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

Document Title: Informed Consent Form – Study No. SCR-009

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CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY
AND
AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Sponsor/Study Title:	**US Food and Drug Administration / "Clinical Study to Investigate the Effect of the Combination of Psychotropic Drugs and an Opioid on Ventilation."**
Protocol Number:	**SCR-009**
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SUBJECT SCREENING #_____

Please read this form carefully. Take time to ask the study doctor or study staff as many questions about the study as you would like. The study doctor or study staff can explain words or information that you do not understand. Reading this form and talking to the study doctor or study staff may help you decide whether to take part or not. If you decide to take part in this study, you must sign your name and date at the end of this form. You cannot take part in this research study until you sign and date this form.

WHAT IS A VOLUNTEER INFORMED CONSENT?

Please read this consent form carefully. This consent form provides important information about participating in a research study to help you decide whether or not you would like to participate as a research subject. This form contains important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject. You may discuss your decision with your family, your friends and/or your doctor. Take time to ask the study doctor or study staff as many questions about the study as you would like. The study doctor or study staff can explain words or information that you do not understand. If you decide to take part in this study, you must sign your name and date at the end of this form. Your participation is entirely voluntary. If you choose to participate you can change your mind at any time and withdraw from the study. You will not be penalized in any way or lose any benefits to which you would otherwise be entitled if you choose not to participate in this study or if you choose to withdraw. You cannot take part in this research study until you sign and date this form. A copy of the signed and dated form will be provided to you for your record.

You are being asked to take part in a research study which will look at three things:

- How three different study drugs (paroxetine, quetiapine and midazolam) affect the blood level of a fourth study drug (oxycodone) in the body.
- Whether four study drugs (paroxetine, quetiapine, midazolam and oxycodone) on their own affect breathing (for example, if the amount of air you breathe in one minute is less with one of these study drugs compared to how much air you breathe normally).

- Whether there is an interaction between one of three study drugs (paroxetine, quetiapine and midazolam) and oxycodone on breathing, and if there is, what the effects are (that is, if there is a change in the amount of air you breathe when taking oxycodone, is there an additional change seen when also taking one of the additional study drugs).

Paroxetine, quetiapine, midazolam and oxycodone have been approved by the U.S. Food and Drug Administration (FDA). Paroxetine has been approved for treatment of depression; quetiapine has been approved for treatment of bipolar disorder, depression and other psychiatric conditions; midazolam has been approved for sedation with diagnostic or treatment procedures and at higher doses as an anesthetic for surgical procedures; and oxycodone has been approved for treatment of pain. However, their use in this study is investigational. An investigational use is one that is not approved by the U.S. FDA.

Before you decide to take part, you should understand the possible benefits and risks associated with this study. This process is known as informed consent and means that you will:

- Receive detailed information about this research study.
- Have a chance to ask and receive answers to any questions you may have.
- Be asked to read and sign and date this informed consent, once you understand the study and wish to take part.
- Be given a signed and dated copy of this informed consent to keep.

Taking part in this study is entirely voluntary.

WHY ARE THESE DRUGS BEING STUDIED?

Oxycodone is an opioid drug. A well-known and potentially deadly side effect associated with opioid use, particularly when it is misused, or when given in combination with certain other drugs is that people 'stop breathing'. It is thought that this is caused by the inability of the body to breathe hard enough to reduce the amount of carbon dioxide in the body which builds up when a person does not breath efficiently. Opioids and benzodiazepines have a warning on their packaging – known as a "boxed warning" - for possible effect on breathing when used together.

There is a need to assess the effects of opioids and other drugs when used together on breathing. The outcome of this study may inform on the risk of combining opioids with other drugs and lead to a standardized approach for assessing the effects of new drugs being developed on breathing.

Special Procedure: Read Rebreathing Procedure

As part of this study, you will be given doses of study drugs that do not typically have significant effects on breathing. In order to study what might happen when higher doses are given, the study doctors will use equipment – a tight fitting face mask attached to oxygen, carbon dioxide and measuring equipment – to copy the effect of reduced breathing caused by opioid drugs (see Figure 1). Through the face mask, covering your nose and mouth, you will be given a mix of oxygen and carbon dioxide that is higher than is normally in the air – 93% oxygen (normally 21% in room air) and 7% carbon dioxide (normally 0.4% in room air). The higher level of carbon dioxide breathed in will result in you feeling like you need to breathe faster. This technique is called Read Rebreathing. Read Rebreathing has been used in previous studies and has proven to be safe and able to study how opioids and other drugs affect breathing. By

doing this and giving the drugs in the study as outlined in this informed consent form (ICF), the data collected will help the FDA to understand better how these drugs can be given more safely. This procedure is non-invasive, meaning no pieces of equipment enter your body.

You will have Read Rebreathing explained to you at length during the ICF process, and you will have time to ask as many questions about this as you wish. The procedure will be conducted under medical supervision. You will also be shown the Read Rebreathing equipment and be trained how to use it to see if you can tolerate it (comfort level to breathe into a mask- similar to a sleep apnea (CPAP) mask) before being enrolled in the study.

Figure 1: Rebreathing Procedure Equipment Setup

HOW WILL THIS STUDY BE DONE?

This study will be divided into three parts: Lead In, Part 1 and Part 2. You will not be allowed to select which part of the study you are in. If you are selected for the Lead In portion, after your participation is completed you would be eligible to rescreen for participation in Part 1 or Part 2 if desired.

Lead In

The Lead In part will have up to 10 healthy volunteers and will enable the study doctor to check if any changes need to be made to the way the study is conducted. There will be no study drugs given during this part of the study, but you will be expected to have the Read Rebreathing procedure. For the Lead In part of the study you will be confined at Spaulding Clinical from day -1 through day 3.

Part 1

In Part 1 of the study, 20 healthy volunteers will be enrolled who will receive four groups of study drugs or dose assignments (labeled A, B, C, D below) in a random order on days 1, 4, 7 and 10 with a washout period (meaning no study drugs are given) of two days in between each dose day.

Oxycodone

The initial dose selected for oral oxycodone is 10 mg IR (Immediate Release) tablet. Based on the results of the first 5 subjects, the dose may be increased to 15 mg IR.

Midazolam

The initial dose selected for midazolam is 0.0375 mg/kg intravenously (IV). Based on the results of the first 5 subjects, the dose may be increased to 0.075 mg/kg IV.

