Study Title: Clinical Study to Investigate the Pharmacokinetics of Multiple Repeated Doses of Intranasal Naloxone

Document Title: Informed Consent Form – Study No. SCR-011

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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 pharmacokinetics of multiple repeated doses of intranasal naloxone"**
Protocol Number:	**SCR-011**
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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.

CLINICAL STUDY SUMMARY:

Purpose of this clinical study	You are being asked to take part in a research study which will look at how different repeated doses of the study drug (naloxone nasal spray) affects the level of naloxone in the blood. Naloxone nasal spray is used to treat patients with known or suspected opioid overdoses. Your participation in this clinical study is voluntary.
Duration of participation	You can be expected to be confined at the research institution for a total of 9 days, 8 nights.
Risks and/or discomforts from the study drug (as seen in previous clinical studies using this study drug)	• Increased blood pressure • Constipation • Toothache • Muscle spasms • Musculoskeletal pain • Headache

	• Nasal dryness • Nasal edema (swelling) • Nasal congestion • Nasal inflammation/bleeding • Rhinalgia (pain in the nose) • Xeroderma (dryness of the skin or nose)
Other foreseeable risks and/or discomforts	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.
Benefits to your participation in this clinical 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 study. 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.
Stipend	If you complete the screening process for this study, you will receive up to $55. If you are selected for participation in this study and complete the entire study (Day -1 to Day 8), you will receive up to $3,645.00

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. 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 the following:

- How different repeated doses of the study drug (naloxone) affect the level of naloxone in the blood.
- Determine the impact of multiple doses of naloxone on the mean time to rescue patients from opioid overdoses using a pre-determined model.

Naloxone (trade name Narcan) has been approved by the U.S. Food and Drug Administration (FDA) and is commonly used in reversing opioid overdose. Naloxone is available in multiple formulations, including intravenous, intramuscular, and intranasal (inhaled through the nose). In this study, the administration of naloxone will be intranasal.

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 IS THIS STUDY DRUG BEING STUDIED?

Naloxone is a fast-acting drug that is commonly used in reversing opioid overdose. The use of intranasal (through the nose) naloxone is of interest as there is a need for naloxone formulations for community use by caregivers and first responders/law enforcement who do not have medical training. It is critical to administer naloxone as quickly as possible in the event of an opioid overdose to prevent irreversible brain damage and death.

There is a need to assess the body's exposure to naloxone when given intranasally over multiple doses. Your contribution to the study is of major importance to agencies like the U.S. Food and Drug Administration to understand how the body processes multiple repeated doses of intranasal naloxone.

HOW WILL THIS STUDY BE DONE?

This study will be conducted in one part, with three treatment periods. Approximately 20 healthy subjects will be enrolled who will receive study drug treatment according to the table below. Subjects will receive study treatment (study treatment group A, B, or C) in a random order on days 1, 4, and 7 with a washout period (meaning no study drug is given) of two days in between each dosing day. There will be no placebo used in this study. The table below describe the 3 dose regimens that you will get in random order.

Study Treatment	Description
A	Four 4 mg IN naloxone doses (1 dose every 2.5 min; L at 0 min, R at 2.5 min, L at 5 min, R at 7.5 min)
B	Four 4 mg IN naloxone doses (2 doses every 2.5 min; L and R at 0* min, L and R at 2.5* min)
C	Two 4 mg IN naloxone doses (L at 0 min, R at 2.5 min)

*IN = intranasal, L = Left Nostril, R = Right Nostril, *L and R doses will be ~5 seconds apart (one after the other)*

For this study, you will be confined at Spaulding Clinical from Day -1 through the morning of Day 8 (a total of 9 days).

WHO IS BEING ASKED TO TAKE PART IN THIS STUDY?

Approximately 20 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 55 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 one study treatment period of 9 days and 8 nights.

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 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 (FSH blood test) at screening, or
- You have a vasectomized partner who has been documented to no longer produce sperm, or
- You are using TWO highly effective methods of contraception to avoid pregnancy at least 1 month before study entry, throughout the study, and for at least 1 month after last study drug administration. Highly effective methods of birth control include:

    - Hormonal implants/patch,
    - Oral hormonal contraceptives,
    - Injectable hormones,
    - Intrauterine 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 study will have a pregnancy test performed at screening, at check-in on Day -1 and check out on Day 8.

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 SUBJECTS

The effect of the study drug on male sperm is unknown. Therefore, it is recommended to avoid fathering a child for 30 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 vital signs including 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).
- 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); blood sample to measure FSH (for postmenopausal female subjects only); 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.

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. <u>Check-in (Day -1)</u>

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
- Weight collection
- Clinical laboratory tests (urine and blood samples), including screening for drugs, alcohol, and pregnancy tests (all female subjects)
- Assessment of vital signs including blood pressure, respiratory rate, heart rate, and oral temperature
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart)
- 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 be provided meals
- Inclusion/Exclusion assessment and preparation for randomization

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

2. <u>Study Treatment (Days 1, 4, and 7)</u>

- Adverse event assessment (check for side effects) and changes in concomitant medications (medicines you are currently taking).
- Randomization (assignment to an order of study treatments)
- Collection of 3 electrocardiograms (ECG) at pre-dose, 1 hour, and 6 hour time points.
- Assessment of vital signs including blood pressure, respiratory rate, heart rate, and oral temperature at pre-dose, 0.5 hour, 1 hour, and 6 hour time points.
- Administration of study drug.
- Blood collection to look at levels of study drug in your blood.
- Meals.
- Nasal irritation assessment.

