Study Title: Clinical Study to investigate the effect of administration of selective serotonin reuptake inhibitors and an opioid on ventilation

Document Title: Informed Consent Form – Study No. SCR-012

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

Sponsor/Study Title:	**U.S. Food and Drug Administration, "Clinical Study to Investigate the Effect of Administration of Selective Serotonin Reuptake Inhibitors and an Opioid on Ventilation"**
Protocol Number:	**SCR-012**
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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 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?

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

- Assess whether dosing of two different selective serotonin reuptake inhibitors (SSRIs) viz. paroxetine and escitalopram combined with oxycodone (narcotic analgesic) affect breathing compared to oxycodone alone under different gas levels (hyperoxic [more oxygen] and hypoxic [less oxygen] conditions),
- Assess whether dosing of SSRIs combined with oxycodone has effects on breathing compared to oxycodone alone under different gas levels, and
- Assess whether dosing of SSRIs has effects on breathing compared to placebo under different gas levels.

Oxycodone HCl (referred to throughout this document as oxycodone), Paroxetine HCl (referred to throughout this document as paroxetine), and Escitalopram oxalate (referred to throughout this document as escitalopram) have been approved by the U.S. Food and Drug Administration. Oxycodone is used for the management of pain severe enough to require an opioid. Paroxetine is used for the treatment of major depressive disorder. Escitalopram is used for acute and maintenance treatment of major depressive disorder and acute treatment of generalized anxiety disorder. However, their use in this study is

investigational. An investigational use is one that is not approved by the U.S. Food and Drug Administration.

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 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?

A well-known and potentially fatal adverse reaction (side effect) associated with opioid administration, particularly in the scenario of misuse, abuse, or when co-administered with certain other drugs is that people 'stop breathing'. Research suggests this is caused by a reduced breathing response to counteract increasing levels of carbon dioxide (CO_2). In August 2016, the U.S. Food and Drug Administration included boxed warnings about increased potential for decreased breathing with co-use of benzodiazepines and opioids. In response to this action, concerns were raised because patients may be prescribed other psychotropic drugs (drugs that affect a person's mental state) that may have similar negative reactions when combined with opioids.

Non-clinical and clinical studies have shown different SSRIs can have independent effects on breathing, though SSRIs have not been shown to cause severe decreased breathing on their own. This supports the need for additional investigation on the effects of serotonergic drugs (paroxetine and escitalopram).

Special Procedure: Duffin Rebreathing Procedure

You will be participating in the Duffin rebreathing procedure where you will breathe a hyperoxic (more oxygen)-hypercapnic (more carbon dioxide) (24% O_2, 6% CO_2, N_2 balanced) or hypoxic (less oxygen)-hypercapnic (more carbon dioxide) (6% O_2, 6% CO_2, N_2 balanced) gas mixture through a tight-fitting mask. This mixture of oxygen, carbon dioxide and nitrogen provided will be different than is normally found in room air (21% O_2, 0.04% CO_2, N_2 balanced with minor amounts of other gasses). The different gas mixtures, in particular the higher level of carbon dioxide breathed in, may result in a feeling of needing to breathe faster or more deeply. This procedure has been used in many previous studies and is non-invasive, meaning no pieces of equipment enter your body. During screening, you will be shown the rebreathing equipment and will be trained how to use it to understand if the procedure is tolerable. By performing this and receiving the drugs in the study as outlined in this informed consent form (ICF), the data collected will help the U.S. Food and Drug Administration to better understand how these drugs can be given more safely.

You will have Duffin 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.

Figure 1: Rebreathing Procedure Equipment Setup

WHO IS BEING ASKED TO TAKE PART IN THIS STUDY?

Approximately 25 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 18-50 (inclusive) years of age, have no history of heart or liver disease, no history of allergies, 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 3 inpatient periods. Each period will last for 23 days/22 nights. There will be 21 days between each inpatient period. By the end of this study you will have spent at least 69 days and 66 nights in the clinic, with at least 21 days off in between each period.

The duration of your participation in the study from screening to final follow-up will be up to 134 days.

