISS indicates PCS values <1% for glucose, BUN, creatinine, Free T3, Free T4, phosphate, potassium, and TSH low. For urate and TSH high, the percentages were 1.5 and 1.7 respectively. If these values were not reported as TEAEs or no pre-existing contributors were listed in the medical history, a narrative was provided. As such, narratives for glucose, potassium, and thyroid function tests were reviewed. This was an uncontrolled study, patients were on numerous concomitant medications, and many had co-morbid conditions; therefore it is not prudent to draw conclusions.

Thyroid Function Tests

JMP line listings from the Placebo-controlled, Phase 3 database were reviewed. Overall conclusions regarding thyroid function indicated that changes in laboratory test results suggesting possible treatment-emergent hypothyroidism or hyperthyroidism occurred no more frequently in subjects who received vilazodone than subjects who received placebo.

b. Hematology

Phase 1

The applicant reported no values of clinical concern for the Phase 1 studies.

Phase 2 and 3 Placebo-controlled Database

1. Mean Change from Baseline

In the all placebo controlled database variations in means were minimal and within expected limits of normal variation for all hematology parameters. There were no clinically significant mean changes from baseline when the vilazodone groups were compared with the placebo groups. The following table represents the mean change

from baseline LOCF for the two pivotal trials compared with placebo. Similar results were observed for the 5 Phase 2 studies.

Table 7.4.7 Hematology: Mean Change from Baseline Placebo-controlled Phase 3

Parameter	N	BL baseline	change from baseline	N	BL baseline	change from baseline
WBC (white blood cell) x 10 ⁹ /L	435	7.1	-0.08	426	7.3	-0.08
RBC (red blood cell) x 10 ¹² /L	436	4.6	-0.02	430	4.68	-0.05
HGB (hemoglobin) g/dL	433	13.9	-0.63	430	14.1	-1.12
HCT (hematocrit) %	432	41.7	-0.16	430	42.0	-0.32
PLT (platelet) x 10 ⁹ /L	431	272	-0.44	426	278	-1.18

Source: Appendix 2 Table 17.2 (ISS)

2. Outliers

The applicant provided tables of the 'PCS' hematology results. The JMP line listings of the two pivotal studies were reviewed; low and high abnormal results were selected and checked against baseline results and/or history. There were no obvious treatment-associated changes in hematology parameters nor were there any significant outliers. This reviewer does not perceive a difference in the vilazodone group compared with the placebo group on hematology parameters, specifically hemoglobin, hematocrit, WBC, or PLT.

Phase 3 Uncontrolled, Long-term Safety Database

The variations in means were minimal and within the expected limits of normal variation. There were no clinically significant mean changes from baseline in the uncontrolled safety database.

c. Urinalysis

Phase 1

The applicant's report indicates no changes of clinical concern for the Phase 1 studies.

Phase 2 and 3 Placebo Controlled

For the 'all doses' of vilazodone exposure (5 phase 2 and 2 phase 3 trials) the percentage of patients with glycosuria was 3% for both placebo and vilazodone. Proteinuria was present in approximately 5% of those in the vilazodone group as compared with about 3% in the placebo group. The PCS urinary abnormalities are

similar between the two groups. The serum creatinine and BUN results of the vilazodone exposed urinalysis PCS cases were reviewed; no associated elevation in serum creatinine or BUN was found. There does not appear to be a clinically significant difference between the vilazodone and placebo groups for proteinuria or glycosuria.

Table 7.4.8 Urinalysis: Phase 2 and 3 Glucose and Protein Outliers

	Vilazodone 40 mg/day N 357 (%)	Vilazodone All dose N 528 (%)	Placebo N 469 (%)
	Glucose		
Negative	343 (96)	509 (97)	456 (97)
Trace	8 (2.2)	8 (1.5)	5 (1)
1+	0	1 (0.2)	1 (0.2)
2+	0	2 (0.4)	1 (0.2)
3+	6 (1.7)	7 (1.3)	6 (1.3)
	Protein		
Negative/Trace	341 (96)	502 (95)	455 (97)
1+	12 (3.4)	21 (4)	14 (3)
2+	3 (0.8)	4 (0.8)	0
3+	1 (0.3)	1 (0.2)	0

Source: Appendix 2 Table 19.1 ISS

Phase 3 Uncontrolled, Long-term

Urinalysis results in the Long-term, uncontrolled study were similar to the results for the placebo-controlled study with 15/526 (2.9%) of patients with glycosuria and 12/526 (2.3%) of patients with proteinuria. Of these, 9 glucose (1.7%) and 5 protein (1%) were considered PCS.

7.4.3 Vital Signs

Phase 1

The Phase One studies safety assessments were not pooled to be reported in any of the four safety databases.

Phase 2 and 3 Placebo-controlled

A. Vital Sign Assessments

In the 5 phase 2 and 2 phase 3 placebo-controlled studies, vital sign measurements included blood pressure (sitting) and heart rate at screening, baseline, and each follow-up visit. Respiratory rate was included in the phase 3 studies but not in the phase 2

studies. Oral temperature was included in the phase 2 studies but not in the phase 3 studies.

B. Potentially Clinically Significant Vital Sign Changes

1. Mean Change from Baseline

The applicant provided summary tables for means and mean changes from baseline for systolic blood pressure, diastolic blood pressure, heart rate (pulse), body temperature, and body weight for the all placebo controlled database. The appendices also listed individual subject data. The following table illustrates minimal changes which are considered to be clinically insignificant for the mean change from baseline.

Table 7.4.9 Vital Signs: Means and Mean Change from Baseline, All PC Database

	Vilazodone All doses N=1577		Vilazodone <40 mg/d N=903		Vilazodone 40 mg/d N=440		Vilazodone >40 mg/d N=227		Placebo N=997	
	BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ
SBP mmHg	120	-0.3	121	-0.7	120	-0.1	119	0.7	120	-0.2
DBP mmHg	77	0.3	77	0.2	76	0.4	76	0.5	76	-0.3
Pulse bpm	74	0.7	75	0.5	73	0.7	75	1.6	73	1.0

Source: Appendix 2 Table 23.1 (ISS)

2. Outliers

The applicant provided summary tables of the incidence of treatment-emergent PCS vital signs for SPB, DBP, HR, and body weight in the all placebo-controlled database, where treatment with vilazodone or placebo was up to 8 weeks' duration.

The applicant's PCS criteria were as follows:

- SBP: PCS high= ≥ 180 mmHg or increase ≥ 20 mmHg; PCS low= ≤ 80 mmHg or decrease ≤ 20 mmHg.
- DBP: PCS high= ≥ 110 mmHg or increase ≥ 10 mmHg; PCS low= ≤ 50 mmHg or decrease ≤ 15 mmHg.
- HR (pulse): PCS high= ≥ 120 bpm or increase ≥ 15 bpm; PCS low= ≤ 50 bpm or decrease ≤ 15 bpm.
- Weight: PCS high= $\geq 10\%$ increase; PCS low= $\leq 10\%$ decrease.

The number of PCS values for systolic and diastolic blood pressure and heart rate was low, less than 1% for all doses of vilazodone and placebo. Over all doses, vilazodone did not appear to be significantly different from placebo on blood pressure or heart rate.

Table 7.4.10 Vital Signs: Incidence of Treatment Emergent PCS All Placebo-controlled Database

H=high L=low		Vilazodone All doses		Vilazodone <40 mg/d		Vilazodone 40 mg/d		Vilazodone >40 mg/d		Placebo	
		n	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)
SBP mmHg	H	1570	0	899	0	439	0	226	0	993	0
	L	1570	8(0.5)	898	5(0.6)	439	3(0.7)	227	0	992	2(0.2)
DBP mmHg	H	1568	2(0.1)	898	1(0.1)	438	0	226	1(0.4)	991	1(0.1)
	L	1569	3(0.2)	898	3(0.3)	438	0	227	0	991	4(0.4)
HR bpm	H	1567	4(0.3)	895	4(0.4)	439	0	227	0	990	4(0.4)
	L	1572	3(0.2)	899	1(0.1)	440	2(0.5)	227	0	993	3(0.3)
Weight kg	H	1484	6(0.4)	811	4(0.5)	440	1(0.2)	227	1(0.4)	954	4(0.4)
	L	1484	3(0.2)	811	1(0.1)	440	1(0.2)	227	1(0.4)	954	4(0.4)

Source: Appendix 2, Table 22.1 (ISS)

The applicant's definition of PCS seemed overly stringent and therefore the vital sign JMP tables for pivotal study GNSC-04-DP-02 were reviewed using: SPB >140, DBP>80, and HR >100. The tables contained data for 205 subjects in the vilazodone group and 205 subjects in the placebo group. SBP values of >140 mmHg were noted in 15% (30/205) of the vilazodone group compared with 7% (15/205) of the placebo group. However, 100% of the subjects in the vilazodone group had SBP>140 at screening or baseline, prior to exposure. For DBP, 53% (108/205) subjects in the vilazodone group had DBP >80 compared with 48% (99/205) in the placebo group. All of the subjects in the vilazodone group had DBP >80 prior to exposure. Pulse (HR) >100 was noted in 4% (8/205) of the vilazodone subjects compared with 4% (9/205) of the placebo group.

Phase 3 Long-term, Uncontrolled Safety Database

In the long-term, uncontrolled safety database vital sign measurements included systolic and diastolic blood pressure, heart rate and respiratory rate. Measurements were taken at screening, baseline, and each scheduled visit. A review of the JMP line listings and the applicant's reports indicates no clinically relevant changes in vitals signs in this cohort of patients with multiple co-morbidities and concomitant medications.

The data submitted for weight change indicated 11/597 (1.8%) for PCS low values and 39/597 (6.5%) for high weight change. This was based on PCS of $\geq 10\%$ decrease for PCS low and $\geq 10\%$ increase for PCS high. The reported incidence of weight increased was 10% (57 subjects) and for weight decreased was 2% (10 subjects). Eight subjects shifted from normal to overweight and from overweight to obese during the course of the study. Although the numbers could be significant, it is not prudent to draw conclusions from this uncontrolled study.

C. Dropouts Due to Vital Sign Abnormalities

Overall, a clinically insignificant number of patients discontinued due to vital sign abnormalities.

One patient (EMD 68843-010) in a Phase 2 study discontinued due to a hypertension.

Patient ID **035-1470** was a 68-year-old Caucasian female with no documented history of hypertension (although blood pressure at screening was 133/90 and at visit 2 was 138/90) who was randomized to the high dose vilazodone treatment arm; she received the first dose of study medication on November 17, 1998. On [REDACTED]^{(b) (6)} the patient was hospitalized for treatment of hypertension. The report indicates that on December 9, 1998 she complained of a migraine headache with musical hallucinations and poorly formed visual hallucinations. On [REDACTED]^{(b) (6)} her BP was 160/100, repeat BP was 182/100 and she reported palpitations and a 'heavy feeling' in her chest. She was given two doses of clonidine with good results and she was discharged from the hospital on [REDACTED]^{(b) (6)}. Medication history included (but not limited to): amitriptyline, Prozac, Celexa, and Synthroid. This SAE is considered likely to be related to the study medication. Review of the CRF indicates a BP of 135/90 at Screening and no history of cardiovascular disease.

Three patients (0.5%) in the Phase 3 Uncontrolled, Long-term study CLDA-07-DP-04 discontinued due hypertension (2 – 'blood pressure increased' and 1- hypertension).

7.4.4 Electrocardiograms (ECGs)

A. ECG Assessments

It is the opinion of this reviewer that although the data provided are acceptable, the applicant's case would be more persuasive if quantitative interval measurements for the Phase 2 safety database would have been provided. In the current submission from the Placebo-controlled Phase 3 Database, 384 ECGs were reported with baseline and on-treatment results read by a cardiologist. From the Uncontrolled, Long-term Phase 3

Database, 541 ECGs were reported with baseline and on-treatment results read by a cardiologist.

Based on review of the information provided by the applicant and the opinion rendered by the QT-IRT, this reviewer concurs with the applicant's assessment that at doses below 80 mg, vilazodone does not appear to have clinically significant effects on ECG parameters or a signal of proarrhythmic potential.

Phase 1

PGxHealth conducted a Phase 1, single-site, double-blind, randomized, placebo and active controlled, 3-arm; parallel study (PGX-08-P1-06) to assess the effects of vilazodone on QT interval. The review of PGX-08-P1-06 is covered in section 7.4.5 of this document. The QT-IRT consultative review indicated "No significant QTc prolongation effect of vilazodone was detected in this TQT study."

Phase 2 and 3

The ECGs were assessed differently across the studies. Quantitative interval measurements were available for the Phase 3 studies only. Across the placebo-controlled Phase 3 database, the all placebo-controlled database, and the uncontrolled long-term safety database, the data were summarized using categories of normal and 3 categories of abnormal. The 3 categories of abnormal included: NCS (not clinically significant), CS (clinically significant), and UNK (unknown).

For studies EMD 68843-009 and EMD 68843-010, the ECG result at screening and Week 8/ET was collected as a normal/abnormal, yes/no response. If the answer was yes, the ECG was classified as normal. If the answer was no, then the ECG is classified as abnormal UNK.

For studies SB-659746-A002, SB-659746-003, and SB-659746-014, the ECG at Screening was collected as a yes/no response to the question "Were there any clinically significant abnormalities detected?" If the answer was no, the ECG is classified as normal; if the answer was yes, the ECG is classified as abnormal, CS. At Week 8/ET, the question is "Were there any clinically significant worsening since the last examination?" If the question was answered yes, the ECG result is classified as abnormal, CS. If the answer was no, then the screening ECG result is used as the Week 8/ET result.

For the Phase 3, pivotal studies, GNSC-04-DP-02 and CLDA-07-DP-02, the ECG assessment at both screening and at Week 8/ET was collected as 'normal', 'abnormal not clinically significant', or 'abnormal, clinically significant'. The assessment was similar in the 52-week, long-term study with additional ECGs collected at Weeks 24, 36, and 52/ET.

Only subjects with both screening/baseline and end of study ECG results are included in the analysis. The incidence of treatment emergent PCS values for ECG parameters were summarized based on the pre-determined criteria.

B. Potentially Clinically Significant ECG Changes

The QTc intervals corrected using Fredericia's formula (QTcF) were used for PCS determination. The ECG PCS criteria were:

- QRS interval: PCS high= ≥ 150 ms
- PR interval: PCS high= ≥ 250 ms
- QTc interval: PCS high= ≥ 500 ms
- HR: PCS high= ≥ 120 bpm or increase ≥ 15 bpm
- HR: PCS low= ≤ 50 bpm or decrease ≤ 15 bpm

1. Mean Change from Baseline

Phase 1 Studies

The thorough QT study is discussed in Section 7.4.5 of this review.

Phase 2 and 3 Studies

As described previously, the method of ECG collection for the all placebo-controlled database did not include pooling information from all of the phase 2 and phase 3 (total of 7) studies. Therefore, this review will focus on the phase 3 placebo-controlled database.

The applicant summarized interval measurements change from baseline to final visit for the placebo-controlled Phase 3 database and the uncontrolled, long-term safety database. In the placebo-controlled Phase 3 database, statistical comparisons between the 40 mg/day vilazodone and placebo treatment groups were made on the changes from baseline. ANCOVA terms for treatment, baseline value, and study were applied, and p-values from testing the treatment effect contrasts were reported for descriptive purposes. When presented in this manner, there is no statistically significant difference between the treatment groups except for the between group difference in QRS interval.

**Table 7.4.11 ECG Parameters: Change from Baseline to Week 8
Placebo-controlled Phase 3 Database**

Parameter	Vilazodone 40 mg/day n=436	Placebo n=433	p-value ¹
Heart rate (bpm)			
n	386	388	
LS mean	1.894	2.97	0.0879
SE	0.450	0.449	
PR Interval (ms)			
n	384	385	
LS Mean	-0.87	-0.20	0.4282
SE	0.605	0.604	
QRS Interval (ms)			
n	384	386	
LS mean	-1.25	-0.11	0.0217
SE	0.352	0.351	
QTC-Bazett (ms)			
n	384	386	
LS mean	-0.56	1.66	0.0724
SE	0.874	0.871	
QTC-Fredericia (ms)			
n	384	386	
LS Mean	-2.37	-1.30	0.3088
SE	0.751	0.748	
QT Interval (ms)			
n	384	386	
LS Mean	-5.66	-6.75	0.4806
SE	1.100	1.097	

¹p-value for treatment effect on mean change from baseline from linear model with terms for treatment, study, and baseline value, Type III sum of squares
Source: Appendix 2 Table 26.1 (ISS)

The Integrated Summary of Safety provides tables which indicate the mean change from baseline to last observation for the Placebo-controlled Phase 3 database as summarized below. On average, the changes in heart rate and interval measurements were minimal, similar to placebo, and not clinically significant. The changes for the long-term, uncontrolled study (CLDA-07-DP-04) were similar to those in the controlled studies, although the mean delta for QTcF was -8.0 msec; the clinical relevance of this is not known.

Table 7.4.12 Mean Change from Baseline to Last Observation: Placebo-Controlled, Phase 3 Database (GNSC-04-DP-02 and CLDA-07-DP-02)

	Vilazodone 40 mg			Placebo		
	n	BL	Δ	n	BL	Δ
Heart Rate (bpm)	436	67.3	1.7	433	66.9	3.2
PR Interval (msec)	436	155.2	-0.7	431	157.0	-0.4
QRS Interval (msec)	436	88.6	-1.3	432	87.7	0
QT Interval (msec)	436	386.2	-5.9	432	384.3	-6.7
QTcB Interval (msec)	436	405.6	-1.2	432	403.1	2.1
QTcF Interval (msec)	436	398.9	-2.8	432	396.7	-1.0

Source: Appendix 2 Table 26.1 (ISS)

Table 7.4.13 Mean Change from Baseline to Last Observation: Uncontrolled, Long-Term Safety Database (CLDA-07-DP-04)

	Vilazodone 40 mg/day		
	n	BL	Δ
HR bpm	599	66.7	3.6
PR Interval msec	599	158.4	-1.7
QRS Interval msec	599	87.5	-0.9
QT Interval msec	599	401.6	2.1
QTcB Interval msec	599	395.6	-1.3
QTcF Interval msec	599	383.9	-8.0

Source: Appendix 2 Table 26.2 (ISS)

Shifts in ECG results were summarized from baseline to Week 8/ET. At each timepoint, the ECG result was classified as Normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS). Shifts that would be considered a worsening of parameters: normal to abnormal (NCS or CS) and abnormal (NCS) to abnormal (CS) are represented in the following table. The percentages of subjects shifting from normal to abnormal are essentially the same. There appears to be no difference in the vilazodone group when compared with the placebo group. The number of abnormal NCS to Abnormal CS for the vilazodone group is nearly two times the placebo group.

**Table 7.4.14 Changes in ECG Results from Baseline to Final Visit
(Placebo-controlled Phase 3 Database Safety Population)**

ECG Change from Baseline to Final Visit	Vilazodone n=384 (%)	Placebo n=386 (%)
Normal to Abnormal NCS	45 (11.7)	46 (11.9)
Normal to Abnormal CS	2 (0.5)	2 (0.5)
Abnormal NCS to Abnormal CS	5 (1.3)	3 (0.8)

KEY: CS=clinically significant; NCS=not clinically significant.

Source: Appendix 2, Table 24.2.

2. Outliers

Phase 1

As indicated in the ISS, the specific outlier criteria consisted of a new abnormal U wave, new >500 ms absolute QTc duration, and a >60 ms change from baseline. For QTcI, none of the subjects met these criteria. The nonspecific outlier criterion was a 30-60 ms change from baseline, which showed no imbalance between placebo and vilazodone groups.

Phase 2 and 3 Studies

In the placebo-controlled Phase 3 database, the applicant reported no clinically meaningful differences between the placebo and vilazodone groups. In the uncontrolled, long-term safety database, no subject had ECG results change from Normal to Abnormal CS, and less than 1% of subjects had ECG results change from Abnormal NCS to Abnormal CS.

For the placebo-controlled, Phase 3 database, no subject taking either placebo or vilazodone had a treatment-emergent PCS abnormality for PR, QRS, or QTcF interval. One subject in each group (vilazodone and placebo) had a treatment-emergent PCS abnormality for HR (low HR in each subject).

In the Uncontrolled, Long-term Database PCS change was seen for HR in two (0.4%) patients and a QRS high for one (0.2%) patient. PCS changes were not observed for heart rate (high), PR Interval (high) or QTcF (high).

C. Discontinuations Due to ECG Abnormalities

There were no dropouts due to ECG abnormalities.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT Study

The applicant conducted a thorough QT study, PGX-08-P1-06, "A Double-Blind, Randomized, Parallel Study to Define the ECG Effects of Vilazodone Using a Clinical and a Supratherapeutic Dose Compared to a Placebo and Moxifloxacin in Healthy Volunteers: A Thorough ECG Study"

The primary objective of this study was to determine the time-matched change from baseline in QTc based on an individual correction (QTcI) method. The secondary objective was to evaluate the safety and tolerability of vilazodone in healthy volunteers as compared to subjects receiving placebo or moxifloxacin.

This was a Phase 1, single study, randomized, double-blind (except moxifloxacin), placebo and active control, 3-arm parallel study to assess the effects of vilazodone on QT interval in healthy males and females. It was hoped to achieve 20 males and 20 females in each treatment arm.

Subjects were randomized to one of three treatments: placebo from Day 1-15, Moxifloxacin 400 mg given on Days 6, 9, 12, and 15 to match each of the doses on vilazodone in which ECG and PK sampling was done, with placebo given on the remaining days; vilazodone starting at 10mg for 3 days, followed by 20 mg for 3 days, then 40 mg for 3 days, then 60 mg for 3 days and concluding with 80 mg/day for 3 days. Subjects in each of the 3 treatment arms received the study drug as a single daily dose following a high fat breakfast.

The effect of vilazodone on ECG parameter (heart rate, PR, QRS, QT, QTc intervals) were evaluated and compare with placebo and moxifloxacin treatment arms. Plasma PK of vilazodone and safety monitoring were also monitored by treatment arm.

Summary of QT Interdisciplinary Review Team Consult

In this randomized, double-blind study, one-hundred and forty subjects received vilazodone in doses from 10 mg to 80 mg (all, moxifloxacin 400 mg, and placebo). The summary of findings is provided in the following table (taken from the IRT review).

Table 7.4.15 QT-IRT Point Estimates and CIs

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound of $\Delta\Delta QTcI$ for Vilazodone and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta QTcI$ (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

The largest lower bounds after Bonferroni adjustment for 4 timepoints are 6.8 ms, 5.8 ms, 2.9 ms, and 3.4 ms, respectively for Days 6, 9, 12, and 15.

The overall assessment by the QT-IRT reviewer was that no significant QTc prolongation effect of vilazodone was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between vilazodone and placebo were below 10 ms. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta QTcI$ for moxifloxacin was greater than 5 ms at Day 6, and the moxifloxacin profile over time is adequate, indicating that assay sensitivity was established.

Study Description

A Phase 1, single-site, randomized, double-blind (except Moxifloxacin), placebo and active controlled, 3, arm, parallel study. The positive control was not double-blinded. Subjects were enrolled at one site and randomized to receive one of three treatments:

- Placebo – given (PO) Day 1-15
- Moxifloxacin 400 mg PO on Days 6, 9, 12, and 15 to match each dose of vilazodone in which ECG and PK sampling was done, placebo was given on remaining days (1-5, 7-8, 10-11, and 13-14).
- Vilazodone starting at 10 mg/day PO for 3 days, followed by 20 mg/day for 3 days, then 40 mg/day for 3 days, then 60 mg/day for 3 days and concluding with 80 mg/day for 3 days. If fewer than 40 subjects were able to complete the scheduled 3 days of dosing and associated PK and ECG activities at a vilazodone dose level, study conduct was interpreted to have identified the MTD for vilazodone and there would be no further increase in the dose. Of note, the MTD was not reached in this study.

Doses of study medication were administered with food, which is shown to increase exposure by approximately 50%. It is curious to note that the doses were titrated every 3 days, but in order to approach steady-state they should have studied each dose for a minimum of 4 days (the half life is assumed to be 8-36 hours). Discussion with the

clinical pharmacology reviewer indicated that on average, steady state is achieved in 3 days for vilazodone.

Table 7.4.16 ECG and PK Assessment Schedule

Study Day	-1	1-3	4, 5	6	7, 8	9	10, 11	12	13, 14	15
Intervention	None	10 mg dose QD	20 mg dose QD		40 mg dose QD		60 mg dose QD		80 mg dose QD	
12-Lead ECGs[#]	Record ECGs	None	None	Record ECGs						
PK Samples for drug^{##}	None	None	None	Collected	None	Collected	None	Collected	None	Collected

[#] ECGs will be obtained digitally using a Mortara Instrument (Milwaukee, WI) H-12+ ECG continuous 12 lead digital recorder ECGs (3 ECGs within 5 minutes) 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours post-dose on Days -1 and 6, 9, 12, and 15.

^{##} PK samples will be collected 5 minutes before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dose.

A total of 157 subjects were enrolled and randomized with 140 subjects (42 placebo, 42 moxifloxacin, and 56 vilazodone) were evaluable for ECG assessments. The reasons for premature discontinuation were 'withdrawal of consent' in 9 subjects and AE in 8 subjects. In the vilazodone group 56 of the 66 (85%) received all 15 doses.

The QT-IRT recommended two labeling changes:

- Deletion of Section 6 ECG
- Section 12.2: The effect of vilazodone 20, 40, 50, 80 mg on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel thorough QTc study in 157 healthy subjects. In the study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern. However, whether 80 mg is adequate to represent the high clinical exposure scenario is unknown.

Safety Issues in the TQT Study

- At the 80 mg dose of vilazodone 10 (18%) subjects met outlier criteria for tachycardia compared with 2 (5%) in the placebo group. None of the subjects in the other vilazodone dose groups met PCS tachycardia criteria.
- TEAEs of hypertension in three subjects and increased blood pressure in two subjects were reported for the vilazodone group only.
- TEAEs of palpitations in four subjects and tachycardia in 6 subjects were reported in the vilazodone group compared with 1 subject in the placebo and 0 in the moxifloxacin groups.

One subject discontinued due to AEs of dizziness, palpitations, hypertension, and tachycardia. He is described as a healthy subject, not taking concomitant medication. The applicant provides the following description of the event:

This subject was a 42-year-old white (Hispanic or Latino) male experienced palpitations which led to his premature discontinuation from the study. He was randomized to the vilazodone treatment arm and received his first dose of vilazodone 10 mg PO on 23 Nov 2008 (Day 1). The subject's heart rate at baseline (Day -1) was 60 beats/minute and blood pressure was 119/69 mmHg. On Day 5 (vilazodone 20 mg), the subject reported mild palpitations, which continued until Day 10 (vilazodone 60 mg). The scheduled heart rate measurement on Day 5 was 60 bpm and the scheduled blood pressure result was 112/70 mmHg. On Day 10, the subject also reported mild dizziness and experienced mild elevated blood pressure (171/100 mmHg) and tachycardia (108 bpm). The events of dizziness, elevated blood pressure, and tachycardia resolved the same day without treatment. The next day (Day 11), about 4 hours after the dose of vilazodone 60 mg, the subject again reported feeling mild palpitations (heart rate, 86 bpm) and dizziness, and experienced increased blood pressure (158/107 mmHg); study drug was discontinued due to the palpitations. Palpitations resolved within 48 minutes without treatment, and elevated blood pressure and dizziness resolved later that day; heart rate and blood pressure findings at the time of resolution were not provided. The investigator considered the events of palpitations, as well as the events of dizziness (first event), tachycardia, and elevated blood pressure, as possibly related to vilazodone; the second event of dizziness was assessed as probably related to vilazodone.

QT-IRT reviewer comments:

"Taking the results together, small effects on BP and HR are possible. However, given the minimal number of significant AEs reported in the phase 3 clinical trial database we believe description of the vital signs and AEs with the clinical trials experience should be sufficient. Precautions with regular monitoring of symptoms, along with blood pressure and pulse rate in patients with hypertension or pre-existing heart disease should be considered."

Although in the Placebo-controlled Database the mean change from baseline and the outliers for heart rate and blood pressure were not significantly different for vilazodone compared with placebo, recommendations to monitor blood pressure and pulse rate in patients with hypertension or pre-existing heart disease should be considered. Concurrence is based on the opinion that it is necessary to further characterize the pharmacokinetic profile of vilazodone with regard to drug-disease interactions and dose response. As noted above, at the 80 mg dose of vilazodone, 18% of patients met tachycardia outlier criteria as compared with 5% in the placebo group. Current data regarding food effect, dose-response, and drug-disease interaction (severe hepatic and severe renal impairment) indicate that it may be difficult to predict exposure.

7.5 Other Safety Explorations

Sexual Function

Antidepressant induced sexual dysfunction is common, under-reported and may result in treatment noncompliance or discontinuation. The Arizona Sexual Experiences Scale (ASEX) and the Changes in Sexual Functioning Questionnaire (CSFQ) have been developed in response to a need for quantitative evaluations of changes in sexual function. The ASEX was assessed in study GNSC-04-DP-02 and the CSFQ was administered in study CLDA-07-DP-02. Outlier and subgroup information might be helpful to provide a more meaningful interpretation of the results. Again, spontaneous reports of sexual AEs indicate a higher incidence of sexual dysfunction for vilazodone over placebo in both males and females.

GNSC-04-DP-02

The ASEX was administered in the Phase 3 study GNSC-04-DP-02. The ASEX was assessed in patients at baseline (Visit 2) and each subsequent visit throughout the study. The ASEX is a 5-item rating scale that quantifies 5 areas of sexual function. The total scores can range from 5 to 30, with increasing scores indicating diminished sexual function and decreasing scores indicate improvement. A mean change of >2 points on the total score is considered to be clinically significant. For the ASEX, sexual dysfunction is defined as a total score of >19, a score of >5 on any one item, or a score of ≥ 4 on 3 or more items.

Results

The Integrated Summary of Safety report indicates that in both treatment groups, mean scores at Week 8 were slightly lower than at baseline for both male and female patient groups.

For males, the least squares (LS) mean change from baseline in ASEX total score at End of Treatment (EOT) was -1.03 in the placebo group and +0.80 for males taking vilazodone 40 mg (higher score indicates lower functioning). The difference in the LS means between the vilazodone and placebo groups was statistically significant; although the applicant points out that neither group demonstrated a clinically important reduction in the mean change of at least 2 points.

For females, the LS mean change from baseline in the ASEX total score at EOT was +0.07 in the placebo groups and -1.14 for the vilazodone group (higher score indicates lower functioning), this difference was not statistically significant. There were no relevant distinctions between the vilazodone and placebo groups on any of the ASEX domain and neither group demonstrated a reduction in mean change of at least 2 points.

When males and females are assessed separately, there is a tendency toward diminished sexual functioning for the males. As expected for this class of therapeutic agents, the spontaneous reports of sexual AEs indicate a higher incidence of sexual dysfunction for vilazodone over placebo in both males and females.

CLDA-07-DP-02

The Changes in Sexual Functioning Questionnaire (CSFQ) is a 14-item questionnaire that uses 5-point Likert scales to assess sexual function. The CSFQ was included as a safety measure to evaluate the impact of vilazodone on this known adverse event associated with antidepressants. The instrument includes subscale scores for males and females. Higher scores indicate higher levels of sexual functioning. A mean change of 3 points on the total score and/or 0.5 points on subscales is considered clinically significant. For the CSFQ, sexual dysfunction is defined as a total score ≤ 47 in men and ≤ 41 in women. The CSFQ was administered in the Phase 3 study CLDA-07-DP-02 and in the long-term study CLDA-07-DP-04.

Results

For males, the LS mean changes in CSFQ total score was increased for both the vilazodone and placebo groups. The LS mean change was higher (higher scores indicate higher functioning) for the placebo group than for the vilazodone group; although, neither group demonstrated a mean change increase of at least 3 points. The difference in the LS mean changes was not statistically significant.

For females, the LS mean changes in CSFQ total score was increased for both the vilazodone and placebo groups. The LS mean change was higher for the placebo group than for the vilazodone group; although, neither group demonstrated a mean change increase of at least 3 points. The difference in the LS mean changes was not statistically significant.

Outlier and subgroup information might be helpful to fully interpret the results of this study. Again, spontaneous reports of sexual AEs indicate a higher incidence of sexual dysfunction for vilazodone over placebo in both males and females.

CLDA-DP-07-04 (open-label, long-term safety)

For males in the uncontrolled, long-term safety database, the mean change from baseline in the CSFQ total score at EOT was +1.5. For females, the mean change from baseline at EOT was +2.7. These numbers did not reach statistical significance.

TEAES pertaining to sexual functioning occurred 9 times more frequently in vilazodone (9%) patients than in placebo (1%) patients. The safety population for the placebo-controlled phase 3 studies indicate decreased libido in 16 (4%) patients (8 males and 8 females) for the vilazodone group and 2 (0.5%) patients (1 male and 1 female) in the

placebo group. Overall, sexual dysfunction is a significant adverse event associated with antidepressants and not an unexpected finding for an SSRI such as vilazodone.

The adverse events were coded per MedDRA version 11.1 and as such, the preferred terms (PT/AETERM) decreased libido, delayed orgasm, anorgasmia, and low libido map to the system organ class (SOC/AEBODSYS) 'Psychiatric Disorders'. The preferred terms sexual dysfunction, delayed ejaculation, and erectile dysfunction map to the SOC "Reproductive System and Breast Disorders." To provide more informative information for labeling, the AEs have been combined as 'sexual adverse events' and presented in tabular format.

Spontaneous reports of sexual adverse events from the JMP datasets in the placebo-controlled phase 3 studies are summarized in the following table.

Table 7.5.1 Sexual Adverse Events – Placebo Controlled Phase 3 (07 and 04)

Adverse Event	All Patients N (%)		Males N (%)		Females N (%)	
	V40 N=440	PBO N=437	V40 N=174	PBO N=183	V40 N=266	PBO N=254
Anorgasmia	6 (1.4)	0	2 (1.1)	0	4 (1.5)	0
Delayed Ejaculation	4 (0.9)	0	4 (2.3)	0	0	0
Erectile Dysfunction	4 (0.9)	1 (0.2)	4 (2.3)	1 (0.5)	0	0
Decreased Libido	16 (3.6)	2 (0.5)	8 (4.6)	1 (0.5)	8 (3.0)	1 (0.4)
Abnormal Orgasm	7 (1.6)	0	6 (3.4)	0	1 (0.4)	0
Sexual Dysfunction	4 (1)	1(0.2)	3 (1.7)	0	1 (0.4)	1 (0.4)

7.5.3 Drug-Demographic Interactions

Among vilazodone subjects from the all placebo-controlled database, the incidence of TEAEs was similar for subjects who were <55 years of age and subjects ≥55 years of age. Although diarrhea occurred at a higher rate for the older age group and nausea occurred more frequently in the younger age group.

Adverse events appeared to occur nearly two times more frequently in the >55 years age group than in the <55 years group for both vilazodone and placebo. It should be

noted that of the 2177 patients in the clinical program, only 37 (1.7%) were 65 years of age or older; 272 (12%) were between 55 and 64 years of age.

7.5.4 Drug-Disease Interactions

The clinical data are currently being reviewed by Clinical Pharmacology. The evaluation of vilazodone in patients with renal or hepatic impairment is limited. Few patients were studied at a 20 mg dose. Patients included in the studies were with mild to moderate impairment. Patients with severe renal or hepatic impairment were not studied.

7.5.5 Drug-Drug Interactions

The Clinical Pharmacology review provides more comprehensive information regarding drug-drug interactions.

