Study Title: Clinical Study to Investigate the Urinary Excretion of N-nitrosodimethylamine (NDMA) after Ranitidine Administration

Document Title: Informed Consent Form - Study No. SCR-010

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

Sponsor/Study Title:	**US Food and Drug Administration / "Clinical Study to Investigate the Urinary Excretion of N-nitrosodimethylamine (NDMA) after Ranitidine Administration."**
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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 and date it. You cannot take part in this research study until you sign and date this form.

WHAT IS A SUBJECT INFORMED CONSENT?

You are being asked to take part in a research study of a drug called ranitidine in oral pill formulation. This drug is already approved by the U.S. Food and Drug Administration (FDA). Over-the-counter (OTC) ranitidine is approved to prevent and relieve heartburn associated with acid ingestion and sour stomach and prescription ranitidine is approved for multiple indications including treatment and prevention of ulcers of the stomach and intestines and treatment of gastroesophageal reflux disease (GRDS) related conditions. This research study will look at what happens to ranitidine after you take it with different diets. 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 DRUG BEING STUDIED?

This is a clinical research study. This study is sponsored by The US Food and Drug Administration, based in Maryland, USA.

The U.S. Food and Drug Administration has learned that some ranitidine products, including some products commonly known as the brand-name drug Zantac, contain low levels of an impurity called N-nitrosodimethylamine (NDMA). NDMA is a substance that possibly causes cancer based on results from laboratory tests. NDMA is known to be in the environment and is found in water and foods, including meats, dairy products, and vegetables.

The U.S. Food and Drug Administration has requested removal of all ranitidine products from the market because some ranitidine products have NDMA levels above the acceptable limits (96 nanograms per day or 0.32 ppm for 300 mg per day of ranitidine). At the acceptable limit, there is approximately a 1 in 100,000 chance of cancer after 70 years of exposure to that level. The ranitidine you will take in this study has been tested and shown to have NDMA levels well below the acceptable limits and these levels are stable on repeated testing.

It is unknown whether NDMA is formed in the body after ranitidine is given and whether administering ranitidine with certain foods affects this. The goal of this study is to use a single prescription dose of ranitidine (300 mg) to test whether there is increased level of NDMA in your urine in the 24 hours following dosing with ranitidine compared to when you are dosed with a placebo. This will be done when ranitidine is given once with meals low in NDMA and nitrites (common preservative in meats and found in other foods), and when given once with meals high in NDMA and nitrites.

WHO IS BEING ASKED TO TAKE PART IN THIS STUDY?

Approximately eighteen 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 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 and remain there for four dosing periods. You will check-in on day -2, have a “washout day” on day -1 and then receive study treatment on days 1, 3, 5 and 7. There will be additional “washout days” on days 2, 4, and 6. Altogether you will be in house from day -2 to day 8, for a total of 10 days and 9 nights in house.

The duration of your participation in the study from screening to final follow-up will be up to 38 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 have had a hysterectomy (uterus removed) or bilateral oophorectomy (ovaries removed), confirmed with documentation, or
- You are of post-menopausal age and have not had a menstrual period for 2 years, confirmed with hormone level at screening, or
- You have a vasectomized partner who has been documented to no longer produce sperm, or
- You are using TWO highly reliable methods of contraception to avoid pregnancy throughout the study and for at least 1 month after last study drug administration. Highly reliable methods of birth control include:

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

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

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

All females enrolled in the study will have a pregnancy test performed at screening and at check-in on Day -2.

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

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

Periodic abstinence and withdrawal are not acceptable methods of contraception.

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

At the beginning of the Screening visit, Informed Consent will be obtained. You may need to visit the study site more than once to complete the screening tests.

You will need to fast for at least 8 hours prior to your arrival at Spaulding Clinical Research, LLC. for the clinical laboratory tests and H-pylori breath test for screening, meaning you should not eat any food and should only have water to drink.

