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INTEGREVIEW IRB
SEPTEMBER 4, 2020

Informed Consent Document

PROTOCOL NUMBER AND TITLE OF STUDY:	S-16-14; "A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intramuscular Administration of Scopolamine Hydrobromide Trihydrate, Injection"
SPONSOR:	The Surgeon General, Department of the Army (TSG-DA)
NAME OF PERSON IN CHARGE OF THE RESEARCH STUDY (STUDY DOCTOR/ INVESTIGATOR):	Paolo DePetrillo, M.D.
DAYTIME TELEPHONE:	410-706-8801
AFTER WORK HOURS:	301-961-5667

CONTACT INFORMATION:

The contact information is a resource if you have questions about the study, your participation in the study, the investigational drug used in the study, any side effect, possible payment for participation in the study, your rights as a study participant, and your safety. You may also withdraw your Health Insurance Portability and Accountability Act (HIPAA) Authorization by contacting the study doctor, who is known as the Principal Investigator (PI).

The PI should be contacted for questions about an injury related to the research study, side effects, the study drug, payment due to injury, or to revoke in writing the HIPAA Authorization.

The study will be conducted at Pharmaron by Dr. Paolo DePetrillo. The sponsor of the study is The Surgeon General, Department of the Army (TSG-DA).

The Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense is funding this research. Pharmaron is being paid to conduct this study.

You must be honest with the investigator about your health history or you may harm yourself by participating in this study.

You are being asked to participate in this research study because you are a healthy adult male or female living in the greater Baltimore area.

The following table summarizes some key points about the study. After reading this summary, if you think you might be interested in participating, please read the rest of the consent form for more details about the study.

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Research Study Summary	
Informed Consent	It is important that you understand what will be done in this research study, as well as the possible risks to you, so you can make an informed decision about participation. This process is called informed consent. • Please ask questions about anything you do not understand. • The study staff will explain anything you do not understand, including the study procedures and risks. • Take as much time as you need to review this document. • Feel free to talk with your family, friends, or others before you make a decision. • After your questions have been answered, you will be asked if you want to participate. If you agree, you will sign this consent form. • After signing, you will be given a test to ensure you understand the study and procedures. You will have three tries to pass the test. In between tries, the study staff will discuss any incorrect answers with you. • You will be given a copy of this form to keep for reference. • The study staff will talk with you about the information in this consent form at any time during the study.
Voluntary Participation	You do not have to take part in this research. It is your choice. • You can choose to withdraw (stop participating) at any time during the study. • Your refusal to participate or withdrawal will involve no penalty or loss of any benefits to which you are otherwise entitled.
Purpose	• The main purpose of this study is to evaluate the safety and tolerability of an investigational drug. • Another purpose is to evaluate how much of the drug remains in your system over time.
Study Duration	You will be in this study for about 2 months, including the screening period.
Main Study Procedures	While you are in the study, the main procedures are: • One screening visit, one inpatient stay of 4 days and 3 nights followed by 2 follow-up telephone calls, and 1 outpatient visit. • One injection (shot) of active study drug or placebo (inactive or "dummy" drug) into one of your thighs. • Safety testing to monitor your physical and mental health throughout the study. • Blood and urine collection for standard lab tests to check your health and measure how much study drug stays in your system. • See *"What Is Involved in Being in This Study"* for a complete description of procedures and tests by study day.

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Research Study Summary	
Investigational Drug	The investigational drug in this study is Scopolamine Hydrobromide Trihydrate, Injection (Scopolamine HBT, Injection). Scopolamine is approved by the US Food and Drug Administration (FDA) for use as a skin patch where the drug is absorbed through the skin to treat nausea and vomiting. However, Scopolamine HBT has not been approved by the FDA to be given as an intramuscular injection, or to treat conditions other than nausea and vomiting. Therefore, the Scopolamine HBT you will receive during this study is considered an investigational drug.
Main Study Risks	The main risks from being in this study are: • Local reactions at the site of injection: pain, itching, rashes, tingling or numbness, tenderness, redness, swelling, bruising, muscle stiffness, or feeling of burning, warmth or coldness. • Systemic reactions due to the study drug include: o Dry mouth, thirst, difficulty swallowing, decreased sweating, and/or dry skin o Dilation of the pupils and blurred vision o Cognitive and memory disturbances (including disorientation or mental confusion), euphoria, and amnesia o Dizziness, headaches, restlessness, tremors, fatigue, and gait disturbances (such as stumbling) o See *"Non Local Reactions"* for a complete description
Benefits	There is no direct benefit to you for participating in this study.
Compensation	You may receive compensation for participating in this study.
ClinicalTrials.gov	A description of this clinical study will be available on http://www.ClinicalTrials.gov, as required by US 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.