The drug interaction study with ketoconazole was studied with suboptimal doses of both vilazodone and ketoconazole (this reviewer's opinion). Interpretation is deferred to the clinical pharmacologist.

7.6 Additional Safety Evaluations

Suicidality

There were two suicides during the clinical development program for vilazodone. Both occurred in Phase 2 studies; as indicated in the following narratives, neither patient was receiving vilazodone at the time of death.

1. 026-1231 – Suicide by Gun Shot

This patient was a 54-year-old Caucasian male. He was randomized to receive placebo and was scheduled for his first dose on Aug. 6, 1998. On [REDACTED] (b) (6) he died from a self-inflicted **gun shot to the head**. The patient's medical history included anxiety, major depressive disorder, alcohol abuse, renal lithiasis, and surgery for herniated disk. This death is not related to the study medication.

2. 027-G01 – Suicide by Carbon Monoxide

This patient was a 47-year-old male who had not been randomized to a study medication when his death occurred. The patient had signed informed consent, but no procedures were performed because he failed to attend the screening visit. On [REDACTED] (b) (6) it was reported that the patient had attempted **suicide by carbon monoxide** inhalation. He was hospitalized for three weeks and died on [REDACTED] (b) (6) as a result of CO poisoning. The death is not related to the study medication.

Methods

The applicant provided a thorough evaluation of suicidality (ISS Appendix 4) using data from Phases 1 through 3. The data consisted of AEs, Columbia Classification Algorithm of Suicide Assessment (C-CASA) scores derived from both database text string search (TSS) of AEs and Columbia-Suicide Severity Rating Scale (C-SSRS) data, HAM-D suicide item score and MADRS suicidal thoughts item score.

The TSS included verbatim, preferred terms, and any associated CRF comments for the following terms: accident-, attempt, burn, cut, drown, gas, gun, hang, hung, immolate, injur-, jump, monoxide, mutilat-, overdos-, self damag-, self harm, self inflict, self injur-, shoot, slash, sui, poison, asphyxiation, suffocation, and firearm.

Phase 1

For the Phase 1 studies, a search of treatment emergent adverse events (TEAEs) associated with suicidality was done. The subjects in Phase 1 were healthy volunteers, not identified to have MDD.

Phase 2 and Phase 3

Of the eight Phase 2 and 3 studies, CLDA-07-DP-02 was the only placebo controlled study that used the C-SSRS. The long-term study CLDA-07-DP-04 implemented the instrument mid-study. Therefore, a comprehensive blinded text string search of all text fields was conducted for the evaluation of suicidality. The TSS hits were evaluated and blinded narratives were prepared for assignment of C-CASA scores by an independent group. Sensitivity analyses were performed using HAM-D and MADRS items and C-SSRS data mapped to C-CASA.

Results

No TEAEs associated with suicidality were reported for the subjects in Phase 1 studies. One subject in the placebo group of a Phase 2 study completed suicide. There were no suicides in subjects receiving vilazodone.

In the placebo controlled Phase 3 database, there was one suicide attempt in the vilazodone group and one event of suicidal behavior in the placebo group. In the all placebo-controlled database, suicidal behavior was identified in 4 subjects (0.4%) in the placebo group and 2 subjects (0.1%) in the all-doses vilazodone group.

Table 7.6.1 C-SSRS CLDA-07-DP-02

Table 3: Contribution of Columbia-Suicide Severity Rating Scale and Text String Search Findings to Columbia Classification Algorithm of Suicide Assessment Results in Study CLDA-07-DP-02 (Safety Population)

Columbia Classification Algorithm of Suicide Assessment (C-CASA) Code / Category		Placebo N=233 n (%)			Vilazodone 40 mg/day N=235 n (%)		
		C-SSRS	TSS	C-SSRS or TSS	C-SSRS	TSS	C-SSRS or TSS
1	Completed Suicide	0	0	0	0	0	0
2	Suicide Attempt	0	0	0	0	0	0
3	Preparatory Acts Toward Imminent Suicidal Behavior	0	0	0	0	0	0
4	Suicidal Ideation	62 (26.6)	0	62 (26.6)	51 (21.7)	0	51 (21.7)
5	Self-injurious Behavior, Intent Unknown	0	0	0	0	0	0
6	Not Enough Information (Death)	0	0	0	0	0	0
7	Non-suicidal Self-injurious Behavior	1 (0.4)	0	1 (0.4)	0	0	0
8	Other (Accident, Psychiatric, Medical)	0	2 (0.9)	1 (0.4)	0	5 (2.1)	3 (1.3)
9	Not Enough Information (Non-Death)	0	0	0	0	0	0
0	No Suicidal Behavior Observed	170 (73.0)	231 (99.1)	169 (72.5)	184 (78.3)	230 (97.9)	181 (77.0)

Note: Subjects were assigned the worst C-CASA category obtained from the Columbia-Suicide Severity Rating Scale (C-SSRS) mapping and from the evaluation of text string search (TSS) findings, respectively. The worst of these 2 scores was reported in the combined C-SSRS or TSS column.

Source: [Appendix 2: Table 40.4](#)

Reproduced from the Applicant's submission 5.3.5.3.2 ISS p.12

Table 7.6.2 C-SSRS Placebo – Controlled Phase 3 Database

Table 2: Columbia Classification Algorithm of Suicide Assessment (Placebo-controlled, Phase 3 Database; Safety Population)

Columbia Classification Algorithm of Suicide Assessment (C-CASA) Code / Category		Primary Evaluation ^a		Secondary Evaluation ^b	
		Placebo N=433 n (%)	Vilazodone 40 mg/day N=436 n (%)	Placebo N=433 n (%)	Vilazodone 40 mg/day N=436 n (%)
1	Completed Suicide	0	0	0	0
2	Suicide Attempt	0	1 (0.2)	0	1 (0.2)
3	Preparatory Acts Toward Imminent Suicidal Behavior	1 (0.2)	0	1 (0.2)	0
4	Suicidal Ideation	64 (14.8)	51 (11.7)	2 (0.5)	0
5	Self-injurious Behavior, Intent Unknown	0	0	0	0
6	Not Enough Information (Death)	0	0	0	0
7	Non-suicidal Self-injurious Behavior	2 (0.5)	0	1 (0.2)	0
8	Other (Accident, Psychiatric, Medical)	3 (0.7)	7 (1.6)	4 (0.9)	9 (2.1)
9	Not Enough Information (Non-Death)	0	0	0	0
0	No Suicidal Behavior Observed	363 (83.8)	377 (86.5)	425 (98.2)	426 (97.7)

^a For the primary evaluation, subjects were assigned the worst C-CASA category obtained from either the Columbia-Suicide Severity Rating Scale (C-SSRS) mapping or from evaluation of text string search findings.

^b For the secondary evaluation, subjects were assigned the worst C-CASA category from evaluation of text string search findings only.

Source: [Appendix 2: Table 40.2](#) (Primary Evaluation) and [Table 41.2](#) (Secondary Evaluation)

Reproduced from the applicant's submission 5.3.5.3.2 ISS p.10

Overall, the incidence of suicide and suicidality was as expected for the disease under investigation. The applicant has complied with the recommendations of the division to include a thorough evaluation of suicidality which is now requested for all clinical development programs for review by DPP.

Although there is no specific signal for increased suicidality was noted in this application, as a member of the class SSRI, a boxed warning will be included in the label.

7.6.1 Human Carcinogenicity

The overall incidence of adverse events in the SOC – Neoplasms benign, malignant, and unspecified – was reviewed to determine if there might be a signal for human carcinogenicity in the vilazodone development program. No signal was observed when these AEs were reviewed. There were 2 thyroid nodules, one in the placebo group and one in the vilazodone group.

The studies in the clinical development program were of short duration, and not well-suited to detect cancer. No human carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

Eleven (11) pregnancies were reported during the clinical development of vilazodone. There were eight (8) in the vilazodone group and three (3) in the placebo group. One (1) patient had a positive pregnancy test at screening and was not randomized. The outcomes of the pregnancies included five (5) elective terminations, five (5) continued pregnancies, and one (1) ruptured ectopic pregnancy. Further details regarding the outcomes are not available.

Phase 1

No (0) pregnancies were reported in the Phase 1 studies.

Phase 2

Ten (10) pregnancies were reported in the Phase 2 studies.

One patient had a positive pregnancy test at screening and was not randomized. Five patients elected termination and four patients elected to continue the pregnancy. The outcome of the pregnancies is not known, one patient was taking vilazodone 20 mg/day, one patient was taking vilazodone 10 mg/day, and two patients were taking placebo.

Phase 3

There was one pregnancy in the placebo group of GNSC-04 (8-week pivotal). There was one ruptured ectopic pregnancy in a patient taking vilazodone 40 mg/day group of the open-label study.

Phase 3 Uncontrolled Long-Term Study

Patient 4090-008 had a negative pregnancy test through Week 8, but a positive result about a month later. Follow up information revealed that a healthy female was delivered on [REDACTED] (b) (6) at 38 weeks gestation. The infant weighed 8 pound 0 ounces, and was 21 inches in length. The infant was noted to be jaundiced at birth but was “within normal limits” after 7 days.

Patient 4130-010 had pregnancy test results that were negative through Week 12, but positive on 25 June 2008. Follow-up indicated a delivery date of [REDACTED] (b) (6) at 32 weeks and 1 day. The male infant weighed 5 pounds and 0 ounces and was 17 inches in length. APGAR scores were 8 at one minute and 9 at 5 minutes.

Patient 4160-004 had a negative pregnancy test results through Week 28, but positive on 26 Sept 2008. The patient was lost to follow up and no addition information the outcome of the pregnancy is available.

Patient 4242-010 had pregnancy test results that were negative through Week 44, but positive approximately 4 weeks later. On [REDACTED] (b) (6) the subject underwent elective termination of the pregnancy.

Patient 4130-008 had pregnancy test results that were negative through Week 2 and at a visit 9 days later. This patient was prematurely discontinued from the study due to a ruptured ectopic pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Vilazodone has not been tested in subjects below the age of 18 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Overdose experience is detailed in Section 7.3.5.2; narratives are provided. Overall, none of the overdoses related to vilazodone were lethal, the exposure to vilazodone was low and there were few episodes. There were no reports of overdose in the Phase 1 studies.

The data provided regarding renal impairment and hepatic impairment are limited and provide no additional information regarding overdose.

Drug Abuse Potential

At this time, the CSS consult was not available for review.

The applicant submitted within the Integrated Summary of Safety, Appendix 7 – Assessment of Drug Abuse Potential. The assessment of the abuse potential was prepared by the applicant in response to an FDA request in accordance with 21 CFR 314.50(d)(5)(vii).

No double-blind clinical investigation in human volunteers with a history of recreational drug or alcohol use was conducted. The procedure used to evaluate the potential for abuse involved a search of the TEAEs from Phase 1, 2, and 3 studies. Summary tables were provided.

It is noted that in the all placebo controlled database, the incidence of ‘euphoria related’ terms for all doses of vilazodone was nearly twice that of the placebo group. This was primarily due to the TEAE “dizziness.” Taken together (although split in the table provided) somnolence and sedation were higher for the all vilazodone doses group 2.7% (42/1578) than the placebo group 1.4% (14/997). The incidence of dissociative/psychotic terms was slightly higher, although not considered to be significant.

Based on the information provided, the adverse event profile and potential for abuse appear to be similar to the serotonin reuptake inhibitors. The applicant did not specifically study or assess withdrawal emergent signs and symptoms during drug taper or discontinuation. It is recommended that this be studied in the post-marketing period, as there have been reports of serious discontinuation symptoms with SSRIs.

8 Postmarket Experience

Vilazodone is not marketed in any country.

9 Appendices

9.2 Labeling Recommendations

Recommendations for labeling will be provided as an addendum to this review.

9.3 Advisory Committee Meeting

Vilazodone is a serotonin specific reuptake inhibitor (SSRI) with a very similar efficacy and adverse events profile to others in the class. Therefore, the Division did not take this NDA to the Psychopharmacological Drugs Advisory Committee.

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

/s/

CHERI Y LINDBERG
01/20/2011

ROBERT L LEVIN
01/20/2011
Refer to Cross-Disciplinary Team Leader Memo

January 21, 2011

***Section 3.3 Financial Disclosures* is incomplete re the Phase 3 studies.**

***Section 7.3.2 Nonfatal Serious Adverse Events* requires a table for the subjects with serious adverse events that compares drug to placebo for all Phase 2 and 3 studies, arranged by system organ class and the preferred team.**

The 1/20/2011 REV-CLINICAL-03 (General Review) corrects these issues. It supersedes this review.

CLINICAL REVIEW

Application Type NDA
Application Number(s) 022567
Related IND 054613
Priority or Standard Standard

Submit Date(s) March 22, 2010
Received Date(s) March 22, 2010
PDUFA Goal Date January 22, 2011
Division / Office DPP/ODE1

Reviewer Name(s) Cheri Lindberg, MD
Review Completion Date December 2, 2010

Established Name Vilazodone HCl
(Proposed) Trade Name Viibryd
Therapeutic Class Antidepressant
Applicant PGxHealth, LLC

Formulation(s) 10, 20, 40 mg tablet
Dosing Regimen Once daily – oral
Indication(s) Major Depressive Disorder
Intended Population(s) Adult

APPEARS THIS WAY ON ORIGINAL

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, approval is recommended (with revisions to the proposed label) of NDA 022567 Viibryd (vilazodone) for the treatment of Major Depressive Disorder in adult patients.

1.2 Risk Benefit Assessment

The efficacy of vilazodone was demonstrated in two (2) of seven (7) controlled trials designed to evaluate vilazodone as a treatment for Major Depressive Disorder in adult outpatients. Review of the safety data submitted by the applicant reveals a safety profile that is similar to other serotonin reuptake inhibitors; with the exception of ophthalmologic abnormalities, there were no unexpected findings.

The efficacy of only one dose of vilazodone, 40 mg qd, was explored. It is the opinion of this reviewer that the dose-response relationship of vilazodone has not been adequately characterized. This should be explored as a post-marketing commitment with a fixed-dose design to provide a valid and rigorous examination of dose-response relationships for efficacy as well as safety and tolerability.

Post-marketing commitments will help elucidate tolerance and withdrawal effects of vilazodone and provide a more thorough understanding of the drug in patients with renal and hepatic impairment.

The labeling should include recommendations to [REDACTED] (b) (4)

[REDACTED] Although in the Placebo-controlled Database, the mean change from baseline and outliers for heart rate and blood pressure were not significantly different for vilazodone compared with placebo; this reviewer concurs with recommendations of the QT-IRT to monitor blood pressure and pulse rate in patients with hypertension or pre-existing heart disease. Concurrence is based on this reviewer's opinion that it is necessary to further characterize the pharmacokinetic profile of vilazodone with regard to drug-disease interactions and dose response. In the thorough QT study, at the 80 mg dose of vilazodone, 18% of patients met tachycardia outlier criteria as compared with 5% in the placebo group. It is this reviewer's opinion that current data regarding food effect, dose-response, and drug-disease interaction (severe hepatic and severe renal impairment) indicate that it may be difficult to predict exposure.

Overall, in view of the potential clinical benefit, the risk-benefit assessment is favorable for vilazodone 40 mg/day for the treatment of Major Depressive Disorder in the adult population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In accordance with section 505-1(a) of FDCA, it has been determined that a REMS is **necessary for vilazodone HCL to ensure the benefits of the drug outweigh the increased** risk of suicidality in children, adolescents, and young adults as observed in short-term studies of major depressive disorder (MDD) and other psychiatric disorders.

Pursuant to 21 CFR 208, FDA has determined that vilazodone HCL poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of vilazodone HCL. FDA has determined that vilazodone HCL is a product for which patient labeling could help prevent serious adverse effects and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved.

1.4 Recommendations for Postmarket Requirements and Commitments

Because the efficacy of only one dose of vilazodone, 40 mg qd, was studied, the dose-response of this drug has not been adequately explored. Therefore, the applicant should conduct a clinical trial evaluating vilazodone compared with placebo in fixed doses of 10 mg/day, 20 mg/day, 30 mg/day, and 40 mg/day.

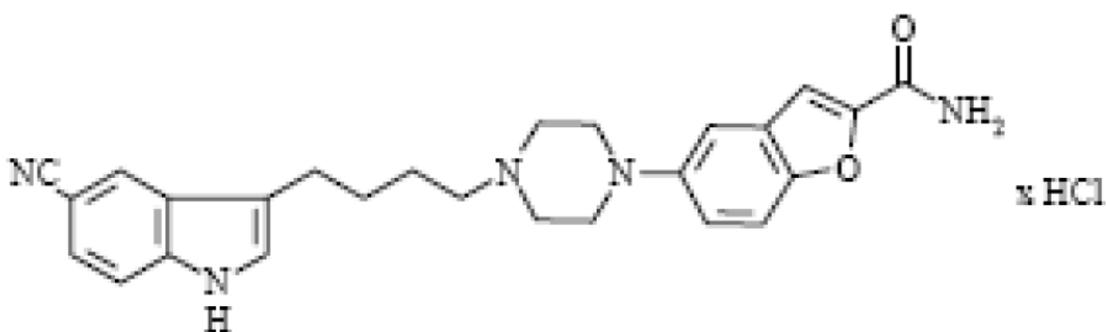
The applicant should also conduct a placebo-controlled, randomized withdrawal trial to assess the occurrence of withdrawal and rebound during taper and discontinuation.

The applicant should also adequately characterize vilazodone with regard to hepatic and renal impairment. The current trials have assessed a small number of patients with mild to moderate impairment of hepatic and renal impairment; no patients with severe impairment have been studied.

2 Introduction and Regulatory Background

2.1 Product Information

USAN: Vilazodone hydrochloride
Molecular Formula: C₂₆H₂₇N₅O₂HCl



Vilazodone hydrochloride is a new molecular entity with putative antidepressant activity as a serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist. Vilazodone has greater in vitro potency and selectivity for serotonin reuptake than fluoxetine. In vitro binding studies also indicate that vilazodone has a greater potency at the 5-HT_{1A} receptor than specific 5-HT_{1A} ligands such as buspirone, an accepted adjunctive treatment for Major Depressive Disorder.

Proposed Trade Name (established name): Viibryd is the proposed trade name and vilazodone HCl is the established name adopted by the United States Adopted Names (USAN) Council.

Chemical Class: New Molecular Entity – belongs to the structural chemical group of the indolalkylamines and is formulated at 10, 20, and 40 mg tablets for oral administration.

Pharmacologic Class: Selective Serotonin Reuptake Inhibitor (b) (4)

Proposed Indications: Treatment of Major Depressive Disorder

Proposed Age Group: Adults

Proposed Dosage and Administration: The recommended dose for vilazodone is 40 mg once daily. Vilazodone should be titrated to the 40 mg dose, starting with an initial dose of 10 mg once daily for 7 days followed by 20 mg once daily for an additional 7 days. Vilazodone should be taken with food.

2.2 Tables of Currently Available Treatments for Proposed Indications

A number of antidepressant medications are available for the treatment of Major Depressive Disorder, including:

Tricyclic Antidepressants	imipramine, desipramine, amitriptyline, nortriptyline, doxepin, amoxapine, trimipramine, protriptyline, maprotiline.
Monoamine Oxidase Inhibitors (MAOI)	phenylzine, tranylcypromine, isocarboxazid, maprotiline, selegiline patch
Selective Serotonin Reuptake Inhibitors (SSRI)	fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram
Serotonin and Norepinephrine Reuptake Inhibitors	venlafaxine, duloxetine, desvenlafaxine
Other Antidepressants	bupropion HCl, bupropion HBr, trazadone, nefazodone, mirtazepine

Electroconvulsive therapy is also available for the treatment of MDD.

2.3 Availability of Proposed Active Ingredient in the United States

This product is a new molecular entity under development for licensing by the applicant and is currently not marketed in the United States. The applicant indicates that the drug product would be readily available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Safety issues of concern with vilazodone are similar to other SSRIs:

- Suicidality
- Serotonin syndrome
- Seizures
- Abnormal bleeding
- Activation of mania or hypomania
- Hyponatremia
- Discontinuation syndrome

These issues are specifically addressed in Section 7 Review of Safety.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Type of Meeting/Correspondence (Meeting Date) [Correspondence Finalized]	FDA recommendations/comments
Initial IND 54613 (11/21/1997) [12/21/1997]	<ul style="list-style-type: none"> Per telephone conversation of 12/21/1997, recommend ophthalmology monitoring because of corneal opacities in the six-month dog study. Request verification of 26 week rat study mammary gland findings.
IND 54613 Type C Meeting (August 7, 2006) [August, 15 2006]	<ul style="list-style-type: none"> Regarding adequacy of the Phase 1 studies: “the <i>adequacy of the studies will be a review</i> issue. It is suggested the sponsor consider exploring the relationship between vilazodone exposure (e.g. concentration, dose) and response (e.g. efficacy, safety)”. The sponsor should also refer to the Guidance on drug interaction studies on the FDA website.
IND 54613 Type B Meeting (May 11, 2009) [May 19, 2009]	<ul style="list-style-type: none"> Discussion of pivotal trial CLDA-07-DP-02 The sponsor agreed to send... the identifying data on the 2 phase II studies that have already been submitted. The information from three trials undertaken by GSK will be submitted, however, the sponsor reported that some appendices were unable to be located. We requested that the primary efficacy results including the MADRS endpoint and the HAM-D17 endpoint be sent to us. The sponsor confirmed that all data will be submitted as part of the filing to the new drug application. We consider Study CLDA-07-DP-02 the first pivotal to confirm the findings on (b) (4) genetic marker... findings need to be replicated before they could be considered in support of a labeling claim.

<p>IND 54613 Type B Teleconference (June 17,2009)</p>	<ul style="list-style-type: none"> • The data from the two pivotal studies will be presented separately and discussed in the clinical summary of efficacy. PGxHealth does not intend to pool the efficacy data from the two pivotal studies other than for the purposes of subgroup analyses. • Data from the five Phase II studies conducted under the sponsorship of Merck and GSK are not considered supportive for the proposed dose and indication.
<p>IND 54613 Email [July 31, 2009]</p>	<p style="text-align: right;">(b) (4)</p>

2.6 Other Relevant Background Information

The ownership of vilazodone has been transferred among several sponsors, as indicated below:

<p style="text-align: center;">November 11, 1997 Initial IND 54613 Submission Lipha Pharmaceuticals, Inc (an Associate of Merck)</p>
<p style="text-align: center;">August 26, 1998 Transfer of ownership from Lipha Pharmaceuticals, NY to Merck KGaA, DE Authorization of PPD Pharmaco as US Agent for IND 54613</p>
<p style="text-align: center;">May 1, 2001 Transfer of Ownership from Merck to GSK</p>
<p style="text-align: center;">February 11, 2003 Transfer of ownership from GSK to Merck KGaA</p>
<p style="text-align: center;">November 7, 2003 Notice of establishment of EMD Pharmaceuticals, Inc. as IND Agent</p>
<p style="text-align: center;">October 25, 2004 Transfer of ownership of IND 54613 from EMD to GNSC</p>

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was appropriately organized to allow information to be reviewed in an acceptable manner. The responses of PGxHealth to all of FDA's requests were timely and well organized.

3.2 Compliance with Good Clinical Practices

According to statements included in the reports for the pivotal trials the applicant certified that the studies were conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

The Division of Scientific Investigation (DSI) inspected four clinical sites that participated in the pivotal Phase 3 trials and did not find any regulatory violations over the course of the audits of these sites. Audits of the applicant revealed no discrepancies or regulatory violations in terms of oversight and monitoring of the pivotal Phase 3 studies, test article accountability, qualifications of investigators and site monitors, transfer of obligations, adverse event reports, and handling of data.

During this inspection, records and documents included, but were not limited to: organization and personnel; conduct of regulatory responsibilities; appropriate transfer of regulatory responsibilities, contracts, work orders, and agreements; investigator selection; FDA 1572's; clinical investigator training; monitoring procedures; data verification; adverse event reporting procedures; primary efficacy process and verification; eligibility assessment; data collection and computerized systems and use of e-CRF's; test article accountability and reconciliation; and sponsor correspondence.

One Form FDA 483 was issued to Dr. Arifulla Khan. The inspection was performed as a data audit for Protocol CLDA-07-SP-02. At the end of the inspection a Form FDA 483 was issued, indicating that the investigation was not conducted in accordance with the investigational plan, and that the investigator did not maintain adequate histories or data pertinent to the research investigation. Dr. Khan responded adequately to the inspectional findings in a letter dated July 13, 2010. The minor regulatory violations are not considered to have an impact on data integrity and patient safety. The study

appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

The DSI inspection reports indicate that the applicant appears to have executed responsibilities appropriately, and no significant issues were noted. The studies appear to have been conducted adequately, and the data generated appear acceptable in support of the proposed indication.

3.3 Financial Disclosures

Vilazodone was licensed to two previous sponsors (Merck and GSK). Two of the five Phase 2 trials did not collect financial disclosures. PGxHealth obtained a letter from a previous sponsor regarding financial disclosures. The division's response indicated that this is acceptable only if the two Phase 2 trials without financial disclosure are not pivotal studies that support the labeling claims in the NDA. None of the Phase 2 trials are considered pivotal studies for this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry, manufacturing and controls data were reviewed by Dr. Pei-I Chu. The reviewer considered the NDA approvable from a CMC perspective pending satisfactory responses from the applicant regarding issues of drug substance and drug product questions. At the time of this writing, the response had not been received.

There are no recommendations for post-marketing commitments, agreements, or risk management steps.

The Office of Compliance has determined that pre-approval inspections for the drug substance, drug product and packaging sites are not needed based on the drug profile.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology data was reviewed by Violetta Klimek, Ph. D. At the time of this writing, the review was not available. The review team held several status meetings during the course of this NDA and no significant issues were identified by the pharmacology/toxicology reviewer.

4.4 Clinical Pharmacology

The clinical pharmacology data was reviewed by Bei Yu, Ph. D. At the time this review was completed, the clinical pharmacology review was not available. The review team held many status meetings during the course of this NDA and no significant issues were identified by the clinical pharmacology reviewer.

4.4.1 Mechanism of Action

The applicant reports “vilazodone is a potent and selective inhibitor of serotonin reuptake and a potent and selective partial agonist at the 5HT-1A subtype of serotonin receptors”. It is thought to optimize the regulation of the 5-HT circuitry at both pre- and post-synaptic sites to augment 5-HT transmission, putatively producing antidepressant effect.

Reviewer comment: The in vivo 5-HT1A receptor binding study of vilazodone failed to provide compelling evidence of 5-HT1A binding activity. The meeting minutes from the End of Phase 2 Meeting on December 20, 2005 indicate: “The Office of Clinical Pharmacology noted that the PET study utilizing a 40 mg dose produced mean receptor occupancy of < 30%, whereas the common thought is that at least 80% occupancy may be needed for antidepressant efficacy.”

(b) (4)

4.4.2 Pharmacodynamics

The clinical study report indicates vilazodone binds in vitro with high affinity to the human 5-HT reuptake site (5-HT transporter) with a $K_i=0.1\text{nM}$ and shows lower affinity for the norepinephrine and dopamine reuptake sites. Vilazodone also potently binds to the rat 5-HT transporter and inhibits with high affinity both rat and human 5-HT reuptake. Functionally, vilazodone is a centrally-active 5-HT reuptake inhibitor.

The study report also indicates that vilazodone binds with high affinity to the rat and human 5-HT1A receptor binding sites and is 60 times more potent than buspirone.

In vivo studies provide a functional profile for vilazodone that is characteristic of a 5-HT1A partial agonist.

In cardiovascular studies, vilazodone was not active in a human hERG (human ether-a-go-go related gene) channel assay, nor did it have activity indicative of potential proarrhythmic effects in guinea-pig papillary muscles.

4.4.3 Pharmacokinetics

Absorption

Vilazodone is absorbed after oral administration with T_{max} occurring at 4 to 6 hours. Vilazodone has linear pharmacokinetics with single doses of 2.5 mg to 80 mg and with repeated doses of 20 mg to 80 mg. In the presence of a high fat breakfast the C_{max} values are approximately 150% higher and AUC values approximately 60-90% higher.

Distribution

Vilazodone is highly protein bound, ranging from 96-99% in human serum.

Metabolism

Vilazodone is extensively metabolized by the liver. CYP3A4 is the major enzyme responsible for vilazodone metabolism with minor contributions from CYP2C19 AND CYP2D6. The use of vilazodone 10 mg with ketoconazole 200 mg resulted in a 50% increase in C_{max} and AUC. The use of vilazodone with inducers of CYP3A4 may reduce vilazodone concentrations.

Excretion

The purported elimination half-life is, on average, about 24 hours. The range in various studies is from 8.5 to 36 hours. The half-life for vilazodone following a single 40 mg dose in healthy young adults ranged from 13 – 30 hours. Shorter half-lives were seen in studies where drug concentrations were measured for only 24 hours post-dose. Some studies reported half-lives from approximately 24 – 29 hours with multiple dosing while another study reported a range of 28 – 37 hours. The majority of vilazodone is eliminated in the feces, presumably via secretion of the parent and metabolites into bile.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program of vilazodone for the treatment of MDD in adults included 24 Phase 1 studies, five Phase 2 studies, and three Phase 3 studies during which 2898 subjects received vilazodone.

Phase 1

Table 5.1 Phase 1 Clinical Trials in Healthy Subjects

Protocol	Study Design	Subjects M/F (ITT)	Treatment Arms	Duration/Applicant's Conclusions
EMD 68 843-007 Single dose Food Effect	Single-center OL, R, 2-way crossover of fed and fasting	16/0 Healthy Subjects (19-39 yrs)	Vilazodone 20mg Oral	1 day in each of 2 periods Conclusion: <i>Clear demonstration of food effect – higher exposures with food.</i>
SB-659746/004 Single dose Bioavailability	Open-label, randomized, 3- period crossover	2/12 Healthy subjects 2/13 Healthy subjects 2/11 Healthy subjects	Vilazodone 10mg micronized tablet Vilazodone 10mg non-micronized tablet Vilazodone 10mg micronized capsule	1 day in each of 3 periods Conclusion: <i>Bioavailabilities were similar among the three formulations</i>
SB-659746/013 Single dose Bioequivalence	OL, R, 2 session crossover	18/10 Healthy subjects 19/10 Healthy subjects	Vilazodone 20mg phase II capsule Vilazodone 20mg Phase III capsule	1 day in each session 1 day in each of 3 sessions Conclusion: <i>Bioequivalence criteria met.</i>
SB 659746/047 Single dose Bioequivalence	OL, R, 3 session crossover	17/9 16/12 17/13	Vilazodone 20mg Phase II capsule Vilazodone 20mg Form IV capsule Vilazodone 20mg (b) (4)	1 day in each of 3 sessions Conclusion: (b) (4) .

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		Healthy subjects		
SB-659746/050 Single dose Bioequivalence	OL, R, 2 period crossover	13/17 12/16 Healthy subjects	Vilazodone 20mg tablet Vilazodone 20mg Phase III tablet	1 day in each of 2 periods Conclusion: <i>BE criteria met</i>
(b) (4) R06-1586 Single dose Bioequivalence	DB, R, 2-way crossover	50/23 50/26 Healthy subjects	Vilazodone 40mg (b) (4) tab Vilazodone 40mg (b) (4) tab	1 day in each of 2 periods Conclusion: <i>BE criteria met (high drop out rate d/t nausea and vomiting)</i>
PGX-08-P1-05 Single dose Food Effect Bioavailability	OL, R, 3 period crossover	11/9 Healthy subjects	Vilazodone 20mg tablet	1 day in each of 3 periods Conclusion: <i>Food increased oral bioavailability</i>
PGX-08-P1-08 Single dose Bioavailability	OL, R, 2 period crossover	7/5 7/5 Healthy subjects	Vilazodone 20mg tablet Vilazodone 5 mg IV formulation	1 day in each of 2 periods Conclusion: <i>BA of oral:IV was 72%:81% per dose normalized AUC</i>
PGX-08-P1-07 PK - ADME	OL	7/0 Healthy subjects	Vilazodone 20 mg solution (oral) µCi radiation	1 day Conclusion: <i>85% radioactivity recovered, 20% urine, 65% feces</i>

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GPP-007-CLN-CP1-2003-234 Multiple dose Drug interaction	Single center, OL, single sequence, 2 session	22/23 Healthy subjects	Vilazodone 20mg capsule Nifedipine 20 mg capsule CYP cocktail: Debrisoquine Mepheytoin Flurbiprofen Caffeine Oral	10 days: 3 day on CYP drugs only, wash-out followed by 7 days of vilazodone alone, then vilazodone plus CYP drugs Conclusion: <i>20 mg dose is not likely to cause clinically significant drug interactions with 1A2, 2C9, 2C19, 2D6, 3A4</i>
GPP-007-CLN-CP1-2003-240 Single dose Drug interaction	A: single center, R, DB, 2-part crossover B: single center, R, DB, PC	A: 8/7 B: 11/11 Healthy subjects	Vilazodone 5 mg Vilazodone 10mg Ketocon. 200 mg Placebo oral	A: 1 day vilazodone; 13 days ketoconazole B: 13 days ketoconazole or 13 days placebo Conclusion: <i>A: systemic exposure increased by 45% B: systemic exposure increased 50% with ketoconazole at steady state</i>
PGX-08-P1-1 PK study renal impairment Single dose	Multicenter OL, SD	22/10 Subjects with mild/mod renal impairment and normal renal function	Vilazodone 20mg Oral tablet	1 day Conclusion: Mild or moderate renal impairment has little effect on pK after 20 mg dose
PGX-08-P1-02 PK Study Hepatic impairment Single dose	Multicenter, OL, SD	23/10 Subjects with mild/mod hepatic impairment and normal function	Vilazodone 20mg Oral tablet	1 day Mild or moderate hepatic impairment has little or no effect on the PK after a single oral dose of 20 mg

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GPP-007-CLN-CP1-1998-230 PK MD	SC, DB, R, PC, multiple ascending dose	9/0 12/0 12/0 12/0 Healthy subjects	Placebo capsule Vilazodone 10mg Vilazodone 20mg Vilazodone 40mg Oral	11 days – single dose vilazodone or placebo followed by multiple oral doses vilazodone or placebo Conclusion: The 20 mg dose can be considered max tolerated dose in healthy males.
GPP-007-CLN-CP1-1996-231 PK SD	DB, PC, R, single ascending dose (SAD) in 2 parts	6/0 6/0 6/0 6/0 6/0 Healthy subjects	1: Placebo Vilazodone 2.5mg Vilazodone 5 mg Vilazodone 10mg Vilazodone 20mg 2: Planned but not performed Placebo Vilazodone 40 mg Vilazodone 80 mg Oral	1 day A dose dependent increase in number and intensity of AEs, mainly GI.
GPP-007-CLN-CP1-1997-232 PK SD	DB, PC, R, SAD	9/0 9/0 9/0 9/0 Healthy subjects	Placebo Vilazodone 20mg Vilazodone 40mg Vilazodone 80mg Oral	1 day Conclusion: This study indicates a longer $t^{1/2}$ 20-24 hours. Dose dependent increase in hGH was observed.
GPP-007-CLN-CP1-2003-237 PK SD MD Elderly	MC, SB,R, PC, parallel group, SAD, and MAD	5/6 1/3 2/3 5/3 5/2 3/5 Healthy subjects	Placebo, elderly Placebo, young Vilazodone 5mg elderly Vilazodone 10mg elderly Vilazodone 20mg Elderly Vilazodone 20mg young	Session 1: 1 day of vilazodone or placebo Session 2: 7 days of vilazodone or placebo

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NDA 022567
Vilazodone

GPP-007-CLN-CPI-2001-255 PET Study Receptor occupancy	Single center, single dose 2 scan	2/0 4/0 Healthy subjects	Vilazodone 20mg Vilazodone 40mg	2 days (day 0 and day 7)
GPP-007-CLN-CP1-2001-241 Multiple dose REM suppression study	Single center, DB, PC, randomized, crossover	7/8 Healthy subjects	Placebo capsule Vilazodone 1 mg Vilazodone 5 mg Vilazodone 10mg oral	12 days of vilazodone, 3 days of placebo and 1 day of no dose for 4- 1week periods
PGX-08-P1-06 TQT – ECG	DB, R, PC, Moxifloxacin controlled, 3- arm, ascending dose parallel group	23/22-pbo 30/36-vil 22/23-mox Healthy subjects	Placebo Vilazodone 10mg Vilazodone 20mg Vilazodone 40mg Vilazodone 60mg Vilazodone 80mg Moxiflox. 400mg Oral	15 days of placebo or 4 days of moxifloxacin and 11 days of placebo or 15 days of vilazodone Conclusion: Vilazodone had no effect on HR, PR, QRS or cardiac morphology. Up to 80 mg showed no increase in QTcl.
GPP-007-CLN-CP1-2003-238 Multiple dose effects on ejaculation latency	Multi-center, DB, R, PC, double- dummy parallel group	22/0 21/0 23/0 Healthy subjects	Placebo to match fluoxetine and vilazodone vilazodone 20mg fluoxetine 20 mg	28 days of fluoxetine, vilazodone or placebo
PGX-08-PI-04 Ethanol effect Bioavailability	Single center, OL 2-period crossover, multiple dose	27/10 Healthy subjects	Vilazodone 40mg Ethanol 30 mL Oral	2 days Vilazodone plus ethanol followed by a ten day washout, then vilazodone alone
PGX-08-P1-03 BA Effect of gastric pH	OL 2-period crossover, multiple dose	16/21 Healthy subjects	Placebo Vilazodone 20mg Oral	8 days (1 day vilazodone; 7 days pantoprazole; the last was vilazodone + pantoprazole

GPP-007-CLP-CP1-2001-235 PD Sleep EEG	DB, R, PC, Crossover	10/0 Healthy subjects	Placebo Vilazodone 20 mg Oral	2 days Vilazodone or placebo on Days 8 and 15
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5.2 Review Strategy

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

The applicant conducted two adequate and well-controlled trials, Studies **GNSC-04-DP-02** and **CLDA-07-DP-02**, in support of this application. Additionally, the applicant submitted the results of a 52-week, uncontrolled, long-term safety study, **CLDA-07-DP-04**.

