Effect of Ketamine on Laboratory-induced Stress in Healthy Subjects: A Proof-of-Concept Translational Study

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Statistical Analysis Plan (2/26/2021): Demographic and clinical characteristics, blood, salivary biomarkers, and behavioral measures will be summarized by randomization group using descriptive statistics. Mean, standard deviation, median, interquartile range and range will be reported as appropriate for continuous measures. Numbers and percentages will be reported for categorical measures. Safety and tolerability data will also be summarized descriptively by randomization group. Adverse events will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Separate tabulations and listings will be produced for related adverse events, serious adverse events, discontinuation due to adverse events and events of at least grade 3 severities.

The *primary behavioral outcome* is the change in the anxious-composed subscale score of the POMS-Bipolar in response to an acute stress (the +0 time point) from pre-TSST (the -25-minute time point). The primary endpoint will be compared between randomization groups using a linear regression model of the change score and randomization group adjusted for baseline score. The primary behavioral null hypothesis is that the regression coefficient for randomization group will be equal to zero. The null hypothesis will be tested using a two-sided, 0.05 level Wald test.

Secondary analyses of the POMS-Bipolar scale will compare the trajectory of scores across each study time point by randomization group using linear mixed-effects models. These models will include a random intercept for patient and fixed effects for randomization group, time, and a randomization group-by-time interaction. *Secondary behavioral outcomes* including other POMS-Bi subscale scores, PANAS, VAS, and BAI will be analyzed in the same manner described above for the behavioral primary outcome.

The *primary biological outcome* is HPA activity, as measured by salivary concentration of the stress hormone cortisol. The trajectory of this measure over each study time point will be compared between randomization groups using a linear mixed effects model. The model will include a random intercept for patient and fixed effects for randomization group, time, and a randomization group-by-time interaction. The primary biological null hypothesis is that there is no interaction between time and randomization group. The null hypothesis will be tested using a type III test of fixed effects with a two-sided, 0.05 level F-test. *Secondary biological outcomes* including alpha amylase will be analyzed in the same manner described above for the biological primary outcome.

All analyses will be conducted at the 0.05 significance level. No formal adjustment for multiple testing will be made as this is a pilot study and all secondary analyses are considered hypothesis generating.