INFORMATION FOR FEMALE SUBJECTS

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 are of non-childbearing potential (confirmed with a blood draw to measure follicle-stimulating hormone levels greater than 40 mIU/mL)
- You have been strictly abstinent for 1 month before check-in (Day -1) and agree to remain strictly abstinent for the duration of the study and for at least 1 month after the last application of study drug.
- You are using two adequate methods of contraception to avoid pregnancy throughout the study and for at least 1 month after last study drug administration.

Adequate methods of contraception include use of two of the following categories of which one (1) must be a barrier method from at least 1 month before check-in (Day -1) until at least 1 month after the end of the study.

- 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

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 this study will have a pregnancy test performed at screening, before admission periods (Day -1, Day 42, and Day 84) and/or early exit visits.

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.

INFORMATION FOR MALE SUBJECTS

You must agree to practice 2 highly effective methods of birth control (as listed above) from at least 1 month before check-in (Day -1) until at least 2 months after the last dose of study drug. 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 2 months after the last dose of the study drug.

Periodic abstinence and withdrawal are not acceptable methods of contraception.

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

You will need to fast for at least 8 hours prior to your arrival at Spaulding Clinical Research, LLC. for your screening visit, meaning you should not eat any food and should only have water to drink.

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 and pulse oximetry.
- A complete history of relevant allergies or drug sensitivities.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- You will be asked if you have taken any medication recently.
- 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), 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.
- Perform Duffin's Rebreathing under hyperoxic and hypoxic conditions

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.

HOW WILL THE STUDY BE DONE?

Approximately 25 healthy adult subjects, both male and female will be enrolled in this study. The study will consist of 3 treatment periods of 23 days/ 22 nights each with a 21-day wash-out in between each period. All subjects will be randomized (placed by chance) into a treatment group. Subjects will receive the following 3 treatments in a randomized order over the 3 treatment periods:

Study Treatment	**Day**					
	1-5	6	7-11	12	13-20	21
A	Placebo QD	Placebo + 10 mg oxycodone	Placebo QD	Placebo + 10 mg oxycodone	Placebo QD	Placebo + 10 mg oxycodone
B	40 mg paroxetine QD	40 mg paroxetine + 10 mg oxycodone	60 mg paroxetine QD	60 mg paroxetine + 10 mg oxycodone	60 mg paroxetine QD	60 mg paroxetine + 10 mg oxycodone
C	20 mg escitalopram QD	20 mg escitalopram + 10 mg oxycodone	30 mg escitalopram QD	30 mg escitalopram + 10 mg oxycodone	30 mg escitalopram QD	30 mg escitalopram + 10 mg oxycodone

Once the study doctor determines that you are eligible to participate, you will be enrolled into one of the groups above for the first period. You will not be allowed to choose your group or the order in which you receive the study treatments. Because this is a double blinded study, neither you nor the study doctor or study staff will know which study treatment you are receiving.

A placebo is a medically inactive substance which looks like the study drug.

QD means to take the medication once daily.

Ondansetron will also be administered prior to all oxycodone doses to reduce potential nausea/vomiting side effects.

You will have received all 3 of the above study treatments by the end of the study. There will be about 21 days in between each study treatment period.

You will go through the same tests and procedures described below for any of the study treatments you receive.

WHAT TESTS AND PROCEDURES WILL BE USED IN THE STUDY?

Check In (Days -1, 42, and 84)

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 need to fast for at least 8 hours prior to your arrival at Spaulding Clinical Research, LLC. for your check-in, meaning you should not eat any food and should only have water to drink.

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.
- Perform Duffin's Rebreathing under hyperoxic and hypoxic conditions.
- You will be provided meals (lunch, dinner and a snack).
- Inclusion/Exclusion assessment and preparation for randomization (Day -1). 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.

Study Treatment (Days 1 to 21, 43 to 63, and 85 to 105)

- Adverse event assessment and changes in concomitant medications.
- Pharmacokinetic (PK) blood sampling.
- Meals (after last Duffin Rebreathing procedure – lunch, dinner and a snack).
- Clinical laboratory tests (urine and blood samples)
- Assessment of blood pressure, heart rate, respiratory rate and oral temperature.
- Administration of study product.
- Continuous ECG (continuous, painless recordings of your heart's rhythm)
- Continuous pulse oximetry monitoring.
- Duffin Rebreathing procedure by trained study staff.
- Eye assessments to measure pupil size.
- Sedation assessments to measure whether you feel awake/alert vs. sedated.

