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Impact of Paroxetine, a Strong CYP2D6 Inhibitor, on SPN-812 (Viloxazine Extended-Release) Pharmacokinetics in Healthy Adults

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Abstract

SPN-812 (viloxazine extended-release) is a novel nonstimulant recently approved as a treatment for attention-deficit/hyperactivity disorder in children and adolescents. Given that SPN-812 is metabolized by CYP2D6 and may be coadministered with CYP2D6 inhibitors, this trial investigated the pharmacokinetics and safety of SPN-812 coadministered with the potent CYP2D6 inhibitor paroxetine. In this single-sequence, 3-treatment period study in healthy volunteers, subjects received a single oral dose of 700 mg SPN-812 alone (period 1), 20 mg daily paroxetine (10 days, period 2), followed by concurrent administration of SPN-812 and paroxetine (period 3). Blood samples were collected for 72 hours post-SPN-812 dosing and analyzed for viloxazine and its primary metabolite, 5-HVLX-gluc. Twenty-two healthy adults were enrolled; all completed the trial. The potential for drug interaction between SPN-812 and paroxetine was assessed using analysis of variance on the log-transformed pharmacokinetic parameters C_{max}, $AUC_{0\text{-}t}$, and AUC_{inf}. The least-squares geometric mean ratios for viloxazine were (reported as the ratio of combination/SPN-812 alone) C_{max}, 116.04%; 90%CI, 109.49%-122.99%; $AUC_{0\text{-}t}$, 134.65%; 90%CI, 127.65-142.03; and AUC_{inf}, 134.80%; 90%CI, 127.94%-142.03%. CYP2D6 inhibition resulted in a modest change (<35%) on viloxazine AUCs with no change in C_{max}. All adverse events were mild in severity.

Keywords

attention-deficit/hyperactivity disorder, CYP2D6, paroxetine, pharmacokinetics, SPN-812, viloxazine

Viloxazine was originally approved in Europe as an antidepressant in 1974 and marketed for 28 years before being discontinued in the early 2000s (for reasons unrelated to safety or efficacy).[1] A novel extended-release version of viloxazine, SPN-812, has recently been approved by the U.S. Food and Drug Administration as a nonstimulant treatment for attention deficit/hyperactivity disorder (ADHD) in children and adolescents.[2–6] Recent in vitro and in vivo animal studies have elucidated a multimodal mechanism of action, with demonstrated activity on norepinephrine and serotonin.[7]

A recent study of viloxazine describing its structure (and that of its metabolites) demonstrated that its primary metabolic route in humans is through 5-hydroxylation followed by glucuronidation.[8] Based on in vitro data from this study, the major enzyme contributing to the formation of 5-hydroxyviloxazine is cytochrome isoenzyme P450 (CYP) 2D6, with minor involvement of CYP1A2, CYP2B6,

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This trial was conducted in accordance with the Helsinki Declaration and the International Council for Harmonization Note for Guidance on Good Clinical Practice. The trial conduct was reviewed and approved by IntegReview Institutional Review Board (Austin, Texas). Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data.

CYP2C9, CYP2C19, and CYP3A4, with subsequent glucuronidation to 5-hydroxyviloxazine glucuronide (5-HVLX-gluc) mediated by uridine 5′-diphosphoglucuronosyltransferase (UGT) 1A9 and UGT2B15. This study also demonstrated that viloxazine is an inhibitor of CYP1A2 (reversible inhibition IC_{50}, 0.269 μM; time-dependent inhibition IC_{50}, 0.0436 μM after 30 minute preincubation with nicotinamide adenine dinucleotide phosphate), and, to a much lesser extent, CYP2B6, CYP2D6, and CYP3A4/5 (with IC_{50} values of 184, 141, 221, and 352 μM, respectively), but not CYP2C8, CYP2C9, or CYP2C19 (all IC_{50} values > 1010 μM).[8]

Paroxetine is a selective serotonin reuptake inhibitor (SSRI)[9] with currently approved indications for the treatment of depression, obsessive compulsive disorder, panic disorder, anxiety disorders, and posttraumatic stress disorder. It is rapidly absorbed, undergoes extensive first-pass metabolism, and is both a substrate and potent inhibitor of CYP2D6.[10] In addition to having one of the highest-known affinities for the serotonin transporter ($K_d < 1$ nM), paroxetine has the highest inhibitory constant among any currently used antidepressant ($K_i = 0.065$-4.65 μM).[10–16] It has an elimination half-life ($t_{1/2}$) of 21 hours, with steady-state generally achieved after 7-14 days of once-daily dosing.[17]

Because it is a strong CYP2D6 inhibitor, paroxetine is commonly used to assess the potential for drug-drug interactions (DDIs) in clinical research, with daily dosing over multiple days used to ensure steady-state[17] and full CYP2D6 inhibition.[13,18,19] Because the half-life of CYP2D6 is ≈46–51 hours, based on in vitro data, the time-dependent inhibition of paroxetine toward CYP2D6-mediated biotransformation of viloxazine is likely to be a significant contributor to impeding viloxazine clearance.[20] Consequently, the clinical drug interaction mediated by CYP2D6 is a composite of the competitive (reversible) inhibition of 2D6 (IC_{50}, 2.54 μM) and the time-dependent (irreversible) inhibition of CYP2D6 (IC_{50}, 0.34 μM).[20] Because of the intransigent binding and the modified IC_{50} shift following preincubation, the observed drug interaction is most likely the result of time-dependent inhibition, more so than reversible inhibition.