Group	Study Drugs
A	Oxycodone + placebo IV: oxycodone tablets plus an intravenous injection of placebo over 5 minutes once per dose day
B	Oral placebo + midazolam IV: placebo tablets plus an intravenous injection of midazolam over 5 minutes once per dose day
C	Oxycodone + midazolam IV: oxycodone tablets plus an intravenous injection of midazolam over 5 minutes once per dose day
D	Oral placebo + placebo IV: placebo tablets plus an intravenous injection of placebo over 5 minutes once per dose day

To counter any possible nausea caused by oxycodone you will be given an anti-sickness medication – ondansetron as an oral tablet – 30 minutes prior to receiving the dose. You will also be expected to have the Read Rebreathing procedure as well as blood draws during the dose days.

For Part 1 of the study, you will be confined at Spaulding Clinical from day -1 through day 11.

<u>Part 2</u>
In Part 2 of the study, 20 healthy volunteers will be enrolled who will complete three different study drug treatment groups (labeled E, F, and G below). Each study treatment group will have 5 days of dosing followed by 7 days of washout in each period. Subjects will complete each of these study treatment groups in a random order. For example, you may be assigned to complete Study Treatment Group G first, followed by E and F.

- Oxycodone (10 or 15 mg IR tablet on the first and last day of each period)
- Paroxetine (40 mg IR tablet daily for five days)
- Quetiapine (50 mg twice a day on the first day, 100 mg twice a day on second day, 150 mg twice a day on the third day, 200 mg twice a day on the fourth day, and 200 mg once on the fifth day, tablet form)

Group	**Days 1, 13, 25**	**Days 2,14, 26**	**Days 3, 15, 27**	**Days 4, 16, 28**	**Days 5, 17, 29**
E	**Morning**: Placebo + Oxycodone **Evening**: Placebo	**Morning**: Placebo **Evening:** Placebo	**Morning**: Placebo **Evening:** Placebo	**Morning**: Placebo **Evening:** Placebo	**Morning:** Placebo + Oxycodone

F	**Morning**: Paroxetine + Oxycodone **Evening**: Placebo	**Morning:** Paroxetine **Evening:** Placebo	**Morning:** Paroxetine **Evening:** Placebo	**Morning:** Paroxetine **Evening:** Placebo	**Morning:** Paroxetine + Oxycodone
G	**Morning:** Quetiapine + Oxycodone **Evening:** Quetiapine	**Morning:** Quetiapine **Evening:** Quetiapine	**Morning:** Quetiapine **Evening:** Quetiapine	**Morning:** Quetiapine **Evening:** Quetiapine	**Morning:** Quetiapine + Oxycodone

The three study treatment arms will be completed over time periods from day -1 through day 5 followed by a 7-day washout; day 13 through 17 followed by a 7-day washout: and day 25 through day 30. You will be confined at Spaulding Clinical for each of the study treatment periods (day -1 through the morning of day 6; the evening of day 12 through the morning of day 18; and the evening of day 24 through the morning of day 30). You will be released from Spaulding clinical for each 7-day washout period and return to the clinical site the evening before the start of the next study treatment period.

Day -1	**Days 1-5**	**Days 6-12**	**Days 13-17**	**Days 18-24**	**Day 25-29**
Check-in	Period 1	Washout (check-in Day 12)	Period 2	Washout (check-in Day 24)	Period 3

To counter any possible nausea caused by oxycodone you will be given an anti-sickness medication – ondansetron as an oral tablet – 30 minutes prior to receiving the dose. You will also be expected to have the Read Rebreathing procedure and blood draws during the study treatment periods.

WHO IS BEING ASKED TO TAKE PART IN THIS STUDY?

Approximately 50 healthy male and female adult subjects, who meet the requirements following a screening visit, will be enrolled in the study.

You have been asked to take part in this study because you are in general good health, are between 18 and 50 years of age, have no history of heart or liver disease, no history of allergies, no symptoms consistent with coronavirus disease of 2019 (COVID-19), no underlying medical conditions that put you at higher risk for COVID-19 complications and have not participated in another research study for an experimental drug (or a medical device) within 30 days of the first dose of study drug.

HOW MUCH TIME IS REQUIRED TO TAKE PART IN THE STUDY?

If you decide to take part in the study, you will be asked to attend a screening visit. If you pass the screening visit, you will return to the clinic for either one period of 4 days and 3 nights (for the Lead In part of the study), one period of 12 days and 11 nights (for Part 1 of the study) or three 7-day and 6-night periods with 6 days of washout in between each period (where you will not stay at the clinic) in Part 2 of the study.

The duration of your participation in the study from screening to final follow-up will be up to 58 days.

INFORMATION FOR FEMALE VOLUNTEERS

You should not screen for this study if:

- There is any possibility that you may become, or are pregnant,

- You have given birth in the last 3 months, or
- You are breast feeding.

You may screen for this study if:

- You have had a hysterectomy (uterus removed) or bilateral oophorectomy (ovaries removed), confirmed with documentation, or
- You are of post-menopausal age and have not had a menstrual period for 2 years, confirmed with hormone level at screening, or
- You have a vasectomized partner who has been documented to no longer produce sperm, or
- You are using TWO highly reliable methods of contraception to avoid pregnancy throughout the study and for at least 1 month after last study drug administration. Highly reliable methods of birth control include:

    - Hormonal implants/patch,
    - Oral hormonal contraceptives,
    - Injectable hormones,
    - Intra-uterine device (IUD),
    - Approved cervical ring,
    - Diaphragm with spermicide or condom (female or male) with spermicide

One of the methods of birth control used must be a barrier method. The use of spermicide alone and condom alone are not acceptable methods of contraception.

Except for continuous abstinence (no sexual intercourse with a male partner), no method of birth control can be considered 100% reliable in preventing pregnancy. Although the risk of becoming pregnant is low with many methods, unplanned pregnancies may occur with all birth control methods. Most occur because of improper or irregular use of the birth control method. If you are usually not sexually active but become sexually active, you must follow the advice documented above regarding contraceptive methods.

All females enrolled in the Lead-in part of the study will have a pregnancy test performed at screening, at check-in on Day -1 and check out on Day 3. All females enrolled in Part 1 of the study will have a pregnancy test performed at screening, at check-in on Day -1 and check out on Day 11. All females enrolled in Part 2 of the study will have a pregnancy test performed at screening, at check-in on Day -1, Day 12, Day 24, and check out on Day 30.

Please be aware that a pregnancy test may not be positive until 12 days after conception (fertilization of the egg by sperm). Therefore, if you do not follow the study birth control requirements and/or your birth control method has failed, you will not be able to count on a negative test to confirm that you are not pregnant.

