CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022567Orig1s000

OTHER REVIEW(S)

Medical Officer's Consultative Review of NDA 22-567
Ophthalmology Consult

NDA 22-567		**Submission date:**	7/7/10
Ophthalmology Consult		**Review date:**	1/7/11

Sponsor: PGxHealth, LLC

Drug: Vilazodone

Pharmacologic Category: Serotonin reuptake inhibitor

Proposed Indication: Major depressive disorders

Requested:

The sponsor has submitted an original NDA (22567) for vilazodone in the treatment of depression. Vilazodone has two serotonergic mechanisms of action: it is an SSRI as well as an agonist at the 5-HT1A receptor. We would appreciate your assessment of the ophthalmologic findings and conclusions submitted by the sponsor.

Background:

The sponsor has provided data from five 8-week clinical studies and one 52-week open-label study of vilazodone. In addition, the sponsor has provided an independent expert's review of the ophthalmologic data. In the sponsor's opinion, the results of the ophthalmologic assessments did not demonstrate clinically significant changes in 'eye health' or ocular function in subjects treated with vilazodone. The report indicates that the presence of treatment-emergent cataracts was identified by slit-lamp biomicroscopy in 22 subject-eyes among 12 subjects. For cortical, nuclear sclerotic, and posterior subcapsular cataract types, the number of subject-eyes that shifted from negative at baseline to positive at the end of treatment was 'small'. Of 110 subjects with cataract at baseline, the overall cataract severity was determined to have worsened for 14 (12.7%) subjects and to have remained stable (change in summed score <0) for 96 (87.3%) subjects at end of treatment.

In a zip file, we have included: two previous ophthalmology consults, two safety summaries containing relevant ophthalmologic data, and the study report for the 52-week clinical study.

We have the following questions:
1) What is your assessment of the ophthalmologic findings?
2) Has the sponsor adequately assessed the ophthalmologic safety profile of vilazodone?
3) Could the ophthalmologic risks be managed through labeling? Would you recommend any specific labeling?
4) Would you recommend that we request any additional information from the sponsor?

The Clinical reviewer is Cheri Lindberg, M.D., and the TL is Robert Levin, M.D.; the Pharmacology/Toxicology (non-clinical) reviewer is Violetta Klimek, Ph.D., and the TL is Linda Fossom, Ph.D. Let me know if you have any questions to send to the sponsor. The link to the NDA original application can be found at: \\CDSESUB1\EVSPROD\NDA022567\022567.ENX
We will also send a zip file that contains relevant summaries and data.

Reviewer's Comments: *Responses in this consult will be limited to areas of ophthalmologic concern.*

Phase 2 Studies:

Table 5: Ocular Drying Effects

Treatment	Days on Medication	Eyes per category	Schirmer Value < 10 mm			Schirmer Value < 5 mm		
			# eyes	%	% change from previous visit	# eyes	%	% change from previous visit
Placebo	Baseline	n=1130	278	24.60%		92	8.14%	
	Visit 2	n=972	232	23.87%	-0.73%	82	8.44%	0.29%
	Visit 3	n=812	192	23.65%	-0.96%	66	8.13%	-0.01%
Citalopram	Baseline	n=248	48	19.35%		15	6.05%	
	Visit 2	n=202	35	17.33%	-2.03%	9	4.46%	-1.59%
	Visit 3	n=160	48	30.00%	10.65%	10	6.25%	0.20%
Fluoxetine	Baseline	n=358	112	31.28%		49	13.69%	
	Visit 2	n=276	97	35.14%	3.86%	42	15.22%	1.53%
	Visit 3	n=276	86	31.16%	-0.13%	37	13.41%	-0.28%
Vilazodone 5 mg	Baseline	n=288	50	17.36%		18	6.25%	
	Visit 2	n=236	68	28.81%	11.45%	26	11.02%	4.77%
	Visit 3	n=254	81	31.89%	14.53%	22	8.66%	2.41%
Vilazodone 10 mg	Baseline	n=522	128	24.52%		44	8.43%	
	Visit 2	n=432	112	25.93%	1.40%	49	11.34%	2.91%
	Visit 3	n=424	131	30.90%	6.38%	55	12.97%	4.54%
Vilazodone 20 mg	Baseline	n=928	238	25.65%		78	8.41%	
	Visit 2	n=777	206	26.51%	0.87%	71	9.14%	0.73%
	Visit 3	n=716	194	27.09%	1.45%	62	8.66%	0.25%
Vilazodone 40-60 mg	Baseline	n=188	44	23.40%		13	6.91%	
	Visit 2	n=128	30	23.44%	0.03%	5	3.91%	-3.01%
	Visit 3	n=130	42	32.31%	8.90%	9	6.92%	0.01%
Vilazodone 80-100 mg	Baseline	n=224	83	37.05%		27	12.05%	
	Visit 2	n=122	48	39.34%	2.29%	18	14.75%	2.70%
	Visit 3	n=112	31	27.68%	-9.38%	10	8.93%	-3.13%

Table 5: Schirmer results are broken down per treatment arm to track any progressive effect of the test articles on lacrimation. The columnar values '# eyes' represents the number of eyes which had Schirmer scores of less than 10 mm. The percent is the incidence under 10 mm per treatment arm pre visit, and the '%change from previous visit' represents the increase in incidence of Schirmer values under 10 mm at that visit. Cells highlighted in red represent notable increases in incidence of dry eye at that visit.

Reviewer's Comments: *Multiple dose levels demonstrate decreasing tear product following use of vilazodone. Tear film deficiencies may account for some of the decreased vision and some of the corneal abnormalities.*

The following funduscopy findings were reported:

Retinal hemorrhage – 3 reports
Floaters -1 report
Abnormal cup – 2 reports
Vitreous detachment – 1
Microaneurysm – 1

Reviewer's Comments: *The relatively few reports and the nature of the reports do not suggest any retinal or vitreous problem related to the drug product.*

Study CLDA-07-DP-04

A One Year Open-Label Study Assessing the Safety and Tolerability of Vilazodone in Patients with Major Depressive Disorder

Ophthalmologic examinations were performed at baseline (Visit 1) and subsequently at Visits 11 (Week 24) and 18 (Week 52). Exams were performed at the early termination visits for patients withdrawing from the study. Evaluations included assessment of best corrected visual acuity as measured by manifest refraction and Snellen scoring, as well as slit-lamp biomicroscopy of the conjunctiva, iris, cornea, and lens. Dilated fundoscopy examinations of the macula, disc, and retinal vessels were performed and the presence/absence of pigments/naevi, exudates, microaneurysms, and/or hemorrhages were noted. Intraocular pressure was also measured at baseline and Week 52 (or at Early Termination [ET]).

Treatment emergent Adverse Events pertaining to the eye occurred in 97 patients (16.2%), the most common of which included dry eye (4.7%), vision blurred (4.0%), and lacrimation increased (1.2%).

Reviewer's Comments: *Dry eye can be contribute to both blurred vision and increased lacrimation.*

			Vilazodone Treatment Result			
			Right Eye		Left Eye	
Corneal Findings	N	Baseline	Normal	Abnormal	Normal	Abnormal
Visit 11/Week 24	310	Normal	288	5	288	5
		Abnormal	2	15	3	14
Visit 18/Week 52	247	Normal	231	4	227	8
		Abnormal	2	10	3	9

Reviewer's Comments: *These corneal findings are likely to be a result of the dry eye abnormalities.*

Lens/Cataract			Absent	Present	Absent	Present
Visit 11/Week 24	310	Absent	222	5	227	4
		Present	10	73	9	70
Visit 18/Week 52	247	Absent	171	6	175	6
		Present	8	62	7	59

Change from Baseline to End of Treatment in Overall Cataract Severity
All Patients with Cataracts at Baseline

Eye	N	Stable	Worsened
Right	110	100 (90.9%)	10 (9.1%)
Left	110	99 (90.0%)	11 (10.0%)
More Severe	110	96 (87.3%)	14 (12.7%)

Reviewer's Comments: *A 9-10% rate of cataract progression in one year is considered high. It is not possible to distinguish without a control group whether this is due a higher than normal rate in this population or due to the drug product.*

	N	Stable	2 Level Decrease	>2 Level Decrease
Right Eye				
Visit 11/Week 24	270	268	0	2
Visit 18/Week 52	213	212	1	0
Visit 18/Early Termination	118	117	0	1
End of Treatment	385	382	1	2
Left Eye				
Visit 11/Week 24	269	264	3	2
Visit 18/Week 52	214	210	4	0
Visit 18/Early Termination	115	112	2	1
End of Treatment	383	375	6	2

Other Ocular Adverse Events:
Among rare TEAEs, 1 subject (0.2%) reported an abnormal sensation in eye, considered mild in severity. Mild blepharitis was reported by 1 subject (0.2%). Mild eye irritation was reported by 2 subjects (0.3%). Increased lacrimation, rated as mild or moderate in severity, occurred in 7 subjects (1.2%). One subject temporarily discontinued study drug due to increased lacrimation. Photophobia was reported by 4 subjects (0.7%), and was considered to be mild or moderate in severity. No subject discontinued due to photophobia. Mild punctate keratitis was reported in 1 subject (0.2%). Reduced visual acuity, mild in intensity, was reported in 4 subjects (0.7%). Other reported events included moderate blepharospasm (1, 0.2%), mild-to-moderate transient blindness/temporary loss of vision (2, 0.3%), mild to moderate eye pain (4, 0.7%), mild eye swelling (2, 0.3%), mild eyelid disorder (2, 0.3%), mild eyelid margin crusting (2, 0.3%), mild myodesopsia (1, 0.2%), “mild” oculogyric crisis (1, 0.2%), mild eye pruritus (3, 0.5%), accommodation disorder (1, 0.2%), arteriosclerotic retinopathy (1, 0.2%), cataract (3, 0.5%), cortical cataract (1, 0.2%), conjunctival hemorrhage (3, 0.5%), conjunctivitis (4, 0.7%), allergic conjunctivitis (2, 0.3%), corneal infiltrates (1, 0.2%), corneal neovascularization (1, 0.2%), acquired dacryostenosis (1, 0.2), eye discharge (2, 0.3%), eye hemorrhage (1, 0.2%), giant papillary conjunctivitis (1, 0.2%), lacrimal disorder (1, 0.2%), ocular hyperaemia (2, 0.3%), ocular hypertension (1, 0.2%), retinal hemorrhage (1, 0.2%), and retinal tear (1, 0.2%)and mild-to-moderate visual impairment (4, 0.7%). One subject temporarily discontinued, and another subject permanently discontinued due to moderate visual impairment.

Reviewer's Comments: *There is no particular pattern to these events and the frequency is consistent with events typically seen in a population of this age range (Mean Age was 43 ±13, Range 18-70, Median 44).*

Responses to Questions:
Question 1) What is your assessment of the ophthalmologic findings?

Response:
The increase in dry eye seems to be real and consistent with other products which cause dry eyes such as many antihistamines. The retinal abnormalities do not appear to be any different than the expected rates in a normal population. The cataract progression rate is higher than I would have expected, but without a concurrent control group, it is not possible to determine whether the product definitely increases the rate of cataracts or the population being studied had a higher than expected reported rate because they were looking for it.

Question 2) Has the sponsor adequately assessed the ophthalmologic safety profile of vilazodone?

Response: *Yes*

Question 3) Could the ophthalmologic risks be managed through labeling? Would you recommend any specific labeling?

Response: *Yes, the ophthalmologic risks can be managed through labeling.*

Question 4) Would you recommend that we request any additional information from the sponsor?

Response: *While it is possible to include information on cataract progression, it would be useful to distinguish whether the higher cataract rate observed in this population is a function of the drug product, a reflection of the baseline rate of cataract formation in the intended population or both. A controlled clinical trial in which patients were maintained on therapy for a period of two years or more would be necessary to make this determination.*

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
01/07/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 6, 2011
To:	Thomas Laughren, MD, Director Division of Psychiatry Products
Through:	Kristina A. Toliver, PharmD, Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Viibryd (Vilazodone) Tablets 10 mg, 20 mg, and 40 mg
Application Type/Number:	NDA 022567
Applicant:	PGxHealth, LLC
OSE RCM #:	2010-826

Contents

1 INTRODUCTION

This review summarizes DMEPA's evaluation of the container labels, carton and insert labeling for Viibryd (Vilazodone HCl) Tablets, 10 mg, 20 mg, and 40 mg (NDA 022567). The Division of Psychiatry Products requested DMEPA's assessment for medication error potential.

2 METHODS AND MATERIALS

DMEPA uses Failure Mode and Effects Analysis (FMEA) and lessons learned from post-marketing experiences to evaluate container labels, carton and insert labeling. This review focuses on the container labels, carton and insert labeling submitted by the Applicant on December 13, 2010 (see Appendices B through F).

- Trade (10 mg, 20 mg, and 40 mg tablets)
    - Container labels: 30-count, 90-count, 500-count
    - Blister card labels: 10-count
    - Carton labeling: Ten 10-count blister cards
    - Patient Starter Package: (contains 10 mg, 20 mg, and 40 mg tablets), 30-count
- Physician Sample Package (contains 10 mg and 20 mg tablets), 14-count

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. Section 3.1 *Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.1 be communicated to the Applicant prior to approval.

Appendix A provides our recommendation concerning the insert labeling that was previously communicated to the review division in a Viibryd labeling meeting held on November 30, 2010.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sandra Griffith, at 301-796-2445.

3.1 COMMENTS TO THE APPLICANT

A. General Comments for All Container Labels and Blister Carton Labeling

1. Ensure the established name is at least ½ the size of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features [21 CFR 201.10(g)(2)].
2. The dosage form statement "Tablets" appears more prominent than the active ingredient statement. The dosage form statement is a part of the established name, therefore, ensure it is commensurate in size, font, etc. to the active ingredient statement.

B. Container Labels, 10 mg, 20 mg, and 40 mg (30-count, 90-count, and 500-count)

1. The net quantity statement is too prominent. Therefore, we request you decrease the prominence by unbolding the statement and reducing its size.
2. The Medication Guide statement is not prominent. Separate the Medication Guide statement from the Usual Dosage and "Dispense in...container" statements (e.g., use a

line to separate these statements). Additionally, increase the prominence of the Medication Guide statement with the use of bold type.

3. The statement "Each tablet contains..." is located on the principal display panel and detracts from important product identifying information such as the proprietary name, established name, and strength. Relocate this statement to one of the side panels.

C. Blister Carton

1. The active ingredient statement "vilazodone HCl" is printed in a light grey color that lacks sufficient contrast against the white background and is, thus, difficult to see. Additionally, the dosage form statement "Tablets" appears more prominent than the active ingredient statement because it appears in a dark green font color. The active ingredient and dosage form statements make up the established name and, thus, ensure they appear in the same color and are commensurate in size, font, etc.
2. The statement of strength is left justified on the front and two side panels. For improved readability, center the statement of strength on these panels. In order to make space for this, relocate the "Each tablet contains..." statement to the back panel.

D. Blister Labels, 10 mg, 20 mg, and 40 mg (10-count unit dose blisters)

1. Increase the prominence of the proprietary name and established name.
2. Relocate the statement of strength to the usual position which is immediately below the established name. In its current position, it looks like the blister number rather than the product strength.
3. Decrease the prominence of the lot number and expiration date.
4. The blister labels look identical for all three strengths. Differentiate the strengths with the use of color, different box shapes, or some other means.
5. Delete the statement "Each tablet contains..." This statement crowds the label and it is not necessary because the label is too small.

E. Patient Starter Package and Physician Sample Package

1. As currently presented, the tablet layout is confusing for the following reasons:

   - The tablets to be taken for each week are lined up in vertical columns that are adjacent to one another and there is no line or other demarcation to separate them.
   - Under each vertical column there is a boxed statement of strength and it is not immediately clear why they are positioned under the vertical columns.
   - It is not immediately clear where a patient should start and in which direction a patient should go as the tablets are taken (i.e., should a patient progress across in a row or down in a column).

   We request you provide data to support the proposed configuration. Provide the results of an FMEA and usability testing that demonstrate the current layout is not confusing and patients can follow the dosing schedule as provided. If you do not have data to support your proposed configuration, we recommend you revise the format as follows:

   Reconfigure the tablet layout so that one week of therapy is contained on one panel or each week of therapy is separated and distinct from the other (see example below).

Ensure that for each day of therapy, the numerical day of the week is stated (i.e., Day 1, Day 2, Day 3, etc.) and placed in close proximity to the respective dose (see example below) rather than the current presentation of "Days X-Y".

Week 1

Day 1 Day 2 Day 3 Day 4

Day 5 Day 6 Day 7

Week 2

Day 1 Day 2 Day 3 Day 4

Day 5 Day 6 Day 7

2. The letters "A" and "B", and "A", "B", and C" are on the patient starter package and physician sample package, respectively. Each letter is accompanied by a circle that encloses one of the tablet strengths, however, there are no instructions that explain the meaning of these letters. Explain the intended meaning of these letters and whether these letters were tested to ensure they can be understood. If tested, provide the results of the testing.
3. The instructions to the patient about how the package should be used do not appear complete. These are some of the questions that should be answered in the instructions to the patient:
   a. What is the procedure for removing the tablets from the package?
   b. Where does the patient start (e.g., show the patient which tablet, week, and day to start with; consider using the statement "start here" along with an arrow pointing to the tablet that should be used first)?

   In the instructions under "How to take Viibryd (vilazodone HCl) Tablets", the tablet strengths have a dash between the number and unit of measure (i.e., 10-mg, 20-mg, 40-mg). This may be confusing. Delete the dash that separates the number and unit of measure (e.g., 10 mg, 20 mg, and 40 mg)
4. The package does not state the number of weeks or days of therapy it contains. Revise to include the number of weeks or days of therapy that the package contains and place this statement on the principal display panel.
5. The starter package and physician sample do not have a net quantity statement. The principal display panel contains only the three strengths without reference to how many tablets of each strength are contained in the pack. Revise to include a net quantity statement on the principal display panel. Revise the statement of strength to reflect the number of tablets of each strength included in the package. For example:

   Each starter pack contains:
   XX tablets containing XX mg—Week 1
   XX tablets containing XX mg—Week 2
   XX tablets containing XX mg—Week 3

6. It is not clear how the tablet strengths will appear on the packages. Each tablet position is represented by a circle and inside the circle the respective tablet strength is specified (i.e., 10, 20, or 40). However, it is unclear whether this information will be printed on the package or how it will appear on the marketed package. Please clarify. We recommend you print the individual tablet strengths on the front card immediately below each tablet in order to help minimize confusion by ensuring that the information is easily seen. Additionally, ensure the dosage unit is also specified (e.g., revise "10" to read "10 mg" and "20" to read "20 mg", etc.)
7. The active ingredient statement "vilazodone HCl" is printed in a light grey color that lacks sufficient contrast against the white background and is, thus, difficult to see. Additionally, the dosage form statement "Tablets" appears more prominent than the active ingredient statement because it is presented in a dark green font color. The active ingredient and dosage form statements make up the established name and, thus, ensure they appear in the same color and are commensurate in size, font, etc.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LORETTA HOLMES
01/06/2011

KRISTINA C ARNWINE
01/06/2011

CAROL A HOLQUIST
01/07/2011

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 5, 2011

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D. Pharmacologist
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

Subject: Vilazodone (NDA 022-567)
Indication: Major Depressive Disorder
Dosages: 40 mg daily
Sponsor: PGx Health, LLC

Materials reviewed: NDA submission located at: **\\CDSESUB1\EVSPROD\NDA022567**
Abuse potential materials including Appendix 7: "Assessment of drug abuse potential", a self-administration study, physical dependence study, and conditioned place preference study in rodents.
Medical officer review by Cheri Lindberg, M.D.
Pharmacology/toxicology review by Violetta Klimek, Ph.D.