Washout (Days 23 to 41 and 65 to 83)

- 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 Out (Day 22 and 64)

- Adverse event assessment and changes in concomitant medications.
- Physical examination.
- Pharmacokinetic (PK) blood sampling.
- Assessment of blood pressure, heart rate, respiratory rate, pulse oximetry and oral temperature.

Discharge (Day 106)

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

WHAT TESTS AND PROCEDURES WILL BE USED IN THE STUDY?

Blood Sampling

Blood samples will be collected for measurement of levels of oxycodone and oxymorphone (Days 6, 12 and 21 of each study period) as well as paroxetine and escitalopram (Days 2, 5, 6, 11, 12, 16, 20, and 21 of each study period) at approximately the following times:

- Day 5, 6, 11, 12, 20, 21 at pre-dose (0 hour), 3, 4, 5, and 8 for a total of approximately 30 blood collections for determining study drug levels.
- Day 6, 12, and 21 at 24 hrs for a total of approximately 3 blood collections for determining study drug levels.
- Day 2 and 16 at 0 (pre-dose), 2, 3, 4, 5, 6, 8, 12, and 24 hrs post-dose for a total of approximately 18 blood collections for determining study drug levels.
- The total number of blood draws is approximately 153 blood collections.

You will have numerous blood samples drawn during the entire study for study drug levels as shown above, and 8 safety laboratory draws throughout the study. 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 for the entire study will be approximately 808 mL or about 3.5 cups for the entire study.

Urine Sampling

You will have urine samples collected at screening, each check-in day (Day -1, Day 42, Day 84) and Day 106 (Check Out). These will be used to screen for either alcohol or drugs, and for routine safety analysis.

ECG Measurements

Safety ECG measurements will occur at your screening visit, Day -1 (Check In), and Day 106 (Check Out). On Days 1, 2 and 16 of each study period you will have telemetry (continuous, painless recordings of your heart's rhythm). There will be periods of time where you will need to lie very still to get precise readings of your heart's rhythm. You will have an ECG assessment on Day 1 of each study period at 0 (pre-dose) hr. You will have continuous ECG monitoring on Days 2 and Day 16 of each study period and

will require you to lay still for approximately 20 minutes at the following time points (based on the time of the study drug dose): 0 hr (Predose), 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 8 hr, 12 hr, and 24 hr.

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 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 study confinement.

Pulse Oximetry

You will have continuous pulse oximetry monitoring (continuous, painless monitoring of oxygen levels in your blood) on each of the rebreathing days (Days 5, 6, 11, 12, 20, and 21 of each study period) for 24 hours. You will also have pulse oximetry measurements with each vital signs collection.

Sedation Assessments

You will have sedation assessments 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.

Duffin 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 (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 Duffin 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.

Eye Measurements

You will have measurements of your eye done at specified times before and after the Duffin 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 staff 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 repeated on the same 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	24 hours of check-in of all study periods.
Caffeine or other xanthine containing products (for example, coffee, tea, cola or chocolate)	24 hours of check-in of all study periods.
Grapefruit	24 hours of check-in of all study periods.
Prescription medication	14 days prior to dose until final check out.
NSAIDs (Ibuprofen, Naproxen)	14 days prior to dose until final check out.
Complementary and alternative medicines	28 days prior to first dose of study drug until final check out.
Nicotine containing products	6 weeks prior to screening until final check out.
Participation in another clinical study of an investigational drug or treatment with an investigational drug.	30 days prior to screening until final check out.

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

You will be required to fast for at least 8 hours prior to study drug administration.

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 Duffin Rebreathing procedure will be performed (including screening).

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

- Subjects should be encouraged to wear masks except when in a private room without anyone else present or for a limited time for a study procedure (for example, study drug administration, switching to rebreathing mask) when instructed by study staff.
- Subjects must practice social distancing, which will include having a maximum of 2 subjects per room for overnight stays and access to common areas will be per clinical research site standards. While subjects are in house, meals will be served per clinical research site standards. Subjects will spend most of their time in their rooms except for specified times for walking in the halls (with masks recommended).
- 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.