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

- A complete medical history and physical examination (including height and weight measurements for Body Mass Index (BMI, a way to tell if your weight is proportional to your height).
- Assessment of blood pressure, respiratory rate, heart rate, and oral temperature.
- A complete history of relevant allergies or drug sensitivities.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- 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.
- You will be given an H-pylori breath test to find out whether you have the H. pylori bacteria in your gut. If you do you cannot be in this trial. You will have to fast before the test then have a drink of water into which a granulated powder has been dissolved. Once this solution is in your stomach, if it mixes with H. pylori bacteria it can be picked up in the breath you exhale through a breath test instrument. The test is safe and painless.

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 potentially antibody screening for coronavirus.

HOW WILL THE STUDY BE DONE?

Eighteen healthy adult subjects, both male and female will be enrolled in this study. The study will consist of four study treatment periods of one day each. There will be a washout period (a period of time to allow the study drug to leave your system) of one day after each dose day, but you will remain at Spaulding Clinical Research for the entire duration of the study. This will be 10 days and 9 nights in total. All subjects will receive the following four study treatments in a randomized (by chance) order over the four study treatment periods:

A. Ranitidine + low nitrite/NDMA meals;
B. Placebo + low nitrite/NDMA meals;
C. Ranitidine + high nitrite/NDMA meals;
D. Placebo + high nitrite/NDMA meals.

Once the study doctor determines that you are eligible to participate, you will be enrolled and randomized to receive either study treatment A or study treatment B for the first and second periods and to receive either study treatment C or study treatment D for the third and fourth periods. You will not be allowed to choose your study group or the order in which you receive the dosing regimens. Because this is a double blinded study, neither you nor the study doctor or study staff will know which study treatment you are receiving. However, your study doctor can find out which group you are in if there is an emergency. When you receive the study drug you will be asked to wear a blindfold so that you are unable to see the study drug or placebo. A placebo is a medically inactive substance, which looks like the study drug.

You will have received all of the above regimens by the end of the study. There will be one day in between each regimen. 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?

Day –2 Admission

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 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).
- 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.
- Meals (lunch, dinner and a small snack).
- 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. None of these tests are investigational and are commonly performed during routine medical care.

Study Treatment (Days 1, 3, 5 and 7)

- Adverse event assessment (check for side effects) and changes in concomitant medications (medicines you are currently taking).
- Randomization (assignment to a dose group) Period 1 only.
- Assessment of temperature, blood pressure and heart rate.
- Administration of study drug or placebo.
- Breakfast within 2 minutes of taking the study drug or placebo.
- Meals (lunch, dinner, and a small snack).
- Pharmacokinetic (PK) blood and urine sampling (blood and urine samples for determination of study drug levels, NDMA and other constituents). Pharmacokinetics looks at how your body:
    - Takes the study drug into your bloodstream.
    - Delivers the study drug through the blood.
    - Breaks down or processes the study drug.
    - Removes the study drug.
- In order to assess the amount of NDMA in your urine you will have all your urine collected at multiple timepoints over 24 hours after you take ranitidine or placebo. You will be encouraged to pass urine only at the specific timepoints, however, all urine will be captured over the 24-hour period.

Washout (Days 2, 4 and 6)

- Adverse event assessment and changes in concomitant medications.
- PK blood and urine collection in the morning only for determination of study drug levels, NDMA, and other constituents.
- Meals (Breakfast, Lunch, Dinner and a small snack).
- Assessment of blood pressure, heart rate, and oral temperature.

Discharge (Day 8)

- Adverse event assessment and changes in concomitant medications.
- PK blood and urine collection in the morning only for determination of study drug levels, NDMA, and other constituents.
- Breakfast.
- Clinical laboratory tests (urine and blood samples) for safety and also for drugs and alcohol and pregnancy.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- Physical examination.
- Assessment of blood pressure, heart rate, and oral temperature.
- Discharge from Spaulding Clinical.

INFORMATION OBTAINED DURING THE STUDY

Blood Sampling

Blood samples will be collected for measurement of levels of ranitidine, NDMA and other constituents **in every study treatment period** at the following times:

- Days 1, 3, 5 and 7 at: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 11, 14, and 24 hrs post-dose for a total of approximately 52 blood collections for determining study drug and NDMA levels.
- The total number of blood draws including screening and safety laboratory draws is approximately 55 blood collections.