If you know that you have not followed the study birth control requirements outlined above, then you must immediately inform us. You must not take any dose of the study drug if you have not followed these requirements. If you become pregnant, your pregnancy will be followed to document the outcome. All live births must be followed for a minimum of 30 days or until the first well-baby visit.

INFORMATION FOR MALE VOLUNTEERS

The effect of the study drug on male sperm is unknown. In rare cases, drugs may damage sperm in ways that affect a child that is fathered. Affected sperm may be present in the semen for about 2 months. Therefore, it is recommended to avoid fathering a child for 90 days after the last dose of the study drug.

Male subjects must ensure that TWO acceptable methods of contraception are used for the entire duration of the study, one of which must be a barrier method, up to the study follow-up visit, if applicable.

Periodic abstinence and withdrawal are not acceptable methods of contraception.

HOW WILL YOU KNOW IF YOU ARE ELIGIBLE TO TAKE PART?

You will NOT need to fast prior to your arrival at Spaulding Clinical Research, LLC. for your screening visit. You may eat and drink as normal prior to arrival.

At the beginning of the Screening visit, Informed Consent will be obtained.

Before starting the study, the following screening procedures will be performed:

- A complete medical history and physical examination (including height and weight measurements for Body Mass Index (BMI, a way to tell if your weight is proportional to your height).
- Assessment of blood pressure, respiratory rate, heart rate, and oral temperature.
- A complete history of relevant allergies or drug sensitivities.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- A pulse oximetry recording (painless recording of the oxygen concentration in your blood).
- You will be asked if you have taken any medication recently, including some eye drops.
- You will be asked if you have been feeling ill recently.
- Clinical laboratory tests (urine and blood samples), including screening for drugs, alcohol, and pregnancy tests (all female subjects); screening for how your body processes certain drugs; and testing for HIV, hepatitis B and C. Positive results of HIV or hepatitis tests will be reported to local health authorities as required by state law.
- Training on the Read Rebreathing procedure so you know what to expect and to ensure you can tolerate it.

If you meet the “entry criteria” of the study, according to the study doctor, you will be tested again when you are admitted to Spaulding Clinical Research, LLC. You will have the entry criteria reviewed again to ensure that you still are eligible for the study.

In addition, prior to admission you will have a diagnostic test performed to detect severe acute respiratory syndrome coronavirus 2 (called “coronavirus” from now on), which is the virus that causes COVID-19. Depending on the time required to return results, this may be performed ~2 days before check-in or may be performed on the check-in day. You will only be allowed to be admitted if your coronavirus test is negative. In addition, when entering the building for screening and check-in, triage for COVID-19 will take place. The exact details of what will occur at triage may change as additional information or testing is available, however as of now it is planned to include asking about any potential contacts with COVID-19, signs and symptoms associated with COVID-19, temperature monitoring and antibody screening for coronavirus.

WHAT TESTS AND PROCEDURES WILL BE USED IN THE STUDY?

1. Lead In Study

1.1. Check-in (Day -1)

Upon admission to Spaulding Clinical Research, LLC., you will be given an identity band to wear throughout your entire stay in the unit.

You will NOT need to fast prior to your arrival meaning you should eat and drink as normal.

The following admission procedures will be performed:

- Perform/review results from coronavirus test
- Medical history updates.
- Physical examination.
- Clinical laboratory tests (urine and blood samples), including screening for drugs, alcohol, and pregnancy tests (all female subjects).
- Assessment of blood pressure, respiratory rate, heart rate, and oral temperature.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- A pulse oximetry recording (painless recording of the oxygen levels in your blood).
- You will be asked for details of any medication taken since the screening or previous visit.
- You will be asked if you have been ill since the screening or previous visit.
- You will be asked if you complied with study restrictions.
- You will have further training to the Read Rebreathing procedure
- You will be provided meals (lunch, dinner and a snack).
- Inclusion/Exclusion assessment.

The results from these tests will help the study staff determine whether you are still eligible to enter the study.

1.2. Study Treatment (Days 1 and 2)

- Adverse event assessment (check for side effects) and changes in concomitant medications (medicines you are currently taking).
- Read Rebreathing procedure (5 times per day).
- Eye assessments to measure pupil size.
- Blood collection to look at levels of proteins and other constituents of your blood.
- Meals (after last Read Rebreathing procedure – lunch, dinner and a snack).

1.3. Check Out (Day 3)

- A complete physical examination.
- Assessment of blood pressure, respiratory rate, heart rate, and oral temperature.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- A pulse oximetry recording (painless recording of the oxygen levels in your blood).
- You will be asked if you have taken any medication recently, including some eye drops.
- You will be asked if you have been feeling ill recently.

Clinical laboratory tests (urine and blood samples), including pregnancy tests (all female subjects).

2. Part 1

2.1. Check In (Day -1)

Upon admission to Spaulding Clinical Research, LLC., you will be given an identity band to wear throughout your entire stay in the unit.

You will NOT need to fast prior to your arrival meaning you should eat and drink as normal.

The following admission procedures will be performed:

- Perform/review results from coronavirus test.
- Medical history updates.
- Physical examination.
- Clinical laboratory tests (urine and blood samples), including screening for drugs, alcohol, and pregnancy tests (all female subjects).
- Assessment of blood pressure, respiratory rate, heart rate, and oral temperature.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- A pulse oximetry recording (painless recording of the oxygen levels in your blood).
- You will be asked for details of any medication taken since the screening or previous visit.
- You will be asked if you have been ill since the screening or previous visit.
- You will be asked if you complied with study restrictions.
- You will have further training to the Read Rebreathing procedure.
- Blood collection to look at levels of proteins and other constituents of your blood.
- You will be provided meals (after last Read Rebreathing procedure – lunch, dinner and a snack).
- Inclusion/Exclusion assessment and preparation for randomization. Randomization means that you will be assigned by chance, like the flip of a coin, to either study group.

The results from these tests will help the study staff determine whether you are still eligible to enter the study.

2.2. Study Treatment (Days 1, 4, 7 and 10)

- Adverse event assessment and changes in concomitant medications.
- Pharmacokinetic (PK) blood sampling.
- Meals (after last Read Rebreathing procedure –, lunch, dinner and a snack).
- Assessment of blood pressure, heart rate, respiratory rate and oral temperature.
- Administration of study product.
- Blood collection to look at levels of proteins and other constituents of your blood.
- Telemetry (continuous, painless recordings of your heart's rhythm).
- Continuous pulse oximetry monitoring (continuous, painless monitoring of oxygen levels in your blood).
- Read Rebreathing procedure with one-on-one monitoring by trained study staff during the procedure (7 times per day).

