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Vilazodone Pharmacokinetics in Subjects With Mild to Moderate Hepatic Impairment

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Abstract

Objective

Vilazodone HCl (VLZ) is a dual-acting selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist in development for the treatment of major depressive disorder. The primary objective of this study was to assess the pharmacokinetics (PK) of VLZ in subjects with mild or moderate hepatic impairment.

Method

32 subjects aged 18-70 completed this phase 1, open-label, single-dose study: 8 with mild hepatic impairment (Child-Pugh 5-6 points), 8 with moderate impairment (7-9 points), and 16 with normal hepatic function individually matched for age, sex, and BMI. Subjects received a 20-mg dose of VLZ. PK and safety measures were performed predose to 7 days postdose.

Results

Mean C_{max} and AUC were similar among groups. Terminal elimination half-lives (30.6 and 29.4 h for mild and moderate impaired subjects vs 25.9 and 25.4 h for healthy control groups) and total drug clearance (25.5 and 29.4 vs 21.7 and 26.8 L/h) were similar for hepatically impaired and healthy subjects, as was mean recovery of VLZ in urine over 96 h (1.30%-0.92% vs 0.84%-1.13% of administered dose). VLZ was extensively bound to plasma proteins, with mean free fraction of 1.59% and 1.64% in mild and moderate hepatically impaired and 0.99% in subgroups of healthy subjects. Due to the observed high variability (CV, 22%-65%) there was no substantial difference in protein binding, and total drug clearance was not affected. Mean serum albumin was within normal range for all groups. No differences in safety outcomes were observed.

Conclusions

Vilazodone PK are similar in healthy and mild or moderate hepatically impaired subjects. Observed differences are small and of no clinical relevance. Peak exposure and drug accumulation with chronic dosing are not expected to be affected by mild or moderate hepatic impairment. Safety and tolerability of vilazodone were comparable in all groups. Thus, in mild or moderate hepatically impaired subjects no dosage adjustment seems to be required.

Introduction

- Vilazodone HCl is a dual-acting potent and selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist that exerts its effects at the serotonin transporter and at pre- and post-synaptic 5-HT_{1A} receptors[1,2]
  - The unique dual modulation of serotonin neurotransmission by vilazodone is hypothesized to decrease endogenous serotonin negative feedback and enhance post-synaptic 5-HT effects
- Data (on file) from phase 1 studies in healthy volunteers indicate
  - Peak serum concentrations of orally administered vilazodone typically are achieved 3 to 6 hours after dose
  - The terminal elimination half-life of vilazodone is 23.0 to 25.3 hours after a single dose and 28.9 to 30.9 hours after 10 days of dosing at 10 to 40 mg once daily
  - Vilazodone has a dose-proportional effect on C_{max} and AUC for doses up to 80 mg
  - Vilazodone is highly bound (96%-99%) to plasma proteins
  - A nominal amount of vilazodone is recovered as unchanged drug (0.2%) or identified metabolites (~4%) in the urine of subjects with normal hepatic function
- The effect of hepatic impairment on the pharmacokinetics (PK) of vilazodone has not been previously studied. The purpose of this study was to investigate the PK of a single oral 20-mg dose of vilazodone in subjects with mild or moderate hepatic impairment compared with the PK in healthy volunteers

Objectives

- Primary
  - To determine the plasma PK of a single orally administered dose of vilazodone in subjects with mild or moderate hepatic impairment
- Secondary
  - To compare the safety and tolerability of vilazodone in subjects with mild or moderate hepatic impairment with healthy volunteers

Methods

- All subjects provided written informed consent before study procedures were initiated
- The study was approved by the institutional review board at each investigational center

Study Subjects

- Male and female subjects 18 to 70 years of age
- Subjects with hepatic dysfunction were classified according to the Child-Pugh hepatic dysfunction staging system[3] as having mild (5-6 points) or moderate (7-9 points) hepatic impairment
- Healthy subjects with normal hepatic function were individually matched for sex, age (±10 y), and body mass index (±15%) to subjects with mild or moderate hepatic impairment
- The PK population included all subjects who received a single dose of vilazodone, completed PK evaluations, and were matched with another subject who also completed PK evaluations
- The safety population included all subjects exposed to vilazodone and who had at least 1 postdose safety measure

Study Design

- Phase 1, open-label, single-dose, multicenter study
- Subjects received a single oral dose of 20 mg vilazodone
- Study included a screening period, inpatient treatment period (day –1 through day 5), outpatient visits (days 6 and 7), and 1 follow-up visit (day 14 ± 1 day)
- Blood samples and urine were collected before and after dosing (blood, 0-144 hours; urine, 0-96 hours)
- Concomitant substances
  - Subjects with hepatic impairment were allowed to continue medically necessary medications during the study if the dosage regimen had been stable for at least 14 days
  - For all subjects, use of the following medications was prohibited or restricted during the study: psychoactive medication, monoamine oxidase inhibitors, migraine drugs with a serotonergic mechanism of action, CYP3A4 inhibitors (food, beverage, or medication), and drugs affecting coagulation (eg, NSAIDs, aspirin >325 mg/day, warfarin, clopidogrel)
  - Use of herbal supplements and alcoholic beverages also was prohibited

