NCT05053126

Protocol *A0081365*

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

Statistical Analysis Plan
(SAP)

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TABLE OF CONTENTS

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 12 Nov 2020	Original 12 Nov 2020	N/A	N/A
1.1/ 14 Mar 2022	2.0/ 24 Dec 2020	To update the sample size of Enrolled and Completer populations To include information of safety endpoint To update the definition of completer population and evaluable population To outline how to handle repeated VAS values	• Section 2.2: updated sample size of Enrolled and Completer populations • Section 3.5: Repeated VAS values will be averaged for statistical analysis • Section 3.6: added definition of AE • Section 3.6: added listing of clinical safety laboratory test • Section 3.6: added parameter of ECG and physical examination, specified the potential clinical concern • Section 3.6: added ECG as part of standard safety summary • Section 4: Completer population definition updated to be more in line with FDA guidance for abuse liability studies. • Section 3.8: added the electrocardiogram analyses • Section 7: added the exploratory analyses
2.0/ 05 Oct 2022	3.0/ 17 Nov 2021	To add Study Treatment To update secondary endpoint To modify Evaluable Population and Completer for Sensitivity Analysis Defining PK based Protocol Deviation Missing pre-dose VAS score Format Change	• Section 2.3: Study Treatment • Section 3.2: Add Feeling Sick", "Nausea", "Sleepy", and "Dizzy" as part of secondary endpoint • Section 4: Change the Evaluable Population to be based on Modified Completer Population • Section 4: Remove Completer for Sensitivity Analysis • PK deviations are pre-defined based on PK results according to PK expectation. • The neutral VAS score will be used as the baseline value for Emax and AUEC calculation when the pre-dose VAS is missing. • Updated sponsor name, fix typo

		Clarify the statistical model will be used in 6.4 Treatment by period interaction testing Levene's Test	• ANOVA was changed to linear mixed-effects model per FDA guidance and comment. • The treatment by period interaction testing was removed from the text in this plan, as it is not possible to test in this study as it is confounded with Carryover effect. • Proc mixed model with Kenward-Roger method will be used, the Levene's test will not be performed
3.0/ 26 Oct. 2022	3.0/ 17 Nov 2021	Clarify major PK deviations and evaluable population	• Adding high pre-dose criteria. • Clarify the Major PK deviation introduced Evaluable population.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study A0081365. 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.

LYRICA® (pregabalin) immediate release (IR) is indicated for neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, neuropathic pain associated with spinal cord injury and adjunctive therapy for the treatment of partial onset seizures in patients 1 month of age and older.

Pregabalin is an analogue of the neurotransmitter gamma-amino butyric acid (GABA). Its mechanism of action has not been established, but it has a similar pharmacological profile to that of gabapentin. Despite being a derivative of GABA, it is not active at GABA receptors and does not appear to mimic GABA physiologically. Pregabalin is not known to be active at receptor sites associated with drugs of abuse; however, several animal models of anxiolytic activity have demonstrated that pregabalin may have antianxiety effects similar to classic benzodiazepines. Pregabalin is not known to be active at receptor sites associated with drugs of abuse; however, pregabalin is associated with central nervous system adverse effects such as somnolence and confusion,[1] and might cause decreased respiratory rate and the combined use of pregabalin and opioids may increase overdose risk.[2] The abuse potential of pregabalin has been shown to be particularly high among opioid addicts and other substance-dependent patients.[3-4]

In a study of recreational users (N=15) of sedative/hypnotic drugs (Protocol Clinical Study Report [CSR] 720-30015, 1008-098: Abuse Liability of Pregabalin (CI-1008) in Recreational Sedative/Alcohol Users), including alcohol, pregabalin (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose).[5] In controlled clinical studies in over 5500 patients, 4% of pregabalin treated patients and 1% of placebo treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1% to 12%.[6]

Pregabalin is a Schedule V controlled substance. Since Lyrica® was approved on 30 December, 2004, the epidemiological studies showed that pregabalin may be used in conjunction with opioids to enhance the 'high' obtained from opioids.7-9 In addition, observational studies have suggested pregabalin is associated with drug overdose death among individuals with concomitant opioid use.3,10 A clinical trial (rather than a nonclinical or observational study) is required to evaluate the abuse potential of pregabalin. As a consequence, the FDA requires this post-authorization safety study (PASS) to evaluate pregabalin in a cross-over design with comparison to placebo and a positive control, oxycodone hydrochloride (HCl), regarding abuse-related subjective responses, physiological responses (including an assessment of respiratory depression), and drug pharmacokinetics (PK) in a healthy non-drug dependent population with drug abuse experience.