Why Is This Investigational Drug Being Offered?

As part of the continued search for better treatment options, the US Army Medical Research and Development Command (USAMRDC) is developing this drug as an additional therapy for the treatment of chemical warfare nerve agent exposure. Nerve agents are organic chemicals that attack the nervous system of the human body by disrupting the way your nerves send messages to your organs. **You will not be exposed to any nerve agents during your participation in this research study**.

What Is the Purpose of the Study?

The main purpose of this study is to evaluate the safety and tolerability of this investigational drug. Another purpose is to evaluate how much of the drug remains in your system over time (this is called pharmacokinetics).

In this study, "Investigational" means the study drug formulation being tested is not approved by the FDA for intramuscular injection, or to treat chemical warfare nerve agent exposure.

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In this document, you may see the terms "medication," "treatment," and "treatment period;" these are terms used in research studies as mentioned above and does not mean that you will be receiving medical treatment for any condition. These terms apply to the study drug and parts of the study where you will receive the investigational product.

What Is the Design of the Study?

This is a dose-escalation study and involves a total of 5 dose levels (or groups). Dose escalation means that the first group of participants will be randomly (by chance) assigned to receive the lowest dose of the active study drug or placebo (inactive or dummy drug), and the second group will be randomly assigned to receive the next higher dose of the active study drug or placebo. After all participants in the first group are dosed, the findings for the entire group will be evaluated. If no concerning side effects are seen, the second group of participants will be enrolled. This procedure will be repeated until all 5 groups have been enrolled.

A minimum of 40 and a maximum of 60 participants will be enrolled in this study. Overall, up to 240 subjects may be screened for this study. In each group, 6 participants will receive the active study drug and 2 will receive the inactive placebo. If certain side effects are seen in any of the groups, 4 additional subjects (3 active and 1 placebo) may be added to each group. Each group will have at least 3 female and 3 male subjects enrolled.

You have a 3 to 1 chance of receiving the active study drug. You will not have a choice as to which dose level (group) you are assigned nor will you have a choice as to the assignment of active drug or placebo. Neither you nor the study staff will know if you are assigned to receive the active study drug or the placebo. This information can be obtained if it becomes medically necessary.

One screening visit is required within 30 days of the start of the study. The purpose of the screening visit is to make sure that you are qualified (eligible) and willing to participate in the study. If the study doctor determines that you are eligible and you agree to participate, the study will require one inpatient clinic stay of 4 days and 3 nights followed by 2 follow-up telephone calls and 1 outpatient visit.

What Is the Length of Study Participation?

The length of your participation in this study is approximately 2 months, including the screening period.

What Is the Investigational Product?

The investigational drug in this study is scopolamine hydrobromide trihydrate, injection (Scopolamine HBT, Injection).

How Will the Drug Be Given?

Scopolamine HBT or placebo will be given as an injection (shot) into the muscle of one of your thighs. Each participant will receive one injection.

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What Are the Requirements to Be in the Study?

To be eligible for this research study, you must meet the following requirements:

- Male or female, 18 to 55 years of age
- Able to read, speak, and comprehend English and willing to sign this informed consent
- A body mass index (BMI) of ≥ 19.0 and ≤ 30.0
- A weight range of 55.0 to 85.0 kg
- Generally healthy and medically cleared for participation by a study doctor based on a physical exam, medical history review, and laboratory, neuropsychiatric and other tests
- Negative results on drug and alcohol tests at screening and prior to study drug administration
- Non-smoker and a non-tobacco/nicotine product (including e-cigarette) user within 3 months of dosing and throughout the study period
- If female, nonpregnant and nonbreastfeeding with a negative blood pregnancy test at screening and prior to dosing. Females should also not plan to become pregnant for the duration of the study.
- If female of childbearing potential, must have been using adequate contraception for at least 3 months prior to drug administration and agree to use an adequate method of contraception for at least 30 days following drug administration
- If female of nonchildbearing potential, must be postmenopausal (no menstrual period for 24 months) or surgically sterile (bilateral tubal ligation [both tubes cut], bilateral removal of ovaries, or total hysterectomy [uterus removed])
- If male with a female partner of childbearing potential, must agree to use a barrier method of contraception (defined as condoms with spermicide) for at least 30 days following drug administration
- Must not have received any other investigational drug within 30 days prior to drug administration
- Must not have donated > 480 mL of blood within 8 weeks of drug administration

