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Conclusions: In this sample of participants seeking treatment for OUD, the subgroup with exposure to fentanyl prior to randomization exhibited markers of greater severity of illness at baseline (more heroin use, more co-occurring non-opioid drug use) and fewer opioid negative urine results during treatment. Consistent with previous post-hoc analyses of subgroups reporting heroin or IV drug use at baseline, treatment with CAM2038 resulted in a greater percentage of urine samples negative for illicit opioids in participants with evidence of fentanyl use prior to randomization vs SL BPN/NX. CAM2038 may have an advantage over SL BPN/NX on illicit opioid use outcome among difficult-to-treat patient population, including those who test positive for fentanyl at treatment initiation. As these are post-hoc analyses from a randomized study, results should be interpreted with caution as further studies are needed to confirm the improved effectiveness of CAM2038 in these subgroups.

RANDOMIZED DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO EVALUATE NV-5138/SPN-820 (NV-5138), AN MTORC1 ACTIVATOR, BY QUANTITATIVE EEG (QEEG) IN HEALTHY VOLUNTEERS, SUPPORTS TARGET ENGAGEMENT AND TRANSLATIONAL STRATEGY

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Abstract: Introduction: NV-5138, a direct mTORC1 activator demonstrates rapid and long-lasting 'antidepressant' effects comparable to ketamine in pre-clinical models. Ketamine and other antidepressants have been investigated for their effects on qEEG and this study was performed to understand the effects of NV-5138 in comparison with those agents as a possible valuable measurement of central pharmacological activity. qEEG may be useful to characterize the CNS impact of NV-5138 including confirmation of meaningful CNS target engagement and a dose to be carried forward to proof-of-concept.

Methods: 25 healthy male subjects were randomly assigned to a single dose of either placebo or 2400 mg NV-5138 on Day 1, and the same treatment on Day 3. Tolerability and PK were evaluated. Baseline (Day -1) and Days 1 and 3 time matched qEEGs (5 minutes each eyes closed (EC); eyes open (EO)) corresponding to 1 hour pre-dose and 1, 4, and 8 hours post-dose, were recorded. Spectral band amplitudes, frequency-derived measures, and magnitude squared coherence were assessed. Recording specs: Compumedics Grael 4k V2 EEG amplifiers, Curry 8E Software, 23 electrodes (International 10-20 system). Standard pre-processing of 2 second segments using a fast Fourier transformation and Irregular-Resampling Auto-Spectral Analysis (IRASA) to separate oscillatory and fractal components was performed (delta through gamma3 bands). Salient changes in end points for drug vs placebo on Days 1 and 3, were classified as small, medium or large, confirmed by MMRM. The pre-dose baseline time point was used as a covariate. The study was performed in accordance with all applicable requirements, including informed consent and IRB oversight.

Results: 56 subjects were screened, with a total of 25 randomized (13 placebo/12 drug). 24 subjects completed the study (1 participant withdrew consent on Day 1 (placebo)). The two sequential doses of NV-5138 were well tolerated, with no incidents of death, no serious adverse events, or discontinuations due to adverse events. Dissociative effects were evaluated with the

CADSS, and there were no clinically meaningful abnormalities in laboratory or physical exam parameters. The strongest changes in qEEG parameters occurred in the NV-5138 group, on both days, 1-hour post-dose (approximately at the time of NV-5138 Tmax). These assessments revealed a decrease in low-frequency EEG bands (delta and theta) and an increase in high-frequency EEG bands (gamma), while alpha bands exhibited decreased amplitudes (or desynchronization) around Tmax. At later time points alpha 1, alpha 2 and beta 1 bands increased in amplitudes, with a resultant decrease in Theta/Beta ratio and increased Alpha Slow-wave Index, linked to increasing arousal and cognitive processing and effects on mood. Salient changes observed in the fractal part of the EEG spectrum included increases in amplitudes for high beta, gamma, gamma 1, gamma 2, and gamma 3 bands (greatest change). Increased inter- and intrahemispheric coherence occurred at several specific electrode pairs, and were more prominent in the high-beta through gamma bands. Changes in qEEG in the placebo group were minimal and not related to treatment. Consistent with the increased beta through gamma band amplitudes and coherences, NV-5138 might increase perceptual and cognitive processing.

Conclusion: NV-5138 was generally safe, well tolerated. NV-5138 actively modulated neural activity as measured by qEEG band amplitudes and coherences. The pattern of electrophysiology changes on drug was consistent with desired antidepressant effects. Limitations include small sample size and use of healthy male volunteers precluding conclusions in females or in patients with depression.

EFFECTS OF SINGLE-DOSE L-THEANINE ON MOTOR CORTEX EXCITABILITY IN HEALTHY SUBJECTS: A DOUBLE-BLINDED, RANDOMIZED ORDER, CROSS-OVER PAIRED-PULSE TMS STUDY

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Abstract: **Background:** L-theanine (N5-ethyl-L-glutamine) is the primary psychoactive component uniquely in green tea. Epidemiological studies support that green tea consumption is an independent factor associated with lower prevalence of depression. Preclinical studies have demonstrated anti-depressant effect of L-theanine in rodents and provided evidences for its pharmacological properties of N- methyl-D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) agonism. Yet these effects have not been proven in humans. We propose using pair-pulse transcranial magnetic stimulation (ppTMS) to probe how L-theanine may manipulate the glutamatergic and GABA systems in the frontal region by changing cortical excitability first in healthy subjects. ppTMS is a well-established technique to investigate frontal motor cortical excitability mediated by the inter-neuron NMDA and GABA receptors. Specific changes of ppTMS measures, including impaired short-term and long-term intracortical inhibition (SICI, mediated by GABA-A receptor; LICI, mediated by GABA-B receptor) and intracortical facilitation (ICF, mediated by NMDA receptor), have been demonstrated in MDD. Using this technique, we plan to investigate the neurobiological effects of L-theanine in healthy subjects first. Given the potential NMDA and GABA agonistic effects of L-theanine, we hypothesize that it increases intracortical inhibition and