On certain study days you may be required to get up very early (between 4 and 6 am) in order to complete study events. This will only be done when absolutely necessary and while it is important that you have sufficient rest during the study sometimes an early start to the day is unavoidable.

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

Please be advised that non-pharmacological (non-drug or medication) treatments (such as heating pack, stretches, hydration, etc.) are our first line of therapy for mild adverse events (side effects). The study doctor will be notified if a concomitant medication may be needed to treat an adverse event (AE). Following the protocol guidelines, the study doctor will assess your AE and develop a treatment plan.

Risks are possible side effects of the study drug, the positive control medicine, and those of taking blood and other medical procedures:

<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, hair loss

<u>For Escitalopram</u>

- Abdominal effects – Nausea, diarrhea, constipation, and indigestion
- Neurological effects – Decreased libido (sexual desire), headache, and dizziness, drowsiness
- General effects – Insomnia, ejaculation disorder, sweating increased, fatigue (feeling tired), somnolence (tiredness), impotence and anorgasmia (difficulty having an orgasm), dry mouth, hair loss
- Less common, but serious adverse events include:
    - Allergic reactions – Hypersensitivity reactions
    - Neurological effects – Syncope (fainting), seizures
    - Heart/blood vessel effects – QT interval prolongation (abnormal ECG), irregular heartbeat, abnormal blood clotting

- Abdominal effects – Increased liver enzymes (possible liver damage)
- Serotonin syndrome (usually when prescribed with another serotoninergic [SSRI] medication which will not be done in this study – leads to fever, sweating, diarrhea and potential complications including seizures and muscle breakdown)

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 (feeling tired)
- Less common side effects include:
    - Allergic reactions – Hypersensitivity reactions including anaphylaxis and bronchospasm (difficulty breathing due to narrowing of the airways) (serious allergic reactions)
    - Heart/blood vessel effects: QT interval prolongation (abnormal ECG) and Torsade de Pointes (abnormal heart rhythm)
    - Serotonin syndrome (usually when prescribed with another serotoninergic [SSRI] 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 an additional drug that is used as a 'rescue' (reversing) medication. Naloxone may be administered if respiratory depression occurs following opioid administration. Side effects of this medication 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 – trembling/shaking, seizures, restlessness, irritability, agitation
- General effects – sweating, body aches, fever
- Less common side effects include:
    - Ventricular tachycardia/fibrillation (Serious, abnormal heart rhythms) and pulmonary edema (accumulation of fluid in lungs)

It is possible that you could experience a potentially serious irregularity in your heart rhythm during the study. For this reason, we will be monitoring your heart rhythm closely throughout the study, and we will have immediate medical care available for you if any problems occur.

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 nurse, a doctor, or a 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 the state law.

Risks or side effects associated with Duffin's 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 (feeling tired), 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
- 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 closely monitored during the course of 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, Hepatitis B and C, and COVID-19 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, Hepatitis B and C, and COVID-19 test results must be reported to health authorities under state law. A positive HIV, Hepatitis B or C and/or COVID-19 result will exclude you from participation in the study.

Reproductive Risks

The effects of the test 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 2 months 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).

Partners of male subjects who become pregnant will be asked to sign a separate consent form to allow collection of the information listed above. Your information will be kept confidential in accordance with state and HIPAA law.

COVID-19 Risks

Despite the extra precautions (for example, 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 (feeling tired)
- 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 subjects, 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 U.S. Food and Drug Administration is the Sponsor of the study.

The U.S. 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 U.S. Food and Drug Administration pays for them.

Information about this study is confidential. This information belongs to the U.S. 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:

- $170.00 if you qualify and take part in a study. $170.00 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 that complete the entire study (Day -1 to the Period 3 checkout (Day 106)), you will receive up to $31,000.00. This payment will be made in 4 separate payments as follows:

- $8,833.00 will be paid after all check out procedures have been completed at the end of Period 1.
- $8,833.00 will be paid after all check out procedures have been completed at the end of Period 2.
- $8,834.00 will be paid after all check out procedures have been completed at the end of Period 3.
- The remaining $4,500.00 will be paid after any additional follow up procedures are completed, and all results are reviewed. Once follow up procedures have been completed and accepted by study doctor, your final payment will be processed and mailed within 14 calendar days.