The purpose of the current study was to evaluate if CYP2D6 inhibition might impact the pharmacokinetics (PK) of SPN-812. Because mood disorders such as depression are thought to co-occur in 20%-45% of patients with ADHD,[21–23] the evaluation of potential DDIs between SPN-812 and SSRIs—many of which are CYP inhibitors[10]—may have direct clinical safety and efficacy implications for patients. Therefore, using clinically relevant doses, the PK of a single dose of SPN-812 alone and SPN-812 coadministered with multiple doses of paroxetine was assessed in healthy adults with CYP2D6 extensive metabolizer (ie, normal) phenotypes. Safety was also evaluated.

Methods

Study Design Overview

This study was approved by IntegReview Institutional Review Board (Austin, Texas), and conducted in agreement with the Helsinki Declaration and the International Council for Harmonization Note for Guidance on Good Clinical Practice. Subjects provided written informed consent. The trial was conducted by Worldwide Clinical Trials, Early Phase Services, LLC (San Antonio, Texas).

This was a single-center open-label, 1-sequence, 3-treatment-period study in healthy adults. This study evaluated the PK of single-dose SPN-812 before and after coadministration with multiple doses of paroxetine. Subjects received each of the treatments in a single standardized sequence (Figure 1). Within 28 days of screening, subjects were admitted to the clinic on day −1 (entry day) to confirm eligibility prior to enrollment on day 1 of period 1. During 1 continuous 17-day clinic residency, subjects received treatment across 3 different treatment periods: SPN-812 alone (period 1, days 1-3), paroxetine alone (period 2, days 4-13), and combination paroxetine and SPN-812 (period 3, days 14-16); see the Treatments section, below, for details.

After a baseline blood draw on day −1 in period 1, subjects received a single dose of SPN-812, and blood samples for SPN-812 PK were collected starting on day 1 for 72 hours (see Sample Collection section, below). In period 2, subjects received a single dose of paroxetine each morning at the same time for a total of 10 doses (20 mg once daily). In period 3, paroxetine dosing continued as in period 2 for study days 14-16. On day 14, SPN-812 was administered 30 minutes after paroxetine dosing. Blood samples for SPN-812 PK were collected for 72 hours post-SPN-812 dosing (study days 14-16). End-of-study (EOS) procedures were completed at the end of period 3 (study day 17) or prior to study discontinuation in the case of early withdrawal and discharge.

Study Subjects

Healthy adult subjects between 18 and 55 years of age were recruited for the trial. Inclusion criteria required subjects to be nonsmokers, CYP2D6 extensive-metabolizer phenotypes, with a body mass index (BMI) of 18-30 kg/m^2 (inclusive). Women of childbearing ability had to be using acceptable birth control or be abstinent. Exclusion criteria have been described in detail elsewhere.[24,25]

To assess CYP2D6 metabolizer status, an oral buccal swab was used to collect DNA to be later extracted

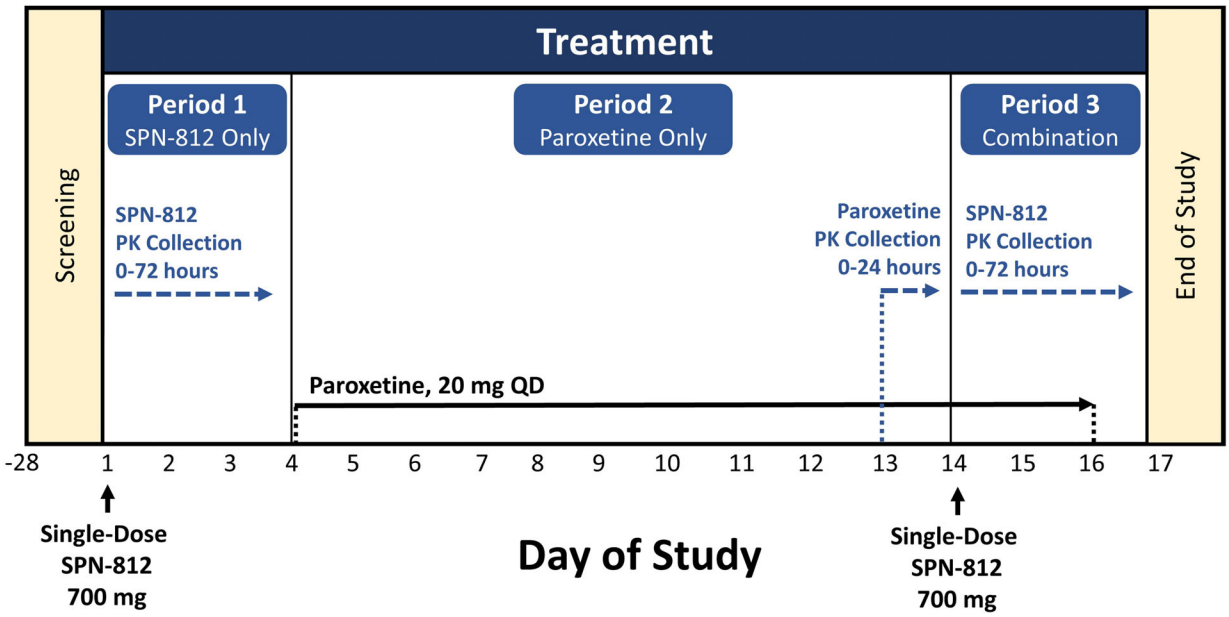

Figure 1. Study schematic. Sequence of the trial with 3 treatment periods: period 1, single-dose SPN-812 only; period 2, multiple daily doses of paroxetine; period 3, single-dose SPN-812 + daily doses of paroxetine. PK, pharmacokinetic; QD, once daily.

for genetic analysis to determine the CYP2D6 single-nucleotide polymorphism. DNA extraction and genotyping were performed by Worldwide Clinical Trials. Only CYP2D6 extensive (ie, normal enzyme activity) metabolizers were enrolled in the study; ultrarapid, extensive-intermediate, intermediate, or poor metabolizers were not included.