- Eye assessments to measure pupil size.
- Sedation assessments to measure whether you feel awake/alert vs. sedated.

2.3. Washout (Days 2, 3, 5, 6, 8 and 9)

- Adverse event assessment and changes in concomitant medications.
- Meals (breakfast, lunch, dinner and a snack).

2.4. Check Out (Day 11)

- Adverse event assessment and changes in concomitant medications.
- Clinical laboratory tests (urine and blood samples)
- Physical examination.
- Assessment of blood pressure, heart rate, respiratory rate and oral temperature.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- A pulse oximetry recording (painless recording of the oxygen levels in your blood).
- Discharge from Spaulding Clinical after all events are completed.

3. Part 2

3.1. Check In (Day -1):

Upon admission to Spaulding Clinical Research, LLC., you will be given an identity band to wear throughout your entire stay in the unit.

You will NOT need to fast prior to your arrival meaning you should eat and drink as normal.

The following admission procedures will be performed:

- Perform/review results from coronavirus test.
- Medical history updates.
- Physical examination.
- Clinical laboratory tests (urine and blood samples), including screening for drugs, alcohol, and pregnancy tests (all female subjects).
- Assessment of blood pressure, respiratory rate, heart rate, and oral temperature.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- A pulse oximetry recording (painless recording of the oxygen levels in your blood).
- You will be asked for details of any medication taken since the screening or previous visit.
- You will be asked if you have been ill since the screening or previous visit.
- You will be asked if you complied with study restrictions.
- You will have further training to the Read Rebreathing procedure.
- You will be provided meals (lunch, dinner and a snack).
- Inclusion/Exclusion assessment and preparation for randomization. Randomization means that you will be assigned by chance, like the flip of a coin, to either study group.

The results from these tests will help the study staff determine whether you are still eligible to enter the study.

3.2. Study Treatment (Days 1 to 5, 13 to 17, and 25 to 29)

- Adverse event assessment and changes in concomitant medications.
- Pharmacokinetic (PK) blood sampling (Days 1, 4, 5, 13, 16, 17, 25, 28, and 29 only).
- Meals (after last Read Rebreathing procedure – lunch, dinner and a snack).
    - On Days 1, 5, 13, 17, 25 and 29 an additional light snack will be provided between the last two Read Rebreathing procedures of the day.
- Assessment of blood pressure, heart rate, respiratory rate and oral temperature.
- Administration of study product.
- Blood collection to look at levels of proteins and other constituents of your blood (Days 1, 4, 5, 13, 16, 17, 25, 28, and 29 only).
- Telemetry (continuous, painless recordings of your heart's rhythm) (Days 1, 5, 13, 17, 25, and 29 only).
- Continuous pulse oximetry monitoring (continuous, painless monitoring of oxygen levels in your blood) (Days 1, 4, 5, 13, 16, 17, 25, 28 and 29 only).
- Read Rebreathing procedure with one-on-one monitoring by trained study staff (6 times per day on days 1, 5, 13, 17, 25, and 29; 5 times per day on days 4, 16 and 28 only).
- Eye assessments to measure pupil size (Days 1, 4, 5, 13, 16, 17, 25, 28, and 29 only).
- Sedation assessments to measure whether you feel awake/alert vs. sedated (Days 1, 4, 5, 13, 16, 17, 25, 28, and 29 only).

3.3. Washout (Days 6 to 12 and 18 to 24)

- Check-out days (Days 6 and 18)
    - Adverse event assessment.
    - Physical examination.
    - Assessment of blood pressure, heart rate, respiratory rate and oral temperature.
    - A pulse oximetry recording (painless recording of the oxygen levels in your blood).
- Check-in days (Days 12 and 24)
    - Perform/review results from coronavirus test.
    - Physical examination.
    - Changes in concomitant medications.
    - Clinical laboratory tests (urine and blood samples) including screening for drugs and alcohol and pregnancy testing for all female subjects.
    - Assessment of blood pressure, heart rate, respiratory rate and oral temperature.
    - A pulse oximetry recording (painless recording of the oxygen levels in your blood).

3.4. Check Out (Day 30)

- Adverse event assessment and changes in concomitant medications.
- Clinical laboratory tests (urine and blood samples) including pregnancy testing for all female subjects.
- Physical examination.
- Assessment of blood pressure, heart rate, respiratory rate and oral temperature.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- A pulse oximetry recording (painless recording of the oxygen levels in your blood).
- Discharge from Spaulding Clinical after all events are completed.

INFORMATION OBTAINED DURING THE STUDY

Blood Sampling

In Part 1 blood samples will be collected for measurement of levels of study drug at the following times:

- Day 1: 0 (pre-dose), 1, 2, 3, 4, 6, 8, 12 and 24 hours after dosing on days 1, 4, 7 and 10 for a total of 36 blood collections for determining study drug levels.

In Part 2 blood samples will be collected for measurement of levels of study drug at the following times:

- Day 1: 0 (pre-dose), 3, 4, 5, 6, 8, 9, 12 and 24 hours after dosing on days 1, 4, 5, 13, 16, 17, 25, 28 and 29 for a total of 81 blood collections for determining study drug levels.

Blood samples will be collected for measurement of proteins and other constituents of your blood at the following times:

- Lead-in: Days 1 and 2 – time 0
- Part 1: Days 1, 4, 7, 10 – time 0
- Part 2: Days 1, 4, 5, 13, 16, 17, 25, 28, 29 – time 0
- Total of 15 blood collections for measuring proteins and other constituents of your blood

You will have numerous blood samples drawn during the entire study as shown above, and 2 safety laboratory draws in Part 1 or 4 safety laboratory draws in Part 2. The blood samples may be taken by individual needle sticks into one of your arm veins, or, if necessary, by an indwelling catheter (a thin plastic tube placed in a vein in your arm).

The total amount of blood taken will be approximately 215 ml or 1 cup in Part 1 or 495 ml or 2 cups in Part 2.

Some of the samples collected may undergo pharmacogenetic testing. Pharmacogenetics is the study of differences in how our bodies respond to or handle drugs. This research will look at genetic differences to better understand why people react or respond differently when they get the same drug. Any personal health information about you, including any genetic information, will be kept confidential.

Urine Sampling

You will have urine samples collected at screening, Day -1 (Check In), the last study day and on two additional days during the study if you are in Part 2. These will be used to screen for either alcohol or drugs or for routine safety analysis.

