Study Title: Clinical study to investigate the effect of the combination of psychotropic drugs and an opioid on ventilation

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Statistical Analysis Plan

SCR-009: Clinical study to investigate the effect of the combination of psychotropic drugs and an opioid on ventilation

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Contents

Table of Abbreviation

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
CI	confidence interval
CV	coefficient of variation
C_{max}	maximum observed concentration
ECG	electrocardiogram
eCRFs	electronic case report forms
FDA	Food and Drug Administration
IV	intravenous
K_{el}	elimination rate
pCO_2	partial pressure of carbon dioxide
$P_{ET}CO_2$	end-tidal pCO_2
PD	pharmacodynamic
PK	pharmacokinetic
SD	standard deviation
SOP	standard operating procedures
TEAE	treatment-emergent adverse event
T_{max}	time of maximum concentration (C_{max})
$t_{1/2}$	terminal half-life
VE55	minute ventilation at 55 mm Hg $P_{ET}CO_2$
ΔVE55	baseline-adjusted VE55
VRT	Ventilatory recruitment threshold

Change Log

Version	Section	Changes
2.0	General	**Number of subjects/cohort** Language has been added to account for flexibility in enrolling subjects in the event that 5 subjects are not eligible to enroll at check-in (e.g., "Participants will enter the clinic on a staggered basis in cohorts of approximately five…")
	5	**Definition of a complete rebreathing procedure** Language has been added to define what is needed for a procedure to be included in the planned analysis (e.g., "A rebreathing assessment will be considered complete if the subject makes it through the entire procedure at a specific timepoint, if there are no identifiable issues with how the procedure was conducted, and if the VE55 regression converges. Potential issues with how the procedure was conducted can include …"
	7.3.1.1	**Examples of poor-quality rebreathing procedure results added to the protocol** "If the subject's data do not follow these trends due to a leak in the apparatus (e.g., incomplete seal between the mask and subject's face), inaccurate readings from the pneumotach, or due to issues in operator recording of the data, the run will not be considered completed and will be excluded from subsequent data analysis."
	7.3.1.1	**Data regression and outlier handling** Language added to allow for linear regression or additional removal of outliers if the initial nonlinear regression fails to converge.
	7.3.1.2, 7.3.1.3, 7.3.1.4	**Missing baseline values** Language has been added to describe how missing subject baseline values will be handled throughout the study (e.g., "Part 1: If a subject's baseline VE55 for a treatment period is not available, then the baseline value for that period will be calculated based on the median of all other baseline values for that subject from other study periods. If a subject does not have any completed baseline VE55 data, the subject will be assigned a baseline VE55 equal to the median of the Part 1 population.…")
	General	**Typographical changes included throughout**
3.0	3.1.3	**PD assessment timepoints for Part 2** Rebreathing assessment timepoints for Days 1, 4, and 5 of each treatment period in part 2 of the study have been updated as per the protocol.
	4.3	**Exploratory endpoints clarification** Additional exploratory endpoints were added based on review of other published studies. Language has been added to clarify that the exploratory endpoints will be calculated for all stages of each rebreathing assessment

5	**Procedures for blinded review of rebreathing assessments** Language was added outlining that all rebreathing assessments will undergo blinded review for assessing completeness of the rebreathing data including individual physiologic components/measurements.
6	**Exclusion of anomalous results for pupillometry assessment** Language has been added to clarify that measurements automatically flagged as anomalous by the quantitative pupillometer device will not be used in analysis (per device manufacturer and manual recommendations).
7.3.1.1	**Identification of Outlying Data Points for Regressions and Exploratory Endpoint Calculations** In addition to automated approaches, outlying values for the linear regression and exploratory endpoints will be identified during blinded review. Any automatically calculated values that do not accurately capture the underlying data will be flagged and both blinded reviewers will confer to determine if removal of outliers should be performed, and automated calculations will be re-run.
7.3.1.1, 9.2	**Regression method for calculating VE55** Review of blinded data revealed that the nonlinear regression method does not always converge. Linear regression on the rebreathing data where minute ventilation increases linearly as end-tidal pCO2 increases will be used as the primary method for determining VE55.
General	**Typographical changes included throughout**

1. Introduction

This document outlines the proposed statistical methods for data analysis of data collection from Protocol 'SCR-009 Clinical study to investigate the effect of the combination of psychotropic drugs and an opioid on ventilation'.

2. Study Objectives

2.1 Primary Objective

The primary objective is to study whether combining psychotropic drugs (Part 1 – midazolam; Part 2 - paroxetine, quetiapine) with an opioid (oxycodone) decreases the ventilatory response to hypercapnia compared to an opioid alone.

2.2 Secondary Objectives

Secondary objectives include the following:

- To study whether each psychotropic drug (paroxetine, quetiapine, or midazolam) affects the pharmacokinetics (PK) of oxycodone.
- To study whether each drug (oxycodone, paroxetine, quetiapine, or midazolam) decreases the ventilatory response to hypercapnia on its own.

2.3 Exploratory Objectives

Exploratory objectives include the following:

- To study whether there is a direct pharmacodynamic (PD) interaction between each psychotropic drug and oxycodone.
- To summarize additional PK parameters and PD measurements collected during the study.

3. Study Overview

The study will be divided into a Lead-in reproducibility assessment phase and two main parts: Part 1 and Part 2. Each of the parts is briefly described below.

3.1 Study Design

3.1.1 Lead-In

The Lead-in reproducibility assessment will have up to 10 healthy volunteer participants. Up to five participants will undergo the reproducibility assessment, and data analysis will be performed. If any changes in study procedures are needed, they will be made at this point. Then,

additional participants will be undergoing the reproducibility assessment (up to a total of 10 in the Lead-in phase), and data will be analyzed.

For the reproducibility assessment, participants will check-in on Day -1, have PD assessments on Day 1 and Day 2 and check-out on Day 3. PD assessments will be performed on Day 1 and 2 at 0, 2, 3, 5, and 6 h. PD assessments will include a Read rebreathing assessment and pupillometry assessments before and after each rebreathing assessment. No dosing or PK sampling is planned for the Lead-In.

