SUBJECT INFORMATION AND CONSENT FORM AND AUTHORIZATION FOR RELEASE OF PROTECTED HEALTH INFORMATION

TITLE: Adaptive Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of Kratom in Healthy, Nondependent, Adult Recreational Polydrug Users with Opioid Experience

PROTOCOL NO.: 75F40121C00199
Altasciences Protocol No.: FDU-P4-117
IRB Protocol No.: Pro00072762

STUDY SPONSOR: Food and Drug Administration (FDA), USA

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STUDY RELATED PHONE NUMBER(S): 913-696-1601 (24 hours)

SUMMARY - KEY INFORMATION

The following is a short summary of this research study. More detailed information is provided later in this form. For purposes of this research, you will be referred to as a "subject".

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you.
- If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you.
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

Why are you being invited to take part in this research study?

You are invited to take part of this study because you are a healthy, male or female between the ages of 18 and 59 who is a non-dependent recreational drug user with experience with opioid drugs.

Why is this research being done?

The name of the investigational drug that you will receive in this study is kratom. An investigational drug is a drug that has not been approved by the U.S. Food and Drug Administration (FDA). Kratom is an herbal substance that comes from the leaves of a tree called *Mitragyna speciosa* which grows in Southeast Asia. It is currently sold in the United States and is used as an energy booster, a mood enhancer, a pain reliever and an antidote for opioid withdrawal.

The intent of this research study is to evaluate the safety and tolerability of a single, escalating oral dose of kratom in healthy, non-dependent (someone who has no physical dependence on a substance or drug) recreational drug users with experience with the use of opioid drugs (for example, heroin, oxycodone, morphine, fentanyl, etc). Another objective of the study is to evaluate the pharmacokinetics and pharmacodynamics of kratom. Pharmacokinetics is the study of how a drug is absorbed into the blood, circulated, broken down, and eventually eliminated by the body. Pharmacodynamics is the study of the drug's effects on the body.

How long will I be in this research?

The duration of your participation in this study will be approximately 37 days including the screening visit and follow-up visit. Screening will occur within 28 days prior to you taking the study treatment. You will stay at the research site for 4 days and 3 nights. The follow-up visit will occur 4 days after your discharge from the research site.

What happens to me if I agree to take part in this research?

The general procedures of the study include:

- Screening visit for eligibility
- Administration of the study treatment orally (by mouth)
- Blood and urine samples collection for laboratory tests, pharmacokinetic analysis, etc. The blood samples will be taken by single needle-sticks or by intravenous (IV) catheter, as determined by the study staff.
- Completion of study questionnaires
- ECG, a test to monitor the electrical activity of your heart (male subjects may be required to have their chest shaved for the ECG; female subjects may not be allowed to wear a bra for the ECG)
- Continuous monitoring of the amount of oxygen in your blood while wearing a device
- Vital signs measurements
- Physical examinations
- Measurement of the size of your pupil

- Follow-up visit

Could being in this research hurt me?

The following side effects were the most commonly reported in people using kratom (10% or more). These side effects may have been reported in chronic (long-term) users of kratom, in people using kratom in combination with other drugs, or in people using different doses of kratom than what will be used during this study. Therefore, you may or may not experience the same side effects.

- Kidney injury
- Agitation
- Altered consciousness (a state in which your perception of yourself or of the world changes)
- Anxiety
- Lack of emotion
- Loss of appetite
- Changes in blood pressure (increased or decreased)
- Feeling confused
- Constipation
- Feeling hot
- Dizziness
- Drowsiness, feeling tired
- Difficulty breathing
- Hallucinations
- Headache
- Heart rate increased
- Difficulty sleeping
- Feeling drunk or like you are under the influence of drugs (intoxicated)
- Feeling irritable
- Elevated cholesterol
- Decrease of sexual desire/sexual performance
- Shrinking or dilation of the pupils
- Decreased motivation
- Nausea
- Irregular heartbeat
- Physical pain
- Respiratory failure
- Stomachache or abdominal pain
- Tongue numbness
- Shaking
- Weight loss
- Vomiting
- Depression