To be eligible for this study, you must agree to the following restrictions:

- May not consume Seville orange (bitter orange), grapefruit, grapefruit juice, other grapefruit-containing products, or starfruit within 7 days prior to dosing and through Day 3
- May not consume alcohol within 72 hours prior to dosing and through Day 3
- May not consume caffeine or other xanthine-containing products (such as chocolate) within 7 days prior to dosing and through Day 3
- May not do strenuous physical activity of any kind (such as lifting weights, working out, or dancing) from 48 hours prior to admission on Day -1 and until after the Day 8 visit
- May not take antimuscarinic drugs, such as phenothiazines, tricyclic antidepressants, antihistamines (including meclizine), meperidine, or other anticholinergics that have weak antimuscarinic activity or that cause drowsiness, including antidepressants, benzodiazepines, alcohol, sedatives (used to treat insomnia), pain relievers, anxiety medicines, and muscle relaxants within 72 hours prior to dosing
- May not take any prescription or nonprescription medication (including home remedies, herbal supplements, or nutritional supplements) within 14 days of planned dosing. Note: hormonal birth control methods are allowed
- May not donate blood or other blood components for 8 weeks after completion of the study

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What Is the Potential Benefit of the Study, and Is There an Alternative to Participating?

There is no direct benefit to you for participating in this study. The alternative to participating is to choose not to participate.

What Are the Potential Risks and Discomforts of the Study Drug?

If you do not understand what any of these side effects mean, please ask the investigator or study staff to explain these terms to you.

Because this drug is investigational, all of its side effects may not be known. There may be rare and unknown side effects. Some of these may be life threatening.

You must tell the investigator or study staff about all side effects that you have. If you are not honest about your side effects, you may harm yourself by staying in this study.

Until you know how the drug(s) will affect you, you should use caution by avoiding stairs, not driving a car or working with machinery.

Local Injection site Reactions:

Potential risks associated with the injection of Scopolamine HBT or placebo with a syringe may include the following local effects at the site of injection: pain (which may be severe), itching, rashes, tingling or numbness, tenderness, redness, swelling, bruising, muscle stiffness, or a feeling of burning, warmth, or coldness.

Non local Reactions:

Typically, dry mouth is the first notable reaction followed by dry skin. Thirst and difficulty in swallowing may occur when the mouth and esophagus become sufficiently dry. Decreased sweating occurs, which also may cause flushing and limit your body's ability to tolerate heat; this can lead to heat exhaustion or heat stroke in a hot environment. Dilation of the pupils of the eyes is expected; sensitivity to light and blurring of vision are effects of this dilation. At the same time your pupils dilate, the muscles that allow your vision to accommodate may be impaired, which also leads to blurred vision. In susceptible persons, especially the elderly, the impaired function of the eye muscles may contribute to an elevation of eye pressures. Difficulty in urination and urinary retention may occur. Tachycardia (ie, rapid heart rate) is a common side effect. Bradycardia (ie, low heart rate) at lower doses, hypotension (low blood pressure), and arrhythmias (irregular heart rhythms) may also occur. Scopolamine HBT reduces salivary secretion, gastric secretion (both the volume and acid content), and also inhibits the motor activity of the stomach and intestines, which may lead to constipation that may be severe. Nausea and vomiting may also occur.