Treatments

Subjects received SPN-812 and paroxetine over 3 treatment periods (Figure 1): in period 1, day 1, subjects received a single oral dose of 700 mg SPN-812; in period 2 (days 4-13), subjects received once-daily oral doses of 20 mg paroxetine; in period 3 (days 14-16), subjects continued once-daily dosing of 20 mg paroxetine and, on day 14 only, received a single oral dose of 700 mg SPN-812 30 minutes after the paroxetine dose. Daily 20 mg paroxetine continued for days 15 and 16.

The 700 mg SPN-812 dose used in the present study was based on prior usage in children, adolescents, and adults. SPN-812 has been evaluated for treatment of ADHD at doses of 100-400 mg in children 6-11 years of age[3,4] and 200-600 mg in adolescents 12-17 years of age,[5,6] and 700 mg has been previously used to assess the potential for DDIs in healthy adults.[24,25] Thus, this trial used 700 mg SPN-812 to safely assess the potential for DDIs at concentrations likely to be used in a clinical setting. The present study administered paroxetine using a therapeutic dose of 20 mg once daily, as this dosage has been previously used to assess CYP2D6 inhibition in healthy adult subjects,[11,13] administered over 10 days to ensure steady-state[17] and full CYP2D6 inhibition.[13,18,19]

Treatment was orally administered after an overnight fast of a minimum of 10 hours, with fasting continuing for at least 4 hours after dosing during periods 1 and 3. During the repeated paroxetine dosing of period 2 in day 4 through day 12, a postdose fast of 2 hours was allowed. Only 240 mL of water was allowed at the time of dosing; otherwise, fluid was restricted 1 hour before and after dosing to minimize absorption variability. For the duration of the study, participants were limited or prohibited from consuming the following foods or beverages through EOS: alcohol-based products, products containing xanthine derivatives or xanthine-related compounds (eg, caffeine), or energy drinks, garlic supplements, pomelo, grapefruit, and food containing poppy seeds (for details, see prior publications[24,25]).

Sample Collection

Sample collection procedures have been previously described.[25] Briefly, blood samples for viloxazine PK were collected in period 1 (days 1-4) and period 3 (days 14-17) and were collected relative to SPN-812 administration at predose (baseline, time 0) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, 60, and 72 hours postdose. The actual time and date of each blood sample collection was recorded. As an alternative procedure to multiple blood draws, a catheter may have been inserted into the arm if judged necessary by the Investigator. Each blood sample for PK was collected in a 4-mL K_2-ethylenediaminetetraacetic acid (purple-top) tube and gently inverted 8-10 times. Blood samples were then centrifuged at 3000 rpm for 10 minutes at ≈4°C

within 30 minutes of blood collection. The resulting plasma was aliquoted in approximately equal amounts into 2 appropriately labeled 3-mL polypropylene screw-cap tubes. Samples were frozen in an upright position at approximately −70°C within 60 minutes of blood collection pending analysis.

Bioanalytical Methods

Plasma concentrations of viloxazine, 5-HVLX-gluc (viloxazine's active metabolite), and steady-state paroxetine were quantified using validated liquid chromatographic-tandem mass spectrometry (LC-MS/MS). Bioanalytical methods for viloxazine and 5-HVLX-gluc have been previously published.[24,25] The plasma bioanalysis of paroxetine was performed at Worldwide Clinical Trials, using a proprietary LC-MS-MS method validated for paroxetine. Study samples were analyzed on a Sciex API 4000 equipped with Agilent Technologies, Pursuit Diphenyl 3-µm, 4.6 × 50 mm high-pressure liquid chromatography column using Analyst (version 1.6.1; Applied Biosystems/MDS Sciex, Framingham, Massachusetts) and Watson Laboratory Information Management System (version 7.2.0.03; Thermo Fisher Scientific, Waltham, Massachusetts) software.

Plasma samples were analyzed for paroxetine using a method validated for a range of 0.100-60.0 ng/mL based on the analysis of 0.200 mL of plasma. Human plasma samples containing paroxetine and the stable isotope-labeled internal standard, namely, paroxetine-D6, were extracted by liquid-liquid extraction, after basification of plasma with 1.0 M ammonium hydroxide (aqueous) and the addition of cyclohexane/ethyl acetate (1:4) as organic solvents. After swirl-mixing well and centrifugation of the samples, the organic phase was carefully transferred into clean tubes and evaporated under a stream of N2 at 40°C. The dried residues were reconstituted in the mobile phase, namely, acetonitrile/methanol/water/acetic acid/ammonium hydroxide (300:200:400:3:0.5). The peaks of interest were eluted under isocratic conditions on a diphenyl column, and the column effluent monitored under multiple reaction monitoring on an API 4000 under atmospheric pressure chemical ionization (heated nebulizer). The peak area of m/z 330→192 was monitored for paroxetine and the peak area of the m/z 336→198 for paroxetine-D6. Quantitation was performed using a weighted $1/\times^2$ linear least-squares regression analyses generated from calibration standards.

Pharmacokinetic Analyses

The analyses compared the PK profiles of single doses of SPN-812 with and without multiple doses of paroxetine. The primary outcome measure was the relative bioavailability of viloxazine with and without paroxetine, as evaluated by the area under the concentration–time curve from time 0 to the last measurable concentration time ($AUC_{0\text{-}t}$), area under the concentration–time curve from time 0 to infinity (AUC_{inf}), and maximum observed plasma concentration (C_{max}). Secondary outcomes were to assess the PK of viloxazine and 5-HVLX-gluc using the following measures: C_{max}, $AUC_{0\text{-}t}$, AUC_{inf}, time to reach maximum concentration (T_{max}), and $t_{1/2}$. Another secondary outcome was to describe the PK of paroxetine at steady state ($_{ss}$) using AUC over the 24-hour dosing interval (AUC_{tau}), $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, and the average plasma concentration ($C_{avg,ss}$). Calculation of the 5-HVLX-gluc-to-viloxazine (metabolite-to-parent) ratios for C_{max}, $AUC_{0\text{-}t}$, and AUC_{inf}; ratios was adjusted based on the molecular weights of viloxazine (237 g/mol) and 5-HVLX-gluc (429 g/mol).