Pharmacokinetic Analytical Methods and Parameters

- Vilazodone concentrations in plasma and urine were determined by a liquid chromatography with tandem mass spectrometry method and validated for the following ranges:
  - Plasma, 0.8119 to 270.6 ng/mL
  - Urine, 1.0 to 200 ng/mL
- The following vilazodone PK parameters were determined for each subject using noncompartmental methods:
  - Maximum plasma concentration (C_{max})
  - Time to maximum plasma concentration (T_{max})
  - Area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24})
  - Area under the plasma concentration-time curve from time 0 to the last measurable concentration (AUC_{0-t})
  - Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
  - Oral clearance (CL/F), calculated as dose/$AUC_{0-\infty}$
  - Terminal elimination rate constant (λ_z)
  - Terminal elimination half-life ($t_{1/2}$)
  - Free fraction in plasma (f_p)
  - Apparent free drug clearance (CLu/F), calculated as (CL/F)/f_p
  - Amount recovered in urine (Au) and percentage of dose recovered in urine (% dose recovered)
  - Renal clearance (CLr), estimated by Au/AUC_{0-96}
  - Volume of distribution (Vz/F), calculated as dose/(λz · $AUC_{0-\infty}$)

Safety

- Safety assessments included evaluations of adverse events (AEs), laboratory tests (chemistry, hematology, and urinalysis), electrocardiography (ECG), and vital signs

Statistical Analysis

- Analysis of variance (ANOVA) was performed on the natural logarithms of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}, with hepatic group (mild hepatic impairment, moderate hepatic impairment, and their matched healthy subject groups) as a fixed effect
  - Comparisons of hepatic impairment group versus the corresponding matched healthy group were made using appropriate contrast statements
  - Point estimate and 90% confidence interval (CI) for the least-square (LS) mean difference between groups in PK parameters on the log scale were exponentiated to obtain estimates for ratios of LS geometric means on the original scale
- Safety assessments were summarized, with no statistical comparisons performed

Results

Baseline Demographics

- Thirty-three subjects were screened and received vilazodone (**Table 1**); 32 subjects were evaluated for the PK analysis

Table 1. Demographics and Baseline Characteristics (Safety Population)

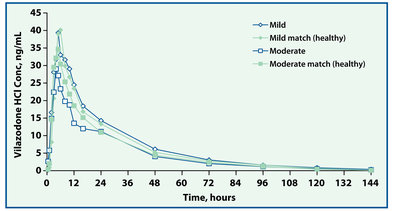
Parameter	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Mild n = 8	Healthy Match n = 9	Moderate n = 8	Healthy Match n = 8
Age, y				
Mean (SD)	48.5 (6.2)	44.3 (7.9)	57.8 (2.2)	55.3 (5.8)
Median (range)	50 (39-55)	45 (29- 53)	57 (54- 60)	56 (47- 64)
Sex, n (%)				
Male	5 (62.5)	6 (66.7)	6 (75.0)	6 (75.0)
Female	3 (37.5)	3 (33.3)	2 (25.0)	2 (25.0)
Race, n (%)				
White	4 (50.0)	8 (88.9)	8 (100.0)	6 (75.0)
Black	4 (50.0)	1 (11.1)	0 (0)	2 (25.0)
Height, cm				
Mean (SD)	172.4 (9.6)	175.6 (4.9)	175.5 (8.9)	171.4 (7.5)
Median (range)	170.0 (163-188)	176.0 (168-183)	174.5 (165-188)	173.0 (155-180)
Weight, kg				
Mean (SD)	80.6 (15.6)	85.3 (15.1)	83.5 (16.2)	80.5 (13.8)
Median (range)	79.5 (58-112)	86.0 (62-109)	84.5 (66-110)	79.0 (65-111)
BMI, kg/m²				
Mean (SD)	27.1 (3.8)	27.7 (4.8)	27.0 (5.0)	27.4 (4.4)
Median (range)	27.5 (22-32)	27.0 (21-36)	25.0 (23-38)	26.5 (24-38)
Serum albumin, g/dL				
Mean (SD)	3.9 (0.5)	4.5 (0.3)	3.4 (0.6)	4.3 (0.2)
Median (range)	4.1 (3.0-4.5)	4.5 (3.9-4.9)	3.4 (2.5-4.3)	4.2 (4.1-4.7)
Child-Pugh score				
Mean (SD)	5.4 (0.5)		7.8 (0.7)	
Median (range)	5.0 (5.0-6.0)		8.0 (7.0-9.0)	

BMI, body mass index.

Pharmacokinetic Parameters in Hepatically Impaired Subjects Compared With Healthy Subjects

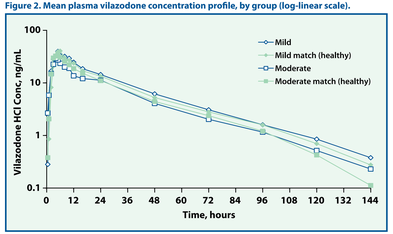
- Mean plasma vilazodone concentration-time profiles were similar between subjects with mild or moderate hepatic impairment and their matched healthy controls (**Figures 1** and **2**)

Figure 1. Mean plasma vilazodone concentration profile, by group (linear scale).



Conc, concentration; HCl, hydrochloride.

Figure 2. Mean plasma vilazodone concentration profile, by group (log-linear scale).



Conc, concentration; HCl, hydrochloride.