3.1.2 Part 1

The study Part 1 will assess the primary, secondary and exploratory endpoints for oxycodone and midazolam and will inform oxycodone dose selection for study Part 2. The study will be a 4-period randomized crossover study with planned dosing of approximately 20 healthy volunteer participants with the following design:

Day -1	Day 1	Days 2-3	Day 4	Days 5-6	Day 7	Days 8-9	Day 10	Day 11
Check-In	Period 1	Washout	Period 2	Washout	Period 3	Washout	Period 4	Checkout

The following 4 treatments will be evaluated over the four study periods. Each subject will be randomized to one of four sequences (i.e., ABCD, BDAC, CADB, DCBA). Participants will enter the clinic on a staggered basis in cohorts of approximately five (i.e., only approximately five participants will undergo dosing, PK assessments, and PD assessments on any given day).

Treatment Code	Treatment
A	Oxycodone + placebo intravenous (IV)
B	Oral placebo + midazolam IV
C	Oxycodone + midazolam IV
D	Oral placebo + placebo IV

Participants will check-in on Day -1 and receive dosing for the four respective periods on Days 1, 4, 7, and 10. There will be two days of washout between each period. Participants will be confined in the study clinic from Day -1 until the morning of Day 11. On dosing days, the dosing, PK, and PD assessments will occur at the following time points:

- Dosing times: 0 h oxycodone, 115 min midazolam
- PK assessment: 0 (pre-dose), 1, 2, 3, 4, 6, 8, 12, 24 h
- PD assessment: 0 (pre-dose), 1, **2**, 3, 4, 6, 24 h

PD assessments will include a Read rebreathing assessment and pupillometry assessments before and after each rebreathing assessment. In addition, pulse oximeter recordings (heart rate and O_2 saturation) will be collected over a 24-h period on each treatment day. The 2-hour time point (bold/underlined above) is when the primary endpoint will be assessed.

The total number of participants to be enrolled is approximately 20. Interim analyses will be performed after approximately 5 subjects finish and the doses of oxycodone and/or midazolam may be adjusted at that time. The oxycodone dose may be increased if the conditional power of concluding a decrease in oxycodone from placebo is less than 90%. Likewise, midazolam dose may be increased from 0.0375 mg/kg to 0.075 mg/kg if the conditional power of concluding a decrease of the combined effect of oxycodone and midazolam compared to oxycodone is less than 80%. The decision to dose escalate either drug will also consider clinical evaluations and whether stopping criteria was attained in any of the participants (refer to study protocol for full list of clinical evaluations and safety stopping criteria). The remaining subjects will complete the study at the updated doses in cohorts of approximately five participants each.

The primary analysis will occur at the 2 h timepoint. If dose adjustments are not needed, the analysis will be based on all subjects. Otherwise, the analysis will be limited to the subjects administered updated doses of oxycodone and/or midazolam.

3.1.3 Part 2

The study Part 2 will assess the primary, secondary and exploratory endpoints for paroxetine, quetiapine and oxycodone. The study will be a 3-period randomized crossover study with planned dosing of approximately 20 healthy volunteer participants. Each treatment period will have 5 days of dosing followed by 7 days of washout between periods.

Day -1	Days 1-5	Days 6 7-11 12	Days 13-17	Days 18 19-23 24	Day 25-29	Day 30
Check-in	Period 1	Checkout Washout Check-in	Period 2	Checkout Washout Check-in	Period 3	Checkout

The following 3-treatments will be evaluated over the three study periods. Each subject will be randomized to one of treatment six sequences (i.e., GEF, FEG, EGF, GFE, FGE, EFG). Participants will enter the clinic on a staggered basis in cohorts of up to approximately five (i.e., only approximately five participants will undergo dosing, PK assessments, and PD assessments on any given day).

Treatment Code	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
E	Check-in	Oxycodone + Placebo	Placebo	Placebo	Placebo	Oxycodone + Placebo	Checkout
F	Check-in	Paroxetine + Oxycodone	Paroxetine	Paroxetine	Paroxetine	Paroxetine + Oxycodone	Checkout
G	Check-in	Quetiapine + Oxycodone	Quetiapine	Quetiapine	Quetiapine	Quetiapine + Oxycodone	Checkout

Participants will check-in on Day -1 and checkout on the morning of Day 6 for each period. Dosing of the 3 drugs will be staggered so that time of maximum concentration (T_{max}) occurs at 5 h for all drugs and the 5-h time point will be used for primary analyses. PD and PK assessments on Days 1, 4, and 5 of each treatment period will occur at the following time points. Paroxetine (or placebo) doses will be administered at time 0 on each day. The first daily dose of quetiapine (or placebo) will occur at 3 h on dosing days, which will also include oxycodone on Days 1 and 5; the second daily dose of quetiapine (or placebo) will be administered at approximately 14 h on Days 1 through 4:

- PK assessment: 0 (pre-dose), 3, 4, 5, 6, 8, 9, 12, 24 h
- PD assessment:
  - Day 1 and 5 of each period: 0 (pre-dose), 4, **5**, 6, 8, 24 h
  - Day 4 of each period: 0 (pre-dose), 4, **5**, 6, 24* h

*Note: The 24h assessment on Day 4 and 0h (pre-dose) assessment on Day 5 will be the same assessment and will only be collected once.

PD assessments will include a Read rebreathing assessment and pupillometry assessments before and after each rebreathing assessment. In addition, pulse oximeter recordings (heart rate and O_2 saturation) will be collected over a 24-h period on Day 1, 4, and 5.

Primary assessments for the two psychotropic drugs (paroxetine or quetiapine) combined with oxycodone versus oxycodone alone will occur on Days 1 and 5. Each statistical test is planned to be conducted separately and will report on drug effects after a single dose (Day 1) or approaching steady state drug concentration (Day 5). The comparisons for paroxetine and quetiapine versus placebo will occur on Day 4.

3.2 Sample Size

Approximately 50 healthy participants are planned for enrollment. For this study a participant is considered enrolled if they completed screening and check-in and have been randomized/assigned to one of the study treatments. Up to ten healthy participants are planned for enrollment for the Lead-In Reproducibility Assessment. Approximately 20 healthy participants will be enrolled for the study Part 1 and approximately 20 healthy subjects for the study Part 2. The planned number of subjects allows for a 10% drop out rate during Part 1 and a 20% drop out rate during Part 2.