5.3 Discussion of Individual Studies/Clinical Trials

The efficacy of vilazodone as an antidepressant was evaluated by the applicant in two Phase 3 clinical efficacy trials, GNSC-04-DP-02 and CLDA-07-DP-04, which are discussed in Section 6.

The individual study results for the 5 Phase 2 studies conducted by Merck and GSK are not considered supportive of efficacy claims because (b) (4)

However, these Phase 2 studies provided information with regard to dose selection and safety.

The efficacy results of the 5 Phase 2 studies are presented in the following table, reproduced from the Biostatistics Review.

Table 5.2.1 Biostatistics Review/Confirmation Table – HAM-D

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 [†]
(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
(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)		

GPP-007-CLN-CP2-2001-244

Study EMD 68 843 [vilazodone]-009

This was a randomized, double-blind, multicenter (13 U.S. sites) parallel group, phase II study comparing vilazodone, titrated over a two week period to a maximum tolerated dose of 20, 40, 60, 80, or 100 mg/day to placebo and the active comparator, fluoxetine 20 mg/day, in adult patients meeting DSM-IV criteria for Major Depressive Disorder (single or recurrent episode). Patients completed a 3 to 7-day, single-blind, placebo period followed by a double-blind treatment period of approximately 8 weeks. All treatments were to be administered orally, once daily. The protocol instructed subjects to take the medication with food.

The study was conducted in men and women who met DSM-IV criteria for Major Depressive Disorder (MDD), single or recurrent episode. Patients were to have a HAM-D total score, 17-item assessment of ≥ 20 at Screening and Baseline and could not have a decrease $>20\%$ in the HAM-D assessment from Screening to Baseline.

All patients were to take part in each of the three study phases:

Phase 1

Patients were screened and if qualified, were enrolled in the study. Upon enrollment, patients started the first phase of the study, a 7 day, single-blind, washout in which they received an oral placebo dose once daily.

Phase 2

A two-week, double-blind, dose-titration period in which patients assigned to EMD 68 843 received 10 mg on Day 1. Thereafter, if the current dose was tolerated, the dose was to be increased from 20 mg to 100 mg once daily (over approximately 3 days per dose level). Patients assigned to fluoxetine or placebo received 20 mg of fluoxetine or placebo, respectively, once daily throughout the titration period.

Phase 3

The third phase consisted of a six-week, double-blind, dose-maintenance period. By Day 15, the investigator was to establish a maximum dose level for each patient based on tolerability. Patients in the EMD group treatment received doses ranging from 20 mg to 100 mg once daily, patients in the fluoxetine or placebo treatments received 20 mg of fluoxetine or placebo until Visit 8 (Day 56).

Efficacy Variables

The efficacy measures included the Hamilton Rating Scale for Depression (HAM-D-17), the Montgomery-Asberg Depression Rating Scale (MADRS) total score, HAM-D Depressed Mood score (item 1 of HAM-D), CGI-Severity, and CGI-Improvement.

The primary efficacy variable was the HAM-D-17 total score, which can range from 0 to 50 (based on 0-4 or 0-2 scale for 17 items assessing depressive symptoms). Secondary efficacy variables included the HAM-D-1 Depressed Mood score, MADRS (which can range from 0 to 60 based on ten items assessing depressive symptoms). The review focused on the intent-to-treat sample, defined as all patients who were randomized and received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one follow-up time.

The primary efficacy objective of this study was to reject the null hypothesis that EMD has equal efficacy to placebo in the ITT population using the HAM-D-17 total score change from Baseline to Endpoint (LOCF). The main effects analysis of variance (ANOVA) model with treatment and center was to be used and a full model, including the treatment by centre interaction, was to be used for exploratory analysis of the interaction. If ANOVA assumptions were violated, additional appropriate non-parametric statistical analysis was to be performed. The estimate of treatment effect was to be presented as a two-sided 95% confidence interval for the contrast comparing vilazodone with placebo.

Secondary measures were also employed including: CGI and MADRS. Baseline severity of illness was assessed using CGI-S (a 1-7 ranking of severity of illness where 1=normal, not ill at all and 7=among the most extremely ill). Global improvement throughout the study was assessed with CGI-I.

Study Results

In total, 420 patients were enrolled, 89% entered the single-blind placebo period and 289/420 (69%) were randomized. Of the randomized patients 99% were evaluable for safety, 93% participated in at least one efficacy evaluation and were classified as ITT. Although the number of patients randomized to the three treatment groups was similar, the number of patients in the per-protocol population was lower in the vilazodone group (n=34) than in the placebo group (n=58). For placebo, the per-protocol number was 58.

Table 5.2.2 Study 68843-009 Safety Population

MAIN REASONS	Number of patients (safety population)					
	Placebo N= 97		Fluoxetine N= 95		EMD 68 843 N= 95	
	n	%	n	%	n	%
Adverse events	5	5.2	14	14.7	15	15.8
Insufficient efficacy	6	6.2	3	3.2	2	2.1
Withdrawal of consent	6	6.2	9	9.5	10	10.5
Failure to attend	4	4.1	8	8.4	8	8.4
Other reason	12	12.4	5	5.3	14	14.7
Total Discontinued	33	34.0	39	41.1	49	51.6

Source: CSR EMD 68843-009

The demographic characteristics among the three treatment groups were similar, although the vilazodone group tended to be older than the placebo group. The mean Baseline HAM-D-17 score for the safety population was approximately 24 for each of the three treatment groups. The use of pain relievers as concomitant medications was prevalent in all groups. Fewer subjects in the vilazodone group were considered to be compliant with dosing, specifically, 73% placebo, 71% fluoxetine, and 57% vilazodone.

Efficacy Findings

The applicant's report indicates that the mean improvement in the HAM-D-17 total score from Baseline to Endpoint was not different for the vilazodone treatment group compared with the placebo group. A large placebo effect was observed.

Table 5.2.3 Change from Baseline for Primary and Secondary Efficacy Measures

Table 5.2.3: Efficacy score changes from Baseline to Endpoint (ITT population)

ASSESSMENT	Baseline and change from Baseline						EMD 68 843 vs. placebo p-value	EMD 68 843 vs. fluoxetine p-value
	Placebo N= 95		Fluoxetine N= 89		EMD 68 843 N= 86			
	Mean	(SD)	Mean	(SD)	Mean	(SD)		
HAM-D total								
Baseline	24.0	(3.1)	24.4	(3.2)	23.4	(2.9)		
Change at Endpoint	-9.3	(7.8)	-9.1	(7.4)	-8.9	(7.7)	0.4885	0.7042
HAM-D depressed mood								
Baseline	3.0	(0.5)	3.1	(0.6)	2.9	(0.6)		
Change at Endpoint	-1.2	(1.1)	-1.4	(1.1)	-1.3	(1.2)	0.7041	0.5241
MADRS								
Baseline	30.0	(3.8)	30.8	(4.2)	30.2	(4.0)		
Change at Endpoint	-10.4	(9.8)	-11.8	(10.1)	-12.7	(9.9)	0.1745	0.6052
CGI-Severity								
Baseline	4.3	(0.6)	4.4	(0.6)	4.3	(0.6)		
Change at Endpoint	-1.1	(1.4)	-1.2	(1.3)	-1.3	(1.2)	0.4184	0.9121
CGI - Improvement Endpoint	2.8	(1.3)	2.6	(1.2)	2.7	(1.2)	0.5754	0.8713
PGI - Improvement Endpoint	3.3	(1.4)	3.0	(1.4)	2.8	(1.3)	0.0251	0.3339
MEL								
Baseline	12.3	(2.9)	12.2	(3.1)	12.5	(2.6)		
Change at Endpoint	-3.4	(4.8)	-4.7	(4.6)	-5.0	(4.2)	0.0405	0.6970

Data from end-of-text [Table 9.2.7](#).
For HAM-D (total and mood), MADRS, CGI-S and MEL scores, more improvement from Baseline corresponds to a larger negative value. For CGI-I and PGI scores more improvement from Baseline corresponds to a smaller positive value.

Source: CSR EMD 68843-009

The applicant reports a dose-response comparison was not appropriate because during the dose-maintenance period, most (52/66, 78%) patients received 80-100 mg/day.

Discussion

This first phase II study was to establish the upper limit of the dose range of the compound in terms of tolerability, and if efficacy at such a dose was observed. The study was not designed to provide dose-response information; there is evidence of intolerable adverse events at the higher doses.

The impression is that this trial did not demonstrate a difference among the three treatment groups. The mean change in the primary efficacy variable was greater for placebo than for the active comparator and vilazodone. The active comparator group did not demonstrate statistical superiority to placebo; therefore, it appears that this study lacks the sensitivity to detect a drug effect and conclusions of effectiveness cannot be drawn from this study.

GPP-0070-CLN-CP2-2001-245

EMD 68 843-010

A Double-Blind, Randomized, Multicenter, Parallel Design Study to Evaluate the Efficacy and Safety of **Three Dose Ranges of EMD 68 843 [vilazodone] in Comparison with Placebo and Fluoxetine in Outpatients with Major Depressive Disorder (MDD)**

Principal Investigator: James Claghorn, MD
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Primary Objective

To evaluate the therapeutic efficacy and safety of EMD 68 843, at three dose ranges compared to placebo and fluoxetine, 20 mg, in patients with MDD, as measured by the Hamilton Depression Rating Scale, first 17 items (HAM-D-17).

Subjects

Male or female outpatients between the ages of 18 and 70 years with a primary diagnosis of MDD, single or recurrent episode from 21 U.S. centers were eligible to participate.

An expected enrollment of 625 patients was thought to result in a sufficient number of patients in the double-blind treatment phase to achieve 80 patients per treatment arm.

Key Inclusion Criteria

Male or female outpatients 18 to 70 years of age with a primary diagnosis of MDD
No other Axis I or II disorders
Females with negative pregnancy test and use of double-barrier contraception
HAM-D-17 ≥ 20 at Screening and Baseline; $< 20\%$ decrease from Screening to Baseline
MADRS ≥ 25 at Baseline
No ECG abnormalities

Key Exclusion Criteria

Unresponsive to two previous courses of antidepressant treatment
Actively suicidal or likely to require hospitalization during the trial
Substance abuse within six months
Patients requiring other psychotropic medication
Patients with history of ECT or psychosurgery

Patients with history of clinically significant cardiac, renal, neurologic, cerebrovascular, metabolic, or pulmonary disease
Pregnant or lactating females

Concomitant medication

Patients taking fluoxetine were to be drug free for 4 weeks prior to enrollment. A drug free period of 2 weeks was required for patients receiving any of the following classes of drugs: antidepressant drugs including SSRI (except fluoxetine), tricyclic, tetracyclic, MAO inhibitor, bupropion, and trazadone; pindolol, lithium, anticonvulsants, benzodiazepines, antipsychotics, methylphenidate or other stimulants, barbiturates, steroids; buspirone.

Study Design

EMD 68 843-010 was a double-blind, randomized, multicenter (21 U. S. sites), parallel-group phase II study with a placebo and active control group. The study was conducted in male and female outpatients, aged 18-70 years. Patients meeting the DSM IV criteria for MDD, single or recurrent and protocol inclusion criteria completed a 7 day single-blind placebo period followed by an 8 week treatment period. The study was comprised of five treatment arms, three dose groups (10-20 mg/day, 40-60 mg/day, 80-100 mg/day) of EMD, placebo, and a 20 mg fluoxetine control group. During the double-blind treatment phase, efficacy and safety was evaluated at Visits 1, 2, 3, 4, 5, 6, 7, and 8. A post-study safety visit occurred on Day 63.

The primary efficacy variable was the change from Baseline to Endpoint in the 17-item HAMD-D assessment for the low and medium dose EMD compared to placebo.

The secondary efficacy variables included the change from Baseline to Endpoint in HAM-D Depressed Mood score, MADRS total score, CGI-S, and CGI-I, among others. Secondary efficacy variables also included response to treatment using HAM-D total (>50% decrease), MADRS (>50% decrease) and CGI-S (≥2 points decrease), and remission rates (HAM-D total ≤7 points).

Patients completed a 7-day, single blind placebo period followed by a double-blind treatment period of 8 weeks. There were five treatment arms: EMD 10-20 mg/day (low dose), EMD 40-60 mg/day (medium dose), EMD 80-100 mg/day (high dose), fluoxetine 20 mg/day, and placebo. All treatments were administered orally (it is not indicated if the patients are fed or fasted). Efficacy and safety were evaluated at Screening, Baseline, Day 7, Day 14, Day 21, Day 28, Day 42, and Day 56 with a post-study safety visit on Day 63.

Each patient participated in at least 3 study phases. During the first visit patients were screened and, if qualified, enrolled in the study.

Phase One was a single-blind, washout period of 7 days in which the patients received placebo, once daily. At the end of this phase, Baseline values were recorded and the patients were randomized to one of the five treatment arms.

Phase Two was a 14 day titration according to assigned treatment arm as follows:

Low Dose – EMD 10-20 mg:

Received 10 mg/day for 14 days – if no improvement¹ at Day 14, the dose was increased to 20 mg/day on Day 15

Medium Dose – EMD 40-60 mg:

Received 10 mg on Day 1, 20 mg/day on Days 2 and 3, 40 mg/day for Days 4-14; if no clinical improvement was seen at Day 14, the dose was to be increased to 60 mg/day on Day 15

High Dose – EMD 80-100 mg:

Received 10 mg on Day 1, 20 mg/day on Days 2 and 3, 40 mg/day from Days 4-6 and 80 mg/day for Days 7-14; if no clinical improvement was seen at Day 14, the dose was to be increased to 100 mg/day on Day 15

Fluoxetine – 20 mg

On Day 1 and all subsequent days the patients received a matching oral treatment of fluoxetine 20 mg

Placebo

On Day 1 and all subsequent days the patients received a matching oral placebo treatment

Phase Three dose levels of EMD administered on Day 15 were maintained throughout the third phase of the study (Days 15-56) unless the tolerance level was unacceptable. If at any time the tolerability was not acceptable, patients could revert to the lowest dose within the respective range. The total study duration for each patient was a maximum of 10 weeks. Tolerability of the drug was based on subjective complaints and the clinical assessment of the investigator.

¹ According to IND protocol amendment 1: “Clinical improvement will be defined as follows: >50% decrease in HAM-D score, CGI improvement of +2 or minimal symptoms, and clinical judgment of the investigator.

Study Results

In total, 960 patients were enrolled, 517 (54%) were randomized. Of the randomized patients 485 (94%) participated in at least one efficacy evaluation and were evaluated as the ITT (intent-to-treat) population. Similar numbers of patients were randomized among the five treatment groups. Higher numbers of patient withdrawals occurred in all vilazodone groups as compared to placebo and fluoxetine groups. Most of the withdrawals were due to adverse events.

The applicant did not provide a table of the demographic characteristics of the ITT population. In the safety population, the demographic characteristics were similar for all treatment groups, most of the patients were Caucasian, female and between the ages of 31-60 years. The median Baseline HAM-D-17 score was 23 for each treatment group, with the means ranging from 23.4 – 23.9. Medical histories, psychiatric histories and concomitant medications were similar for each group. Treatment compliance was approximately 80% for the placebo, fluoxetine, and low-dose groups and progressively declined in the medium and high dose groups.

Efficacy Findings

The mean improvement in the HAM-D total score from Baseline to Endpoint was not different for the low and medium vilazodone treatment groups compared with the placebo treatment group. A large placebo effect was observed in the change from Baseline to Endpoint (see table 5.2.1).

Protocol amendment 3 of June 11, 1999 states: “remove the 80 – 100 mg EMD 68843 dose group from the confirmatory statistical analysis, which made the confirmatory analysis be between the 10-20 mg and 40-60 mg dose groups and placebo only”.

According to the applicant, a large placebo effect was observed for most efficacy assessments. Fluoxetine, at a recommended dose, failed to show superiority compared with placebo.

Discussion

The impression is that this is a ‘failed study’ (b) (4)



GPP-007-CLN-CP2-2003-246

SB-659746-A/003

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy and Safety of SB-659746-A (10 and 20 mg/day) and Citalopram (20 mg/day) in patients with Major Depressive Disorder

Sponsor: GlaxoSmithKline
Compound: SB-659746-A – vilazodone
Initiation 08Oct2001
Completion 01Nov2002

Primary Objective

To evaluate the antidepressant efficacy of vilazodone, 10 mg/day and 20 mg/day compared with placebo in outpatients with Major Depressive Disorder (MDD). The primary efficacy measure was the change from Baseline to Week 8, last observation carried forward (LOCF) endpoint in the HAM-D-17 total score.

Secondary Objectives

To assess the safety and tolerability of vilazodone
To provide preliminary data on the time to onset of therapeutic effect of vilazodone
To provide preliminary data on the anxiolytic effect of vilazodone

Subjects

Outpatients from 39 U. S. Centers were eligible for enrollment in the trial. Randomization of 508 evaluable subjects was thought to be sufficient to provide 127 patients in each of the 4 treatment arms.

Key Inclusion Criteria

- Male or female outpatients between 18-65 years of age with MDD
- MDE of less than one year's duration
- HAM-D-17 ≥ 20 at Screening and Baseline
- Females of child bearing potential with negative pregnancy test and using double barrier contraceptive measures

Key Exclusion Criteria

- HAM-D-17 decreased by $\geq 25\%$ between Screening and Baseline
- Co-morbid Axis I diagnosis
- Actively suicidal or likely to require hospitalization during the trial
- ECT within six months of Screening
- Patients requiring other psychotropic medications
- Patients with clinically significant cardiac, renal, neurologic, cerebrovascular, metabolic or pulmonary disease

- Pregnant or lactating females
- Patients previously unresponsive to SSRIs

Prohibited Medications

Insulin treatment was prohibited, although oral hypoglycemic agents were allowed. Migraine medications with a serotonergic mechanism of action were prohibited. Psychotropic medications were prohibited.

Study Design

This was an 8-week, 4-arm, parallel group, placebo and active comparator controlled, fixed dose study. The four treatment groups were: vilazodone 10 mg/day, vilazodone 20 mg/day, citalopram 20 mg/day, and placebo.

Screening – Visit 1

Screening assessments were performed and patients were provided with one bottle of single-blind placebo for the 7-day placebo washout/run-in period.

Baseline – Visit 2

Following the one week single-blind placebo phase, baseline evaluations were conducted to determine eligibility to enter the 8-week double-blind treatment phase. Those eligible were randomized to one of the 4 treatment arms (1:1:1:1).

The patients were instructed to take the study medication once daily, in the morning, with food.

Patients randomized to receive the 20 mg dose of vilazodone received 10 mg/day for the first 7 days of double-blind treatment period, after which the dose was increased to 20 mg/day.

Double-Blind Treatment – Visits 3-8 (Weeks 1-8)

Treatment phase visits were scheduled at the end of Weeks 1, 2, 4, 6, and 8. A mandatory Follow Up was scheduled for 14 days after the last dose of double-blind study medication. A 28 day follow up was scheduled if there were any ongoing adverse events at the 14 day follow up assessment. If a patient completed the 28 day Follow-Up Visit, the maximum amount of time participated in the study was 13 weeks.

Efficacy Variables

Assessments included the HAM-D-17 as the primary efficacy variable; several measures, including, Hospital Anxiety and Depression Scale (HAD), MADRS, CGI, Sheehan Disability Scale (SDS) were listed as secondary endpoints although none were regarded as 'key secondary endpoints'.

Study Results

Patients in the intent to treat (ITT) dataset were between 18 and 64 years old, with a mean age of 38 years. Seventy-nine (79) percent were Caucasian, ten percent were African-American, one percent were classified as Oriental and nine percent were classified as other. Sixty (60) percent were female. The treatment groups were comparable at baseline on the demographic and key efficacy variables.

A total of 511 patients were randomized, 3 subjects at center 022 were excluded from the safety and efficacy tables on the recommendation of GSK Worldwide Regulatory Compliance. The remaining subjects were randomized, of which 68% completed the 8-week treatment phase. The ITT population consisted of 96% of those randomized.

Table 5.2.4 HAM-D-17 Total Score Change from Baseline
HAM-D-17 Total Score

Group	Baseline	LOCF Wk 8 ¹	Difference	Difference ² (adjusted LSM)	P-value
Placebo N=128	23.3	13.1	10.2		
Vilazodone 10 N=119	23.8	13.0	10.8	-0.5	0.585
Vilazodone 20 N=121	23.7	12.6	11.1	-0.8	0.407
Citalopram 20 N=115	23.1	12.3	10.8	-0.7	0.511

¹primary analysis; ²difference in adjusted least squares means

Source: CSR SB659746-A003

Discussion

The impression is that this is a 'failed study'.

(b) (4)

GPP-007-CLN-CP2-2003-247

SB-659746-014

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Flexible-dose Study Evaluating the Efficacy and Safety of SB-659746-A in Patients with Major Depressive Disorder

Sponsor: GlaxoSmithKline
Compound: SB-659746-A – **vilazodone**
Initiation: 05-Nov-2001
Completion: 08-Nov-2002

Primary Objective

- To evaluate the antidepressant efficacy of flexible doses of vilazodone (5-20 mg/day) compared with placebo in outpatients with Major Depressive Disorder (MDD)

Secondary Objectives

- To assess the safety and tolerability of vilazodone
- To provide preliminary data on the anxiolytic effect of vilazodone

Subjects

Outpatients from 27 centers in the U. S. and Canada with a diagnosis of MDD were eligible for enrollment. The target for randomization was 216 subjects to yield 108 patients in each treatment group.

Key Inclusion Criteria

- Male or female outpatients, 18-65 years of age with MDD
- MDD of less than one year's duration
- HAM-D-17 ≥ 20 at Screening and Baseline
- Females of child bearing potential with negative pregnancy test and using double barrier contraceptive measures

Key Exclusion Criteria

- HAM-D-17 decreased by $\geq 25\%$ between Screening and Baseline
- Co-morbid Axis I diagnosis
- Actively suicidal or likely to require hospitalization during the trial
- ECT within 6 months of Screening
- Patients requiring other psychotropic medications
- Patients with clinically significant cardiac, renal, neurologic, cerebrovascular, metabolic or pulmonary disease
- Pregnant or lactating females
- Patients previously unresponsive to SSRIs

Prohibited Medications

Insulin treatment was prohibited, although oral agents for the treatment of diabetes were allowed. Migraine medications with serotonergic mechanism of action were prohibited as were psychotropic medications.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of flexible doses of vilazodone (5 to 20 mg/day).

Screening – Visit 1

Approximately 7 days prior to the Baseline Visit Informed Consent was obtained and screening assessments were performed to determine eligibility to be enrolled in the study. If eligible, patients were provided with one bottle of single-blind placebo for the 7-day placebo washout/run-in period.

Baseline – Visit 2

Following the one-week single-blind placebo phase, baseline evaluations were conducted to determine eligibility to enter the 8-week double-blind treatment phase. The subjects meeting all inclusion and no exclusion criteria were randomized 1:1 to either vilazodone or placebo.

The patients were instructed to take the study medication once daily, in the morning, with food.

Double-Blind Treatment – Visits 3-8 (Weeks 1-8)

All patients in the vilazodone arm received 5mg for the first week of the treatment phase. The dose could then be increased to 10 mg followed by 20 mg at the discretion of the investigator, based on clinical response and tolerability. Dose levels could only be increased by one level at 7 day intervals. The highest dose level obtainable during the treatment phase was: Week 1 – 5 mg (Level 1), Week 2 – 10 mg (Level 2), Week 3 – 20 mg (Level 3).

A dose level reduction during the treatment phase was permitted in the event of an intolerable adverse event (AE); however, this was permitted only once during the course of the study.

Treatment phase visits were scheduled at the end of Weeks 1, 2, 3, 4, 6, and 8. A 14-Day Follow-Up Visit occurred at the end of Week 8 or upon early termination. A 28-Day Follow-Up visit was scheduled if there were ongoing AEs.

If a patient completed the 28-Day Follow-Up visit, the maximum amount of time in study was 13 weeks.

Efficacy Variables

The primary efficacy variable was the change from Baseline to Week 8, LOCF, in the HAM-D-17 total score, comparing vilazodone to placebo. Several secondary efficacy variables were employed, although none were pre-specified as key secondary efficacy

variables. The secondary efficacy variables were: HAM-D-1, HAM-D anxiety item scores, CGI-S and CGI-I, SDS, and MADRS.

Study Results

Patients in the intent to treat (ITT) dataset were between 18 and 64 years old, with a mean age of 34 years. Eighty-four (84) percent were Caucasian, eight percent were African-American, two percent were classified as Oriental and seven percent were classified as other. Sixty-two (62) percent were female. The treatment groups were comparable at baseline on the demographic and key efficacy variables.

A total of 228 patients were randomized, 113 to the vilazodone group and 115 to the placebo group. Of the randomized population, 161 (71%) subjects completed the 8-week treatment phase and 67 (29%) patients withdrew early. The ITT population consisted of 96% of those randomized. The number of patients in the ITT population was evenly distributed between the two treatment groups. The following table taken from the applicant’s submission indicates study completers in the ITT population.

Table 5.2.5 Study Completers - 659746-014

Reason for Study Conclusion	Treatment Group n (%)		
	Vilazodone (N = 109)	Placebo (N = 111)	Total (N = 220)
Completed Study ¹	75 (68.8)	86 (77.5)	161 (73.2)
Total Number of Withdrawals	34 (31.2)	25 (22.5)	59 (26.8)
Adverse Event ²	10 (9.2)	2 (1.8)	12 (5.5)
Insufficient Therapeutic Effect	5 (4.6)	9 (8.1)	14 (6.4)
Protocol Deviation (Incl. Non-Compliance)	3 (2.8)	2 (1.8)	5 (2.3)
Lost to Follow-up	9 (8.3)	5 (4.5)	14 (6.4)
Other ³	7 (6.4)	7 (6.3)	14 (6.4)

Data Source: [Table 12.7, Section 12](#)

1. A subject was considered to have completed if they remained in the study up to and including Visit 8 (week 8).
2. Including death as an outcome
3. Including unknown and non-study-related personal reasons

Source: CSR 659746-014

Discussion

The impression is that this is a negative study, [REDACTED] (b) (4)

[REDACTED] There was no active control to assess the sensitivity of this study to detect a drug effect.

According to the applicant report, the adjusted mean difference between vilazodone and placebo HAM-D-17 at Week 8 LOCF was -1.0 point (p=0.272). Therefore, “there was no statistically significant evidence indicating a difference in the change from baseline to Week 8 LOCF endpoint in HAM-D total score between placebo and vilazodone.”

Of note, the study was not designed to provide dose-response information and the statistical information provided in this report did not provide a summary analysis on the basis of vilazodone dose.

GPP-007-CLN-CP2-2003-248

SB-659746-A/002

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating Efficacy and Safety of Three Doses of Vilazodone (5 mg, 10 mg, and 20 mg) in Patients with Major Depressive Disorder

Sponsor: GlaxoSmithKline
Compound: SB-659746-A – **vilazodone**
Initiation: 24-Sep-2001
Completion: 30-Aug-2002

Primary Objective

- To evaluate the antidepressant efficacy of three doses of vilazodone compared to placebo in outpatients with Major Depressive Disorder (MDD)

Secondary Objectives

- To assess the safety and tolerability of vilazodone
- To provide preliminary data on the time to onset of therapeutic effect
- To provide preliminary data on the anxiolytic effect of vilazodone

Subjects

A target of 552 outpatients with a diagnosis of MDD from 39 centers in the United States was proposed to yield 138 patients in each treatment group.

Key Inclusion Criteria

- Male or female outpatients, 18-65 years of age with MDD
- MDD of less than one year's duration
- HAM-D-17 ≥ 20 at Screening and Baseline
- HAM-D-1 (depressed mood) ≥ 2 at Screening and Baseline

Key Exclusion Criteria

- HAM-D-17 decreased by $\geq 25\%$ between Screening and Baseline
- Co-morbid Axis I diagnosis
- Actively suicidal or likely to require hospitalization during the trial
- ECT within 6 months of Screening
- Patients requiring other psychotropic medications
- Patients with clinically significant cardiac, renal, neurologic, cerebrovascular, metabolic or pulmonary disease
- Pregnant or lactating females (females of childbearing potential must have negative pregnancy test and use acceptable contraception)
- Patients previously unresponsive to SSRIs

Prohibited Medications

- Insulin (oral agents acceptable)
- Migraine medication with serotonergic mechanism of action
- Psychotropic medications

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of three doses of vilazodone (5, 10, and 20 mg/day) compared with placebo.

Screening – Visit 1

One week prior to the Baseline Visit, informed consent was documented and screening assessments were performed to determine eligibility for the one week, single-blind placebo run-in phase. If eligible, the patient was registered, the placebo was dispensed, and the Baseline Visit was scheduled for one week later.

Baseline – Visit 2

Baseline evaluations were conducted to determine eligibility to enter the 8-week, double-blind treatment phase. The subjects meeting all inclusion and no exclusion criteria were randomized to one of 4 treatment arms: vilazodone 5 mg, 10 mg, 20 mg, or placebo. They were instructed to take the study medication once daily in the morning with food. During the run-in phase and throughout the treatment phase no other psychotropic medications were allowed.

Double-Blind Treatment – Visits 3-8 (Weeks 1-8)

Patients randomized to the 20 mg dose received 10 mg/day for the first 7 days of the double-blind treatment and then had the dose increased to 20 mg/day, for other treatment arms, the starting dose was the final dose. Treatment phase visits were scheduled at the end of Week 1, 2, 3, 4, 6, and 8. A mandatory 14-Day Follow-Up Visit occurred 2 weeks after the last dose of study medication at the end of Week 8 or Early Termination. A 28-day Follow-Up Visit was also scheduled if there were any ongoing adverse events at the 14-Day Follow-Up Visit.

If a patient completed the 28 day Follow-Up Visit, the maximum amount of time participated in the study was 13 weeks.

Efficacy Variables

The primary efficacy variable was the change from Baseline to Week 8, LOCF, in the HAM-D-17 total score. The primary comparisons of interest were vilazodone 5, 10, and 20 mg/day compared to placebo.

Secondary efficacy variables included comparisons of each dose of vilazodone to placebo at Week 8 OC and LOCF for several variables, none of which were considered to be 'key secondary efficacy variables'. The list of variables included the following, among others: HAM-D-1 (depressed mood), HAM-D anxiety items, MADRS, CGI-I and CGI-S and response and remission assessments.

Study Results

Patients in the intent to treat (ITT) dataset were between 18 and 64 years old, with a mean age of 34 years. Eighty-four (84) percent were Caucasian, eight (8) percent were African-American, two (2) percent were classified as Oriental and seven (7) percent were classified as other. Sixty-two (62) percent were female. The treatment groups were comparable at baseline on the demographic and key efficacy variables.

Table 5.2.6 Study Completers - 659746 A002

Table 3 Number (%) of Subjects Who Completed the Study or were Withdrawn by Reason for Withdrawal (ITT Population)

Reason for Study Conclusion	n (%)				Total (N = 533)
	SB659746-A 20 mg (N = 132)	SB659746-A 10 mg (N = 133)	SB659746-A 5 mg (N = 140)	Placebo (N = 128)	
Completed Study ¹	90 (68.2)	105 (78.9)	112 (80.0)	97 (75.8)	404 (75.8)
Total Number of Withdrawals	42 (31.8)	28 (21.1)	28 (20.0)	31 (24.2)	129 (24.2)
Adverse Event	4 (3.0)	4 (3.0)	5 (3.6)	2 (1.6)	15 (2.8)
Insufficient Therapeutic Effect	7 (5.3)	2 (1.5)	7 (5.0)	11 (8.6)	27 (5.1)
Protocol Deviation (Incl. Non-Compliance)	8 (6.1)	5 (3.8)	4 (2.9)	1 (0.8)	18 (3.4)
Lost to Follow-up	12 (9.1)	11 (8.3)	9 (6.4)	8 (6.3)	40 (7.5)
Other ²	11 (8.3)	6 (4.5)	3 (2.1)	9 (7.0)	29 (5.4)

Data Source: [Table 12.7, Section 12](#)

1. A subject was considered to have completed if they remained in the study up to and including Visit 8 (week 8).
2. Including unknown and non-study-related personal reasons.

Source: CSR 659746 A002

A total of 555 patients were randomized, six (6) patients at center 013 were excluded from the safety and efficacy tables upon recommendation of GSK Worldwide Regulatory Compliance. Of the remaining 549 patients in the randomized population, 404 (74%) patients completed the 8-week treatment phase and 145 (26%) patients withdrew early from the treatment phase. The ITT population consisted of 97% of those randomized. The number of patients in the ITT population was evenly distributed among the four treatment groups.

Discussion

The impression is that this is a negative study, (b) (4)

There was no active control group to assess the sensitivity of this study to detect a drug effect.

6 Review of Efficacy

Efficacy Summary

The Division met with the Applicant on June 17, 2009 when it was agreed that data from the five Phase II studies conducted under the sponsorship of Merck and GSK and submitted previously to FDA in submissions to IND 54613 are not considered to be supportive for the proposed dose and indication. The Division agreed that the clinical summary of efficacy should include a brief summary of the primary results for these (Phase II) studies and the results are not required in the side-by-side efficacy evaluations.

