NCT05319756

Protocol A9451180

A PHASE 4, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-AND ACTIVE-CONTROLLED, SINGLE-DOSE, SIX-WAY CROSSOVER STUDY EVALUATING THE ABUSE POTENTIAL OF NEURONTIN® TAKEN ORALLY CONCOMITANTLY WITH OXYCODONE HYDROCHLORIDE IN HEALTHY NON-DRUG DEPENDENT, RECREATIONAL OPIOID USERS

Statistical Analysis Plan
(SAP)

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 21 FEB 2022	2.0 / 12 MAR 2021	N/A	N/A
2/ 16 MAR 2022	2.0 / 12 MAR 2021	Update definition of Completer Population Outline how to handle repeated VAS values.	Completer population definition updated to be more inline with FDA guidance for abuse liability studies. Repeated VAS values will be averaged for statistical analysis.
3/ 19 APR 2022	2.0 / 12 MAR 2021	Modify Evaluable Population Defining PK based Protocol Deviation Missing pre-dose VAS score Completer for Sensitivity Analysis	Change the Evaluable Population to be based on Modified Completer Population PK deviations are pre-defined based on PK results according to PK expection. The neutral VAS score will be used as the baseline value for Emax and AUEC calculation when the pre-dose VAS is missing. Removed.
4/14 SEP 2022	2.0 / 12 MAR 2021	Clarify the statistical model will be used in 6.2.2	ANOVA was changed to linear mixed-effects model per FDA guidance and comment.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study A9451180. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Neurontin® (gabapentin) is indicated for postherpetic neuralgia in adults, adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization in adults and pediatric patients 3 years and older with epilepsy.

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta or kappa), or cannabinoid 1 receptor sites; however, gabapentin abuse has been reported at increasing rates. Individuals abusing gabapentin describe experiences such as euphoria, improved sociability, relaxation and a marijuana-like "high".[1-8]

There are post-marketing reports of abuse and individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most of these individuals were taking higher than recommended doses of gabapentin for unapproved uses and had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

Epidemiological studies have shown that gabapentin may have abuse potential, particularly among individuals with a history of opioid abuse. Gabapentin abuse is reported both alone (ie, without other drugs), and in conjunction with opioids to enhance the 'high' obtained from opioids.[1-3] Further, published data suggest that gabapentin is recorded on death certificates suggesting drug overdose, both as the primary and contributory causes of death, and reported with and without other drugs like opioids, benzodiazepines, and alcohol.[4-7] As a consequence, the FDA requires this post-authorization safety study (PASS) to evaluate gabapentin in combination with a moderate dose of oxycodone hydrochloride (HCl) compared to oxycodone HCl monotherapy and placebo in healthy non-drug dependent, recreational drug users.

2.1. Study Objectives and Endpoints

Objectives	***Endpoints***
Primary:	***Primary:***
• *To determine the abuse potential of orally administered Neurontin® taken concomitantly with oxycodone HCl in non-dependent, recreational opioid users under fasted condition.*	• *Bipolar visual analogue scale (VAS) for "Drug liking" [maximum effect (E_{max})].*
Secondary:	***Secondary:***
• *To evaluate additional pharmacodynamic (PD) effect, pharmacokinetic (PK) and safety of Neurontin® when used alone and concomitantly with oxycodone HCl in non-dependent, recreational opioid users under fasted condition.*	***Pharmacodynamic endpoints:*** • *Bipolar VAS for "Drug liking" [time for E_{max} (TE_{max}), area under the effect-time profile from time zero to the last quantifiable effect ($AUEC_{last}$), and partial AUECs ($AUEC_1$, $AUEC_2$, $AUEC_3$, $AUEC_4$, $AUEC_8$)].* • *Unipolar VAS for "High" (E_{max}, TE_{max} and $AUEC_{last}$), and partial AUEC ($AUEC_1$, $AUEC_2$, $AUEC_3$, $AUEC_4$, $AUEC_8$).* • *Bipolar VAS for "Take Drug Again" at 24, 36 and 48 hours post dose.* • *Bipolar VAS for "Overall Drug Liking" at 24, 36 and 48 hours post dose.* • *Unipolar VAS for "Good Drug Effect".*