2.1. Study Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• *To determine the abuse potential of orally administered pregabalin taken concomitantly with oxycodone HCl in non-dependent, recreational opioid users under a fasted condition.*	• *Bipolar visual analogue scale (VAS) for "Drug Liking" [maxium effect (E_{max})].*
Secondary:	**Secondary:**

• *To evaluate additional pharmacodynamic (PD) effect and PK of pregabalin and oxycodone HCl taken alone and concomitantly in non-dependent, recreational opioid users under a fasted condition.* • *To evaluate safety of pregabalin and oxycodone HCl taken alone and concomitantly in non-dependent, recreational opioid users under a 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 AUEC ($AUEC_1$, $AUEC_2$, $AUEC_3$, $AUEC_4$, $AUEC_8$)].* • *Unipolar VAS for "High" [E_{max}, TE_{max}, AUEClast , and partial AUEC ($AUEC_1$, $AUEC_2$, $AUEC_3$, $AUEC_4$, $AUEC_8$)].* • *Bipolar VAS for "Take Drug Again" at 24, 36, 48 hour postdose.* • *Bipolar VAS for "Overall Drug Liking" at 24, 36 and 48 hours postdose.* • *Unipolar VAS for "Good Drug Effect"* • *Unipolar VAS for "Bad Drug Effect"* • *Unipolar VAS for "Any Drug Effect"* • *Pupil size (diameter).* ***Pharmacokinetic Endpoints:*** • *C_{max}, T_{max}, and area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUC_{last}) of pregabalin and oxycodone.* • *Area under the plasma concentration-time profile from time zero extrapolated to infinity*

	time (AUC_{inf}),)and half-life ($t_{½}$), if data permits,of pregabalin and oxycodone. • *Partial AUCs (AUC_1, AUC_2, AUC_3, AUC_4, AUC_8) of pregabalin and oxycodone.* ***Safety Endpoints:*** • *Vital signs include respiratory rate (RR), blood pressure (BP), pulse rate (PR).* • *Oxygen saturation of hemoglobin (SpO_2).* • *Physical examination.* • *12-lead electrocardiogram (ECG).* • *Clinical labs and AEs.*
Tertiary/Exploratory:	**Tertiary/Exploraory:**
• *Exposure-response relationship between pregabalin 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 pregabalin concentrations and selected PD endpoints (Biploar 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% female) 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 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 SoA from the protocol:

1. *Visit 1, Screening will occur within 28 days prior to Visit 2.*
2. *Visit 2, Qualification Phase will require inpatient stay at the Clinical Research Unit (CRU) for 3 nights:*
    a. *Naloxone Challenge Phase, Day -1;*
    b. *Drug Discrimination, Days 1 and 2 will require inpatient stay at the CRU for 2 nights;*

c. End of Drug Discrimination requires an inpatient stay at the CRU overnight to ensure discharge occurs 24 hours after receiving oxycodone or placebo;

d. 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.

3. Visits 3 to 8, Treatment Phase will require a total of 18 overnight inpatient stays at the CRU:

a. Each visit will require an inpatient stay at the CRU of 3 nights;

b. Each visit will be separated by a washout period of at least 4 days. The washout period is calculated between two subsequent study drug administraitons.

4. End of Study Assessments will be at the CRU to occur 48 hours after completing the last study drug dosing or 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: Placebo single.
- Treatment B: Oxycodone HCl 20 mg.
- Treatment C: Pregabalin 300 mg.
- Treatment D: Pregabalin 450 mg.
- Treatment E: Pregabalin 300 mg + oxycodone HCl 20 mg.
- Treatment F: Pregabalin 450 mg + oxycodone HCl 20 mg.

3. ENDPOINTS AND BASELINE VARIABLES DAY -1: 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 observed effect (E_{last})*	*Linear trapezoidal method*
$AUEC_1$	*Area under the effect-time profile from time zero to 1hour 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", "Sleepy", and "Dizzy" and "Any Drug Effect" as well as pupil size (diameter) will be collected at the time points shown in the SoA of the protocol.

3.3. PK 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.*

		~~*Linear/Log trapezoidal method*~~
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 measurements of psychometric and pupillometry 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 (High only) 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

AE is defined as any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

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 taken.

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

For clinical safety laboratory assessment. Blood and urine samples will be collected at the time points specified in the schedule of activities to conduct hematology, coagulation, chemistry and urinalysis analyses. See Table 4 for the list of clinical safety laboratory tests to be performed:

Table 4. ***Laboratory Test***

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and creatinine	pH	FSH[b]
Hematocrit	Glucose (fasting)	Glucose (qual)	Urine drug screening[c]
RBC count	Calcium	Protein (qual)	Alcohol breathalyzer or
MCV	Sodium	Blood (qual)	urine
MCH	Potassium	Ketones	β-hCG[d]
MCHC	Chloride	Nitrites	Hepatitis B surface
Platelet count	Total CO2 (bicarbonate)	Leukocyte esterase	antigen
WBC count	AST, ALT	Urobilinogen	Hepatitis B core
Total neutrophils (Abs)	Total bilirubin	Urine bilirubin	antibody
Eosinophils (Abs)	Alkaline phosphatase	Microscopy[a]	Hepatitis C core
Monocytes (Abs)	Uric acid		antibody
Basophils (Abs)	Albumin		Human
Lymphocytes (Abs)	Total protein		immunodeficiency virus
	Additional Tests		HAV IgM
	(Needed for Hy's Law)		HAV IgG
	AST, ALT (repeat)		
	Total bilirubin (repeat)		
	Albumin (repeat)		
	Alkaline phosphatase		
	(repeat)		
	Direct bilirubin		
	Indirect bilirubin		
	Creatine kinase		
	GGT		
	PT/INR		
	Total bile acids		
	Acetaminophen drug		
	and/or protein adduct		
	levels		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; HAV IgG = hepatitis A virus immunoglobulin G; HAV IgM = hepatitis A virus immunoglobulin M; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.
a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Serum or urine β-hCG for female participants of childbearing potential.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 to 35 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

For electrocardiograms, twelve (12)-Lead ECGs should be collected at times specified in the Schedule of Activities (SoA) section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. ECG values of potential clinical concern are listed in protocol Appendix 7. Continuous cardiac monitoring will also be performed during the Treatment phase as noted in the SoA. The time, duration, and description of any clinically significant abnormal rhythm will be reported as an adverse event using protocol Appendix 7 as a guide as to what is generally considered to be a drug-related adverse event of potential clinical concern.