The concentration-time data for viloxazine, 5-HVLX-gluc, and paroxetine were analyzed using standard noncompartmental methods in Phoenix WinNonlin (version 8.1; Certara, L.P., Princeton, New Jersey) in conjunction with internet-accessible implementation of Pharsight Knowledgebase ServerTM (version 4.0.4; Certara, L.P.). During the PK analysis, viloxazine, 5-HVLX-gluc, and paroxetine plasma concentrations that were below the limit of quantification (BLQ) were treated as 0 from time 0 to the time at which the first quantifiable concentration was observed; embedded and terminal BLQ values were treated as missing. Actual sample times were used for PK and statistical analyses. PK results were summarized by analyte, period, and day using descriptive statistics including n, arithmetic mean, standard deviation, median, and coefficient of variation (CV). Geometric means were used for calculations of bioavailability.

Statistical Analyses

The potential for the strong CYP2D6 inhibitor paroxetine to impact the metabolism of SPN-812 was evaluated using analysis of variance on log-transformed PK parameters: C_{max}, $AUC_{0\text{-}t}$, and AUC_{inf}. The least-squares mean (LS mean), the difference in the LS means, and the 2-sided 90% confidence intervals (CIs) for each of the SPN-812 collections (period 1 and period 3) were calculated in natural logarithmic scale. These results from the natural log-transformed data were transformed back to the original scale by exponentiation to obtain the 90%CIs for the geometric LS mean ratios, calculated as combination paroxetine with SPN-812 (period 3)/SPN-812 alone (period 1). The absence of a DDI was indicated if the 90%CIs for the ratios were contained within the predefined no-difference limits of 80.0% to 125.0% for C_{max}, $AUC_{0\text{-}t}$, and AUC_{inf} for viloxazine and 5-HVLX-gluc.

The CV for the geometric LS means was calculated for inter- and intrasubject variability. For the comparison of SPN-812 alone versus the com-

bination, intersubject variability was calculated as: (sqrt[exp(covariance for subject[sequence] of the log-transformed data-1)]) × 100; intrasubject variability was calculated as: (sqrt[exp(covariance for residual of the log-transformed data) – 1]) × 100.

Safety Monitoring and Assessments

Baseline measurements included vital signs, physical examination, medical history, clinical laboratory tests (ie, serum chemistry, complete blood count, urinalysis), and the Columbia-Suicide Severity Rating Scale (C-SSRS) suicidality assessment. Vital signs (diastolic/systolic blood pressure, pulse rate, respiratory rate, and temperature) were assessed at screening, entry, 5 hours postdosing, and EOS. Blood pressure and heart rate were taken after the subject had been sitting or supine for a minimum of 5 minutes. Clinical laboratory tests occurred at screening, entry (day −1), and EOS. A single 12-lead electrocardiogram (ECG) was performed while the subject was supine for at least 10 minutes at screening, the end of period 1, the end of period 2, and at EOS. The C-SSRS was administered during screening, end of period 1, end of period 2, and EOS. Assessments were performed as scheduled or at any time deemed necessary by the investigator. Adverse events (AEs) were monitored for the duration of treatment. Safety and tolerability data are summarized using descriptive statistics.

Results

Subject Demographics

Of 79 adults screened for the study, 57 were not eligible (screen failures); thus, 22 healthy adult subjects (15 men, 7 women) were enrolled. Subjects were 38.6 ± 11.1 years (mean ± standard deviation [SD]; range, 22-55 years) and had a BMI of 26.18 ± 2.85 kg/m^2 (mean ± SD), and 54.5% of subjects were Black or African American and 45.5% were white. All 22 subjects completed the study having received all doses of both study drugs.

Descriptive Pharmacokinetics of Viloxazine, 5-HVLX-gluc, and Paroxetine

PK parameters for viloxazine are listed in Table 1, and plasma concentrations over time are shown in Figure 2. Multiple doses of paroxetine administered in combination with a single dose of SPN-812 resulted in an increase in viloxazine exposure as measured by AUCs. Although mean viloxazine C_{max} and $t_{1/2}$ were similar across treatment periods, median viloxazine T_{max} was slightly delayed by ≈1 hour after the combination (T_{max}, 6 hours) compared with that after SPN-812 alone (T_{max}, 5 hours).

PK parameters for 5-HVLX-gluc are listed in Table 2, and plasma concentrations over time are shown

Table 1. Summary of Viloxazine Plasma Pharmacokinetic Parameters

Parameter	SPN-812 Alone[a] (Period 1)	Combination[b] (Period 3)
T_{max} (h)	5.0 (4.0-8.0)	6.0 (4.0-12.0)
C_{max} (μg/mL)	4.2 ± 0.8 (19.7%)	4.9 ± 0.8 (16.9%)
$AUC_{0\text{-}t}$ (μg·h/mL)	84.0 ± 22.9 (27.3%)	112.0 ± 23.9 (21.5%)
AUC_{inf} (μg·h/mL)	84.9 ± 22.8 (26.8%)	113.0 ± 23.9 (21.2%)
$t_{1/2}$ (h)	5.2 ± 2.3 (44.4%)	6.0 ± 1.6 (26.2%)

$AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last measurable time; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum measured plasma concentration; CV%, coefficient of variation; h, hours; PK, pharmacokinetics; QD, once daily; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time of the maximum measured plasma concentration .

All data reported as mean ± SD (CV%), except T_{max}, which is reported as median (range).