Objectives	***Endpoints***
	• *Unipolar VAS for "Bad Drug Effect".* • *Unipolar VAS for "Any Drug Effect".* • *Pupil size (diameter).* ***Pharmacokinetic endpoints:*** • *C_{max}, time for C_{max} (T_{max}), area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUC_{last}) of gabapentin and oxycodone.* • *Area under the plasma concentration-time profile from time zero extrapolated to infinity time ($AUCi_{nf}$) and half-life ($t_{½}$), if data permits, of gabapentin and oxycodone.* • *Partial AUCs (AUC_1, AUC_2, AUC_3, AUC_4, AUC_8) of gabapentin and oxycodone.* ***Safety endpoints:*** • *Vital signs [blood pressure (BP), pulse rate (PR)].* • *Respiratory rate (RR).* • *Oxygen saturation of hemoglobin (SpO2).* • *Physical examination.* • *12-lead electrocardiogram (ECG).* • *Clinical Lab and adverse events (AEs).*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *Exposure-response relationship between gabapentin concentration and selected PD effect in the presence and absence of oxycodone.* • *To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.*	• *Correlation between gabapentin concentrations and selected PD endpoints (bipolar VAS for "Drug Liking", Unipolar VAS for "High", pupil diameter) in the presence and absence of oxycodone, as data permit.* • *Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).*

2.2. Study Design

This will be a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-treatment, 6-period crossover single-dose, Williams square design study in healthy male and/or female adult, non-drug-dependent recreational opioid users. The study includes Screening, a Qualification Phase, a Treatment Phase and Follow-up. This study will randomize approximately 60 adult male and female (at least 20% females) participants (10 participants in each sequence) in the Treatment Phase to ensure at least 48 participants complete the Treatment Phase of the study. Dropouts for non-safety reasons in the Treatment Phase may be replaced at the discretion of the Investigator in consultation with the Sponsor.

The following study visits are required, see Figure 1 and the Schedule of Activities (SoA) from the protocol*:*

- *Visit 1, Screening will occur within 28 days prior to Visit 2.*
- *Visit 2, Qualification Phase will require inpatient stay at the clinical research unit (CRU) for 3 nights:*
    - *Naloxone Challenge Phase, Day 0.*
    - *Drug Discrimination, Days 1 and 2 will require inpatient stay at the CRU for 2 nights.*
    - *End of Drug Discrimination requires an inpatient stay at the CRU overnight to ensure discharge occurs 24 hours after receiving oxycodone or placebo.*
    - *Participant will proceed to Visit 3 after at least 4-day washout but less than 28 days after the last dose of study intervention during Qualification Phase.*
- *Visits 3 to 8, Treatment Phase will require a total of 18 overnight inpatient stays at the CRU:*
    - *Each visit will require an inpatient stay at the CRU of 3 nights.*
    - *Each visit will be separated by a washout period of at least 4 days. Washout period is calculated between two subsequent study drug administrations.*
- *End of Study assessments will be at the CRU and occur 48 hours after the last study drug dosing of period 6 or at the time of early withdrawal.*
- *For the entire study, 21 overnight inpatient stays will be required.*

2.3. Study Treatment

The study treatment code and label are listed below:

- *Treatment A: Oxycodone hydrochloride 20 mg.*

- *Treatment B: Placebo single*
- *Treatment C: Gabapentin 600 mg*
- *Treatment D: Gabapentin 1200 mg*
- *Treatment E: Gabapentin 600 mg + oxycodone hydrochloride 20 mg.*
- *Treatment F: Gabapentin 1200 mg + oxycodone hydrochloride 20 mg.*

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The following parameter will be calculated for VAS for "Drug Liking" during each *Treatment Period:*

- *Maximum (peak) effect (E_{max})* as observed directly from the data.

3.2. Secondary Endpoint(s)

The following parameters will be calculated for VAS for "Drug Liking" and VAS for "High" during each *Treatment Period:*

Table 2. ***Derivation of Pharmacodynamic Parameters***

Parameter	*Definition*	*Method of Determination*
E_{max} (High only)	*Maximum* change from pre-dose response	*Observed directly from data*
TE_{max}	*Time for* E_{max}	*Observed directly from data as time of first occurrence*
$AUEC_{last}$	*Area under the effect-time profile from time zero to the time of the last quantifiable effect* (E_{last})	*Linear trapezoidal method*
$AUEC_1$	*Area under the effect-time profile from time zero to 1 hour postdose*	*Linear trapezoidal method*
$AUEC_2$	*Area under the effect-time profile from time zero to 2 hours postdose*	*Linear trapezoidal method*
$AUEC_3$	*Area under the effect-time profile from time zero to 3 hours postdose*	*Linear trapezoidal method*
$AUEC_4$	*Area under the effect-time profile from time zero to 4 hours postdose*	*Linear trapezoidal method*
$AUEC_8$	*Area under the effect-time profile from time zero to 8 hours postdose*	*Linear trapezoidal method*

Unipolar VAS for "Good Drug Effect", "Bad Drug Effect", "Feeling Sick", "Nausea", "Any Drug Effect", "Sleepy", and "Dizzy" as well as pupil size (diameter) will be collected at the time points shown in the SoA of the protocol.