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. And a brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms. Height and weight will also be measured and recorded as per the Schedule of Activities.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data,*
- *vital signs data,*
- *physical examination,*
- *12-lead electrocardiogram (ECG),*
- *Oxygen Saturation of hemoglobin (SpO2).*

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Table 5. ***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 from 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 0-3.5h postdose (assuming the Tmax of 300/450 mg pregabalin is 1.5h).*
Modified Completer	*The Modified Completer Population will include all randomized participants in the Completer Population, however,will exclude any participant who meet either of the following criteria:* 1. *VAS E_{max} scores are within 5 a 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.*

Population	Description
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 interferewith 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 thatcould potentially affect the PD conclusions of the study. Prior to unblinding the Treatment Phase data, the Sponsor (or designee) will identify protocol violations or 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 pregabalin the following tests will be performed in the order of validation test followed by combination vs. oxycodone and then pregabalin alone vs. oxycodone:

Study Validation:

The sensitivity and integrity of the study will be validated by comparing the mean responsesof 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:

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

$$H_0: \mu_T - \mu_C \geq 0.2(\mu_C - \mu_P) \text{ versus } H_a: \mu_T - \mu_C < 0.2(\mu_C - \mu_P).^{12}$$

The combination of pregabalin 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 pregabalin plus oxycodone – 1.2 * oxycodone alone + 0.2 * placebo to be positive is less than 0.05.

Secondary:

1. *Does pregabalin (L) produce mean responses that show less abuse potential than*

oxycodone HCl (C)?

$$H_0: \mu_C - \mu_L \leq 0.2(\mu_C - 50) \text{ versus } H_a: \mu_C - \mu_L > 0.2(\mu_C - 50).^{13}$$

2. *Does pregabalin (L) produce mean responses that show abuse potential similar to placebo (P)?*

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

3. *Does pregabalin (L) produce mean responses that show less abuse potential than pregabalin plus oxycodone HCl (T)?*

$$H_0: \mu_T - \mu_L \leq 0.2(\mu_T - 50) \text{ versus } H_a: \mu_T - \mu_L > 0.2(\mu_T - 50).^{13}$$

For each of the pregabalin hypothesis, the statistical significance of the test will be assessed for all doses of pregabalin.

5.2. General Methods

Statistically, the study will be evaluated as a safety study. Consequently, the null hypothesis for pregabalin 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 post-dose data; these will be the primary PD analyses.

5.3. Potential Additional Analysis

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

6. ANALYSES AND SUMMARIES

6.1. Study Validity of 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, a carryover variable and sequence as fixed effects, and participant nestedwithin 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 (ie, 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 pregabalin and oxycodone will not be performed.

6.2. Analysis of Primary and Secondary Endpoint

A linear mixed-effects model with treatment, period, 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 Emax) produced by pregabalin, oxycodone HCl and placebo at a significance level of 0.05 (1-sided).

The primary PD endpoint is the Emax of bipolar VAS for "Drug Liking".

The principal parameters for the primary and secondary endpoints will be summarized by treatment using descriptive statistics (mean, standard error [SE], median, first and third quartiles, minimum and maximum). These parameters will be analyzed using a mixed-effect model with treatment, period, 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 95% confidence interval will be provided for the comparisons of pregabalin (300 mg and 450 mg) plus oxycodone versus oxycodone IR 20 mg. Data will be summarized graphically, where appropriate.

The study validation comparisons will be:

- Oxycodone HCl IR 20 mg vs. placebo.

The primary treatment comparisons will be:

- Pregabalin 300 mg plus oxycodone HCl IR 20 mg vs. oxycodone HCl IR 20 mg;
- Pregabalin 450 mg plus oxycodone HCl IR 20 mg vs. oxycodone HCl IR 20 mg.

The secondary treatment comparisons will be:

- Pregabalin 300 mg vs. placebo;
- Pregabalin 450 mg vs. placebo;
- Pregabalin 300 mg plus oxycodone HCl IR 20 mg vs. placebo;
- Pregabalin 450 mg plus oxycodone HCl IR 20 mg vs. placebo;
- Pregabalin 300 mg vs. oxycodone HCl IR 20 mg;
- Pregabalin 450 mg vs. oxycodone HCl IR 20 mg;

- Pregabalin 300 mg plus oxycodone HCl IR 20 mg vs. pregabalin 300 mg;
- Pregabalin 450 mg plus oxycodone HCl IR 20 mg vs. pregabalin 450 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.

6.3. Sensitivity/Supplementary Analyses

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

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[11]:

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

[redacted]

3. Calculate s^2 as follows:

[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.

6.4. 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, 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 meansand 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.

6.5. Exploratory Analysis

As an exploratory analysis, the time course of the different subjective measures in relation to each other (and to abuse-related AEs) may 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.