3. Washout (Days 2, 3, 5, and 6)

- Adverse event assessment (check for side effects) and changes in concomitant medications (medicines you are currently taking).
- Assessment of vital signs including blood pressure, respiratory rate, heart rate, and oral temperature.
- Meals.

4. Check-out (Day 8)

- Adverse event assessment (check for side effects) and changes in concomitant medications (medicines you are currently taking).
- Physical examination.
- Weight collection.
- Clinical laboratory tests (urine and blood samples), including screening for drugs, alcohol, and pregnancy tests (all female subjects).
- Assessment of vital signs including blood pressure, respiratory rate, heart rate, and oral temperature.
- An electrocardiogram (ECG)
- 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.

INFORMATION OBTAINED DURING THE STUDY

Blood Sampling

Blood samples will be collected for measurement of levels of study drug at the following times:

- On dosing days (Day 1, 4, and 7) at: 0 (pre-dose), 2, 4.5, 7, 10, 12.5, 15, 20, 30, 45, 60, 120, 180, 240, 360, and 720 minutes after dosing for a total of 48 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:

- Screening
- Check-in: Day -1
- Check-out: Day 8
- Total of 3 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. 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 480 ml or about 2 cups.

Urine Sampling

You will have urine samples collected at screening, Day -1 (Check-in), and the last study day (Check-out). 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), Day 1, 4, 7, and Day 8 (Check-out). 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 needed, 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.

Nasal Irritation Assessment

You will have nasal irritation assessments at different timepoints during study drug administration. A trained observer will use a pen light to look in your nostrils for signs of irritation or bleeding.

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 or grapefruit juice	48 hours before dose until the end of study visit
Nicotine-containing products	6 weeks prior to screening until end of study visit
Prescription or non-prescription medication (except for oral contraceptives) – note this includes:	14 days prior to dose

• Aspirin or NSAIDs (Ibuprofen, Naproxen) • Any intranasal medication	
Other intranasal spray products	48 hours before dose until the 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.

You must be willing to comply with study rules, including the meal schedule (25 minutes to eat), attempting to void at specified times, remaining quiet, awake, undistracted, motionless, and seated during specified times (for example during ECG extraction times), and avoiding vigorous exercise as directed throughout the duration of the study.

You must be able to take the study drug intranasally and should not have a deviated septum or any previous nasal surgeries that would impact administration of the intranasal drug.

You must remain fully supine for approximately one hour after study drug administration. You will be instructed to not breathe through the nose during administration of the nasal spray into the nose. You will be asked to leave your masks off for twenty minutes after study drug administration.

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

- You must always wear a mask except when in your bed with a curtain drawn in the room or for a limited time for a study procedure (for example, study drug administration when instructed by the study staff).
- You must practice social distancing. Common areas will be closed. You will eat meals socially distanced in the hallway. You will spend most of your time in your rooms except for specified times for walking in the halls (with masks).
- You 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.

The following adverse reactions were observed in a naloxone nasal spray clinical study similar to this one:

- Increased blood pressure
- Constipation
- Toothache
- Muscle spasms
- Musculoskeletal pain
- Headache
- Nasal dryness
- Nasal edema (swelling)
- Nasal congestion
- Nasal inflammation/bleeding
- Rhinalgia (pain in the nose)
- Xeroderma (dryness of the skin or nose)

Additionally, there is a risk of precipitation of severe opioid withdrawal in subjects who are opioid-dependent characterized by the following signs/symptoms:

- Body aches
- Diarrhea
- Tachycardia (increased heart rate)
- Fever
- Runny nose
- Sneezing
- Piloerection (goose bumps)
- Sweating
- Yawning
- Nausea or vomiting
- Nervousness
- Restlessness or irritability
- Shivering or trembling
- Abdominal cramps
- Weakness
- Increased blood pressure

However, opioid-dependent individuals are excluded from this study as subjects cannot use prescription or nonprescription drugs within at least 14 days of study drug administration and a urine drug screen will check for opioids at screening and check-in.

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.

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 30 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 (for a minimum of 30 days or until the first well-baby visit).

COVID-19 Risks

Despite the extra precautions (for example, COVID-19 triage at screening/check-in, coronavirus testing, mandatory masks for study subjects and study staff, social distancing, 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, study 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:

- $55.00 if you qualify and take part in a study. $55.00 for your time and inconvenience if you do not qualify for this 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 Day 8), you will receive up to $3,645.00. This payment will be made in two separate payments as follows:

- $3,000.00 will be paid after all check out procedures have been completed at the end of day 8.
- The remaining $645.00 will be paid after the follow up visit/call, and 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) 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 the pre-dose 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 at the rate of approximately $365 a day.

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; 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 study sponsor, 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. 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 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. The U.S. Food and Drug Administration may keep study samples and data collected for future research. Identifiers might be removed from your identifiable private information or identifiable biospecimens collected during this study and could then be used for future research studies or distributed to another investigator for future research studies without additional informed consent. No additional participation time or procedures will be required beyond what is described above for the primary study. Study samples and data will be de-identified (stripped of identifiers such as name, address, or account number) so that the data cannot be linked to you. The de-identified data from the study 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 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 and will not benefit you. 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 study doctor. 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.

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 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, 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: Pro00049858.

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, U.S. Food and Drug Administration or Advarra IRB 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:

- Serum pregnancy test (female subjects only)
- Adverse events and concomitant medications
- Alcohol and drug screening
- Clinical laboratory (blood) tests and urine collection for urinalysis
- Measurement of vital signs including blood pressure, heart rate, respiratory rate, pulse oximetry and oral body temperature)
- ECG
- Complete physical exam including weight

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 U.S. Food and Drug Administration
- Representatives of Spaulding Clinical Research, LLC.
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study).
- 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.

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 Time (24hr)

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)