3.3. Other Endpoint(s)

PK parameters will be derived from the concentration-time profiles as shown in Table 3.

Table 3. ***Derivation of Pharmacokinetic Parameters***

Parameter	*Definition*	*Method of Determination*
C_{max}	*Maximum plasma concentration*	*Observed directly from data*
T_{max}	*Time for* C_{max}	*Observed directly from data as time of first occurrence*
AUC_{last}	*Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration* (C_{last})	*Linear/Log trapezoidal method*
AUC_{inf}[a]	*Area under the plasma concentration-time profile from time zero extrapolated to infinity time*	$AUC_{last} + (C_{last}*/k_{el})$, *where* $C_{last}*$ *is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.*
AUC_1	*Area under the plasma concentration-time profile from time zero to 1 hour postdose*	*Linear/Log trapezoidal method*
AUC_2	*Area under the plasma concentration-time profile from time zero to 2 hours postdose*	*Linear/Log trapezoidal method*
AUC_3	*Area under the plasma concentration-time profile from time zero to 3 hours postdose*	*Linear/Log trapezoidal method*
AUC_4	*Area under the plasma concentration-time profile from time zero to 4 hours postdose*	*Linear/Log trapezoidal method*
AUC_8	*Area under the plasma concentration-time profile from time zero to 8 hours postdose*	*Linear/Log trapezoidal method*
$t_{1/2}$[a]	*Terminal elimination half-life*	$Log_e(2)/k_{el}$, *where* k_{el} *is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.*

a. If data permit.

3.4. Baseline Variables

The pre-dose psychometric measurements of each period will be the baseline for calculating the changes in these parameters post dose.

When the pre-dose psychometric measures were not collected or missing, the neutral VAS point (50 for Drug liking, 0 for High) will be used as baseline for Emax and AUEC calculation purpose.

3.5. Repeated VAS values

For post-dose VAS data collection, when VAS evaluations were taken within a 10-minute window, the values will be treated as repeated measures. In this case, the mean value will be used for the VAS score; the median time will be used as the data collection time.

For pre-dose VAS data collection, when there were multiple VAS values collected, the values will be averaged to be the baseline values.

3.6. Safety Endpoints

Any adverse events (AEs) occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Adverse events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the previous treatment.

Adverse events will be summarized by treatment and Phase of the study (i.e., Naloxone Challenge Phase, Drug Discrimination Phase, and Treatment Phase).

The following data are considered in standard safety summaries:

- *Adverse events,*
- *Clinical laboratory data,*
- *Vital signs data [blood pressure (BP), pulse rate (PR)],*
- *Respiratory rate (RR),*
- *Oxygen Saturation of hemoglobin (SpO_2),*
- *Physical examination,*
- *12-lead electrocardiogram (ECG).*

4. ANALYSIS SETS

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding, other than the Modified Completer Population and Evaluable Population which will be done after unblinding, and releasing the database and classifications will be documented per standard operating procedures.

Table 4. Analysis Sets

Population	Description
Safety	*The Safety Population will include all participants who receive at least one dose of study drug, beginning with the Naloxone Challenge. This population will be analyzed as treated.*
PK	*The PK population will include all enrolled participants treated who have at least 1 concentration in the Treatment Phase. The PK parameter analysis population will include all enrolled participants treated who have at least 1 of the PK parameters of interest.*
Completer	*The Completer Population will include all randomized participants who complete all 6 periods of the Treatment Phase and who contribute post-dose PD data during each period. These participants must have at least one response on the visual analog scale (VAS) for Drug Liking within 2 hours of Tmax for each treatment in the study; ie, at least one VAS response within the interval 0-3h postdose (assuming the Tmax of 20 mg oxycodone is 1h) and at least one VAS response within the interval 1-5h postdose (assuming the Tmax of 600/1200 mg gabapentin is 3h).*
Modified Completer	*The Modified Completer Population will include all randomized participants in the Completer Population, excluding any participants who meet either or both of the following criteria for Drug Liking VAS:* *1. E_{max} scores are within a 5 point difference across all six treatments (ie, Maximum E_{max} score – Minimum E_{max} score ≤5);* *2. $E_{max}(P) > 60$ AND $E_{max}(P) - E_{max}(Oxy20) \geq 5$;* *where $E_{max}(P)$ and $E_{max}(Oxy20)$ are the VAS E_{max} scores for placebo and oxycodone HCl IR 20 mg, respectively.* *This population will be analyzed as randomized.*
Evaluable	*The Evaluable Population will include all randomized participants in the Modified Completer Population who do not have major protocol violations or adverse events that would interfere with drug absorption such as vomiting within 4 hours of study drug administration. Major protocol violations, including deviations related to study drug intake are defined as those that could potentially affect the PD conclusions of the study. Prior to unblinding the Treatment Phase data, the Sponsor (or designee) will identify protocol violations or*