The efficacy data relevant to the indication of MDD arise from 2 randomized, double-blind, placebo-controlled Phase 3 studies: GNSC-04-DP-02 (**04**) and CLDA-07-DP-2 (**07**). Studies 04 and 07 were conducted by PGxHealth at the proposed dose of 40 mg daily, were adequate, well-controlled, and had acceptable endpoints. This clinical review will summarize the study design and efficacy findings from each of these studies.

Vilazodone at 40 mg taken once daily with food demonstrated efficacy for the treatment of MDD, based on the change from baseline at Week 8, LOCF. Treatment margins (difference of vilazodone – placebo) for LSM change from Baseline to Week 8, LOCF were -3.2 and -2.5 for the primary efficacy endpoint in Studies 04 and 07, respectively. In both trials, vilazodone demonstrated statistically significant improvements compared to the placebo group.

6.1 Indication – Major Depressive Disorder

Pivotal Study #1 **GNSC-04-DP-02**

6.1.1 Methods

Study **GNSC-04-DP-02** was a multicenter, 8 week, randomized, double-blind, placebo-controlled, flexible dose study in adults aged 18-65 years with a DSM-IV-TR diagnosis of Major Depressive Disorder (MDD). This clinical trial took place at 18 sites, all within the United States. The study was initiated February 22, 2006 and completed May 23, 2007.

Primary Objective

The primary objective was to compare the efficacy of vilazodone and placebo in the treatment of MDD as measured by the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) after 8 weeks of treatment. The MADRS is accepted by the Agency as a standard measure for antidepressant clinical trials.

Secondary Objectives

The applicant identified three secondary objectives:

- To assess the safety profile of vilazodone compared with placebo
- To assess the efficacy of vilazodone compared with placebo by using secondary measures of depression, anxiety, and overall clinical impression
- To discover genetic markers associated with treatment response and/or AEs in patients taking vilazodone.

The Arizona Sexual Experiences Scale (ASEX) was employed to evaluate sexual function, because of the known sexual side effects associated with SSRIs.

The Hamilton Rating Scale for Anxiety (HAM-A) was used to measure the severity of anxiety symptoms.

Study Design

This was a randomized, double-blind, placebo-controlled, flexible-dose, multicenter study of treatment with vilazodone in adults with MDD. Before undergoing any study procedures, written, informed consent was obtained from each patient. A washout period of 2 to 12 weeks (depending on the drug being washed out) occurred if the patient was taking another antidepressant or excluded medication. After the washout, screening assessments were performed and the subjects were evaluated according to inclusion and exclusion criteria.

At baseline, the subjects were randomly assigned (1:1 ratio) to receive either vilazodone or matching placebo. The initial dose of vilazodone or matching placebo was 10 mg/day for the first 7 days (Days 1-7), 20 mg/day for the next 7 days (Days 8-14), and 40 mg/day for the remaining 42 days (Days 15-56) of the trial. Two flexible dose options were available to the Investigator if the subject experienced an intolerable AE:

- If the AE occurred during the dose titration period at the 20 mg/day dose, the patient could remain at 20 mg/day until Week 8 (Visit 5) with the option of increasing the dose to 40 mg/day if the AE/s resolved
- If the subject had intolerable AE/s during or after starting the 40 mg/day dose at Day 15, the dose could be reduced to 20 mg/day at any time. If placed on the lower dose, the subject remained on that dose throughout the study

During the 8-week (including the 2-week titration period) treatment period, the subjects received a maximum dosage of 40 mg/day vilazodone or matching placebo in oral tablet form. The assigned treatment was taken with food each morning. The double-blind treatment period was 8 weeks, during which the subjects returned to the study site for efficacy and safety assessments at the end of Weeks 1, 2, 4, 6, and 8.

Table 6.1.1 Study Schedule of Visits

Phase	Pre-Randomized		Double-Blind Treatment				
	Screen	Baseline	Titration Phase		Treatment Phase		
Treatment			10 mg	20 mg	40 mg	40 mg	40 mg
Visit	1	2	3	4	5	6	7
Week	-1	0	1	2	4	6	8 or ET
Day ±	-1	0	7	14	28	42	56

Key Inclusion Criteria:

- Male or female 18-65 years of age
- MDD single or recurrent (DSM-IV-TR)
- HAM-D ≥22 on the first 17 items

Key Exclusion Criteria:

- Serious psychiatric co-morbidity (GAD, social phobia, simple phobia permitted)
- History of inadequate response to 2 consecutive antidepressants
- Serious medical co-morbidity
- Pregnant, lactating or planning to become pregnant females

Results

6.1.2 Demographics

Overall, 561 patients were screened for entry into the study, 410 patients were randomized to either vilazodone or placebo. All patients began the study with a two-week titration; the doses for the final 6 weeks of the study were as follows:

Table 6.1.2 Dose Titration Pattern-Study Completers

Dose at Visit 2/3/4/5/6	Vilazodone N=152 (%)	Placebo N=154 (%)	Total N=360 (%)
10/20/40/40/40	139 (91.4)	149 (96.8)	288 (94.1)
10/20/20/20/20	5 (3.3)	1 (0.6)	6 (2.0)
10/20/20/40/40	3 (2.0)	2 (1.3)	5 (1.6)
10/20/40/20/20	3 (2.0)	1 (0.6)	4 (0.3)
10/20/40/40/20	1 (0.7)	0 (0.0)	1 (0.3)
10/20/40/40/missing	1 (0.7)	1 (0.6)	2 (0.7)

Source: CSR GNCS-04-DP-02 Table 14.3.6.22 p.609

Comment: Some patients were not able to tolerate the 40 mg dose and were maintained at 20 mg for the 6 week post titration, double-blind treatment period. In

discussion with Dr. Dinh, this did not seem to have an effect, as the point estimate is still in favor of the drug over placebo.

The majority of patients in this study were white, females with a mean age of 40 years. Both treatment groups included a greater number of females than males. In both treatment groups, the majority of patients were White; however, the vilazodone group had a higher percentage of White patients.

In both groups, the second most frequent race was Black/African American; however, the percentage of Black patients in the vilazodone groups was approximately half that of the placebo group.

White and Black patients together composed 98% of the patients in the vilazodone group and 95% of the patients in the placebo group. Each of the groups had the same small number of Asian patients.

The remaining race categories (American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, and Other) were more prevalent in the placebo groups, though the numbers were small.

Table 6.1.3 Demographics

Demographic		Treatment Group		Total n=409 (%)
Category	Variable	Vilazodone n=204 (%)	Placebo n=204 (%)	
Gender n (%)	Female	127 (62.0)	130 (63.7)	257 (62.8)
	Male	78 (38.0)	74 (36.3)	152 (37.2)
Race n (%)	White	181 (88.3)	157 (76.9)	338 (82.6)
	Black/African American	20 (9.8)	36 (17.6)	56 (13.7)
	Asian	2 (1.0)	2 (1.0)	4 (1.0)
	American Indian/ Alaskan Native and White	1 (0.5)	3 (1.5)	4 (1.0)
	Native Hawaiian/ Pacific Islander	0	3 (1.5)	3 (0.7)
	Other	1 (0.5)	2 (1.0)	3 (0.7)

Ethnicity n (%)	Hispanic or Latino	17 (8.3)	13 (6.4)	30 (7.3)
	Not Hispanic or Latino	188 (91.7)	191 (93.6)	379 (92.7)
Age (years)	Mean	40.0	39.8	39.9
	Standard Deviation	12.11	12.74	12.41
	Median	40.0	39.0	40.0
	Range	18-63	18-65	18-65

Source: CSR: GNSC-04-DP-02 p.59

Baseline Characteristics

The baseline height and weight were similar between the two groups. The mean patient height was 169.3 cm (SD \pm 9.40) for the vilazodone group and 168.8 cm (SD \pm 10.31) for the placebo group. Mean body weight at the Screening visit was 85.1 kg (SD \pm 22.18) for the vilazodone group and 84.0 kg (SD \pm 22.0) for the placebo group.

The medical and surgical histories revealed no significant differences that would be likely to have an effect on the outcome of the study.

The psychiatric histories of all patients in the safety population revealed similar characteristics for both the vilazodone and placebo groups. As indicated in the table below, the mean age of the first episode was approximately 33 years for the vilazodone group and 32 years for the placebo group. The duration of depressive symptoms was similar between the vilazodone and placebo groups; this was the first MDE in approximately one-third of the subjects in both groups. Severity of symptoms was similar in both groups, 100 percent of the patients in both groups had symptom severity of either moderate or severe.

Table 6.1.3 Baseline Psychiatric History

Major Depressive Episode (MDE)	Vilazodone N=205 (%)	Placebo N=204 (%)	Total N=409 (%)
Duration of MDE:			
1-6 months	107 (52.2)	110 (53.9)	217 (53.1)
6-12 months	68 (33.2)	78 (38.2)	146 (35.7)
>12 months	30 (14.6)	16 (7.8)	46 (11.2)
1 st Lifetime MDE:			
Yes	72 (35.1)	76 (37.3)	148 (36.2)
No	133 (64.9)	128 (62.7)	261 (63.8)
Age (years) of 1 st MDE:			
N			
Mean	205	204	409
SD	33.4	31.9	32.6
Min	13.4	13.8	13.6
Max	6	5	5
	63	64	64
Current MDE severity:			
Mild	0	0	0
Moderate	147 (71.7)	147 (72.1)	294 (71.9)
Severe	58 (28.3)	57 (27.9)	115 (28.1)

Source: CSR: GNSC-04-DP-02 Section 14.3.6.4 p. 464

Prior and Concomitant Medications

Concomitant medications were used by 79% of the vilazodone group and 78% of the placebo group. The majority of the medications used during the trial were over the counter pain relievers, anti-hypertensive medications, and antacids.

The number of patients on prior psychiatric medication was similar between the two groups (vilazodone 14% and placebo 12%); adequate time for washout of prior medications appeared to be adhered to. It seems unlikely that the use of the concomitant medications would have significantly biased the results based on the pharmacology of the medications and roughly equal distributions between the two groups. These prior and concomitant medications are likely to be used in the population for which this drug is intended.

6.1.3 Subject Disposition

Of 561 patients screened, 151 patients failed the screening process. The remaining 410 patients were randomized 1:1 to vilazodone or placebo, resulting in 205 patients in each group. Of the 205 patients randomized, 152 in the vilazodone group completed all visits through Week 8 (Visit 7) and 154 on placebo completed all visits.

The following table is copied from the applicant's submission (CSR/21 December 2007 p. 54) and is a concise representation of subject disposition:

Table 6.1.4 Patient Disposition

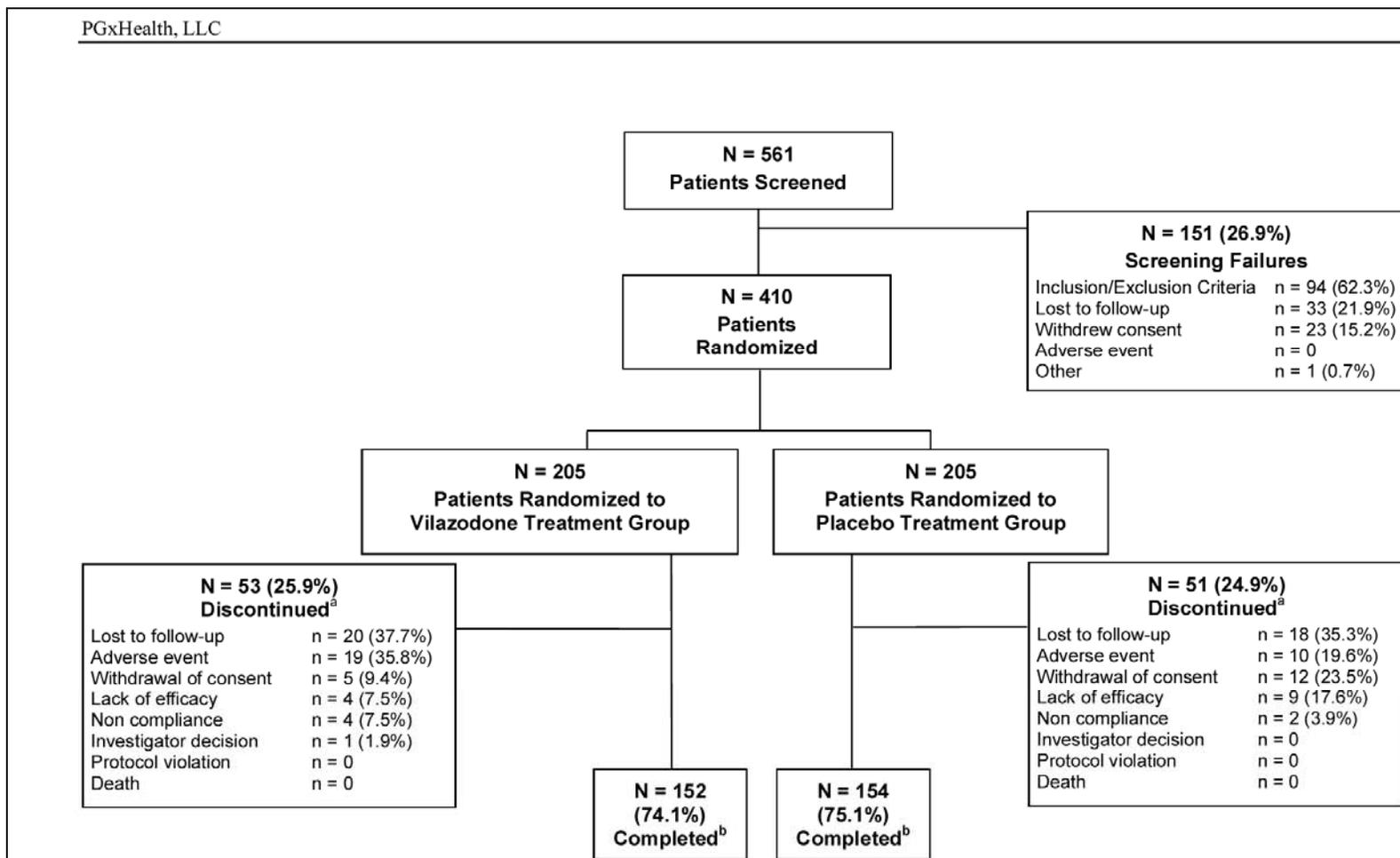


Figure 10-1 Patient Disposition

Source: Section 14.3.6.1, Table 1, Section 14.3.6.3, Table 3, and Section 14.3.6.20, Figure 1

- a. for each reason for discontinuation, percent (%) values in this figure were calculated using a denominator of the total number (N) of patients discontinued in each treatment group
- b. a patient was considered to have completed the study when he/she completed all visits through Week 8 (Visit 7)

Source: CSR: GNSC-04-DP-02 p.54

Of the randomized patients, the numbers of patients who completed the study through Week 8 were similar for the vilazodone and placebo groups; approximately 25% of patients in each treatment group discontinued prior to Week 8. The most common reason for discontinuation was 'lost to follow-up' in both treatment groups. It should be

noted that 20 patients were lost to follow up in the vilazodone group compared with 18 patients in the placebo group.

More patients in the vilazodone group discontinued due to an AE, 19 (9%) for vilazodone and 10 (5%) for placebo. More patients in the placebo group discontinued due to withdrawal of consent, 5 (2%) vilazodone and 12 (6%) for placebo; and lack of efficacy 4 (2%) for vilazodone and 9 (4%) for placebo.

Table 6.1.5 Study Completion Rates

	Vilazodone	Placebo
Randomized	205	205
Early discontinuations	53 (25.9%)	51 (24.9%)
Completed all visits	152 (74.1%)	154 (75.1%)
	Reason for Discontinuation	
	N=53	N=51
Lost to follow up	20 (37.7%)	18 (35.3%)
Adverse event	19 (35.8%)	10 (19.6%)
Withdrawal of consent	5 (9.4%)	12 (23.5%)
Lack of efficacy	4 (7.5%)	9 (17.6%)
Noncompliance	4 (7.5%)	2 (3.9%)
Investigator decision	1 (1.9%)	0

Source: CSR: GNSC-04-DP-02 Fig. 10-1 p.54.

The most common adverse events leading to dropout included diarrhea, headache, depression, suicidal ideation, and heart palpitations.

Protocol Deviations

Review of the data indicates that protocol deviations occurred due to concomitant medications, inclusion/exclusion criteria, study drug dosing, study medication details, study procedures, visit schedule interval, and medication therapy. None of these deviations was considered to be major and patients with protocol deviations were not excluded from the efficacy or safety analyses.

Statistical Plans

The three populations analyzed in this study report are defined by the applicant as:

1. **Intent to treat (ITT)** – all randomized patients that received at least one dose of study medication and had at least one post-baseline efficacy measurement within

7 days of the last dose of study medication with data collected on or before Day 71.

2. **Modified intent to treat (mITT)** – all patients in the ITT population who completed the MADRS (primary efficacy measure) at Week 8.
3. **Safety population** – all randomized patients who took at least one dose of study medication and had at least one safety measurement. This population was used for all safety analyses and all demographic and baseline characteristic analyses.

The ITT population was used for all efficacy analyses; the mITT was used, in addition to ITT, for efficacy analyses of the primary efficacy endpoint and analyses of key secondary endpoints.

Table 6.1.6 Study Populations

Population	Number (%) of Patients by Treatment Group	
	Vilazodone	Placebo
All randomized patients	205 (100)	205 (100)
ITT population	198 (96.6)	199 (97.1)
mITT population	152 (74.1)	154 (75.1)
Safety population	205 (100)	204 (99.5)

Source: CSR: GNSC-04-DP-02 Table 11-1 p.56

Three patients (2 vilazodone and 1 placebo) received at least one dose of study medication and had at least one post-baseline efficacy assessment, but were not included in the ITT analyses because each of the three had only one efficacy assessment and that assessment was outside of the predefined treatment window.

Analysis of the primary efficacy endpoint, change in MADRS total score from Baseline to Week 8 was a single comparison and therefore there was no multiplicity issue. The main secondary efficacy variables for inferential analyses were MADRS response, MADRS remission, and HAM-A total score. The analyses for these main secondary variables were performed on both the ITT and the mITT populations.

Analysis of HAM-A results included evaluation of a subgroup of clinical anxiety patients; clinical anxiety patients were defined as those patients with a Baseline HAM-A total score ≥ 18 .

Efficacy Findings

For efficacy results, missing values were imputed using the last observation carried forward (LOCF) approach. Only assessments done after dosing were used in the LOCF

procedure. Primary and Secondary endpoint analyses included only those measurements obtained while patients were receiving active treatment with either vilazodone or placebo.

The results from the primary analysis indicate that patients treated with vilazodone demonstrate improvement on the total MADRS score when compared to the patients treated with placebo. The mean change from baseline in the MADRS total score at Week 8 was analyzed using ANCOVA with terms for treatment, center, and Baseline MADRS total score. The ITT population (LOCF), mean change from baseline was -12.9 for the vilazodone group and -9.6 for the placebo group, to yield a difference between groups (vilazodone-placebo) of -3.3.

Table 6.1.7 Least Squares Mean Change in MADRS Total Score

Least Square Mean Change in MADRS total score: Treatment Group Difference by Study Visit						
	ITT Population			mITT Population		
Study Week	Value	P-value	95%CI	Value	P-Value	95% CI
1	-1.7	0.0002	-2.5, -0.8	-1.7	0.0005	-2.7, -0.8
2	-1.5	0.0127	-2.7, -0.3	-1.4	0.0395	-2.8, -0.1
4	-2.6	0.0011	-4.1, -1.0	-2.5	0.0049	-4.2, -0.8
6	-3.6	0.0001	-5.3, -1.8	-3.7	0.0002	-5.6, -1.8
8	-3.2	0.0010	-5.2, -1.3	-3.3	0.0027	-5.4, -1.1

Source: CSR GNSC-04-DP-02 Table 11-9 p.71

6.1.4 Analysis of Primary Endpoint(s)

The results from the primary analysis indicate that patients treated with vilazodone demonstrate improvement on the total MADRS score when compared to the patients treated with placebo. The mean change from baseline in the MADRS total score at Week 8 was analyzed using ANCOVA with terms for treatment, center, and Baseline MADRS total score. The ITT population (LOCF), mean change from baseline was -12.9 for the vilazodone group and -9.7 for the placebo group, to yield a difference between groups (vilazodone-placebo) of -3.2. The following table extracted from the Biometrics review of Dr. Dinh illustrates these findings.

Table 6.1.8 Change from Baseline to Week 8 LOCF – MADRS

Table 10. 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		
<i>Mean (Standard deviation)</i>	30.7 (3.9)	30.8 (3.9)
<i>Median (Min – Max)</i>	31 (20 – 41)	31 (21 – 43)
Change from baseline		
<i>LS Means</i>	-9.7	-12.9
<i>Difference from placebo (SE)</i>		-3.2 (0.99)
<i>(95% confidence interval)</i>		(-5.1, -1.2)
<i>P-value</i>		0.001

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

The difference was similar between treatment groups when mITT population was analyzed. The mean change from Baseline for the mITT population was a difference between groups of -3.3, (-15.6 vilazodone and -12.3 placebo).

The Applicant reports a statistically and clinically significant difference between treatment groups for both ITT (p=0.0010) and mITT (p=0.0027) populations. The improvement in vilazodone-treated patients relative to placebo was observed as early as the first week of treatment with greatest relative response at Weeks 6 and 8.

6.1.5 Analysis of Secondary Endpoints(s)

The main secondary efficacy variables for inferential analyses were MADRS response, MADRS remission, and HAM-A total score in a subset of patients with HAM-A total score ≥18. The analyses for these variables were performed on both the ITT and mITT populations. Response and remission rates, based on pre-defined criteria, were determined using MADRS and HAM-D results. Response rates were also determined using CGI-I data.

MADRS Response

There were more MADRS responders in the vilazodone group. In the ITT population LOCF analyses, 80 (40.4%) patients in the vilazodone groups and 56 (28.1%) patients in the placebo group met MADRS response criteria (≥50% reduction in total score from Baseline at Week 8).

The results of MADRS Response were insignificant for the ITT population; however, notable in that the adjusted p value for the treatment group difference was 0.0464 for the mITT population. The mITT includes all ITT patients who completed the MADRS at Week 8. For the mITT population vilazodone n=152 and placebo n=154.

MADRS Remission

Remission on the MADRS was defined as a total score of <10 at Week 8. There were more MADRS remitters in the vilazodone group than in the placebo group; however, the difference between treatment groups in remission rate was not statistically significant (raw p=0.0506, adjusted p=0.1012). Similar estimates of remission were found in the mITT population.

HAM-A total score

The primary analysis of HAM-A was a change from Baseline to Week 8 analyses (ANCOVA, LOCF) performed using only the patients with a HAM-A total score ≥ 18 at Baseline, suggesting a co-occurring condition of 'clinical anxiety'.

The mean change in HAM-A total score from Baseline to Week 8 was greater in the vilazodone group. However, the mean treatment group difference was not statistically significant for either the ITT or the mITT.

Conclusions

The impression is that the 40 mg/day dose of vilazodone is superior to placebo in the LOCF primary efficacy analysis at the 8-week endpoint. The effect size, as measured by difference between drug and placebo on change from baseline is likely to be clinically meaningful. Overall, it is considered to be a positive study.

Pivotal Study #2 **CLDA-07-DP-02**

6.1.1 Methods

Study **CLDA-07-DP-02** is a multicenter, randomized, double-blind, placebo-controlled, fixed titration, 8-week clinical trial designed to assess the efficacy and safety of vilazodone in the treatment of adults (18-70 years of age, inclusive) diagnosed with MDD according to DSM-IV-TR criteria. This study was conducted by qualified principal investigators at fifteen sites in the United States under the sponsorship of PGxHealth.

The first patient was randomized March 31, 2008, the last patient completed the study February 10, 2009; the report was released November 3, 2009.

Primary Objective

To compare the efficacy of vilazodone and placebo in the treatment of MDD as measured by the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at Week 8 or End of Treatment Visits. The MADRS is accepted by the Agency as a standard measure for antidepressant trials.

Secondary Objectives

The Applicant identified three secondary objectives:

- To assess the safety profile of vilazodone compared with placebo
- To analyze a pre-specified genetic biomarker, referred to as (b) (4), associated with treatment response to vilazodone and to conduct further exploratory analyses of genetic biomarkers related to vilazodone
- Secondary efficacy and safety analyses using the MADRS, HAM-D and subscales, Hamilton Anxiety Scale (HAM-A), Clinical Global Impressions (CGI), Changes in Sexual Functioning Questionnaire (CSFQ), and Columbia-Suicide Severity Rating Scale (C-SSRS)

Study Design

CLDA-07-DP-02 enrolled approximately 470 patients randomly assigned to vilazodone or placebo, 40 mg, taken orally, once daily with food each morning. The study was divided into three periods: a washout period, a screening period, and an 8-week-double-blind treatment period. The washout period permitted the time for discontinuation of current antidepressants or any additional medications that were prohibited by the protocol. At Visit 2 (Week 0), baseline assessments were performed, the patients were randomized, and study drug was dispensed. After the baseline visit, there were five scheduled visits at which safety and efficacy measurements were administered.

- The initial dose of vilazodone or matching placebo for all patients was 10 mg/day for the first 7 days (Days 1-7), 20 mg/day for the next 7 days (Days 8-14), and 40 mg/day for the remaining 42 days (Days 15-56) of the trial.

Key Inclusion Criteria

- Male or female (of child-bearing potential using adequate and reliable methods of birth control) patients 18-70 years of age, inclusive
- MDD per DSM-IV-TR with current MDE of at least 4 weeks but no more than 2 years duration
- MDD diagnosis confirmed at baseline by MINI
- HAM-D score ≥ 22 on the first 17 items of the 21-item HAM-D at screening and baseline

Key Exclusion Criteria

- Current Axis I disorder of PTSD, Eating Disorder, Obsessive Compulsive Disorder (Generalized Anxiety Disorder, Social Phobia, or Simple Phobia permitted)
- Patients with history of Schizophrenia, Schizoaffective Disorder or Bipolar I or II Disorder (with a history of hypomanic or manic episodes)
- Patients who met DSM-IV-TR criteria for substance abuse (alcohol or drugs) within 3 months prior to screening or substance dependence within 6 months prior to screening
- Patients who met criteria for any of the following DSM-IV specifiers: catatonic features, postpartum onset, seasonal pattern, psychotic features
- ECT within the past 6 months
- Psychotherapy within the past 6 months
- Patients with inadequate response to at least 2 consecutive, within the same episode, antidepressants from different classes given at adequate doses for an adequate duration
- Patients with a history of clinically significant cardiac, renal, neurologic, cerebrovascular, hepatic, hematologic, metabolic or pulmonary disorders
- Pregnant (or intending to become pregnant) or lactating females

Prohibited Medications

- Monoamine oxidase inhibitors (MAOIs), fluoxetine
- All other antidepressants, sedative, hypnotics, beta adrenergic blockers, benzodiazepines or other psychoactive medications, including herbal preparations
- Triptans and ergot derivatives
- CYP450 3A4 inhibitors such as grapefruit juice, ketaconazole, diltiazem, and macrolide antibiotics
- Singulair (montelukast)
- Previous vilazodone treatment

There were three protocol amendments to the study that primarily involved the genetic biomarker section of the protocol; although minor changes were also made in the exclusion criteria and descriptive text.

Results

6.1.2 Demographics

There were more females (56.2%) than males (43.8%). The percentage of females was slightly higher in the vilazodone group. The mean age of 41.7 years was similar in the vilazodone and placebo groups. The majority, 79.7%, of enrolled patients were white in

both the vilazodone and placebo groups. Ethnicity was identified as 'Not Hispanic or Latino' for more than 90% of patients in both groups.

Table 6.1.9 Demographics CLDA 07-DP-02

Table 9: Demographic and Baseline Characteristics (Safety Population): Sex, Race, and Ethnicity			
	Vilazodone N=235	Placebo N=233	Total N=468
Parameter	n (%)	n (%)	n (%)
Sex			
Male	96 (40.9)	109 (46.8)	205 (43.8)
Female	139 (59.1)	124 (53.2)	263 (56.2)
Race			
American Indian or Alaskan Native	7 (3.0)	0	7 (1.5)
Asian	8 (3.4)	8 (3.4)	16 (3.4)
Black or African American	35 (14.9)	31 (13.3)	66 (14.1)
Native Hawaiian or other Pacific Islander	2 (0.9)	1 (0.4)	3 (0.6)
White	182 (77.4)	191 (82.0)	373 (79.7)
American Indian or Alaskan Native, Asian, White	1 (0.4)	0	1 (0.2)
American Indian or Alaskan Native, White	0	2 (0.9)	2 (0.4)
Ethnicity			
Hispanic or Latino	14 (6.0)	16 (6.9)	30 (6.4)
Not Hispanic or Latino	221 (94.0)	217 (93.1)	438 (93.6)

Note: The data for Patient IDs of 2080-058 and 2020-173 were excluded from analysis. Patient IDs 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient and the patient participation was consecutive. Patient IDs 2020-173 (placebo) and 2080-074 (vilazodone) were the same patient and the patient participation was overlapping.
Source: Table 14.1.4.1
Cross-reference: Listing 16.2.4.1

Source: CSR CLDA-07-DP-02 p54

Baseline Characteristics

The baseline height and weight were similar between the two groups. The mean patient height was 168 cm for the vilazodone group and 170 cm for the placebo group. Mean body weight at the Screening Visit was 192 pounds for the vilazodone group and 195 pounds for the placebo group.

The medical and surgical histories revealed no significant differences that would be likely to have an effect on the outcome of the study.

The psychiatric histories of all patients in the safety population revealed similar characteristics for both the vilazodone and placebo groups. As indicated in the table below, the mean age of the first MDE was approximately 32 years for the vilazodone group and 33 years for the placebo group. The duration of depressive symptoms was similar between the two groups; this was the first MDE in approximately 66.5% of the subjects in both groups. Severity of symptoms was similar in both groups and 100 percent of the patients in both groups had symptom severity of either moderate or severe.

Table 6.1.10 Baseline Characteristics

Baseline Psychiatric History			
Major Depressive Episode (MDE)	Vilazodone N=235(%)	Placebo N=233(%)	Total N=468(%)
Duration of MDE			
1-6 months	110 (46.8)	120 (51.5)	230 (49.1)
6-12 months	61 (26.0)	59 (25.3)	120 (25.6)
>12 months	63 (26.8)	54 (23.2)	117 (25.0)
1st Lifetime MDE			
Yes	66 (28.1)	67 (28.8)	133 (28.4)
No	169 (71.9)	166 (71.2)	335 (71.6)
Age of 1st MDE			
N	235	233	468
Mean	32.0	33.2	32.6
SD	13.4	14.1	13.8
Min	6	8	6
Max	64	70	70
Current MDE			
Mild	0	0	0
Moderate	175 (74.5)	165 (70.8)	340 (72.6)
Severe	60 (25.5)	68 (29.2)	128 (27.4)

Source: CSR CLDA-07-DP-02 Table 14.1.5 p.126

Prior and Concomitant Medications

Psychotropic medications, including antidepressants (other than study drug), mood stabilizers, benzodiazepines, and antipsychotics could not be used during the study. Eligible patients were instructed by the investigator to discontinue their current antidepressant medication for the specified and appropriate washout period.

Other medications initiated before the double-blind period were permitted at the discretion of the investigator, but were to remain at a stable dose throughout the study. The list of medications was reviewed and it seems unlikely that the use of concomitant medications would have significantly biased the results based on the roughly equal distributions between the two groups. These prior and concomitant medications are likely to be used in the population for which the drug is intended.

Treatment Compliance

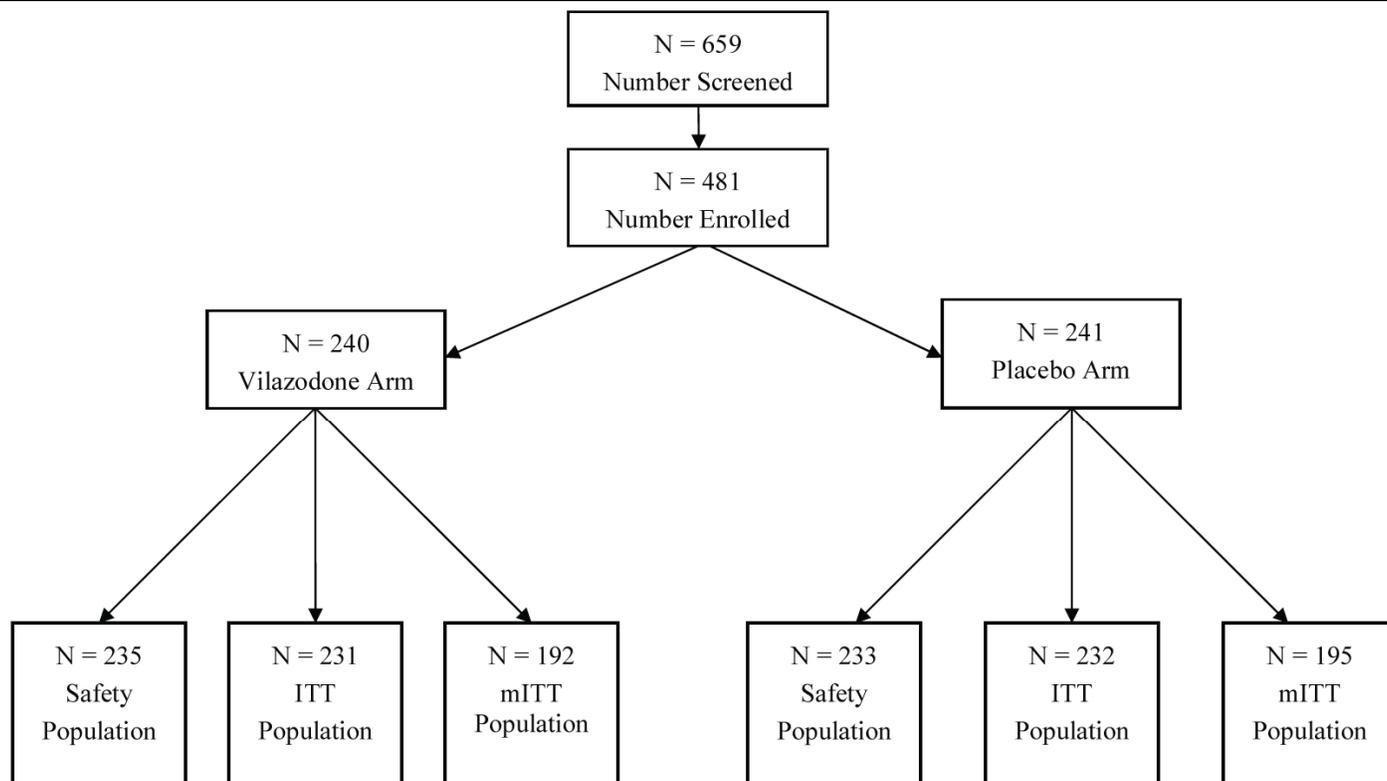
Treatment compliance was defined as 80-120% of prescribed drug taken during any evaluation period. For both treatment groups more than 90% of patients were compliant at each time point. Treatment compliance was similar between vilazodone and placebo groups at each visit. Over, 88% of vilazodone and 94% of placebo patients were compliant.

6.1.3 Subject Disposition

Overall, 659 patients were screened for entry into the study, 481 were randomized to either vilazodone treatment (n=240) or placebo (n=241). Of the total 659 patients, 178 (27%) were screen failures. Nearly half (n=87, 48.9%) did not meet the inclusion/exclusion criteria, 37 patients (20.8%) withdrew consent, 25 patients (14.0%) were lost to follow up and "other" was listed as the reason for screen failure of 29 (16.3%) patients.