Scopolamine HBT also often causes cognitive and memory disturbances (including disorientation or mental confusion), euphoria (a feeling or state of intense excitement and happiness), amnesia (a partial or total loss of memory), and dreamless sleep with a reduction in rapid-eye-movement sleep. Scopolamine HBT may cause drowsiness, fatigue, dizziness, headaches, tremors, and gait disturbances (such as stumbling). Less commonly, Scopolamine HBT may cause excitement, restlessness, insomnia (inability to sleep), delirium (altered mental status), hallucinations, and/or paranoia (suspicion and mistrust of people), especially in the presence of severe pain.

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Rarely, Scopolamine HBT may cause neuroleptic malignant syndrome (includes seizures and fever) and the risk of seizures. Emergency equipment and rescue medications will be available at the bedside in case of seizures or other side effects.

A specific rescue medication to treat Scopolamine HBT effects will be available. This medication is called physostigmine, a drug that has been used to reverse the side effects of Scopolamine HBT, such as memory disturbances, paranoia, and hallucinations. After receiving your injection of Scopolamine HBT or placebo, you will be monitored carefully by a study doctor. Depending on your symptoms, the study doctor will determine whether you need to receive a dose of physostigmine to relieve the side effects. If used, medical staff will administer one dose of physostigmine intravenously (IV). Three more doses may be given every 5 minutes (for a total of 4 doses), if needed to relieve the symptoms.

Additional rescue medications, atropine and a benzodiazepine (diazepam or lorazepam), will be available at the bedside.

Allergic Reaction:

As with any study drug administration and no matter what precautions are taken, there is always the risk of a more serious, or even life-threatening, allergic reaction. Emergency equipment is available in the clinic to handle emergencies per standard medical practice. For these reactions, initial emergency medical treatment will begin in the clinic, and if indicated, 911 will be called for further treatment and possible transport to a local hospital emergency room.

What Are the Potential Risks and Discomforts of the Study Procedures?

Needle Stick:

Blood sampling carries a minimal risk of minor discomfort, the possibility of minor bruising at the needle puncture site, and the possibility of lightheadedness or fainting. Rarely, there is also the possibility of infection at the needle puncture site or inflammation of the vein.

ECG:

The adhesive on the ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement and removal of ECG leads.

Blood Oxygen Level:

A finger clip sensor will be used to measure the amount of oxygen in your blood. The clip will fit snugly on your index finger and should cause minimal, if any, discomfort. While causing minimal discomfort, you should be aware that your oxygen levels will be monitored for 24 hours after you receive the study drug.

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Are There Unknown Risks to Participating in This Study?

Unknown/Unforeseeable Risks:

As with all research, there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

You will be informed in a timely manner both verbally and in writing of any new information, findings, or changes to the way the research will be performed that might influence your willingness to continue your participation in this study.

Risks to the Unborn:

The effects of the study drug on an unborn child are unknown and may be hazardous. You should not receive this investigational drug if you are pregnant, or think you may be pregnant, and you should not become pregnant for at least 30 days after drug administration.

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you will be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study staff will follow your pregnancy to term for safety reasons via periodic telephone contact. The updates you provide to study staff on your pregnancy and pregnancy outcome (delivery or other outcome) will be reported to the sponsor and the Institutional Review Board (IRB). There is a possibility that it may be necessary to access your medical records in order to obtain more information about your pregnancy and/or pregnancy outcome.

The birth control requirements for males and females who participate in this study are described below.

Birth Control Requirements:

Females:

You may not participate in this study if you are pregnant or breastfeeding. As part of giving your consent you must agree to have a serum (blood) pregnancy test at screening, prior to dosing, and at the end of the study, regardless of your childbearing potential. You must also agree to use an acceptable means of birth control during this study unless you are post-menopausal for at least 2 years or are surgically sterile (have had a bilateral oophorectomy [both ovaries removed], bilateral tubal ligation [both tubes cut], or total hysterectomy [uterus removed]).

Acceptable means of birth control for females include the regular use of hormonal contraceptives (ie, oral, implant, injection, patch, or vaginal ring), barrier methods with spermicide (ie, condom, diaphragm, cervical cap with spermicidal gel, cream, or foam), or an intrauterine device (IUD). If you are using an acceptable means of birth control, you must have been using the same method for at least 3 months prior to receiving the study drug, and you must continue this method for at least 30 days after study drug administration.

Please note that birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUDs, or sperm-killing products are not completely effective in preventing pregnancy.