Table 4. Analysis Sets

Population	Description
	adverse events that would disqualify a participant from the evaluable population and determine which participants or participant visits will be excluded. This population will be analyzed as randomized.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

To assess the abuse potential of gabapentin, the following tests will be performed in the order of validation test followed by combination vs. oxycodone and then gabapentin alone vs. oxycodone:

Study Validation:

1. *The sensitivity and integrity of the study will be validated by comparing the mean responses of oxycodone HCl, the positive control (C), to the placebo:*

$$H_0: \mu_C - \mu_P \leq \delta_1 \text{ versus } H_a: \mu_C - \mu_P > \delta_1 \text{ where } \delta_1 = 15.$$

The study will be considered validated if the one-sided p-value for the validation hypothesis test is less than 0.05.

Primary:

2. *Does gabapentin plus oxycodone HCl (T) produce mean responses that show abuse potential that is no higher than oxycodone HCl (C)?*

$$H_0: \mu_T - \mu_C \geq 0.2\ (\mu_C - \mu_p) \text{ versus } H_a: \mu_T - \mu_C < 0.2\ (\mu_C - \mu_p).$$

The combination of gabapentin plus oxycodone will be considered to not have an additive effect for abuse potential compared to oxycodone alone if the one-sided p-value for gabapentin plus oxycodone – 1.2 * oxycodone alone + 0.2 * placebo to be positive is less than 0.05.

Secondary:

3. *Does gabapentin (G) produce mean responses that show less abuse potential than oxycodone HCl (C)?*

$$H_0: \mu_C - \mu_G \leq 0.2\ (\mu_C - 50) \text{ versus } H_a: \mu_C - \mu_G > 0.2\ (\mu_C - 50).$$[9]

4. *Does gabapentin (G) produce mean responses that show abuse potential similar to placebo(P)?*

$$H_0: \mu_G - \mu_p \geq \delta_2 \text{ versus } H_a: \mu_G - \mu_p < \delta_2 \text{ where } \delta_2 = 11.$$

5. *Does gabapentin (G) produce mean responses that show less abuse potential than gabapentin plus oxycodone HCl (T)?*

$$H_0: \mu_T - \mu_G \leq 0.2\,(\mu_T - 50) \text{ versus } H_a: \mu_T - \mu_G > 0.2\,(\mu_T - 50).[9]$$

For each of the gabapentin hypotheses, the statistical significance of the test will be assessed for all doses of gabapentin.

All hypothesis testing is based on one-sided test with alpha level of 0.05.

5.2. General Methods

Statistically, the study will be evaluated as a safety study. Consequently, the null hypothesis for gabapentin alone and when used concomitantly with oxycodone HCl will be constructed on the presumption that these treatments produce abuse potential similar to oxycodone HCl and therefore differentiates from placebo. To demonstrate that these treatments have no abuse potential, the null hypothesis will be statistically rejected.

All PD analyses will be performed using the Modified Completer Population and all available postdose data; these will be the primary PD analyses.

5.3. Potential Additional Analysis

Key PD analyses may be repeated on the Evaluable Population using all available post-dose data.

6. ANALYSES AND SUMMARIES

6.1. Study Validity Analysis of Endpoints

*Study validity will first be confirmed through the comparison of mean E_{max} for "Drug Liking" between oxycodone and placebo administered during the Treatment Phase. This comparison will be made using a mixed-effect model with treatment, period, treatment * period interaction, a carryover variable, and sequence as fixed effects, and participant nested within sequence as a random effect. If the p-value for the carryover variable is >0.25, a reduced mixed model will be used with treatment, period and sequence as fixed effects, and participant nested within sequence as a random effect. If the treatment comparison of oxycodone vs. placebo is statistically significant (i.e., one-sided $p \leq 0.05$) in the appropriate direction and confidence intervals exclude differences of <15 points for "Drug Liking" E_{max}, it will confirm the sensitivity of the study. If study validity is not confirmed, comparisons between gabapentin and oxycodone will not be performed.*

6.2. Analysis of Primary and Secondary Endpoints

*A linear mixed-effect model with treatment, period, treatment * period interaction, a carryover variable, and sequence as fixed effects, and participant nested within sequence as*

a random effect. If the p-value for the carryover variable is >0.25, a reduced mixed model will be used with treatment, period and sequence as fixed effects, and participant nested within sequence as a random effect. The primary analyses of abuse potential will be based on testing the differences between the means from the primary measure(s) at the peak of drug response effects (VAS E_{max}) produced by gabapentin, oxycodone HCl and placebo at a significance level of 0.05 (1-sided).