ECG Measurements

Safety ECG measurements will occur at your screening visit, Day -1 (Check In), and the last study day. For Part 1, you will have telemetry (continuous, painless recordings of your heart's rhythm) on each of the study treatment days (Days 1, 4, 7, 10) for 24 hours. For Part 2, you will have telemetry on Days 1, 5, 13, 17, 25, and 29 for 24 hours. There will be periods of time where you will need to lie very still to get precise readings of your heart's rhythm.

Some individuals may develop redness, irritation, or discoloration of the skin at the site of ECG electrodes placed on the chest/body. This may develop due to sensitivity to the electrodes or to our skin

preparation procedure. In order to get the quality results we need, it is necessary for us to lightly scrub the skin with an abrasive pad to remove any skin impedance such as oil, dead skin cells and lotions. We may trace each electrode site with a permanent marker to assure electrodes are placed in the same place on the body for each ECG event to maintain quality and consistent results. This tracing may occur as often as once a day during confinement.

Pulse Oximetry

For Part 1, you will have continuous pulse oximetry monitoring (continuous, painless monitoring of oxygen levels in your blood) on each of the study treatment days (Days 1, 4, 7, 10) for 24 hours. For Part 2, you will have continuous pulse oximetry monitoring on Days 1, 4, 5, 12, 13, 16, 17, 25, 28 and 29 for 24 hours. You will also have pulse oximetry quickly checked (not continuous) at screening and on check-in and check-out days.

Sedation Assessments

You will have sedation assessments during Part 1 and Part 2 of the study prior to the start of each Rebreathing procedure. You will be asked to look at a visual scale and describe your level of sedation from awake and alert to very sedated. An observer will also be documenting your sedation level prior to the start of each rebreathing procedure.

Read Rebreathing

You will have measurements of your breathing done at specified times during the study through a device that controls and measures the amount of oxygen and carbon dioxide you receive through a close-fitting face mask. This device in non-invasive.

During the procedure you will be given instructions on how to breathe (either large deep breaths, quicker breaths, or normal breaths). During screening you will be allowed to see the equipment to be used for the procedure and you will also be trained on the procedure by study staff so that you know what to expect and to see if you can tolerate it.

The Read Rebreathing procedure will be overseen by study staff who have been fully trained on the procedure. You will be overseen by a study doctor for up to 6 hours after dosing with oxycodone or midazolam.

Eye Measurements

You will have measurements of your eye done at specified times before and after the Read Rebreathing procedure by an automated device that takes a picture of your pupil and measures how it changes from a brief light stimulus. This is called pupillometry. The study team will compare the changes in pupil measurements to the changes in breathing measurements. The device is held up to one of your eyes while the other eye is covered and then the same is done with the opposite eye. The recording time on each eye takes less than 10 seconds and the procedure is painless.

WHAT ARE YOUR RESTRICTIONS DURING THE STUDY?

You will need to avoid the following while taking part in this study, and most importantly from the time of your screening visit until you check in:

Restricted Item:	**Duration:**
Alcohol	48 hours before dose until the end of study visit.
Caffeine or other xanthine containing products (for example, coffee, tea, cola or chocolate)	48 hours before dose until the end of study visit.
Grapefruit	48 hours before dose until the end of study visit.
Prescription medication	14 days prior to dose
NSAIDs (Ibuprofen, Naproxen)	14 days prior to dose.
Nicotine containing products	6 weeks prior to screening until end of study visit.

You will receive a diet that does not contain any alcohol or caffeine. You must eat all of each meal that is served to you and eat at a reasonable pace (within 25 minutes).

You may eat only meals and snacks that are provided to you during the periods of your stay. After checking out of the clinic, there are no dietary restrictions aside from what is listed in the table above.

You must be willing to comply with study rules, including the meal schedule (25 minutes to eat), attempting to void at specified times (for example, before rebreathing assessment windows), remaining quiet, awake, undistracted, motionless, and seated during specified times, and avoiding vigorous exercise as directed throughout the duration of the study. Subjects will not be allowed to sleep during any rebreathing assessment periods.

You must not have facial hair (be clean shaven) on all days when the Read Rebreathing procedure will be performed (including screening).

Due to current precautions being taken for COVID-19, the following restrictions will be in place:

- Subjects must always wear masks except when in a private room without anyone else present or for a limited time for a study procedure (e.g. study drug administration, switching to rebreathing mask) when instructed by staff.
- Subjects must practice social distancing, which will include having 1 subject per room for overnight stays and having common areas closed. Food will be served at subjects' rooms with subjects sitting at their doorway to eat. Subjects will spend most of their time in their rooms except for specified times for walking in the halls (with masks).
- Subjects must practice regular handwashing with soap and water, scrubbing hands for at least 20 seconds or with approved hand sanitizer as supplied by study staff.

If new information becomes available, there could be other precautions that lead to additional restrictions.

ARE THERE RISKS TO YOU IF YOU ARE IN THIS STUDY?

Please be advised that non-pharmacological treatments (such as heating pack, stretches, hydration, etc.) are our first line of therapy for mild adverse events. The study doctor will be notified if a subsequent

medication may be needed to treat an adverse event. Following the study plan guidelines, the study doctor will assess your adverse event and develop a treatment plan.

Oxycodone and midazolam can reduce breathing and the effect can be increased when they are taken together. You will be given low doses that have a minimal effect when you are going about your normal activities. As described above, when you undergo the Read Rebreathing procedure the carbon dioxide levels that you breathe will be increased and it may make you breathe faster or deeper (which lasts 3-15 minutes). If you are taking oxycodone, midazolam, and/or one of the other drugs in the study, you may not increase your breathing as much. Before, during, and after the procedure, you will be closely monitored by study staff, and you will have continuous, painless recordings of your heart's rhythm and oxygen levels in your blood. If needed, the study staff can administer oxygen and drugs to counteract effects from oxycodone and midazolam.

