Disorders, 5th edition (DSM-5) ADHD diagnosis, ADHD-Rating Scale-5 (ADHD-RS-5) score ≥28, Clinical Global Impression-Severity score ≥4, and be free of ADHD medication ≥1 week before randomization. This investigation was conducted at 34 study sites in the United States. Subjects (N=310) were randomized 1:1:1 to placebo:200 mg SPN-812:400 mg SPN-812. The treatment period included up to 1 week of titration and 5 weeks of maintenance (intent-to-treat population: N=301; placebo=104, 200 mg=94, 400 mg=103). The primary efficacy endpoint was change from baseline (CFB) at end of study (EOS) in ADHD-RS-5 total score. Key secondary endpoints included Clinical Global Impression-Improvement (CGI-I) score at EOS, and CFB at EOS in Conners 3-Parent Short Form (Conners 3-PS) Composite T-score and Weiss Functional Impairment Rating Scale-Parent Form (WFIRS-P) total average score. Safety assessments included adverse events (AEs), laboratory tests, vital signs, physical exams, electrocardiograms, and the Columbia-Suicide Severity Rating Scale.

RESULTS: Compared to placebo, a significantly greater improvement in ADHD-RS-5 total score was observed in the 200 mg and 400 mg SPN-812 treatment group at EOS (p=0.0232, p=0.0091; respectively). Significant improvement in CGI-I score at EOS for both 200 mg and 400 mg SPN-812 compared to placebo was also observed (p=0.0042, p=0.0003; respectively). No significant change was observed at either dose compared to placebo in the Conners 3-PS Composite T-score (p=0.6854, p=0.0518; respectively), or the WFIRS-P total average score (p=0.2062, p=0.0519; respectively). The most common (≥5%) treatment-related AEs were somnolence, decreased appetite, fatigue, headache, and nausea.

CONCLUSIONS: In this study, SPN-812 met the primary objective for both the 200 and 400 mg doses, and a key secondary objective (CGI-I) for both the 200 and 400 mg doses. AE-related dropouts were ≤5%, indicating SPN-812 treatment was well tolerated.

This study is an encore of a poster presentation at the 2019 Annual Meeting of the American Academy of Child and Adolescent Psychiatry (AACAP).

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Phase 3, Randomized, Double-Blind, Placebo-Controlled Study (P303) Assessing Efficacy and Safety of Extended-Release Viloxazine in Children with ADHD

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ABSTRACT: Study Objective: SPN-812 (extended-release viloxazine) is a structurally distinct, bicyclic, Serotonin Norepinephrine Modulating Agent (SNMA) in development as a treatment for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. This Phase 3, randomized, double-blind study (P303) evaluated the efficacy and safety of once-daily SPN-812 at doses of 200 and 400 mg compared to placebo in children ages 6-11yrs with ADHD.

METHOD: Inclusion criteria required subjects have a confirmed Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) ADHD diagnosis, ADHD-Rating Scale-5 (ADHD-RS-5) score ≥28, Clinical Global Impression-Severity score ≥4, and be free of ADHD medication ≥1 week before randomization. Subjects were enrolled at 31 study sites in the United States. Subjects (N=313) were randomized 1:1:1 to placebo:200 mg SPN-812:400 mg SPN-812. Treatment included up to 3 weeks of titration and 5 weeks of maintenance (intent-to-treat population: N=301; placebo=97, 200 mg=107, 400 mg=97). The primary efficacy endpoint was change from baseline (CFB) at end of study (EOS) in ADHD-RS-5 total score. Key secondary endpoints included Clinical Global Impression-Improvement (CGI-I) score at EOS, and CFB at EOS in Conners 3-Parent Short Form (Conners 3-PS) Composite T-score and in Weiss Functional Impairment Rating Scale-Parent Form (WFIRS-P) total average score. Safety assessments included adverse events (AEs) among other measures.