The primary endpoint is a comparison of minute ventilation at the 55 mm Hg end tidal pCO_2 (VE55), termed VE55, between two treatments (oxycodone with the concomitant medication versus oxycodone alone) at protocol specified timepoints (Part 1: 2 h; Part 2: 5 h on Day 1 and Day 5). Part 1 is powered with consideration to the effect of oxycodone plus midazolam versus oxycodone. After the first cohort has completed, results from both oxycodone versus placebo and oxycodone plus midazolam versus oxycodone will be considered in determining whether the

oxycodone dose, midazolam dose, or both doses need to be changed. Assuming at least a -4 L/min effect size on VE55 and standard deviation (SD) of 5 L/min, there is greater than 90% power at a one-sided significance level. This estimated effect size and variability was determined based on publications using 20 mg oxycodone and a similar experimental technique (Van der Schrier et al, 2017a; Van der Schrier et al, 2017b) where peak VE55 effects of 12-18 L/min were observed with a reported SD of 4 L/min. Because of uncertainty regarding variability with the experimental technique, the effect size at 10 mg oxycodone, and the effect when adding midazolam, the current study utilized putative assumptions for effect size and variability from these published values. In the event that dose escalation of either oxycodone or midazolam are needed, the study has greater than 80% power at a one-sided significant level assuming these same effect sizes at the higher dose or doses and at least 12 subjects with the necessary data. Part 1 is not designed to terminate early for futility or success based on assessment of the first cohort.

Part 2 is powered with consideration to the effect of oxycodone plus concomitant medication (quetiapine or paroxetine) versus oxycodone on day 1 and day 5. Assuming a -4 L/min effect size on VE55 and SD of 5 L/min, there is greater than 90% power at a one-side significance level. The same assumptions and sample size calculations used to design Part 1 were also utilized to design Part 2. Both concomitant medications will be considered as separate tests. Comparisons for Day 1 and Day 5 are considered multiple primary endpoints and will have an adjustment for multiplicity.

This study does not pre-specify enrollment of replacement subjects due to discontinuations. In the event that higher than anticipated discontinuations are noted, the statistical analysis plan may be amended to allow for replacement subjects in specific parts of the study.

4. Study Endpoints

4.1 Primary Endpoints

The primary endpoint is a comparison of the minute ventilation at the 55 mm Hg end tidal pCO_2 point (VE55) of each psychotropic drug (paroxetine, quetiapine, or midazolam) combined with oxycodone vs. oxycodone alone. Part 2 will include a comparison at both Day 1 and Day 5 of treatment.

4.2 Secondary Endpoints

Secondary endpoints are:

- Comparison of VE55 of each psychotropic drug (oxycodone, paroxetine, quetiapine, or midazolam) on its own compared to placebo. Oxycodone and midazolam will be assessed in Part 1, while paroxetine and quetiapine will be assessed in Part 2. For Part 2, this is a comparison of study result on Day 4 from each treatment period.

- The maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of oxycodone alone versus oxycodone in combination with a psychotropic drug (paroxetine or quetiapine or midazolam).

4.3 Exploratory Endpoints

Exploratory endpoints are:

- The PK/PD relationship for study drugs when administered alone vs. in combination.
- Additional pharmacokinetic and pharmacodynamic measures that will be evaluated include:
    - Pharmacokinetics
        - T_{max}
        - Elimination rate constant (K_{el})
        - Terminal half-life ($t_{1/2}$)
    - Pharmacodynamics (respiratory and cardiovascular)
        - Minute ventilation, tidal volume, respiratory rate, $P_{ET}CO_2$, oxygen saturation and heart rate during each stage of the rebreathing assessment
        - Number of apneic events lasting > 10 s (during relaxed baseline breathing with room air and 100% O_2)
        - Slope of the minute ventilation / end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) regression line
        - X-axis intercept of the minute ventilation / $P_{ET}CO_2$ regression line
        - Intercept of mean baseline minute ventilation during 100% O2 breathing with the minute ventilation / $P_{ET}CO_2$ regression line
    - Pharmacodynamics (pupillary) (before and after rebreathing assessments)
        - Maximum pupil diameter before constriction
        - Dynamic pupillary measurements after a light stimulus
            - Minimum diameter at peak constriction
            - Percent change between min/max diameter
            - Latency of constriction
            - Average constriction velocity
            - Maximum constriction velocity
            - Dilation velocity after peak constriction
            - Time to reach 75% recovery of maximum diameter
    - Pharmacodynamics (sedation scores)
        - Ramsey Sedation Scale
        - Visual Analogue Scale

5. Analysis Populations

The rebreathing analysis population for Lead-In, Part 1, and Part 2 will include all subjects who completed at least one rebreathing assessment on any day or at any timepoint.

For calculating the primary endpoint for Part 1 and Part 2, the rebreathing analysis population will be subset to those subjects with data from at least two treatments and rebreathing assessments up to the primary PD endpoint timepoint (2 h for Part 1 and 5 h for Part 2) resulting in complete data for calculating VE55 at the primary PD endpoint timepoint. In Part 2, a subject who discontinues dosing after the primary timepoint on Day 1 but before the primary timepoint on Day 5, would be part of the analysis population for the primary endpoint on Day 1 but not for Day 5.

Subjects in the rebreathing analysis population will be used for the planned primary and secondary analyses related to evaluating drugs effects on the ventilatory response to hypercapnia. If a subject does not contribute data from all treatments due to early discontinuations or other reasons, only those comparisons where the subject has all required data will be performed. For example, to be included in the primary analysis from Part 1 it is necessary that a subject have a completed rebreathing assessment at 2 h for oxycodone with midazolam and oxycodone alone.

A rebreathing assessment will be considered complete if the subject makes it through the entire procedure (e.g., subject makes it to the rebreathing stage with sufficient data collected to estimate VE55) and if there are no identifiable issues with how the procedure was conducted. Potential issues with how the procedure was conducted can include, but are not limited to, a leak from the system (e.g., substantially decreasing O_2 during rebreathing or no evidence of an increase in CO_2 during rebreathing), inaccurate readings from the pneumotach (e.g., non-physiologic baseline minute ventilation readings), or a subject suddenly increasing minute ventilation without subsequent increases in minute ventilation as end tidal pCO_2 increases (suggesting stress-associated or other non-CO_2 mediated hyperventilation confounding the ventilatory response to hypercapnia through $[H^+]$ chemoreceptors). Determination of the completeness of each rebreathing assessment and its individual components/measurements will be performed manually by two members blinded from treatment information (see Section 7.3).