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Males:

As part of giving your consent, you must agree to use a barrier form of birth control (ie, condoms with spermicide) from the time of screening to 30 days after study drug administration.

A pregnancy test isn't always right, especially in the early stages of pregnancy. If you or your partner are pregnant, become pregnant, or breastfeed during the study, the study drug may have unforeseen effects on the unborn or breastfed baby.

What Is Involved in Being in This Study?

Screening Visit and Tests:

After all of your questions have been answered, and if you are interested in participating and sign the informed consent form, the following screening tests and activities will be done:

- Complete medical and surgical history, including past and current medications and treatments, and past and current illnesses (including psychiatric history)
- Complete physical exam including weight, height, body mass index (BMI) calculation, and vital signs (blood pressure, heart rate, respiration rate, body temperature, and blood oxygen level)
- Electrocardiogram (ECG): measures the electrical activity of your heart and monitors your heart rhythm)
- Brief Psychiatric Rating Scale: you will be asked a set of questions about how you are feeling. This will only take a few minutes and study staff and will note your answers.
- Suicidality Rating Scale: you will be asked questions to determine if you have ever had any wishes to harm yourself, or if you have made any attempts to harm yourself in the past. The interview will take only a few minutes and study staff will note your responses.
- Structured Clinical Interview (done at Day -1 admission): clinical staff will ask you questions relating to your mental health. The interview may take up to approximately one hour.
- Digit Symbol Substitution Test is a short 'paper and pencil test' administered by study staff to help determine if the study drug has caused any changes to your cognitive or memory functions. The test takes around 3 minutes.
- Blood samples (fasting [no food] $\geq$ 8 hours) for standard lab tests to check your health, (includes hepatitis B and C, HIV, and syphilis testing), and pregnancy testing for all females regardless of childbearing potential
- Urine sample for urinalysis and drugs of abuse screening
- Alcohol breath test
- Review of inclusion/exclusion criteria
- Discussion of study restrictions

You will be told at the end of the screening visit if any of the completed tests will exclude you from the study. If you are not excluded during the screening visit, you will be contacted by telephone a few days later and told whether you qualify for the study (after all test results have been reviewed). If you do not qualify at any time, you will be told the reason(s) for your exclusion.

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If you are found to be positive for hepatitis B or C, HIV, or syphilis you will be asked to return to the study site to discuss the results with a study doctor. You will be given counseling and referrals to the appropriate healthcare providers. Please be aware that any positive results from these tests will be reported to the local health department, as required by state law.

Inpatient Stay and Dosing:

If you are eligible after all screening test results have been reviewed, you will be asked to return to the study site for an inpatient stay of 4 days and 3 nights. You will be considered an alternate for this study until such time as you receive the study drug.

Day -1:

You will check into the study site on the day before dosing (Day -1) to begin your inpatient stay. Blood and urine samples will be collected for laboratory tests, screening for drugs of abuse, and pregnancy testing for all females. Breath alcohol testing, three ECGs, vital signs, and a physical exam including weight with BMI calculation will be done. The Brief Psychiatric Rating Scale, Suicidality Rating Scale, the Digit Symbol Substitution Test, and the Structured Clinical Interview will be administered, and you will be asked if you have taken any medications since the screening visit. Your medical history will be reviewed and your eligibility will be assessed again.

If you are still eligible, starting on the evening of Day -1, you will be asked to fast overnight (no food for at least 8 hours prior to dosing), but water and clear liquids will be allowed.

Eligible subjects who are not dosed on Day 1 may be asked to return for dosing on another day. If this happens, your Day-1 tests will be repeated (except for the Structured Clinical Interview).

Day 1:

You will continue to fast for 1 hour after dosing (total fast of at least 9 hours). Liquids will be allowed until 1 hour before dosing and again at 1 hour after dosing. Prior to dosing, you will be placed on continuous cardiovascular (heart and vital signs) monitoring for approximately 24 hours, a blood sample will be collected, and three ECGs and vital sign measurements will be done. You will begin to collect all of your urine for the next 24 hours in containers provided by the study staff. You will then receive your dose of study drug as an injection in your thigh, and you will be asked to rate any injection site symptoms (pain, itching, tingling, or numbness) using a scale of 0 to 10.