[a] SPN-812 alone: single-dose SPN-812 (700 mg); PK samples collected for 72 hours beginning on day 1.

[b] Combination: single-dose SPN-812 (700 mg) + paroxetine once daily (20 mg); PK samples collected for 72 hours beginning on day 14.

Table 2. Summary of 5-HVLX-gluc Plasma Pharmacokinetic Parameters

Parameter	SPN-812 Alone[a] (Period 1)	Combination[b] (Period 3)
T_{max} (h)	7.0 (5.0-12.0)	10.0 (5.0-12.0)
C_{max} (μg/mL)	3.5 ± 0.8 (24.2%)	2.9 ± 0.7 (24.6%)
$AUC_{0\text{-}t}$ (μg·h/mL)	70.5 ± 19.6 (27.8%)	62.1 ± 16.1 (25.9%)
AUC_{inf} (μg·h/mL)	70.7 ± 19.7 (27.9%)	62.3 ± 16.1 (25.8%)
$t_{1/2}$ (h)	5.7 ± 1.7 (29.6%)	6.4 ± 2.0 (32.0%)
Metabolite-to-parent (5-HVLX-gluc to viloxazine) ratios[c]		
MPR C_{max}	0.47 ± 0.12 (27.4%)	0.33 ± 0.06 (19.2%)
MPR $AUC_{0\text{-}t}$	0.49 ± 0.15 (31.1%)	0.31 ± 0.08 (25.2%)
MPR AUC_{inf}	0.48 ± 0.15 (31.5%)	0.31 ± 0.08 (25.1%)

$AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last measurable time; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum measured plasma concentration; CV%, coefficient of variation; h, hours; MPR, metabolite-to-parent ratio; PK, pharmacokinetics; QD, once daily; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time of the maximum measured plasma concentration.

All data reported as mean ± SD (CV%), except T_{max}, which is reported as median (range).

[a] SPN-812 alone: single-dose SPN-812 (700 mg); PK samples collected for 72 hours beginning on day 1.

[b] Combination: single-dose SPN-812 (700 mg) + paroxetine once daily (20 mg); PK samples collected for 72 hours beginning on day 14.

[c] Metabolite-to-parent ratios are adjusted based on the molecular weights of viloxazine (237) and 5-HVLX-gluc (429).

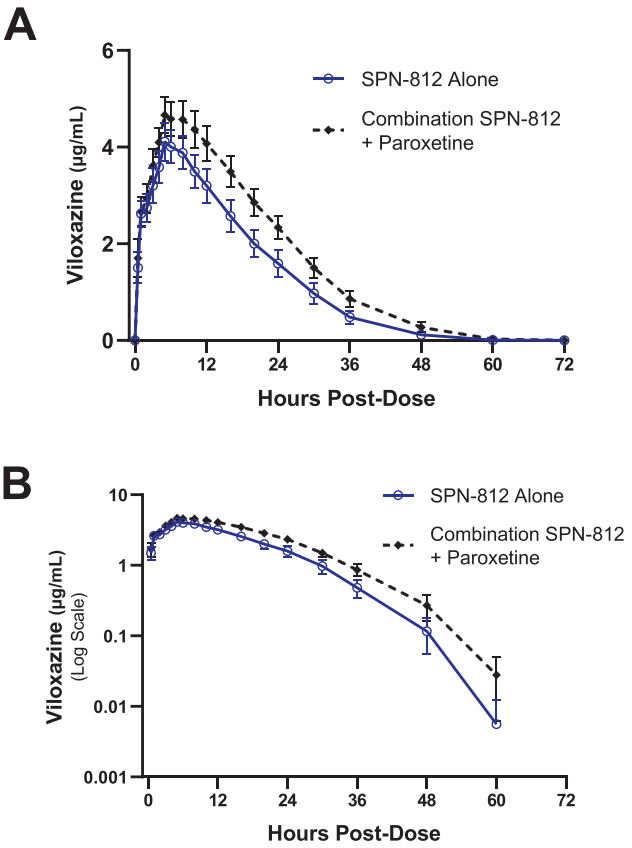

Figure 2. Viloxazine concentration-time profiles. Viloxazine concentration-time profiles after 700 mg SPN-812 alone (period 1, day 1; open circles) and combination 700 mg SPN-812 + 20 mg paroxetine once daily (period 3, day 14; black diamonds) on linear (A) and semilogarithmic (B) scales. Means ± 95% confidence intervals.

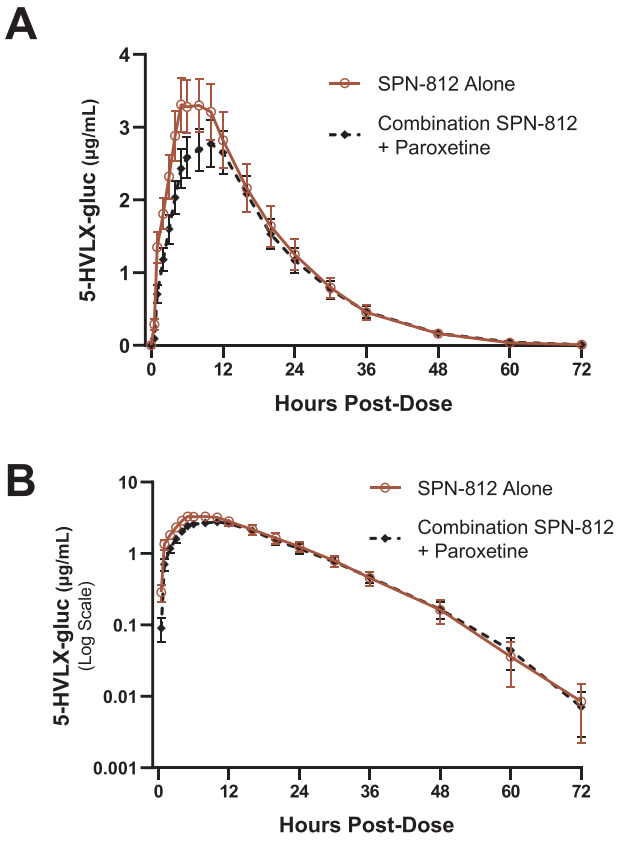

Figure 3. 5-HVLX-gluc concentration-time profiles. 5-HVLX-gluc concentration-time profiles after 700 mg SPN-812 alone (period 1, day 1; open circles) and combination 700 mg SPN-812 + 20 mg paroxetine once daily (period 3, day 14; black diamonds) on linear (A) and semilogarithmic (B) scales. Means ± 95% confidence intervals.