If you withdraw from the study early, you will only be paid for the visits you completed ($384.00 per visit day).

NOTE: You may be required to return to the clinic for repeat blood test or other assessment (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 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; Advarra Institutional Review Board, health authority inspectors, such as the U.S. Food & Drug Administration and the European Medicines Agency; 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 U.S. 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. Any data and/or biospecimens provided to the U.S. Food and Drug Administration will be coded (stripped of identifiers such as name, address, or account number) and the key allowing the code to be linked to your personal information will be kept by the study team and never released to the agency. Therefore, the U.S. Food and Drug Administration will not be able to re-identify you. The U.S. Food and Drug Administration may share your coded information, as necessary, with the U.S. Food and Drug Administration affiliates who work within the scope of this consent;

Advarra IRB and Regulatory agencies such as 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 U.S. 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 U.S. Food and Drug Administration has also entered into agreements with third parties working for the U.S. 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.. The U.S. Food and Drug Administration may keep study samples and data collected for future research. Identifiers will be removed from your identifiable private information or identifiable biospecimens collected during this study so that data cannot be linked to you. The coded data and/or biospecimen could then be used for future research studies or distributed to another investigator for future research studies without additional informed consent .You will not be contacted about each of these future uses for additional informed consent. No additional participation time or procedures will be required beyond what is described above for the primary study. The coded data from the study will be replaced with a unique identifier and may be released to a data warehouse (location that will store the data) or used as part of a publication. It may be shared broadly for research purposes outside of the U.S. Food and Drug Administration and Spaulding Clinical Research, LLC. Other investigators study doctors will have access to limited clinical and biological data such as age, gender, and disease status. Your samples will only be used for research purposes. It is also possible that your samples and data will never be used. Results of research done on your samples and data will not be available to your personal doctor. If the results of this study are published or presented in a meeting, you will not be named and nobody will be able to tell that you were in the study from the publication or presentation.

WHO CAN YOU CONTACT FOR MORE INFORMATION ABOUT THIS STUDY?

You can ask questions about this consent form or the study (before you decide to start the study, at any time during the study, or after completion of the study). Questions may include:

Who to contact in the case of a research-related injury or illness;

- Payment or compensation for being in the study, if any;
- Your responsibilities as a study subject;
- Eligibility to participate in the research;
- The study doctor's or study site's decision to exclude you from participation;
- Results of tests and/or procedures;
- Other questions, concerns, or complaints.

Contact the study doctor or study staff <u>listed on the first page of this form</u> with any questions, concerns or complaints.

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 such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a research subject;
- Eligibility to participate in the study;
- The study doctor's or study site's decision to exclude you from participation;
- Results of tests and/or procedures;

Please contact the study doctor 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, contact:

- By **mail**:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00064533.

An IRB is a group of people who review research studies to protect the rights and welfare of research subjects.

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 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 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 for the following study procedures:

- Physical examination.
- Pregnancy test (if necessary).
- Body weight and body temperature.
- Blood pressure and pulse rate.
- Pulse oximetry (measurement of blood oxygen levels)
- ECG.
- Blood draws for hematology and chemistry.
- Blood draws for PK.
- Urine will be collected for urinalysis.
- Assessment for adverse events and concomitant medications (if you are taking any medications at the same time you were participating in the study)

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 of 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 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.

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

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 U.S. Food and Drug Administration (such as representatives who may audit the research or receive reports of adverse events).
- Representatives of Spaulding Clinical Research, LLC.
- Representatives of Advarra IRB. (an Institutional Review Board that reviews this study)
- Other U.S. 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 U.S. Food and Drug Administration and those working for the U.S. Food and Drug Administration may use the coded 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 on December 31, 2060.

You may take back your permission to use and share health data about you at any time by writing to the study doctor. 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 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 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.

_____ ____/____/____

Initials of Person Obtaining Authorization Date