Of the 481 randomized patients, 388 (80.7%) completed the study. The number of completers was similar in both the vilazodone and placebo groups.

Table 6.1.11 Patient Disposition CLDA-07-CP-02



Source CSR CLDA-07-DP-02 p50

Table reproduced from the Applicant's submission CSR LDA-07-DP-02 p. 50

The three populations analyzed in this study report are defined by the applicant as:

1. **Intent to treat (ITT)** – all randomized patients that received at least one dose of study medication and had at least one post-baseline efficacy measurement.
2. **Modified intent to treat (mITT)** – all patients in the ITT population who completed the MADRS (primary efficacy measure) at Week 8.
3. **Safety population** – all randomized patients who took at least one dose of study medication and had at least one safety measurement. This population was used for all safety analyses and all demographic and baseline characteristic analyses.

Of the 481 randomized patients, 388 patients (80.7%) completed the study. The number of patients who completed the study was similar in the vilazodone and placebo groups. For the 93 (19%) of patients who discontinued, the most frequent reasons were lost to

follow up (36% vilazodone and 37% placebo) and withdrawal of consent (23% vilazodone and 24% placebo). Of those patients who discontinued due to an adverse event, 12 (26%) were in the vilazodone group and 4 (9%) were in the placebo group. Three patients (6%) in the vilazodone group effect and 7 (15%) patients in the placebo group discontinued due to patient-reported lack of therapeutic effect.

The most common adverse events leading to discontinuation in the vilazodone group included two patients with nausea and 1 of each of the following: palpitations, delirium, angina, pneumonia, dyspepsia, vomiting, feeling abnormal, feeling jittery, dizziness, and migraine. Discontinuation due to AEs in the placebo group included 1 of each: irritability, anxiety, tension, and skin reaction.

Protocol Deviations

No patient was discontinued from this trial for a protocol deviation. The most frequent protocol deviations were study medication non-compliance (57 patients) and study visit outside of visit window (43 patients). These protocol deviations were not excluded from the efficacy or safety analyses.

It should be noted that Patient 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient and the patient participation was consecutive. Patient 2020-0173 (placebo) and 2080-074 (vilazodone) were the same patient and the patient participation was overlapping. The data for Patient 2080-058 and 2020-173 were excluded from efficacy and safety analyses.

Statistical Plans

The primary efficacy endpoint was the change from baseline in MADRS total score at Week 8. The intent-to-treat (ITT) population was used for the primary efficacy analysis using LOCF methods. The model was an analysis of covariance (ANCOVA), with terms for treatment and center, adjusting for baseline MADRS.

A mixed-effects model repeated measures (MMRM) analysis was performed. 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 value and baseline-by-visit interaction. The treatment group comparisons were based on evaluating the difference in LS means between groups at each post-baseline visit. If patients discontinued early and between visits, the last observation was carried forward to the next scheduled visit for the analysis.

All analyses were performed on the ITT and the modified ITT populations. The ITT population consisted of patients who were randomized, took at least one dose of study drug, and had at least one post-baseline efficacy endpoint measurement. The mITT

population consisted of the subset of the ITT population who completed their Week 8 MADRS assessment.

The secondary efficacy endpoints included the 17-item HAM-D, 21-item HAM-D, and HAM-A total scores, CGI-S and CGI-I scores, MADRS and 17-item HAM-D response and remission rates.

MADRS response was defined as a decrease in total score by at least 50% from the baseline at endpoint. MADRS remission was defined as final MADRS total of <10. The 17-item HAM-D response was defined as a decrease in the 17-item HAM-D total score by at least 50% from baseline. HAM-D remission was defined as a final 17-item HAM-D total of <7. Cochran-Mantel-Haenszel tests were used for these analyses comparing response and remission rates for the treatment groups, stratifying by center.

The 17-item HAM-D, 21-item HAM-D, and HAM-A total scores, as well as the CGI-S score were analyzed using the same models as MADRS total score. As a subgroup, the change from baseline to endpoint between treatment groups in HAM-A total was assessed in patients with baseline HAM-A scores ≥ 18 .

Study Results

For efficacy results, missing values were imputed using the last observation carried forward (LOCF) approach. Only assessments done after dosing were used in the LOCF procedure. Primary and Secondary endpoint analyses included only those measurements obtained while patients were receiving active treatment with either vilazodone or placebo.

6.1.4 Analysis of Primary Endpoint

The results from the primary analysis indicate that patients treated with vilazodone demonstrate improvement on the total MADRS score when compared to the patients treated with placebo. The mean change from baseline in the MADRS total score at Week 8 was analyzed using ANCOVA with terms for treatment, center, and a Baseline MADRS total score. The ITT population (LOCF), mean change from baseline was -13.3 for the vilazodone group and -10.8 for the placebo group, to yield a difference between groups (vilazodone-placebo) of -2.5. This difference resulted in statistically significant finding with a p-value of 0.009.

Table 6.1.12 Change from Baseline to Week 8 LOCF – MADRS

Table 3. 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		
<i>Mean (Standard deviation)</i>	32.0 (3.6)	31.9 (3.5)
<i>Median (Min – Max)</i>	32 (24 – 42)	32 (22 – 42)
Change from baseline		
<i>LS Means</i>	-10.8	-13.3
<i>Difference from placebo (SE)</i>		-2.5 (0.96)
<i>(95% confidence interval)</i>		(-4.4, -0.6)
<i>P-value</i>		0.009

The data for Patient IDs of 2080-058, 2020-173, and 2080-074 were excluded from analysis. Patient IDs 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient enrolled at 2 different clinical sites and participation was consecutive. Patient IDs 2020-173 (placebo) and 2080-074 (vilazodone) were the same patient and participation was overlapping at 2 different clinical sites.

(Source: CLDA-07-DP-02 Study Report; Table 11, page 57)

Conclusion

The impression is that the 40 mg/day dose of vilazodone is superior to placebo in the LOCF primary efficacy analysis at the 8-week endpoint. The effect size, as measured by difference between drug and placebo on change from baseline, is only marginally impressive but still could be clinically meaningful. Overall, it is considered to be a positive study.

6.1.5 Analysis of Secondary Endpoints

The main secondary efficacy variables for inferential analyses were MADRS response, MADRS remission, and HAM-A total score. The analyses for these variables were performed on the ITT population. Response and remission rates, based on pre-defined criteria, were determined using MADRS total scores.

MADRS Response

There were more MADRS responders in the vilazodone group. In the ITT population LOCF analyses, 100 (43.7%) patients in the vilazodone group and 70 (30.3%) patients in the placebo group met response criteria (defined as ≥50% reduction in MADRS total

score from Baseline at Week 8). The difference between the two treatment groups was statistically significant, $p=0.0024$.

MADRS Remission

There were more MADRS remitters in the vilazodone group. In the ITT population LOCF analyses, 63 (27.3%) patients in the vilazodone group and 47 (20.3%) patients in the placebo group met remission criteria (defined as MADRS total score at Week 8 <10). The difference between the two groups was not statistically significant, $p=0.0662$.

HAM-A total score

The HAM-A total score least-squares mean change from baseline at Week 8, ITT population, LOCF, was -7.0 for the vilazodone group and -5.7 for the placebo group. The difference of -1.2 between the groups was statistically significant, $p=0.037$. The HAM-A total score change from baseline at Week 8 are presented in the following table.

Table 6.1.13 HAM-A Change from Baseline to Week 8

Table 15: Hamilton Anxiety Scale Total Score Change at Week 8 (Intent-to-Treat Population; Last Observation Carried Forward)			
Statistic	Vilazodone N=231	Placebo N=232	P-value
Model A ^a			
n	231	231	
LS-Mean (SE)	-7.0 (0.55)	-5.7 (0.55)	
95% CI (LS-Mean)	-8.0, -5.9	-6.8, -4.7	
LS-Mean Treatment Difference		-1.2	0.0371
95% CI (LS-Mean Treatment Difference)		-2.4, -0.1	
Treatment Effect			0.0371
Center Effect			0.2173
Baseline HAM-A Effect			<0.0001
Model B ^b			
Treatment Effect			0.0035
Center Effect			0.1986
Treatment*Center Interaction			0.1014
Baseline HAM-A Effect			<0.0001

^a Analysis of covariance (ANCOVA) test including treatment, center and baseline Hamilton Anxiety Scale (HAM-A) total score in the model.
^b ANCOVA test including treatment, center, treatment-by-center interaction and baseline HAM-A total score in the model.
Note: The data for Patient IDs of 2080-058, 2020-173, and 2080-074 were excluded from analysis. Patient IDs 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient enrolled at 2 different clinical sites and the patient participation was consecutive. Patient IDs 2020-173 (placebo) and 2080-074 (vilazodone) were the same patient and the patient participation was overlapping at 2 different clinical sites.
CI = confidence interval; LS = least squares; SE = standard error.
Source: Table 14.2.4.1
Cross-reference: Listing 16.2.6.3

Source: CSR CLDA-07-DP-02 p.66

6.1.6 Analysis of Other Endpoints

In an analysis of a **subset of patients with baseline HAM-A scores ≥ 18** (ITT) the HAM-A total score least-squares mean change from baseline at Week 8 LOCF was -9.5 for the vilazodone group and -8.7 for the placebo group. The difference between the treatment groups of -0.8 was not statistically significant, $p=0.401$. Using the same population of patients (ITT), a repeated measures analysis demonstrated that differences between treatment groups were not statistically significant at any time point.

Crosscutting Issues

6.1.7 Subpopulations

GNSC-04-DP-02

Patients in the ITT dataset (total n=397) were between the ages of 18 and 65 years old, inclusive, with a mean age of 40 years. Eighty-three (83%) percent were Caucasian, 14% were African-American, 1% were Asian, and approximately 2% were American Indian or Pacific Islander. Sixty-three (63%) percent of the patients were female. Seven (7%) percent were Hispanic or Latino. Treatment groups were comparable at baseline on the demographic variables.

The subgroup analysis for gender indicated numerical improvements in the change from baseline MADRS scores for both males and females, with a slightly greater difference from placebo in the male population (-3.4 males and -2.9 females). The subgroup analysis for race indicated a numerical improvement for white patients; whereas the treatment effect is null for non-whites. The subgroup analysis for age, ≤ 40 years or > 40 years, indicated numerical improvements in both groups with a greater difference from placebo in the older group.

CLDA-07-DP-02

Patients in the ITT dataset (total n=463) were between the ages of 18 and 70 years old, inclusive, with a mean age of 42 years. Eighty (80%) percent were Caucasian, 14% were African-American, 4% were Asian, and approximately 2% were American Indian or Pacific Islander. Fifty-six (56%) of the patients were female. Six (6%) percent were Hispanic or Latino. Treatment groups were comparable at baseline on the demographic variables.

The subgroup analysis for gender indicated a greater change from baseline for females. In this study, only 1% of the subjects were over the age of 65 years. When stratified as ≤ 40 years or > 40 years, the greater improvement was seen in the older age group. Subgroup analysis for race was analyzed as white and non-white. There was a more favorable response in the white group. Overall, it appears that a greater sample size yields a more favorable vilazodone outcome.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In the pivotal trials, the applicant evaluated the efficacy of only one dose of vilazodone, 40 mg qd. The dose-response of this drug has not been adequately explored as previous studies were not designed to provide reliable dose-response information. Neither of the pivotal trials was designed to investigate the effectiveness of the 20 mg qd dose; doses higher than 40 mg qd have been associated with significant GI and psychiatric adverse events. There is also a significant food effect with this medication which could lead to variable exposures if labeling recommendations are not followed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The two pivotal studies, 04 and 07, were of 8 week's duration and in the opinion of this reviewer, were not designed to assess the persistence of efficacy and/or tolerance effects.

Study **CLDA-07-DP-04**, a 52-week uncontrolled study was conducted to assess the long-term safety of vilazodone in patients with MDD. This study included male or female patients, 18 to 70 years of age with HAM-D-17 \geq 18.

A secondary objective of this study was to assess the effectiveness of vilazodone during longer-term treatment. The efficacy variables were the change in MADRS total score from baseline to Week 8, change in CGI-S score from Baseline to Week 8 and the change in the two scores over time.

The 'Effectiveness Population' consisted of enrolled subjects who took study drug and had a post-baseline effectiveness measurement. This population was used for the effectiveness analyses. The mean response at each assessment visit was computed using observed case values only. Two-sided 95% CIs were computed for the mean.

The mean MADRS total scores decreased (change from Baseline at Week 52 was -22.8) over time. Because this was an uncontrolled study, the results are speculative. Therefore, the persistence of efficacy and or tolerance effects has not been adequately evaluated for vilazodone.

6.2.0 Efficacy Conclusions

The impression is that the 40 mg/day dose of vilazodone is superior to placebo in the LOCF primary efficacy analyses at the 8-week endpoint. The effect size, as measured by difference between drug and placebo on change from baseline is likely to be clinically meaningful.

7 Review of Safety

Safety Summary

7.1 Methods

The following safety evaluation of vilazodone consisted of a review of the deaths, serious adverse events, adverse events that led to early discontinuation, common adverse events, clinical laboratory results, vitals, ECG findings, and safety findings specifically related to antidepressants from 24 Phase 1 studies, 5 Phase 2 studies, and 3 Phase 3 studies. Consultations were requested to assess ocular findings, abuse potential, and the thorough QT study.

Overarching Summary

This safety summary focuses primarily on findings of the Phase 2/3 studies, though Phase 1 studies were also reviewed and are included in the body of the review. The Phase 2/3 placebo controlled studies pooled data provide placebo comparisons. This data includes the 2 pivotal trials (CLDA-07-DP-02 and GNSC-04-DP02) and 5 Phase 2 studies that were done by Merck and GSK which were not included in the efficacy assessment due to issues that were discussed earlier in this review. These 5 clinical trials also provide placebo comparisons.

A total of 2898 subjects were exposed to vilazodone in the clinical development program for the treatment of Major Depressive Disorder. In the controlled, short-term trials 1578 patients were exposed to vilazodone. In the long-term, open-label study, 599 subjects were exposed to vilazodone. The total vilazodone exposure in clinical studies was 551 subject-years. The vilazodone exposure was 203 subject-years in the short-term, controlled trials, and the exposure was 348 subject years in the long-term study.

Short-term treatment with vilazodone appears to have been reasonably safe in the MDD population studied. Generally, the types of adverse events related to vilazodone treatment are similar to those seen with other SSRIs. There is the issue of lens opacities and cataracts for which ophthalmology has been consulted.

Deaths

A total of three deaths occurred during the clinical development program of vilazodone. One death was a homicide in the Phase 1 “thorough QT study” and 2 deaths were suicides. One suicide occurred after consent was signed but prior to randomization and one suicide occurred in a patient who was randomized to placebo. None of the subjects who died had received vilazodone.

Nonfatal Serious Adverse Events

In the Phase 1 studies, 5 serious adverse events (SAEs) were reported. One patient experienced a “paranoid reaction” 5 days after he completed the 8-week double blind arm of vilazodone. There is insufficient evidence to assume causality. One episode of syncope was reported; the narrative is included in the safety review.

In the Phase 2 studies, 44 serious adverse events were reported by 41 patients. Of the 44 serious adverse events, 23 were reported in the vilazodone treatment groups, 13 in the placebo groups, 5 in the active comparator groups, and 3 were reported prior to study medication randomization.

In the two placebo-controlled Phase 3 studies 11 SAEs in 9 patients were reported in the vilazodone group and 9 SAEs in 7 patients were reported in the placebo group. For the vilazodone group the 11 SAEs included two malignancies, one concussion (related to alcohol consumption), one suicide attempt, one psychotic episode, one angina (pre-existing cardiovascular disease). Of those, three are considered by this reviewer as possibly related to vilazodone: depression with psychotic features, angina and atypical chest pain. Sufficient information is not available to establish causality. The SAEs in the placebo group are significant as suicidal ideation is likely related to the condition being studied.

Discontinuations due to Adverse Events

The treatment emergent adverse events leading to discontinuation were predominantly within the gastrointestinal and nervous systems. During Phase 1 development, the applicant reports 88 subjects who discontinued due to an AE, of those, 24 were discontinued for vomiting. During the Phase 2 and 3 studies discontinuations due to TEAEs followed the same pattern of GI, psychiatric, and nervous system. The symptom of palpitations was a reason for discontinuation in 2%, these were subjective reports without documentation of cardiac rhythm.

Common Adverse Events

Adverse events occurring in $\geq 2\%$ of patients treated with vilazodone and with an incidence greater than placebo included diarrhea (28%), nausea (23%), vomiting (5%), dizziness (8%), somnolence/sedation (5%), and restlessness/akathisia (3%). Due to coding inconsistencies, this reviewer’s report of somnolence/sedation and restlessness/akathisia reflects a higher incidence than the applicant reported.

Examining the dose-relatedness of adverse events, the GI adverse events appeared to be relatively consistent across the dose ranges, although a very slight increase was noted as the dose reached 40 mg/day and higher. The psychiatric and nervous system AEs (dizziness, somnolence, tremor, insomnia, abnormal dreams, anxiety, and nightmares) more than doubled with doses exceeding 40 mg/day.

Laboratory Analysis

No significant differences were noted between vilazodone and placebo for chemistry, hematology, and urinalysis parameters. No cases that met criteria for Hy's Law were reported or discovered in review.

Weight

The difference between the vilazodone groups and the placebo group for weight mean change from baseline or PCS values was insignificant. However, the applicant used 10% (not the usual 7%) as the limit for PCS weight changes. The mean weight increased by 0.16 kg in the vilazodone group and 0.18 kg in the placebo group.

Vital Signs

The mean change from baseline for vital signs was unremarkable; the number of PCS values for systolic and diastolic blood pressure and heart rate was low, less than 1% for all doses of vilazodone and placebo. Over all doses, no significant differences were noted between the placebo group and the vilazodone groups.

Electrocardiogram

The applicant conducted a TQT (thorough QT) study; the overall assessment by the QT-IRT reviewer was that no significant QTc prolongation effect of vilazodone was detected in this TQT study.

In the placebo-controlled, Phase 3 database, no subject taking either placebo or vilazodone had a treatment-emergent PCS abnormality for PR, QRS, or QTcF interval. One subject in each group (vilazodone and placebo) had a treatment-emergent PCS abnormality for HR (low HR in each subject).

Ocular Findings

Verbal communication with Dr. Chambers indicates that a conclusion cannot be drawn from the data provided by the applicant for the assessment of cataracts. A written report is being prepared.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For the ISS, the applicant submitted pooled data only from the five Phase 2 and three Phase 3 studies. The safety of vilazodone in the 24 Phase 1 studies was provided as individual study reports and the safety data was not pooled for analysis in the ISS.

Phase 1 data was not described in the ISS unless it was 'germane to specific section topics' for example, renal and hepatic impairment studies; drug-drug interactions, and special safety topics. Statistical tests comparing placebo with vilazodone treatment were conducted for two pooled, placebo-controlled Phase 3 studies only.

7.1.2 Categorization of Adverse Events

The ISS indicates that each verbatim AE term was coded at the study level to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 11.1.

To ensure consistency in reporting adverse events across studies, re-coding of AEs from legacy studies was performed by (b) (4) using MedDRA version 11.1. General conventions were consistent with ICH-endorsed guidelines for choosing MedDRA terms. PGxHealth reviewed and approved all terms that were split.

The JMP file for adverse events was reviewed with an emphasis on verbatim to the preferred term coding. It appeared that most verbatim terms were appropriately coded to preferred terms.

Concomitant medications were coded using the September 2008 version of the World Health Organization Drug Dictionary (WHODD).

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Summary analyses of the Phase 2 and Phase 3 studies were generated using 4 safety subsets from an integrated database of all Phase 2 and 3 studies. The 4 subsets include:

Placebo-controlled Phase 3 Database (GNSC-04-DP-02 and CLDA-07-DP-02)

Each subject receiving vilazodone in the Phase 3 pivotal studies was titrated to 40 mg/day of vilazodone. In study GNSC-04-DP-02, subjects could be down-titrated or maintained at 20 mg/day according to the discretion of the investigator (this was not an option in study CLDA-07-DP-02). All subjects were considered part of the 40 mg/day group. Statistical tests comparing placebo with vilazodone treatment were conducted for this database only.

All Placebo controlled Database (all Phase 2 studies and the two pivotal studies)

The groups were divided according to study drug and dose. Subjects in the Placebo-controlled Phase 3 database who did not titrate to vilazodone 40 mg/day were assigned to the vilazodone <40 mg/day group.

Uncontrolled, Long-term Safety Database (CLDA-07-DP-04)

This group consisted of one arm, vilazodone 40 mg/day.

All Vilazodone Exposure Database (vilazodone subjects from all Phase 2 and 3 studies)

This database consists of all subjects receiving vilazodone from all Phase 2 and 3 studies combined. Only demographics, disposition, exposure, AEs, SAEs, and AEs leading to discontinuation were summarized for the All Vilazodone Exposures database. Active comparator treatment groups are not included in any summaries.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In general, the overall exposure is considered to be adequate based on the number of subjects exposed to vilazodone at the proposed dose of 40 mg/day. However, the demographics indicate that most of the exposure was in white females, younger than 55 years of age. Although this is likely representative of the target population for treatment it would be useful to have more information pertaining to gender, age, race, and ethnicity.

In the Phase 1 clinical development program, 721 male and female subjects were exposed to doses of vilazodone ranging from 1 to 80 mg in single and repeat dose studies. Most subjects were healthy volunteers, although a small number of subjects with mild to moderate hepatic and renal impairment were also evaluated.

Table 7.2.1 Vilazodone Exposure All Placebo-Controlled Phase 2 and 3 Studies

	Placebo N= 997	Vilazodone <40 mg/day N=903	Vilazodone 40 mg/day N=441	Vilazodone >40 mg/day N=227	Vilazodone All doses N=1578
Subject-years exposure ¹	136.1	113.8	60.9	28.8	203.5
Duration of exposure (days)					
n	994	903	441	227	1571
Mean	50.0	46.0	50.4	46.4	47.3
SD	14.51	18.38	14.92	16.76	17.34
Median	56.0	56.0	56.0	56.0	56.0
Min	1	1	4	7	1
Max	77	76	90	70	90
Duration of exposure (%)					
N	994	903	441	227	1571
>0 days	994(100)	903 (100)	441 (100)	227 (100)	1571 (100)
≥7 days	985 (99)	868 (96)	432 (98)	227 (100)	1527 (97)
≥14 days	952 (96)	799 (89)	419 (95)	215 (95)	1433 (91)
≥28 days	876 (88)	717 (79)	392 (89)	179 (78)	1288 (82)
≥42 days	818 (82)	671 (74)	375 (85)	165 (73)	1211 (77)
≥56 days	615 (62)	468 (52)	282 (64)	114 (50)	864 (55)
Unknown/Missing	3	0	0	0	7
¹ calculated by summing days of exposure over all subjects and dividing by 365.25					

Exposure in the open-label, long-term safety database is illustrated in the following table. As indicated, by six months nearly half of the subjects had dropped out of vilazodone treatment and by the one year mark, only 20% of the subjects remained in the study.

Table 7.2.2 Vilazodone exposure open-label long-term study

	Vilazodone 40 mg/day N=599
Subject-years of exposure [†]	348.2
Duration of exposure (days)	
N	599
Mean	212.3
SD	146.95
Median	214.0
Min	1
Max	392
Duration of exposure, n (%)	599
> 0 days	599 (100)
≥ 7 days	594 (99)
≥14 days	576 (96)
≥28 days	529 (88)
≥42 days	498 (83)
≥56 days	464 (83)
≥3 months	389 (65)
≥6 months	314 (52)
≥9 months	277 (46)
≥10 months	265 (44)
≥11 months	261 (44)
≥12 months	118 (20)
[†] subject-years calculated by summing days of exposure and dividing by 365.25	

7.2.2 Explorations for Dose Response

Vilazodone across doses of 1 mg to 80 mg was investigated in the Phase 1 studies. Throughout the clinical development program, more AEs were reported with higher doses of vilazodone. In a repeat dose study with placebo or vilazodone at doses of 20, 40, and 80 mg/day for 10 days, a dose-dependent increase in the number of TEAEs was observed, most commonly, GI TEAEs. During the Phase 1 studies, regardless of the dose, the most common TEAEs were nausea, diarrhea, vomiting, headache, and dizziness.

Dose-related increases in the frequency of TEAEs were observed throughout the Phase 2 and Phase 3 studies with the most frequent TEAEs being diarrhea, nausea, vomiting, dizziness, and insomnia. For the most part, when the vilazodone dose was increased to >40 mg/day there were more AEs leading to discontinuation.

Both pivotal trials were designed to study only one dose of vilazodone, 40 mg/day. Study GNSC-04-DP-02 (pivotal trial) included an option for the investigator to maintain a

dose of 10 or 20 mg/day if an 'unacceptable adverse event' precluded titration to 40 mg/day. As a result, 13 of 152 patients in the vilazodone arm and 5 of 154 patients in the placebo arm were not titrated to the 40 mg/day target.

7.2.3 Special Animal and/or In Vitro Testing

Clinical trials included specific laboratory testing to determine whether vilazodone exerted any demonstrable effect on thyroid function. This special analysis was designed in response to the observation in a single carcinogenicity study of thyroid adenomas and follicular hyperplasia associated in mice. Overall conclusions regarding thyroid function included the fact that changes in laboratory test results suggesting possible treatment-emergent hypothyroidism or hyperthyroidism occurred no more frequently in subjects who received vilazodone than subjects who received placebo.

Protocols for mouse and rat carcinogenicity studies were presented to the Executive CAC in July 1998 and at a second meeting in April 2000.

Executive CAC recommendations and conclusions:

Mouse Carcinogenicity Study – The committee concurred that the increased incidences of mammary adenocarcinomas and adenoacanthomas in females at the high dose and hepatocellular neoplasms in male mice at the high dose were drug related.

Rat Carcinogenicity Study – No biologically relevant, drug-related increases in neoplasm incidence were observed in rats administered vilazodone.

Further interpretation of this matter will be addressed in the Pharmacology/Toxicology reviews. The Pharmacology Toxicology review was not available at the time of this writing.

7.2.4 Routine Clinical Testing

The clinical trials program included routine clinical testing at screening, baseline, at various timepoints during the studies. There was no scheduled follow-up to assess clinical testing after the Week 8 visit for the two pivotal studies. The following clinical laboratory assessments were included:

Hematology: WBC with differential, RBC with indices, hemoglobin, hematocrit, platelet

Chemistry: ALT, AST, albumin, ALP, bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, GGT, glucose, magnesium, phosphorus, potassium, total protein, sodium, thyroid function tests, and uric acid

Urinalysis: color, appearance, specific gravity, pH, protein, urobilinogen, nitrite, glucose, ketones, bilirubin, occult blood, microscopic examination, and leukocyte esterase

Urine drug screen: amphetamines, barbiturates, cocaine, marijuana, methadone, opiates, phencyclidine, benzodiazepines, and propoxyphene

Pregnancy tests: Screening serum pregnancy tests were analyzed by the central laboratory. Urine pregnancy tests were done at Baseline, Week 2, and Week 8 (Visit 7 or early termination) by the study staff.

Ophthalmologic evaluations: slit lamp biomicroscopy, dilated funduscopy, tests of visual acuity, intraocular pressure, and Schirmer's test for decreased lacrimation. The ocular monitoring was conducted only in the five Phase 2 studies and the uncontrolled, long-term Phase 3 study.

Electrocardiograms: 12 lead ECGs were assessed periodically and in a 'Thorough QT Study' PGX-08-P1-06.

Vital signs: systolic blood pressure, diastolic blood pressure, pulse, respiratory rate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the comprehensive review by Biopharmaceutics.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Serotonin Reuptake Inhibitors, as a class, are contraindicated in patients taking monoamine oxidase inhibitors. Warnings and precautions for the use of SSRIs include clinical worsening, suicide risk, anxiety, insomnia, discontinuation symptoms, activation of mania or hypomania, hyponatremia, seizures, and abnormal bleeding.

Potential Serotonin Toxicity

Because Serotonin Syndrome is a known complication of treatment with SSRIs, the AEs in the Phase 2 and Phase 3 studies were searched for preferred terms that might indicate serotonin syndrome. When the terms were identified, Hunter's serotonin toxicity criteria were applied to identify patients with possible serotonin toxicity. The JMP line listings were reviewed to confirm the applicant's assessment. Two subjects were identified with probable vilazodone related serotonin toxicity and are described in the following narratives.

CLDA-07-SP-04-4040-0001

A 24-year-old African American female in the 52-week, long-term, open-label study, who received vilazodone 10 mg/day x 1 week; vilazodone 20 mg/day x 1 week, and vilazodone 40 mg/day for the next 262 days. On the last day of study medication she experienced anxiety, visual hallucinations, and became combative. Vitals: blood pressure 152/79 mmHg, heart rate 155, and temperature 98.4°. She reportedly had missed 'a couple of days of medication and took 5-6 pills to catch up'. This patient took an overdose and experienced signs and symptoms consistent with serotonin toxicity.

GPP-007-CLN-CP2-2001-245/EMD-68843-010/0038-1358

A 42-year-old white male in an 8-week, Phase 2 study received vilazodone 10 mg/day x one day, 20 mg/day x 2 days, 40 mg/day x 3 days, and 80 mg/day x 6 days. He experienced middle insomnia throughout the dosing period. On Day 12 (the final dose), he experienced derealization, flushed feeling, hypnogogic hallucinations, olfactory hallucinations, and myoclonic jerks. It is likely that the patient was experiencing serotonin toxicity due to the rapid dose titration.

Seizures

Review of the entire vilazodone exposure database indicates one seizure which is described in Section 7.3.2 Nonfatal SAEs.

Hyponatremia

Review of the JMP line listing for sodium values revealed only one result lower than 130 mmol/L, this was a screening result of 129 mmol/L. In the all Phase 2 and Phase 3 database there was no evidence of hyponatremia.

Activation of Mania or Hypomania

Activation of mania or hypomania is a known complication of antidepressant use. The applicant identified ten subjects from a search that included at least one incidence of 3 or more of the following TEAEs: affect lability, aggression, agitation, anger, delusions, euphoria, flight of ideas, grandiosity, hallucinations, irritability, and hostility, among others. Using these criteria, 8 subjects receiving vilazodone and 2 subjects receiving placebo were identified from the database search of all Phase 2 and 3 studies. Further assessment of patterns of TEAEs, medical history, concomitant medications, and comorbidity yielded six (6) subjects with potential manic or hypomanic symptoms, 5 received vilazodone and 1 received placebo.

Review of the JMP line listing of AEs and narrative reports supports the applicant's assessment that the incidence of activation of manic/hypomanic symptoms associated with vilazodone use during treatment of MDD are within or below the expectations observed with other antidepressants.

Abnormal Bleeding

The TEAEs related to bleeding occurred in <1% of subjects in the Phase 2 and 3 database. For the all placebo-controlled database, 2.8% of those in placebo group and 2.8% of those in the vilazodone group experienced a TEAE in various SOCs related to bleeding. Of those subjects, 2.0% of the TEAEs in the vilazodone group (31/31 females) and 1.8% in the placebo group (2/18 males) were due to hematuria or blood in the urine. Two subjects receiving vilazodone and one receiving placebo experienced a bleeding episode (hemorrhagic diarrhea, epistaxis, and hematuria) that led to withdrawal from the study. Three subjects had events that resulted in treatment with concomitant medication.

One bleeding event in the long-term study was identified as an SAE. Subject CLDA-07-DP-04-4040-0016, a 46-year-old female, developed exacerbation of menometrorrhagia after 146 days on vilazodone 40 mg/day. Her medical history included menorrhagia and uterine fibroids; she underwent an elective hysterectomy. The subject continued on vilazodone and completed the study. The menometrorrhagia is most likely related to uterine fibroids, although it is possible that vilazodone was a contributing factor.

From a clinical perspective, the bleeding events in the subjects taking vilazodone appear to be minor and not necessarily attributable to the drug. The majority of the TEAEs were related to hematuria or blood in the urine; most of the subjects were female.

7.3 Major Safety Results

There were 3 deaths across all of the Phase 1, 2, and 3 studies. One subject in the Phase 1 study (TQT) PGX-08-P1-06 (moxifloxacin arm) was murdered 25 days after completing treatment. There was one suicide in the Phase 2 study GPP-007-CLN-CP2 2001-245 in the placebo study arm. One patient had signed informed consent to participate but had not been randomized in the Phase 2 study GPP-007-CLN-CP2 2001-245 committed suicide.

Of the 74 patients who experienced an SAE in the Phase 2 and 3 studies, the percentage taking vilazodone was 2.4% and the percentage taking placebo was 2.1%. The percentage of SAEs was nearly doubled for the >55 years age group (3.9%) compared with <55 years (2.2%).

For the all vilazodone exposure database, nearly twice as many patients taking vilazodone experienced a TEAE that led to discontinuation. The percentage of subjects with a TEAE that led to discontinuation was similar for subjects taking <40 mg/day and 40mg/day, with the highest incidence of TEAE in the patients taking >40 mg/day.

7.3.1 Deaths

Phase 1

One subject in study PGX-08-P1-06 died during the study due to a fatal stab wound. The narrative report indicates this 29-year-old white (Hispanic or Latino) female received a fatal stab wound. She was randomized to the moxifloxacin treatment arm (never received vilazodone) and completed treatment on [REDACTED] (b) (6). On [REDACTED] (b) (6), 25 days after completing the study drug, she was fatally stabbed in her home during a domestic dispute.

Phase 2/3

Two deaths occurred in GPP-007-CLN-CP2-2001-245; however, neither patient was receiving active treatment with vilazodone. **Both of the deaths were suicides.** One patient died during the pre-treatment phase and one patient was receiving placebo.

1. 026-1231 – Suicide by Gun Shot

This patient was a 54-year-old Caucasian male. He was randomized to receive placebo and was scheduled for his first dose on Aug. 6, 1998. On [REDACTED] (b) (6) he died from a self-inflicted **gun shot to the head**. The patient's medical history included anxiety, major depressive disorder, alcohol abuse, renal lithiasis, and surgery for herniated disk. This death is not related to the study medication.

2. 027-G01 – Suicide by Carbon Monoxide

This patient was a 47-year-old male who had not been randomized to a study medication when his death occurred. The patient had signed informed consent, but no procedures were performed because he failed to attend the screening visit. On [REDACTED] (b) (6) it was reported that the patient had attempted **suicide by carbon monoxide** inhalation. He was hospitalized for three weeks and died on [REDACTED] (b) (6) as a result of CO poisoning. The death is not related to the study medication.

7.3.2 Nonfatal Serious Adverse Events

Phase 1

In the Phase 1 studies 5 serious adverse events (SAEs) were reported. Narrative reports follow the table for each of the events. One patient experienced a "paranoid reaction" 5 days after he completed the 8-week double blind arm of vilazodone. There is insufficient evidence to assume causality. Subject 230-202 experienced many AEs that appear to be associated with the study medication, vilazodone 40 mg/day.