Table of Contents

I. Summary

A. Background

This memo responds to the Division of Psychiatry Products consult regarding the abuse potential of vilazodone (NDA 22-567). Vilazodone is a new chemical entity (NCE). According to the Sponsor, vilazodone is an orally administered, dual-acting, selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist. Vilazodone is being developed for the treatment of major depressive disorder.

There is evidence suggesting the involvement of serotonin (5-HT) in several psychiatric disorders including depression. Depression may be due, in part, to a deficiency of 5-HT neurotransmission. Selective serotonin reuptake inhibitors (SSRI's) are thought to achieve therapeutic efficacy via an increase in 5-HT neurotransmission. However, the increase in 5-HT may result in feedback inhibition via autoinhibitory 5-HT1A receptors.

According to the Sponsor, the combination of an SSRI and 5-HT1A partial agonist may more robustly normalize 5-HT neurotransmission relative to either mechanism of action alone, and alleviate the symptoms of major depression.

B. Conclusions:

1. Receptor binding studies indicate that vilazodone does not have significant affinity for receptor sites associated with abuse potential.
2. Drugs with a mechanism of action similar to vilazodone such as selective serotonin reuptake inhibitors (SSRI's) and 5-HT1A agonists have a low abuse potential.
3. Vilazodone produces antidepressant-like behavioral effects in preclinical models of depression.
4. Animal self-administration studies indicate that vilazodone has a low potential for abuse.
5. Animal conditioned place preference studies indicate that vilazodone has a low potential for abuse.
6. Animal physical dependence studies indicate that vilazodone produces physical dependence. However, physical dependence is unlikely to contribute to the abuse potential of vilazodone at clinically relevant doses.
7. The Sponsor has not studied vilazodone for abuse potential in a human abuse potential pharmacology laboratory study.
8. However, an analysis of abuse-related AEs from completed clinical studies suggests that vilazodone affects CNS activity, but does not indicate that vilazodone has the potential for abuse, in that minimal euphoria and hallucinations were reported. Vilazodone produces somnolence and sedation in humans.
9. In summary, preclinical and clinical data indicate the vilazodone produces CNS depressant effects, but appears to have a very low potential for abuse.

C. Recommendations:

CSS recommends that the following text be added to section 9.2 of the label: "An analysis of abuse related adverse events from clinical studies suggests that VIIBRYD has a low potential for abuse".

II. Appendix

D. Pharmacology of drug substance and active metabolites

1. Product description

Upon approval, vilazodone will be available in 10, 20, and 40 mg immediate-release, oval, film-coated tablets manufactured from a (b) (4) with total tablet weights of 103 mg, 206 mg and 412 mg, respectively. The 10 mg tablets are pink; the 20 mg, orange; and the 40 mg, blue. The tablets are debossed with the strength on one side and plain on the other. The tablets are packaged in 30-count, 90-count and 500-count high-density polyethylene (HDPE) bottles, and in film/aluminum foil blisters.

2. In vitro studies

The pharmacology of vilazodone has been studied to characterize its serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibition, receptor binding profile, and regulation of 5-HT neurotransmission. Sponsor information and DPP reviews are summarized below:

- Receptor binding studies

According to the pharmacology and toxicology review by Violetta Klimek, Ph.D., Vilazodone binds with high affinity to the serotonin reuptake site (Ki= 0.1 nM), but not to the norepinephrine (Ki=56 nM) or dopamine (Ki=37 nM) reuptake sites. Vilazodone inhibits reuptake of serotonin (IC50 = 1.6 nM and binds to 5HT1A receptors with similar affinity (IC50 = 2.1 nM) and is 5HT1A receptor partial agonist.

Additional information summarized by the Sponsor appears below:

In study GPP-007-NCD- PCL-1999-065, the affinity of vilazodone for various receptors was assessed. Vilazodone has high affinity for 5-HT1A receptors from rat cerebral cortex (IC 50 = 1.6 nM) and human recombinant 5-HT1A receptors expressed in CHO cells (IC 50 = 2.1 nM). Vilazodone also displays high affinity (0.14 nM) for the 5-HT reuptake transporter and does not demonstrate significant affinity for any other receptor subtypes in this study.

In study GPP-007-NCD-PCL-1995-046, vilazodone demonstrates high affinity for 5-HT1A (IC 50 = 0.5 nM) receptors, D3 receptors (IC 50 = 140 nM), 5-HT4 receptors (IC 50 = 100 nM) and σ receptors (IC 50 = 16 nM). In this study, vilazodone has higher affinity for rat hippocampal 5-HT1A receptors than the prototypical 5-HT1A agonist 8-OH-DPAT, and the anxiolytics ipsapirone and

buspirone. This study also demonstrates vilazodone's activity in inhibiting 5-HT uptake (IC50 = 0.2 nM).

The receptor binding profiles of the three major metabolites of vilazodone (EMD, 87409, EMD 80 546, and EMD 122 230) were also assessed. All were shown to have less affinity or be less potent than the parent compound.

3. Safety pharmacology findings

- General behavioral responses

Studies examining the ability of vilazodone to produce physical dependence and withdrawal are described below (see: Animal behavioral studies).

The Sponsor examined the effect of vilazodone on locomotor activity and 8-OH-DPAT-induced hyperlocomotor activity in male rats (study GPP-007-NCD-PCL-2003-134). The locomotor study did not include a positive control with a known abuse potential. Because a positive control was not used in the locomotor study, the results do not provide information directly applicable to the abuse potential assessment of vilazodone.

Male rats were administered vilazodone (3.0, 10, or 30 mg/kg p.o.) or vehicle prior to an injection of either 8-OH-DPAT (0.1 mg/kg s.c.) or vehicle. Animals were then placed into runway boxes under red light conditions and the number of travels monitored for 30 minutes. No dose of vilazodone had a significant effect on locomotor activity. In contrast, 8-OH-DPAT significantly increased the number of travels recorded.

These data demonstrate that vilazodone does not affect locomotor activity at the doses tested. The locomotor study data also suggest that vilazodone produces behavioral effects that are distinct from the prototypical 5-HT1A agonist, 8-OH-DPAT. The preceding suggestion is consistent with the partial agonist profile of vilazodone at the 5-HT1A receptor. The rationale for the selection of doses of vilazodone and the two hour pretreatment time was not provided.

4. Animal behavioral studies

- Self administration studies

Study GPP-007-NCD-PCL-2003-120 was a self-administration study to evaluate the abuse potential of vilazodone. The self administration study suggests that vilazodone is not reinforcing and has a low potential for abuse. Despite several deficiencies, the overall self-administration study design was appropriate. The doses of vilazodone used in the self administration study included doses that are equivalent to the proposed clinical dose (on a weight adjusted basis) and appear sufficient to assess the reinforcing properties of vilazodone. The highest dose of vilazodone produced self-administration levels that were lower than placebo, and suggests that this dose was behaviorally active and sufficiently large.

Heroin was used as the self-administration training agent although the rationale for the use of heroin as the training agent was not provided. This is an important consideration as the immediate drug history of an animal may affect the results of self administration studies (Ator and Griffiths 2003). Twenty-five male rats were trained to press on a fixed-ratio 5 (FR 5) schedule for heroin injections (0.1 mg/kg). Vilazodone failed to maintain self-administration at any dose tested with 1.8 ± 0.4, 1.5 ±0.4, and 0.2 ±0.1 injections at the 0.5, 1.75 and 6.12 mg/kg/infusion dose levels. The highest dose of vilazodone (6.12 mg/kg/infusion) produced self-administration levels that were lower than placebo, which may indicate aversive effects.

The rationale for the doses used in the self-administration study was not provided. In addition, blood plasma levels of vilazodone were not measured during sessions. It is unknown how the plasma levels of vilazodone in the self-administration study compare to plasma levels that will be achieved clinically. At the two highest doses of vilazodone, (1.75 and 6.12 mg/kg/infusion) the pH of the solution was maintained at 5.0. It is unknown whether the acidic nature of the solution produced aversive effects that masked the reinforcing properties of vilazodone.

- Conditioned place preference study

The Sponsor assessed the rewarding properties of vilazodone using conditioned place preference (CPP) (study GPP-007-NCD-PCL-2003-118). Despite several limitations, the CPP results indicate that vilazodone is not reinforcing and has a low potential for abuse.

Rodents were trained for eight days with placebo, the positive control morphine (64 mg/kg), or vilazodone (5 or 25 mg/kg) p.o., administered 60 min before testing. Morphine administration resulted in a significant increase in time spent in the drug-paired compartment as compared to vehicle treated animals (663.5 ± 36.3 seconds versus 650.3 ± 31.8 seconds for placebo $p< 0.05$). In contrast, neither dose of vilazodone (5 or 25 mg/kg) resulted in an increase in time spent in the drug-associated compartment (594.5±24.7 and 530.8±29.7 seconds).

Although the overall study design was appropriate, the rationale for the selection of dose, pretreatment time, and route of administration were not provided. It is possible that lower doses of vilazodone are reinforcing but were not tested by the Sponsor. The vilazodone doses tested in the CPP paradigm are much higher than the anticipated clinical dose. The proposed human dose (40 mg/day) in an average 70 kg person, is equivalent to about 0.6 mg/kg. The highest tested dose in the CPP paradigm (25 mg/kg) is about 42 times the planned therapeutic dose.

An assessment of drug plasma levels in rodents would determine the relative dose of vilazodone used in the CPP study. Plasma level assessments would also verify that CPP assessments were performed using the appropriate pretreatment times (e.g. during the Cmax of vilazodone).

- Drug discrimination study

In a rodent drug discrimination study (study GPP-007-NCD-PCL-1997-091), rats were trained to discriminate 0.4 mg/kg (8-hydroxy-2-(id-n-propylamino)tetralin) (8-OH-DPAT) from saline.

The results of the drug discrimination study suggest that some component of the stimulus effects of vilazodone may be shared with 8-OH-DPAT, and mediated via agonist effects at the 5-HT1A receptor. However, the interpretation of partial generalization in drug discrimination studies is problematic and open to interpretation. While the design of the drug discrimination study was appropriate, the study results have little relevance to the abuse potential of vilazodone because the abuse potential of 8-OH-DPAT in humans is completely unknown.

All drugs were administered i.p. with a 15 min pretreatment time. Once reliable 8-OH-DPAT discrimination was obtained, substitution tests with vilazodone were performed. Vilazodone increased drug-appropriate responding in a dose dependent manner. At the maximum dose of 4 mg/kg, vilazodone produced 54% 8-OH-DPAT-appropriate responding (i.e. intermediate substitution or partial generalization). The proportion of rats emitting ≥77% 8-OH-DPAT-appropriate responding also increased in a dose related manner, with five of twelve animals selecting the drug-appropriate lever at the highest dose (4 mg/kg). Higher doses of vilazodone resulted in behavioral impairment.

- Physical dependence study

Physical dependence was evaluated in male wistar rats (study GPP-007-NCD-PCL-2003-119). Changes in rectal temperature and body weight were observed and suggest the occurrence of physiological changes after chronic administration of vilazodone. However, given the high doses employed in the study, the physiological changes observed are unlikely to be clinically relevant. Thus, the ability of vilazodone to produce physical dependence is unlikely to increase the abuse potential of vilazodone.

Male Wistar rats were administered 5 or 25 mg/kg/day vilazodone in three equal subdoses for 30 days. The 30-day dosing regimen and dose selection are appropriate for an assessment of physical dependence. Morphine was used as a positive control (128 mg/kg/day) and administered under identical conditions. Beginning with the last 3 days of the treatment period (e.g., days 28, 29, and 30), animals were observed for signs of physical withdrawal. Observations continued for 8 days after the final injection (e.g., days 31- 38). Food consumption, body weight, and rectal temperature were assessed as markers of physical dependence.

Vilazodone administration did not change food consumption during the last three days of the drug treatment period. At day four of the post-dose cessation period (day 34), food intake was increased in the 25 mg/kg/day vilazodone group. The increase in food consumption persisted for the duration of the observation period (e.g., food consumption was still increased on day 38). In the 5 mg/kg/day vilazodone group, an increase in food consumption was observed on days 32, 36,

and 38 of the study (e.g., cessation days 2, 6, and 8). Morphine administration resulted in a significant decrease in food consumption during the last 3 days of the treatment period. This effect persisted for the first 4 days of the cessation period (days 31-34). During the last three days of the cessation period (days 37-39), food intake was increased in morphine treated animals relative to vehicle treated controls.

Relative to placebo, neither dose of vilazodone caused a significant change in body weight at any point in the study. Morphine administration resulted in a significant decrease in body weight at every point assessed in the study.

The high dose of vilazodone caused a decrease in rectal temperature on the first observed day of the treatment period (e.g. day 28). During the cessation period, the high dose of vilazodone increased rectal temperate from day 4 through the end of the study. Morphine caused a decrease in rectal temperature during the first two observation days of the dosing period. No other changes were observed.

Other "behavioral and physiological symptoms" were qualitatively observed. The Sponsor concluded that vilazodone showed no behavioral effects during the treatment or withdrawal phase.

To evaluate the ability of vilazodone to produce opioid-like withdrawal effects, the Sponsor examined vilazodone in the Saelens' jump test (study GPP-007-NCD-PCL-2000-096). The findings suggest that vilazodone does not produce opioid-like physical dependence. However, the negative results from the Saelens' test are expected given vilazodone's mechanism of action.

According to the Sponsor, the Saelans jump test is a commonly used measure of opioid-like withdrawal. Mice were treated with vilazodone doses of 3, 10, and 30 mg/kg administered p.o., 5 times on Day 1, and 2 times on Day 2. The administration of vilazodone on Day 2 was followed by treatment with naloxone (10 mg/kg i.p.) to induce opioid withdrawal. Morphine, (64 mg/kg) was administered under identical conditions as a positive control. Vilazodone treated mice displayed a decrease in the number of jumps in response to naloxone challenge, this decrease was not significant. In contrast, morphine produced a statistically significant increase in the number of jumps precipitated by naloxone treatment.

E. Clinical pharmacology

Clinical pharmacology finds are summarized below.

1. Absorption

Vilazodone is intended for oral administration. In human studies, the Sponsor has not assessed the absorption, pharmacokinetics, or metabolism of vilazodone administered by alternate routes (e.g. injection, buccal administration, or "snorting").

2. Metabolism

Vilazodone is metabolized by the liver. CYP3A4 is the major cytochrome P450 (CYP) isoenzyme responsible for vilazodone metabolism.

Study GPP-007-CLN-ANR-1997-019 was a pilot study done in healthy volunteers to determine the metabolites of vilazodone. Subjects received a single oral administration of vilazodone (either 2.5 to 80 mg). In this study, the half life was between 13 h and 18 h and the tmax range was 3-6 hours.

3. Elimination

The primary route of elimination of vilazodone is through feces, probably via secretion into bile. In a study measuring the metabolites of vilazodone in healthy males after a single, oral dose of 14C-vilazodone (PGX-08-P1-07), 65% of the dose was recovered in feces, with 1.8% as unchanged vilazodone. Recovery of radioactivity in urine through 14 days postdosing was 19.9% of the administered label, with 1.1% of the dose recovered as unchanged vilazodone. Mean overall recovery of the administered radiolabel from both urine and feces through 14 days postdosing totals was 85%, with 3% recovered as unchanged vilazodone.

Vilazodone urine concentrations were assayed in 2 single ascending-dose studies (GPP-007-CLN-CP1-1996-231, GPP-007-CLN-CP1-1997-232), 2 special-population studies (PGX-08-P1-01, PGX-08-P1-02) and a 14C-vilazodone mass-balance study (PGX-08-P1-07). The elimination half-life for vilazodone following a single 40 mg dose is approximately 24 hours, although average values in healthy normals ranged from approximately 13 hours to nearly 30 hours.

4. Pharmacokinetics / pharmacodynamic parameters of parent drug & active metabolites

- Comparison with similar drug products or formulations

Vilazodone is a purported SSRI and 5-HT1A partial agonist. The half life of currently marketed SSRI's is variable. For example, fluvoxamine has a half life of about 18 hours, while citalopram has a half life of about 36 hours (Goodman et al. 2006). Clinically useful anxiolytics with 5-HT1A activity such as buspirone have an elimination half life of 2-4 hours (Katzung 2009). Vilazodone is only available as an oral formulation

- Cmax, Tmax, Emax

Vilazodone displays a consistent PK profile across studies with a median Tmax generally occurring 4-6 hours post-dose, whether administered as a single dose, repeated doses, capsule, or tablet. Vilazodone AUC values show dose proportionality over the range of doses studied (2.5 to 80 mg as single doses, and 20 mg to 80 mg qd as repeated doses). The mean AUC 0-24 at steady state produced by vilazodone 40 mg qd was 1645 ng/hr/mL (PGX-08-P1-06).

Cmax values show dose proportionality from 2.5 mg to 80 mg when administered as a single dose (GPP-007-CLN-CP1-1996-231; GPP-007-CLN-CP1-1997-232).

With repeated dosing, vilazodone plasma concentrations reach steady-state levels within approximately 3 days and result in peak steady-state concentrations that are 60-80% greater than single dose administrations (GPP-007-CLN-CP1-1998-230; GPP-007-CLN-CP1-2003-237).

Vilazodone exposure is greater when administered with food in comparison to fasting conditions. Single doses of vilazodone (40 mg tablets) with a meal result in a mean steady-state Cmax of 156 mg/mL. When vilazodone is administered with food, Cmax values are increased approximately 50% to 150%, and AUC values are approximately 50% to 90% greater than when given under fasting conditions.

The elimination half-life of vilazodone after a single 40 mg dose is approximately 24 hours (CLDA-07-DP-01) although values in healthy young adults range from 13 (GPP-007-CLN-CP1-1996-231) to nearly 30 hours (GPP-007-CLN-CP1-2003-237). The elimination half-life may be slightly longer following repeated dosing. An increase in the elimination half-life from 24.5 hours to 28.9 hours was reported with multiple dosing in study GPP-007-CLN-CP1-1998-230, and an increase from 28.3 hours to 36.6 hours was reported in study GPP-007-CLN-CP1-2003-237. The Sponsor feels that the increase in the terminal elimination half-life is an artifact of vilazodone concentrations being sampled and/or quantified for a longer period of time when studied in the multiple dose setting.