- Mean C_{max}, T_{max}, AUC_{∞}, $t_{1/2}$, oral clearance, and Au were each similar between hepatic impaired and healthy subjects (**Table 2**)

Table 2. Vilazodone PK Parameters (PK Population)

Parameter	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Mild n = 8	Healthy Match n = 8	Moderate n = 8	Healthy Match n = 8
C_{max}, ng/mL				
Mean (SD)	44.1 (16.5)	43.1 (13.1)	34.2 (8.2)	35.8 (10.7)
Median (range)	43.8 (14.3-69.8)	39.9 (28.2-63.1)	35.2 (22.4-45.3)	38.3 (17.9-48.7)
CV, %	37.4	30.3	23.9	29.9
T_{max}, h				
Mean (SD)	4.63 (1.60)	5.00 (1.51)	4.13 (1.81)	4.88 (0.84)
Median (range)	4.50 (3.00-8.00)	5.00 (3.00-8.00)	4.00 (2.00-8.00)	5.00 (4.00-6.00)
CV, %	34.6	30.2	43.8	17.1
AUC_{0-24}, ng·h/mL				
Mean (SD)	537 (249)	501 (121)	370 (70)	446 (123)
Median (range)	506 (166-1030)	498 (371-722)	378 (269-492)	442 (259-609)
CV, %	46.3	24.2	19.0	27.5
AUC_{0-t}, ng·h/mL				
Mean (SD)	984 (505)	898 (168)	683 (190)	768 (229)
Median (range)	907 (280-1940)	891 (665-1240)	650 (421-938)	708 (420-1110)
CV, %	51.3	18.7	27.9	29.9
$AUC_{0-\infty}$, ng·h/mL				
Mean (SD)	1030 (506)	945 (169)	727 (196)	809 (231)
Median (range)	961 (305-1980)	952 (714-1290)	695 (471-1020)	753 (448-1160)
CV, %	49.2	17.9	26.9	28.6
λ_z, 1/h				
Mean (SD)	0.0243 (0.0070)	0.0280 (0.0061)	0.0265 (0.0093)	0.0286 (0.0067)
Median (range)	0.0223 (0.0170-0.0356)	0.0278 (0.0189-0.0380)	0.0264 (0.0130-0.0448)	0.0259 (0.0214-0.0400)
CV, %	28.9	21.8	35.2	23.4
$t_{1/2}$, h				
Mean (SD)	30.6 (8.2)	25.9 (5.9)	29.4 (11.4)	25.4 (5.5)
Median (range)	31.3 (19.5-40.8)	25.1 (18.2-36.6)	26.4 (15.5-53.5)	27.0 (17.3-32.4)
CV, %	26.9	22.8	38.8	21.5
Vz/F, L				
Mean (SD)	1048 (493)	801 (183)	1176 (331)	948 (244)
Median (range)	1050 (335-1840)	821 (542-1110)	1155 (771-1680)	835 (721-1340)
CV, %	47.1	22.8	28.2	25.7
CL/F, L/h				
Mean (SD)	25.5 (17.3)	21.7 (3.7)	29.4 (8.0)	26.8 (8.7)
Median (range)	20.9 (10.1-65.6)	21.0 (15.5-28.0)	29.0 (19.7-42.5)	26.6 (17.3-44.7)
CV, %	68.1	17.0	27.1	32.5
Au, mg				
Mean (SD)	0.259 (0.169)	0.167 (0.096)	0.183 (0.105)	0.226 (0.108)
Median (range)	0.256 (0.033-0.452)	0.126 (0.073-0.354)	0.161 (0.050-0.407)	0.205 (0.094-0.452)
CV, %	65.0	57.4	57.3	47.9
Dose recovered in urine, %				
Mean (SD)	1.297 (0.845)	0.835 (0.479)	0.915 (0.525)	1.131 (0.541)
Median (range)	1.297 (0.165-2.260)	0.629 (0.366-1.770)	0.802 (0.252-2.040)	1.029 (0.470-2.260)
CV, %	65.1	57.3	57.4	47.9
CLr, L/h				
Mean (SD)	0.264 (0.136)	0.202 (0.123)	0.299 (0.206)	0.296 (0.091)
Median (range)	0.269 (0.039-0.451)	0.166 (0.061-0.448)	0.264 (0.077-0.743)	0.279 (0.164-0.418)
CV, %	51.6	61.1	68.9	30.9

- Vilazodone was extensively bound to plasma proteins, with mean free fraction of 1.59% to 1.64% in subjects with mild to moderate hepatic impairment and 0.99% in healthy subjects (**Table 3**)
- The observed ranges in vilazodone free fraction for the 3 groups of subjects were similar, suggesting there were no substantial differences in protein binding among the hepatic impaired and healthy groups
  - Oral clearance was not affected by mild or moderate hepatic impairment, supporting that free fraction was not altered with mild or moderate hepatic impairment, or was not critical to vilazodone clearance

Table 3. PK Parameters Related to Vilazodone and Protein Binding (PK Population)

	Mild Hepatic Impairment	Moderate Hepatic Impairment	Healthy
	n = 8	n = 8	n = 8
Mean f_p, %			
Mean (SD)	1.590 (0.767)	1.635 (0.361)	0.985 (0.644)
Median (range)	1.645 (0.630-2.670)	1.600 (1.050-2.210)	0.790 (0.610-2.550)
CV, %	48.2	22.1	65.4
CLu/F, L/h			
Mean (SD)	n = 8	n = 8	n = 4
Median (range)	1719 (798)	1879 (681)	2583 (634)
CV, %	1650 (823-3090)	1610 (1080-3060)	2710 (1750-3160)
	46.4	36.2	24.5

- Mean serum albumin levels at baseline were 3.9 g/dL and 3.4 g/dL in mild and moderate impairment groups, respectively, and 4.3 to 4.5 g/dL in healthy subjects. These mean values were within the normal range (3.4-4.5 g/dL)
- Ratios of vilazodone C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for both hepatic impairment groups compared with their healthy matches were similar (**Table 4**)