Following dosing, you will have pharmacokinetic blood samples taken 11 times over the next 12 hours to see how much study drug is in your blood stream. Periodically during the next 24 hours, your vital signs will be measured, and ECGs and physical exams will be performed. You will be asked how you are feeling, if you are experiencing any injection site symptoms, and if you have taken any medications. The Brief Psychiatric Rating Scale will be administered and you will be monitored for any potential side effects. The study staff will also monitor your injection site.

Note: You will not be able to shower during the 24-26 hours you are on continuous cardiovascular monitoring (starting 1-2 hours prior to dosing on Day 1 and until after the morning activities on Day 2).

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Note: To ensure that you stay hydrated, you will be asked to drink at least 1000 mL (1 liter) of water within 24 hours prior to administration of study drug and 1000 mL (1 liter) during the 24 hours following the administration of study drug.

Days 2 and 3:

The continuous cardiovascular monitoring will end on the morning of Day 2. On Days 2 and 3, blood and urine samples will be collected, and ECGs and vital sign measurements will be done. You will be asked how you are feeling, if you are experiencing any injection site symptoms, and if you have taken any medications. On Day 3, you will also have a physician exam and the Brief Psychiatric Rating Scale and the Digit Symbol Substitution Test will be administered again. You will be discharged from the clinic after you have completed all of the study procedures on Day 3. Before you leave, study staff will schedule your follow-up telephone calls and outpatient visit, and remind you about the birth control requirements and all applicable study restrictions.

The study doctor may determine that you require longer observation in the clinic or additional laboratory testing based on the effects of the drug or the results of the laboratory tests as necessary.

Day 4:

You will be contacted for a follow-up telephone call. Study staff will ask how you are feeling, if you are experiencing any injection site symptoms, and if you have taken any medications since your last visit. You will be reminded about the Day 8 follow-up visit, birth control requirements, and all applicable study restrictions.

Day 8:

You will return to the research center for an outpatient visit. You will have a physical exam and an ECG, and vital signs including blood oxygen level will be measured. Blood and urine samples will be collected for clinical laboratory tests, and your urine will be tested for drugs of abuse. A pregnancy test will be performed for all women, regardless of childbearing potential. You will be asked how you are feeling, if you are experiencing any injection site symptoms, and if you have taken any medications since the Day 4 telephone call. The Brief Psychiatric Rating Scale, Suicidality Rating Scale, and Digit Symbol Substitution Test will be administered. You will be reminded about the Day 30 follow-up telephone call, birth control requirements, and all applicable study restrictions.

Day 30:

You will be contacted for a follow-up telephone call. Study staff will ask how you are feeling, if you are experiencing any injection site symptoms, and if you have taken any medications since your last visit. You will be reminded to refrain from donating blood or other blood components for 8 weeks after study completion.

Withdrawal Procedures:

If you withdraw early from the study, for any reason, you will be asked to complete the lab testing and discharge procedures described previously in the Day 8 study procedures.

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Meals:

Standardized meals and snacks will be served at regular times during your clinic stay except when fasting is required or otherwise noted. Please tell study staff if you have any dietary requirements or if you do not eat certain foods.

Blood Sampling:

The total amount of blood to be collected in this study is approximately 250 milliliters (a little more than 1 cup). This amount includes tests to check your health and pharmacokinetic testing to see how much of the drug is in your blood stream. For comparison, a standard blood donation is about 2 cups of blood. Additional blood may be drawn during the study if the study doctor considers it necessary for monitoring your health. It is possible that more than one attempt to obtain a blood sample may be necessary.

During your inpatient stay, an intravenous catheter (a small flexible tube) may be inserted into a vein (by a needle) in your arm to collect blood samples without sticking you multiple times. The catheter will be checked, maintained, and may be changed if necessary.

What Happens if I Am Injured as a Result of Taking Part in This Treatment Protocol?

You may choose to seek care under your own health insurance, and it is also possible that you may have workers' compensation/disability coverage that applies to your injury. No reimbursement will be offered if you incur medical expenses to treat research-related injuries. No compensation will be offered for research-related injuries. If you believe you have sustained a research-related injury, please contact the PI.

Please be aware that some insurance plans may not pay for research-related injuries. You should contact your insurance company for more information.