You will have numerous blood samples drawn during the entire study for study drug levels as shown above, and three 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 464 mL (416 mL for the determination of ranitidine, NDMA and other constituent concentrations, and approximately 48 mL for clinical laboratory tests) or about 2 cups for the entire study. For comparison, a standard blood donation (once every 56 days) is 470 mL or about 2 cups taken at one time.

Urine Sampling

You will have urine samples collected at screening, check in on day -2 and at check out on day 8. These will be used to screen for either alcohol or drugs, and for routine safety analysis.

On days 1, 3, 5 and 7 all your urine will be collected for 24 hours for measurement of study drug, NDMA, and other constituents for assessment of your body's response. Your urine will be collected at specific timepoints and you will be encouraged to pass urine only at these timepoints.

ECG Measurements

Safety ECG measurements will occur at your screening visit, check in on day -2 and at check out on day 8.

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 confinement.

WHAT ARE YOUR RESTRICTIONS DURING THE STUDY?

You will need to avoid the following while taking part in this study (including between screening and check in), and for some of the following you will need to confirm you have not taken certain medications within a certain time prior to screening:

- Subjects should not use antacids or heart burn medications for 2 weeks before screening.

- Subjects should not use prescription or non-prescription drugs, including antacids, heart burn medications, aspirin or NSAIDs (like ibuprofen and naproxen) excluding oral contraceptives or acetaminophen (Tylenol) for 28 days prior to the first dose until they have completed study participation.
- Subjects should not use mouthwash from day -2 until they have completed study participation.
- Subjects should not consume alcohol, grapefruit or grapefruit juice, caffeine or other methylxanthines (for example, coffee, tea, cola or chocolate) for 24 hr prior to first dose until they have completed study participation.
- Male and female subjects must adhere to contraception methods as previously stated.
- All subjects will fast for a minimum of 12 hours overnight ahead of dosing on days 1,3, 5 and 7, and will fast for 8 hours before safety labs are drawn at screening, day -2 and day 8.

You will receive a diet that does not contain any alcohol or caffeine. You must eat all of each meal, snack and drink that is served to you and eat at a reasonable pace (within 25 minutes) throughout the entire study from the morning of day -1 until the end of day 7. You will be shown the menu for this study in full during your screening visit. If you think you may be unable to eat each meal in full throughout the entire study you should not agree to be part of this study. While you are at Spaulding Clinical you will be provided only distilled water to drink, not water from a tap or water fountain.

You may eat only meals and snacks that are provided to you during periods of your stay.

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

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

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

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

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

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

For Ranitidine (study drug):

Headache, sometimes severe, is the most common adverse effect. The following additional adverse events have been reported in patients taking ranitidine, but whether they were caused by ranitidine has been unclear in many cases:

- Neurological effects: Rarely malaise (general discomfort), dizziness, somnolence (sleepiness), insomnia (difficulty sleeping), vertigo (dizziness). Rare cases of reversible mental confusion (confusion that goes away after stopping the study drug), agitation, depression, hallucinations mainly in severely ill elderly patients, reversible blurred vision, or reversible involuntary motor disturbances.
- Heart effects: Rare reports of abnormal heart rhythms.
- Abdominal effects: Constipation, diarrhea, nausea/vomiting and abdominal discomfort/pain. Occasional reports of hepatitis (liver inflammation). Rare cases of liver failure or pancreatitis (inflammation of pancreas).
- Musculoskeletal effects: Rare reports of arthralgias (joint pain) and myalgias (muscle aches).
- Blood/vessel effects: Leukopenia, granulocytopenia and thrombocytopenia (decreased blood cell counts) in a few patients. Rare cases of vasculitis (blood vessel inflammation), agranulocytosis or pancytopenia (more severe decreased blood counts), and exceedingly rare cases of acquired immune hemolytic anemia (low red blood cell count).
- Sexual effects: Controlled studies have shown no hormone effects, however, occasional cases of impotence (erectile dysfunction), and loss of libido (sex drive) have been reported in males, but the rates did not differ from that in the general population. Rare cases of breast symptoms and conditions, including galactorrhea (milky nipple discharge) and gynecomastia (enlarged breast tissue).
- Skin/hair effects: Rash, including rare cases of erythema multiforme (skin or mouth lesions). Rare cases of alopecia (hair loss).
- Lung effects: Potential increased risk of pneumonia (lung infection).
- Other: Rare cases of hypersensitivity reactions (exaggerated immune response that can cause trouble breathing, fever, rash or increased blood counts), anaphylaxis (severe allergic reaction), angioneurotic edema (swelling under the skin), acute interstitial nephritis (kidney inflammation), and small increases in serum creatinine (effect on kidneys).

