Document Coversheet

Study Title: Modulation of Drug Intake: Evaluation of Opioid and Cannabinoid Interactions on Drug Self-Administration

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Modulation of Drug Intake: Evaluation of Opioid and Cannabinoid Interactions on Drug Self-Administration

Protocol Number: 45017

Statistical Analysis Plan

All analyses will be conducted using SAS Version 9.4 (SAS Institute, Inc; Cary, NC, USA), and all hypothesis testing will be two-sided with a significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be represented as <0.001.

Continuous data will be summarized using descriptive statistics: number of observations (n), arithmetic mean, standard error, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) outcomes. Means and standard errors will be presented to two decimal places.

Analysis Populations

Two study populations will be defined for analysis.

Enrolled Population - All subjects who sign the Informed Consent Form.

Completer Population - Subjects in the who complete the entire Study Phase.

Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized; no statistical comparisons will be made on demographic or baseline characteristics. The demographic and baseline characteristics will consist of age, sex, race, ethnicity, height (cm), weight (kg), and BMI (kg/m^2).

Continuous variables (age, height, weight, BMI) will be summarized by n, mean, standard deviation, min, median, and max. Frequencies and percentages will be used to describe categorical (discrete) variables including gender, race, and ethnicity.

Analysis of Primary Outcomes

The primary analyses will be performed based on the Completer Population.

-Primary: Self-Administration of Drug Units Earned

Through a progressive-ratio self-administration model given once per treatment condition, participants work for some, none, or all of the available drug dose. For each dose condition, the number of drug units (out of a total of 7) completed for drug was pulled from the raw data and averaged to yield one mean (SEM). The primary outcome will be analyzed in a mixed model including the 12 drug conditions with a compound symmetry covariance structure. Within each

model, subject will be treated as random effects, and the remaining parameter as fixed effects. Mixed models are suited for data with repeated measures, correlations among observations within an individual subject, and the presence of missing data. The response of individual subjects is first modeled, and then the estimates for each individual are combined in a group analysis (Singer, 1998; Ballinger 2004; Diggle et al. 1996; Gibbons et al. 1993; Kreft and De Leeuw 1998). Tukey post-hoc tests will compare active doses to placebo and other relevant active dose comparisons.

Analysis of Secondary Outcomes

Secondary analyses will be performed based on the Completer Population. Secondary pharmacodynamic outcomes will include:

- Raw time course data of VAS items (e.g., High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, Desire to Use Opioids), subjective opioid adjectives, street value, observer adjectives, DSST, cold pressor test, cold water VAS, flicker/fusion, balance task, heart rate, systolic blood pressure, diastolic blood pressure, respiration rate, oxygen saturation, end tidal carbon dioxide, and pupil diameter from the 12 dose conditions.
- Emax and Emin (where appropriate) on the VAS items, subjective opioid adjectives, street value, observer adjectives, DSST, cold pressor test, cold water VAS, flicker/fusion, heart rate, systolic blood pressure, diastolic blood pressure, respiration rate, oxygen saturation, end tidal carbon dioxide, and pupil diameter from the 12 dose conditions.

Secondary analyses will be completed in mixed models that include drug condition and time (when appropriate with an autoregressive covariance structure) with an autoregressive (AR1) covariance structure. Subject will be treated as random effects and the remaining parameters fixed. Tukey post-hoc tests will compare active doses to placebo and other relevant active dose comparisons.

Safety and Tolerability Analyses

Adverse events (AEs) recorded after signing informed consent but prior to the first dose will be recorded as baseline AEs and will be listed by subject but will not be included in the summary safety analysis. AEs will be summarized by relationship to study drug and severity.

Missing Data

Within-session missing data are expected to be less than 3% for each outcome. Inspection of missing data and correlates of missingness will be examined upon study completion. The use of mixed models as an analytic strategy obviates the need for the missing values to be imputed.

Identification and Summary of Protocol Deviations

Major protocol deviations from the participant's entry criteria through study completion will be documented and summarized as far as they can be extracted from the numeric and coded study data.

References:

Ballinger GA (2004) Using generalized estimating equations for longitudinal data analysis. Organizational Research Methods 7(2): 127-150.

Diggle PJ, Liang K, Zeger SL (1996) Analysis of Longitudinal Data. Oxford University Press, Inc., Oxford University Press, Inc.

Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, Shea MT, Imber SD, Sotsky SM, Watkins JT (1993) Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of Depression Collaborative Research Program dataset. Arch Gen Psychiatry 50: 739-50.

Kreft I, De Leeuw J (1998) Introducing Multilevel Modeling. Sage Publications, Ltd., Sage Publications, Ltd.

Singer JD (1998) Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. J Educ Behav Stat 24: 323-355.