You should understand that this does not constitute a waiver or release of legal rights.

What Happens if I Want to Leave the Study?

Your participation in this study is completely voluntary. You may choose not to take part at all, or you may choose to stop your participation at any time after you have begun the study. If you stop participating in this study, you will not be penalized or lose any benefits to which you are otherwise entitled. If you decide to leave this study early, we ask that you notify the PI or a designee as soon as possible. You may be asked to schedule a clinic visit.

The investigator, the sponsor company, IntegReview, or the FDA, if applicable, may take you out of the study without your permission, at any time, for the following reasons:

- If you do not follow the investigator's instructions
- If we find out you should not be in the study
- If the study is stopped
- If it becomes harmful to your health

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If you leave the study or if you are taken out of the study, you may be asked to return for a final visit to have some end of study evaluations or tests. If information generated from this study is published or presented, your identity will not be revealed. If you leave the study, no more information about you will be collected for this study. However, all of the information you gave us before you left the study will still be used.

What Are the Safeguards for My Protection?

All study procedures will be performed by qualified, trained study personnel.

Volunteer Registry Data Sheet:

USAMRDC requires that data sheets (Volunteer Registry Data Sheet, Form 60-R) be completed for entry into the Command's Volunteer Registry Database for all individuals participating in research studies. This information includes the volunteer's name, address, social security number, study identity, and dates of participation. The intent of this database is twofold: first, to readily answer questions about an individual's participation in research sponsored by USAMRDC and second, to ensure that USAMRDC can exercise its obligation to ensure that all research study participants are adequately warned (duty to warn) of risks and to provide new information as it becomes available. This information will be stored at USAMRDC for a minimum of 75 years and is kept confidential. The Volunteer Registry Data Base is separate from and not linked to the study database.

Will I Be Compensated for My Participation in the Study?

You will be paid up to $2500.00 for your participation in this study. You will be paid for the visits that you complete based on the following:

Study Timeline and Payment Breakdown	
Screening Visit	$50.00
Inpatient Stay (4 days/3 nights in the clinic)	
Day -1: Admission	$300.00
Day 1: Dosing	$350.00
Day 2: In-Clinic Day	$300.00
Day 3: Discharge	$300.00
Day 4: Follow-up Telephone Call	$150.00
Day 8: Outpatient Visit	$300.00
Day 30: Follow-up Telephone Call	$150.00
Study Completion	$600.00
TOTAL	$2500.00

You will not be paid for the screening visit if you test positive for drugs or alcohol. You will be withdrawn from the study if you test positive for drugs and/or alcohol at any other time during the study and paid only for your completed portion of the study.

You will receive $50.00 for each unscheduled visit requested by a study physician (such as when lab tests need to be repeated). You will receive payment within 7 days of the completion of your participation in the study. If you are designated as an alternate (admitted on Day -1 but not dosed on Day 1), you will be paid $200.00. Alternates who remain eligible may be asked to return to the clinic on the next admission date.

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SEPTEMBER 4, 2020**

In agreeing to participate in this study, you will be acting as an independent contractor, not as an employee of Pharmaron. Because payments made to you for participating in this study will be reported to the Internal Revenue Service as income as required by law, you are required to provide your social security number. No deductions for any state or federal withholding or any other similar taxes will be made. It is the responsibility of the participant to report this compensation (payment) on state and federal tax returns and for the payment of any taxes that are due on this compensation.

What about My Confidentiality?

Confidentiality:

All data and medical information obtained about you as an individual will be considered privileged and held in confidence. We may need to request your medical or hospital records to monitor your safety. You will not be identified by name in any published report or in any presentation of the results. Information bearing on your health may be required to be reported to appropriate medical or military authorities. Representatives from other regulatory agencies, such as the FDA, USAMRDC and its subordinate commands, IntegReview IRB and study personnel are eligible to review research records as part of their responsibility to protect human participants in research and to carry out their obligations relating to the study. Representatives from the USAMRDC may review your research record. By signing this consent document, you agree to such inspection and disclosure.

The Institutional Review Board (IRB), IntegReview, and accrediting agencies may inspect and copy your records, which may have your name on them. Therefore, total confidentiality cannot be guaranteed. If the study results are presented at meetings or printed in publications, your name will not be used.