The primary PD endpoint is the E_{max} of bipolar VAS for "Drug Liking".

*The principal parameters for the primary and secondary endpoints will be summarized by treatment using descriptive statistics (mean, SE, median, first and third quartiles, minimum and maximum). These parameters will be analyzed using a mixed-effect model with treatment, period, treatment * period interaction, a carryover variable, and sequence as fixed effects, and participant nested within sequence as a random effect. If the p-value for the carryover variable is >0.25, a reduced mixed model will be used with treatment, period and sequence as fixed effects, and participant nested within sequence as a random effect. Analyses of endpoints with baseline (pre-dose) measurements will include the baseline measurement as a covariate in the model. Least squares means, standard errors, and one-sided 95% confidence intervals will be provided for each treatment and for the difference between treatments. P-values will be provided for each hypothesis. A two-sided 90% confidence interval will be provided for the comparisons of gabapentin (600 mg and 1200 mg) plus oxycodone versus oxycodone alone. Data will be summarized graphically, where appropriate.*

The study validation comparisons will be:

- *oxycodone 20 mg vs. placebo;*

The primary treatment comparisons will be:

- *gabapentin 600 mg plus oxycodone 20 mg vs. oxycodone 20 mg;*
- *gabapentin 1200 mg plus oxycodone 20 mg vs. oxycodone 20 mg;*

The secondary treatment comparisons will be:

- *gabapentin 600 mg vs. placebo;*
- *gabapentin 1200 mg vs. placebo;*
- *gabapentin 600 mg plus oxycodone 20 mg vs. placebo;*
- *gabapentin 1200 mg plus oxycodone 20 mg vs. placebo;*
- *gabapentin 600 mg vs. oxycodone 20 mg;*
- *gabapentin 1200 mg vs. oxycodone 20 mg;*

- *gabapentin 600 mg plus oxycodone 20 mg vs. gabapentin 600 mg;*
- *gabapentin 1200 mg plus oxycodone 20 mg vs. gabapentin 1200 mg.*

Statistical significance of all treatment differences will be reported. All statistical tests will be conducted using one tailed significance criteria. These comparisons will be used to assess the primary study objective.

The VAS for "Overall Drug Liking", "Take Drug Again", "Good Drug Effect", "Bad Drug Effect", and "Any Drug Effect" will be summarized by timepoints.

Mean time plots (linear scale) against nominal time postdose by treatment (all treatments on the same plot) of VAS for "Drug Liking", "High", "Overall Drug Liking", "Take Drug Again", "Good Drug Effect", "Bad Drug Effect", and "Any Drug Effect" and pupil size will be presented.

6.2.1. Sensitivity/Supplementary Analyses

Regression diagnostics will be performed to verify model assumptions and adequacy of the fitted linear models for the primary endpoints. Levene's test will be used to diagnose potential heterogeneity of variance and the Shapiro–Wilk test will be used to diagnose potential non-normality of the model residuals.

If the resulting p-value from Levene's test is ≤0.05, the null hypothesis of equal variances is rejected and it will be concluded that there is a difference between the treatment group variances. An unequal variance model will then be applied using the Satterthwaite method in order to produce an accurate F-approximation.

If the resulting p-value from the Shapiro-Wilk test is ≤0.05, symmetry of the distribution of paired differences will be tested using the Triples Test and either the t test (symmetry) or sign test (asymmetry) will be performed.

If needed (Shapiro-Wilk test has a p-value ≤0.05), symmetry will be tested for each of the primary comparisons using the Triples Test in the following manner[10]:

1. Calculate the paired differences of the treatments being compared
2. Calculate T as follows:

[redacted]

where sign(y) = -1, 0, or 1 if y is less than, equal to or greater than 0, respectively. For each set of triples, if $\text{sign}(X_i + X_j - 2X_k) + \text{sign}(X_i + X_k - 2X_j) + \text{sign}(X_j + X_k - 2X_i) = -1$, it is a left triple; if it is 0, it is neither a left nor a right triple; and, if it is 1, it is a right triple.

3. Calculate s^2 as follows:

[redacted]

[redacted]

where [redacted]

[redacted]

4. Calculate the test statistic

[redacted]

5. If [redacted], then the distribution of the differences in responses will be considered asymmetric; otherwise, they will be considered symmetric.

The test for median of differences for each treatment comparison and endpoint (E_{max}) will be determined by the t test if the paired differences are symmetric, or by the Sign Test if the paired differences are asymmetric.