6.6. Pharmacokinetic Analysis

Pregabalin and oxycodone PK parameters (Table 3) will be calculated for each participant/period/analyte using noncompartmental analysis of concentration-time data. Samples below the LLOQ were set to 0 for analysis. Actual sample collection times were used for the PK analysis.

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 Pregabalin concentration, the 300 mg dose period (either mono- or combo- dose) will be used as the reference geometric mean.

Any period with the pre-dose concentration over 5% of the Cmax of the same period will be defined as major protocol deviation for that period.

A subject at any period classified as a major protocol deviation will be further excluded from the Evaluable Population for that period.

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 (eg, group averages, standard deviation [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 pregabalin and oxycodone will be presented. Concentrations will be listed and summarized by PK sampling time and treatment for each analyte.

6.7. 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, continuous cardiac monitoring, SpO_2 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.

6.8. Electrocardiogram Analyses

Electrocardiogram results collected at Screening will be listed.

7. EXPLORATORY ANALYSES

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

8. INTERIM ANALYSES

8.1. Introduction

No formal interim analysis will be conducted for this study.

9. REFERENCES

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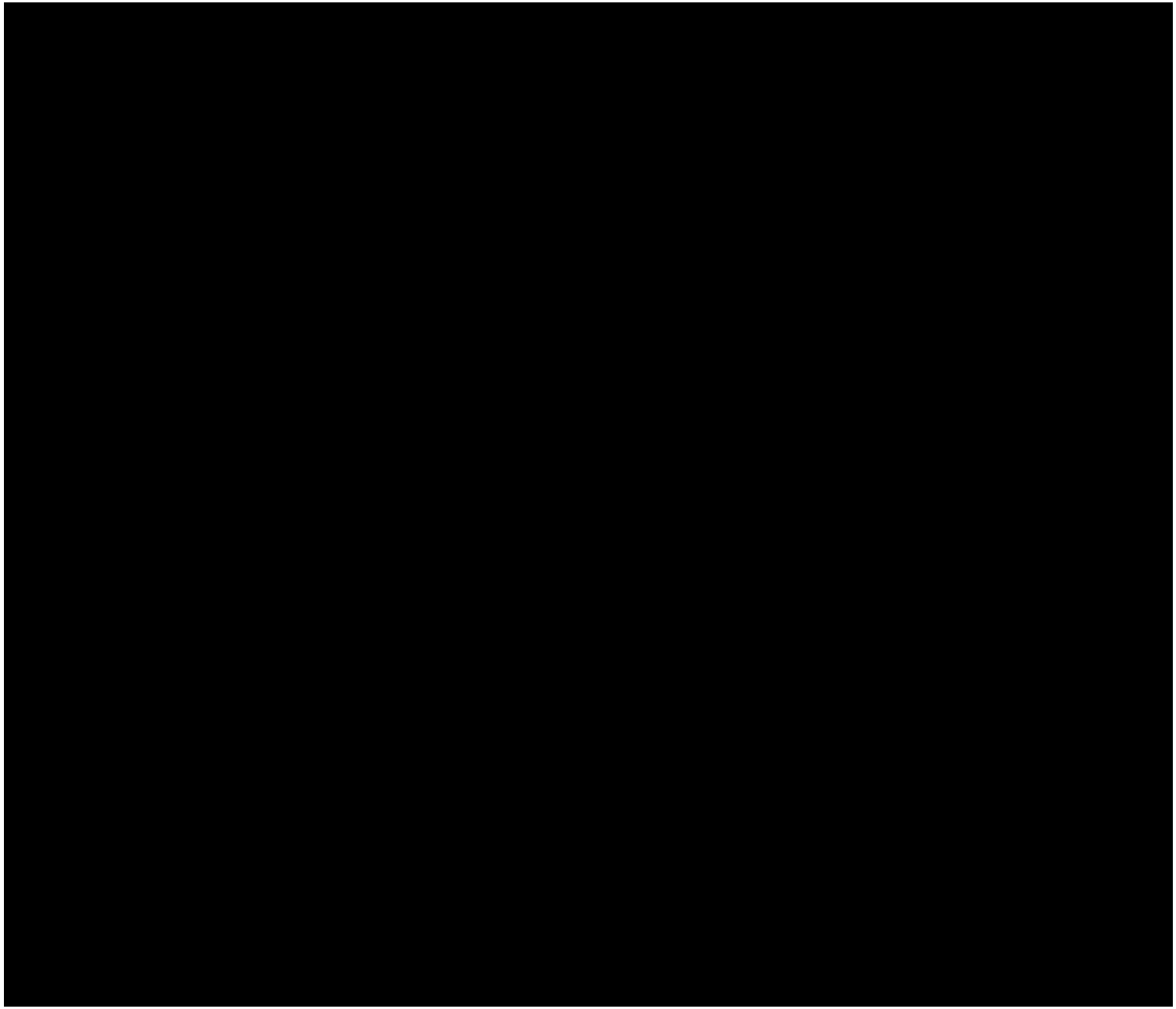
Appendix 1. SAS Code