Table 4. Vilazodone PK Comparisons Between Impaired and Healthy Match Groups (PK Population)

Comparison	Ratio	90% CI
C_{max}		
Mild/healthy match	0.978	0.724, 1.323
Moderate/healthy match	0.972	0.719, 1.314
AUC_{∞}		
Mild/healthy match	0.977	0.713, 1.338
Moderate/healthy match	0.895	0.653, 1.226
AUC_{0-t}		
Mild/healthy match	0.980	0.724, 1.326
Moderate/healthy match	0.905	0.669, 1.225

- The 90% CIs for these PK parameters are outside the 0.80 to 1.25 range normally designated as proving bioequivalence (**Table 4**), most likely because of the small number of subjects

Safety

- All TEAEs were mild to moderate in intensity (**Table 5**); there were no SAEs
- No subject discontinued because of a TEAE

Table 5. Incidence of TEAEs Occurring in More than 1 Subject by Preferred Term (Safety Population)

Preferred Term[a]	Subjects, n (%)			
	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Mild n = 8	Healthy Match n = 9	Moderate n = 8	Healthy Match n = 8
Diarrhea	5 (62.5)	1 (11.1)	2 (25.0)	2 (25.0)
Dizziness	1 (12.5)	1 (11.1)	3 (37.5)	1 (12.5)
Nausea	1 (12.5)	2 (22.2)	1 (12.5)	1 (12.5)
Headache	0	0	1 (12.5)	1 (12.5)
Back pain	1 (12.5)	0	1 (12.5)	0

[a]Subjects might have reported more than 1 event per preferred term.

- No clinically significant changes in laboratory parameters were noted in any group
- Mean changes from baseline in vital signs were small, similar among groups, and not considered clinically significant (**Table 6**)
- No clinically significant abnormalities were noted on 12-lead ECGs

Table 6. Blood Pressure and Pulse at Baseline and Change From Baseline at 4 Hours After Dose and EOS/ET (Safety Population)

Parameter	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Mild n = 8	Healthy Match n = 8	Moderate n = 8	Healthy Match n = 8
SBP, mm Hg				
Baseline				
Mean (SD)	114.3 (10.1)	125.1 (14.0)	124.0 (16.0)	119.9 (16.4)
Median (range)	114.5 (102.0-129.0)	121.0 (100.0-143.0)	133.0 (98.0-138.0)	121.5 (98.0-140.0)
4 Hours after dose[a]				
Mean (SD)	1.8 (4.0)	–7.4 (11.3)	0.0 (10.9)	–7.9 (13.9)
Median (range)	3.0 (–6.0-5.0)	–3.0 (–30.0-6.0)	0.5 (–17.0-16.0)	–7.5 (–31.0-10.0)
EOS/ET[b]				
Mean (SD)	7.0 (7.5)	0.2 (9.4)	0.1 (12.0)	0.4 (12.9)
Median (range)	8.5 (–6.0-15.0)	–1.0 (–11.0-19.0)	1.0 (–26.0-13.0)	4.0 (–27.0-15.0)
DBP, mm Hg				
Baseline				
Mean (SD)	71.2 (9.9)	72.3 (9.4)	74.3 (6.8)	75.1 (11.5)
Median (range)	72.5 (58.0-85.0)	74.0 (51.0-82.0)	77.0 (63.0-82.0)	73.5 (62.0-95.0)
4 Hours after dose[a]				
Mean (SD)	–1.8 (6.3)	–1.3 (4.4)	0.3 (4.2)	–7.4 (12.4)
Median (range)	–2.5 (–10.0-8.0)	–1.0 (–9.0-6.0)	0.5 (–7.0-8.0)	–5.5 (–27.0-8.0)
EOS/ET[b]				
Mean (SD)	7.0 (7.5)	1.9 (6.1)	2.5 (7.7)	–0.8 (6.9)
Median (range)	10.0 (–8.0-12.0)	4.0 (–8.0-11.0)	0.0 (–4.0-20.0)	–0.5 (–12.0-10.0)
Pulse, bpm				
Baseline				
Mean (SD)	68.7 (11.2)	71.0 (9.1)	68.6 (9.6)	68.4 (11.9)
Median (range)	71.0 (54.0-82.0)	70.0 (57.0-89.0)	68.5 (56.0-86.0)	63.0 (56.0-91.0)
4 Hours after dose[a,b]				
Mean (SD)	–4.8 (5.3)	–1.9 (8.7)	–1.3 (8.2)	–4.9 (7.9)
Median (range)	–4.5 (–14.0-2.0)	–1.0 (–14.0-13.0)	–1.0 (–12.0-12.0)	–2.0 (–22.0-2.0)
EOS/ET[a,b]				
Mean (SD)	–4.7 (10.2)	0.6 (11.9)	4.8 (6.5)	3.8 (9.3)
Median (range)	–3.5 (–20.0-11.0)	–4.0 (–12.0-22.0)	6.5 (–8.0-13.0)	4.5 (–11.0-19.0)

bpm, beats per minute; DBP, diastolic blood pressure; EOS/ET, end of study/early termination; SBP, systolic blood pressure.
[a]Mean change from baseline.
[b]n = 6.

