Study Title: Prescription Medication Interactions

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Statistical Analysis Plan for Primary Study

1. Introduction

The purpose of this document is to provide details about the study population, how missing data will be handled, and the statistical methodologies that will be used to analyze the data for the primary study.

2. General Conventions

All analyses will be conducted using SAS Version 9.3 or higher (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.

3. Analysis Populations

Two study populations will be defined for analysis.

3.1 Enrolled Population

All subjects who sign the Informed Consent Form.

3.2 Completer Population

Subjects in the who complete the entire Study Phase.

4. Subjects and Demographics

4.1 Disposition and Withdrawals

Subject disposition will be summarized using the number and percent of subjects who are in the Enrolled Population and Completer Population.

4.2 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Completer Population. 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.

5. Pharmacodynamic Analyses

5.1 Primary Pharmacodynamic Analyses

The primary analyses will be performed based on the Completer Population. The primary Emax VAS item Drug Liking and will be analyzed in a mixed model including the nine 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.

5.2 Secondary Pharmacodynamic Analyses

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 nine 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, balance task, heart rate, systolic blood pressure, diastolic blood pressure, respiration rate, oxygen saturation, end tidal carbon dioxide, and pupil diameter from the nine dose conditions.

Secondary analyses will be completed in mixed models that include drug condition and time (when appropriate with an autoregressive covariance structure) with a compound symmetry 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.

5.2.1 Drug Identification Assessments: Drug identification assessments completed during the experimental dose sessions will be summarized by frequencies and percentages to describe categorical outcomes.

6. Safety and Tolerability Analyses

Safety analyses will be performed on the Enrolled Population. 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.

The numbers and frequencies of subjects reporting AEs, including abuse-related AEs, will be summarized. If the same AE (preferred term) is reported more than once for the same subject, it will only appear once in the summary tables and the highest severity grade and strongest relationship to treatment will be included in the summary. Any AEs leading to a study discontinuation will be summarized.

All deaths, other SAEs, and AEs will be listed.

Other safety variables, including clinically significant changes in the participant's physical examination, vital signs, electrocardiograms, and clinical laboratory results, will be tabulated and presented by study drug received.

7. 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.

8. 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.

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

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