

dose group in the WFIRS-P total average score ($p=0.0651$, $p=0.1680$; respectively). The most common ($\geq 5\%$) 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 $\leq 5\%$, 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).

Funding Acknowledgements: This research was funded by Supernus Pharmaceuticals, Inc., Rockville, MD.

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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 suprathreshold 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 (suprathreshold 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, $\Delta\Delta$ QTcI (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 $\Delta\Delta$ QTcI to demonstrate assay sensitivity; and changes in ECG morphology. Safety endpoints included assessment of adverse events and other parameters.

RESULTS: The relationship between $\Delta\Delta$ QTcI and viloxazine plasma concentration demonstrated a negative slope ($p=0.0012$). Predicted mean $\Delta\Delta$ QTcI (2-sided 90% CI) for SPN-812 was -9.7 ms (-11.3, -8.1) at the mean C_{max} of 12.4 $\mu\text{g/mL}$. The relationship of 5-HVLX-gluc and $\Delta\Delta$ QTcI similarly demonstrated a predicted negative slope ($p=0.0007$) with a predicted mean $\Delta\Delta$ QTcI (2-sided 90% CI) of -9.2 ms (-10.8, -7.8) at the mean C_{max} of 10.0 $\mu\text{g/mL}$. 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 suprathreshold 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.

Funding Acknowledgements: This research was funded by Supernus Pharmaceuticals, Inc., Rockville, MD.