- Drug/product interactions (alcohol, drugs, food, dietary supplements, etc.)

Vilazodone exposure is greater when the dose is administered with food in comparison to fasting conditions. When vilazodone is administered with food Cmax values are approximately 50% to 150% greater, and AUC values are approximately 50% to 90% greater.

- Pharmacogenetic considerations (metabolizer status)

Vilazodone did not induce CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, or CYP3A5 isoforms in an in vitro study in cultured human hepatocytes. The Sponsor feels that this is an indication that vilazodone is unlikely to induce of any of the major CYP isoenzymes (GPP-007-CLN-ANR-1999-027) or result in pharmacogenetic differences.

- Does the drug produce tolerance in humans?

No clinical assessments of withdrawal or tolerance effects were performed. The Sponsor recommends upward titration to a dose of 40 mg/day. This titration schedule suggests the development of some degree of physiological tolerance. A withdrawal syndrome is associated with the discontinuation of several SSRI's (Black et al. 2000; Haddad 1998). Vilazodone may produce a similar tolerance and withdrawal profile.

F. Clinical Studies

Twenty-four Phase 1 studies, five Phase 2 studies, and three Phase 3 studies were performed with vilazodone. A total of 2,898 subjects received vilazodone during development. A clinical abuse potential study was not performed.

1. Adverse event profile through all phases of development- particularly those related to abuse potential

In response to a Controlled Substance Staff information request, the Sponsor summarized abuse-related AEs that occurred during clinical development. In a summary analysis, the Sponsor included an analysis of AEs that occurred during Phase 1 studies, Phase 2 and Phase 3 studies, and an overall summary of AEs from uncontrolled long-term studies (e.g. uncontrolled Phase 2 and 3 studies). No statistical analyses were performed.

- Phase 1 studies

There were 24 phase 1 studies with a total of 715 subjects exposed to vilazodone. An analysis of abuse related AEs from Phase 1 studies suggests that vilazodone has a low abuse potential, even at doses up to two times the proposed clinical dose. Vilazodone doses ranged from 2.5-80 mg. Table 1 shows abuse related AEs that occurred during Phase 1 studies.

In Phase 1 studies there were no occurrences of euphoric mood and few AEs occurred in more than 1% of the volunteers that received vilazodone. The most common AE was "dizziness" which was experienced by 110 of the 715 participants (15.4%). However, "dizziness" is not considered an abuse related AE unless reported with the verbatim term "giddiness". "Disturbance in attention" was the second most common abuse related AE, experienced by 9 (1.3%) of the volunteers. These results indicate that vilazodone has a low abuse potential, even at doses up to two times the proposed clinical dose.

- Phase 2/3 studies

Analyzing abuse related AEs from Phase 2 and Phase 3 presents several difficulties because of the subject population. In particular, it may be difficult to distinguish reports of "euphoric mood" from the resolution of depression. Thus, conclusions from the abuse related AE analysis of Phase 2 and Phase 3 studies are limited.

The analysis of abuse related AEs from Phase 2 and Phase 3 studies suggests that vilazodone has a low potential for abuse. Table two displays the incidence of abuse-related AEs from placebo controlled, Phase 2 and Phase 3 studies. There were five Phase 2 studies and three Phase 3 studies. All of the Phase 2 and Phase 3 studies were placebo-controlled, except for one long-term Phase 3 study (study CLDA-07-DP-04) that is displayed separately.

Similar to Phase 1 studies, "dizziness" was the most common AE and experienced by 34 (15%) of individuals receiving greater than 40 mg/day vilazodone. "Euphoric mood" was experienced by one volunteer at the 40 mg/day dose, and 2 individuals that received placebo.

Table 3 shows the abuse-related AE profile for study (CLDA-07-DP-04). Study (CLDA-07-DP-04) is the only uncontrolled Phase 3 study, and is not included in Table 2. Similar to the pooled analysis, of placebo controlled Phase 2 and 3 studies, "dizziness" was the most common abuse-related AE.

"Dizziness" was experienced by 46 (8.2%) of individuals and "sedation" was experienced by 21 (3.7%) of volunteers. "Euphoric mood" was reported by 7 (1.2%) participants. According to the Sponsor, all events coded to euphoric mood were mild except for 1 subject who had an event described as "hyperserotonergia" of moderate severity on Day 4 of treatment. This subject had "tremors of upper extremities bilaterally," insomnia, somnolence, and abnormal dreams. The subject was treated with eszopiclone, and vilazodone was reduced from 40 mg to 20 mg. The insomnia, somnolence, and abnormal dreams resolved within a few weeks; however, the euphoric mood AE persisted for approximately 1 year until study completion, at which time the subject was noted as having recovered without sequelae.

Although the incidence of "euphoric mood" in this single study (1.2%) was higher than the pooled analysis of Phase 2 and Phase 3 studies (0.2%), the lack of placebo control makes the interpretation of these results difficult.

- Prospective evaluation of physical dependence in phase 3 studies

No prospective studies of physical dependence or withdrawal were performed. However, during vilazodone discontinuation in clinical studies, downward titration of dosing was not performed and only 2 withdrawal-related AE's were reported within 30 days of study discontinuation.

One of the withdrawal-related events occurred after a Phase 1 study. Ten days after the last dose of study drug, a subject reported that he was unhappy in his relationship. One day later the subject became paranoid and started asking questions about his wife. He developed a conspiracy theory around his wife being a pharmacist and how he might get poisoned. The subject did not experience any hallucinations or other perceptual abnormalities but did act on his paranoid beliefs. The subject visited a psychiatrist 21 days after the last dose of study medication and was described as fully recovered. The Investigator considered these paranoid delusions as possibly related to study drug.

A second patient was hospitalized with an AE of worsening depression with psychotic features approximately 25 days after receiving her last dose of vilazodone while participating in a Phase 3 study (study GNSC-04-DP-02). The subject reported that she felt as though an implant was in her head, and the case report form described her thoughts that "her cats were cameras of terrorists, and were following her". She was discharged from the hospital 7 days later and recovered fully.

SSRI's, which have a mechanism of action similar to vilazodone, are known to produce withdrawal upon abrupt discontinuation (Black et al. 2000; Haddad 1997; Haddad 1998; Lejoyeux et al. 1992; Lejoyeux and Ades 1997). Withdrawal symptoms typically seen after discontinuation of SSRIs include dizziness, nausea, emesis, fatigue, gait instability, and insomnia. Behavioral symptoms such as aggressive or impulsive behavior have also been seen during SSRI discontinuation.

Based on the known SSRI withdrawal symptoms and the similar mechanism of action of vilazodone, it is likely that vilazodone produces some degree of physical dependence. The AEs described above appear consistent with withdrawal symptoms due to SSRI discontinuation. However, 1035 individuals were treated with vilazodone during Phase 3 studies. Although not formally tested with statistical measures, the two reports of withdrawal-related AEs are unlikely to be clinically relevant.

2. Safety profile

The Sponsor reports that there were 5 subjects who potentially experienced study drug overdose, including 1 non-subject, the child of a research subject. The Sponsor defined "overdose" as taking more study drug than directed. One of the 5 subjects reported to have experienced overdose was recorded under the TEAE of "serotonin syndrome". Cases of study drug overdose are described below:

A 25 year old female reported moderate disorientation and restless after taking a "double-dose" of the study drug. She fully recovered the same day that the dose was taken. There was no change in vilazodone dose (40 mg) and no further study action taken.

A 51-year old male experienced overdose while taking 10 mg vilazodone. He recovered the same day and no action was taken by the study investigator. No CRF's were found for this patient in the NDA submission.

A 49-year old female subject experienced a mild overdose on two separate occasions while taking 5 mg/day vilazodone. On both occasions, she recovered the same day. For the study protocol of interest, the primary investigator was required to report any irregularity in drug accountability as a potential study drug overdose. For one of the two events that were classified as a potential study drug overdose, the volunteer misplaced a study medication bottle. Because the misplaced study medication bottle was unaccounted for, it was classified as a

study drug overdose. Twenty four days later, the volunteer returned three unused capsules of the study medication to the primary investigator. Since these three capsules were unaccounted for, they were classified as a study drug overdose. For both events, no action was taken by the study investigator. Although both instances were coded as a potential study drug overdose, neither appears to be an actual overdose.

One subject was reported as experiencing an AE of "serotonin syndrome." A 24 year old African American female reported taking 5-6 pills of 40 mg vilazodone in order to "catch up" on missed doses. She presented to the ER anxious, seeing things, picking at her face, mute, and combative. Her blood pressure was 152/79 mm Hg, heart rate 155 bpm, and body temperature was 98.4 C°. She was admitted to the hospital, treated, and discharged the next day. She discontinued from the study several days later.

A pediatric overdose occurred in a 21-month old child. The child was estimated to have ingested 5-7, 40 mg pills. The child was taken to the emergency room and received activated charcoal and experienced several episodes of emesis. After 45 minutes, the child appeared sleepy and lethargic. The child was transferred to a children's ER and returned to "baseline" in a few hours. He was discharged the next day.

Overdose associated with intentional misuse and abuse was not reported.

3. Evidence of misuse and diversion in clinical trials

The Sponsor did not perform an analysis of study drug diversion during clinical trials. As a class, selective serotonin reuptake inhibitors (SSRI's) and 5-HT1A agonists are not scheduled, and not typically associated with abuse.

- Study dropout analysis

The Sponsor reports that in placebo controlled Phase 3 studies, the percentage of subjects that discontinued treatment due to a TEAE was 7.1% for vilazodone and 3.2% for placebo. No single TEAE led to discontinuation in greater than 1% of subjects.

G. Integrated abuse potential assessment

1. Findings

- Risks of substance and formulation

Based on the preclinical receptor binding profile, animal studies, and AE analysis, vilazodone appears to have a minimal abuse potential and presents minimal risk.

- Sponsor identified -are risks appropriately identified in label

In the label, the Sponsor appropriately acknowledges the lack of human abuse potential data. In the "DRUG ABUSE AND DEPENDENCE" section of the label, physicians are advised to carefully evaluate patients for a history of drug

abuse and to follow them closely, observing them for signs of drug misuse and abuse. CSS has provided recommendations for additional text to be added to the label (See: C. Recommendations)

- FDA/scientific literature

The scientific literature provides several reports regarding the efficacy of vilazodone in treating major depressive disorder. There are no reports on the abuse potential of vilazodone.

There have been case reports of fluoxetine (an SSRI) abuse (Pagliaro and Pagliaro 1993; Tinsley et al. 1994) however this appears to be an extremeley rare occurence.

Because vilazodone is not marketed in any country, there is no postmarketing experience.

Table 1. Pooled Analysis of Abuse-Related AEs from Phase 1 Studies	
Abuse potential category preferred term	vilazodone, All doses N= 715 (%)
Number of subjects with at least one AE	125 (17.5)
Total number of abuse-related AEs	188
Euphoria-related terms	**114 (15.9)**
Dizziness*	110 (15.4)
Feeling abnormal	7 (1.0)
Feeling drunk	1 (0.1)
Inappropriate affect	1 (0.1)
Terms indicative of impaired attention, cognition, mood, and psychomotor events	**15 (2.1)**
Disturbance in attention	9 (1.3)
Mood swings	2 (0.3)
Somnolence	2 (0.3)
Emotional distress	1 (0.1)
Memory impairment	1 (0.1)
Dissociative /psychotic terms	**7 (1.0)**
Disorientation	6 (0.8)
Agitation	1 (0.1)
*"Dizziness" should not be considered an abuse related AE unless reported with the verbatim term "giddiness".	

Table 2. Pooled Abuse-Related AEs for Phase 2 and Phase 3, Placebo Controlled Studies					
Abuse Potential Preferred Term	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 (%)
Number of subjects with at least 1 abuse potential related AE	88 (8.8)	93 (10.3)	52 (11.8)	64 (28.2)	211 (13.4)
Total number of abuse potential related AEs	105	124	62	97	285
Euphoria-related terms	**38 (3.8)**	**41 (4.5)**	**31 (7.0)**	**38 (16.7)**	**111 (7.0)**
Dizziness*	34 (3.4)	38 (4.2)	27 (6.1)	34 (15.0)	100 (6.3)
Feeling abnormal	2 (0.2)	3 (0.3)	3 (0.7)	1 (0.4)	7 (0.4)
Hypnagogic hallucination	0	0	0	2 (0.9)	2 (0.1)
Euphoric mood	2 (0.2)	0	1 (0.2)	0	1 (0.1)
Hallucination	0	0	0	1 (0.4)	1 (0.1)
Hallucination, auditory	0	0	1 (0.2)	0	1 (0.1)
Hallucination, olfactory	0	0	0	1 (0.4)	1 (0.1)
Terms indicative of impaired attention, cognition, mood, and psychomotor events	**45 (4.5)**	**51 (5.6)**	**18 (4.1)**	**26 (11.5)**	**95 (6.0)**
Irritability	21 (2.1)	21 (2.3)	4 (0.9)	7 (3.1)	32 (2.0)
Sedation	10 (1.0)	11 (1.2)	6 (1.4)	7 (3.1)	24 (1.5)
Somnolence	4 (0.4)	9 (1.0)	3 (0.7)	6 (2.6)	18 (1.1)
Disturbance in attention	9 (0.9)	3 (0.3)	5 (1.1)	7 (3.1)	15 (1.0)
Memory impairment	3 (0.3)	7 (0.8)	1 (0.2)	1 (0.4)	9 (0.6)
Amnesia	0	1 (0.1)	0	0	1 (0.1)
Emotional disorder	1 (0.1)	0	0	0	0
Mood swings	1 (0.1)	0	0	0	0
Dissociative/psychotic terms	11 (1.1)	13 (1.4)	6 (1.4)	13 (5.7)	33 (2.1)
Agitation	5 (0.5)	2 (0.2)	1 (0.2)	5 (2.2)	8 (0.5)
Disorientation	0	1 (0.1)	1 (0.2)	5 (2.2)	8 (0.5)
Confusional state	2 (0.2)	2 (0.2)	2 (0.5)	2 (0.9)	6 (0.4)
Anger	1 (0.1)	4 (0.4)	1 (0.2)	0	5 (0.3)
Depersonalization	2 (0.2)	2 (0.2)	0	0	2 (0.1)
Derealisation	0	1 (0.1)	0	1 (0.4)	2 (0.1)
Dissociation	1 (0.1)	0	1 (0.2)	0	1 (0.1)
Paranoia	1 (0.1)	1 (0.1)	0	0	1 (0.1)
*"Dizziness" should not be considered an abuse related AE unless reported with the verbatim term "giddiness".					

Table 3. Incidence of Abuse-related AEs from the Uncontrolled Phase 3 Study (CLDA-07-DP-04)				
Abuse Potential Category Preferred Term	vilazodone 10 mg/day N=13 (%)	vilazodone 20 mg/day N=24 (%)	vilazodone 40 mg/day N=562 (%)	vilazodone All Doses N=599 (%)
Number of subjects with at least 1 abuse potential TEAE	2 (15.4)	3 (12.5)	130 (23.1)	135 (22.5)
Total number of abuse potential TEAEs	3	4	170	177
Euphoria-related terms	1 (7.7)	3 (12.5)	56 (10.0)	60 (10.0)
Dizziness*	1 (7.7)	3 (12.5)	46 (8.2)	50 (8.3)
Euphoric mood	0	0	7 (1.2)	7 (1.2)
Feeling abnormal	0	0	2 (0.4)	2 (0.3)
Hallucination, auditory	0	0	1 (0.2)	1 (0.2)
Hallucination, visual	0	0	1 (0.2)	1 (0.2)
Terms indicative of impaired attention, cognition, mood, and psychomotor events	1 (7.7)	1 (4.2)	73 (13.0)	75 (12.5)
Sedation	0	0	21 (3.7)	21 (3.5)
Disturbance in attention	0	1 (4.2)	17 (3.0)	18 (3.0)
Irritability	1 (7.7)	0	17 (3.0)	18 (3.0)
Somnolence	0	0	17 (3.0)	17 (2.8)
Memory impairment	0	0	4 (0.7)	4 (0.7)
Emotional disorder	0	0	1 (0.2)	1 (0.2)
Mood altered	0	0	1 (0.2)	1 (0.2)
Mood swings	1 (7.7)	0	0	1 (0.2)
Dissociative/psychotic terms	0	0	15 (2.7)	15 (2.5)
Agitation	0	0	6 (1.1)	6 (1.0)
Mental disorder	0	0	3 (0.5)	3 (0.5)
Anger	0	0	2 (0.4)	2 (0.3)
Derealisation	0	0	2 (0.4)	2 (0.3)
Confusional state	0	0	1 (0.2)	1 (0.2)
Depersonalization	0	0	1 (0.2)	1 (0.2)
Disorientation	0	0	1 (0.2)	1 (0.2)
Dissociation	0	0	1 (0.2)	1 (0.2)
Paranoia	0	0	1 (0.2)	1 (0.2)
*"Dizziness" should not be considered an abuse related AE unless reported with the verbatim term "giddiness".				

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/s/

CHAD REISSIG
01/05/2011

LORI A LOVE
01/05/2011

MICHAEL KLEIN
01/05/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Patient Labeling Review

Date:	December 16, 2010
To:	Thomas Laughren, M.D., Ph.D., Director **Division of Psychiatry Products (DPP)**
Through:	Sharon Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Risk Management** Melissa Hulett, MSBA, BSN, RN Patient Labeling Reviewer **Division of Risk Management**
From:	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name:	VIIBRYD (vilazodone hydrochloride)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 22-567
Applicant/sponsor:	PGx Health, LLC.
OSE RCM #:	2010-784

1 INTRODUCTION

On March 22, 2010 the Applicant submitted an original New Drug Application, NDA 22-567 for Viibryd (vilazodone hydrochloride) tablets. The proposed indication for VIIBRYD (vildazodone hydrochloride) tablets is for the treatment of major depressive disorder (MDD). This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Risk Management and Evaluation Strategy (REMS) submitted for that NDA.

The DRISK review of the REMS was provided under a separate cover on December 3, 2010.

During the VIIBRYD team meeting on November 30, 2010, DPP requested that DRISK use the most recently proposed FDA version of the Aplenzin MG as a comparator for the VIIBRYD MG.