The PK population will include all subjects who receive study drug and have at least 1 estimable PK parameter after dosing.

The safety population will include all subjects who receive at least 1 dose of any of the study drugs.

6. Data Screening and Acceptance

6.1 Handling of Missing or Incomplete Data

The following will be performed:

- PK measurements below the quantification limits will be considered equal to zero for all analyses.
- Missing PK or PD data (e.g., subject discontinued from study; subject could not successfully complete rebreathing at a time point) will not be imputed.
- Pupillometry data collected from the PLR®-3000 pupillometer device flagged as being anomalous based on device error codes will be excluded from analyses.

7. General Statistical Considerations

All data will be presented in data listings by part (i.e., Lead-In, Part 1, and Part 2). Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics.

7.1 Subject Disposition

The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment by study part will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized.

7.2 Demographic and Baseline Characteristics

Continuous demographic and baseline characteristic variables (age, height, weight, and body mass index) will be summarized by study part and by treatment using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). The number and percentage of subjects in each class of categorical demographic and baseline characteristic variables will also be summarized.

7.3 Pharmacodynamic Analyses

7.3.1 Rebreathing Analyses

The primary endpoint is a comparison of the VE55 of each psychotropic drug (paroxetine, quetiapine, or midazolam) combined with oxycodone versus oxycodone alone. Part 1 will be a comparison of the VE55 between oxycodone with midazolam versus oxycodone alone. Part 2 will be a comparison of the VE55 comparison of oxycodone with paroxetine or quetiapine versus oxycodone alone on both Day 1 and Day 5. In Part 2, these will each be treated as separate comparisons as the aim is to determine if there is an interaction with either of the test drugs following single-dose (Day 1) or at approximate steady-state drug levels (Day 5).

7.3.1.1 Analysis of the VE55 and Other Pharmacodynamic Endpoints

For Lead-In, Part 1, and Part 2, VE55 will be determined through regression of time course data collected from the planned rebreathing procedure at each time point. Minute ventilation, end-tidal pCO_2, and other pharmacodynamic measures for secondary and exploratory analyses, will be collected following procedural steps outlined in the rebreathing standard operating procedures (SOP) document.

Figure 1 shows a representative time-course result from a rebreathing procedure, with minute ventilation, oxygen percentage, and end-tidal pCO_2 shown from top to bottom. Throughout the procedure subjects will undergo different steps designed to reduce noise and variability. Initially, subjects breathe room air for 5 minutes and relax as much as possible. Around the 5-minute mark, the valve is turned to allow inhalation of 100% oxygen supply (gas flow of 15 L/min) for 3 min after which they are encouraged to hyperventilate for another 1 min to deplete the CO_2 stores. During this test, participants breathe from a bag filled with a specified gas mixture with an elevated level of CO_2 (93%/7% O_2/CO_2) which stimulates increased ventilation. As the participants breathe from the gas bag, above a certain level of CO_2, participants begin to increase their minute ventilation. This point, known as the ventilatory recruitment threshold (VRT), is the pressure of CO_2 dissolved in the blood (known as pCO_2) required to activate the respiratory chemoreceptors. After the VRT, ventilation increases linearly in a CO_2-dependent fashion.

Each of these steps can be noted on the example figure (note, the example figure has different timing than will be used in the experimental procedure for the study). In this example, relaxation with breathing room air was performed for 3-minutes, as evident by O_2% ranging between 21-23%. From 3 to 7 minutes, the test subject inhaled from 100% O_2, and a corresponding jump in O_2% to near 100% is observed. At approximately 7 minutes to 9 minutes, the test subject begins hyperventilation under 100% O_2, and slight decreases in O_2% and pCO_2 with an increase in minute ventilation are observed. Finally, the test subject begins rebreathing from the 93%/7% O_2/CO_2 bag at 9 minutes. After taking deep breaths, pCO_2 in the rebreathing circuit and the lungs equilibrate and then pCO_2 increases linearly to approximately 55 mm Hg at the end of rebreathing in this subject. During rebreathing, at a certain point an increase in minute ventilation is triggered, and both measures increase until completion of the procedure based on subject tolerability or until other procedure stopping criteria are reached, such as reaching an $P_{ET}CO_2$ 67.5 mmHg; see protocol for full list. If the subject's data does not follow these trends due to a leak in the apparatus (e.g., incomplete seal between the mask and subject's face), inaccurate readings from the pneumotach, issues in operator recording of the data, or the subject not having a linear increase in minute ventilation as end tidal pCO_2 increases prior to reaching pCO2 of 55 mm Hg, the run will not be considered completed and will be excluded from subsequent data analysis that is dependent on the minute ventilation / $P_{ET}CO_2$ regression line.

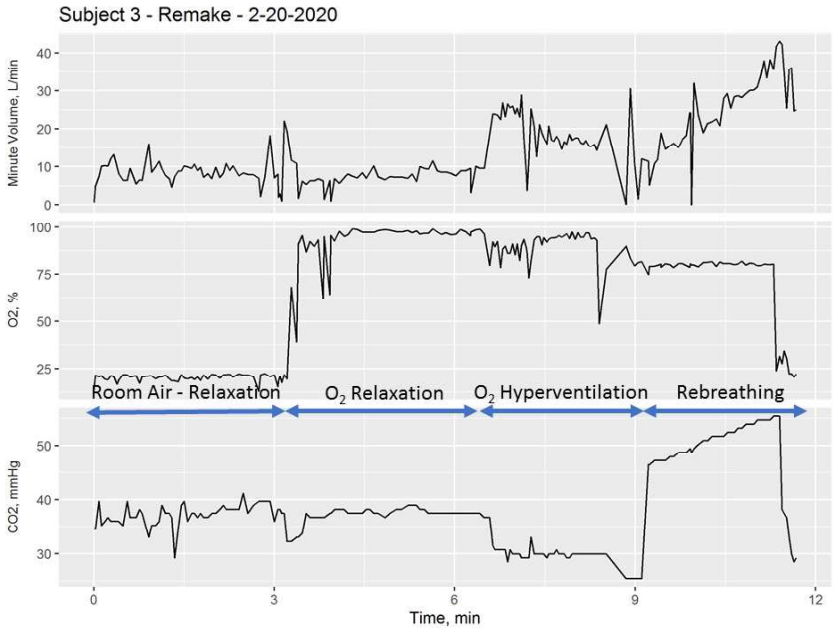

Figure 1: Sample data from a test subject during relaxation, hyperventilation and rebreathing, with minute ventilation, O_2 percentage, and pCO_2 mm Hg over time during these experimental steps.