in Figure 3. Multiple doses of paroxetine administered in combination with a single dose of SPN-812 resulted in a decrease in overall 5-HVLX-gluc exposure (relative to SPN-812 alone). Although mean 5-HVLX-gluc $t_{1/2}$, $AUC_{0\text{-}t}$, and AUC_{inf} were similar across treatment periods, mean C_{max} was lower and median T_{max} was delayed by ≈3 hours after the combination (T_{max}, 10 hours) compared with that after SPN-812 alone (T_{max}, 7 hours). Minor differences in metabolite-to-parent ratios were observed across treatment periods, with mean ratios lower when SPN-812 was administered in combination with paroxetine, relative to SPN-812 administered alone (Table 2).

On day 13, after multiple daily doses of paroxetine, median T_{max} at steady state was 6.00 hours (range, 5.00-8.01 hours). Mean ± SD $C_{max,ss}$ and $C_{min,ss}$ were 39.0 ± 19.0 ng/mL (48.8% CV) and 22.3 ± 13.4 ng/mL (60.2% CV), respectively. Mean ± SD C_{avg} was 29.6 ± 15.7 ng/mL (53.2% CV), and mean ± SD AUC_{tau} was 709.0 ± 377.0 ng·h/mL (53.2% CV).

Statistical Comparison of Viloxazine and 5-HVLX-gluc Bioavailability With and Without Paroxetine Coadministration

Using the geometric means, the ratios (with 90%CIs) of the combination treatment divided by SPN-812 alone for viloxazine were C_{max}, 116.04% (90%CI, 109.49%-122.99%); $AUC_{0\text{-}t}$, 134.65% (90%CI, 127.65%-142.03%); and AUC_{inf}, 134.80% (90%CI, 127.94%-142.03%); see Table 3 and Figure 4. The 90%CI for viloxazine C_{max} (109.49-122.99) was fully contained within the predetermined no-difference limits of 80.0%-125.0%, but the 90%CIs for $AUC_{0\text{-}t}$ and AUC_{inf} were outside the limits (CIs for both parameters were ~127%-142%). The ratios (90%CIs) for 5-HVLX-gluc were C_{max}, 83.05% (78.52%-87.85%); $AUC_{0\text{-}t}$, 88.75% (84.20%-93.55%); and AUC_{inf}, 88.77% (84.20%-93.60%). The 90%CIs for 5-HVLX-gluc $AUC_{0\text{-}t}$ and AUC_{inf} (~84% to 94% for both parameters) were contained within the predetermined no-difference limits of 80.0% to 125.0%, but the lower-bound 90%CI for C_{max} (78.52%-87.75%) was below the limit.

Table 3. Relative Bioavailability of Viloxazine and 5-HVLX-gluc

Parameter	SPN-812 Alone[a] (Period 1)	Combination[b] (Period 3)	Ratio[c] (%)	90%CI
Viloxazine				
C_{max}	4.1	4.8	116.0	109.5-123.0
AUC_{0-t}	81.1	109.0	134.7	127.7-142.0
AUC_{inf}	82.0	111.0	134.8	127.9-142.0
5-HVLX-gluc				
C_{max}	3.4	2.8	83.1	78.5-87.9
AUC_{0-t}	67.8	60.1	88.8	84.2-93.6
AUC_{inf}	67.9	60.3	88.8	84.2-93.6

AUC_{0-t}, area under the concentration-time curve from time 0 to the last measurable time; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum measured plasma concentration; QD, once daily.
Values are the geometric means, based on least-squares means of log-transformed parameter values.
[a] SPN-812 alone: single-dose SPN-812 (700 mg); PK samples collected for 72 hours beginning on day 1.
[b] Combination: single-dose SPN-812 (700 mg) + paroxetine once daily (20 mg); PK samples collected for 72 hours beginning on day 14.
[c] Ratio (%): combination/SPN-812 alone (using geometric means).

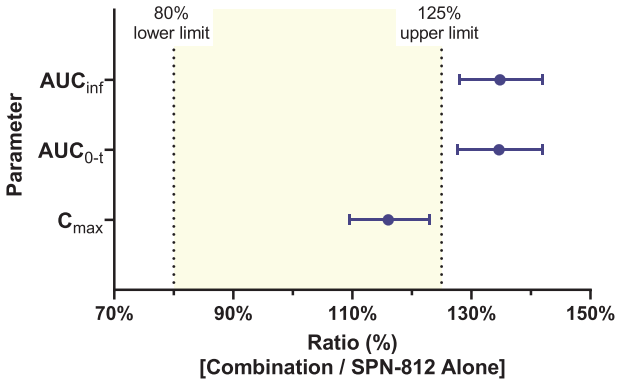

Figure 4. Relative bioavailability of plasma viloxazine. Ratio (%) of the relative bioavailability of viloxazine in plasma (geometric means ± 90% confidence intervals, based on least-squares means of log-transformed parameter values). Yellow-shaded area represents the predetermined no-difference limits of 80% to 125%.