2 MATERIALS REVIEWED

- Draft VIIBRYD (vilazodone hydrochloride) tablets Prescribing Information (PI) submitted on March 22, 2010, revised by DPP throughout the review cycle and received by DRISK on December 1, 2010
- Draft VIIBRYD (vilazodone hydrochloride) tablets Medication Guide (MG) submitted on March 22, 2010 and received by DRISK on November 24, 2010
- DRISK Aplenzin (bupropion hydrobromide) extended-release tablets MG review for 18 month REMS assessment dated December 7, 2010
- DPP/DRISK agreed upon MG template for MDD products dated March 2010 and Complete Response letters for MDD class products dated September 24, 2010

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the SSRI MG template issued with CR letters to Applicants with approved current generation MDD class products dated September 24, 2010 as appropriate.
- ensured that the MG is consistent with the Aplenzin (bupropion hydrobromide) extended-release tablets MG review for 18 month REMS assessment dated December 7, 2010 where applicable

4 DISCUSSION

A MG template was recently completed for all current generation drugs indicated to treat MDD. On March 15, 2010, DPP provided DRISK with the agreed upon DPP/DRISK SSRI template that they intended to send to the Applicants as stated above. DPP requested submission of Prior Approval Supplements by all Applicants of drugs in the MDD class to convert currently approved MGs to comprehensive MGs. Complete Response letters were issued by DPP to Applicants of all approved drugs in the class, on September 24, 2010. The CR letters included an MDD MG template.

During the course of our review of the VIIBRYD MG, DRISK noted that the proposed MG for VIIBRYD was not developed according to the March 15, 2010 agreed upon template. The MG for the currently approved comparator product, Aplenzin, (bupropion hydrobromide) extended-release tablets, also does not follow this template. DRISK consulted with DPP for clarification and was advised to follow the template as much as possible, but to also assure that the MG followed the information in the VIIBRYD PI.

DRISK then did a side by side comparison of the agreed upon SSRI template with the template provided to Applicants in the September 24, 2010 CR letter. We determined that the CR letters included a different version of the template than the March 2010 agreed-upon MDD MG template. Differences were noted that DRISK was not previously aware of. The major difference that was noted in the September 24, 2010 template was the addition of information about drug interactions at the beginning of the MG section "What should I tell my healthcare provider before taking VIIBRYD?" This represents new language and placement subsequent to the DPP/DRISK agreed upon template that DRISK does not agree with.

Other differences that were noted in comparing the templates include the addition of highlighted instructions to Applicants about including specific

information as appropriate to the labeling of individual products in the September 24, 2010 version.

As a result of the differences that were noted, DRISK used the template provided in the letter to Applicants as the template for reviewing the VIIBRYD MG review, with the exception of the following: we moved information regarding drug interactions further down in the section "What should I tell my healthcare provider before taking VIIBRYD?" under "Especially tell your healthcare provider if you take...". This is consistent placement across patient labeling when drug interactions do not rise to the level of being placed in the "What is the most important section..." of the MG. Additionally, we revised the information, as appropriate, to be consistent with the Drug Interactions section of the PI.

5 CONCLUSIONS

The MG is acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence
- Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.
- In light of differences in the current SSRI template that DRISK was not previously aware of, further discussion of the template is warranted to reach agreement between DPP and DRISK on the template for future use.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
12/16/2010

SHARON R MILLS
12/16/2010
I concur

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: **December 14, 2010**

To: William Bender
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Jessica Cleck Derenick, PhD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC Comments VIIBRYD™ (vilazodone hydrochloride) label**
NDA 022567

DDMAC has reviewed the proposed product labeling (PI) for VIIBRYD™ (vilazodone hydrochloride) tablets submitted for DDMAC review on December 8, 2010.

The following comments, using the proposed PI sent via email on December 8, 2010, by William Bender, are provided directly on the marked up version of the label attached below.

If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

JESSICA N CLECK DERENICK
12/14/2010

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: October 4, 2010

TO: William Bender, Regulatory Project Manager
Cheri Y. Lindberg, MD, Medical Officer
Robert L. Levine, MD, Lead Medical Officer
Division of Psychiatry Products, HFD-130

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Anthony Orencia, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-567

APPLICANT: PGx Health, LLC

DRUG: vilazodone

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of Major Depressive Disorder (MDD) in Adult Patients

CONSULTATION REQUEST DATE: May 12, 2010

DIVISION ACTION GOAL DATE: December 4, 2010

PDUFA DATE: January 22, 2011

I. BACKGROUND:
Inter-individual variability in response to FDA-approved antidepressants has been well-documented, with about 30% to 40% of depressed patients not responding to initial treatment. Vilazodone, a selective serotonin reuptake inhibitor (SSRI) that has partial 5-hydroxytryptamine (serotonin) type 1A (5-HT1A) receptor agonist properties, is a new molecular entity submitted for the proposed indication of treatment of Major Depressive Disorder (MDD) in adult patients.

Two adequate and well-controlled studies were submitted in support of this NDA for the major depressive disorder indication. Two clinical sites per protocol were selected for field inspection.

STUDY Protocol CLDA-07-dp-02
This randomized, double-blind, placebo-controlled, multicenter, 8-week clinical trial was designed to assess the efficacy and safety of vilazodone, and to evaluate a genetic biomarker of treatment response associated with vilazodone as used in adults diagnosed with MDD by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria. This study was designed to enroll approximately 470 patients across 15 U.S. clinical centers. The first patient was randomized on March 31, 2008. The last patient completed on February 10, 2009.

The primary objective was to compare the efficacy between vilazodone and placebo treated groups using change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 8. The secondary objectives were (a) to assess the safety profile of vilazodone compared with placebo, (b) 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, and (c) to conduct secondary efficacy and safety analysis utilizing 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). The primary efficacy variable was the change in MADRS total score from baseline to Week 8.

STUDY Protocol GNSC-04-dp-02
This was a randomized, double-blind, placebo-controlled, multicenter study of treatment with vilazodone in adults with MDD, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR), across 18 centers in the United States. The first patient enrolled on February 22, 2006 and the last patient completed on May 23, 2007.

The primary objective was to compare the efficacy of vilazodone and placebo in the treatment of MDD, as measured by mean change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score after 8 weeks of treatment. The secondary objectives were (a) to assess the safety profile of vilazodone compared with placebo, (b) to assess the efficacy of vilazodone compared with placebo using secondary measures of depression, anxiety, and overall clinical impressions of severity and improvement, and (c)

to discover genetic markers associated with treatment response and/or with AEs in patients taking vilazodone. The primary efficacy variable was mean change in MADRS total score from Baseline to Week 8.

Vilazodone is a new molecular entity proposed for acute treatment for major depressive disorder. While no clinical investigator sites were identified that could potentially influence efficacy findings in isolation, as advised by the review division clinical and biostatistics teams during the filing meeting, the sites selected represent clinical sites that had enrollment of large numbers of study subjects for each of the two sites per protocol.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Arifulla Khan, M.D./ Site #2020	Bellevue, WA	CLDA-07-dp-02	6/16-7/1, 2010	7/19/2010	Voluntary Action Indicated (VAI)
Jerry C. Steiert, M.D./ Site #2080	Seattle, WA	CLDA-07-dp-02	7/6-7/20, 2010	8/16/2010	VAI
Nader Oskooilar, M.D./Site: #2030	Newport Beach, CA	GNSC-04-dp-02	6/9-23/2010	7/12/2010	NAI
Karl Rickels, M.D./ Site: #0400	Philadelphia, PA	GNSC-04-dp-02	7/20-26, 2010	8/20/2010	NAI
PGx Health, LLC/Sponsor	New Haven, CT		6/7-6/11, 2010	8/16/2010	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.
Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

Protocol CLDA-07-dp-02

1. Arifulla Khan, M.D.
Northwest Clinical Research Center
1951 152nd Place NE Suite 200
Bellevue, WA 98007

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811, from June 16 – July 1, 2010. A total of 217 subjects were screened; 162 subjects were randomized and 125 subjects completed the study. An audit of 52 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, electronic case report forms, study endpoints, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection
None.

c. General observations/commentary
Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. A two-item observation Form FDA 483 was issued at the end of the inspection. Examples of specific findings:

- Subject 2020-135 had a positive urine drug screen for opiates (i.e., not allowed within a 30 day exclusion window for a positive drug test per protocol eligibility criteria) on 10/13/2008, but patient was dispensed study drug on 10/16/2008 (The patient had dental pain for which he took hydrocodone).
- Subject 2020-109 had repeat screening 21 days later (10/7/2008), but was randomized and dispensed study drug on the same day before laboratory reports were reviewed.
- Similarly, Subject 2020-088 had repeat screening 15 days later (9/3/2008), but was randomized and dispensed study drug on the same day prior to review of the lab report.
- Cafergot was listed as a prohibited drug for the study, however, Subject 2020-200 was prescribed this ergotamine derivative, and study drug was dispensed (12/3/2008), and
- Subject 2020-164's Ortho Tricyclin, a birth control pill, was not listed as a concomitant medication on the study subject log or e-CRF.

The clinical investigator responded adequately to the ORA findings on July 14, 2010. A quality assurance program was instituted as part of Dr. Khan's corrective action plan.

d. Data acceptability/reliability for consideration in the NDA review decision.
Although regulatory violations were noted, these are considered isolated in nature and unlikely to impact data integrity and/or patient subject safety. The data, in support of clinical efficacy and safety at this clinical site, appear acceptable for this specific indication.

2. Jerry C. Steiert, M.D.
Summit Research Network (Seattle)
Seattle, WA 98104

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811, from July 6-20, 2010. A total 84 subjects were screened; 65 subjects were enrolled and randomized, and 55 subjects completed the study. An audit of 30 study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, electronic case report forms, study endpoints, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection
None.

c. General observations/commentary
Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. A two-item observation Form FDA 483 was issued at the end of the inspection. Specifically, for Subject 2080-018, there was lack of full documentation that the washout period for Valerian was completed. Additionally for this subject, this psychoactive herbal drug was not recorded in the e-CRF as medication taken 12 weeks prior to screening.

Dr. Steiert responded adequately on August 5, 2010 to prevent future occurrences of any observed minor regulatory deficiency.

d. Data acceptability/reliability for consideration in the NDA review decision.
The minor regulatory deficiency observed for Subject 2080-018 is unlikely to have an impact on data integrity. The data, in support of clinical efficacy and safety at this clinical site, appears acceptable for this specific indication.

Protocol GNSC-04-dp-02
3. Nader Oskooilar, M.D., Ph.D.
Pharmacology Research Institute
1601 Dove Street Suite 290
Newport Beach, CA 92660

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811 from June 9-23, 2010. There were three investigational sites used to conduct this study. A total of 62 subjects at three sites were screened and enrolled. Forty-four (44) subjects

completed the study. A 100% review of the informed consent forms for all three sites (i.e., #200, #201 and #203) for the 62 subjects enrolled was performed. An in depth audit of 25 subjects' records (i.e., Site #201: 6 records and Site #203: 19 records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study endpoints, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection
None.

c. General observations/commentary
Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. In general, the study appears to have been conducted adequately at this site.

This clinical site appeared to be in compliance with Good Clinical Practices. A form FDA 483 was not issued.

d. Data acceptability/reliability for consideration in the NDA review decision.
The data, in support of clinical efficacy and safety at this clinical site, appears acceptable for this specific indication.

4. Karl Rickels, M.D.
University Department of Psychiatry
Mood and Anxiety Disorders Section
3535 Market Street, Suite 670
Philadelphia, PA 19104-3309

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811 from July 20-26, 2010. A total of 29 subjects were screened, 22 were randomized, and 17 subjects completed the study. One Serious Adverse Event was reported for Subject 400-016 (suicide ideation). An audit of 29 of enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study endpoints, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection
None.

c. General observations/commentary
Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings, and no discrepancies were noted.

This clinical site appeared to be in compliance with Good Clinical Practices. A form FDA 483 was not issued.

d. Data acceptability/reliability for consideration in the NDA review decision.
The data, in support of clinical efficacy and safety at this clinical site, appears acceptable for this specific indication.

5. PGx Health, LLC (Sponsor)
5 Science Park
New Haven, CT 06511

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.810 from June 7-11. The inspection evaluated the following documents: organization and personnel, responsibility, transfer of responsibilities, contracts, work orders, and agreements, investigator selection; FDA 1572's; training; monitoring procedures; data verification; adverse event procedures, primary efficacy process and verification, eligibility assessment; data collection and computerized systems, CRF's, test article accountability and reconciliation.

b. Limitations of inspection
None.

c. General observations/commentary
No significant issues were noted in the adherence to sponsor responsibilities in the conduct of the "pivotal" clinical trials and the sponsor appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was not issued.

d. Data acceptability/reliability for consideration in the NDA review decision.
The data, in support of clinical efficacy and safety at this Sponsor site, appear acceptable for this specific indication.

MISCELLANEOUS FDA COMMUNICATIONS

On August 20, 2010, DSI received an anonymous outside mail complaint via the Office of Commissioner's Office of Good Clinical Practices (OGCP), purporting about the possibility of "skewed data" in favor of the efficacy for vilazodone, along with another drug not related to this NDA submission. Further, OGCP stated that DSI may want to make DPP aware of this claim. DSI communicated with the review division medical as well as biostatistics groups to seek input about possible high-yield inspection strategies to guide ORA field office inspections.

A DPP mid-cycle meeting for vilazodone was held on August 25, 2010. DSI Medical Officer briefed DPP about the four clinical sites inspected that were completed, representing the largest U.S. enrolment sites for this NDA, as well as the sponsor site. Further, the findings would be formally communicated in this Clinical Inspection Summary report. The meeting was well represented including: CDER management, Dr. Robert Temple; Associate Director of Biostatistics, Dr. Sue Jane Wang; ODE I manager, Ellis Unger; Division management and the respective review teams. DPP's Biostatistics review team did not raise any concerns about scientific integrity or data irregularities, based on their extensive analysis and review of the data. DSI sought supplemental input and expertise from the NDA mid-cycle gathering regarding this anonymous complaint.

The vilazodone review team, DPP management, ODE 1 Office management stated that the anonymous letter was sketchy, vague, or poorly written, and that there was no basis or specific items mentioned in this concern. No strategies for inspecting the site were offered, nor will be pursued. Based on the finding by the clinical and statistical teams, DPP Division Director, and other comments received in this mid-cycle meeting, DPP was assured thus far, and that no additional PDUFA inspection consults to DSI would be forthcoming.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As part of the PDUFA-related inspections, four U.S. clinical investigator sites, as well as the sponsor, were inspected in support of this application: two clinical investigator sites were inspected for Protocol CLDA-07-dp-02, and two clinical investigator sites were inspected for Protocol GNSC-04-dp-02. Observed regulatory deficiencies found in Protocol CLDA-07-dp-02 were minor; these had minimal impact on data integrity and protection of human subjects. The data appear reliable for the proposed indication. Inspection findings documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations.

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

ANTHONY J ORENCIA
10/04/2010

TEJASHRI S PUROHIT-SHETH
10/04/2010

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22567
Generic Name	Vilazodone (SB-659746 and EMD 68843)
Sponsor	PGx Health, LLC
Indication	Treatment of major depressive disorder
Dosage Form	Tablets
Drug Class	Selective serotonin reuptake inhibitor (SSRI); anti-depressant
Therapeutic Dosing Regimen	10 mg/day
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	(b) (4) mg/day
Submission Number and Date	SDN 139/10 Nov 2008
Clinical Division	DPP / HFD 130

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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 (doses 10 mg - 80 mg) and placebo were below 10 ms. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms at Day 6, and the moxifloxacin profile over time is adequately demonstrated in Figure 4 (Day 6), indicating that assay sensitivity was established.

In this randomized, double-blind, placebo-controlled, parallel study, one-hundred and forty subjects were received vilazodone (doses 10 mg - 80 mg), moxifloxacin 400 mg, and placebo. The overall summary of findings is presented in Table 1 .

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

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

*Multiple endpoint adjustment was not applied. The largest lower bounds after Bonferroni adjustment for

4 time points are 6.8 ms, 5.8 ms, 2.9 ms, and 3.4 ms, respectively, for Day 6, 9, 12 and 15, respectively.

The supratherapeutic dose (80 mg) produces mean C_{max} and AUC values 2.0-fold higher than the observed C_{max} for the studied therapeutic dose (40 mg). This increase in exposures is expected to be greater than exposures increase due to drug-drug interaction with ketoconazole (1.5-fold increase). However, no hepatic impairment study was conducted to identify whether exposures are increased for patients with liver dysfunction. Further only one drug-drug interaction study (with ketoconazole) has been conducted. It is unclear whether other drugs may increase the exposure of vilazodone more.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- As mentioned in section 4.2.8.3, one subject in the TQT study experienced convulsive syncope while having her blood drawn. This was reported as convulsive syncope of vasovagal etiology. ECG taken soon after the episode was reported normal. However this event also had temporal association to study drug and may be due to non-arrhythmogenic mechanisms.
- It is noted that baseline-corrected, placebo-adjusted QTc intervals in both moxifloxacin and vilazodone groups decrease over time following long term treatment (Figure 1). The reason is unclear.

Comments regarding Heart rate and BP effects (requested by DDDP medical reviewer)

- In the placebo controlled phase 3 database:
  - there were several cases of palpitations with vilazodone compared to placebo. However, considering clinically relevant arrhythmias, there was only one case of atrial fibrillation was reported as SAE for one subject on vilazodone in the phase 2/phase 3 studies. No other significant supra-ventricular or ventricular tachycardia or arrhythmias are reported.
  - The sponsor reports that mean change from baseline DBP data at the Week 8/ET visit demonstrated a statistically significant but minimal difference for subjects who received placebo (mean change of -0.6 mmHg) compared with subjects who received vilazodone 40 mg qd (mean change of + 0.6 mmHg). No significant differences for mean SBP and HR are reported. The direction of change for potentially clinically significant (PCS) values for each vital sign were similar when comparing vilazodone and placebo groups.
- In the TQT study:
  - no mean changes in heart rate were noted. At the highest vilazodone dose (80 mg), 10 (18%) subjects met tachycardic outlier criteria versus 2 (5%) subjects on placebo suggesting a possible increase effect on heart rate. None of the subjects in the other vilazodone dose groups met PCS tachycardia criteria.
  - TEAEs of hypertension (3), blood pressure increased (2) were reported for the vilazodone group only. TEAEs of palpitations (4) tachycardia (2) and sinus tachycardia (3) were reported with greater frequency in the vilazodone group compared to one report in the placebo group and none in the

moxifloxacin group. One subject in the vilazodone group was discontinued due to the AEs of dizziness, palpitation, hypertension and tachycardia.

- 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.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

The sponsor has proposed the following language in the current label.