RESULTS: Compared to placebo, a significantly greater improvement in ADHD-RS-5 total score was observed in the 200 mg and 400 mg SPN-812 treatment group at EOS (p=0.0038, p=0.0063; respectively). Significant improvement in CGI-I score at EOS for both 200 mg and 400 mg SPN-812 was also observed (p=0.0028, p=0.0099; respectively). Significant improvement was observed for the 200 mg SPN-812 dose compared to placebo in the Conners 3-PS Composite T-score (p=0.0064), but not for the 400 mg dose (p=0.0917). No significant improvement was observed in either

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dose group in the WFIRS-P total average score (p=0.0651, p=0.1680; respectively). The most common (≥5%) treatment-related AEs were somnolence, decreased appetite, fatigue, headache, and upper abdominal pain.

CONCLUSIONS: In this study, SPN-812 met the primary objective for both the 200 and 400 mg doses and the key secondary objective (CGI-I) for both the 200 and 400 mg doses with statistical significance. A second key secondary objective (Conners 3-PS) for the 200 mg dose was also met. AE-related dropouts were ≤5%, indicating SPN-812 treatment was well tolerated.
This study is an encore of a poster presentation at the 2019 Annual Meeting of the American Academy of Child and Adolescent Psychiatry (AACAP).
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An Assessment of QTc Effects With SPN-812 (Extended-Release Viloxazine) in Healthy Adults

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ABSTRACT: Study Objective: SPN-812 (extended-release viloxazine) is a structurally distinct, bicyclic, Serotonin Norepinephrine Modulating Agent (SNMA) under investigation as a treatment for attention-deficit/hyperactivity disorder (ADHD). One concern for any new drug is prolongation of the QT interval, which is associated with increased risk for potentially very harmful ventricular cardiac arrhythmias such as torsades de pointes (TdP). The objective of this study was to assess the effects of SPN-812 at a supratherapeutic dose (1800 mg once daily [QD]) on cardiac repolarization (QTc) in healthy adults.

METHOD: This study was a Phase 1, double-blind (except for the positive control moxifloxacin), randomized, 3-period, 6-sequence crossover design in healthy adult male and female subjects evaluating the electrocardiographic effects of SPN-812. Subjects were randomized to receive a sequence of all 3 treatments – placebo, 400 mg moxifloxacin (positive control), and 1800 mg SPN-812 (supratherapeutic dose). Treatment was given for 2 consecutive days (separated by a washout of at least 4 days). The primary endpoint was based on concentration-QTc effect modeling, evaluating the relationship between plasma concentrations of SPN-812 and its metabolite 5-hydroxyviloxazine glucuronide (5-HVLX-gluc) with the placebo-adjusted change from baseline in QTcI, ΔΔQTcI (QT interval corrected for HR based on the individual-specific QT interval correction method). Secondary endpoints included time point change from baseline in QTcI, QTcF, HR, PR, and QRS; evaluation of the relationship between the plasma concentration of viloxazine and 5-HVLX-gluc and the placebo-adjusted change from baseline in HR, PR, QRS, and QTcF; evaluation of the relationship between the plasma concentration of moxifloxacin and ΔΔQTcI to demonstrate assay sensitivity; and changes in ECG morphology. Safety endpoints included assessment of adverse events and other parameters.

RESULTS: The relationship between ΔΔQTcI and viloxazine plasma concentration demonstrated a negative slope (p=0.0012). Predicted mean ΔΔQTcI (2-sided 90% CI) for SPN-812 was -9.7 ms (-11.3, -8.1) at the mean Cmax of 12.4 µg/mL. The relationship of 5-HVLX-gluc and ΔΔQTcI similarly demonstrated a predicted negative slope (p=0.0007) with a predicted mean ΔΔQTcI (2-sided 90% CI) of -9.2 ms (-10.8, -7.8) at the mean Cmax of 10.0 µg/mL. Assay sensitivity was confirmed. Concentration-effect modeling demonstrated no relationship between plasma concentrations of viloxazine and 5-HVLX-gluc and other ECG parameters. The secondary time point analyses demonstrated no effect of SPN-812 on QTcI or other ECG intervals. SPN-812 produced no changes in ECG T wave or U wave morphology.

CONCLUSIONS: Data from this Phase 1 thorough QT study demonstrate that a supratherapeutic dose of SPN-812, 1800 mg QD, has no effect on cardiac repolarization or other ECG parameters, and is thus not associated with a risk for cardiac arrhythmias such as TdP.
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