From these results, minute ventilation and $P_{ET}CO_2$ levels over time will be matched. $P_{ET}CO_2$ will be calculated as the product of the % CO_2 and the barometric pressure. A linear regression will be fit to data from when subjects are rebreathing from the 93%/7% O_2/CO_2 bag (rebreathing stage). Because of potential inconsistencies in when the stage transition may have been flagged by the device operator (pressed while hyperventilation was still ongoing) and as initial breathing with the rebreathing circuit may be below the VRT, the first 15 seconds of data from the rebreathing stage will be removed when calculating the linear regression. In addition, all other pharmacodynamic endpoints listed in Section 4.3 will be automatically calculated.

Because of the potential for outlying data points in the minute ventilation and/or end-tidal pCO_2 signal at each individual breath, it is sometimes necessary to exclude outlying data points from the regression. Such outlying data points can be introduced by subject postural changes, sighing, hiccups, talking, or faulty sensors. In addition, there may be a need to remove additional data at the beginning of rebreathing (e.g., nonlinearity before VRT has been reached) or to remove data at the end of rebreathing (e.g., nonlinearity as subject approaches or exceeds $P_{ET}CO_2$ 55 mmHg).

Outlying values for the linear regression will be identified automatically through evaluation of standardized residuals after performing the initial regression (i.e., standardized residuals > 2). Then, two team members will be provided with time course plots from the full assessment (all rebreathing procedure stages with stage transitions marked) and a linear regression using data

from the rebreathing stage. The two team members will evaluate the completeness of the rebreathing assessment and visually assess the automatically calculated values in comparison to the underlying data. Any automatically calculated values that do not accurately capture the underlying data will be flagged and both reviewers will confer to determine if removal of outliers/noise should be performed, and automated calculations will be re-run. A subject may have incomplete rebreathing data not supporting calculation of VE55 and other linear regression-dependent measures at a specific time point, but other endpoint measures would still be used for exploratory analyses (or the reverse).

The estimated VE55 from the linear regression will be used for primary endpoint analyses in all study parts. All modeling analyses for the regressions will be performed in statistical software.

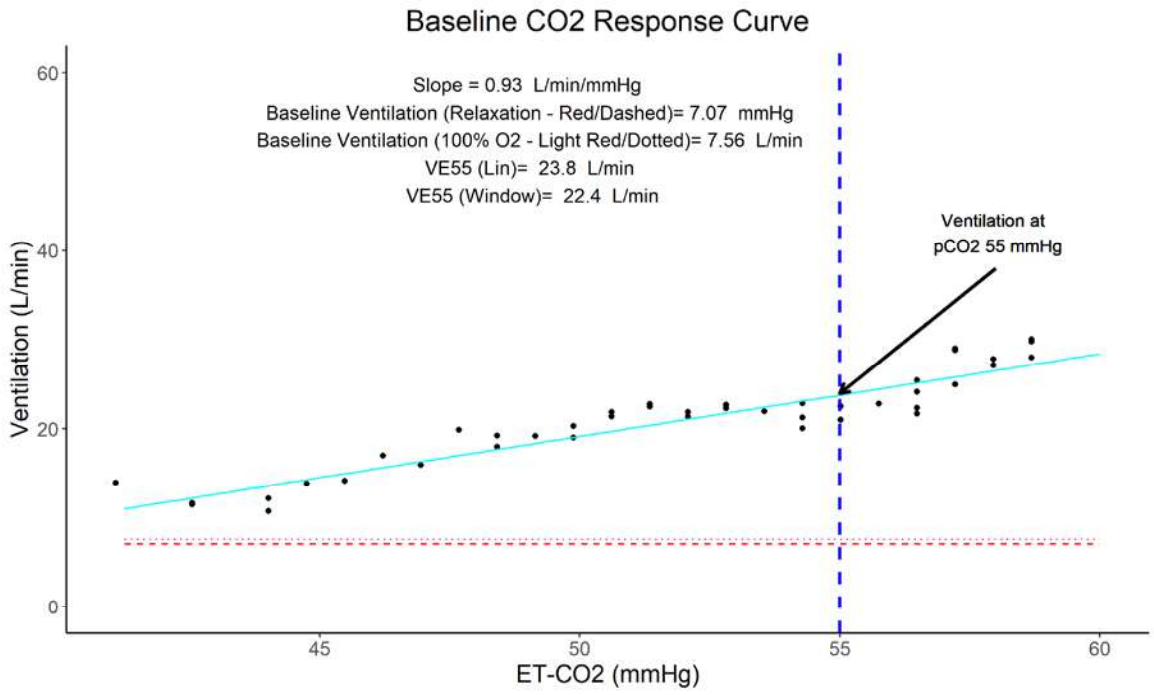

Figure 2: Sample linear regression between minute ventilation and $P_{ET}CO_2$.

This model will be used to predict minute ventilation at pCO_2 of 55 mmHg (i.e. VE55). If a subject does not reach 55 mmHg, the model will be extrapolated to predict the on-treatment minute ventilation at 55 mmHg. Baseline-adjusted VE55 (ΔVE55) will be calculated for each subject at each time point by subtracting on-treatment VE55 from baseline (i.e., time 0 h for Day 1 and 2 in the Lead-In, time 0 h from each period for Part 1, and time 0 h from Day 1 for Part 2).