Section 6:
ECG

(b) (4)

Reviewer's comments: We recommend that Section 6 be removed (b) (4)

2.2 QT-IRT RECOMMENDATIONS

We recommend that the Section 6 in the current label be replaced by a (b) (4)

(b) (4)

3 BACKGROUND

Vilazodone HCl is a NME that has selective serotonin reuptake inhibitor (SSRI) as well as 5-HT1A partial agonist properties. The sponsor has submitted an original NDA for vilazodone in the treatment of adults with a diagnosis of Major Depressive Disorder

3.1 MARKET APPROVAL STATUS

Vilazodone is not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

Source: Non-Clinical Summary, eCTD 2.6.2

> **"hERG Channel Assay**
>
> Vilazodone (0.01 – 1.0 µM) was tested at hERG K^+ channels stably expressed in Chinese hamster ovary cells (GPP-007-NCD-PCL-2000-100). Vilazodone had no effect at any concentration tested, indicating low potential for producing increases in QT_c interval duration and related arrhythmias in vivo.
>
> **"Papillary Muscles of Guinea Pig Heart**
>
> The putative risk for drug-induced arrythmogenic side effects was investigated by examining the effect of vilazodone on action potentials in isolated right ventricular papillary muscles of the guinea pig heart (GPP-007-NCD-PCL-2000-099). Due to the limited solubility of vilazodone, effects could not be studied at concentrations higher than 3 µM. None of the parameters studied, resting membrane potential, action potential amplitude, and action potential duration at 90% and 20% repolarization (APD_{90} and APD_{20}, respectively) were affected by vilazodone relative to vehicle. Thus, a pronounced prolonging effect of vilazodone was not found, indicating that proarrhythmogenic properties are unlikely.
>
> **"Blood Pressure Effects**
>
> Orally administered vilazodone (30, 100 mg/kg) was tested for effects on blood pressure in conscious, spontaneously hypertensive rats. Vilazodone did not affect mean arterial pressure or heart rate relative to vehicle during the 210 min post-dosing test session (GPP-007-NCD-PCL- 1995-101).
>
> "The effects of slow intravenous administration of 0.1 mg/kg, 1 mg/kg and 3 mg/kg vilazodone in propanediol solvent on hemodynamic parameters and blood-gas values in anesthetized normotensive pigs were investigated (GPP-007-NCD-PCL-1995-102). During a test period of 3 h and at doses up to 3.0 mg/kg, vilazodone displayed mild and short-term effects on the cardiovascular and blood-gas parameters recorded that were also seen with approximately equal intensity following administration of the solvent propanediol. Thus, vilazodone produced no changes in the measured and calculated cardiovascular values in anesthetized pigs following intravenous administration of up to 3.0 mg/kg."

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety, eCTD 2.7.4 and ISS

The safety of vilazodone was assessed through 24 Phase 1 studies, 5 Phase 2 studies, and 3 Phase 3 studies, during which 2898 subjects received vilazodone.

There were 2 subjects who died during the clinical development program. There was 1 subject in a Phase 1 study and 1 subject in a Phase 2 study. Neither subject received vilazodone.

For cardiac disorders, the incidence of TEAEs was greater in subjects who received vilazodone 40 mg (2.8%) compared with subjects who received placebo (1 subject, 0.2%). Palpitations was the TEAE associated with this difference, in 9 versus 1 subjects receiving vilazodone versus placebo. Other cardiac TEAEs, reported in few subjects in the vilazodone group (and not in the placebo group), were ventricular extrasystoles (in 2 subjects), and angina pectoris, sinus bradycardia, and tachycardia (in 1 subject each).

ECGs

Placebo-controlled Phase 3 Database

Table 7 presents changes in ECG results from baseline to final visit for the placebo-controlled Phase 3 database. Less than 12% of subjects had ECG changes that would be considered worsening, and there was no difference between the vilazodone and placebo groups.

Table 7: Changes in ECG Results from Baseline to Final Visit (Placebo-controlled, Phase 3 Database Safety Population)

ECG Change from Baseline to Final Visit	Placebo N = 386 n (%)	Vilazodone 40 mg/day N = 384 n (%)
Normal to Abnormal NCS	46 (11.9)	45 (11.7)
Normal to Abnormal CS	2 (0.5)	2 (0.5)
Abnormal NCS to Abnormal CS	3 (0.8)	5 (1.3)
P-value[a]		0.5104
P-value[b]		0.5714

[a] P-value from a Cochran-Mantel-Haentzel test stratified by study comparing the proportion of subjects with treatment-emergent abnormal EGC results between vilazodone and placebo groups.

[b] P-value from Fisher's Exact test comparing the proportions of subjects with treatment-emergent abnormal ECG results between vilazodone and placebo groups.

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

Source: Module 5.3.5.3.2, Appendix 2: Table 24.2.

For the placebo-controlled, Phase 3 database, the sponsor reports that 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). No clinically important differences between placebo and vilazodone were seen for any ECG parameters.

Uncontrolled, Long-term Safety Database

For the 541 subjects with ECG recordings while receiving vilazodone for up to 52-weeks in the sponsor's uncontrolled long term safety database, no subjects had ECG changes from Normal to Abnormal CS and 5 subjects (0.9%) had ECG changes from Abnormal NCS to Abnormal CS from baseline to final visit. The sponsor reports that there were no clinically meaningful mean changes in any measured ECG parameter. A PCS change was seen for HR (low values) for 2 subjects (0.4%) and for QRS interval (high values) for 1 subject (0.2%).

Reviewer's Comments:

- *There are no reports of sudden death, seizures or significant ventricular arrhythmias with vilazodone.*
- *There are a few reports of syncope and/or palpitations reported as moderate or severe mainly in the HV studies. Only one case of syncope is reported in the placebo controlled phase 3 database.*
- *As indicated above there were several cases of palpitations with vilazodone compared to placebo in the phase 3 trial. Atrial fibrillation was reported as SAE for one subject on vilazodone in the phase 2/phase 3 studies. No other clinically relevant supra-ventricular or ventricular tachycardia or arrhythmias are reported.*
- *In the placebo-controlled Phase 3 database, sponsor reports that mean change from baseline DBP data at the Week 8/ET visit demonstrated a statistically significant but minimal difference for subjects who received placebo (mean change of -0.6 mmHg) compared with subjects who received vilazodone 40 mg qd (mean change of + 0.6 mmHg). Similar minimal changes, lacking statistical or clinical significance between groups, were observed in mean change from baseline data for SBP, HR, and body weight. The sponsor reports no clinically meaningful constellation of abnormal vital sign results. Also, the direction of change for PCS values for each vital sign were similar when comparing vilazodone and placebo groups.*

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocols (conducted under IND 54613) prior to conducting this study. The sponsor submitted the study report PGX-08-P1-06 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind Randomized Parallel Study to Define the ECG Effects of Vilazodone Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin in Healthy Volunteers: A Thorough ECG Study

4.2.2 Protocol Number

PGX-08-P1-06

4.2.3 Study Dates

First Subject Enrollment: 25 September 2008
Last Subject Enrollment: 12 January 2009

4.2.4 Objectives

Primary Objectives:
The primary objective of this study was to determine the time-matched change from baseline in QTc based on an individual correction (QTcI) method that provides an optimization of QT correction for heart rate as compared to fixed exponent approaches as Bazett (QTcB) or Fridericia (QTcF).

Secondary Objectives:
The secondary objective was to evaluate the safety and tolerability of vilazodone in healthy volunteers as compared to subjects receiving placebo or moxifloxacin.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase I, single-site, randomized, double-blind (except for the use of moxifloxacin), placebo and active controlled, 3-arm, parallel study designed to assess the effects of vilazodone on QT interval in healthy male and female subjects.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not double blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were enrolled at one investigational site and randomized to receive 1 of the following 3 treatments:

- Placebo PO (Oral) given from Day 1 through Day 15.
- Moxifloxacin 400 mg PO given on Days 6, 9, 12, and 15 to match each of the doses of vilazodone in which ECG and PK sampling was done, with placebo given on the remaining days (ie, Days 1-5, 7-8, 10-11, and 13-14).
- Vilazodone starting at 10 mg/day PO x 3 days, followed by 20 mg/day x 3 days, then 40 mg/day x 3 days, then 60 mg/day x 3 days, and concluding with 80 mg/day x 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 given the designated administration regimen. There would be no further increase in dose. Of note, the MTD was not reached in this study.

4.2.6.2 Sponsor's Justification for Doses

The clinical dose of vilazodone is 40 mg/day and the supratherapeutic doses included in this study (60 mg/day and 80 mg/day) were designed to test the maximum tolerated chronic dosing regimen, which is achieved by titration from 10 mg/day to doses above the 40 mg/day clinical dose. Hence, the supratherapeutic dose of vilazodone was to be defined in

the results of this trial as the highest tolerable dose achieved (eg, 60 mg/day or, if sufficient subjects reached this level, 80 mg/day). A target supratherapeutic dose of 80 mg/day was selected as it is 2 x the clinical dose and covers the range of potential increases associated with QT effect modifiers, as well as metabolic and absorption interactions. Vilazodone concentrations potentially can be increased by approximately 50% by metabolic drug-drug interactions (eg, ketoconazole), or by 50% to 90% by taking the tablet with a meal as compared to while fasting. The absolute bioavailability of vilazodone tablets when administered with a meal (standard or high fat) is approximately 70% to 75%, thus limiting the total impact of combination of interactions to an approximately 30% to 50% increase. Irrespective of the number of subjects who reached 80 mg/day, ECG and PK sampling was to be done, but the primary evaluation was to be on the MTD dose, which was defined as the highest dose reached for which at least 40 subjects had evaluable ECG and PK data. ECG and PK sampling was to be done at all clinically relevant doses (20, 40, 60, and 80 mg) with concomitant placebo and positive control (moxifloxacin) to obtain a full range of pharmacokinetic/pharmacodynamic (PK/PD) relationships as well.

Vilazodone was dosed for 3 days at each dose level to achieve steady-state conditions under the assumption that active metabolites have a similar profile as parent (although not precisely defined) and the need for chronic drug administration in the target indications. Sequentially increasing doses of vilazodone were utilized to facilitate the subjects' accommodation to vilazodone and reduce the incidence of AEs that might lead to early discontinuation.

Reviewer's Comment: The supratherapeutic dose (80 mg) produces mean C_{max} and AUC values 2.0-fold higher than the observed C_{max} for the studied therapeutic dose (40 mg). This increase in exposures is expected to be greater than that for the highest exposures from the drug-drug interaction with ketoconazole (1.5-fold increase). It is good that the sponsor administered the dose with a high-fat meal, as administration with food has been shown to increase vilazodone's systemic exposure by 50–90% when compared dosing while fasting. However, exposures of vilazodone in patients with hepatic impairment or for patients with other drug-drug interactions remain unclear.

4.2.6.3 Instructions with Regard to Meals

Doses were administered with a high-fat breakfast. Meals were to be consumed and doses were to be taken at the same time on each occasion. Within 30 minutes of starting the high fat breakfast, subjects were administered a single PO dose of study drug with 240 mL of room temperature tap water.

Reviewer's Comment: As administration with high-fat meals is shown to increase vilazodone exposure by as much as 49% (highest clinically relevant exposures), it is reasonable to study this scenario to observe the full range of clinically relevant exposures and effects on the QT interval.

4.2.6.4 ECG and PK Assessments

Table 2: 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	None	Record ECGs	None	Record ECGs	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.

Reviewer's Comment: Timing of both ECG and PK samples were acceptable. The sampling was frequent, captured the C_{max} of vilazodone concentrations, and covered the duration of elimination of vilazodone concentrations. It would have been better if the sponsor had studied each dose for a minimum of 4 days. Four days would allow vilazodone to reach near steady-state concentrations since it has a half life of 21 hours.

4.2.6.5 Baseline

The sponsor used time-matched Day -1 QTc values as baseline.

4.2.7 ECG Collection

ECGs were obtained digitally using a Mortara Instrument (Milwaukee, WI) H-12+ ECG continuous 12-lead digital recorder, which was placed to record all ECGs in each of the 3 treatment arms. The ECGs were stored on a flash card about every 10 seconds and were not available for review until the card was received by the central ECG laboratory.

ECGs used in the analysis were selected by the predetermined time points and were read centrally using a high resolution manual on-screen caliper manual adjudication method with annotations. Three 12-lead ECGs were downloaded from the H-12 flash card within about 5 minutes (providing 3 ECGs for each time point) at baseline (Day –1), and then again on Days 6, 9, 12, and 15 at the time points specified above. Subjects were supine for at least 10 minutes before each of the time points for the ECGs.

The ECG analysis were conducted in Lead II, and when not analyzable in Lead V5 or the most appropriate lead. ECG readers were blinded to subject identifiers, treatment, and visit. All ECGs for a given subject were analyzed by the same reader.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

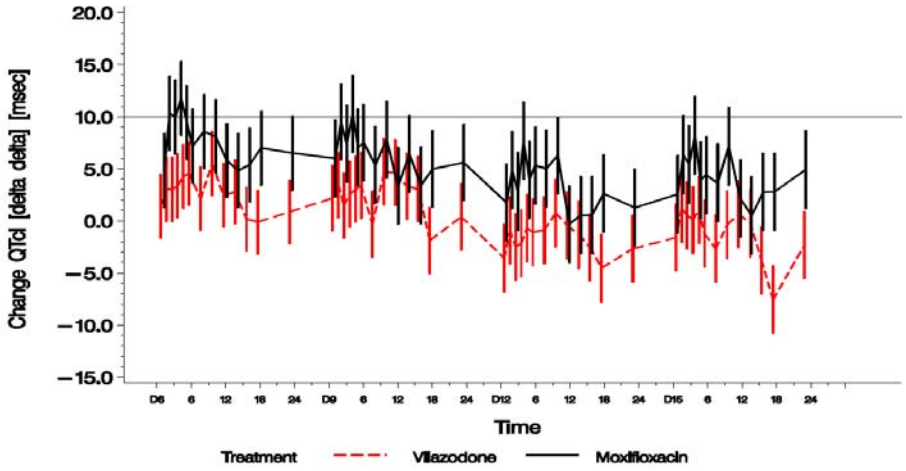
Up to 220 healthy subjects (half female by stratification) were planned to be enrolled into the study to achieve a total of 120 subjects evaluable for ECG and PK assessments (ie, 40 per group). A total of 157 subjects (45 in the placebo group, 46 in the moxifloxacin group, and 66 in the vilazodone group) were actually enrolled and randomized and 140 subjects (42 in the placebo group, 42 in the moxifloxacin group, and 56 in the vilazodone) were evaluable for the ECG assessments. The reasons for premature discontinuation were withdrawal of consent in 9 subjects and an AE in 8 subjects.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the time-matched change from baseline mean differences between vilazodone (doses 10 mg - 80 mg) and placebo in QTcI. The sponsor used ANCOVA model. Figure 1 presents sponsor's time course of ΔΔQTcI for vilazodone (doses 10 mg – 80 mg) and moxifloxacin treatment groups. The upper bounds of the 2-sided 90% CIs for the mean differences between vilazodone and placebo were less than 10 ms. For moxifloxacin 400 mg, the largest lower bounds of the 2-dised 90% CI for the mean differences ranged from 4.2 to 7.8 ms.

Figure 1: Sponsor's Time Course of ΔΔQTcI for Vilazodone (doses 10 mg - 80 mg) and Moxifloxacin 400 mg



Source: Sponsor's CSR Figure 1on Page 53/446.

Reviewer's Comments: We will provide our independent analysis results in section 5.2.

4.2.8.2.2 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc>450 ms, >480 ms, and >500 ms, and changes from baseline QTc >30 ms and >60 ms. No subject's absolute QTc > 480 ms and ΔQTc > 60 ms.

4.2.8.3 Safety Analysis

- One subject in the moxifloxacin group died post-study completion as the result of injury (fatal stab wound). The event occurred 25 days after the last dose of study drug
- Two additional subjects experienced nonfatal SAEs (convulsion in the moxifloxacin group and convulsive syncope in the vilazodone group [Day 9, 40 mg]).
    - Subject 0601-106 in the moxifloxacin group experienced convulsion on Day 7. Moxifloxacin was given on Days 6, 9, 12, and 15 and placebo was given on Days 1-5, 7-8, 10-11, and 13-14. On Day 7, approximately 11 hours after the dose of study drug (placebo), the subject experienced a seizure, which lasted 45-60 seconds. The event lasted 1 minute and was assessed by the investigator as moderate in severity and not related to study drug. The subject had a history of a seizure disorder since the age of 13.

    - Subject 0601-183, a 36 year old female in the vilazodone group experienced convulsive syncope on Day 9. About 3 hours after the dose of vilazodone 40 mg on 01 Dec 2008 (Day 9), while having her blood drawn, the subject experienced an apparent seizure (generalized tonic/clonic) while in bed at the CRU that lasted approximately 20 seconds. The paramedic witness stated that the subject suddenly arched her back throwing her arms over her head and had several tonic movements of her extremities while lying in bed. She was placed with her legs in a Trendelenburg position. The subject's eyes were tonic to the right and she was not responsive to pain to deep pressure at the tibia or shoulder. Within 2 minutes, the subject became more responsive; however, she had no recollection of the event. On examination, she was lethargic with a finger stick glucose of 85 mg/dL, blood pressure 172/77 mm Hg, pulse 91 beats/minute, respiratory rate 20 breaths/minute, and temperature 36.7°C. She had a supple neck, no neurological deficits, clear lungs, regular cardiac rate and rhythm, and a normal ECG. Further w/u was negative. Neurology consultation indicated that the subject had a history of migraines, with no past history of convulsions or a family history of epilepsy. The subject noted that she became very confused and dizzy waiting for blood to be drawn. She bit her tongue during the episode; however, she did not have urinary or bowel incontinence. Neurological examination was within normal limits. The neurologist considered the most likely diagnoses as convulsive syncope and migraines. The neurologist confirmed that the episode was not seizure activity and did not recommend antiepileptic medication.

    - Study drug was discontinued due to AEs in 8 subjects overall, including 4 (6.1%) vilazodone subjects, 3 (6.5%) moxifloxacin subjects, and 1 (2.2%) placebo subject;
    - Emesis was the reason for study drug discontinuation in 4 of the 8 subjects (2 subjects in the vilazodone group). The other events that led to study drug discontinuation in the vilazodone group were syncope in Subject 0601-183 and palpitations in Subject 0601-245.

- Subject 0601-245, a 42 year old white male, experienced palpitations which led to his premature discontinuation from the study. 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.

- TEAEs of hypertension (3), blood pressure increased (2) were reported for the vilazodone group only
- TEAEs of palpitations (4) tachycardia (2) and sinus tachycardia (3) were reported with greater frequency in the vilazodone group compared to one report in the placebo group and none in the moxifloxacin group.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The sponsor's pharmacokinetic parameters for vilzaodone at the studied doses are shown in Table 3. Both AUC and C_{max} values increase linearly with increasing dose and T_{max} values were consistent for all dose amounts.