6.2.2. Pharmacodynamic Analysis

*Pharmacodynamic parameter values that will be evaluated are listed in Table 2. The pre-dose measurements of psychometric and pupillometry of each period will be the baseline for calculating the changes in these parameters post dose. Descriptive statistics for the changes from baseline will be reported by treatment and by hours postdose. The changes from baseline will be analyzed with linear mixed-efforts model consisting of: Sequence, Period, Treatment, Time, Period*Time and Treatment*Time terms as fixed effects, and a participant (Sequence) term as a random effect. To accommodate the repeated measures aspect of the design, a compound symmetric covariance matrix will be employed, with the participant set to Period*Participant (Sequence). The Treatment*Time least-squares means and differences among them will be assessed for trends likely to be of clinical relevance.*

Descriptive statistics of the mean, standard error, and other summary statistics such as minimum, first quartile (Q1), median, third quartile (Q3) and maximum for each subjective measure, each treatment and each paired difference among treatments will be calculated and used to create tables and graphs.

Pupil size will be summarized by time points.

6.2.3. Pharmacokinetic Analysis

Blood samples will be collected throughout the study session in order to monitor drug PK. This will be done to primarily confirm that plasma levels of the drug are equivalent between participants and to evaluate whether subjective measures and AEs can be correlated with drug levels over time. Typically, blood will be drawn immediately after the collection of subjective measures are completed at each time point. If an analysis shows that a participant had low plasma levels of a drug, it may account for a lack of subjective responses in a drug session.

A subject/period which lacks of any measurable concentrations or only has very low plasma concentrations on a supposed non-placebo period(s) will be defined as a major protocol deviation. A subject/period is considered to have very low plasma concentrations if its AUC is less than 5% of the corresponding analyte/treatment geometric mean AUC (which should be calculated without inclusion of data from the outlying subject).

A subject/period, with significant measurable concentrations on the placebo period or a specific treatment period in which the drug was not administered, will be defined as a major protocol deviation. A subject/period is considered to have significant plasma concentrations if its AUC is more than 5% of corresponding analyte and treatment geometric mean AUC. In the case of gabapentin concentration, the 600 mg dose period (either mono- or combo- dose) will be used as the reference geometric mean.

A subject with any period classified as a major protocol devation will be further excluded from the Evaulable Population.

Gabapentin and oxycodone PK parameter values will be calculated for each non-placebo treatment and each participant using noncompartmental analysis of concentration-time data. PK parameter values that will be evaluated are listed in Table 3. The PK parameters (AUC_{inf}, AUC_{last}, C_{max}, T_{max}, $t_{½}$, partial AUCs [AUC_1, AUC_2, AUC_3, AUC_4, AUC_8]) will be derived for each participant/period/analyte and will be summarized by treatment and analyte. Individual participant PK parameters, as well as summary statistics (e.g., group averages, SD, geometric means, coefficient of variation [CV] and geometric CV%) by treatment will be reported for PK parameters, as appropriate. Plasma concentration-time profiles of gabapentin and oxycodone will be presented. Concentrations will be listed and summarized by PK sampling time and treatment for each analyte.

6.3. Safety Summaries and Analyses

All safety analyses will be performed on the safety population.

The safety data will be described and summarized in accordance with the sponsor's Data Standards.

AEs, ECGs, BP, pulse rate, RR, SpO_2 continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

6.4. Exploratory Analysis

Exploratory analysis will be conducted to evaluate the correlation between gabapentin concentrations and selected PD endpoints (Bipolar VAS for "Drug Liking", Unipolar VAS for "High", pupil diameter) in the presence and absence of oxycodone, as data permit.

As an exploratory analysis, the time course of the different subjective measures in relation to each other (and to abuse-related AEs) will evaluate the outcome of positive or negative assessments of the drug before, during and after the peak of drug effects. The physiological effects such as pulse rate, blood pressure, respiratory rate and pupil size will be monitored over the course of the study session and correlated to both the drug dose administered and the PK of the drug.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study.

8. REFERENCES

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9. APPENDICES

Appendix 1. SAS Code

Sample SAS code for PROC MIXED:
Create a dummy variable, “carryover”, for Periods 2, 3, 4, 5, and 6, carryover is assigned as follows:

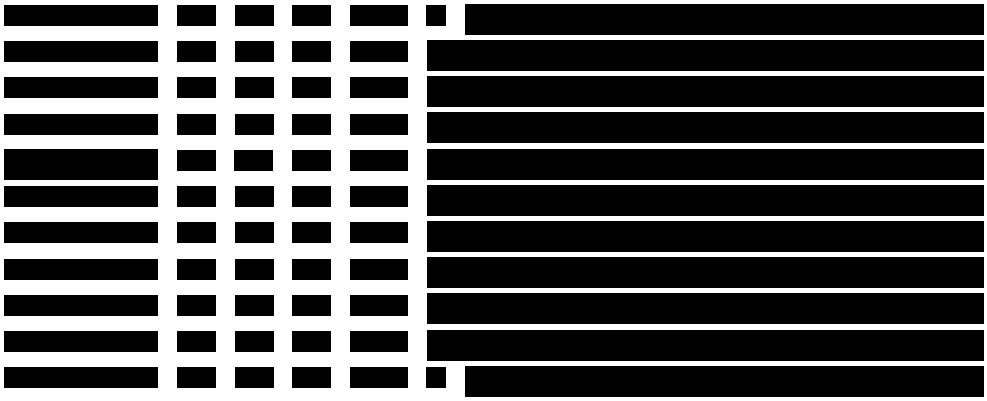
Treatment	Carryover
A	1
B	2
C	3
D	4
E	5
F	6

For Period 1, carryover = 1 regardless of the Treatment.

[redacted]

[redacted]

[redacted]