7.3.1.2 Lead-In Reproducibility Analysis

VE55 data will be summarized by day and time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Both VE55 and ΔVE55 time course profiles will be calculated and plotted for the overall group and individuals. Linear-mixed effect modeling will be used to determine between-occasion variability and between-subject variability from all Lead-In subject data (example below), where USUBJID and OCC are the subject identifier and measurements obtained at different times across the two-day period, respectively. Fixed effects will include baseline VE55 (i.e., VE55 obtained at 0 h of each day). If a subject's baseline VE55 for a specific day is not available, then the baseline value from the other assessment day will be used. If neither is available, the subject will be assigned a baseline VE55 equal to the median of the Lead-In population:

$$VE55 \sim VE55_{base} + (1|USUBJID/OCC)$$

7.3.1.3 Part 1

The primary endpoint (see Section 4.1) for the VE55 analysis in Part 1 will be VE55 at 2 h for oxycodone with midazolam compared to oxycodone alone. VE55 will be compared between treatments using a linear mixed effects model. Fixed effects will include treatment, period, sequence, and baseline VE55 (i.e., VE55 obtained at 0 h on the treatment day). Subject will be included as a random effect on the intercept. If a subject's baseline VE55 for a treatment period is not available, then the baseline value for that period will be calculated based on the median of all other baseline values for that subject from other study periods. If a subject does not have any completed baseline VE55 data, the subject will be assigned a baseline VE55 equal to the median of the Part 1 population. All subjects contributing assessments from both treatments will be included in the analysis. To demonstrate an effect of oxycodone with midazolam ('oxy+mid') compared to oxycodone alone ('oxy'), it is necessary that the lower bound of the one-sided 95% confidence interval (CI) in the least-square mean VE55 difference between treatments < 0 L/min

- H_0: $VE55_{oxy+mid} - VE55_{oxy} \geq 0$ L/min
- H_A: $VE55_{oxy+mid} - VE55_{oxy} < 0$ L/min

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for tests of fixed effects. Normality assumption will be verified using the Shapiro-Wilke test for normality. Homogeneity of variances will be verified using Levene's test. If the data in its original or transformed form does not satisfy assumptions for normality and homogeneity, a Wilcoxon signed-rank test will be used for all comparisons rather than a linear mixed effect model.

For the secondary endpoint (see Section 4.2), VE55 at 2 h for midazolam or oxycodone compared to placebo will be compared using a linear mixed effect model. A significant increase for each treatment compared to be placebo will be concluded if the lower bound of the one-sided

CI of the least-square mean VE55 difference between treatment versus placebo <0 L/min. These comparisons will be performed separately (i.e., 'trt' as 'oxycodone' or 'midazolam') and will be completed regardless of if the primary endpoint passes.

- H_0: $VE55_{trt}$ - $VE55_{placebo} \geq 0$ L/min
- H_A: $VE55_{trt}$ - $VE55_{placebo} < 0$ L/min

Part 1 has a planned interim analysis after approximately 5 subjects complete. The purpose of this assessment will be to determine the conditional power for the study to succeed based upon current assumptions and results obtained from approximately 5 subjects. The analysis does not allow for early termination of the study due to success or futility and will only be used to inform decisions about changing the oxycodone and/or the midazolam dosing. For this determination both the treatment effect for oxycodone compared to placebo and oxycodone with midazolam compared to oxycodone alone will be considered.

As oxycodone alone has been evaluated in previous publications, there is an expectation that oxycodone 10 mg will have a sufficient effect size to differentiate from placebo. However, in the event that the conditional power <90% for concluding the lower bound of the one-sided 95% CI of the least-square mean VE55 difference between oxycodone and placebo < 0 L/min, the oxycodone dose may be escalated to 15 mg. Similarly, if the conditional power <80% for concluding the lower bound of the one-sided 95% CI of the least-square mean VE55 difference between oxycodone and midazolam versus oxycodone alone < 0 L/min, the midazolam dose may be escalated to 0.075 mg/kg. Conditional power calculations will be based on methodology from Jennison and Turnbull (2000):

$$P_{lk}(\theta) = \Phi\left(\frac{-Z_k\sqrt{I_k} - z_{1-\alpha}\sqrt{I_K} - \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right)$$

Where k is the interim stage (k=1 for the present case), K is the stage at which the study will complete (K=2 for the present case), Z_k is the test statistic calculated from the observed data at stage k, θ is the expected difference under the alternative hypothesis, I_k is the interim information level (number_subjects_cohort_1/$SD_{interim}^2$ for the present case) and I_K is the final information level (total_N/[interim_N L/min]^2 for the present case). The decision to dose escalate will also consider observed safety signals from the initial cohort and will not conclude to increase dose solely because conditional power is not achieved.

If either the oxycodone or midazolam dose is increased, the primary and secondary analyses will be based on the remaining subjects in Part 1 and proceed as described above. If neither the oxycodone nor midazolam dose is increased, the planned analyses will use all subjects. As an interim look of the dataset has been performed after the first cohort, the proposed primary and secondary analyses will be updated to only reject the null hypothesis if the lower bound of the

one-sided 95.1% confidence interval < 0 L/min based on the least square mean difference between treatments. This alpha spending allocation follows O'Brien Fleming approach for two planned analyses (i.e., 0.005 for k=1 and 0.0492 for k=2) with the exception that success cannot be concluded at the interim analysis. Testing for normality and homogeneity will proceed as described above.

VE55 data will be summarized by treatment and time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Both VE55 and ΔVE55 time course profiles will be calculated and plotted for the overall treatments and for individuals.

7.3.1.4 Part 2

The multiple primary endpoints (see Section 4.1) for the VE55 analysis in Part 2 will be VE55 at 5 h for oxycodone with paroxetine or quetiapine compared to oxycodone alone on Day 1 and Day 5. VE55 will be compared between treatments using a linear mixed effects model. Fixed effects will include treatment, period, sequence, and baseline VE55 (i.e., VE55 obtained at 0 h on Day 1 for the treatment period). Subject will be included as a random effect on the intercept. Separate linear mixed effects models will be developed for Day 1 and Day 5. If a subject's baseline VE55 for a treatment period is not available, then the baseline value for that period will be calculated based on the median of all other baseline values for that subject from other study periods. If a subject does not have any completed baseline VE55 data, the subject will be assigned a baseline VE55 equal to the median of the Part 2 population. Testing for normality and homogeneity will proceed as described above. In the event that the data does not satisfy assumptions for normality and homogeneity then a Wilcoxon signed-rank test will be used for comparisons.