Table 3: Mean and Median Plasma Vilazodone Pharmacokinetic Parameters (PK Evaluable Population)

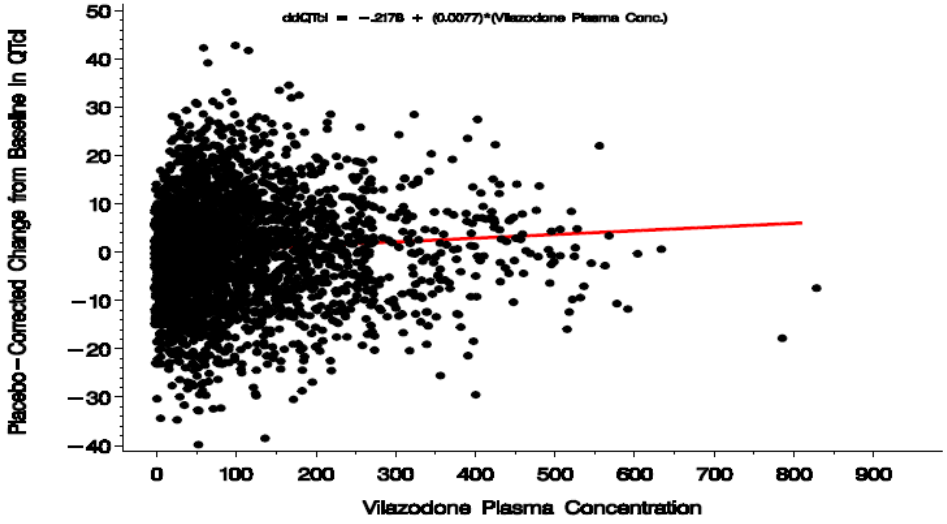
	Vilazodone 20 mg (N = 56)	Vilazodone 40 mg (N = 55)	Vilazodone 60 mg (N = 55)	Vilazodone 80 mg (N = 56)
$AUC_{0\text{-}tlqc}$ (hr x ng/mL)				
Mean (SD)	776.8 (352.0)	1645.3 (720.9)	2506.1 (1107.4)	3269.8 (1720.0)
Median	780.5	1575.8	2557.7	3138.9
C_{max} (ng/mL)				
Mean (SD)	70.1 (30.2)	156.3 (67.6)	253.1 (113.1)	315.4 (169.5)
Median	68.7	143.5	240.9	312.0
T_{max} (hr)				
Mean (SD)	4.8 (1.6)	4.3 (1.7)	4.3 (1.1)	4.5 (1.4)
Median	4.0	4.0	4.0	4.0
CL/F (L/hr)				
Mean (SD)	30.5 (42.6)	34.0 (74.9)	35.8 (60.5)	59.3 (216.3)
Median	21.4	21.7	20.2	21.3

(Source: Sponsor's Thorough QT Study Report, Table 7)

4.2.8.4.2 Exposure-Response Analysis

Figure 2 shows the relationship between QTcI duration and vilazodone plasma concentration from paired samples taken in all vilazodone dose groups.

Figure 2: QTcI Placebo-corrected Change from Baseline versus Vilazodone Plasma Concentrations (ECG Evaluable Population)



(Source: Sponsor's Thorough QT Study Report, Figure 4)

The results of the PK/PD model showed that the slope for QTcI for vilazodone parent was flat and the predicted value at C_{max} (156 ng/mL after 40 mg/day) was < 1 ms. These data do not support any effect of vilazodone parent on cardiac repolarization.

Reviewer's Comment: The sponsor's ΔΔQTcI plot appears to show no clinically meaningful correlation between QT interval prolongation and vilazodone plasma concentration. See Section 5.3 for the reviewer's analysis.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included gender, baseline, RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 4, it appears that QTcI had smaller absolute slopes than QTcF, which indicates that QTcI might be a better correction method for the study data.

Table 4: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI	Diff_p_value
Moxifloxacin	0.0422	0.0313	0.0000
Placebo	0.0287	0.0149	0.0000
Vilazodone (10-80 mg)	0.0189	0.0128	0.0001
All	0.0276	0.0179	0.0000

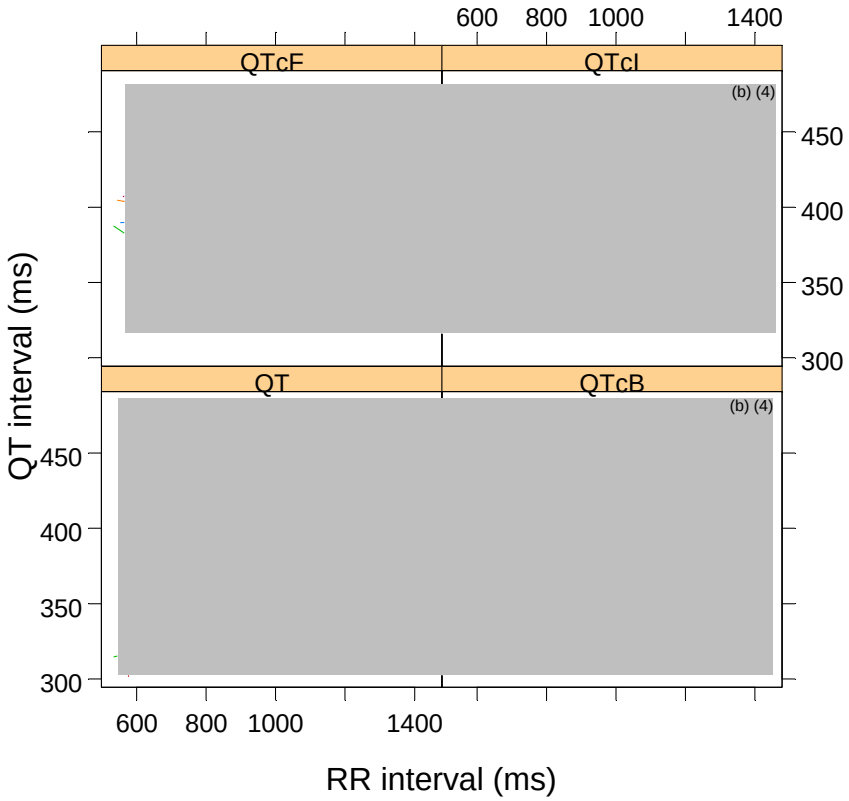
We also confirmed this conclusion by another approach, where we used the mean sum of squared slopes (MSSS) from individual regressions of QTc values versus RR as the criterion. The smaller this value is, the better the correction. Based on the results listed in Table 5, it appears that QTcI is the best correction method. Therefore, this reviewer used QTcI for the primary statistical analysis. This is also consistent with the sponsor's choice for the primary endpoint.

Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Moxifloxacin	46	0.0045	46	0.0027	46	0.0013
Placebo	45	0.0056	45	0.0020	45	0.0011
Vilazodone (20-80 MG)	66	0.0042	66	0.0019	66	0.0012
All	157	0.0047	157	0.0021	157	0.0012

The QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

Figure 3: QT, QTcB, QTcF, and QTcI, vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

The statistical reviewer used mixed model to analyze the ΔQTcI effect. The model included TIME as a fixed effect and BASELINE as a covariate. The analysis results are presented in Table 6. The largest upper bounds of the two-sided 90% CI for the mean differences between vilazodone and placebo are 9.2 ms, 8.9 ms, 5.2 ms, and 5.9 ms, respectively, for Days 6, 9, 12 and 15, respectively.

Table 6: Analysis Results of ΔQTcI and ΔΔQTcI for Vilazodone (doses 10 mg - 80 mg) and Moxifloxacin 400 mg on Days 6, 9, 12 and 15

			Treatment Group						
			Moxifloxacin				Vilazodone (10-80 mg)		
		Placebo	ΔQTc	ΔΔQTc			ΔQTc	ΔΔQTc	
Day	Time (hour)	LS Mean	LS Mean	LS Mean	90% CI	Adj. 90% CI	LS Mean	LS Mean	90% CI
6	1	-8.5	-2.7	5.8	(2.2, 9.4)	(0.8, 10.7)	-6.3	2.2	(-1.1, 5.6)
	2	-3.5	7.8	11.3	(7.6, 14.9)	(6.2, 16.3)	0.4	3.9	(0.4, 7.3)
	3	1.8	12.7	10.9	(7.0, 14.8)	(5.6, 16.2)	5.7	3.8	(0.2, 7.5)
	4	3.2	15.6	12.4	(8.3, 16.5)	(6.8, 17.9)	7.4	4.2	(0.4, 8.0)
	5	0.1	10.3	10.2	(7.1, 13.2)	(6.0, 14.3)	5.0	4.9	(2.1, 7.7)
	6	-0.0	8.0	8.1	(4.7, 11.4)	(3.5, 12.7)	5.1	5.2	(2.0, 8.3)
	8	-0.1	9.1	9.3	(5.6, 12.9)	(4.3, 14.2)	2.6	2.7	(-0.7, 6.1)
	10	-2.5	6.3	8.9	(5.5, 12.3)	(4.2, 13.5)	3.5	6.0	(2.9, 9.2)
	12	0.2	6.6	6.4	(3.2, 9.6)	(2.0, 10.8)	3.3	3.1	(0.1, 6.1)
	14	-0.3	5.2	5.4	(2.0, 8.8)	(0.7, 10.1)	3.1	3.4	(0.2, 6.6)
	16	-0.8	4.7	5.5	(2.1, 8.9)	(0.9, 10.1)	-0.5	0.3	(-2.9, 3.5)
	18	-0.1	7.3	7.5	(3.6, 11.4)	(2.2, 12.8)	0.3	0.4	(-3.2, 4.0)
	23.5	-1.0	6.3	7.3	(3.8, 10.7)	(2.6, 11.9)	0.6	1.5	(-1.7, 4.7)
9	1	-7.2	-0.4	6.8	(2.8, 10.9)	(1.4, 12.3)	-4.3	2.9	(-0.8, 6.6)
	2	-3.1	7.2	10.3	(6.4, 14.2)	(5.0, 15.6)	0.9	4.0	(0.4, 7.6)
	3	1.7	10.3	8.6	(4.7, 12.5)	(3.3, 13.9)	4.0	2.3	(-1.3, 5.9)
	4	3.5	14.5	11.0	(7.2, 14.8)	(5.8, 16.2)	6.8	3.3	(-0.3, 6.9)
	5	1.1	8.7	7.6	(3.9, 11.3)	(2.5, 12.6)	4.4	3.3	(-0.1, 6.7)
	6	-0.1	8.3	8.5	(4.9, 12.1)	(3.5, 13.4)	3.9	4.0	(0.6, 7.3)
	8	0.7	7.2	6.5	(2.5, 10.5)	(1.0, 11.9)	1.2	0.4	(-3.3, 4.2)
	10	-1.1	7.2	8.3	(4.2, 12.5)	(2.7, 14.0)	4.0	5.1	(1.2, 8.9)
	12	-0.1	3.7	3.8	(-0.2, 7.8)	(-1.7, 9.2)	4.8	4.9	(1.1, 8.6)
	14	-0.8	6.3	7.1	(3.8, 10.5)	(2.6, 11.7)	3.0	3.8	(0.7, 6.9)
	16	-2.5	1.1	3.6	(-0.1, 7.4)	(-1.5, 8.7)	0.7	3.2	(-0.3, 6.7)
	18	2.0	7.6	5.6	(1.9, 9.3)	(0.5, 10.7)	0.6	-1.4	(-4.9, 2.1)
	23.5	-0.8	5.7	6.5	(3.2, 9.8)	(2.0, 11.0)	0.3	1.1	(-2.0, 4.2)
12	1	-4.3	-1.7	2.6	(-1.7, 7.0)	(-3.3, 8.6)	-7.1	-2.8	(-6.9, 1.3)
	2	0.2	6.1	5.9	(2.0, 9.8)	(0.5, 11.3)	0.1	-0.1	(-3.7, 3.6)
	3	6.9	10.4	3.5	(-0.5, 7.5)	(-2.0, 8.9)	5.0	-1.9	(-5.7, 1.8)
	4	6.4	14.7	8.3	(4.4, 12.2)	(2.9, 13.6)	5.0	-1.4	(-5.1, 2.3)
	5	2.5	7.2	4.8	(1.0, 8.5)	(-0.4, 9.9)	2.4	-0.1	(-3.6, 3.5)

			Treatment Group						
			Moxifloxacin				Vilazodone (10-80 mg)		
		Placebo	ΔQTc	ΔΔQTc			ΔQTc	ΔΔQTc	
Day	Time (hour)	LS Mean	LS Mean	LS Mean	90% CI	Adj. 90% CI	LS Mean	LS Mean	90% CI
	6	0.9	7.6	6.6	(2.8, 10.5)	(1.3, 11.9)	0.9	-0.0	(-3.6, 3.6)
	8	-0.2	5.7	5.9	(2.1, 9.7)	(0.7, 11.1)	-0.5	-0.2	(-3.8, 3.3)
	10	-2.1	5.1	7.2	(3.4, 11.1)	(2.0, 12.5)	-0.6	1.6	(-2.0, 5.2)
	12	1.5	2.1	0.6	(-3.0, 4.2)	(-4.3, 5.5)	2.0	0.5	(-2.9, 3.8)
	14	2.3	3.6	1.2	(-2.8, 5.2)	(-4.2, 6.7)	1.5	-0.8	(-4.6, 2.9)
	16	1.5	2.1	0.6	(-3.3, 4.6)	(-4.8, 6.1)	-1.1	-2.5	(-6.2, 1.2)
	18	1.2	4.3	3.1	(-1.2, 7.4)	(-2.8, 8.9)	-2.9	-4.2	(-8.2, -0.1)
	23.5	-0.8	1.4	2.2	(-1.3, 5.7)	(-2.6, 7.0)	-2.5	-1.7	(-5.0, 1.6)
15	1	-8.5	-5.4	3.1	(-1.5, 7.8)	(-3.2, 9.5)	-9.6	-1.1	(-5.4, 3.3)
	2	-4.5	3.0	7.6	(3.3, 11.9)	(1.7, 13.4)	-2.6	1.9	(-2.1, 5.9)
	3	2.2	8.7	6.5	(2.1, 10.8)	(0.6, 12.4)	3.3	1.1	(-2.9, 5.2)
	4	3.6	12.8	9.2	(4.9, 13.4)	(3.4, 15.0)	4.5	0.8	(-3.2, 4.8)
	5	1.2	5.2	4.0	(0.3, 7.7)	(-1.0, 9.1)	2.3	1.1	(-2.3, 4.6)
	6	-0.5	4.6	5.1	(1.3, 8.9)	(-0.1, 10.3)	-1.1	-0.7	(-4.2, 2.9)
	8	-1.0	3.3	4.4	(0.4, 8.3)	(-1.0, 9.7)	-3.2	-2.2	(-5.8, 1.5)
	10	-2.2	5.7	7.9	(3.7, 12.0)	(2.2, 13.6)	-1.9	0.2	(-3.6, 4.1)
	12	0.1	2.6	2.5	(-1.8, 6.9)	(-3.4, 8.5)	1.0	1.0	(-3.1, 5.0)
	14	-0.3	0.7	1.0	(-3.1, 5.1)	(-4.6, 6.6)	-0.2	0.1	(-3.7, 4.0)
	16	-2.1	0.8	2.9	(-1.5, 7.3)	(-3.2, 8.9)	-5.8	-3.7	(-7.8, 0.4)
	18	1.6	4.4	2.8	(-1.8, 7.4)	(-3.5, 9.1)	-6.2	-7.8	(-12.2, -3.5)
	23.5	-5.7	0.3	6.0	(2.1, 10.0)	(0.6, 11.4)	-7.1	-1.4	(-5.1, 2.3)

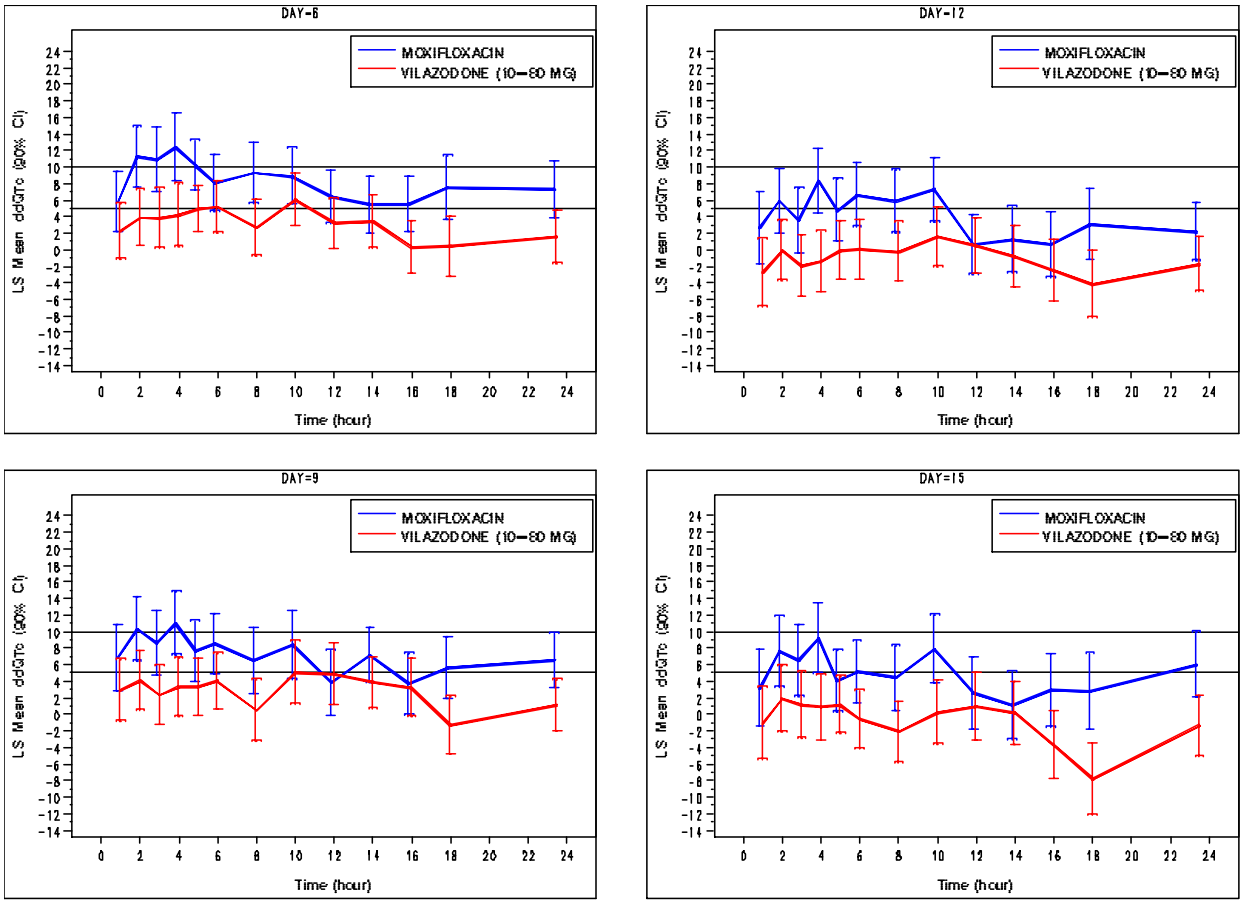
5.2.1.1 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 6. The largest unadjusted 90% lower confidence intervals are 8.3 ms, 7.2 ms, 4.4 ms and 4.9 ms, respectively, for Days 6, 9, 12 and 15, respectively. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence intervals are 6.8 ms, 5.8 ms, 2.9 ms and 3.4 ms, respectively, for Days 6, 9, 12 and 15, respectively.