Table 7.3.1 Phase 1 Serious Adverse Events

ID	Drug	Serious Adverse Event	Intervention	Outcome	D/C from Study	Related to Study Drug
238-140	Vilazodone	Mandibular Fracture (trauma)	Corrective Surgery	Recovered	No	Not Likely
238-018	Vilazodone 20 mg/day	“Paranoid Reaction”	Psychiatric Assessment	Recovered	No	Possibly
230-202	Vilazodone 40 mg/day	Labile Mood Delusional Thought Content	Psychiatric Hospitalization	Recovered	Yes	Yes
0601-183	Vilazodone 40 mg	Syncope (seizure)	Neurology Consult	Recovered	Yes	Possibly
0601-106	Moxifloxacin	Convulsion (history of Seizures)	Medical Evaluation	Resolved	No	No

Study GPP-007-CLN-CP1-2003-238

- Subject 0140 experienced a fractured mandible as a result of trauma; he required corrective surgery. This is considered to be unrelated to the study drug.
- Subject 00018 experienced a ‘paranoid reaction’ five days after the last dose of study medication (unblinding revealed vilazodone treatment from Aug 30 – Sep 27). Although the patient was not hospitalized, psychiatric follow up was required and this was considered an SAE. This is considered to be related to the study drug. The narrative indicates that five days after the last dose of study medication he was ‘clear minded’. Ten days after the last dose of study medication he reported that he was unhappy in his relationship. The following day he started asking questions about his wife and developed ideas focused around his wife being a pharmacist and he might get poisoned. No hallucinations were reported but he refused to eat food that his wife had prepared. He reported normal sleep patterns, mildly depressed mood, reduced concentration, and poor appetite. He continued to work as usual. No concomitant medications were taken during the study and he had no psychiatric history. The subject was seen by a psychiatrist who noted paranoid delusions with initially poor insight. On October 19, 2002 the

psychiatrist assessed improved insight, did not diagnose mania or depression and reported full recovery without the need for treatment.

Study GPP-007-CLN-CP1-1998-230

- Subject 202, a 40-year-old male, experienced 54 AEs of increasing intensity during the course of treatment. Ultimately emotional lability, aggressive behavior, and delusional content of thought resulted in prolonged hospitalization of this 'healthy volunteer'. The narrative indicates that on April 21, 1997 (Day 16) the medication was stopped due to a combination of AEs. The volunteer reported restless legs after every dose of medication but the severity was increasing during the course of treatment. From Day 12 he reported parasthesia/heavy sensations on his back. He was emotionally unstable. He reported vivid, colorful dreams during the night. On Day 15 he reported hyperesthesia (sounds 10 times stronger than normal). The parasthesia in his extremities and back were increasing in intensity. This was an inpatient study, these events required extended hospitalization, and psychiatric treatment was not indicated in the narrative report. The subject reported resolution of all AEs as of May 17, 1997.

Study PGX-08-P1-06 (Thorough QT Study)

- One subject (0601-183) in the vilazodone group experienced syncope on Day 9. This 36-year-old white female (Hispanic or Latino) experienced convulsive syncope and was discontinued from the study. She was randomized to the vilazodone treatment arm and received the first dose of vilazodone 10 mg on Nov 23, 2008. About 3 hours after the dose of vilazodone 40 mg on [REDACTED] (b) (6), while having her blood drawn, the subject experienced an apparent seizure. After further investigation, this was assessed to be convulsive syncope secondary to a vasovagal episode. This is considered to be possibly related to the study drug.
- One subject (0601-106) in the moxifloxacin group experienced convulsion on Day 7. The event lasted one minute and was assessed as not related to the study drug.

Phase 2

In the Phase 2 studies, 44 serious adverse events were reported by 41 patients. Table xxx illustrates the SAEs; narrative reports for pertinent events follow the table. Of the 44 serious adverse events, 23 were reported in the vilazodone treatment groups, 13 in the placebo groups, 5 in the active comparator groups, and 3 were reported prior to study medication randomization.

Table 7.3.2 Phase 2 Placebo-controlled Studies – Serious Adverse Events

ID	Drug	Serious Adverse Event	Intervention	Outcome	D/C From Study	Related To Study Drug
001-1075	(b) (6)	Suicidal Ideation	Hospitalized	Recovered	Yes	Possibly
022-1017		Overdose	Hospitalized	Recovered	Yes	Possibly
025-1376		Diarrhea	Hospitalized	Recovered	Yes	Possibly
033-1260		Depression	Hospitalized	Recovered	Yes	Unlikely
035-1466		Overdose (insomnia)	Emergency Room	Recovered	Yes	Yes
035-1470		HTN	Hospitalized	Recovered	Yes	Yes
042-1598		Pregnancy	Elective Termination	Resolved	Yes	No
001-03565		Pregnancy	Elective Termination	Resolved	No	No
013-02429		Pregnancy (on OCs)	None	Ongoing	Yes	Possibly
002-02046		Pregnancy	None	Ongoing	No	No
017-02545		Tremors	Emergency Room	Resolved	Yes	Possibly
023-02759		Migraine	Unknown	Resolved	Yes	Possibly
021-02713		TIA	Hospitalized	Resolved	Yes	Possibly
026-02866		Fractured R foot	Hospitalized MV accident	Resolved	No	Unlikely
001-04006		Atrial Fibrillation	ECG – med Follow-up	Resolved	No	Possibly
006-04187		Self mutilation	Hospitalized	Recovered	Yes	Unlikely
023-04417		Cervicitis	Hospitalized	Recovered	Yes	Unlikely
005-01334		Suicidal Ideation	Hospitalized	Resolved	Yes	Possibly
036-01704		Pneumonia	Hospitalized	Resolved	Yes	No
008-00245		Pregnancy	None	Resolved	No	No
018-00588	Medication Missing	None	Resolved	No	No	
005-1099	Suicide Attempt	Hospitalized	Alive with sequelae	Yes	No	

006-1219	(b) (6)	Facial fracture	Hospitalized	Recovered	Yes	No
		Pneumo-thorax				
008-1284		Asthma	Hospitalized	Recovered	Yes	No
		Pneumonia	Hospitalized	Recovered		
013-1397		Pregnancy	None	Ongoing	No	No
021-1104		Suicidal Ideation	Hospitalized	Unknown	Yes	No
022-1028		Overdose	Hospitalized	Recovered	Yes	No
031-1544		Pregnancy	None	Unknown	No	No
014-02449		Depression	Hospitalized for psychosis	Resolved	Yes	No
016-02534		Pregnancy	Elective Termination	Resolved	Yes	No
021-03532		Suicidal Ideation	Hospitalized	Resolved	Yes	No
042-03424		Renal Calculus	Hospitalized	Resolved	No	No
024-00793		Pregnancy	Elective Termination	Resolved	No	No
024-00795		Abdominal Hernia	Hospitalized	Resolved	No	No
003-1166		Arrhythmia	Hospitalized CABG Pacemaker Implant	Recovered	Yes	No
		Unstable Angina				
006-1217		Pneumonia	Hospitalized	Recovered	Yes	No
033-1152		Stomach Cramps	Hospitalized	Recovered	Yes	Unlikely
011-02347		Overdose Intentional	Emergency Room	Resolved	Yes	Possibly
027-471		Hernia	Surgery	Recovered	Yes	No
029-285	Pregnancy	Unknown	Unknown	Yes	No	
001-0085	UTI	Unknown	Recovered	Yes	No	

GPP-007-CLN-CP2-2001-244 (EMD 68843-009)

Patient ID **001-1075** was a 20-year-old Caucasian female who was randomized to vilazodone; she received the first dose of study medication on July 24, 1998. On August

10, 1998 she reported suicidal ideation (the dose was 60 mg at the time). She took her last dose of vilazodone on August 15, 1998; she was hospitalized for suicidal ideation on [REDACTED] (b) (6) and was discontinued from the study.

GPP-007-CLN-SP2-2001-245 (EMD 68843-010)

Patient ID **022-1017** was a 19-year-old Caucasian female who was randomized to the medium dose vilazodone treatment arm; she received the first dose on September 29, 1998. On [REDACTED] (b) (6) she attempted suicide by overdose. She consumed 8 Unisom tablets with an undisclosed amount of Tylenol and liquor. She was treated in the emergency room and admitted to the psychiatric unit on [REDACTED] (b) (6). Her medical history includes a previous suicide attempt in 1992. The patient was withdrawn from the study on November 19, 1998.

Patient ID **022-1028** was a 36-year-old Caucasian male who was randomized to the placebo treatment group; he received the first dose of study medication on xxx. On [REDACTED] (b) (6), as a suicide attempt, he ingested a 90-day supply of Zoloft 50 mg, Darvocet N-100 (n=17), flurazepam 15 mg (n=17) and Soma (n=28). The patient was intubated in the emergency room and admitted for treatment and observation. On Day 2 of hospitalization a psychiatric consultation was obtained. The subject was assessed as recovered on [REDACTED] (b) (6). He was discontinued from the study.

Patient ID **033-1260** was a 35-year-old Caucasian female who was randomized to the high dose vilazodone treatment group; she received her first dose of study medication on September 30, 1998. On [REDACTED] (b) (6) she reported worsening of depression for which she was hospitalized. She was in the hospital for one week and was discharged on [REDACTED] (b) (6) when the SAE was considered to be resolved. Her medical history included recurrent depression, fibromyalgia, and IBS. Medication history includes: paroxetine in 1993 and Soma since 1997. While hospitalized she was prescribed Seroquel 150 mg, Effexor, and Buspar. The last dose of study medication was taken on November 2, 1998 and she was withdrawn from the study on December 29, 1998.

Patient ID **035-1466** was a 31-year-old Hispanic male who was randomized to the low dose vilazodone treatment arm; he received the first dose of study medication on October 2, 1998. On [REDACTED] (b) (6) he overdosed. The report indicates that he became frustrated because he was unable to sleep and he took 250 mg chloral hydrate. He still was unable to go to sleep so he took 8000 mg chloral hydrate after which he became concerned and presented to the emergency room. He was evaluated at the emergency room by a crisis worker and released to return home. He was not discontinued from the study at that time and the serious adverse event was considered to be resolved. Within 72 hours of the overdose, the patient presented with profound depression and suicidal ideation which led to discontinuation from the study. His last dose of study medication was on October 23, 1998, he was withdrawn from the study

on November 3, 1998. He was subsequently treated with another antidepressant (Remeron). The event of insomnia is considered to be related to the study medication and the suicidal ideation as possibly related.

Patient ID **035-1470** was a 68-year-old Caucasian female who was randomized to the high dose vilazodone treatment arm; she received the first dose of study medication on November 17, 1998. On [REDACTED] (b) (6) the patient was hospitalized for treatment of hypertension. The report indicates that on December 9, 1998 she complained of a migraine headache with musical hallucinations and poorly formed visual hallucinations. On [REDACTED] (b) (6) her BP was 160/100, repeat BP was 182/100 and she reported palpitations and a 'heavy feeling' in her chest. She was given two doses of clonidine with good results and she was discharged from the hospital on [REDACTED] (b) (6). Medication history included (but not limited to): amitriptyline, Prozac, Celexa, and Synthroid. This SAE is considered likely to be related to the study medication.

GPP-007-CLN-CP2-2003-246 (SB-659746-A)

Patient ID **021-02713** was a 64-year-old female who was randomized to vilazodone treatment; 41 days after the first dose of study medication she developed confusion, agitation, dizziness, stiff neck, and disorientation. ECG was within normal limits and she seemed to improve; however, when she returned home she became more confused and disoriented. She was admitted to the hospital for observation. The following day she did not remember the event. She was alert and oriented and was subsequently diagnosed with a transient ischemic attack (TIA). The study medication was discontinued and the event resolved. She was withdrawn from the study. This is possibly related to the study medication.

Patient ID **017-02545**-The following narrative is copied from the clinical study report: This report refers to a 28-year-old female (patient identification number 003.017.02545). The patient's current medical history included intermittent insomnia. Concomitant medication use included acetylsalicylic acid/caffeine/paracetamol (Excedrin)-last dose 21-Nov-2001.

On 13-Nov-2001, the patient was randomized to study medication. On [REDACTED] (b) (6), the patient was withdrawn from the study due to lack of efficacy and received the last dose of study medication. On [REDACTED] (b) (6), 10 days post the last dose of study medication, the patient was taken to the emergency room due to body tremors. The patient reported a sudden onset of body tremors Wednesday evening, which were "violent" in nature. The patient was treated with intravenous diazepam (Valium), and the tremors subsided "to some degree". The patient was diagnosed with stress. The patient presented on [REDACTED] (b) (6) for further evaluation. Diagnosis of "we don't know what this is" was made. The patient was prescribed alprazolam (Xanax) .05 mg TID and was sent home. CT (computed tomography) scan and complete laboratory work-up reported no findings.

On [REDACTED] (b) (6), the patient came into the clinic for follow-up. The patient's tremors were at her head, neck, torso, arms, and down to her knees. The tremors were described as coarse tremors, three to five beats/second. Due to the tremors, the patient had bruising on her head from hitting it on the floor. The tremors were significant enough that she was unable to drive or perform many of her ADLs (activities of daily living). There appeared to be no obvious cognitive deficits. The patient was sent to a local healthcare facility for a medical and neurological work-up.

In breaking the study medication blind on 17-Dec-2001, the investigator learned that the patient had been randomized to double-blind oral vilazodone (659746) 20 mg. The investigator reported that the patient had never before been treated for depression, and thus had never been exposed to any antidepressant medications, including prior exposure to tricyclics, SSRIs (selective serotonin reuptake inhibitor), and SNRIs (serotonin norepinephrine reuptake inhibitor). The investigator felt the need to break the blind to appropriately evaluate and treat the patient.

The patient was scheduled for a MRI (magnetic resonance imaging) on [REDACTED] (b) (6), but was having trouble getting an appointment with a neurologist since she did not have any medical coverage. The investigator reported that the patient was not taking concomitant medications. She also did not respond to the Xanax, and thus treatment was discontinued. The event resolved on 24-Dec-2001. It was reported that the patient's condition was back to baseline.

GPP-007-CLN-SP2-2001-247 (SB-659746-A)

Patient **ID 001-04006** was a 64-year-old male who was randomized to the vilazodone treatment group. Approximately 8 weeks after beginning the study medication, and on the day of the final dose, the subject had an ECG which revealed bradycardia and normal sinus rhythm. The following day, he had a physical examination and his pulse was noted to be irregular. Another ECG was done which revealed atrial fibrillation. He was referred for internal medicine evaluation – outcome unknown. At the 14-day follow-up visit and ECG revealed normal sinus rhythm.

Patient **ID 006-04187** was a 24-year-old male who was randomized to the vilazodone treatment group; he received the first dose of study medication on August 17, 2002. On [REDACTED] (b) (6) weeks after the first dose of the study medication he experienced self-inflicted lacerations to the forearm after a night of heavy drinking. He was taken to the emergency room where it was determined that his blood alcohol level was elevated. The lacerations were sutured; he was treated with IV fluids and tetanus update. The study medication was stopped and he was discontinued from the trial. His psychiatric history was significant for depression and 'cutting'.

GPP-007-CLN-CP2-2001-248 (SB-659746-A)

Patient ID **005-1334** was a 53-year-old male who was randomized to the vilazodone (20 mg) treatment arm. Approximately 7 weeks after the study medication was initiated, the subject was hospitalized for suicidal ideation. The trial medication was discontinued and the event resolved after 24 days of hospitalization. His medical history includes diabetes, for which he was prescribed metformin.

Phase 3 Placebo Controlled (non-fatal SAEs)

In the two placebo-controlled Phase 3 studies 11 SAEs in 9 patients were reported in the vilazodone group and 9 SAEs in 7 patients were reported in the placebo group. For the vilazodone group the 11 SAEs included two malignancies (possibly three, although it is listed as pleural effusion), one concussion (related to alcohol consumption), one suicide attempt, one psychotic episode, one angina (pre-existing cardiovascular disease). Of those, three are considered by this reviewer as possibly related to vilazodone: depression with psychotic features, angina and atypical chest pain. Sufficient information is not available to establish causality. The SAEs in the placebo group are significant in that the suicidal ideation is likely related to not being in an active treatment arm.

Table 7.3.3 Phase 3 Placebo Controlled SAEs

ID	Drug	Serious Adverse Event	Intervention	Outcome	D/C From Study	Related to Study Drug
0404-004	Vilazodone	Prostate Cancer	Hospitalized	Unknown	Yes	No
0404-012	Vilazodone	Concussion	Hospitalized	Recovered	No	Not Likely
0800-033	Vilazodone	Suicide Attempt (OD Tylenol)	Hospitalized	Recovered	Yes	Not likely
0800-037	Vilazodone	Lymphoma	Hospitalized	Unknown	Yes	No
0800-083	Vilazodone	Depression w/psychotic features	Hospitalized	Resolved at time of hospital discharge	Yes	Possibly
		Psychosis	Hospitalized	Recurrent Psychosis	Yes	Possibly
0400-016	Placebo	Suicidal Ideation	Hospitalized	Recovered	Yes	No
0404-	Placebo	Depression	Unknown	Recovered	Yes	No

003						
0500-012	Placebo	Pregnancy	None Follow-up HCG Negative	Recovered	No	No
0800-022	Placebo	Depression Suicidal Ideation	Hospitalized	Ongoing Suicidality Depressed mood	Yes	No
0800-057	Placebo	Suicidal Ideation	Hospitalized	Recovered	Yes	No
2010-014	Vilazodone	Angina	Hospitalized	Resolved	Yes	Possibly
		AS Carotid Disease	Hospitalized carotid end- arterectomy	Chronic	Yes	No
2020-061	Vilazodone	Pleural Effusion	Hospitalized	Unknown	Yes	Not likely
2020-168	Vilazodone	Chest Pain Atypical	Hospitalized	Resolved	No	Possibly
2070-009	Vilazodone	Cholecystitis	Hospitalized	Recovered	No	Not likely
2050-084	Placebo	Asthma	Hospitalized	Recovered		Not likely
		Asthma	Hospitalized	Recovered		Not likely
2080-019	Placebo	Ankle Fracture	Hospitalized	Not Recovered		Not likely

Study GNSC-04-DP-02

In this study 6 SAEs were reported in 5 patients in the vilazodone group and 6 SAEs were reported in 5 patients in the placebo group. Narrative reports of SAEs were reviewed, those of interest include:

Subject **0404-012** was a 27-year-old white male with a history of nephrectomy, splenectomy, hypertension, and hyperlipidemia. Concomitant medications included ibuprofen, Atacand, rosuvastatin, and Ziac. The patient was randomized to vilazodone and received his first dose of 10 mg on Nov 22, 2006 and was titrated per protocol to 40 mg on Dec 6, 2006. On [REDACTED] (b) (6), the patient suffered a head concussion. The patient was intoxicated and fell, hitting his head on the pavement and losing consciousness. The patient was hospitalized, lacerations required sutures. No action was taken with the study drug in response to the SAE and he completed the study on Jan 16, 2007.

Subject **0800-033** was a 20-year-old white female with a history of IBS, headache, and breast augmentation. Concomitant medications included orthotricyclen and Phenergan. The patient was randomized to vilazodone and received her first dose of 10 mg on Jul 21, 2006 and was titrated per protocol to 40 mg on Aug 4, 2006. On [REDACTED] (b) (6) the patient took an overdose of acetaminophen. Psychiatry consultation revealed a break up with her boyfriend and a history of self injurious behavior (cutting). It was recommended that the patient not be started on psychiatric medications immediately because of the recovering status of her liver. The patient was discharged to home and recovered without sequelae. The patient received her last dose of study medication on [REDACTED] (b) (6) one week prior to the onset of the SAE. At the early termination visit on Sep 21, 2006 there were no notable abnormalities. It is unlikely that this event was related to the study drug.

Subject **0800-083** was a 60-year-old Caucasian female with a history of chronic pain, cardiac murmur and hyperlipidemia. The patient was randomized to the vilazodone treatment group and received the first dose of 10 mg on March 16, 2007. After one week the dose was increased to 20 mg and by March 30, 2007 the dose was increased, per protocol, to 40 mg/day. On April 27, the patient reported 'worsening depression'. Treatment with vilazodone was discontinued by the patient because of depression. She received the last dose of study medication on April 29, 2007. She also received Ambien, lorazepam, aripiprazole, and bupropion for the reported symptoms of 'worsening depression'. On [REDACTED] (b) (6), she was hospitalized for depression with psychotic features. She presented at the emergency room in a confused, guarded, and paranoid state with disorganized thoughts. Urine toxicology was negative, thyroid function tests were within normal limits, and CT scan was unremarkable. Axis I diagnoses included: Psychotic Disorder, NOS; r/o MDD, recurrent, with psychotic features. She was prescribed but refused to take aripiprazole intermittently throughout her hospitalization. Her mood stabilized and affect brightened and on [REDACTED] (b) (6) she was discharged with plans for outpatient follow-up. At the time of her discharge from the hospital she denied hallucinations, delusions, suicidal, or homicidal ideation. The patient was considered recovered without sequelae from the SAE at the time of discharge. Discharge medications included aripiprazole, lorazepam, simvastatin, and medroxyprogesterone acetate.

Subject **0800-057** was a 46-year-old American Indian/Alaskan Native female with a history of cerebral palsy, gestational diabetes, bursitis, headache, rheumatoid arthritis and hypertension. Concomitant medications included Aleve, loratidine, and sertraline (discontinued 10/31/2006). The patient was randomized to placebo (the narrative states vilazodone in the heading and placebo in the text-the dataset indicates placebo) on Nov 21, 2006. On [REDACTED] (b) (6) she experienced SI and presented to the emergency room with suicidal ideation and thoughts of self harm. She was hospitalized for the event. On [REDACTED] (b) (6) she was discharge to home. She received her last dose of the study drug

on Jan 3, 2007. The event was attributed to the disease under study, not related to vilazodone.

Study CLDA-07-DP-02

In this study 5 SAEs were reported in 4 patients in the vilazodone group and 2 SAEs were reported in 3 patients in the placebo group. Narrative reports of SAEs were reviewed, those of interest include:

Subject **2010-014** was a 69 year-old White female with multiple medical problems, including hyperlipidemia, II/IV systolic murmur, GERD, tinnitus, insomnia, and sinus congestion. She was randomized to vilazodone and received 10 mg/day beginning July 22, 2008, the dose was titrated to 40 mg/day by September 3, 2008. Angina was first recorded on August 20, 2008 (at a primary care visit) and on the office visit of (b) (6) she complained of chest tightness and pressure. She appeared diaphoretic and pale, BP 134/66, HR 67 bpm, RR 20 bpm. She was given 0.4 mg SL nitroglycerin and sent to hospital by EMS. On (b) (6) she underwent cardiac catheterization which revealed single vessel disease (LAD). She was discontinued from the study on September 3, 2008. The patient had underlying cardiac disease; however, the event of angina, though unlikely is possibly related to the study drug (reviewer's opinion).

Subject **2020-168** was a 53-year-old Native Hawaiian/Pacific Islander female with hypertension, GERD, steatohepatitis, and headache. She was randomized to vilazodone treatment and received the first dose of 10 mg/day on October 29, 2008. Her dose was increased to 20 mg/day from November 5 to November 11 with treatment interrupted from (b) (6) due to hospitalization (details were not provided in the narrative). The dose was increased to 40 mg from November 12 through December 23. She reported chest pain beginning November 4, 2008. On (b) (6) she presented to the emergency room with a (b) (6) history of chest discomfort. She also reported migraine symptoms. Her blood pressure was 172/108 mmHg, heart rate 67 bpm. It was noted that she had discontinued Cozaar (which she had taken since 2002) against medical advice on August 28, 2008. Pre-existing hypertension was cited as the reason. It is unlikely that this event was related to vilazodone, although it is a possible contributing factor (reviewer's opinion).

Phase 3 Uncontrolled, Long-term Study CLDA-07-DP-04 (Non-fatal SAEs)

There were 33 SAEs that occurred in 23 (4%) patients. The SAE of pneumonia occurred in 2 patients, and all other SAEs occurred in 1 patient each. The most frequent system organ classes consisted of: Infections and Infestations – 5 patients, Respiratory; Thoracic and Mediastinal – 4 patients; Nervous System Disorders – 3 patients; Psychiatric Disorders – 3 patients; and General Disorders and Administration Site Conditions – 3 patients. There was one episode of syncope.

Narrative provided for an episode of syncope:

Patient **4290-040** was a 70 year old white female. Past medical/surgical history included former smoker, facelift, stress test, and benign ovarian tumors removed. Concomitant medical conditions included syncope, hypertension, hiatal hernia, pelvic cystic mass, arthritis, insomnia, hypothyroidism, generalized fatigue, hypercholesterolemia, irregular heartbeat, lipoma on left shoulder, acid reflux, gastroesophageal reflux disease, recurrent urinary tract infections, post menopausal, bursitis, degenerative joint disease, hip pain, trochanteric lumbar spine problem, severe headaches, sleep apnea, and sleep disorder. Her first lifetime episode of MDD occurred at age 56 years and the duration of the current MDD episode (considered severe in severity) was more than 12 months. She received treatment with vilazodone at 10 mg from 28 March to 02 April 2008, at 20 mg from 03 to 07 April 2008, and 40 mg from 08 to 12 April 2008. On [REDACTED] (b) (4), the patient was hospitalized for a syncopal episode which led to study drug discontinuation. The investigator reported that the patient said she had fallen on that date, chipped her tooth, and bit her tongue. The patient reported she had been feeling progressively but mildly weaker in past several weeks, including 3 falls in that time, prior to that day, when she fell in her bathroom, according to Drug Safety records. Those records also indicated that “her vital signs were: blood pressure 93/48 mmHg, pulse 60 bpm, and respiration rate 16 breaths per minute. Laboratory results on [REDACTED] (b) (6) revealed: potassium 3.3 mmol/L [3.6-5.1]; CO2 20 mmol/L [22-32]; BUN 29 mg/dL [8-20]; total protein 5.7 G/dL [6.1-7.9]; albumin 3.3 G/dL [3.5-4.8]; WBC 13.7 thou/mm3 [5.0-10.0]; hemoglobin 16.4 GM/dL [12.0-16.0]; and hematocrit 47.4% [37.0-47.0]. All other results were within normal limits.” The day after hospitalization, she reported feeling dizzy while lying in bed, but examination found no abnormalities at that time. On [REDACTED] (b) (6), her supine blood pressure was 142/75 mmHg, pulse 61 bpm, and standing blood pressure was 119/76 mmHg, pulse 81 bpm, and she complained of severe dizziness and nausea; an echocardiogram on that date revealed an ejection fraction of 60%, normal cardiac chamber size, normal pulmonary pressures at 25-30 mmHg, and trace mitral and tricuspid regurgitation, according to Drug Safety records. These records also indicated that during hospitalization, head CT and chest x-ray were normal, magnetic resonance angiography of the neck revealed no evidence of high-grade stenosis, EEG was within normal, and urinalysis revealed *E. coli*. Although the patient’s atenolol was stopped and she was started on Cozaar (losartan), “she was still noted to have persistent mild bradycardia for several days.” Morphine (start [REDACTED] (b) (6)) was reported as medication used to treat the severe headache related to her syncope and fall. The stop date of the syncopal episode was [REDACTED] (b) (6); she took her last dose of study drug on [REDACTED] (b) (6). The patient was discharged from the hospital on [REDACTED] (b) (6) and she was recovered with sequelae (no details provided).

Study ECG at screening (17 March 2008) was abnormal but not clinically significant, with normal sinus rhythm with nonspecific ST and T wave abnormality and QTcB borderline prolonged; QTcB was 473 ms and QTcF was 459 ms. Study ECG at early termination (23 April 2009) was abnormal but not clinically significant, with an overall

similar interpretation; QTcB was 493 ms and QTcF was 465 ms. Vital signs included blood pressure 144/89 mmHg and pulse 66 bpm at screening, and blood pressure 114/81 mmHg and pulse 98 bpm at early termination, on 23 April 2008. Additional AEs reported for this patient that were related to this syncopal episode: orthostatic hypertension [sic], worsening severe headache (both deemed severe but not related to study drug) and bruising under both eyes, deemed unlikely related to study drug (all with onset 12 April 2008).

Concomitant medications reported at the onset of this SAE included aspirin, atenolol, Lasix (furosemide), and Synthroid (levothyroxine); the atenolol was stopped immediately after the syncopal episode.

The investigator considered the syncopal episode to be serious due to hospitalization. The event was considered severe in intensity and unlikely related to study drug; however, no alternate causality was reported. Syncopal episode was reported as the primary reason for study drug discontinuation; the patient was discontinued from the study on 23 April 2008.

7.3.3 Dropouts and/or Discontinuations

In the Phase 1 development program for vilazodone, 721 male and female subjects were exposed to doses of vilazodone ranging from 1 to 80 mg in single and repeat dose studies. Most subjects were healthy volunteers, although subjects with mild to moderate hepatic and renal impairment were also evaluated.

The treatment emergent adverse events leading to discontinuation were predominantly within the gastrointestinal and nervous systems. During Phase 1 development, the applicant reports 88 subjects who discontinued due to an AE, of those, 24 were discontinued for vomiting.

Comment: Phase 1 AEs were not pooled as a group or with Phase 2 and 3 studies – the Phase 1 studies were reported individually only.

Phase 3 Placebo Controlled Studies (safety population)

In the Phase 3 placebo-controlled trials, 31(7%) patients in the vilazodone group discontinued due to an adverse event compared with 14 (3%) in the placebo group. The most common adverse events leading to discontinuation in the phase 3 studies were gastrointestinal complaints (2%), and the most concerning adverse events leading to discontinuation were cardiac disorders (1%). Four patients on vilazodone and zero patients on placebo discontinued due to palpitations. One event of pneumonia was reported, however, review of the narrative indicates the patient had a pleural effusion and liver mass.

Table 7.3.4 AEs Leading to Discontinuation – Phase 3 Placebo-Controlled

System Organ Class Preferred Term	Vilazodone 40 mg/day N=436	Placebo N=433	
Gastrointestinal disorders	10 (2.3)	1 (0.2)	
Diarrhea	4 (0.9)	0	
Nausea	2 (0.5)	1 (0.2)	
Abdominal discomfort	1 (0.2)	0	
Abdominal pain	1 (0.2)	0	
Dyspepsia	1 (0.2)	0	
Vomiting	1 (0.2)	0	
General disorders	6 (1.4)	1 (0.2)	
Fatigue	2 (0.5)	0	
Asthenia	1 (0.2)	0	
Chest pain	1 (0.2)	0	
Feeling abnormal	1 (0.2)	0	
Feeling jittery	1 (0.2)	0	
Irritability	0	1 (0.2)	
Cardiac disorders	5 (1.1)	0	
Palpitations	4 (0.9)	0	
Angina pectoris	1 (0.2)	0	
Ventricular extrasystoles	1 (0.2)	0	
Psychiatric disorders	4 (0.9)	6 (1.4)	
Depression	2 (0.5)	1 (0.2)	
Confusional state	1 (0.2)	0	
Panic attack	1 (0.2)	0	
Anxiety	0	1 (0.2)	
Suicidal ideation	0	3 (0.7)	
Tension	0	1 (0.2)	
Nervous system disorders	2 (0.5)	4 (0.9)	
Dizziness	1 (0.2)	0	
Migraine	1 (0.2)	0	
Headache	0	3 (0.7)	
Tension headache	0	1 (0.2)	
Blood and lymphatic system disorders	1 (0.2)	0	
Lymphadenopathy	1 (0.2)	0	
Infections and infestations	1 (0.2)	0	
Pneumonia *(actually pleural effusion)	1 (0.2)	0	
Neoplasm, benign, malignant and unspecified	1 (0.2)	0	
Prostate cancer	1 (0.2)	0	
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	
Dyspnea	1 (0.2)	0	
Musculoskeletal and connective tissue disorders	0	1 (0.2)	
Muscular weakness	0	1 (0.2)	
Skin and subcutaneous disorders	0	1 (0.2)	
Skin reaction	0	1 (0.2)	

Table 7.3.5 TEAEs by SOC for Phase 3 Placebo-Controlled Safety Database

System Organ Class Preferred Term	Vilazodone 40 mg/day N=436 N (%)	Placebo N=433 N (%)
Gastrointestinal disorders	234 (53.7)	101 (23.3)
Diarrhea	122 (28.0)	40 (9.2)
Nausea	102 (23.4)	22 (5.1)
Vomiting	20 (4.6)	5 (1.2)
Nervous System disorders	142 (32.6)	101 (23.3)
Dizziness	37 (8.5)	20 (4.6)
Restless legs syndrome	7 (1.6)	0
Tremor	7 (1.6)	0
Psychiatric disorders	87 (20.0)	35 (8.1)
Insomnia	26 (6.0)	9 (2.1)
Abnormal dreams	18 (4.1)	5 (1.2)
Libido decreased	16 (3.7)	1 (0.2)
Orgasm abnormal	7 (1.6)	0
Anorgasmia	6 (1.4)	0
Reproductive system and breast disorders	18 (4.1)	10 (2.3)
Ejaculation delay	4 (0.9)	0
Cardiac disorders	12 (2.8)	1 (0.2)
Palpitations	9 (2.1)	1 (0.2)

Phase 3 Uncontrolled Study

There were 124 patients (21%) who had a TEAE that led to discontinuation in this study. The applicant provided a summary table of discontinuations with incidence of >1%. The most frequent TEAEs leading to discontinuation were as expected, nausea 8 (1.3%) and diarrhea 7 (1.2%), followed by anxiety 6 (1%) and insomnia 5 (1%). Interestingly, after insomnia, palpitations was the next most frequent with 4 (1%). The narratives for these AEs were perused, it is difficult to interpret the association as these patients had multiple medical conditions and were taking numerous concomitant medications.

Four patients had a positive pregnancy test during the treatment period. All 4 had negative pregnancy tests at screening and baseline, during the treatment period had a positive test and was discontinued prematurely due to pregnancy. A fifth patient had a

ruptured ectopic pregnancy. Follow up on these pregnancies can be found in Section 7.6.2 of this review.

7.3.5.1 Ocular Findings

Background

During the development of vilazodone, questions have been raised concerning four potential ocular problems: lens opacities, retinal lesions, corneal opacities, and ocular dryness. The Division of Anti-Infective and Ophthalmology has been consulted to review this data. At the time of this writing the consult has not been completed.

Systematic ophthalmologic evaluation of patients in the clinical studies began when dose dependent occurrence of corneal opacities was demonstrated in dogs. (b) (4)

At that time, Dr. Wiley Chambers concluded that ocular testing had detected abnormalities in tear production, cataract formation and retinal abnormalities. The results from the corneal studies were deemed inconclusive due to inconsistent data. Dr Chambers recommended that ocular testing continue.

Two ophthalmology consults have been completed for IND 54613. The first consultation, dated May 6, 2001 included the review of a 52-week toxicology study (which confirmed transient corneal opacities in dogs), and the review of slit lamp and funduscopy findings from studies EMD 68843-009 and -010.

The Reviewer's comments were as follows:

1. It is not clear how the data has been reported and this 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.
3. The retina abnormalities should be explained.
4. Reduction in tear production demonstrated a dose dependent effect.

The second ophthalmology consult is, dated December 19, 2005, regarding the End of Phase 2 Meeting states:

- The potential of vilazodone to cause cataract and retinal lesions needs to be evaluated in longer term studies.
- 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 following text is taken from minutes of the End of Phase 2 meeting on December 20, 2005:

Does the agency concur that detailed ophthalmologic examinations are not needed in this trial? Does the agency concur that detailed ophthalmologic examinations are no longer necessary in the development program for vilazodone?

Comment: *We agreed that detailed ophthalmologic examinations are not needed in this trial because it would be too short in any case to detect lenticular or retinal changes. However, we did inform them that for longer term exposures they will need to include baseline and every 6 months slit lamp exams and dilated funduscopy to assess for possible lenticular or retinal changes.*

Applicant response

The applicant engaged an independent 'expert' to review data from the visual assessments performed in the five 8-week Phase 2 clinical studies and TEAE data from the Phase 2 clinical program. The applicant's independent expert noted that data collection methods in the Phase 2 studies for cataracts and funduscopy were not optimal in that there was no requirement for the evaluations to be performed by the same examiner, which complicated the interpretation of the results. Nevertheless, the expert concluded that the data collected provided sufficient support that vilazodone did not cause cataracts or deleterious funduscopy findings over the 8-week treatment period in Phase 2.