Additional risks are possible side effects of the study drugs and those of taking blood and other study procedures:

<u>For Midazolam</u>

- Heart/blood vessel effects – minor variations in blood pressure and heart rate
- Lung effects - non-life-threatening decrease in tidal volume (amount of air moved with each breath), decrease in respiratory rate (fewer breaths), apnea (pause in breathing), aspiration (inhaling contents into lungs such as saliva), cough
- Abdominal effects – nausea, vomiting, hiccups
- Neurological effects – headache, drowsiness, over sedation (tiredness)

<u>For Oxycodone</u>

- Abdominal effects – nausea, vomiting, constipation
- Neurological effects – headache, insomnia (difficulty sleeping), asthenia (general weakness), lightheadedness, dizziness, drowsiness, agitation, anxiety, hallucinations, nightmares, somnolence (being sleepy)
- Skin effects - itching
- Less common, but serious adverse events include:
    - Lung effects -- respiratory depression/arrest (decreased/stopped breathing)
    - Heart/blood vessel effects –blood circulatory depression and hypotension (decreased blood pressure), cardiac arrest and/or shock (heart, lung, and circulatory changes that are potentially life threatening)

<u>For Paroxetine</u>

- Abdominal effects – nausea, diarrhea, vomiting, flatulence (passing gas), loss of appetite, dry mouth, constipation
- Neurological effects – weakness, drowsiness, dizziness, anxiety, agitation, asthenia (general weakness), yawning, nervousness, tremors (shaking), insomnia (difficulty falling and/or staying asleep)
- Eye effects - vision changes
- Sexual effects - erectile dysfunction; delayed ejaculation; vaginal paresthesia (change in sensation), itching, and discharge; impotence; decreased libido (sex drive)
- General effects – infection, sweating

For Quetiapine

- Heart/blood vessel effects - postural hypotension (low blood pressure with change in position)
- Abdominal effects – pharyngitis (sore throat), dyspepsia (heartburn), constipation, dry mouth, stomach pain, constipation, nausea, vomiting
- Neurological effects – Drowsiness, asthenia (general weakness), lethargy, dizziness
- General effects - weight gain
- Liver effects - ALT increased (increased liver stress)

For Ondansetron

- Heart/blood vessel effects - hypoxia (decrease in oxygen to areas of the body)
- Abdominal effects – diarrhea, constipation
- Neurological effects – headache
- General effects – fever, malaise (feeling of discomfort), fatigue
- Additional, less common side effects include:
    - Allergic reactions – Hypersensitivity reactions including anaphylaxis and bronchospasm (serious allergic reactions)
    - Heart/blood vessel effects: QT interval prolongation and Torsade de Pointes (abnormal heart rhythm)
    - Serotonin syndrome (usually when prescribed with another serotoninergic medication which will not be done in this study – leads to fever, sweating, diarrhea and potential complications including seizures and muscle breakdown)

You may be exposed to two additional drugs that are used as 'rescue' (reversing) medications. Naloxone may be administered if respiratory depression occurs following opioid administration. Additionally, flumazenil may be administered if needed to reverse the effects of midazolam. Side effects of these medications may include:

For Naloxone

- Heart/blood vessel effects – tachycardia (faster heart rate), hypertension (high blood pressure)
- Lung effects - dyspnea (difficulty taking breaths)
- Abdominal effects – nausea, vomiting, abdominal cramps
- Neurological effects – tremulousness (trembling/shaking), seizures, restlessness, irritability, agitation
- General effects – sweating, body aches, fever
- Additional, less common side effects include:
    - Ventricular tachycardia/fibrillation (Serious, abnormal heart rhythms) and pulmonary edema (accumulation of fluid in lungs)

For flumazenil

- Heart/blood vessel effects – abnormal heart rhythm
- Abdominal effects – nausea, vomiting
- Neurological effects – agitation, tremors, dizziness, headaches, abnormal sensations, seizures, fatigue
- Eye effects – blurred vision
- Ear effects – abnormal hearing such as tinnitus (ringing in the ears)
- General effects - injection site irritation, flushing, excessive sweating

Problems or side effects that are not now known could also occur. You will be given any new information that may affect your willingness to start or continue in the study.

The tests done at each visit are standard medical tests. The most unpleasant is often having blood samples taken. The risks of taking blood may include:

- Fainting
- Pain
- Bruising
- Rarely, there may be a small blood clot or infection at the site of the needle puncture

The blood pressure cuff may also cause discomfort or bruising to the upper arm.

In rare instances where a study nurse, a study doctor, or a study technician, sustains an exposure to your blood, tissue or body fluids by needle stick, cut or splash to mucosa or damaged skin, it may be necessary to test your blood, tissue, or body fluid sample for certain viral infections including Hepatitis B and C and HIV on the sample already available. This is to enable that person to receive appropriate counseling, monitoring and treatment if necessary. In this instance, the study doctor or designee will offer you the information relevant to your health and advise you on the next steps. Confidentiality of your data will be respected at all times according to the state law.

Risks or side effects associated with Read Rebreathing procedure include:

- Heart/blood vessel effects – rapid heart rate, increased blood pressure, chest pain
- Lung effects – difficulty breathing
- Neurological effects – headache, dizziness, confusion
- Abdominal effects – nausea, vomiting
- General effects - muscle twitches, fatigue, sweating

Unknown Risks

As with any drug, it is possible that you could experience an allergic reaction to the study drug used in this study. Symptoms of any allergic reaction can include:

- Rash
- Hives
- Itching
- Angioedema:
    - Difficulty breathing
    - Closing of the throat
    - Swelling of the lips, tongue or face
- Rarely, death

If you think you are having a severe allergic reaction, while outside the study center call 9-1-1 and seek medical attention immediately.

It is very important that you tell the study doctor and the study staff about any side effects that you might experience.

You may experience side effects or discomforts that are not listed on this form. Tell your study doctor or study staff immediately if you have any problems. Your safety will be our priority and closely monitored throughout the study.

For ECG Monitoring

It is possible to be sensitive to the adhesives used on the electrodes that are applied to your chest when having an ECG performed. If this is the case, you could develop a temporary redness, irritation, or discoloration of the skin where the electrodes were applied.

HIV and Hepatitis B and C Testing

The risks of HIV and Hepatitis B and C testing include psychological and social risks. A positive test can lead to restrictions in freedom of travel to some countries and possible prejudices in job employment, insurance eligibility, housing and other forms of discrimination. Positive HIV and Hepatitis B and C test results must be reported to health authorities under state law. A positive HIV and/or Hepatitis B or C result will exclude you from participation in the study.

Reproductive Risks

The effects of the study drug on human pregnancy and the unborn child (fetus) are unknown. Therefore, it is very important that you do everything within your power not to become pregnant, or father a child during this study and for 60 days following the last dose. Please ensure that you follow the study birth control requirements outlined in the sections regarding information for male and female subjects above.

If you become pregnant during the course of the study, you will be withdrawn from the study immediately. Neither Spaulding Clinical Research, LLC. nor the sponsor will be responsible for the cost of any obstetric or related care, or for your child's care. Female subjects are agreeing, by signing and dating this form, that information about your pregnancy and birth of your child may be collected. The information collected will include your health and the health of your unborn child during pregnancy, pregnancy outcome (miscarriage, termination, live birth, etc.), and the health of the baby after it is born (up to 6 weeks after delivery).

