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STATISTICAL ANALYSIS PLAN

OFFICIAL TITLE: Glutamate Reducing Interventions in Schizophrenia

NCT NUMBER: NCT03321617

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Statistical Analysis

Sample size and randomization: For the sample (n=3 subjects per 4 doses) the randomization sequences will be balanced in blocks of 4.

Primary outcome: Change (hypothesized decrease) in left CA1 CBV from baseline to 14 days. Adherence, dropouts, and missing data: As this is a dose finding trial it is highly important that analyses be done on subjects who adhere closely to taking the study drug across the 14 days and who have complete data. We have set a threshold of adherence at >80% compliance. Subjects who are non-adherent, dropout, or who have unusable CA1 values at baseline or 14 days will be replaced.

Hypothesis testing (Go No-Go Criteria): The hypothesis to be tested is that at least one of the 4 doses shows a mean decrease in left CA1 CBV from baseline to 14 days of at least 0.33 standard deviations. Given that this is a dose finding study, to confirm the hypothesis we will not require a statistically significant test (e.g. $p<.05$), but instead will require the estimated mean decrease across the 3 patients in any one dose to be at least 0.33 standard deviations (standardized change will be used as the effect size measure). One-way ANOVA of the change scores on the 4 dose levels will be used to estimate the mean changes for each dose level standardized by the pooled standard deviation of change. Based on our prior data, the test-retest reliability of CA1 CBV (taken across 3 weeks in 4 patients on placebo) is very high (ICC = 0.85) providing confidence in the specificity of our measure of change and justification for including 3 patients at each level.

The target mean decrease of 0.33 standard deviations was chosen based on: 1) it represents half of the difference found between healthy controls and CHR patients in previous work and 2) we expect any decrease in CA1 CBV to be related to improvement in symptoms given our finding of a linear relationship between CA1 CBV and symptoms in CHR.

Similar analyses will be conducted for our secondary measures of hippocampal Glx (MRS). The clinical symptoms (SIPS) and cognitive measures (Matrics) are measured at 7 and 14 days and will be modeled with repeated measures ANOVA summarizing average change by dose over the study period. The safety measures (e.g. side effects) will be measured similarly throughout the study and will similarly be modeled with repeated measures ANOVA providing estimates at each time point and also aggregated across the study.