Conclusions

- Vilazodone PK after a single 20 mg oral dose was not substantially different in subjects with mild or moderate hepatic impairment compared with matched healthy subjects with normal hepatic function
  - Observed differences were small and unlikely to be clinically relevant
- Mild or moderate hepatic impairment was not associated with any pattern of increased incidence of TEAEs or clinically significant changes in laboratory values, vital signs, or ECG parameters, compared with subjects with normal hepatic function
- These findings suggest that no dose adjustment of vilazodone would be required for patients with mild or moderate hepatic impairment

References

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- The study was approved by the institutional review board at each investigational center

Study Subjects

- Male and female subjects 18 to 70 years of age
- Subjects with hepatic dysfunction were classified according to the Child-Pugh hepatic dysfunction staging system[3] as having mild (5-6 points) or moderate (7-9 points) hepatic impairment
- Healthy subjects with normal hepatic function were individually matched for sex, age (±10 y), and body mass index (±15%) to subjects with mild or moderate hepatic impairment
- The PK population included all subjects who received a single dose of vilazodone, completed PK evaluations, and were matched with another subject who also completed PK evaluations
- The safety population included all subjects exposed to vilazodone and who had at least 1 postdose safety measure

Study Design

- Phase 1, open-label, single-dose, multicenter study
- Subjects received a single oral dose of 20 mg vilazodone
- Study included a screening period, inpatient treatment period (day –1 through day 5), outpatient visits (days 6 and 7), and 1 follow-up visit (day 14 ± 1 day)
- Blood samples and urine were collected before and after dosing (blood, 0-144 hours; urine, 0-96 hours)
- Concomitant substances
  - Subjects with hepatic impairment were allowed to continue medically necessary medications during the study if the dosage regimen had been stable for at least 14 days
  - For all subjects, use of the following medications was prohibited or restricted during the study: psychoactive medication, monoamine oxidase inhibitors, migraine drugs with a serotonergic mechanism of action, CYP3A4 inhibitors (food, beverage, or medication), and drugs affecting coagulation (eg, NSAIDs, aspirin >325 mg/day, warfarin, clopidogrel)
  - Use of herbal supplements and alcoholic beverages also was prohibited

Pharmacokinetic Analytical Methods and Parameters

- Vilazodone concentrations in plasma and urine were determined by a liquid chromatography with tandem mass spectrometry method and validated for the following ranges:
  - Plasma, 0.8119 to 270.6 ng/mL
  - Urine, 1.0 to 200 ng/mL
- The following vilazodone PK parameters were determined for each subject using noncompartmental methods:
  - Maximum plasma concentration (C_{max})
  - Time to maximum plasma concentration (T_{max})
  - Area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24})
  - Area under the plasma concentration-time curve from time 0 to the last measurable concentration (AUC_{0-t})
  - Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
  - Oral clearance (CL/F), calculated as dose/$AUC_{0-\infty}$
  - Terminal elimination rate constant (λ_z)
  - Terminal elimination half-life ($t_{½}$)
  - Free fraction in plasma (f_p)
  - Apparent free drug clearance (CLu/F), calculated as (CL/F)/f_p
  - Amount recovered in urine (Au) and percentage of dose recovered in urine (% dose recovered)
  - Renal clearance (CLr), estimated by Au/AUC_{0-96}
  - Volume of distribution (Vz/F), calculated as dose/($\lambda z \cdot AUC_{0-\infty}$)

Safety

- Safety assessments included evaluations of adverse events (AEs), laboratory tests (chemistry, hematology, and urinalysis), electrocardiography (ECG), and vital signs

Statistical Analysis

- Analysis of variance (ANOVA) was performed on the natural logarithms of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}, with hepatic group (mild hepatic impairment, moderate hepatic impairment, and their matched healthy subject groups) as a fixed effect
  - Comparisons of hepatic impairment group versus the corresponding matched healthy group were made using appropriate contrast statements
  - Point estimate and 90% confidence interval (CI) for the least-square (LS) mean difference between groups in PK parameters on the log scale were exponentiated to obtain estimates for ratios of LS geometric means on the original scale
- Safety assessments were summarized, with no statistical comparisons performed

Results

Baseline Demographics

- Thirty-three subjects were screened and received vilazodone (**Table 1**); 32 subjects were evaluated for the PK analysis

Table 1. Demographics and Baseline Characteristics (Safety Population)