Safety

All subjects who received at least 1 dose of study drug were included in the safety population (n = 22). All reported AEs were mild; there were no serious AEs, AEs that led to subject withdrawal, or deaths. A total of 12 subjects (54.5%) reported AEs over the course of the study. Six subjects (27.3%) reported AEs that were considered treatment related by the investigator: 2 (9.1%) during period 1 (SPN-812 alone), 3 (13.6%) during period 2 (paroxetine alone), and 2 (9.1%) during period 3 (after the combination); see Table 4. There were no clinically significant abnormal results for clinical laboratory test results, ECGs, vital signs (Figure 5), or physical examinations and no increase in suicidality as measured by the C-SSRS at EOS. Three subjects (13.6%) had normal ECG interpretation at baseline but had an abnormal ECG interpretation at EOS. All abnormal ECG results were evaluated as not clinically significant by the investigator. There were no AEs related to clinical laboratory test results.

Discussion

We report modest impact of the strong CYP2D6 inhibitor paroxetine on the PK of viloxazine and 5-HVLX-gluc after a single dose of SPN-812 in healthy adults with extensive (ie, normal) CYP2D6 phenotypes. Specifically, although the increase in viloxazine C_{max} after the combination (versus SPN-812 alone) was minimal (16%, with CIs well contained within the 80.0% to 125.0% no-difference limits), AUC_{0-t} and AUC_{inf} both increased by just under 35%, resulting in CIs falling outside the upper limit of 125.0% (Figure 4). However, paroxetine coadministration did not appear to significantly impact the PK of viloxazine's primary metabolite, 5-HVLX-gluc: AUC_{0-t} and AUC_{inf} decreased by only 12%, with CIs clearly contained within the predetermined no-difference limits, and C_{max} decreased by 17%, with the lower-bound 90%CI falling just outside the 80.0% limit (78.5%); see Table 3. Further, all treatments were safe and appeared to be well tolerated, with a low incidence of AEs and no reported serious AEs. The combination did not appear to increase the frequency or severity of reported AEs (Table 4) or alter vital signs such as blood pressure, heart rate, or respiration (Figure 5), relative to either SPN-812 alone or paroxetine alone.

Like many psychiatric drugs, SPN-812 has a metabolism that relies primarily on the CYP2D6 enzyme as its primary metabolic pathway, with minor involvement from CYP1A2, CYP2B6, CYP2C9, 2C19, and CYP3A4.[8] Of these CYP enzymes, CYP2D6 is thought to account for <50% of the formation of 5-hydroxyviloxazine, whereas subsequent glucuronidation to 5-HVLX-gluc is mediated by UGT1A9 and UGT2B15.[8] Thus, viloxazine metabolism does not rely

Table 4. Treatment-Related Adverse Events in Healthy Adult Subjects

	SPN-812 Alone (n = 22), n (%)	Paroxetine Alone (n = 22), n (%)	Combination (n = 22), n (%)	Overall (n = 22), n (%)
Any adverse event	2 (9.1%)	3 (13.6%)	2 (9.1%)	6 (27.3%)
Diarrhea	0	3 (13.6%)	0	3 (13.6%)
Abnormal dreams	1 (4.5%)	0	0	1 (4.5%)
Decreased appetite	0	0	1 (4.5%)	1 (4.5%)
Dysgeusia	0	0	1 (4.5%)	1 (4.5%)
Palpitations	0	0	1 (4.5%)	1 (4.5%)
Somnolence	1 (4.5%)	0	0	1 (4.5%)