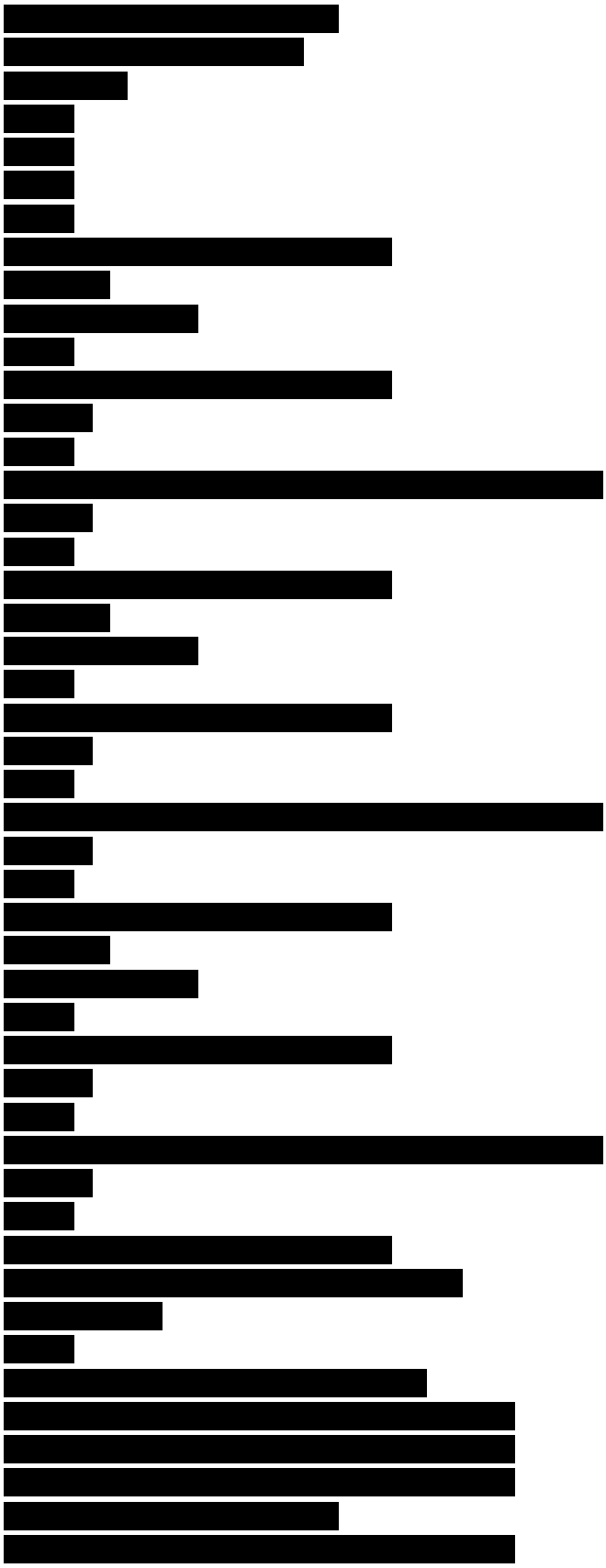


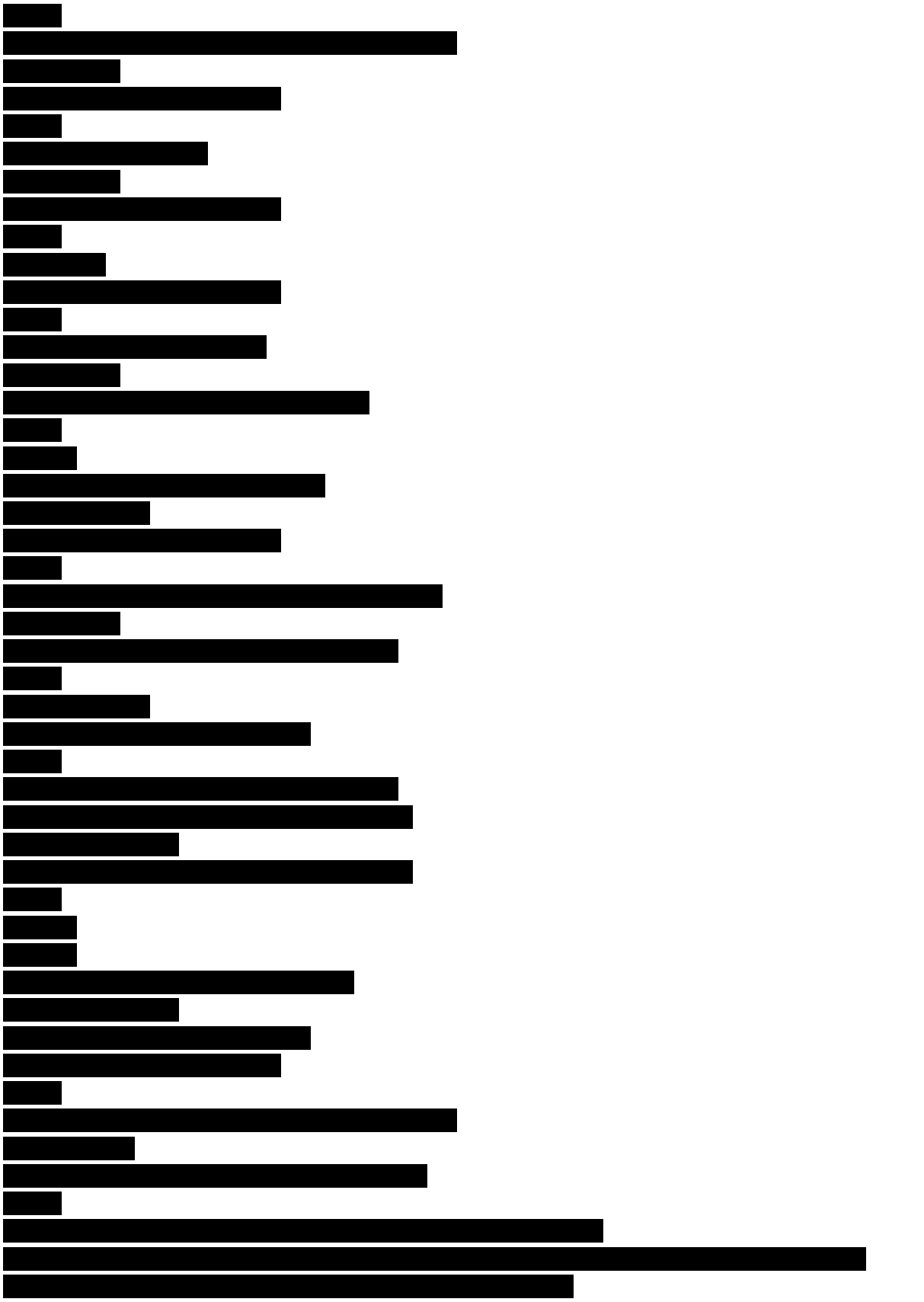
[redacted]

Letter assignments for treatments (trt) within the estimate statement above are as follows:

Treatment A: Oxycodone hydrochloride 20 mg single dose orally while fasting.
Treatment B: Placebo single dose orally while fasting.
Treatment C: Gabapentin 600 mg single dose orally while fasting.
Treatment D: Gabapentin 1200 mg single dose orally while fasting.
Treatment E: Gabapentin 600 mg + oxycodone hydrochloride 20 mg single dose orally while fasting.
Treatment F: Gabapentin 1200 mg + oxycodone hydrochloride 20 mg single dose orally while fasting.

Sample SAS code for Triples Test:





[redacted]

Appendix 2. List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC	area under the curve
AUEC	area under the effect-time profile from time zero to the last quantifiable effect
BP	blood pressure
C_{max}	maximum observed concentration
CRU	clinical research unit
CV	coefficient of variation
ECG	electrocardiogram
E_{max}	maximum effect
GABA	gamma-amino butyric acid
HCl	hydrochloride
IR	immediate release
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	pulse rate
Q_1	first quartile (25^{th} percentile)
Q_3	third quartile (75^{th} percentile)
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SD	standard deviation
SoA	Schedule of Activities
T_{max}	time of maximum concentration
VAS	visual analog scale