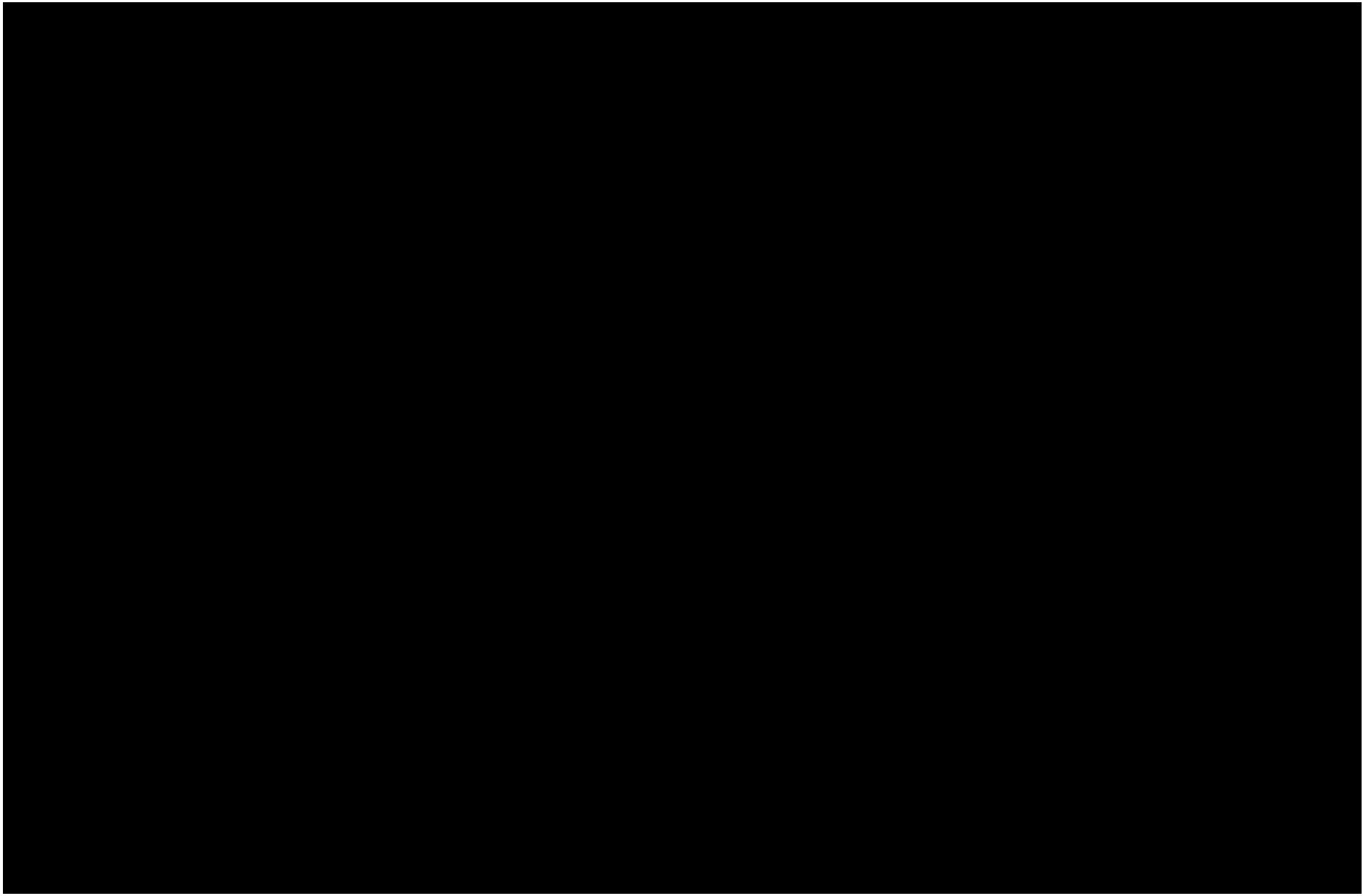
Sample SAS code for PROC MIXED:

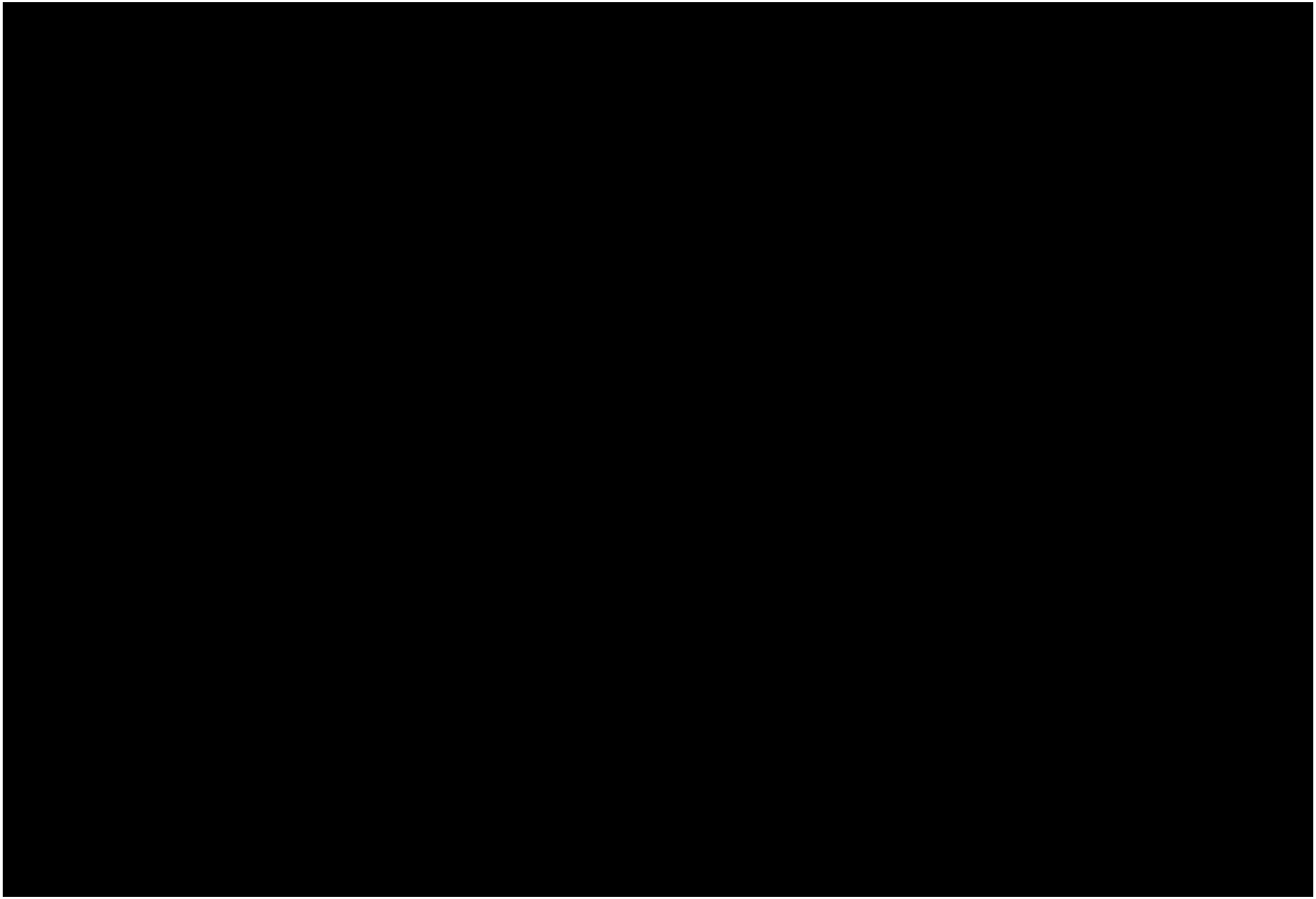
Create a dummy variable, “carryover”, for Periods 2, 3, 4, 5, and 6, carryover is assigned as follows:

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

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





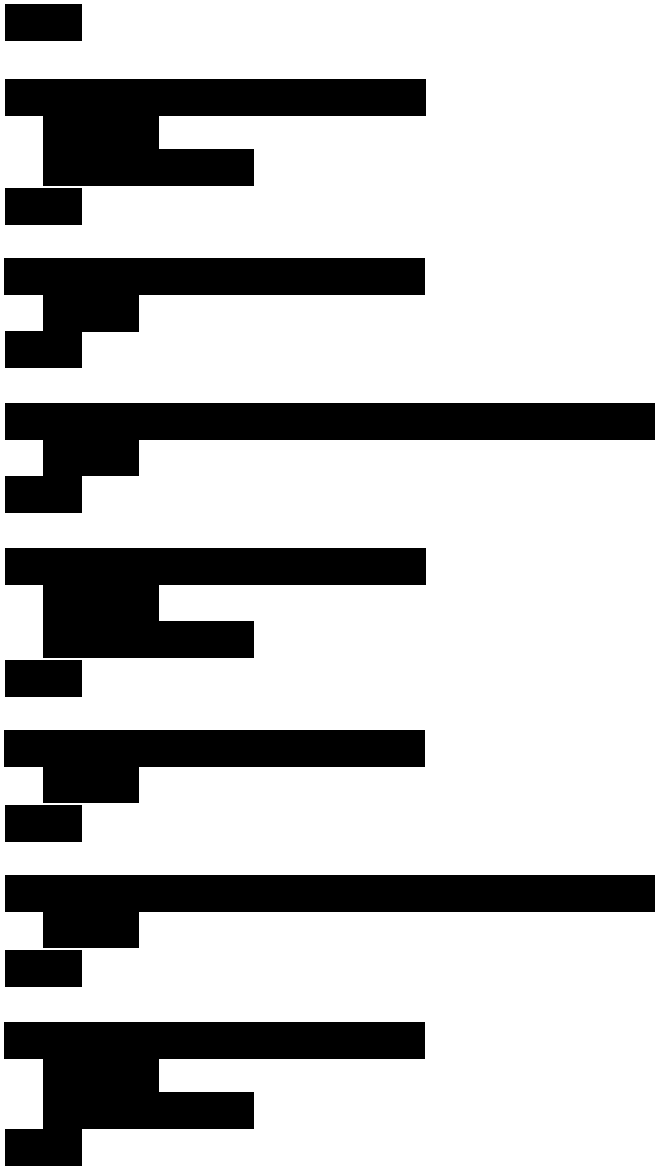


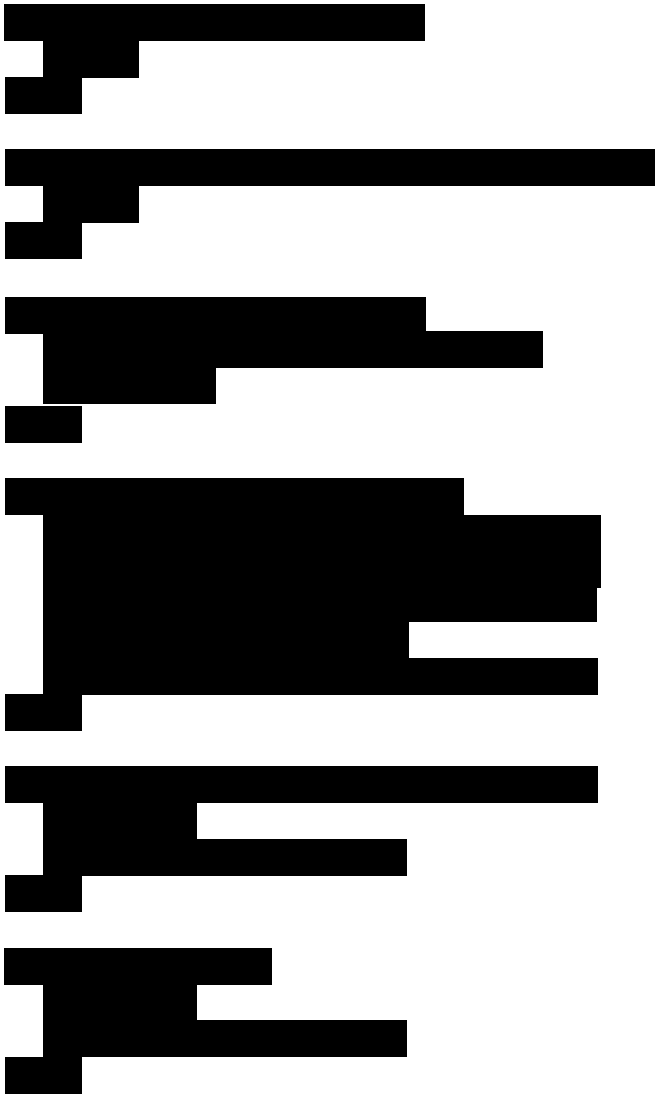
[redacted]

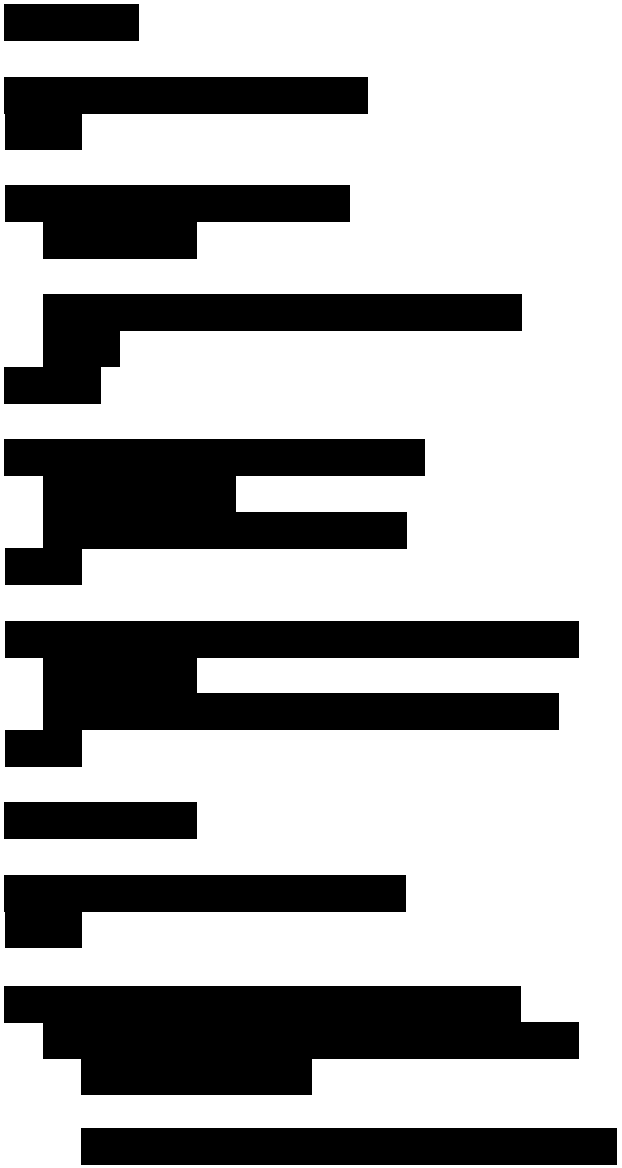
Letter assignments for treatments (trt) within the estimate statement above are as follows:

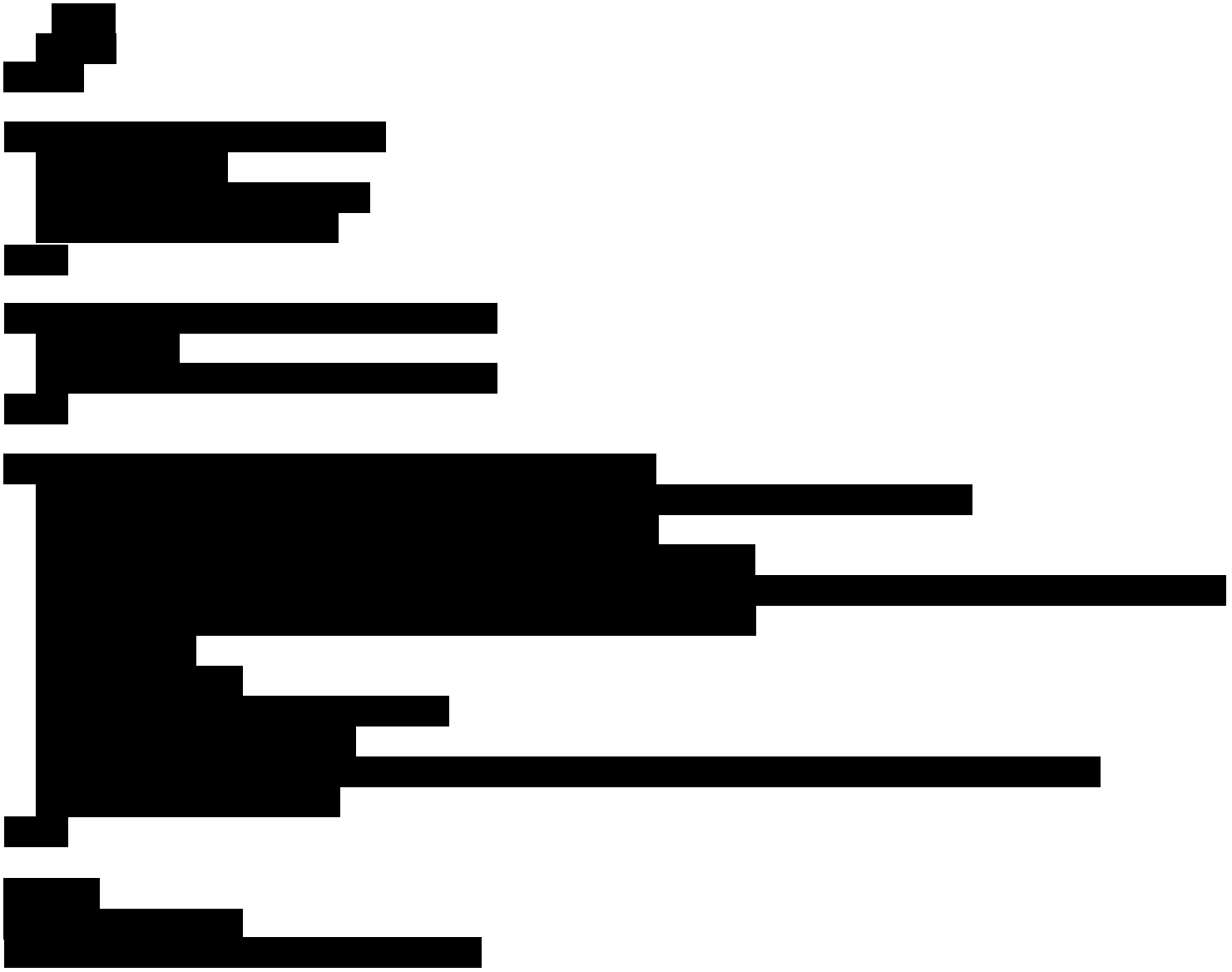
Treatment A: Placebo single dose orally while fasting.
Treatment B: Oxycodone HCl 20 mg single dose orally while fasting.
Treatment C: Pregabalin 300 mg single dose orally while fasting.
Treatment D: Pregabalin 450 mg single dose orally while fasting.
Treatment E: Pregabalin 300 mg + oxycodone HCl 20 mg single dose orally while fasting.
Treatment F: Pregabalin 450 mg + oxycodone HCl 20 mg single dose orally while fasting.

[redacted]









[redacted]

Appendix 2. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUEC	area under the effect-time profile from time zero to the last quantifiable effect
BP	blood pressure
BUN	blood urea nitrogen
β-hCG	beta human chorionic gonadotropin
Cmax	maximum observed concentration
CRU	Clinical Research Unit
CV	coefficient of variation
ECG	electrocardiogram
Emax	maximum effect
Emax(P)	maximum effect for placebo
Emax(Oxy20)	maximum effect for oxycodone HCl IR 20 mg
FSH	follicle stimulating hormone
GABA	gamma-amino butyric acid

GGT	**gamma glutamyl transferase**
HAV IgG	**hepatitis A virus immunoglobulin G**
HAV IgM	**hepatitis A virus immunoglobulin M**
HCl	**hydrochloride**
IR	**immediate release**
INR	**international normalized ratio**
PD	**pharmacodynamic(s)**
PR	**pulse rate**
PT	**prothrombin time**
QTc	**corrected QT**
MCH	**mean corpuscular hemoglobin**
MCHC	**mean corpuscular hemoglobin concentration**
MCV	**mean corpuscular volume**
RBC	**red blood cell**
WBC	**white blood cell**
PK	**pharmacokinetic(s)**
PR	**pulse rate**
Q1	**first quartile (25th percentile)**
Q3	**third quartile (75th percentile)**
RR	**respiratory rate**
SAE	**serious adverse event**
SAP	**statistical analysis plan**
SD	**standard deviation**
SoA	**Schedule of Activities**
Tmax	**time of maximum concentration**