All subjects contributing assessments from both treatments necessary for a comparison will be included in the analysis. To demonstrate an effect when oxycodone is combined with paroxetine (or quetiapine) compared to oxycodone alone it is necessary that the lower bound of the one-sided 97.5% CI of the least-square mean VE55 difference between treatments be < 0 L/min. Each comparison will be performed separately (i.e., 'trt' as 'paroxetine' or 'quetiapine' and 'day' as 'Day 1' or 'Day 5'). In all, four separate comparisons will be performed:

- H_0: $VE55_{oxy+trt/day}$ - $VE55_{oxy/day} \geq 0$ L/min
- H_A: $VE55_{oxy+trt/day}$ - $VE55_{oxy/day} < 0$ L/min

For the secondary endpoint (see Section 4.2), VE55 at 5 h on Day 4 will be compared between oxycodone with paroxetine or quetiapine and oxycodone with placebo using a linear mixed effect model. Fixed effects will include treatment, period, sequence, and baseline VE55 (i.e., VE55 obtained at 0 h on Day 1 of the treatment period). Subject will be included as a random effect on the intercept. Note, that by Day 4, oxycodone has not been administered since Day 1 and should have washed out. As such, the comparison on Day 4 is viewed as a comparison of

either paroxetine or quetiapine alone versus placebo. Testing for normality and homogeneity will proceed as described above. In the event that the data does not satisfy assumptions for normality and homogeneity then a Wilcoxon signed-rank test will be used for comparisons. A significant increase for each treatment compared to be placebo will be concluded if the lower bound of the one-sided CI of the least square means VE55 difference between treatment versus placebo <0 L/min. These comparisons will be performed separately (i.e., 'trt' as 'paroxetine' or 'quetiapine') and will be completed regardless of if the primary endpoint passes.

- H_0: $VE55_{trt} - VE55_{placebo} \geq 0$ L/min
- H_A: $VE55_{trt} - VE55_{placebo} < 0$ L/min

VE55 data will be summarized by treatment, treatment day (Day 1, 4, and 5), and time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Both VE55 and ΔVE55 time course profiles will be calculated and plotted for the overall treatments and for individuals.

7.3.2 Exploratory Ventilation Measures

Other exploratory respiratory measures will be calculated and summarized from information collected during planned rebreathing procedures (see Section 4.3). Data collected during the procedure will be used to calculate the slope of the minute ventilation / $P_{ET}CO_2$ regression line (output from regression). Data from the initial relaxation/resting portions of the procedure will be used to calculate ventilation, tidal volume and $P_{ET}CO_2$. All measures will be summary by day, treatment, and time, as appropriate for Lead-In, Part 1, and Part 2, respectively, using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Time course profiles for all measures will be calculated and plotted.

Apneic events lasting > 10 seconds will be determined using data collected during the relaxation and preparation portion of the rebreathing procedure (i.e., all recorded data prior to hyperventilation on 100% O_2). An event is defined as the absence of inspiratory flow (as measured by the pneumotachograph) for at least 10 s during this period. These parameters will be summarized using descriptive statistics (number of subjects, number of events) by study part, treatment, day, and time, as appropriate.

7.3.3 Pupillometry Analyses

Maximum pupil diameter before constriction and dynamic pupillary measurements after a light stimulus will be measured during relaxation and after each rebreathing assessment. This will include measurements before and after the rebreathing assessment and from the left and right eye. These exploratory parameters (see Section 4.3) will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum), and time courses summaries of each pupillary measurement will be generated for all treatment groups. Pupillary changes will be compared to baseline measurements (Day 1, 0 h for Part 1 and Part 2; Day 1 or

Day 2, 0 h for Lead-In) and between treatments to evaluate the effect of different interventions on pupillary changes. In addition, time course pupillary changes will be compared to time course ventilatory changes across treatments to evaluate concordance between these measures when subjects receive different drugs and drug combinations.

7.3.4 Sedation Score Analyses

Ramsay Sedation Scale is an observer-based assessment of sedation that will be collected for each subject as during the relaxation period of each rebreathing procedure in Part 1 and Part 2. In addition, subjects will be asked to provide their own assessment of sedation using the Visual Analog Scale during the same relaxation period. These are two measures for assessing an individual's level of sedation and will provide a subjective assessment of how sedated the subject is during the study. These exploratory parameters will be summarized using descriptive statistics, and time courses summaries of both scores will be generated for all treatments from Part 1, and Part 2 (Day 1, 4, and 5).

7.4 Pharmacokinetic Analyses

7.4.1 Plasma Pharmacokinetics

PK parameters will be calculated for the different drugs and metabolites and study days based on data collected from the time of drug administration to the 24-h sample on the specified day. C_{max} and AUC (i.e. AUC_{0-24} for oxycodone, Part 1; $AUC_{3-24,Day1}$ and $AUC_{3-24,Day5}$ for oxycodone, Part 2) will be computed for oxycodone on the specified days (i.e., Day 1 for Part 1 and Day 1 and 5 for Part 2) as part of the secondary endpoints for this study (see Section 4.2). AUC and C_{max} will be calculated for midazolam (Part 1, Day 1) and quetiapine and paroxetine (Part 2, Day 1, 4, and 5) and relevant metabolites as exploratory PK parameters (see Section 4.3).

Additionally, the following exploratory PK parameters will be determined for oxycodone, midazolam, quetiapine, paroxetine, and metabolites on each specified day:

- T_{max} (Part 1 and Part 2 Day 1, 4, and 5)
- Elimination rate constant (K_{el}) (Part 1 and Part 2 Day 1 [oxycodone and metabolites only] and Day 5)
- Terminal half-life ($t_{1/2}$) (Part 1 and Part 2 Day 1 [oxycodone and metabolites only] and Day 5)

The PK parameters will be analyzed using noncompartmental methods based on actual sampling times. All parameters will be calculated using R software and the PKNCA package. Serum concentrations below the limits of quantification will be set to zero for the purpose of this analysis (see Section 6). K_{el} and $t_{1/2}$ for each analyte and subject will only be included if the subject has 3 or more concentration values on the terminal portion of the pharmacokinetic curve

and the linear regression of the log-concentration time curve has an adjusted coefficient of determination (R^2) greater than 0.80.

In Part 1, oxycodone C_{max} and AUC will be log-transformed and the values from oxycodone alone versus oxycodone with midazolam will be compared using a linear mixed effects model (i.e., treatment as fixed effects and subject as random effects) to determine if oxycodone exposures differ between the two treatments. The geometric mean ratio will be determined and no difference in exposure will be concluded if the two-sided 90% confidence interval includes 1. Similar comparisons will be performed between oxycodone with quetiapine or with paroxetine and oxycodone alone based on C_{max} and AUC from Day 1 and Day 5 (separate comparisons) in Part 2.