HIPAA Authorization:

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires that researchers obtain the participant's permission (called an Authorization) to use and disclose protected health information (PHI) about the participant that is either created by or used in connection with this research. This Authorization has no expiration date. **By signing this consent form, you are agreeing to the use and disclosure of your PHI by the PI and the research staff**, including results of physical exams, blood tests, and other diagnostic and medical procedures as well as vaccination and medical history. Your PHI may also be viewed and used by other regulatory and medical representatives, including but not limited to representatives from FDA and USAMRDC and the study Medical Monitor and Research Monitor.

Subject records will be maintained in accordance with applicable FDA guidelines and HIPAA requirements. Your PHI may also be used by others who do not necessarily work under HIPAA rules. De-identified subject data will be maintained permanently in electronic format by the sponsor.

If you choose not to authorize these uses and disclosure of your PHI by signing this form, you will not be eligible to participate in this study. However, your decision not to sign this consent form will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits. You may also change your mind and cancel this Authorization at any time by sending a written notice to the PI. Cancellation of this Authorization will not alter disclosure of PHI that has already been collected; however, no further PHI about you will be collected by or disclosed to the researcher for this study.

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Consent for the Use of Your Samples/Information

There is a chance that your pharmacokinetic blood samples collected during this study may be used in other future studies and may have some commercial value. Should your sample(s) lead to the development of a commercial drug, the US government will own it and may patent and license the drug. You will not receive compensation for any future value that the samples you have given may be found to have. You will not be contacted if your samples are used for the purposes defined in this study. However, you will be notified if your samples are used for research purposes that are not defined in this study, and your identity will not be associated with these samples.

No genetic testing will be performed (now or in the future) on any samples collected during this study.

Please indicate your willingness to permit the use of your samples for future research purposes that are not defined in this study by initialing beside the appropriate statement below:

_____ Yes, my stored pharmacokinetic blood samples MAY be used for future research purposes that are not defined in this study.

_____ No, my stored pharmacokinetic blood samples MAY NOT be used for future research purposes and may only be used for the research purposes defined in this study (protocol # S-16-14).

Even if you initial "Yes" above, you may withdraw your consent at any time for the use of your blood samples in future research. To withdraw your consent, please contact a study team member.

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 PI:

Paolo DePetrillo, M.D.
410-706-8801 daytime telephone number
301-961-5667 after hours number

If you are unable to reach anyone at the number(s) listed above and you require immediate (life threatening) medical attention, please go to the nearest emergency room.

If you seek emergency care or hospitalization is required, inform the treating physician that you are participating in this research study.

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If you do not want to talk to the investigator or study staff if you have concerns or complaints about the research or want to ask questions about your rights as a study subject you may contact the IntegReview IRB. The IntegReview IRB is a group of people that has reviewed this study. The main goal of this review is to protect the rights and well-being of the human subjects participating in the study. IntegReview's policy indicates that all concerns/complaints are to be submitted in writing for review at a convened IRB meeting to:

Mailing Address	E-mail Address
Chairperson IntegReview IRB 3815 S. Capital of Texas Highway Suite 320 Austin, Texas 78704	integreview@integreview.com

If you are unable to provide your concerns/complaints in writing or if this is an emergency situation, you may contact IntegReview at:

512-326-3001
or toll free at 1-877-562-1589
between 8 a.m. and 5 p.m. Central Time.

IntegReview has approved the information in this consent form and has given approval for the investigator to do the study. This does not mean IntegReview has approved your being in the study. You must consider the information in this consent form for yourself and decide if you want to be in this study.

**APPROVED BY
INTEGREVIEW IRB
SEPTEMBER 4, 2020**

Consent for Participation in the Research Study

Your signature on this form indicates that you have read this consent form, that the research study has been explained to you and your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

SIGNATURES

Printed Full Name of Study Participant

Signature of Study Participant | Date

Printed Name of Person Conducting Informed Consent Discussion

Signature of Person Conducting Informed Consent Discussion | Date

THIS IS AN IMPORTANT DOCUMENT - KEEP FOR FUTURE REFERENCE

VERSION CONTROL
jr/1-24-20 sab/4-20-20 lng/6-5-20 jm/8-31-20 ar/9-4-20