COVID-19 Risks

Despite the extra precautions (e.g. COVID-19 triage at screening/check-in, coronavirus testing, mandatory masks for study subjects and staff, social distancing including single-occupancy rooms, extra hand washing) that will be in place, there is still a risk of developing COVID-19 just as there is when you are not at Spaulding Clinical. Tell your study doctor or study staff about any new symptoms you develop during the study.

The U.S. Centers for Disease Control and Prevention (CDC) currently highlights that people with the following symptoms may have COVID-19:

- Cough
- Shortness of breath or difficulty breathing
- Fever or chills
- Fatigue
- Muscle or body aches
- Headache
- Sore throat
- New loss of taste or smell
- Congestion or runny nose
- Nausea or vomiting

- Diarrhea

It is important to note that COVID-19 can also present with other symptoms and just because you develop any of the above symptoms does not mean that you have COVID-19. Your study doctor will evaluate if your symptoms warrant further isolation from other study subjects/staff, additional coronavirus testing, and/or any treatment.

NEW FINDINGS

Your study doctor will tell you of any information learned during the course of the study that might cause you to change your mind about taking part in the study. You may contact the study doctor at any time after your participation ends to find out if any new information about this study has become available.

WHAT IS THE ALTERNATIVE TO BEING IN THE STUDY?

Since this is a study involving healthy volunteers, your alternative is not to take part.

WILL YOU BENEFIT FROM TAKING PART IN THE STUDY?

You will not receive direct medical benefit from receiving the study drug. You may benefit by having your medical history recorded, undergoing a physical examination, and having blood and urine tests as they apply to this research project.

Just by taking part in this research study, you may be helping future patients by providing important information about the study drug and by contributing to medical knowledge.

WHO IS PAYING FOR THIS STUDY?

The US Food and Drug Administration is the Sponsor of the study.

The US Food and Drug Administration pays the study doctor to run this study.

The study drug and all tests, procedures and visits required by the study are provided at no cost to you. The sponsor, the US Food and Drug Administration pays for them.

Information about this study is confidential. This information belongs to the US Food and Drug Administration. We ask that you keep it private. You can discuss this information in private with your doctor or family to talk about your healthcare or to decide about taking part in this study.

WILL YOU BE PAID FOR BEING IN THIS STUDY?

Compensation for screening is as follows:

- $100.00 if you qualify and take part in a study. $100.00 for your time and inconvenience if you do not qualify for a study.
- If the results of the drug and alcohol tests are positive, or if you attempt to falsify your drug screen you will not receive any compensation.
- If you screen for the study, qualify and are enrolled, your screening payment will be included in your first stipend payment. If you are not accepted into the study your screening payment will be processed and mailed within 7 calendar days of study enrollment.

Compensation for this study is as follows:

For subjects in the Lead In part of the study that complete the entire study (Day -1 to Day 3), you will receive up to $1,700.00 This payment will be made in two separate payments as follows:

- $1,200.00 will be paid after all check out procedures have been completed at the end of day 3,
- The remaining $500.00 will be paid after any additional follow up procedures are completed, and all results are reviewed.

For subjects in Part 1 that complete the entire study (Day -1 to Day 11), you will receive up to $4,900.00 This payment will be made in two separate payments as follows:

- $4000.00 will be paid after all check out procedures have been completed at the end of day 11,
- The remaining $900.00 will be paid after any additional follow up procedures are completed, and all results are reviewed.

For subjects in Part 2 that complete the entire study (Day -1 to Day 30), you will receive up to $8,900.00. This payment will be made in three separate payments as follows:

- $3,950.00 will be paid after all check out procedures have been completed at the end of day 17.
- $3,450.00 will be paid after all check out procedures have been completed at the end of day 30.
- The remaining $1,500.00 will be paid after any additional follow up procedures are completed, and all results are reviewed.

If you withdraw from the study early, you will only be paid for the visits you completed. You will receive $100.00 for each full day that you were in-house.

NOTE: You may be required to return to the clinic for repeat blood test or other assessments (for example, ECG, physical, vital signs) in between periods or after the final check out. This is considered part of the study and no additional compensation is available. Your final payment will not be released until all follow up procedures have been completed and accepted by the study doctor. Once follow up procedures have been completed and accepted by study doctor, your final payment will be processed and mailed within 14 calendar days.

NOTE: If you meet eligibility criteria you may be asked to be an alternate subject. Alternate subjects are eligible subjects that are in addition to the number of subjects in the event an enrolled subject drops out before their dose can take place or in the event it is not safe for a subject to move forward with dosing. If you are selected as an alternate subject and you agree to participate as an alternate subject, you may receive up to $250 if you are not needed to dose. If you are needed to replace a subject, you will be paid as stated for participating in and completing the study. If you agree to be an alternate subject, you will have all of the predose procedures as the enrolled subjects so that if you are needed, you will be ready to participate. If you are not needed you will be discharged shortly after completion of the dosing round.

No deductions for any state or federal withholding or any other similar taxes will be made, and you are solely responsible for reporting such payments on your state and federal income tax returns.

If you need to stay at Spaulding Clinical Research, LLC. for a longer period of time for safety reasons, you will be compensated at a rate proportional to the entire compensation for the study.

If you are dismissed from the study for medical reasons OR if the study is temporarily or permanently halted, your compensation will be proportional to the time you spend in the study.

If you are dismissed from the study because you have not complied with the instructions of the study staff, no compensation is available. Non-compliance includes, but is not limited to, improper conduct, taking alcohol and/or any drugs (including recreational drugs), tampering with the study drug, or consuming any foods/beverages not allowed in the study.

Subjects may be reimbursed for travels expenses depending on need and Sponsor approval.

By signing and dating this consent, you expressly agree that you are an Independent Contractor for Spaulding Clinical Research, LLC. As an Independent Contractor, you will receive a 1099 form from Spaulding Clinical Research, LLC. The 1099 form shall document and report all payments and/or study stipends you received as an Independent Contractor for Spaulding Clinical Research, LLC. In addition, because you are an Independent Contractor and will be receiving payments and/or study stipends, those earnings are subject to wage garnishment. If Spaulding Clinical receives an Earnings Garnishment Notice (or similar) from a State or Federal legal entity, we will adhere to that garnishment.

COMPENSATION FOR INJURY

It is important that you follow carefully all the instructions given by the study doctor and his/her study staff regarding this study.

If you become ill or are physically injured as a result of participation in this study, please contact the study doctor right away at the telephone number listed on page one of this consent form. He/she will treat you or refer you for treatment.