The applicant indicates that in the uncontrolled long-term study, visual acuity scores remained stable at End of Treatment for 98% of the subjects and 'few subjects' had abnormal findings on slit-lamp biomicroscopy, corneal evaluations, or dilated funduscopy.

The applicant asserts that the results of detailed ophthalmologic exams did not demonstrate clinically significant eye changes and except for a mild drying effect on the eye, there are no indications of any clinically important ophthalmologic effects of vilazodone.

Reviewer assessment

The data presented in the five Phase 2 studies and the long-term, open-label study is difficult to interpret. Slit lamp and fundoscopic evaluations collected for each eye were assessed as normal or abnormal within each region and sub-region. Treatment-emergent abnormalities were enumerated and summarized with frequencies and percentages at the end of study visit. An end of study assessment of abnormal for a region or sub-region was considered treatment emergent only if the baseline assessment is present and normal. The denominator for percentages is the number of subjects with a normal baseline assessment and a post-baseline assessment. If a region of a particular eye is marked normal but one or more of its sub-regions are marked abnormal, then the region of that eye will be considered abnormal. This reviewer found it very difficult to confirm the data reported by the applicant.

Because of the serious implications of ocular pathology, the division has requested ophthalmology consultation to assist with interpretation.

At the time of this writing, Dr. Chamber's consult was not available. However, during the status meeting of November 30, 2010 he informed the review team of the his opinion. This reviewer interprets his comments as:

1. A definitive answer regarding the development of cataracts in association with vilazodone cannot be provided because a placebo controlled trial of one year's duration would be necessary to provide an answer. This is not a reason for a Post Marketing Requirement. The information regarding the possible association with cataract development should be provided in adverse reactions section of labeling.
2. The finding of retinal lesions is negative – retinal lesions did not occur more frequently in the vilazodone group than in the placebo group.
3. Vilazodone is associated with dry eye and should be labeled to indicate this finding.

Vilazodone Overdose

Overall, none of the overdoses related to vilazodone were lethal, the exposure to vilazodone was low and there were few episodes.

To confirm the applicant's report, JMP table line listings of all SAEs were referenced to identify reports of overdose, ingestion, toxicity, and suicide attempts. Narrative reports pertaining to overdoses of vilazodone are provided in the following text. Narrative reports regarding the overdose of other substances are provided in Section 7.3.2 Nonfatal SAEs.

Phase 1

There were no reports of overdose in the Phase 1 studies.

Phase 2 and Phase 3

According to the Integrated Summary of Safety, overdose of study medication occurred in 8 subjects and the child of one subject. Five of the eight ingested vilazodone study drug product and four subjects ingested a substance other than the study drug. One subject was not reported as an overdose, but the TEAE was reported as 'serotonin syndrome'. In some cases, an irregularity in drug accountability was reported as an overdose.

Subject CLDA-07-DP-**04-4040-0001**(long-term, open-label study) – A 24-year-old African American female presented in a mute and combative state with symptoms of agitation and visual hallucinations. Vitals were reported as: blood pressure 152/79 mmHg, HR 155 bpm, and temperature 98.4°. The history indicates that she had "missed

a couple of days and took 5 or 6 pills to catch up” the night prior to the event. She was given the following medications: haldol, lorazepam, midazolam, charcoal, famotidine, magnesium sulfate, and potassium. She was medically stabilized and discharged home in less than 48 hours. She was subsequently discharged from the study.

Subject **0010-1094** (EMD68843-009) – A 25-year-old Caucasian female inadvertently took a double-dose of study medication after approximately one month on study drug. The same day as the ingestion she reported two episodes of disorientation and restlessness. No action was taken and the subject recovered without event.

Subject **0035-1161** (SB 659746-002) – A 51-year-old Caucasian male, “experienced a mild overdose” while taking vilazodone 10 mg/day. The narrative does not indicate the amount of drug taken. No action was taken and he “recovered the same day”.

Subject **0018-0588** (SB 659746-002) – A 49-year-old Caucasian female “experienced a mild overdose (verbatim term=potential study drug overdose) after 32 days of taking vilazodone 5 mg/day”. The narrative does not indicate the amount of drug taken. The event was repeated a few days later. For both events, no action was taken and the subject fully recovered.

Subject CLDA-07-DP-**04-4180-004** (long-term, open-label study) – A 21-year-old Caucasian female, discovered that her 21-month-old son had obtained her study medication bottle (vilazodone 40 mg). She found him chewing on a “couple of pills” and she was able to remove 1 tablet from his mouth. She estimated that he had ingested 5 to 7 pills. The child was taken to the emergency room, given activated charcoal and subsequently had several episodes of emesis. The record indicates that after about 45 minutes he was noted to be very sleepy and lethargic. No seizure activity was noted. The subject was a Caucasian male, 35 inches tall and 26.4 pounds at the time of the event. Hematology and chemistry (including LFTs) lab values were within normal limits. He was admitted to a local children’s hospital with temperature 98.6, HR 132 bpm, RR 36 breaths per minute and blood pressure 130/69 mmHg. Within a few hours of arrival he was noted to be back to his usual baseline and taking appropriate hydration. At admission and the following day, ECG revealed normal sinus rhythm. He was discharged home on the day following the incident.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase 1 Studies

Phase 1 consisted of 24 studies with short-term exposure in healthy subjects and subjects with hepatic or renal impairment. There were 721 subjects who received

vilazodone at any dose during the Phase 1 studies. The applicant did not pool data from the Phase 1 studies in any safety database. The JMP tables for the Phase 1 studies were reviewed to assess the incidence of adverse events. As expected, the most frequent AEs were nausea, headache, diarrhea, dizziness, and vomiting.

Table 7.4.1 AEs Reported in ≥5% of Vilazodone Subjects – Phase 1

AEDECOD	N	% n=459
Nausea	240	52
Headache	199	43
Diarrhea	157	34
Dizziness	128	28
Vomiting	112	24
Fatigue	65	14
Abdominal pain or discomfort	34	7
Somnolence	29	6
Hyperhidrosis	26	6
Feeling hot	22	5

Phase 2/3 Studies

A number of commonly reported adverse events appeared to be related to vilazodone treatment. The following AEs occurred in at least 5% of vilazodone subjects and were reported at least twice as commonly in the placebo group: diarrhea 28%, nausea 23%, vomiting 5%, sexual dysfunction 9%, and abnormal dreams 5%. Insomnia was reported more than two times as frequently in the vilazodone treated patients.

The safety population for the phase 2 and 3 placebo controlled studies consisted of 433 patients in the placebo groups and 436 patients in the vilazodone groups. The most significant finding when reviewing the two pivotal studies is the high rate of gastrointestinal adverse events. The design for the two pivotal studies allowed for a dose titration phase and specified the drug to be taken with food. However, titration did not completely eliminate the adverse GI effects associated with vilazodone. More than half of the patients exposed to vilazodone experienced a gastrointestinal adverse event. Sexual dysfunction was captured in the spontaneous adverse event reporting at approximately 10% and is addressed later in the safety review.

Table 7.4.2 AEs Reported in ≥2% of Vilazodone Treated Subjects Phase 3 Placebo-Controlled Database

AEBODSYS	Vilazodone n=436 n (%)	Placebo n=433 n (%)
Gastrointestinal disorders	234 (54)	102 (24)
Diarrhea	122 (28)	40 (9)
Nausea	102 (23)	22 (5)
Vomiting	20 (5)	5 (1)

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Gastroenteritis ¹	16 (4)	4 (1)
Nervous system disorders	218 (50)	101 (23)
Headache	66 (15)	62 (14)
Dizziness	37 (8)	20 (5)
Somnolence or sedation	21 (5)	12 (3)
Restlessness or akathisia ³	15 (3)	1 (0)
Tremor	7 (2)	0
Infections and infestations ²	74 (17)	77 (18)
Upper respiratory infection	15 (3)	32 (7)
Common cold	10 (2)	12 (3)
Psychiatric disorders	87 (20)	36 (8)
Insomnia	31 (7)	12 (3)
Anxiety (anxiety or panic)	7 (2)	6 (1)
Abnormal dreams	22 (5)	7 (2)
Sexual (abnormal orgasm or libido)	28 (6)	2 (0)
Musculoskeletal and connective tissue disorders	37 (8)	36 (8)
Pain	24 (6)	30 (7)
General disorders and administration site conditions	40 (9)	34 (8)
Fatigue	16 (4)	13 (3)
Skin and subcutaneous tissue disorders	18 (4)	13 (3)
Rash	5 (1)	5 (1)
Diaphoresis/sweating	10 (2)	3 (1)
Respiratory, thoracic and mediastinal disorders	15 (3)	10 (2)
Nasal congestion/inflammation	6 (1)	2 (0)
Sore throat	4 (1)	4 (1)
Injury, poisoning and procedural complications	18 (4)	18 (4)
Investigations ⁴	15 (3)	13 (3)
Abnormal lab results	5 (1)	2 (0)
Abnormal ECG or blood pressure	2 (0)	5 (1)
Weight gain	4 (1)	4 (1)
Metabolism and nutrition disorders	17 (4)	10 (2)
Increased appetite	10 (2)	4 (1)
Reproductive system and breast disorders	18 (4)	10 (2)
Erectile dysfunction	12 (3)	2 (0)
Cardiac disorders	12 (3)	1 (0)
Palpitations	8 (2)	1 (0)

¹ There were sixteen cases of “gastroenteritis” coded as infections and infestation, it is the opinion of this reviewer they should be coded as GI AEs.

² The 16 cases of gastroenteritis in vilazodone groups and 4 cases in placebo groups were subtracted from infections and infestations (90-16=74 and 81-4=77).

³ Restlessness was coded as psychiatric, nervous system disorders, and ‘restless legs’, in this table all are combined with akathisia and coded as restlessness.

⁴ Reports are reviewed and discussed in specific areas of the Safety Review.

The following tables illustrate the incidence of TEAEs by SOC and PT for the all placebo-controlled database. The same patterns of adverse events seem to persist across all dose levels. The gastrointestinal AEs appear to be more consistent across the dose range whereas the nervous system and psychiatric AEs show a significant dose-related increase. The rate of diarrhea and vomiting remained stable across the dose ranges; a small dose related increase was seen with nausea and dry mouth. The incidence of insomnia tripled from 6% to 18% from the 40 mg dose to >40 mg. There

was also a substantial increase in the incidence of anxiety when the dose increased to >40 mg.

Table 7.4.3 Incidence of TEAEs by SOC and Preferred Term Reported by ≥5% of Subject All Placebo-Controlled Database

System Organ Class ^{a,b} Preferred Term ^{a,b}	Placebo N=997 n (%)	Vilazodone <40 mg/day N=903 n (%)	Vilazodone 40 mg/day N=441 n (%)	Vilazodone >40 mg/day N=227 n (%)	Vilazodone All Doses N=1578 n (%)
All Subjects^a					
Number of subjects with at least 1 TEAE	732 (73.4)	734 (81.3)	368 (83.4)	210 (92.5)	1318 (83.5)
Total Number of TEAEs	2218	2761	1199	1109	5087
Gastrointestinal Disorders	310 (31.1)	445 (49.3)	247 (56.0)	135 (59.5)	830 (52.6)
Diarrhoea	98 (9.8)	195 (21.6)	130 (29.5)	61 (26.9)	387 (24.5)
Nausea	84 (8.4)	146 (16.2)	112 (25.4)	67 (29.5)	328 (20.8)
Dry mouth	62 (6.2)	80 (8.9)	38 (8.6)	28 (12.3)	146 (9.3)
Dyspepsia	36 (3.6)	52 (5.8)	14 (3.2)	10 (4.4)	76 (4.8)
Vomiting	21 (2.1)	27 (3.0)	27 (6.1)	15 (6.6)	71 (4.5)
Nervous System Disorders	298 (29.9)	294 (32.6)	153 (34.7)	128 (56.4)	577 (36.6)
Headache	182 (18.3)	170 (18.8)	66 (15.0)	49 (21.6)	285 (18.1)
Dizziness	45 (4.5)	54 (6.0)	37 (8.4)	43 (18.9)	135 (8.6)
Somnolence	30 (3.0)	33 (3.7)	14 (3.2)	23 (10.1)	71 (4.5)
Tremor	5 (0.5)	10 (1.1)	7 (1.6)	13 (5.7)	30 (1.9)
Psychiatric Disorders	141 (14.1)	186 (20.6)	96 (21.8)	114 (50.2)	400 (25.3)
Insomnia	43 (4.3)	68 (7.5)	27 (6.1)	40 (17.6)	137 (8.7)
Abnormal dreams	22 (2.2)	26 (2.9)	20 (4.5)	25 (11.0)	71 (4.5)
Anxiety	25 (2.5)	32 (3.5)	5 (1.1)	18 (7.9)	55 (3.5)
Nightmare	8 (0.8)	11 (1.2)	5 (1.1)	14 (6.2)	30 (1.9)
Infections and Infestations	190 (19.1)	176 (19.5)	85 (19.3)	50 (22.0)	311 (19.7)
Nasopharyngitis	57 (5.7)	47 (5.2)	21 (4.8)	11 (4.8)	79 (5.0)
Upper respiratory tract infection	56 (5.6)	34 (3.8)	20 (4.5)	12 (5.3)	66 (4.2)
General Disorders and Administration Site Conditions	95 (9.5)	114 (12.6)	43 (9.8)	42 (18.5)	199 (12.6)
Fatigue	34 (3.4)	39 (4.3)	15 (3.4)	15 (6.6)	69 (4.4)

Table 7.4.4 Incidence of TEAEs by SOC and Preferred Term Reported by ≥5% of Subject All Placebo-Controlled Database

System Organ Class ^{a,b} Preferred Term ^{a,b}	Placebo N=997 n (%)	Vilazodone <40 mg/day N=903 n (%)	Vilazodone 40 mg/day N=441 n (%)	Vilazodone >40 mg/day N=227 n (%)	Vilazodone All Doses N=1578 n (%)
Musculoskeletal and Connective Tissue Disorders	125 (12.5)	83 (9.2)	42 (9.5)	32 (14.1)	158 (10.0)
Eye Disorders	76 (7.6)	97 (10.7)	12 (2.7)	29 (12.8)	139 (8.8)
Skin and Subcutaneous Tissue Disorders	59 (5.9)	72 (8.0)	20 (4.5)	47 (20.7)	140 (8.9)
Hyperhidrosis	10 (1.0)	21 (2.3)	5 (1.1)	14 (6.2)	41 (2.6)
Pruritus	5 (0.5)	6 (0.7)	4 (0.9)	12 (5.3)	22 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	63 (6.3)	63 (7.0)	14 (3.2)	18 (7.9)	95 (6.0)
Metabolism and Nutrition Disorders	26 (2.6)	51 (5.6)	19 (4.3)	9 (4.0)	79 (5.0)
Investigations	81 (8.1)	100 (11.1)	22 (5.0)	31 (13.7)	154 (9.8)
Reproductive System and Breast Disorders	34 (3.4)	31 (3.4)	19 (4.3)	16 (7.0)	66 (4.2)
Injury, Poisoning and Procedural Complications	37 (3.7)	36 (4.0)	15 (3.4)	13 (5.7)	65 (4.1)
Renal and Urinary Disorders	16 (1.6)	26 (2.9)	9 (2.0)	13 (5.7)	48 (3.0)

a MedDRA version 11.1. Subjects were counted once at each level of summarization (overall, system organ class, and preferred term).

b All SOC and preferred terms with incidence ≥5.0% in any treatment group are displayed.

KEY: SOC=system, organ class; TEAE=treatment-emergent adverse event.

Source: [Appendix 2, Table 5.1.1.](#)

7.4.2 Laboratory Findings

Mean Change from Baseline

a. Clinical Chemistry

Phase 1

No values of clinical concern were reported by the applicant for the Phase 1 studies.

Phase 2 and 3

1. Mean Change from Baseline

The applicant provided several tables to illustrate the findings from the phase 2 and 3 studies which were reviewed along with the JMP line listings. Overall, based on review of the data as submitted, it does not appear that there is a clinically significant difference between vilazodone and placebo in the mean change from baseline chemistry parameters.

Table 7.4.5 Chemistry: Mean Change from Baseline to LOCF Endpoint – All Placebo Controlled (Phase 2 and 3 Studies)*

	All doses vilazodone	<40 mg/day	40 mg/day	>40 mg/day	Placebo
ALT (U/L)					
N	1412	787	401	220	897
Change (SD)	0.34 (10.7)	0.01 (10.5)	1.36 (11.4)	-0.32 (9.7)	0.12 (9.7)
AST (U/L)					
N	1412	787	401	220	897
Change (SD)	0.49 (7.4)	0.15 (7.6)	1.51 (7.9)	-0.15 (5.7)	0.17 (6.9)
ALP (U/L)					
N	1412	787	401	220	898
Change (SD)	0.50 (10.8)	0.21 (10.5)	0.63 (12.0)	1.33 (8.9)	-0.41 (9.1)
ALB (U/L)					
N	1048	681	367	N/A	713
Change (SD)	-0.56 (2.4)	0.58 (2.2)	-0.52 (2.7)		-0.61
GGT (U/L)					
N	750	126	401	219	569
Change (SD)	-0.26 (13.7)	0.36 (10.5)	-0.62 (14.8)	0.08 (13.2)	-0.57 (13.6)
Bicarb mmol/l					
N	388	20	368	N/A	384
Change (SD)	-0.23 (2.9)	-1.34 (2.9)	-0.17 (2.9)		-0.35 (3.1)
Bili µmol/l					
N	1410	787	400	219	896
Change (SD)	-0.23 (3.8)	-0.18 (4.0)	-0.40 (3.3)	-0.09 (3.9)	-0.09 (3.5)
BUN mmol/l					
N	1412	787	401	220	898
Change (SD)	0.09 (1.4)	0.07 (1.2)	0.13 (1.1)	0.06 (1.2)	0.8 (1.2)
Calc mmol/l					
N	1412	787	401	220	898
Change (SD)	-0.02 (0.1)	-0.02 (0.1)	-0.021 (0.1)	-0.02 (0.1)	-0.02 (0.1)
CK (IU/L)					
N	364	106	34	220	185
Change (SD)	12.9 (81)	5.38 (61.9)	40.6 (76.6)	12.8 (89)	-3.84 (100)
Cl ⁻ mmol/L					
N	1049	681	368	N/A	713
Change (SD)	0.35 (2.7)	0.30 (2.6)	0.45 (2.9)		0.25 (2.5)
Creat µmol/l					
N	1412	787	401	220	898
Change (SD)	3.1 (11.9)	2.0 (11.7)	4.08 (11.9)	5.42 (12.3)	1.03 (11.6)
Glu mmol/l					

N	744	126	394	220	558
Change (SD)	0.15 (1.4)	0.40 (1.2)	0.04 (1.4)	0.2 (1.3)	0.18 (1.2)
K+ mmol/l					
N	1404	786	395	219	887
Change (SD)	-0.04 (0.5)	0.06 (0.4)	-0.13 (0.7)	0.01 (0.4)	-0.6 (0.4)
Phos mmol/l					
N	1041	681	360	N/A	702
Change (SD)	0.00 (0.09)	0.01 (0.1)	-0.01 (0.1)		-0.01 (0.1)
PRL ng/ml	Prolactin				
N	362	105	34	219	185
Change (SD)	1.3 (5.5)	0.66 (4.7)	1.62 (5.8)	1.45 (5.8)	0.9 (7.2)
Na+ mmol/l					
N	1413	787	402	220	898
Change (SD)	0.16 (2.6)	0.02 (2.5)	0.48 (2.9)	0.08 (2.5)	0.01 (2.5)

*Source: Appendix 2 Table 16.1 Integrated Summary of Safety

Review of the individual patient results revealed a number of elevated serum cholesterol and triglyceride results. In the all Placebo-controlled Database of vilazodone all doses, of 361 patients exposed, 5 (1.4%) had PCS results compared with 185 exposed in the placebo group where 0 had PCS results. These were not listed in the table as there was no indication that the patients were fasting at the time of specimen collection, most of the patients with elevated results had abnormal values at Screening, and there was no discernable pattern as the values tended to fluctuate throughout the study period.

2. Outliers

The JMP line listings and CSR laboratory results were assessed for Hy's Law; no cases were reported or discovered to meet Hy's Law criteria. There were some cases of elevated liver enzymes, but many were high at Screening and there did not appear to be a pattern related to vilazodone use.

Table 7.4.6 Chemistry: Incidence of Potentially Clinically Significant Abnormalities – All Placebo Controlled Database, Safety Population

Parameter and Potentially Clinically Significant Criteria	Treatment Groups				
	Vilazodone				PBO
	All doses	<40 mg/d	40 mg/d	>40 mg/d	Placebo
	N PCS (%)	N PCS (%)	N PCS (%)	N PCS (%)	N PCS (%)
ALT (>3xULN)	1417 1 (0.1)	792 1 (0.1)	401 0 (0)	220 0 (0)	899 0 (0)
AST (>3xULN)	1417 1 (0.1)	792 0 (0.1)	401 1 (0.2)	220 0 (0)	899 0 (0)

ALP (2xULN)	1417 0 (0)	792 0 (0)	401 1 (0)	220 0 (0)	899 0 (0)
GGT (3xULN)	746 4 (0.5)	126 1 (0.8)	398 2 (0.5)	218 1 (0.5)	569 1 (0.2)
Bilirubin (1.5xULN)	1411 8 (0.6)	790 3 (0.4)	398 1 (0.3)	219 4 (1.8)	897 4 (0.4)
BUN (>30 mg/dl)	1412 0 (0)	792 0 (0)	396 0 (0)	220 0 (0)	899 2 (0.2)
Creatinine (>2.0 mg/dl)	1417 1 (0.1)	792 0 (0)	401 1 (0.2)	220 0 (0)	900 1 (0.1)
Cholesterol (>1.6xULN)	361 5 (1.4)	105 1 (1.0)	33 0 (0)	219 4 (1.8)	185 0 (0)
Calcium (<0.9xLLN) (<1.1xULN)	1417 1 (0.1) 1417 2 (0.1)	792 0 (0) 792 1 (0.1)	401 1 (0.2) 401 1 (0.2)	220 0 (0) 220 0 (0)	899 1 (0.1) 900 0 (0)
Phosphate (<0.8xLLN) (>1.2xULN)	1045 0 (0) 1046 5 (0.5)	684 0 (0) 685 3 (0.4)	361 0 (0) 361 2 (0.6)	0 0	703 2 (0.3) 703 2 (0.3)
Free T ₄ (<4.5µg/dl) (>12.5µg/dl)	410 1 (0.2) 410 1 (0.2)	45 0 (0) 45 0 (0)	365 1 (0.3) 365 1 (0.3)	0 0	399 0 (0) 399 0 (0)
TSH (<0.35mIU/L) (>5.50mIU/L)	411 2 (0.5) 412 1 (0.2)	45 0 (0) 46 0 (0)	365 2 (0.5) 365 1 (0.3)	1 0 (0) 1 0 (0)	400 2 (0.5) 398 1 (0.3)

Source: Table 65 (ISS 5.3.5.3.2)

Uncontrolled, Long-term Safety Database

The ISS indicates PCS values <1% for glucose, BUN, creatinine, Free T₃, Free T₄, phosphate, potassium, and TSH low. For urate and TSH high, the percentages were 1.5 and 1.7 respectively. If these values were not reported as TEAEs or there was no pre-existing contributors were listed in the medical history, a narrative was provided. As such, narratives for glucose, potassium, and thyroid function tests were reviewed. This was an uncontrolled study, patients were on numerous concomitant medications, and many had co-morbid conditions; therefore it is not prudent to draw conclusions.

Thyroid Function Tests

JMP line listings from the Placebo-controlled, Phase 3 database were reviewed. Overall conclusions regarding thyroid function indicated that changes in laboratory test results suggesting possible treatment-emergent hypothyroidism or hyperthyroidism occurred no more frequently in subjects who received vilazodone than subjects who received placebo.

b. Hematology

Phase 1

The applicant reported no values of clinical concern for the Phase 1 studies.

Phase 2 and 3 Placebo-controlled Database

1. Mean Change from Baseline

In the all placebo controlled database variations in means were minimal and within expected limits of normal variation for all hematology parameters. There were no clinically significant mean changes from baseline when the vilazodone groups were compared with the placebo groups. The following table represents the mean change from baseline LOCF for the two pivotal trials compared with placebo. Similar results were observed for the 5 Phase 2 studies.

Table 7.4.7 Hematology: Mean Change from Baseline Placebo-controlled Phase 3

Parameter	Vilazodone 40 mg			Placebo		
	N	BL	Δ	N	BL	Δ
WBC x 10 ⁹ /L	435	7.1	-0.08	426	7.3	-0.08
RBC x 10 ¹² /L	436	4.6	-0.02	430	4.68	-0.05
HGB mg/dl	433	13.9	-0.63	430	14.1	-1.12
HCT %	432	41.7	-0.16	430	42.0	-0.32
PLT x 10 ⁹ /L	431	272	-0.44	426	278	-1.18

Source: Appendix 2 Table 17.2 (ISS)

2. Outliers

The applicant provided tables of the 'PCS' hematology results. The JMP line listings of the two pivotal studies were reviewed; low and high abnormal results were selected and checked against baseline results and/or history. There were no obvious treatment-associated changes in hematology parameters nor were there any significant outliers. This reviewer does not perceive a difference in the vilazodone group compared with the placebo group on hematology parameters, specifically hemoglobin, hematocrit, WBC, or PLT.

Phase 3 Uncontrolled, Long-term Safety Database

The variations in means were minimal and within the expected limits of normal variation. There were no clinically significant mean changes from baseline in the uncontrolled safety database.

c. Urinalysis

Phase 1

The applicant's report indicates no changes of clinical concern for the Phase 1 studies.

Phase 2 and 3 Placebo Controlled

For the 'all doses' of vilazodone exposure (5 phase 2 and 2 phase 3 trials) the percentage of patients with glycosuria was 3% for both placebo and vilazodone. Proteinuria was present in approximately 5% of those in the vilazodone group as compared with about 3% in the placebo group. The PCS urinary abnormalities are similar between the two groups. The serum creatinine and BUN results of the vilazodone exposed urinalysis PCS cases were reviewed; no associated elevation in serum creatinine or BUN was found. There does not appear to be a clinically significant difference between the vilazodone and placebo groups for proteinuria or glycosuria.

Table 7.4.8 Urinalysis: Phase 2 and 3 Glucose and Protein Outliers

	Vilazodone 40 mg/day N 357 (%)	Vilazodone All dose N 528 (%)	Placebo N 469 (%)
	Glucose		
Negative	343 (96)	509 (97)	456 (97)
Trace	8 (2.2)	8 (1.5)	5 (1)
1+	0	1 (0.2)	1 (0.2)
2+	0	2 (0.4)	1 (0.2)
3+	6 (1.7)	7 (1.3)	6 (1.3)
	Protein		
Neg/Trace	341 (96)	502 (95)	455 (97)
1+	12 (3.4)	21 (4)	14 (3)
2+	3 (0.8)	4 (0.8)	0
3+	1 (0.3)	1 (0.2)	0

Source: Appendix 2 Table 19.1 ISS

Phase 3 Uncontrolled, Long-term

Urinalysis results in the Long-term, uncontrolled study were similar to the results for the placebo-controlled study with 15/526 (2.9%) of patients with glycosuria and 12/526 (2.3%) of patients with proteinuria. Of these, 9 glucose (1.7%) and 5 protein (1%) were considered PCS.

7.4.3 Vital Signs

Phase 1

The Phase One studies safety assessments were not pooled to be reported in any of the four safety databases.

Phase 2 and 3 Placebo-controlled

A. Vital Sign Assessments

In the 5 phase 2 and 2 phase 3 placebo-controlled studies, vital sign measurements included blood pressure (sitting) and heart rate at screening, baseline, and each follow-up visit. Respiratory rate was included in the phase 3 studies but not in the phase 2 studies. Oral temperature was included in the phase 2 studies but not in the phase 3 studies.

B. Potentially Clinically Significant Vital Sign Changes

1. Mean Change from Baseline

The applicant provided summary tables for means and mean changes from baseline for systolic blood pressure, diastolic blood pressure, heart rate (pulse), body temperature, and body weight for the all placebo controlled database. The appendices also listed individual subject data. The following table illustrates minimal changes which are considered to be clinically insignificant for the mean change from baseline.

Table 7.4.9 Vital Signs: Means and Mean Change from Baseline, All PC Database

	Vilazodone All doses N=1577		Vilazodone <40 mg/d N=903		Vilazodone 40 mg/d N=440		Vilazodone >40 mg/d N=227		Placebo N=997	
	BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ
SBP mmHg	120	-0.3	121	-0.7	120	-0.1	119	0.7	120	-0.2
DBP mmHg	77	0.3	77	0.2	76	0.4	76	0.5	76	-0.3
Pulse bpm	74	0.7	75	0.5	73	0.7	75	1.6	73	1.0

Source: Appendix 2 Table 23.1 (ISS)

2. Outliers

The applicant provided summary tables of the incidence of treatment-emergent PCS vital signs for SPB, DBP, HR, and body weight in the all placebo-controlled database, where treatment with vilazodone or placebo was up to 8 weeks' duration.

The applicant's PCS criteria were as follows:

- SBP: PCS high= ≥ 180 mmHg or increase ≥ 20 mmHg; PCS low= ≤ 80 mmHg or decrease ≤ 20 mmHg.
- DBP: PCS high= ≥ 110 mmHg or increase ≥ 10 mmHg; PCS low= ≤ 50 mmHg or decrease ≤ 15 mmHg.
- HR (pulse): PCS high= ≥ 120 bpm or increase ≥ 15 bpm; PCS low= ≤ 50 bpm or decrease ≤ 15 bpm.
- Weight: PCS high= $\geq 10\%$ increase; PCS low= $\leq 10\%$ decrease.

The number of PCS values for systolic and diastolic blood pressure and heart rate was low, less than 1% for all doses of vilazodone and placebo. Over all doses, vilazodone did not appear to be significantly different from placebo on blood pressure or heart rate.

Table 7.4.10 Vital Signs: Incidence of Treatment Emergent PCS All Placebo-controlled Database

H=high L=low		Vilazodone All doses		Vilazodone <40 mg/d		Vilazodone 40 mg/d		Vilazodone >40 mg/d		Placebo	
		n	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)
SBP mmHg	H	1570	0	899	0	439	0	226	0	993	0
	L	1570	8(0.5)	898	5(0.6)	439	3(0.7)	227	0	992	2(0.2)
DBP mmHg	H	1568	2(0.1)	898	1(0.1)	438	0	226	1(0.4)	991	1(0.1)
	L	1569	3(0.2)	898	3(0.3)	438	0	227	0	991	4(0.4)
HR bpm	H	1567	4(0.3)	895	4(0.4)	439	0	227	0	990	4(0.4)
	L	1572	3(0.2)	899	1(0.1)	440	2(0.5)	227	0	993	3(0.3)
Weight kg	H	1484	6(0.4)	811	4(0.5)	440	1(0.2)	227	1(0.4)	954	4(0.4)
	L	1484	3(0.2)	811	1(0.1)	440	1(0.2)	227	1(0.4)	954	4(0.4)

Source: Appendix 2, Table 22.1 (ISS)

Phase 3 Long-term, Uncontrolled Safety Database

In the long-term, uncontrolled safety database vital sign measurements included systolic and diastolic blood pressure, heart rate and respiratory rate. Measurements were taken at screening, baseline, and each scheduled visit. A review of the JMP line listings and the applicant's reports indicates no clinically relevant changes in vitals signs in this cohort of patients with multiple co-morbidities and concomitant medications.

The data submitted for weight change indicated 11/597 (1.8%) for PCS low values and 39/597 (6.5%) for high weight change. This was based on PCS of $\geq 10\%$ decrease for PCS low and $\geq 10\%$ increase for PCS high. The reported incidence of weight increased was 10% (57 subjects) and for weight decreased was 2% (10 subjects). Eight subjects shifted from normal to overweight and from overweight to obese during the course of the study. Although the numbers could be significant, it is not prudent to draw conclusions from this uncontrolled study.

C. Dropouts Due to Vital Sign Abnormalities

Overall, a clinically insignificant number of patients discontinued due to vital sign abnormalities.

One patient (EMD 68843-010) in a Phase 2 study discontinued due to a hypertension.

Patient ID **035-1470** was a 68-year-old Caucasian female who was randomized to the high dose vilazodone treatment arm; she received the first dose of study medication on November 17, 1998. On (b) (6) the patient was hospitalized for treatment of hypertension. The report indicates that on December 9, 1998 she complained of a migraine headache with musical hallucinations and poorly formed visual hallucinations. On (b) (6) her BP was 160/100, repeat BP was 182/100 and she reported palpitations and a 'heavy feeling' in her chest. She was given two doses of clonidine with good results and she was discharged from the hospital on (b) (6). Medication history included (but not limited to): amitriptyline, Prozac, Celexa, and Synthroid. This SAE is considered likely to be related to the study medication. Review of the CRF indicates a BP of 135/90 at Screening and no history of cardiovascular disease.

Three patients (0.5%) in the Phase 3 Uncontrolled, Long-term study CLDA-07-DP-04 discontinued due hypertension (2 – 'blood pressure increased' and 1- hypertension).

7.4.4 Electrocardiograms (ECGs)

A. ECG Assessments

It is the opinion of this reviewer that although the data provided is acceptable, the applicant's case would be more persuasive if quantitative interval measurements for the Phase 2 safety database would have been provided. In the current submission from the Placebo-controlled Phase 3 Database, 384 ECGs were reported with baseline and on-treatment results read by a cardiologist. From the Uncontrolled, Long-term Phase 3 Database, 541 ECGs were reported with baseline and on-treatment results read by a cardiologist.

Based on review of the information provided by the applicant and the opinion rendered by the QT-IRT, this reviewer concurs with the applicant's assessment that at doses below 80 mg, vilazodone does not appear to have clinically significant effects on ECG parameters or a signal of proarrhythmic potential.

Phase 1

PGxHealth conducted a Phase 1, single-site, double-blind, randomized, placebo and active controlled, 3-arm; parallel study (PGX-08-P1-06) to assess the effects of vilazodone on QT interval. The review of PGX-08-P1-06 is covered in section 7.4.5 of this document. The QT-IRT consultative review indicated "No significant QTc prolongation effect of vilazodone was detected in this TQT study."

Phase 2 and 3

The ECGs were assessed differently across the studies. Quantitative interval measurements were available for the Phase 3 studies only. Across the placebo-controlled Phase 3 database, the all placebo-controlled database, and the uncontrolled long-term safety database, the data were summarized using categories of normal and 3 categories of abnormal. The 3 categories of abnormal included: NCS (not clinically significant), CS (clinically significant), and UNK (unknown).

For studies EMD 68843-009 and EMD 68843-010, the ECG result at Screening and Week 8/ET was collected as a normal/abnormal, yes/no response. If the answer was yes, the ECG was classified as normal. If the answer was no, then the ECG is classified as abnormal UNK.

For studies SB-659746-A002, SB-659746-003, and SB-659746-014, the ECG at Screening was collected as a yes/no response to the question "Were there any clinically significant abnormalities detected?" If the answer was no, the ECG is classified as normal; if the answer was yes, the ECG is classified as abnormal, CS. At Week 8/ET, the question is "Were there any clinically significant worsening since the last examination?" If the question was answered yes, the ECG result is classified as abnormal, CS. If the answer was no, then the Screening ECG result is used as the Week 8/ET result.