The PK parameters C_{max}, AUC_{x-24}, T_{max}, and K_{el} will be summarized using descriptive statistics (number of subjects, mean, SD, coefficient of variation [CV], median, minimum, and maximum) on Day 1 for Part 1 and Day 1, 4, and 5 for Part 2 for each active drug and metabolites (note: 'x' for AUC_{x-24} will depend on when the drug is administered and will be 0 h for oxycodone in Part 1, 1.9 h for midazolam in Part 1, 0 h for paroxetine in Part 2, and 3 h for quetiapine and oxycodone in Part 2). Mean and individual concentration-time profiles will be presented in graphs.

7.4.2 PK/PD Analyses

A nonlinear-mixed effect PK/PD model will be developed for ΔVE55 versus time for all treatments (see Section 4.3). The model will be employed using NONMEM modeling software, version 7.3.

The PK/PD analysis will be sequential, first running PK models for each of the four drugs evaluated in this study. These will be one- or two compartment models with linear absorption, as appropriate. The PK modeling will not include covariate exploration but will attempt to model active metabolites for oxycodone and quetiapine that are analyzed. As there is extensive experience with all of these compounds, models from the literature will serve as starting points for model evaluation.

The PD modeling will use predictions from the PK modeling as input. Different model structures will be evaluated, including an effect compartment coupled to an indirect response model or a modified Bateman function. No covariate exploration will be performed for the PD model, though stand-alone interactions between drug effects will be evaluated. A separate modeling analysis plan will be developed for the planned analyses.

7.5 Additional Exploratory Analyses

7.5.1 Sex Hormone Analyses

Estrogen and progesterone levels will be collected at the start of all study days with a rebreathing assessment in the Lead-In, Part 1, and Part 2. These parameters will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) and may be used to explore variation in ventilation and the response to study drugs across the menstrual cycle. Additional details regarding the statistical methods for these analyses will be described in a separate plan.

7.5.2 Genomic Analyses

Gene (genotype) variances may be explored that may contribute to the PK or PD of the study drugs. Additional details regarding the statistical methods for these analyses will be described in a separate plan.

7.6 Safety Analyses

7.6.1 Adverse Events

All adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities. The incidence of treatment-emergent adverse event (TEAEs), organized by system organ class and frequency, will be summarized by seriousness, severity, relationship to treatment, and by treatment at onset of the TEAE. A detailed listing of serious AEs and TEAEs leading to withdrawal will also be provided.

7.6.2 Clinical Laboratory Tests

Clinical laboratory results (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Clinical laboratory results will be classified as normal or abnormal, according to the reference ranges of the individual parameter. The number and percentage of subjects with abnormal laboratory results will be provided. No statistical testing will be performed on clinical laboratory data.

7.6.3 Vital Sign Measurements

Vital sign measurements and changes from baseline will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) by treatment and time point.

7.6.4 Safety 12-lead Electrocardiograms

Safety 12-lead ECG data will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) by treatment and time point.

7.6.5 Pulse Oximetry and Telemetry

Continuous telemetry monitoring will be performed on treatment days for Part 1 and on Days 1 and 5 in Part 2. Events requiring intervention from the staff or discontinuation from the study will be recorded in appropriate logs.

Oxygen saturation measurements obtained from 24-h pulse oximeters recordings will be used to plot time course profiles of oxygen saturation for treatments from Lead-In (Day 1 and 2), Part 1, and Part 2 (Day 1, 4, and 5).

7.6.6 Physical Examinations

Physical examination findings will be presented in a data listing, and abnormal physical examination findings will be recorded as AEs.

7.6.7 Other Safety Data

All concomitant medication usage and medications that changed in daily dose, frequency, or both since the subject provided informed consent will be summarized for each subject.

8. Data Quality Assurance

Completed electronic case report forms (eCRFs) are required for each subject randomly assigned to the study drug. Electronic data entry will be accomplished through the ClinSpark® remote electronic data capture system, which allows for on-site data entry and data management. This system provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for appropriate governmental health or regulatory authorities, without written permission of the sponsor.

9. Appendices

9.1 Randomization Schedule

The study will consist of three separate sections. The first (i.e., Lead-In) will enroll up to10 subjects and has no planned randomization. All subjects will participate in the same set of procedures over two days. No replacement subjects are planned for the Lead-In.

Part 1 is a 4-period, double-blind, crossover study where subjects will be enrolled in cohorts of approximately 5. Subjects will be randomized to one of four sequences (i.e., ABCD, BDAC, CADB, DCBA) where treatment codes and interventions are summarized in the table below. Subjects will be randomized in blocks of 4. The study plans for 1:1 enrollment of males and females, but the randomization will not account for sex and treatment sequence interactions.

Part 2 is a 3-period, double-blind, crossover study where subjects will be enrolled in cohorts of approximately 5. Subjects will be randomized to one of six sequences (i.e., GEF, FEG, EGF, GFE, FGE, EFG) where treatment codes and interventions are summarized in the table below. Subjects will be randomized in blocks of 6. The study plans for 1:1 enrollment of males and females, but the randomization will not account for sex and treatment sequence interactions.

The project biostatistician created the specifications for generating the randomization schedule as described above. A dummy randomization schedule generated in R (version 3.6.3 or later). The project biostatistician will transfer the program used to generate the 'dummy' schedule to the randomization biostatistician (unblinded), who is an independent party and will not be participating in any programming or statistical decisions for the study before breaking the blind. The randomization biostatistician will be responsible for generating the final randomization schedule. The output will be sent only to designated unblinded recipients.

Table 1: Treatment Codes and Treatment Names for Part 1 and Part 2 of SCR-009

SCR-009 Part	Treatment Code	Treatment Name
Part 1	A	Oxycodone/placebo
Part 1	B	Placebo/midazolam
Part 1	C	Oxycodone/midazolam
Part 1	D	Placebo/placebo
Part 2	E	Oxycodone/placebo
Part 2	F	Oxycodone/paroxetine
Part 2	G	Oxycodone/quetiapine

10. References

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