Spaulding Clinical Research, LLC. and/or its affiliated institutions has not set aside funds to provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. You or your insurer will be responsible for the payment of any medical treatments for research related injuries or illness. By signing and dating this consent form, you are not giving up any legal rights. If this research study is conducted in a negligent manner and you are injured as a direct result, you may be able to recover the costs of care and other damages from the individuals or organizations responsible for your injury as you still have the right to seek compensation for injury related to malpractice, negligence, fault, guilt or blame of those involved in the research.

PROTECTING THE PRIVACY OF YOUR HEALTH DATA

Unless required by law, your name will not be disclosed outside the research clinic. Your name will be available only to the following people or agencies: the study doctor and study staff; and authorized representatives of the study doctor; institutional review board, health authority inspectors, such as the US Food & Drug Administration and the European Medicines Agency; the US Food and Drug Administration, study monitors and auditors; and authorized Clinical Research Organization representatives. The above mentioned individuals will use the personal information collected as part of this study, including your medical records (“Study Information”) to check that the study is conducted correctly and to ensure the accuracy of the study information. These people are all obligated to maintain confidentiality by the nature of their work, or are bound by confidentiality agreements. If required, the study doctor may contact your personal doctor to collect additional medical information and your past medical history.

The study doctor may only share your study information with people whom you have permitted to see it. However once your study information is shared as authorized, it may no longer be protected by Federal law and may be re-disclosed without your permission.

While participating in this study, the study doctor will replace your name with a special code that identifies you. This code, along with your study information, will be used by the study sponsor, the US Food and Drug Administration and their representatives, for the study purposes mentioned above and to help establish whether the study drug is safe and effective. The US Food and Drug Administration may share your coded information, as necessary, with the US Food and Drug Administration affiliates who work within the scope of this consent; people and companies who work with the US Food and Drug Administration and who work within the scope of this consent; Advarra IRB and Regulatory agencies such as the US Food & Drug Administration, the National Health Authorities, and the European Medicines Agency.

You should be aware that some countries may not offer the same level of privacy protection as you are used to in the country where you live or where this study is conducted. However, the US Food and Drug Administration will keep any information it receives to the same standard of confidentiality as far as permitted by applicable local law. The US Food and Drug Administration has also entered into agreements with third parties working for the US Food and Drug Administration to secure adequate protection of your data and samples.

The Study Information will be kept confidential within the limits of the law. This may include research performed by researchers outside of the FDA and Spaulding Clinical Research, LLC. This may be done by releasing de-identified data (data not linked to you) from the study to a data warehouse (location that will store the data) or as part of a publication. Researchers would only have access to de-identified data where you cannot be identified. If the results of this study are published or presented in a meeting, you will not be named and no one will be able to tell that you were in the study from the publication or presentation.

Your participation in this study is voluntary and you may cancel this consent at any time and without any reason. If you do so, your participation in the study will end and the study staff will stop collecting information from you, however, you will be asked to come back to the site for an end of study visit. Your samples will then be destroyed. However, the US Food and Drug Administration will continue to retain and use any research results that have already been collected to verify the scientific integrity of the study. If you wish to leave the study inform your study doctor.

You have the right to review your Study Information and medical records and request changes to the Study Information if it is not correct. However, please note that during the study, access to Study Information may be limited if it weakens the integrity of the research. You may have access to the Study Information held by the study doctor at the end of the study.

If you have any questions about the collection and use of information about you, or would like to exercise rights that you may have regarding this information, you should ask your study doctor.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number

listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00041368.

IS YOUR PARTICIPATION VOLUNTARY?

Yes, your participation in this study is strictly voluntary. You may refuse to take part in it, or you may stop participating at any time, even after signing and dating this informed consent. There will be no penalty or loss of benefits to which you are otherwise entitled. However, if you decide to leave the study before it ends, the study doctor will need to see you before you are released from the study.

The study doctor, Sponsor, FDA or Advarra may also decide to remove you from the study at any time without your consent. The study doctor may choose to take you out of the study because of unexpected or serious side effects, or for other scientific, technical, or safety considerations.

Examples why you may be taken out of the study are:
- Staying in the study would be harmful
- You need treatment not allowed in this study
- You failed to follow instructions
- You become pregnant
- The study is cancelled
- Your study treatment arm is stopped

If your participation ends for any reason, you will return to the study site for the following study procedures:
- Physical examination.
- Pregnancy test (if necessary).
- Body weight and body temperature.
- Blood pressure and pulse rate.
- Pulse oximetry.
- ECG.
- Blood draws for hematology and chemistry.
- Blood draws for PK.
- Urine will be collected for urinalysis.
- Adverse events and concomitant medications.

If you should decide to leave the study you should tell the study doctor or study staff. They will make sure that proper procedures are followed and a final visit is made for your safety.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

STATEMENT OF CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____ ____/____/____
Signature of Research Subject Date

_____ _____
Printed Name of Research Subject Time (24hr)

STATEMENT OF PERSON OBTAINING INFORMED CONSENT
I have carefully explained to the subject the nature and purpose of the above study. There has been an opportunity for the subject to ask questions about this research study. I have been available to answer any questions that the subject has about this study.

_____ ____/____/____
Signature of Person Obtaining Informed Consent Date

_____ _____
Printed Name of Person Obtaining Informed Consent Time (24hr)

HIPAA Authorization Agreement
Permission to Review, Use and Release Information about You

If you decide to be in this study, the study doctor and research team will use and share health data about you to conduct the study. Health data may include:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your study visits, including all test results.

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the research team may share health data about you with authorized users. Authorized users may include:

- Representatives of the US Food and Drug Administration
- Representatives of Spaulding Clinical Research, LLC.
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study).
- The Food and Drug Administration (FDA) and other US governmental agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STIs) must be reported.
- Governmental agencies of other countries.
- Labs working with the sponsor on this study.
- Other authorized users.

The sponsor and those working for the sponsor may use the health data sent to them:

- To see if the study drug works and is safe.
- To compare the study drug to other drugs.
- For other research activities related to the study drug.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy laws.

Your permission to use and share health data about you will not end unless required by state law. If state law applies, your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may take back your permission to use and share health data about you at any time by writing to the study doctor at the address listed on page one of this consent form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____ ____/____/____

Signature of Research Subject Date

_____

Printed Name of Research Subject

STATEMENT OF PERSON OBTAINING AUTHORIZATION

I have carefully explained to the subject the nature and purpose of this form. I have been available to answer any questions that the subject has about this form.

_____ ____/____/____

Signature of Person Obtaining Authorization Date

_____ _____

Printed Name of Person Obtaining Informed Consent Time (24hr)