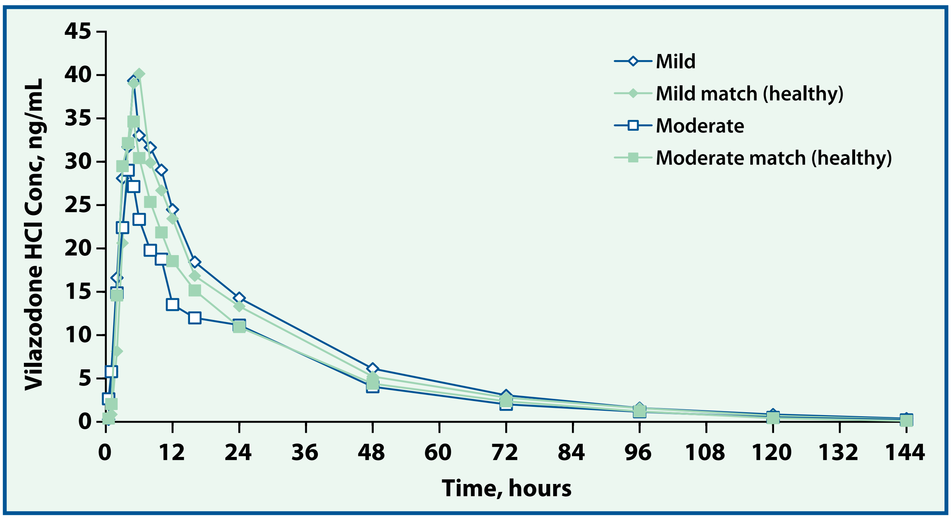
	Mild Hepatic Impairment		Moderate Hepatic Impairment	
Parameter	Mild n = 8	Healthy Match n = 9	Moderate n = 8	Healthy Match n = 8
Age, y				
Mean (SD)	48.5 (6.2)	44.3 (7.9)	57.8 (2.2)	55.3 (5.8)
Median (range)	50 (39-55)	45 (29- 53)	57 (54- 60)	56 (47- 64)
Sex, n (%)				
Male	5 (62.5)	6 (66.7)	6 (75.0)	6 (75.0)
Female	3 (37.5)	3 (33.3)	2 (25.0)	2 (25.0)
Race, n (%)				
White	4 (50.0)	8 (88.9)	8 (100.0)	6 (75.0)
Black	4 (50.0)	1 (11.1)	0 (0)	2 (25.0)
Height, cm				
Mean (SD)	172.4 (9.6)	175.6 (4.9)	175.5 (8.9)	171.4 (7.5)
Median (range)	170.0 (163-188)	176.0 (168-183)	174.5 (165-188)	173.0 (155-180)
Weight, kg				
Mean (SD)	80.6 (15.6)	85.3 (15.1)	83.5 (16.2)	80.5 (13.8)
Median (range)	79.5 (58-112)	86.0 (62-109)	84.5 (66-110)	79.0 (65-111)
BMI, kg/m²				
Mean (SD)	27.1 (3.8)	27.7 (4.8)	27.0 (5.0)	27.4 (4.4)
Median (range)	27.5 (22-32)	27.0 (21-36)	25.0 (23-38)	26.5 (24-38)
Serum albumin, g/dL				
Mean (SD)	3.9 (0.5)	4.5 (0.3)	3.4 (0.6)	4.3 (0.2)
Median (range)	4.1 (3.0-4.5)	4.5 (3.9-4.9)	3.4 (2.5-4.3)	4.2 (4.1-4.7)
Child-Pugh score				
Mean (SD)	5.4 (0.5)		7.8 (0.7)	
Median (range)	5.0 (5.0-6.0)		8.0 (7.0-9.0)	

BMI, body mass index.

Pharmacokinetic Parameters in Hepatically Impaired Subjects Compared With Healthy Subjects

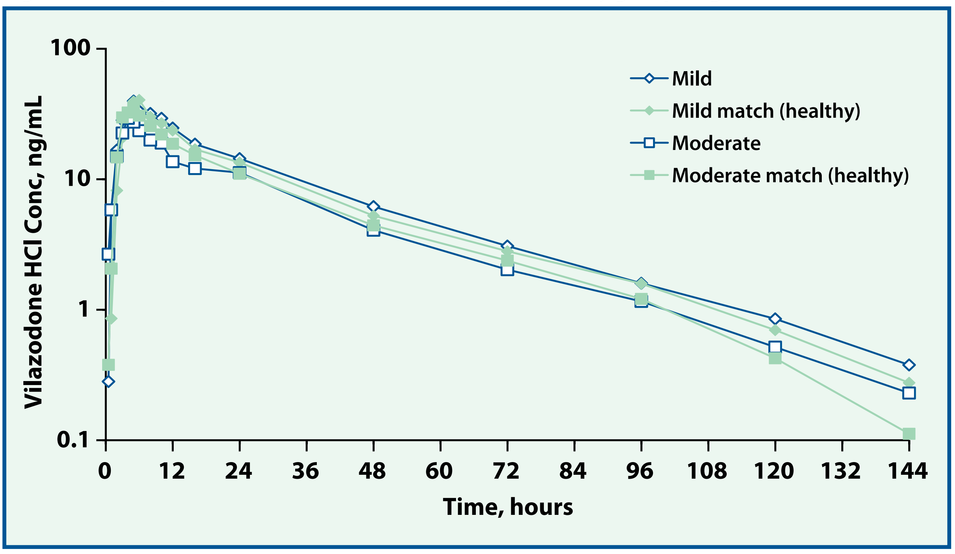
- Mean plasma vilazodone concentration-time profiles were similar between subjects with mild or moderate hepatic impairment and their matched healthy controls (**Figures 1** and **2**)

Figure 1. Mean plasma vilazodone concentration profile, by group (linear scale).



Conc, concentration; HCl, hydrochloride.

Figure 2. Mean plasma vilazodone concentration profile, by group (log-linear scale).



Conc, concentration; HCl, hydrochloride.