5.2.1.2 Graph of ΔΔQTcI Over Time

The following figure displays the time profile of ΔΔQTcI for different treatment groups on Days 6, 9, 12 and 15.

Figure 4: Time Course of Means and 90% CI ΔΔQTcI for Vilazodone (Doses 10 mg - 80 mg) and Moxifloxacin 400 mg on Days 6, 9, 12 and 15



5.2.1.3 Categorical Analysis

Table 7 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcI is above 480 ms.

Table 7: Categorical Analysis for QTcI

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
Moxifloxacin	46	42 (91.3%)	4 (8.7%)
Placebo	44	41 (93.2%)	3 (6.8%)
Vilazodone (10-80 mg)	62	59 (95.2%)	3 (4.8%)

Table 8 lists the categorical analysis results for ΔQTcI. No subject's change from baseline is above 60 ms.

Table 8: Categorical Analysis of ΔQTcI

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
Moxifloxacin	46	31 (67.4%)	15 (32.6%)
Placebo	44	37 (84.1%)	7 (15.9%)
Vilazodone (10-80 mg)	62	52 (83.9%)	10 (16.1%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 9. The largest upper bounds of the two-sided 90% CI for the mean differences between vilazodone and placebo are 3.8 ms, 1.4 ms, 2.1 ms, and 3.6 ms, respectively, for Days 6, 9, 12 and 15, respectively. Table 10 presents the categorical analysis of PR, four subjects in vilazodone treatment groups experienced absolute PR interval greater than 200 ms. Table 11 presents the list of individual subjects with PR ≥ 200 ms in treatment groups.

Table 9: Analysis Results of ΔPR and ΔΔPR for Vilazodone (10 mg -80 mg) and Moxifloxacin 400 mg on Days 6, 9, 12 and 15

			Treatment Group					
			Moxifloxacin			Vilazodone (10-80 mg)		
		Placebo	ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Day	Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
6	1	-1.1	-0.5	0.6	(-2.1, 3.4)	-1.3	-0.2	(-2.8, 2.4)
	2	-0.5	-1.9	-1.4	(-4.4, 1.5)	-1.8	-1.3	(-4.0, 1.5)
	3	1.2	-0.3	-1.5	(-4.1, 1.2)	-0.8	-1.9	(-4.4, 0.6)
	4	0.8	-1.0	-1.8	(-5.1, 1.5)	-0.5	-1.3	(-4.4, 1.8)
	5	2.5	-0.6	-3.1	(-5.8, -0.4)	1.1	-1.4	(-3.9, 1.2)
	6	2.5	-0.5	-3.0	(-5.7, -0.3)	-0.5	-3.1	(-5.6, -0.5)
	8	2.4	-0.1	-2.6	(-5.4, 0.2)	-3.3	-5.7	(-8.4, -3.1)
	10	1.6	-1.9	-3.5	(-6.3, -0.7)	-0.5	-2.2	(-4.8, 0.5)
	12	-0.4	-2.3	-1.9	(-4.5, 0.7)	-0.7	-0.3	(-2.7, 2.1)
	14	-2.0	-0.5	1.5	(-1.1, 4.1)	-0.9	1.0	(-1.4, 3.5)
	16	0.4	1.7	1.3	(-2.0, 4.7)	-0.9	-1.3	(-4.4, 1.8)
	18	-0.5	-0.0	0.5	(-2.7, 3.7)	-1.0	-0.6	(-3.5, 2.4)
	23.5	0.8	1.6	0.8	(-1.9, 3.5)	2.1	1.3	(-1.3, 3.8)
9	1	0.0	2.7	2.6	(-0.2, 5.5)	-1.2	-1.3	(-3.9, 1.4)
	2	2.1	0.2	-2.0	(-4.9, 1.0)	-3.5	-5.6	(-8.3, -2.8)
	3	2.9	0.7	-2.2	(-5.2, 0.9)	-0.7	-3.5	(-6.4, -0.7)
	4	2.6	2.1	-0.5	(-3.7, 2.7)	-1.3	-3.9	(-6.9, -0.9)
	5	3.3	0.1	-3.2	(-6.3, -0.1)	-1.7	-5.0	(-7.9, -2.1)

			Treatment Group					
			Moxifloxacin			Vilazodone (10-80 mg)		
		Placebo	ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Day	Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
	6	4.4	1.5	-3.0	(-5.8, -0.1)	-0.9	-5.3	(-8.0, -2.6)
	8	3.0	2.9	-0.1	(-3.0, 2.9)	-3.1	-6.2	(-8.9, -3.4)
	10	2.5	-0.6	-3.1	(-6.1, -0.1)	-0.9	-3.5	(-6.2, -0.7)
	12	1.5	-0.3	-1.7	(-4.7, 1.2)	-0.3	-1.8	(-4.6, 1.0)
	14	0.7	1.3	0.5	(-2.4, 3.4)	-0.6	-1.4	(-4.1, 1.4)
	16	1.8	2.0	0.2	(-3.3, 3.6)	-1.3	-3.1	(-6.4, 0.1)
	18	3.7	2.4	-1.3	(-4.9, 2.3)	-1.5	-5.1	(-8.5, -1.7)
	23.5	3.9	3.7	-0.2	(-2.7, 2.4)	1.5	-2.4	(-4.8, 0.0)
12	1	2.2	2.6	0.3	(-3.0, 3.7)	-2.0	-4.2	(-7.4, -1.1)
	2	2.0	0.9	-1.1	(-3.8, 1.7)	-3.8	-5.8	(-8.3, -3.2)
	3	3.9	2.6	-1.3	(-4.3, 1.7)	-1.1	-5.0	(-7.8, -2.1)
	4	6.5	2.7	-3.8	(-7.2, -0.4)	-3.3	-9.8	(-13.0, -6.6)
	5	4.8	1.5	-3.4	(-6.4, -0.3)	-0.9	-5.8	(-8.6, -2.9)
	6	5.7	1.0	-4.6	(-7.8, -1.4)	-2.2	-7.8	(-10.8, -4.8)
	8	4.1	-0.5	-4.6	(-8.0, -1.1)	-2.5	-6.6	(-9.8, -3.4)
	10	2.8	-2.0	-4.8	(-7.9, -1.7)	-1.4	-4.1	(-7.0, -1.2)
	12	0.8	-1.7	-2.5	(-5.6, 0.6)	-1.8	-2.5	(-5.5, 0.4)
	14	-0.5	-0.6	-0.1	(-3.3, 3.1)	-1.5	-1.0	(-4.0, 2.1)
	16	2.9	2.5	-0.4	(-4.0, 3.2)	0.3	-2.7	(-6.1, 0.7)
	18	2.3	1.3	-1.0	(-4.8, 2.8)	-3.2	-5.5	(-9.0, -1.9)
	23.5	4.8	2.9	-1.9	(-4.8, 1.0)	0.8	-4.1	(-6.8, -1.3)
15	1	1.2	-0.0	-1.3	(-4.3, 1.8)	-2.6	-3.9	(-6.7, -1.0)
	2	2.3	0.1	-2.1	(-5.6, 1.4)	-3.6	-5.9	(-9.2, -2.6)
	3	3.6	0.7	-2.9	(-6.0, 0.3)	-2.5	-6.0	(-9.0, -3.1)
	4	5.1	1.1	-3.9	(-7.3, -0.6)	-3.5	-8.5	(-11.7, -5.4)
	5	4.8	0.5	-4.3	(-7.3, -1.3)	-2.2	-7.0	(-9.9, -4.2)
	6	5.2	2.3	-2.9	(-6.0, 0.1)	-3.6	-8.8	(-11.7, -6.0)
	8	2.7	0.6	-2.0	(-5.3, 1.2)	-3.3	-6.0	(-9.0, -2.9)
	10	3.3	-0.4	-3.8	(-7.0, -0.5)	-0.6	-4.0	(-7.1, -0.9)
	12	-0.3	-2.0	-1.7	(-4.7, 1.3)	-1.3	-1.0	(-3.8, 1.9)
	14	-0.6	-1.2	-0.6	(-4.0, 2.8)	-0.1	0.4	(-2.8, 3.6)
	16	3.3	4.3	1.1	(-2.7, 4.8)	-0.6	-3.9	(-7.4, -0.4)
	18	2.4	3.1	0.6	(-3.5, 4.7)	-2.4	-4.9	(-8.7, -1.0)
	23.5	2.8	3.0	0.2	(-3.1, 3.5)	0.9	-1.9	(-5.0, 1.2)

Table 10: Categorical Analysis of PR

Treatment Group	Total N	PR < 200 ms	PR >=200 ms
MOXIFLOXACIN	46	41 (89.1%)	5 (10.9%)
PLACEBO	44	38 (86.4%)	6 (13.6%)
VILAZODONE (10-80 MG)	62	58 (93.5%)	4 (6.5%)

Table 11: List of Subjects with PR ≥ 200 ms

Subject ID	Treatment	Day	Time (hour)	PR at Baseline	PR at Post-Dose	PR Change
PGX-08-P1-06-01-1027	VILAZODONE (10-80 MG)	12	16	191.0	205.0	14.0
	VILAZODONE (10-80 MG)	6	18	192.0	207.0	15.0
	VILAZODONE (10-80 MG)	12	18	192.0	213.7	21.7
PGX-08-P1-06-01-2003-1	VILAZODONE (10-80 MG)	12	3	175.3	202.7	27.3
	VILAZODONE (10-80 MG)	9	12	182.0	206.3	24.3
	VILAZODONE (10-80 MG)	9	16	179.7	205.3	25.7
PGX-08-P1-06-01-2043	VILAZODONE (10-80 MG)	15	18	183.7	202.7	19.0
PGX-08-P1-06-01-2044	VILAZODONE (10-80 MG)	6	1	198.3	208.3	10.0
	VILAZODONE (10-80 MG)	9	1	198.3	207.0	8.7
	VILAZODONE (10-80 MG)	12	1	198.3	203.3	5.0
	VILAZODONE (10-80 MG)	6	2	206.0	209.3	3.3
	VILAZODONE (10-80 MG)	12	2	206.0	201.7	-4.3
	VILAZODONE (10-80 MG)	15	2	206.0	200.3	-5.7
	VILAZODONE (10-80 MG)	6	3	185.0	208.7	23.7
	VILAZODONE (10-80 MG)	6	14	207.7	203.0	-4.7
	VILAZODONE (10-80 MG)	9	14	207.7	207.0	-0.7
	VILAZODONE (10-80 MG)	15	14	207.7	206.3	-1.3
	VILAZODONE (10-80 MG)	6	16	207.7	205.7	-2.0
	VILAZODONE (10-80 MG)	12	16	207.7	201.0	-6.7
	VILAZODONE (10-80 MG)	6	18	206.3	217.3	11.0
	VILAZODONE (10-80 MG)	9	18	206.3	203.7	-2.7
	VILAZODONE (10-80 MG)	6	23.5	205.3	205.3	0.0

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper bounds of the two-sided 90% CI for the mean differences between vilazodone and placebo are 2.1 ms, 2.2 ms, 2.3 ms, and 3.5 ms, respectively, for Days 6, 9, 12 and 15, respectively. There is no subjects who experienced absolute QRS interval greater than 110 ms in vilazodone treatment group.

Table 12: Analysis Results of ΔQRS and ΔΔQRS for Vilazodone (10-80 mg) and Moxifloxacin 400 mg on Days 6, 9, 12 and 15

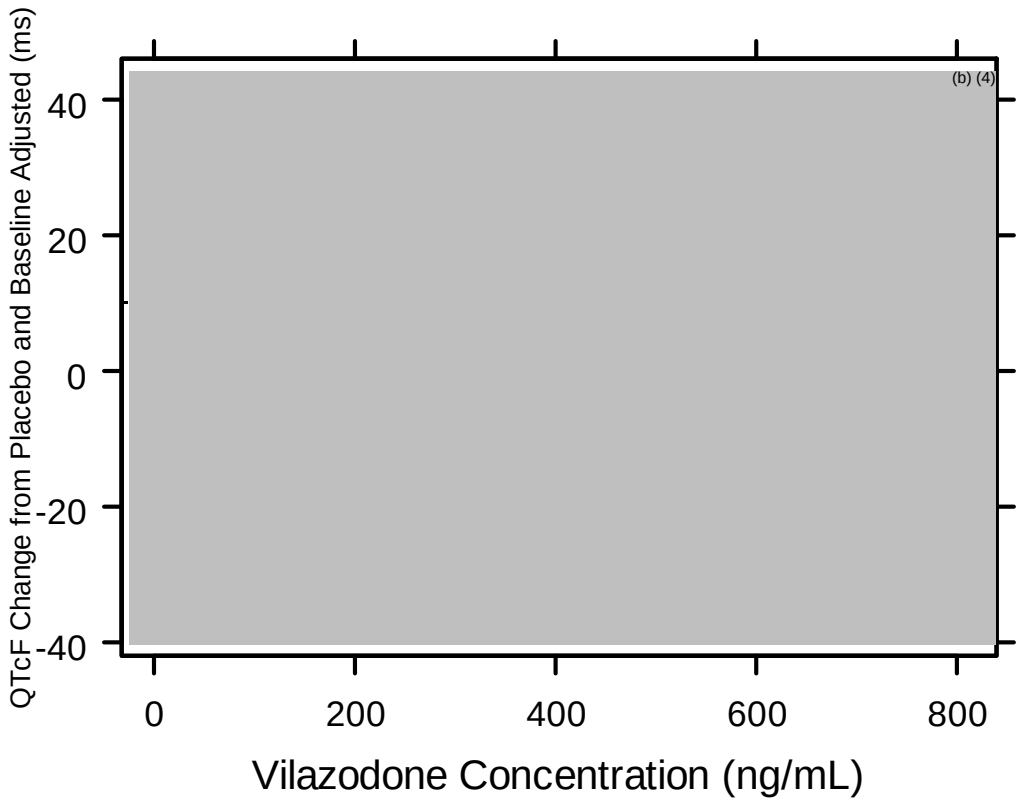
			Treatment Group					
			Moxifloxacin			Vilazodone (10-80 mg)		
		Placebo	ΔQRS	ΔΔQRS		ΔQRS	ΔΔQRS	
Day	Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
6	1	0.1	-0.8	-0.9	(-2.1, 0.3)	0.5	0.3	(-0.8, 1.4)
	2	0.2	0.2	-0.0	(-1.3, 1.3)	0.3	0.1	(-1.1, 1.3)
	3	-0.4	0.2	0.6	(-0.7, 1.9)	0.5	0.9	(-0.3, 2.1)
	4	0.4	1.0	0.6	(-0.5, 1.8)	0.4	0.0	(-1.1, 1.1)
	5	-0.1	-0.1	-0.0	(-1.1, 1.1)	0.4	0.5	(-0.5, 1.5)
	6	0.2	0.4	0.2	(-0.9, 1.3)	1.0	0.8	(-0.2, 1.9)
	8	0.8	-0.3	-1.1	(-2.3, 0.1)	0.8	-0.0	(-1.1, 1.1)
	10	-0.2	-0.2	0.0	(-1.2, 1.2)	0.5	0.7	(-0.4, 1.8)
	12	-0.6	-0.3	0.3	(-0.9, 1.4)	0.3	0.9	(-0.2, 1.9)
	14	0.2	-0.3	-0.5	(-1.6, 0.6)	1.0	0.8	(-0.2, 1.9)
	16	-0.1	-0.2	-0.0	(-1.3, 1.2)	-0.1	0.0	(-1.1, 1.2)
	18	0.1	-0.2	-0.3	(-1.6, 1.0)	0.4	0.3	(-1.0, 1.5)
	23.5	0.1	0.6	0.5	(-0.7, 1.7)	0.9	0.8	(-0.4, 1.9)
9	1	0.3	0.4	0.1	(-1.2, 1.5)	0.5	0.2	(-1.0, 1.5)
	2	-0.3	0.6	0.9	(-0.4, 2.2)	0.2	0.6	(-0.6, 1.7)
	3	0.4	0.8	0.4	(-0.8, 1.7)	0.2	-0.1	(-1.3, 1.0)
	4	0.5	0.9	0.3	(-1.0, 1.6)	0.4	-0.2	(-1.4, 1.0)
	5	0.0	0.3	0.3	(-1.0, 1.6)	0.4	0.4	(-0.8, 1.6)
	6	0.8	0.7	-0.1	(-1.3, 1.1)	0.8	0.0	(-1.1, 1.2)
	8	0.7	0.2	-0.5	(-1.8, 0.8)	0.7	-0.0	(-1.2, 1.2)
	10	0.8	0.1	-0.6	(-1.9, 0.6)	1.1	0.3	(-0.9, 1.4)
	12	-0.7	-0.5	0.2	(-1.0, 1.5)	-0.0	0.7	(-0.4, 1.9)
	14	-0.3	0.8	1.2	(-0.0, 2.4)	0.7	1.1	(-0.0, 2.2)
	16	-0.1	0.5	0.6	(-0.7, 1.9)	-0.4	-0.3	(-1.5, 0.9)
	18	0.3	0.5	0.2	(-1.2, 1.7)	0.4	0.1	(-1.2, 1.4)

			Treatment Group					
			Moxifloxacin			Vilazodone (10-80 mg)		
		Placebo	ΔQRS	ΔΔQRS		ΔQRS	ΔΔQRS	
Day	Time (hrs.)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
	23.5	0.8	1.3	0.5	(-0.7, 1.7)	0.7	-0.1	(-1.2, 1.1)
12	1	0.4	-0.3	-0.6	(-2.1, 0.8)	0.2	-0.2	(-1.5, 1.1)
	2	-0.1	0.1	0.2	(-1.2, 1.6)	0.5	0.5	(-0.7, 1.8)
	3	-0.1	0.7	0.8	(-0.5, 2.1)	-0.4	-0.3	(-1.5, 0.9)
	4	0.2	1.0	0.8	(-0.4, 2.1)	-0.0	-0.2	(-1.4, 1.0)
	5	0.1	-0.7	-0.8	(-2.1, 0.6)	-0.0	-0.1	(-1.3, 1.2)
	6	0.1	-0.1	-0.3	(-1.5, 1.0)	0.1	-0.0	(-1.2, 1.2)
	8	0.2	-0.5	-0.6	(-1.9, 0.6)	0.2	0.0	(-1.1, 1.2)
	10	-0.4	-0.1	0.3	(-1.0, 1.6)	0.8	1.2	(-0.0, 2.3)
	12	-0.6	-1.1	-0.4	(-1.7, 0.9)	0.4	1.1	(-0.2, 2.3)
	14	0.2	-0.1	-0.2	(-1.5, 1.1)	0.9	0.7	(-0.5, 1.9)
	16	-1.1	0.3	1.4	(-0.0, 2.8)	-0.2	0.9	(-0.4, 2.2)
	18	-0.7	0.2	0.9	(-0.4, 2.3)	0.3	1.0	(-0.3, 2.3)
	23.5	-0.1	0.6	0.7	(-0.6, 2.1)	0.0	0.1	(-1.2, 1.4)
15	1	0.5	-0.8	-1.2	(-2.7, 0.3)	0.5	0.1	(-1.3, 1.4)
	2	-0.6	0.4	1.0	(-0.4, 2.3)	0.5	1.1	(-0.2, 2.3)
	3	-0.6	0.5	1.1	(-0.3, 2.5)	0.3	0.9	(-0.4, 2.3)
	4	-0.2	1.4	1.6	(0.2, 3.0)	0.3	0.5	(-0.8, 1.8)
	5	-0.5	-0.3	0.2	(-1.1, 1.4)	0.5	1.0	(-0.2, 2.1)
	6	-0.1	0.1	0.3	(-1.0, 1.5)	0.2	0.3	(-0.8, 1.5)
	8	-0.1	-0.8	-0.6	(-1.9, 0.7)	0.1	0.2	(-0.9, 1.4)
	10	-0.1	-0.3	-0.2	(-1.4, 1.1)	1.0	1.1	(-0.1, 2.2)
	12	-1.7	-1.1	0.6	(-0.8, 2.1)	0.4	2.2	(0.8, 3.5)
	14	0.1	-0.5	-0.5	(-1.8, 0.8)	0.6	0.6	(-0.6, 1.8)
	16	-0.5	-0.1	0.4	(-1.0, 1.8)	-0.5	-0.0	(-1.3, 1.3)
	18	-0.2	0.7	0.8	(-0.7, 2.3)	0.0	0.2	(-1.2, 1.6)
	23.5	-0.2	0.6	0.7	(-0.6, 2.1)	0.0	0.2	(-1.0, 1.4)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔΔQTcI and vilazodone concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5: ΔΔ QTcI vs. Vilazodone Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety Assessments

There were no sudden deaths or significant ventricular arrhythmias in this study.
As reported in section 4.2.8.3 one subject experienced convulsive syncope while having her blood drawn. This was reported as convulsive syncope of vasovagal etiology. ECG taken soon after the episode was reported normal. However this event also had temporal association to study drug and may be due to non-arrhythmogenic mechanisms.
There were 3 other episodes of syncope in the vilazodone group reported as vasovagal. No narratives are available for these events.