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.

You will be asked to fast during this study, and you will not be able to drink alcohol, use nicotine-containing products, or drink beverages containing caffeine or alcohol. This may cause you some discomfort.

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

according to the state law. The study doctor may be required by law to report the result of these tests to the local health authority.

Unknown Risks

As described in the earlier section on "Why is this drug being studied?" some ranitidine products have been found to contain NDMA, which is a substance that possibly causes cancer. However, the ranitidine being used in this study has been tested twice and shown to have NDMA levels well below the acceptable limits. It is possible that some NDMA is formed in the body after taking ranitidine. However, your risk remains very low as at the acceptable limit for NDMA, there is approximately a 1 in 100,000 chance of cancer after 70 years of exposure to that level. During this study, you will only receive two doses of ranitidine.

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 Testing

The risks of HIV 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 test results must be reported to health authorities under state law.

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 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

Or at least two of these symptoms:

- Fever
- Chills
- Repeated shaking with chills
- Muscle pain
- Headache
- Sore throat
- New loss of taste or smell

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 additional testing, further isolation from other study subjects/staff until testing results are obtained, and 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 United States Food and Drug Administration is the Sponsor of the study.

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

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

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

WILL YOU BE PAID FOR BEING IN THIS STUDY?

Compensation for screening is as follows:

- $55.00 if you qualify for a study. $55.00 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 -2 to Day 8), you will receive up to $3,625.00. This payment will be made in two separate payments as follows:

- $1000.00 will be paid after all check out procedures have been completed at the end of Day 8,
- The remaining $2,625.00 will be paid after any additional follow up procedures are completed, and all results are reviewed.

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

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

COMPENSATION FOR INJURY

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

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

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

damages from the individuals or organizations responsible for your injury as you still have the right to seek compensation for injury related to malpractice, negligence, fault, guilt or blame of those involved in the research.

PROTECTING THE PRIVACY OF YOUR HEALTH DATA

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

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

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

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

The Study Information will be kept confidential within the limits of the law and used only for research purposes mentioned above. De-identified data (data not linked to you) from the study may be released to a data warehouse (location that will store the data) or as a part of a publication. Research may be performed by researchers outside of the U.S. Food and Drug Administration and Spaulding Clinical Research, LLC. If the results of this study are published or presented in a meeting, you will not be named and no one will be able to tell that you were in the study from the publication or presentation.

Your participation in this study is voluntary and you may cancel this consent at any time and without any reason. If you do so, your participation in the study will end and the study staff will stop collecting information from you, however, you will be asked to come back to the site for an end of study visit. Your samples will then be destroyed. However, the US Food and Drug Administration will continue to retain

and use any research results that have already been collected to verify the scientific integrity of the study. If you wish to leave the study inform your study doctor.

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

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

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the 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: Pro00043877.

IS YOUR PARTICIPATION VOLUNTARY?

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

The study doctor, Sponsor, FDA or Advarra 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 to you or others.
- 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.
- ECG.
- Blood draws for hematology and chemistry.
- Blood draws for PK.
- Urine will be collected for urinalysis.
- Adverse events and concomitant medications.

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

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. 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 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.

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

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

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

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

Your permission to use and share health data about you will not end unless required by state law. If state law applies, your permission to use and share health data about you will end 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 and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

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

_____ ____/____/____

Signature of Research Subject Date

_____

Printed Name of Research Subject

STATEMENT OF PERSON OBTAINING AUTHORIZATION

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

_____ ____/____/____

Initials of Person Obtaining Authorization Date