- Mean $C_{max,}$ T_{max}, AUC, $t_{½}$, oral clearance, and Au were each similar between hepatic impaired and healthy subjects (**Table 2**)

Table 2. Vilazodone PK Parameters (PK Population)

Parameter	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Mild n = 8	Healthy Match n = 8	Moderate n = 8	Healthy Match n = 8
C_{max}, ng/mL				
Mean (SD)	44.1 (16.5)	43.1 (13.1)	34.2 (8.2)	35.8 (10.7)
Median (range)	43.8 (14.3-69.8)	39.9 (28.2-63.1)	35.2 (22.4-45.3)	38.3 (17.9-48.7)
CV, %	37.4	30.3	23.9	29.9
T_{max}, h				
Mean (SD)	4.63 (1.60)	5.00 (1.51)	4.13 (1.81)	4.88 (0.84)
Median (range)	4.50 (3.00-8.00)	5.00 (3.00-8.00)	4.00 (2.00-8.00)	5.00 (4.00-6.00)
CV, %	34.6	30.2	43.8	17.1
AUC_{0-24}, ng·h/mL				
Mean (SD)	537 (249)	501 (121)	370 (70)	446 (123)
Median (range)	506 (166-1030)	498 (371-722)	378 (269-492)	442 (259-609)
CV, %	46.3	24.2	19.0	27.5
AUC_{0-t}, ng·h/mL				
Mean (SD)	984 (505)	898 (168)	683 (190)	768 (229)
Median (range)	907 (280-1940)	891 (665-1240)	650 (421-938)	708 (420-1110)
CV, %	51.3	18.7	27.9	29.9
$AUC_{0-\infty}$, ng·h/mL				
Mean (SD)	1030 (506)	945 (169)	727 (196)	809 (231)
Median (range)	961 (305-1980)	952 (714-1290)	695 (471-1020)	753 (448-1160)
CV, %	49.2	17.9	26.9	28.6
λ_z, 1/h				
Mean (SD)	0.0243 (0.0070)	0.0280 (0.0061)	0.0265 (0.0093)	0.0286 (0.0067)
Median (range)	0.0223 (0.0170-0.0356)	0.0278 (0.0189-0.0380)	0.0264 (0.0130-0.0448)	0.0259 (0.0214-0.0400)
CV, %	28.9	21.8	35.2	23.4
$t_{½}$, h				
Mean (SD)	30.6 (8.2)	25.9 (5.9)	29.4 (11.4)	25.4 (5.5)
Median (range)	31.3 (19.5-40.8)	25.1 (18.2-36.6)	26.4 (15.5-53.5)	27.0 (17.3-32.4)
CV, %	26.9	22.8	38.8	21.5
Vz/F, L				
Mean (SD)	1048 (493)	801 (183)	1176 (331)	948 (244)
Median (range)	1050 (335-1840)	821 (542-1110)	1155 (771-1680)	835 (721-1340)
CV, %	47.1	22.8	28.2	25.7
CL/F, L/h				
Mean (SD)	25.5 (17.3)	21.7 (3.7)	29.4 (8.0)	26.8 (8.7)
Median (range)	20.9 (10.1-65.6)	21.0 (15.5-28.0)	29.0 (19.7-42.5)	26.6 (17.3-44.7)
CV, %	68.1	17.0	27.1	32.5
Au, mg				
Mean (SD)	0.259 (0.169)	0.167 (0.096)	0.183 (0.105)	0.226 (0.108)
Median (range)	0.256 (0.033-0.452)	0.126 (0.073-0.354)	0.161 (0.050-0.407)	0.205 (0.094-0.452)
CV, %	65.0	57.4	57.3	47.9
Dose recovered in urine, %				
Mean (SD)	1.297 (0.845)	0.835 (0.479)	0.915 (0.525)	1.131 (0.541)
Median (range)	1.297 (0.165-2.260)	0.629 (0.366-1.770)	0.802 (0.252-2.040)	1.029 (0.470-2.260)
CV, %	65.1	57.3	57.4	47.9
CLr, L/h				
Mean (SD)	0.264 (0.136)	0.202 (0.123)	0.299 (0.206)	0.296 (0.091)
Median (range)	0.269 (0.039-0.451)	0.166 (0.061-0.448)	0.264 (0.077-0.743)	0.279 (0.164-0.418)
CV, %	51.6	61.1	68.9	30.9

- Vilazodone was extensively bound to plasma proteins, with mean free fraction of 1.59% to 1.64% in subjects with mild to moderate hepatic impairment and 0.99% in healthy subjects (**Table 3**)
- The observed ranges in vilazodone free fraction for the 3 groups of subjects were similar, suggesting there were no substantial differences in protein binding among the hepatic impaired and healthy groups
  - — Oral clearance was not affected by mild or moderate hepatic impairment, supporting that free fraction was not altered with mild or moderate hepatic impairment, or was not critical to vilazodone clearance

Table 3. PK Parameters Related to Vilazodone and Protein Binding (PK Population)

	Mild Hepatic Impairment	Moderate Hepatic Impairment	Healthy
Mean f_p, %	n = 8	n = 8	n = 8
Mean (SD)	1.590 (0.767)	1.635 (0.361)	0.985 (0.644)
Median (range)	1.645 (0.630-2.670)	1.600 (1.050-2.210)	0.790 (0.610-2.550)
CV, %	48.2	22.1	65.4
CLu/F, L/h	n = 8	n = 8	n = 4
Mean (SD)	1719 (798)	1879 (681)	2583 (634)
Median (range)	1650 (823-3090)	1610 (1080-3060)	2710 (1750-3160)
CV, %	46.4	36.2	24.5

- Mean serum albumin levels at baseline were 3.9 g/dL and 3.4 g/dL in mild and moderate impairment groups, respectively, and 4.3 to 4.5 g/dL in healthy subjects. These mean values were within the normal range (3.4-4.5 g/dL)
- Ratios of vilazodone C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for both hepatic impairment groups compared with their healthy matches were similar (**Table 4**)

Table 4. Vilazodone PK Comparisons Between Impaired and Healthy Match Groups (PK Population)