5.4.2 ECG Acquisition and Interpretation

Waveforms from the ECG ware house were reviewed. According to ECG warehouse statistics, over 95% of the ECGs were analyzed in the primary lead (II). Less than 0.1 % of the ECGs were reported to have significant QT bias, according to the automated algorithm. Overall, ECG acquisition and interpretation in this study seems acceptable,

5.4.3 PR and QRS Interpretation and Heart Rate Effects

As noted in the statistical reviewer's analysis (5.2.2) there were no clinically relevant effects in the PR and QRS intervals. No subject with an absolute PR> 200 ms post-treatment with vilazodone had a change from baseline values over 15%. Vilazodone seems

to decrease the PR interval with maximum effect at day 12, hour 6 [-9.8 ms (-13.0; -6.6)]. We dot believe this finding is clinically relevant.

The sponsor reports that the mean changes from baseline placebo-corrected for heart rate for vilazodone 20 to 80 mg ranged from -3 to +1 bpm; these results were not dose related. One (2%) subject in the 20 mg dose group met bradycardic outlier criteria. At the highest vilazodone dose (80 mg), 10 (18%) subjects met tachycardic outlier criteria versus 2 (5%) subjects on placebo suggesting a possible increase effect on heart rate. None of the subjects in the other vilazodone dose groups met PCS tachycardia criteria.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	40 mg QD	
Maximum tolerated dose	40 mg QD results in 50% emesis if patient is not titrated to that dose in several steps	
Principal adverse events	Emesis, nausea and diarrhea with single, or short term dosing Dyspepsia, nausea, headache, dizziness, insomnia, excessive dreaming, dry mouth, somnolence, increased sweating, vomiting, rhinitis. Nausea, dyspepsia and headache were the most frequent, and most severe, treatment related AEs in patients receiving 80-100 mg QD.	
Maximum dose tested	Single Dose	80 mg
	Multiple Dose	100 mg QD for up 3-42 days (following a 14 day titration regimen to reach 80 mg QD).
Exposures Achieved at Maximum Tested Dose	Single Dose	Cmax: 58.4 ng/ml (47%) at 80 mg AUC: 1151 ng•hr/mL (31%) at 80 mg
	Multiple Dose	Maximum dose with repeat dosing and PK sampling was 40 mg QD Cmax: 59.5 ng/mL (37%) at 40 mg QD AUC: 755 ng•hr/mL (33%) at 40 mg QD
Range of linear PK	2.5 to 80 mg as single dose	
Accumulation at steady state	1.5 to 1.8 over the dosage range of 10-40 mg/QD	

<table>
<tr><td>Metabolites</td><td colspan="2">Four synthetically available metabolites have been characterized regarding their uptake inhibition in vitro. Their potency of 5-HT reuptake inhibition is considerably lower than that of vilazodone; however, minor metabolites EMD 87 409 and EMD 113 084 are in the same potency range as fluoxetine.

Inhibition of Monoamine Reuptake into Rat Brain Synaptosomes (IC_{50}, nM) by Vilazodone, Metabolites, and Fluoxetine
<table><tr><th></th><th>[^{3}H]5-HT</th><th>[^{3}H]NA</th><th>[^{3}H]DA</th></tr><tr><td>EMD 87 409</td><td>10</td><td>>10000</td><td>>10000</td></tr><tr><td>EMD 80 546</td><td>200</td><td>200</td><td>400</td></tr><tr><td>EMD 122 230</td><td>> 10000</td><td>> 10000</td><td>> 10000</td></tr><tr><td>EMD 113 084</td><td>7</td><td>82</td><td>78</td></tr><tr><td>Vilazodone</td><td>0.2</td><td>60</td><td>90</td></tr><tr><td>Fluoxetine</td><td>6</td><td>1000</td><td>3000</td></tr></table></td></tr>
<tr><td rowspan="2">Absorption</td><td>Absolute/Relative Bioavailability</td><td>Not available, but ≤ 70% based on food effect or ketoconazole interaction</td></tr>
<tr><td>Tmax</td><td>Median = 4-5 hr (2-6 hr) for parent
Not Available for metabolites</td></tr>
<tr><td rowspan="2">Distribution</td><td>Vd/F or Vd</td><td>Vd/F: 16.25 L (35%)</td></tr>
<tr><td>% bound</td><td>96% (by ultrafiltration)
99% (by ultracentrifugation)</td></tr>
<tr><td rowspan="3">Elimination</td><td>Route</td><td>Fecal (probably ~95%)
Renal (0.2% as parent,1-4% as M1)</td></tr>
<tr><td>Terminal t½</td><td>21 hr (16%) at 40 mg for parent
Not Available for metabolite</td></tr>
<tr><td>CL/F or CL</td><td>42.6 L/hr (31%)</td></tr>
<tr><td rowspan="4">Intrinsic Factors</td><td>Age</td><td>Cmax 17% lower in elderly
AUC: 19% lower in elderly</td></tr>
<tr><td>Sex</td><td>No apparent difference</td></tr>
<tr><td>Race</td><td>Not available</td></tr>
<tr><td>Hepatic & Renal Impairment</td><td>Not available</td></tr>
</table>

Extrinsic Factors	Drug interactions	200 mg a day ketoconazole : 38% increase in Cmax, 41% increase in AUC of vilazodone 1A2, 2D6, 2C9, 2C19 probes showed no change in presence of vilazodone
	Food Effects	High fat meal resulted in 49% increase in Cmax and 49% increase in AUC compared to fasted dosing
Expected High Clinical Exposure Scenario	Maximum clinical dose is 40 mg QD. Ketoconazole and high fat meal both produce an approximately 50% increase in peak and total exposures. Age decreases exposures. Renal impairment is not expected to affect exposure because of low renal clearances. A supratherapeutic dose of 60 mg (150% of 40 mg) will cover known PK effects. A supratherapeutic dose of 80 mg (200% of 40 mg) provides an additional safety margin for yet uncharacterized PK factors and non-PK factors. Nausea and emesis side effects (generally occurring prior to Tmax) will probably lead to a high incidence of incomplete drug absorption if dosed without allowing time for subject accommodation to the drug. Nausea, dyspepsia and headache were the most frequent, and most severe treatment related AEs in patients receiving 80-100 mg QD following an up-titration accommodation period.	

6.2 TABLE OF STUDY ASSESSMENTS

Table 2: Schedule of visits and study flowchart (Screening through 20 mg treatment)

Study Phase	Screening	Admission	Baseline	Treatment 10 mg			Treatment 20 mg		
Day	-14 to -2	-2	-1	1	2	3	4	5	6
Obtain ICF	X								
Demographics	X								
Inclusion / exclusion criteria	X								
Prior and concomitant medication	X	X		X	X	X	X	X	X
Medical history	X	X							
Physical examination[a]	X	X					X		
Vital signs[b]	X	X	X	X[b]	X	X	X[b]	X	X
Drugs of abuse (including ethanol)	X	X							
Safety laboratory tests	X	X							
HBsAg, HCV, and HIV	X								
Serum pregnancy test[c]	X								
Urine pregnancy test[c]		X							
Blood sample for DNA analysis			X						
Safety digital ECGs at site[d]	X	X				X			X
Randomization			X						
Vilazodone dosing group[e]				X	X	X	X	X	X
Moxifloxacin (400 mg) dosing group[e]						X			X
Placebo group[e]				X	X	X	X	X	X

Table 2: Schedule of visits and study flowchart (Screening through 20 mg treatment) (Continued)

Study Phase	Screening	Admission	Baseline	Treatment 10 mg			Treatment 20 mg		
Day	-14 to -2	-2	-1	1	2	3	4	5	6
12-lead ECG from H-12 (flash card placed in morning)[f]			X						X
PK blood samples[g]									X
Adverse events				X	X	X	X	X	X
End of study									

a Physical exams: full exams at screening, Day -2, and Day 16 or early termination. All other physical exams are symptom directed.

b Vital signs at 30 minutes pre-dose and 4 and 8 hours post-dose on Days 1, 4, 7, 10, and 13. All other vital sign collections should occur within 30 minutes after daily dose.

c For females only: Serum pregnancy test at screening. Urine pregnancy tests at Day-1 and Day 16 or early termination (if applicable).

d Standard digital 12-lead ECGs will be recorded at screening, baseline, and then again approximately 2-3 hour after dosing on Days 3, 6, 9, 12, and 15 of treatment to detect any immediate ECG effects for subject safety. Subjects should remain supine for at least 10 minutes prior to each ECG recording. The ECG extraction is to be completed before the PK sample is drawn.

e Dosing should occur at the same time (± 1 hour) each day. Whenever possible, subjects should be separated from each other for 2 hour after dosing due to emesis effect.

f 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.

g 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGXHEALTH LLC	VILAZODONE HCL

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

/s/

JOANNE ZHANG
09/14/2010

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09/14/2010

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09/14/2010

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09/14/2010

SUCHITRA M BALAKRISHNAN
09/14/2010

NORMAN L STOCKBRIDGE
09/15/2010

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 19, 2010

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

Subject: **INFORMATION REQUEST:** NDA 22-567, Vilazodone HCL
Indication: Major Depressive Disorder
Dosages: 40 mg daily
Sponsor: PGx Health, LLC

Materials reviewed: NDA submission located at: **\\CDSESUB1\EVSPROD\NDA022567**
Abuse potential materials included a self-administration study, and conditioned place preference study in rodents.

This is an Information Request to PGx Health, LLC, to compile and tabulate abuse-related information (adverse events) in the NDA for Vilazodone (NDA 22-567).

According to 21 CFR 314.50(d)(5)(vii), a sponsor must submit in the NDA an assessment of studies and other information related to the potential abuse of a drug and include a proposal for scheduling if the drug affects the central nervous system (CNS), is chemically or pharmacologically similar to other drugs with known abuse potential, or produces psychoactive effects such as sedation, euphoria, and mood changes.

The Sponsor did not perform a clinical abuse potential assessment, provide a recommendation for scheduling, and did not include a dedicated abuse potential section in the NDA. To evaluate the abuse potential of Vilazodone, the Sponsor must submit a formal analysis of abuse-related adverse events (AEs). This analysis should include all clinical studies (e.g. Phase 1, 2 and 3 studies). For each clinical study, AEs should be categorized by dose and presented in tabular format.

The Sponsor must also provide a pooled analysis of abuse-related AEs. The pooled analysis should contain all AEs, collapsed across studies, and categorized by dose.

The specific AEs of interest appear below:

Abuse-Related AE Terms for Use in Clinical Efficacy Studies

All clinical studies should be evaluated for indicators of abuse potential. The list below is a compilation of abuse-related adverse events terms, based on our experience to date. The list includes specific terms that are in the MedDRA 12.0 dictionary as well as frequently used verbatim terms, words or phrases. Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The presence of euphoria or other positive mood changes is a key observation that may influence a recommendation for scheduling. However, the overall behavioral profile and pharmacologic similarity to a scheduled drug is critical in determining whether scheduling will be recommended, and if so, into which schedule the drug will be recommended for placement.

Euphoria-related terms:

Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high*, high* feeling, laughter. (* Exclude terms that clearly are not related or relevant such as "high blood pressure," etc.)

Elevated mood: mood elevated, elation.

Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.

Feeling of relaxation: feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

Dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts.

Hallucination: (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

Inappropriate affect: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laugher, inappropriate mood elevation.

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor.

Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative/psychotic terms:

Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia.

Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGXHEALTH LLC	VILAZODONE HCL

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

/s/

CHAD REISSIG
08/19/2010

LORI A LOVE
08/19/2010

MICHAEL KLEIN
08/19/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22-567 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Vilazodone Hydrochloride Tablets Dosage Form: Tablets Strengths: 10 mg, 20 mg and 40 mg		
Applicant: PGxHealth, LLC Agent for Applicant (if applicable):		
Date of Application: March 22, 2010 Date of Receipt: March 22, 2010 Date clock started after UN:		
PDUFA Goal Date: January 22, 2011	Action Goal Date (if different):	
Filing Date: May 21, 2010	Date of Filing Meeting: May 5, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) New Molecular Entity (1)		
Proposed indication(s)/Proposed change(s): Major Depressive Disorder		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	X 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A				
List referenced IND Number(s): 54,613				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:* **06/28/2010**				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			X	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) X Medication Guide (MedGuide) X Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) Biometrics (4/13/2010); DSI Clinical Sites (5/12/2010); QT consult (5/21/2010); CSS Consult (6/28/2010); Ophthalmology consult (July 7, 2010) ***If yes, specify consult(s) and date(s) sent:***	x			

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** June 17, 2009 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** July 31, 2009 Request for a Written Response in lieu of a meeting ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 28, 2010

BLA/NDA/Supp #: 22-567

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: Vilazodone Hydrochloride Tablets

DOSAGE FORM/STRENGTH: 10 mg, 20 mg and 40 mg tablets

APPLICANT: PGxHealth, LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Major Depressive Disorder

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Bill Bender	Y
	CPMS/TL:	Paul David/Renmeet Grewal	N
Cross-Discipline Team Leader (CDTL)	Robert Levin		Y
Clinical	Reviewer:	Cheri Lindberg	Y
	TL:		
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Bei Yu	Y
	TL:	Raman Baweja	Y
Biostatistics	Reviewer:	Phillip Dinh	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Violetta Klimek	Y
	TL:	Linda Fossom	Y
Statistics (carcinogenicity)	Reviewer:	Mohamed Nagem	N
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Pei-I Chu	Y
	TL:	Thomas Oliver	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	N
	TL:	Kristinal Toliver	N
OSE/DRISK (REMS)	Reviewer:	Robin Duer	N
	TL:	Mary Dempsey	N
Bioresearch Monitoring (DSI)	Reviewer:	Anthony Orencia	Y
	TL:		

Other reviewers	Issam Zineh, Genomics	Y
Other attendees	Yaning Wang, Atul Bhattaram, Huixia Zhang, Hiren Patel	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	 X Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**: None.	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: X NO ☐ To be determined Reason: The application did not raise significant safety or efficacy issues.

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	XNot Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ellis Unger, MD, ODE 1 Deputy Director **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: X No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: X Standard Review ☐ Priority Review
ACTIONS ITEMS	
X	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGXHEALTH LLC	VILAZODONE HCL

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

/s/

WILLIAM H BENDER
07/08/2010

DSI CONSULT: Request for Clinical Inspections

Date: *See Appended Electronic Signature Page*

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2, HFD-47
Anthony Orencia, DSI Primary Reviewer

Through: Thomas Laughren, M.D./Division of Psychiatry Products/HFD-130
Bob Levin, M.D./ Medical Team Leader

From: William Bender, Pharm.D., Senior Regulatory Project Manager
Division of Psychiatry Products/HFD-130

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-567
Sponsor/Sponsor contact information: Kimberly Fabrizio
Phone: (203)786-3502
KFabrizio@pgxhealth.com

Drug: Vilazodone HCL 10 mg, 20 mg, and 40 mg tablets
NME: Yes
Standard or Priority: Standard
Study Population < 17 years of age: No
Pediatric exclusivity: No

Proposed New Indication: Major Depressive Disorder (MDD)

Inspection Summary Goal Date: November 17, 2010
Action Goal Date: December 4, 2010
PDUFA: January 22, 2011

II. Protocol/Site Identification

See Table below for the Protocol Title/# of subjects enrolled and site address:

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Arifulla Khan, M.D. Site #2020 Northwest Clinical Research Center 1951 152nd Place NE Suite 200 Bellevue, WA 98007	CLDA-07-DP-02	217	Major Depressive Disorder in Adults
Jerry C. Steiert, M.D. Site #2080 Summit Research Network (Seattle) Seattle, WA 98104	CLDA-07-DP-02	84	Major Depressive Disorder in Adults
Nader Oskooilar, M.D., Ph.D. Site: #2030 Pharmacology Research Institute 1601 Dove Street Suite 290 Newport Beach, CA 92660	GNSC-04-DP-02	50	Major Depressive Disorder in Adults
Karl Rickels, M.D. Site: #0400 University Department of Psychiatry Mood and Anxiety Disorders Section 3535 Market Street, Suite 670 Philadelphia, PA 19104-3309	GNSC-04-DP-02	72	Major Depressive Disorder in Adults

Please find a copy of clinical study report and the study protocol in the edr at the following link:
\\CDSESUB1\EVSPROD\NDA022567\022567.ENX

III. Site Selection/Rationale

We chose the centers that had the highest number of patients enrolled. .

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

Should you require any additional information, please contact CDR Bill Bender at 301-796-2145 or Cheri Lindberg at 301-796-4963.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGXHEALTH LLC	VILAZODONE HCL

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

/s/

WILLIAM H BENDER
05/12/2010

THOMAS P LAUGHREN
05/12/2010