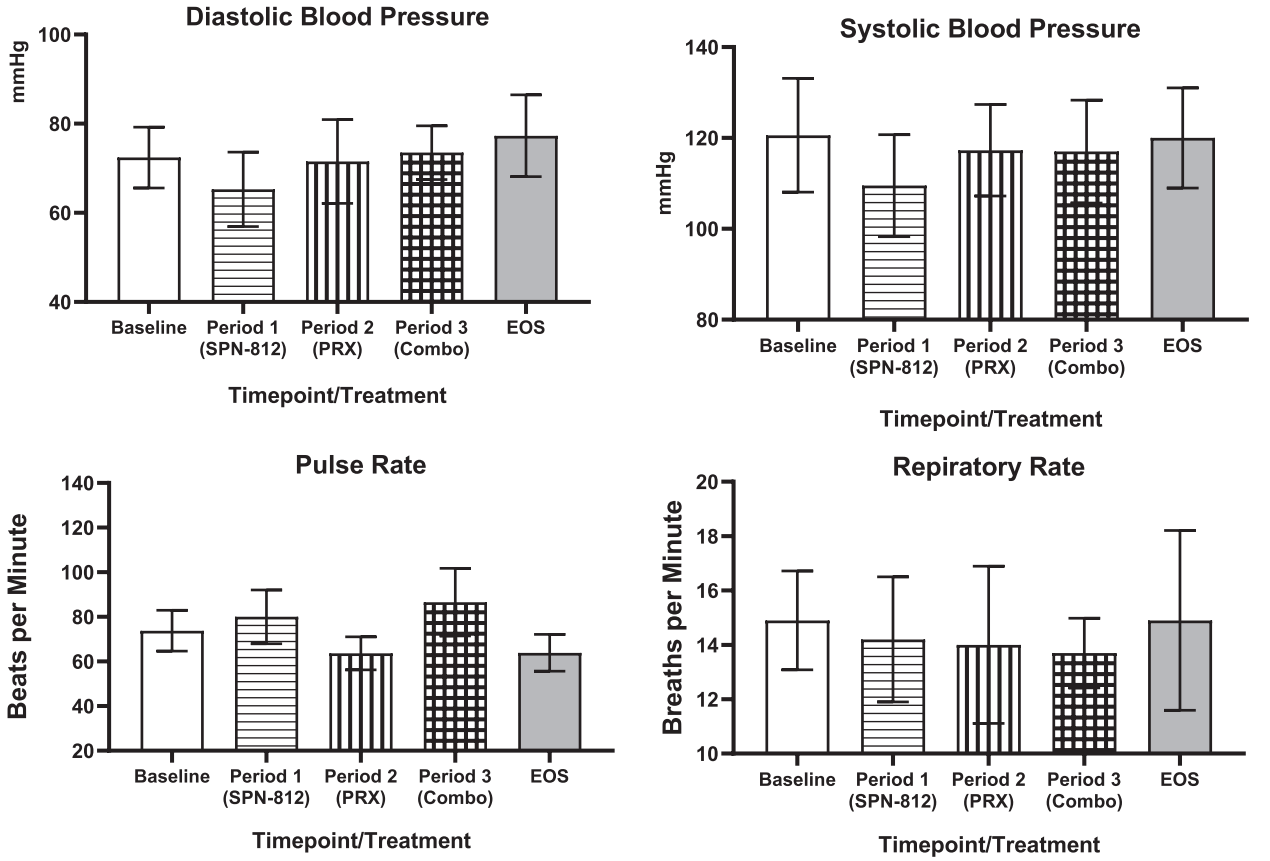

Figure 5. Vital signs. Vital signs assessed at baseline (day −1); period 1, day 1 (single-dose SPN-812); period 2, day 13 (after multiple daily doses of paroxetine); period 3, day 14 (combination daily paroxetine + single-dose SPN-812); and end of study (day 17). Means ± standard deviations. Combo, combination SPN-812 + paroxetine; EOS, end of study; PRX, paroxetine.

exclusively on CYP2D6 and instead uses multiple CYP enzymes (and other minor metabolites such as the carbamoyl glucuronide),[8] which provide for diffuse metabolic pathways (ie, metabolic switching) and, in turn, are likely to modulate the impact of CYP2D6. Because of these multiple metabolic routes, even a potent CYP2D6 inhibitor such as paroxetine would be unlikely to result in a clinically significant PK interaction when combined with SPN-812. These multiple metabolic pathways may account for the modest impact of the combination on the PK results reported here.

Likelihood of Clinically Significant Drug Interactions With SPN-812

CYP-mediated DDIs are a notable concern for psychiatric patients, as they are among the most likely to be taking at least 1 CYP2D6 substrate (relative to other groups such as hospitalized or geriatric patients or the general public), with estimates of ∼50% of psychiatric patients taking at least 1 such drug.[26] This is notable because SSRIs, which are well known to act as CYP inhibitors,[10,27] are increasingly common, approved for patients with not only depression, but also a wide

variety of conditions, including obsessive-compulsive disorder, panic disorder, generalized or social anxiety disorder, and posttraumatic stress disorder. The potential for CYP-mediated DDIs may be particularly relevant for clinicians treating patients with ADHD as many (thought to be as high as 50%) present with psychiatric comorbidities such as anxiety or depressive disorders.[28–31]

The results presented here suggest that the PK of SPN-812 was modestly changed (AUC increased <35%) in the presence of the SSRI paroxetine, notably among the most potent CYP2D6 inhibitors.[10–13] Although a 35% change might be a clinical concern for drugs with a narrow therapeutic index,[32,33] viloxazine has been well documented as safe since its initial use in Europe in the 1970s.[34,35] Specifically, very few major safety concerns have been reported in historical studies using the original instant-release formulation (100-300 mg 1-3 times daily),[34–36] recent studies using the extended-release formulation (ie, SPN-812) in healthy adults (single doses of 700 mg)[24,25] and contemporary studies with repeated dosing in children (100-400 mg/d)[2–4] and adolescents (200-600 mg/d).[5,6] Further, these latter studies in pediatric patients have reported significant reductions in ADHD symptoms at doses of 100-400 mg/d.[2–5] These data suggest that SPN-812 has a relatively large therapeutic window, and a 35% increase in viloxazine exposure is unlikely to warrant dose adjustment. However, it is nonetheless advisable to monitor patients for adverse reactions and adjust dosages as clinically indicated.

Conclusions

This study found a minimal impact of a strong CYP2D6 inhibitor (paroxetine) on the SPN-812 PK profile in healthy adults. There was no impact on safety, as evaluated by AEs, vital signs, serum chemistry, or ECGs. Specifically, although paroxetine coadministration resulted in minimal (<35%) increased exposure (as measured by AUC) coupled with no impact on C_{max}, a carefully considered treatment plan with SPN-812 and CYP2D6 inhibitors is unlikely to result in a clinically significant drug interaction.

Conflicts of Interest

The protocol of the trial was designed by Supernus employees, and the study was conducted by Worldwide Clinical Trials. Z. Wang, A. Kosheleff, L. Adeojo, O. Odebo, T. Adewole, P. Qin, S. Schwabe, and A. Nasser are employees of Supernus Pharmaceuticals, Inc. V. Maletic is an employee of the University of South Carolina School of Medicine. He is a consultant for ACADIA Pharmaceuticals Inc., Alfasigma USA, Inc., Alkermes, Inc., Allergan, Eisai-Purdue, Intra-Cellular Therapies, Janssen, H. Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sage Pharmaceuticals, Sunovion Pharmaceuticals Inc., Supernus Pharmaceuticals, Inc., and Takeda Pharmaceutical Company Limited. He serves on the speakers bureau of ACADIA Pharmaceuticals Inc., Alkermes, Inc., Allergan, Ironshore, Intra-Cellular, Janssen, H. Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sunovion Pharmaceuticals Inc., and Takeda Pharmaceutical Company Limited, and his spouse serves on the speakers bureau of Otsuka America Pharmaceutical, Inc.

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