Comparison	Ratio	90% CI
C_{max}		
Mild/healthy match	0.978	0.724, 1.323
Moderate/healthy match	0.972	0.719, 1.314
AUC_{0-t}		
Mild/healthy match	0.977	0.713, 1.338
Moderate/healthy match	0.895	0.653, 1.226
$AUC_{0-\infty}$		
Mild/healthy match	0.980	0.724, 1.326
Moderate/healthy match	0.905	0.669, 1.225

- The 90% CIs for these PK parameters are outside the 0.80 to 1.25 range normally designated as proving bioequivalence (**Table 4**), most likely because of the small number of subjects

Safety

- All TEAEs were mild to moderate in intensity (**Table 5**); there were no SAEs
- No subject discontinued because of a TEAE

Table 5. Incidence of TEAEs Occurring in More than 1 Subject by Preferred Term (Safety Population)

	Subjects, n (%)			
	Mild Hepatic Impairment		Moderate Hepatic Impairment	
Preferred Term[a]	Mild n = 8	Healthy Match n = 9	Moderate n = 8	Healthy Match n = 8
Diarrhea	5 (62.5)	1 (11.1)	2 (25.0)	2 (25.0)
Dizziness	1 (12.5)	1 (11.1)	3 (37.5)	1 (12.5)
Nausea	1 (12.5)	2 (22.2)	1 (12.5)	1 (12.5)
Headache	0	0	1 (12.5)	1 (12.5)
Back pain	1 (12.5)	0	1 (12.5)	0

[a] Subjects might have reported more than 1 event per preferred term.

- No clinically significant changes in laboratory parameters were noted in any group
- Mean changes from baseline in vital signs were small, similar among groups, and not considered clinically significant (**Table 6**)
- No clinically significant abnormalities were noted on 12-lead ECGs

Table 6. Blood Pressure and Pulse at Baseline and Change From Baseline at 4 Hours After Dose and EOS/ET (Safety Population)

Parameter	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Mild n = 8	Healthy Match n = 8	Moderate n = 8	Healthy Match n = 8
SBP, mm Hg				
Baseline				
Mean (SD)	114.3 (10.1)	125.1 (14.0)	124.0 (16.0)	119.9 (16.4)
Median (range)	114.5 (102.0-129.0)	121.0 (100.0-143.0)	133.0 (98.0-138.0)	121.5 (98.0-140.0)
4 Hours after dose[a]				
Mean (SD)	1.8 (4.0)	–7.4 (11.3)	0.0 (10.9)	–7.9 (13.9)
Median (range)	3.0 (–6.0-5.0)	–3.0 (-30.0-6.0)	0.5 (–17.0-16.0)	–7.5 (–31.0-10.0)
EOS/ET[a]				
Mean (SD)	7.0 (7.5)	0.2 (9.4)	0.1 (12.0)	0.4 (12.9)
Median (range)	8.5 (–6.0-15.0)	–1.0 (–11.0-19.0)	1.0 (–26.0-13.0)	4.0 (–27.0-15.0)
DBP, mm Hg				
Baseline				
Mean (SD)	71.2 (9.9)	72.3 (9.4)	74.3 (6.8)	75.1 (11.5)
Median (range)	72.5 (58.0-85.0)	74.0 (51.0-82.0)	77.0 (63.0-82.0)	73.5 (62.0-95.0)
4 Hours after dose[a]				
Mean (SD)	–1.8 (6.3)	–1.3 (4.4)	0.3 (4.2)	–7.4 (12.4)
Median (range)	–2.5 (–10.0-8.0)	–1.0 (–9.0-6.0)	0.5 (–7.0-8.0)	–5.5 (–27.0-8.0)
EOS/ET[a]				
Mean (SD)	7.0 (7.5)	1.9 (6.1)	2.5 (7.7)	–0.8 (6.9)
Median (range)	10.0 (–8.0-12.0)	4.0 (–8.0-11.0)	0.0 (–4.0-20.0)	–0.5 (–12.0-10.0)
Pulse, bpm				
Baseline				
Mean (SD)	68.7 (11.2)	71.0 (9.1)	68.6 (9.6)	68.4 (11.9)
Median (range)	71.0 (54.0-82.0)	70.0 (57.0-89.0)	68.5 (56.0-86.0)	63.0 (56.0-91.0)
4 Hours after dose[a,b]				
Mean (SD)	–4.8 (5.3)	–1.9 (8.7)	–1.3 (8.2)	–4.9 (7.9)
Median (range)	–4.5 (–14.0-2.0)	–1.0 (–14.0-13.0)	–1.0 (–12.0-12.0)	–2.0 (–22.0-2.0)
EOS/ET[a,b]				
Mean (SD)	–4.7 (10.2)	0.6 (11.9)	4.8 (6.5)	3.8 (9.3)
Median (range)	–3.5 (–20.0-11.0)	–4.0 (–12.0-22.0)	6.5 (–8.0-13.0)	4.5 (–11.0-19.0)

bpm, beats per minute; DBP, diastolic blood pressure; EOS/ET, end of study/early termination; SBP, systolic blood pressure.
[a] Mean change from baseline.
[b] n = 6.

Conclusions

- Vilazodone PK after a single 20 mg oral dose was not substantially different in subjects with mild or moderate hepatic impairment compared with matched healthy subjects with normal hepatic function
  - — Observed differences were small and unlikely to be clinically relevant
- Mild or moderate hepatic impairment was not associated with any pattern of increased incidence of TEAEs or clinically significant changes in laboratory values, vital signs, or ECG parameters, compared with subjects with normal hepatic function
- These findings suggest that no dose adjustment of vilazodone would be required for patients with mild or moderate hepatic impairment

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