For the Phase 3, pivotal studies, GNSC-04-DP-02 and CLDA-07-DP-02, the ECG assessment at both screening and at Week 8/ET was collected as 'normal', 'abnormal not clinically significant', or 'abnormal, clinically significant'. The assessment was similar in the 52-week, long-term study with additional ECGs collected at Weeks 24, 36, and 52/ET.

Only subjects with both screening/baseline and end of study ECG results are included in the analysis. The incidence of treatment emergent PCS values for ECG parameters were summarized based on the pre-determined criteria.

B. Potentially Clinically Significant ECG Changes

The QTc intervals corrected using Fredericia's formula (QTcF) were used for PCS determination. The ECG PCS criteria were:

- QRS interval: PCS high= ≥ 150 ms
- PR interval: PCS high= ≥ 250 ms
- QTc interval: PCS high= ≥ 500 ms
- HR: PCS high= ≥ 120 bpm or increase ≥ 15 bpm
- HR: PCS low= ≤ 50 bpm or decrease ≤ 15 bpm

1. Mean Change from Baseline

Phase 1 Studies

The thorough QT study is discussed in Section 7.4.5 of this review.

Phase 2 and 3 Studies

As described previously, the method of ECG collection for the all placebo-controlled database did not include pooling information from all of the phase 2 and phase 3 (total of 7) studies. Therefore, this review will focus on the phase 3 placebo-controlled database.

The applicant summarized interval measurements change from baseline to final visit for the placebo-controlled Phase 3 database and the uncontrolled, long-term safety database. In the placebo-controlled Phase 3 database, statistical comparisons between the 40 mg/day vilazodone and placebo treatment groups were made on the changes from baseline. ANCOVA terms for treatment, baseline value, and study were applied, and p-values from testing the treatment effect contrasts were reported for descriptive purposes. When presented in this manner, there is no statistically significant difference between the treatment groups except for the between group difference in QRS interval.

**Table 7.4.11 ECG Parameters: Change from Baseline to Week 8
Placebo-controlled Phase 3 Database**

Parameter	Vilazodone 40 mg/day n=436	Placebo n=433	p-value ¹
Heart rate (bpm)			
n	386	388	
LS mean	1.894	2.97	0.0879
SE	0.450	0.449	
PR Interval (ms)			
n	384	385	
LS Mean	-0.87	-0.20	0.4282
SE	0.605	0.604	
QRS Interval (ms)			
n	384	386	
LS mean	-1.25	-0.11	0.0217
SE	0.352	0.351	
QTC-Bazett (ms)			
n	384	386	
LS mean	-0.56	1.66	0.0724
SE	0.874	0.871	
QTC-Fredericia (ms)			
n	384	386	
LS Mean	-2.37	-1.30	0.3088
SE	0.751	0.748	
QT Interval (ms)			
n	384	386	
LS Mean	-5.66	-6.75	0.4806
SE	1.100	1.097	

¹p-value for treatment effect on mean change from baseline from linear model with terms for treatment, study, and baseline value, Type III sum of squares
Source: Appendix 2 Table 26.1 (ISS)

The Integrated Summary of Safety provides tables which indicate the mean change from baseline to last observation for the Placebo-controlled Phase 3 database as summarized below. On average, the changes in heart rate and interval measurements were minimal, similar to placebo, and not clinically significant. The changes for the long-term, uncontrolled study (CLDA-07-DP-04) were similar to those in the controlled studies, although the mean delta for QTcF was -8.0 msec; the clinical relevance of this is not known.

Table 7.4.12 Mean Change from Baseline to Last Observation: Placebo-Controlled, Phase 3 Database (GNSC-04-DP-02 and CLDA-07-DP-02)

	Vilazodone 40 mg			Placebo		
	n	BL	Δ	n	BL	Δ
Heart Rate (bpm)	436	67.3	1.7	433	66.9	3.2
PR Interval (msec)	436	155.2	-0.7	431	157.0	-0.4
QRS Interval (msec)	436	88.6	-1.3	432	87.7	0
QT Interval (msec)	436	386.2	-5.9	432	384.3	-6.7
QTcB Interval (msec)	436	405.6	-1.2	432	403.1	2.1
QTcF Interval (msec)	436	398.9	-2.8	432	396.7	-1.0

Source: Appendix 2 Table 26.1 (ISS)

Table 7.4.13 Mean Change from Baseline to Last Observation: Uncontrolled, Long-Term Safety Database (CLDA-07-DP-04)

	Vilazodone 40 mg/day		
	n	BL	Δ
HR bpm	599	66.7	3.6
PR Interval msec	599	158.4	-1.7
QRS Interval msec	599	87.5	-0.9
QT Interval msec	599	401.6	2.1
QTcB Interval msec	599	395.6	-1.3
QTcF Interval msec	599	383.9	-8.0

Source: Appendix 2 Table 26.2 (ISS)

Shifts in ECG results were summarized from Baseline to Week 8/ET. At each timepoint, the ECG result was classified as Normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS). Shifts that would be considered a worsening of parameters: normal to abnormal (NCS or CS) and abnormal (NCS) to abnormal (CS) are represented in the following table. The percentages of subjects shifting from normal to abnormal are essentially the same. There appears to be no difference in the vilazodone group when compared with the placebo group. The number of abnormal NCS to Abnormal CS for the vilazodone group is nearly two times the placebo group.

**Table 7.4.14 Changes in ECG Results from Baseline to Final Visit
(Placebo-controlled Phase 3 Database Safety Population)**

ECG Change from Baseline to Final Visit	Vilazodone n=384 (%)	Placebo n=386 (%)
Normal to Abnormal NCS	45 (11.7)	46 (11.9)
Normal to Abnormal CS	2 (0.5)	2 (0.5)
Abnormal NCS to Abnormal CS	5 (1.3)	3 (0.8)

KEY: CS=clinically significant; NCS=not clinically significant.

Source: Appendix 2, Table 24.2.

2. Outliers

Phase 1

As indicated in the ISS, the specific outlier criteria consisted of a new abnormal U wave, new >500 ms absolute QTc duration, and a >60 ms change from baseline. For QTcI, none of the subjects met these criteria. The nonspecific outlier criterion was a 30-60 ms change from baseline, which showed no imbalance between placebo and vilazodone groups.

Phase 2 and 3 Studies

In the placebo-controlled Phase 3 database, the applicant reported no clinically meaningful differences between the placebo and vilazodone groups. In the uncontrolled, long-term safety database, no subject had ECG results change from Normal to Abnormal CS, and less than 1% of subjects had ECG results change from Abnormal NCS to Abnormal CS.

For the placebo-controlled, Phase 3 database, no subject taking either placebo or vilazodone had a treatment-emergent PCS abnormality for PR, QRS, or QTcF interval. One subject in each group (vilazodone and placebo) had a treatment-emergent PCS abnormality for HR (low HR in each subject).

In the Uncontrolled, Long-term Database PCS change was seen for HR in two (0.4%) patients and a QRS high for one (0.2%) patient. PCS changes were not observed for heart rate (high), PR Interval (high) or QTcF (high).

C. Discontinuations Due to ECG Abnormalities

There were no dropouts due to ECG abnormalities.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT Study

The applicant conducted a thorough QT study, PGX-08-P1-06, "A Double-Blind, Randomized, Parallel Study to Define the ECG Effects of Vilazodone Using a Clinical and a Supratherapeutic Dose Compared to a Placebo and Moxifloxacin in Healthy Volunteers: A Thorough ECG Study"

The primary objective of this study was to determine the time-matched change from baseline in QTc based on an individual correction (QTcI) method. The secondary objective was to evaluate the safety and tolerability of vilazodone in healthy volunteers as compared to subjects receiving placebo or moxifloxacin.

This was a Phase 1, single study, randomized, double-blind (except moxifloxacin), placebo and active control, 3-arm parallel study to assess the effects of vilazodone on QT interval in healthy males and females. It was hoped to achieve 20 males and 20 females in each treatment arm.

Subjects were randomized to one of three treatments: placebo from Day 1-15, Moxifloxacin 400 mg given on Days 6, 9, 12, and 15 to match each of the doses on vilazodone in which ECG and PK sampling was done, with placebo given on the remaining days; vilazodone starting at 10mg for 3 days, followed by 20 mg for 3 days, then 40 mg for 3 days, then 60 mg for 3 days and concluding with 80 mg/day for 3 days. Subjects in each of the 3 treatment arms received the study drug as a single daily dose following a high fat breakfast.

The effect of vilazodone on ECG parameter (heart rate, PR, QRS, QT, QTc intervals) were evaluated and compare with placebo and moxifloxacin treatment arms. Plasma PK of vilazodone and safety monitoring were also monitored by treatment arm.

Summary of QT Interdisciplinary Review Team Consult

In this randomized, double-blind study, one-hundred and forty subjects received vilazodone in doses from 10 mg to 80 mg (all , moxifloxacin 400 mg, and placebo). The summary of findings is provided in the following table (taken from the IRT review).

Table 7.4.15 QT-IRT Point Estimates and CIs

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound of $\Delta\Delta QTcI$ for Vilazodone and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta QTcI$ (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

The largest lower bounds after Bonferroni adjustment for 4 timepoints are 6.8 ms, 5.8 ms, 2.9 ms, and 3.4 ms, respectively for Days 6, 9, 12, and 15.

The overall assessment by the QT-IRT reviewer was that no significant QTc prolongation effect of vilazodone was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between vilazodone and placebo were below 10 ms. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta QTcI$ for moxifloxacin was greater than 5 ms at Day 6, and the moxifloxacin profile over time is adequate, indicating that assay sensitivity was established.

Study Description

A Phase 1, single-site, randomized, double-blind (except Moxifloxacin), placebo and active controlled, 3, arm, parallel study. The positive control was not double-blinded. Subjects were enrolled at one site and randomized to receive one of three treatments:

- Placebo – given (PO) Day 1-15
- Moxifloxacin 400 mg PO on Days 6, 9, 12, and 15 to match each dose of vilazodone in which ECG and PK sampling was done, placebo was given on remaining days (1-5, 7-8, 10-11, and 13-14).
- Vilazodone starting at 10 mg/day PO for 3 days, followed by 20 mg/day for 3 days, then 40 mg/day for 3 days, then 60 mg/day for 3 days and concluding with 80 mg/day for 3 days. If fewer than 40 subjects were able to complete the scheduled 3 days of dosing and associated PK and ECG activities at a vilazodone dose level, study conduct was interpreted to have identified the MTD for vilazodone and there would be no further increase in the dose. Of note, the MTD was not reached in this study.

Doses of study medication were administered with food, which is shown to increase exposure by approximately 50%. It is curious to note that the doses were titrated every 3 days, but in order to approach steady-state they should have studied each dose for a minimum of 4 days (the half life is assumed to be 8-36 hours). Discussion with the

clinical pharmacology reviewer indicated that on average, steady state is achieved in 3 days for vilazodone.

Table 7.4.16 ECG and PK Assessment Schedule

Study Day	-1	1-3	4, 5	6	7, 8	9	10, 11	12	13, 14	15
Intervention	None	10 mg dose QD	20 mg dose QD		40 mg dose QD		60 mg dose QD		80 mg dose QD	
12-Lead ECGs[#]	Record ECGs	None	None	Record ECGs						
PK Samples for drug^{##}	None	None	None	Collected	None	Collected	None	Collected	None	Collected

[#] ECGs will be obtained digitally using a Mortara Instrument (Milwaukee, WI) H-12+ ECG continuous 12 lead digital recorder ECGs (3 ECGs within 5 minutes) 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours post-dose on Days -1 and 6, 9, 12, and 15.

^{##} PK samples will be collected 5 minutes before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dose.

A total of 157 subjects were enrolled and randomized with 140 subjects (42 placebo, 42 moxifloxacin, and 56 vilazodone) were evaluable for ECG assessments. The reasons for premature discontinuation were 'withdrawal of consent' in 9 subjects and AE in 8 subjects. In the vilazodone group 56 of the 66 (85%) received all 15 doses.

The QT-IRT recommended two labeling changes:

- Deletion of Section 6 ECG
- Section 12.2: The effect of vilazodone 20, 40, 50, 80 mg on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel thorough QTc study in 157 healthy subjects. In the study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern. However, whether 80 mg is adequate to represent the high clinical exposure scenario is unknown.

Safety Issues

- At the 80 mg dose of vilazodone 10 (18%) subjects met outlier criteria for tachycardia compared with 2 (5%) in the placebo group. None of the subjects in the other vilazodone dose groups met PCS tachycardia criteria.
- TEAEs of hypertension in three subjects and increased blood pressure in two subjects were reported for the vilazodone group only.
- TEAEs of palpitations in four subjects and tachycardia in 6 subjects were reported in the vilazodone group compared with 1 subject in the placebo and 0 in the moxifloxacin groups.

One subject discontinued due to AEs of dizziness, palpitations, hypertension, and tachycardia. He is described as a healthy subject, not taking concomitant medication. The applicant provides the following description of the event:

This subject was a 42-year-old white (Hispanic or Latino) male experienced palpitations which led to his premature discontinuation from the study. He was randomized to the vilazodone treatment arm and received his first dose of vilazodone 10 mg PO on 23 Nov 2008 (Day 1). The subject's heart rate at baseline (Day -1) was 60 beats/minute and blood pressure was 119/69 mmHg. On Day 5 (vilazodone 20 mg), the subject reported mild palpitations, which continued until Day 10 (vilazodone 60 mg). The scheduled heart rate measurement on Day 5 was 60 bpm and the scheduled blood pressure result was 112/70 mmHg. On Day 10, the subject also reported mild dizziness and experienced mild elevated blood pressure (171/100 mmHg) and tachycardia (108 bpm). The events of dizziness, elevated blood pressure, and tachycardia resolved the same day without treatment. The next day (Day 11), about 4 hours after the dose of vilazodone 60 mg, the subject again reported feeling mild palpitations (heart rate, 86 bpm) and dizziness, and experienced increased blood pressure (158/107 mmHg); study drug was discontinued due to the palpitations. Palpitations resolved within 48 minutes without treatment, and elevated blood pressure and dizziness resolved later that day; heart rate and blood pressure findings at the time of resolution were not provided. The investigator considered the events of palpitations, as well as the events of dizziness (first event), tachycardia, and elevated blood pressure, as possibly related to vilazodone; the second event of dizziness was assessed as probably related to vilazodone.

QT-IRT reviewer comments:

"Taking the results together, small effects on BP and HR are possible. However, given the minimal number of significant AEs reported in the phase 3 clinical trial database we believe description of the vital signs and AEs with the clinical trials experience should be sufficient. Precautions with regular monitoring of symptoms, along with blood pressure and pulse rate in patients with hypertension or pre-existing heart disease should be considered."

Although in the Placebo-controlled Database the mean change from baseline and the outliers for heart rate and blood pressure were not significantly different for vilazodone compared with placebo, this reviewer concurs with recommendations to monitor blood pressure and pulse rate in patients with hypertension or pre-existing heart disease. Concurrence is based on this reviewer's opinion that it is necessary to further characterize the pharmacokinetic profile of vilazodone with regard to drug-disease interactions and dose response. As noted above, at the 80 mg dose of vilazodone, 18% of patients met tachycardia outlier criteria as compared with 5% in the placebo group. It is this reviewer's opinion that current data regarding food effect, dose-response, and drug-disease interaction (severe hepatic and severe renal impairment) indicate that it may be difficult to predict exposure.

7.5 Other Safety Explorations

Sexual Function

Antidepressant induced sexual dysfunction is common, under-reported and may result in treatment noncompliance or discontinuation. The Arizona Sexual Experiences Scale (ASEX) and the Changes in Sexual Functioning Questionnaire (CSFQ) have been developed in response to a need for quantitative evaluations of changes in sexual function. The ASEX was assessed in study GNSC-04-DP-02 and the CSFQ was administered in study CLDA-07-DP-02. Outlier and subgroup information might be helpful to provide a more meaningful interpret of the results. Again, spontaneous reports of sexual AEs indicate a higher incidence of sexual dysfunction for vilazodone over placebo in both males and females.

GNSC-04-DP-02

The ASEX was administered in the Phase 3 study GNSC-04-DP-02. The ASEX was assessed in patients at Baseline (Visit 2) and each subsequent visit throughout the study. The ASEX is a 5-item rating scale that quantifies 5 areas of sexual function. The total scores can range from 5 to 30, with increasing scores indicating diminished sexual function and decreasing scores indicate improvement. A mean change of >2 points on the total score is considered to be clinically significant. For the ASEX, sexual dysfunction is defined as a total score of >19, a score of >5 on any one item, or a score of ≥ 4 on 3 or more items.

Results

The Integrated Summary of Safety report indicates that in both treatment groups, mean scores at Week 8 were slightly lower than at Baseline for both male and female patient groups.

For males, the least squares (LS) mean change from baseline in ASEX total score at End of Treatment (EOT) was -1.03 in the placebo group and +0.80 for males taking vilazodone 40 mg (higher score indicates lower functioning). The difference in the LS means between the vilazodone and placebo groups was statistically significant; although the applicant points out that neither group demonstrated a clinically important reduction in the mean change of at least 2 points.

For females, the LS mean change from baseline in the ASEX total score at EOT was +0.07 in the placebo groups and -1.14 for the vilazodone group (higher score indicates lower functioning), this difference was not statistically significant. There were no relevant distinctions between the vilazodone and placebo groups on any of the ASEX domain and neither group demonstrated a reduction in mean change of at least 2 points.

When males and females are assessed separately, there is a tendency toward diminished sexual functioning for the males. The applicant concludes that the mean differences between the treatment groups are clinically irrelevant. However, the spontaneous reports of sexual AEs indicate a higher incidence of sexual dysfunction for vilazodone over placebo in both males and females.

CLDA-07-DP-02

The Changes in Sexual Functioning Questionnaire (CSFQ) is a 14-item questionnaire that uses 5-point Likert scales to assess sexual function. The CSFQ was included as a safety measure to evaluate the impact of vilazodone on this known adverse event associated with antidepressants. The instrument includes subscale scores for males and females. Higher scores indicate higher levels of sexual functioning. A mean change of 3 points on the total score and/or 0.5 points on subscales is considered clinically significant. For the CSFQ, sexual dysfunction is defined as a total score ≤ 47 in men and ≤ 41 in women. The CSFQ was administered in the Phase 3 study CLDA-07-DP-02 and in the long-term study CLDA-07-DP-04.

Results

For males, the LS mean changes in CSFQ total score was increased for both the vilazodone and placebo groups. The LS mean change was higher (higher scores indicate higher functioning) for the placebo group than for the vilazodone group; although, neither group demonstrated a mean change increase of at least 3 points. The difference in the LS mean changes was not statistically significant.

For females, the LS mean changes in CSFQ total score was increased for both the vilazodone and placebo groups. The LS mean change was higher for the placebo group than for the vilazodone group; although, neither group demonstrated a mean change increase of at least 3 points. The difference in the LS mean changes was not statistically significant.

Outlier and subgroup information might be helpful to fully interpret the results of this study. Again, spontaneous reports of sexual AEs indicate a higher incidence of sexual dysfunction for vilazodone over placebo in both males and females.

CLDA-DP-07-04 (open-label, long-term safety)

For males in the uncontrolled, long-term safety database, the mean change from baseline in the CSFQ total score at EOT was +1.5. For females, the mean change from baseline at EOT was +2.7. These numbers did not reach statistical significance.

Treatment Emergent Adverse Events Pertaining to Sexual Function

TEAES pertaining to sexual functioning occurred 9 times more frequently in vilazodone (9%) patients than in placebo (1%) patients. The safety population for the placebo-

controlled phase 3 studies indicate decreased libido in 16 (4%) patients (8 males and 8 females) for the vilazodone group and 2 (0.5%) patients (1 male and 1 female) in the placebo group. Overall, sexual dysfunction is a significant adverse event associated with antidepressants and not an unexpected finding in this application.

Table 7.5.1 Sexual Adverse Events for Study GNSC-04-DP-02

Adverse Event	All patients		Males		Females	
	V40 n=205	PBO n=204	V40 n=78	PBO n=74	V40 n=127	PBO n=130
Anorgasmia	4(2.0)	0	1(1.3)	0	3(2.4)	0
Ejaculation Delayed	2(1.0)	0	2(2.6)	0	0	0
Decreased Libido	5(2.4)	1(0.5)	2(2.6)	0	3(2.4)	1(0.8)
Orgasm Abnormal	4(2.0)	0	4(5.1)	0	0	0
Sexual Dysfunction	3(1.5)	1(0.5)	2(2.6)	0	1(0.8)	1(0.8)
Total n (%)	18(8.8)	2(1.0)	11(14.1)	0	7(5.5)	2(1.5)

Table 7.5.2 Sexual Adverse Events for Study CLDA-07-DP-02

Adverse Event	All patients		Males		Females	
	V40 n=235	PBO n=233	V40 n=96	PBO n=109	V40 n=139	PBO n=124
Anorgasmia	2 (0.8)	0	1(1.0)	0	1 (0.7)	0
Ejaculation Delayed	2 (0.8)	0	2 (2.1)	0	0	0
Erectile Dysfunction	4 (1.7)	1 (0.4)	4 (4.2)	1 (0.9)	0	0
Decreased Libido	11(4.7)	1 (0.4)	6 (6.2)	1 (0.9)	5 (3.6)	0
Orgasm Abnormal	3 (1.3)	0	2 (2.1)	0	1 (0.7)	0
Sexual Dysfunction	1 (0.4)	0	1 (1.0)	0	0	0
Total n (%)	23 (9.8)	2 (0.9)	16(16.7)	2 (1.8)	7 (5.0)	0

The adverse events were coded per MedDRA version 11.1 and as such, the preferred terms (PT/AETERM) decreased libido, delayed orgasm, anorgasmia, and low libido map to the system organ class (SOC/AEBODSYS) 'Psychiatric Disorders'. The preferred terms sexual dysfunction, delayed ejaculation, and erectile dysfunction map to the SOC "Reproductive System and Breast Disorders". To provide more informative information for labeling, the AEs have been combined as 'sexual adverse events' and presented in tabular format.

Spontaneous reports of sexual adverse events from the JMP datasets in the placebo-controlled phase 3 studies are summarized in the following table.

Table 7.5.3 Sexual Adverse Events – Placebo Controlled Phase 3 (07 and 04)

Adverse Event	All Patients N (%)		Males N (%)		Females N (%)	
	V40 N=440	PBO N=437	V40 N=174	PBO N=183	V40 N=266	PBO N=254
Anorgasmia	6 (1.4)	0	2 (1.1)	0	4 (1.5)	0
Delayed Ejaculation	4 (0.9)	0	4 (2.3)	0	0	0
Erectile Dysfunction	4 (0.9)	1 (0.2)	4 (2.3)	1 (0.5)	0	0
Decreased Libido	16 (3.6)	2 (0.5)	8 (4.6)	1 (0.5)	8 (3.0)	1 (0.4)
Abnormal Orgasm	7 (1.6)	0	6 (3.4)	0	1 (0.4)	0
Sexual Dysfunction	4 (1)	1(0.2)	3 (1.7)	0	1 (0.4)	1 (0.4)
Total	41 (9.3)	4 (0.9)	27 (15.5)	2 (1)	14 (5.2)	2 (0.8)

7.5.3 Drug-Demographic Interactions

Adverse events appeared to occur nearly two times more frequently in the >55 years age group than in the <55 years group. This may indicate that the older population is more susceptible to the GI and psychiatric AEs – although a dose adjustment is not recommended for the elderly. It should be noted that of the 2177 patients in the clinical program, only 37 (1.7%) were 65 years of age or older; 272 (12%) were between 55 and 64 years of age.

7.5.4 Drug-Disease Interactions

The clinical data are currently being reviewed by Clinical Pharmacology. The evaluation of vilazodone in patients with renal or hepatic impairment is limited. Few patients were studied at a 20 mg dose. Patients included in the studies were with mild to moderate impairment. Patients with severe renal or hepatic impairment were not studied.

7.5.5 Drug-Drug Interactions

The Clinical Pharmacology review provides more comprehensive information regarding drug-drug interactions.

The drug interaction study with ketoconazole was studied with suboptimal doses of both vilazodone and ketoconazole (this reviewer's opinion). Interpretation is deferred to the clinical pharmacologist.

7.6 Additional Safety Evaluations

Suicidality

Overall, the incidence of suicide and suicidality was as expected for the disease under investigation.

There were two suicides during the clinical development program for vilazodone. Both occurred in Phase 2 studies; as indicated in the following narratives, neither patient was receiving vilazodone at the time of death.

1. 026-1231 – Suicide by Gun Shot

This patient was a 54-year-old Caucasian male. He was randomized to receive placebo and was scheduled for his first dose on Aug. 6, 1998. On [REDACTED] (b) (6) he died from a self-inflicted **gun shot to the head**. The patient's medical history included anxiety, major depressive disorder, alcohol abuse, renal lithiasis, and surgery for herniated disk. This death is not related to the study medication.

2. 027-G01 – Suicide by Carbon Monoxide

This patient was a 47-year-old male who had not been randomized to a study medication when his death occurred. The patient had signed informed consent, but no procedures were performed because he failed to attend the screening visit. On [REDACTED] (b) (6) it was reported that the patient had attempted **suicide by carbon monoxide** inhalation. He was hospitalized for three weeks and died on [REDACTED] (b) (6) as a result of CO poisoning. The death is not related to the study medication.

Methods

The applicant provided a thorough evaluation of suicidality (ISS Appendix 4) using data from Phases 1 through 3. The data consisted of AEs, Columbia Classification Algorithm of Suicide Assessment (C-CASA) scores derived from both database text string search (TSS) of AEs and Columbia-Suicide Severity Rating Scale (C-SSRS) data, HAM-D suicide item score and MADRS suicidal thoughts item score.

The TSS included verbatim, preferred terms, and any associated CRF comments for the following terms: accident-, attempt, burn, cut, drown, gas, gun, hang, hung, immolate, injur-, jump, monoxide, mutilat-, overdos-, self damag-, self harm, self inflict, self injur-, shoot, slash, sui, poison, asphyxiation, suffocation, and firearm.

Phase 1

For the Phase 1 studies, a search of treatment emergent adverse events (TEAEs) associated with suicidality was done. The subjects in Phase 1 were healthy volunteers, not identified to have MDD.

Phase 2 and Phase 3

Of the eight Phase 2 and 3 studies, CLDA-07-DP-02 was the only placebo controlled study that used the C-SSRS. The long-term study CLDA-07-DP-04 implemented the instrument mid-study. Therefore, a comprehensive blinded text string search of all text fields was conducted for the evaluation of suicidality. The TSS hits were evaluated and blinded narratives were prepared for assignment of C-CASA scores by an independent group. Sensitivity analyses were performed using HAM-D and MADRS items and C-SSRS data mapped to C-CASA.

Results

No TEAEs associated with suicidality were reported for the subjects in Phase 1 studies. One subject in the placebo group of a Phase 2 study completed suicide. There were no suicides in subjects receiving vilazodone.

In the placebo controlled Phase 3 database, there was one suicide attempt in the vilazodone group and one event of suicidal behavior in the placebo group. In the all placebo-controlled database, suicidal behavior was identified in 4 subjects (0.4%) in the placebo group and 2 subjects (0.1%) in the all-doses vilazodone group.

Table 7.6.1 C-SSRS CLDA-07-DP-02

Table 3: Contribution of Columbia-Suicide Severity Rating Scale and Text String Search Findings to Columbia Classification Algorithm of Suicide Assessment Results in Study CLDA-07-DP-02 (Safety Population)

Columbia Classification Algorithm of Suicide Assessment (C-CASA) Code / Category		Placebo N=233 n (%)			Vilazodone 40 mg/day N=235 n (%)		
		C-SSRS	TSS	C-SSRS or TSS	C-SSRS	TSS	C-SSRS or TSS
1	Completed Suicide	0	0	0	0	0	0
2	Suicide Attempt	0	0	0	0	0	0
3	Preparatory Acts Toward Imminent Suicidal Behavior	0	0	0	0	0	0
4	Suicidal Ideation	62 (26.6)	0	62 (26.6)	51 (21.7)	0	51 (21.7)
5	Self-injurious Behavior, Intent Unknown	0	0	0	0	0	0
6	Not Enough Information (Death)	0	0	0	0	0	0
7	Non-suicidal Self-injurious Behavior	1 (0.4)	0	1 (0.4)	0	0	0
8	Other (Accident, Psychiatric, Medical)	0	2 (0.9)	1 (0.4)	0	5 (2.1)	3 (1.3)
9	Not Enough Information (Non-Death)	0	0	0	0	0	0
0	No Suicidal Behavior Observed	170 (73.0)	231 (99.1)	169 (72.5)	184 (78.3)	230 (97.9)	181 (77.0)

Note: Subjects were assigned the worst C-CASA category obtained from the Columbia-Suicide Severity Rating Scale (C-SSRS) mapping and from the evaluation of text string search (TSS) findings, respectively. The worst of these 2 scores was reported in the combined C-SSRS or TSS column.

Source: [Appendix 2: Table 40.4](#)

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Table 7.6.2 C-SSRS Placebo – Controlled Phase 3 Database

Table 2: Columbia Classification Algorithm of Suicide Assessment (Placebo-controlled, Phase 3 Database; Safety Population)

Columbia Classification Algorithm of Suicide Assessment (C-CASA) Code / Category		Primary Evaluation ^a		Secondary Evaluation ^b	
		Placebo N=433 n (%)	Vilazodone 40 mg/day N=436 n (%)	Placebo N=433 n (%)	Vilazodone 40 mg/day N=436 n (%)
1	Completed Suicide	0	0	0	0
2	Suicide Attempt	0	1 (0.2)	0	1 (0.2)
3	Preparatory Acts Toward Imminent Suicidal Behavior	1 (0.2)	0	1 (0.2)	0
4	Suicidal Ideation	64 (14.8)	51 (11.7)	2 (0.5)	0
5	Self-injurious Behavior, Intent Unknown	0	0	0	0
6	Not Enough Information (Death)	0	0	0	0
7	Non-suicidal Self-injurious Behavior	2 (0.5)	0	1 (0.2)	0
8	Other (Accident, Psychiatric, Medical)	3 (0.7)	7 (1.6)	4 (0.9)	9 (2.1)
9	Not Enough Information (Non-Death)	0	0	0	0
0	No Suicidal Behavior Observed	363 (83.8)	377 (86.5)	425 (98.2)	426 (97.7)

^a For the primary evaluation, subjects were assigned the worst C-CASA category obtained from either the Columbia-Suicide Severity Rating Scale (C-SSRS) mapping or from evaluation of text string search findings.

^b For the secondary evaluation, subjects were assigned the worst C-CASA category from evaluation of text string search findings only.

Source: [Appendix 2: Table 40.2](#) (Primary Evaluation) and [Table 41.2](#) (Secondary Evaluation)

Reproduced from the applicant's submission 5.3.5.3.2 ISS p.10

7.6.1 Human Carcinogenicity

The overall incidence of adverse events in the SOC – Neoplasms benign, malignant, and unspecified – was reviewed to determine if there might be a signal for human carcinogenicity in the vilazodone development program. No signal was observed when these AEs were reviewed. There were 2 thyroid nodules, one in the placebo group and one in the vilazodone group.

No human carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

Eleven (11) pregnancies were reported during the clinical development of vilazodone. There were eight (8) in the vilazodone group and three (3) in the placebo group. One (1) patient had a positive pregnancy test at screening and was not randomized. The outcomes of the pregnancies included five (5) elective terminations, five (5) continued pregnancies, and one (1) ruptured ectopic pregnancy. Further details regarding the outcomes are not available.

Phase 1

No (0) pregnancies were reported in the Phase 1 studies.

Phase 2

Ten (10) pregnancies were reported in the Phase 2 studies.

One patient had a positive pregnancy test at screening and was not randomized. Five patients elected termination and four patients elected to continue the pregnancy. The outcome of the pregnancies is not known, one patient was taking vilazodone 20 mg/day, one patient was taking vilazodone 10 mg/day, and two patients were taking placebo.

Phase 3

There was one pregnancy in the placebo group of GNSC-04 (8-week pivotal). There was one ruptured ectopic pregnancy in a patient taking vilazodone 40 mg/day group of the open-label study.

Phase 3 Uncontrolled Long-Term Study

Patient 4090-008 had a negative pregnancy test through Week 8, but a positive result about a month later. Follow up information revealed that a healthy female was delivered on [REDACTED] (b) (6) at 38 weeks gestation. The infant weighed 8 pound 0 ounces, and was

21 inches in length. The infant was noted to be jaundiced at birth but was “within normal limits” after 7 days.

Patient 4130-010 had pregnancy test results that were negative through Week 12, but positive on 25 June 2008. Follow-up indicated a delivery date of [REDACTED] (b) (6) at 32 weeks and 1 day. The male infant weighed 5 pounds and 0 ounces and was 17 inches in length. APGAR scores were 8 at one minute and 9 at 5 minutes.

Patient 4160-004 had a negative pregnancy test results through Week 28, but positive on 26 Sept 2008. The patient was lost to follow up and no additional information the outcome of the pregnancy is available.

Patient 4242-010 had pregnancy test results that were negative through Week 44, but positive approximately 4 weeks later. On [REDACTED] (b) (6) the subject underwent elective termination of the pregnancy.

Patient 4130-008 had pregnancy test results that were negative through Week 2 and at a visit 9 days later. This patient was prematurely discontinued from the study due to a ruptured ectopic pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Vilazodone has not been tested in subjects below the age of 18 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Overdose experience is detailed in Section 7.3.5.2; narratives are provided. Overall, none of the overdoses related to vilazodone were lethal, the exposure to vilazodone was low and there were few episodes. There were no reports of overdose in the Phase 1 studies.

The data provided regarding renal impairment and hepatic impairment are limited and provide no additional information regarding overdose.

Drug Abuse Potential

At this time, the CSS consult was not available for review.

The applicant submitted within the Integrated Summary of Safety, Appendix 7 – Assessment of Drug Abuse Potential. The assessment of the abuse potential was

prepared by the applicant in response to an FDA request in accordance with 21 CFR 314.50(d)(5)(vii).

No double-blind clinical investigation in human volunteers with a history of recreational drug or alcohol use was conducted. The procedure used to evaluate the potential for abuse involved a search of the TEAEs from Phase 1, 2, and 3 studies. Summary tables were provided.

It is noted that in the all placebo controlled database, the incidence of 'euphoria related' terms for all doses of vilazodone was nearly twice that of the placebo group. This was primarily due to the TEAE "dizziness". Taken together (although split in the table provided) somnolence and sedation were higher for the all vilazodone doses group 2.7% (42/1578) than the placebo group 1.4% (14/997). The incidence of dissociative/psychotic terms was slightly higher, although not considered to be significant.

Based on the information provided, the adverse event profile and potential for abuse appear to be similar to the serotonin reuptake inhibitors. The applicant did not specifically study or assess withdrawal emergent signs and symptoms during drug taper or discontinuation. It is recommended that this be studied in the post-marketing period, as there have been reports of serious discontinuation symptoms with SSRIs.

8 Postmarket Experience

Vilazodone is not marketed in any country.

9 Appendices

9.2 Labeling Recommendations

Recommendations for labeling will be provided as an addendum to this review.

9.3 Advisory Committee Meeting

Vilazodone is a serotonin specific reuptake inhibitor (SSRI) with a very similar efficacy and adverse events profile to others in the class. The Division did not take this NDA to the Psychopharmacological Drugs Advisory Committee.

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/s/

CHERI Y LINDBERG
12/02/2010

ROBERT L LEVIN
12/03/2010