The following serious side effects were also reported in less than 4% of people using kratom:

- Respiratory depression or arrest (breathing disorder characterized by
- Rhabdomyolysis (destruction or degeneration of muscle tissue)
- Coma
- Kidney failure
- Blue/purple discoloration of

slow and ineffective breathing)
- Cardiac arrest (condition in which the heart stops beating)
- Decreased heart rate
- Increased levels of bilirubin in the blood (bilirubin is a yellowish pigment that is made during the normal breakdown of red blood cells)
- the skin (usually the lips, mouth, earlobes and fingernails)

The following serious side effects were also reported in some people using kratom alone (not in combination with other drugs); the frequency of these side effects is unknown:

- Seizure
- Serious liver conditions and injuries
- Bleeding in the brain
- Inflammation and death of the tissues of the intestines
- Involuntary muscle twitches or spasms
- Catatonic state (a state in which someone is awake but does not seem to respond to other people and their environment)

In the United States, some deaths were reported that **may** have been associated with the use of kratom. **However, in these cases, other causes of death could not be completely ruled out, such as the use of other substances in combination with kratom or pre-existing medical conditions.**

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 of ECG patches.

Local pain, bruising, bleeding, inflammation or infection might occur at the site of the needle stick where blood is drawn with the needle-sticks. There is a possibility of dizziness or fainting while your blood is being drawn. Infection, redness, pain, bruising or swelling, vein irritation from the fluids being given, local swelling due to IV fluid accidentally entering the tissue rather than the vein, and blood clots, which may cause inflammation, swelling and pain, might occur at the site where the catheter is inserted. Precautions will be taken to minimize the above complications.

The size of your pupil will be measured with a pupillometer, which is a handheld scanner. The study staff will place the pupillometer in front of one of your eyes in order to measure your pupil. This is a safe and painless procedure.

The study staff will ask you questions about the quality of your life as part of a questionnaire. Some people feel uncomfortable when answering these questions. Though it is always better to have fully completed questionnaires, you do not need to answer any questions that make you feel uncomfortable, however, this may impact your eligibility to participate in the study.

Will being in this research benefit me?
Since the drug in this study is not being given to treat any symptoms or illness, there will be no medical benefit.

What other choices do I have besides taking part in this research?
An alternative would be to not take part in the study.

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM

This Subject Information and Consent Form may contain words you do not understand. Please ask the study staff to explain any words or procedures that you do not understand.

The purpose of this form is to give you information about this research study. This form describes the purpose, procedures, benefits, risks, discomforts, and precautions of this research study. You should only take part in the study if you want to do so. You may refuse to take part in this study, or you may choose to withdraw from this study at any time, without a penalty or loss of the benefits to which you are otherwise entitled. Please take the time to read this Subject Information and Consent Form carefully, ask as many questions as needed, and do not sign this form if you have any questions that have not been answered to your liking. Once you have read this document, if you agree to take part, you will be asked to sign and date the consent form. By signing this document, you are stating that you have been fully informed and give your consent to take part in the study.

A copy of this signed and dated consent form will be given to you to keep. Be sure to take the time to read through this information carefully to decide if you would like to take part in this study.

DESCRIPTION AND PURPOSE OF THE STUDY

The name of the investigational drug that you will receive in this study is kratom. An investigational drug is a drug that has not been approved by the U.S. Food and Drug Administration (FDA). Kratom is an herbal substance that comes from the leaves of a tree called *Mitragyna speciosa* which grows in Southeast Asia. It is currently sold in the United States and is used as an energy booster, a mood enhancer, a pain reliever and an antidote for opioid withdrawal.

During this study, you will receive a single dose of 1 gram (g), 2 g, 4 g, 6 g or 8 g of kratom in powder form (these doses may be increased or decreased). The dosage will be in capsule form and will be taken orally (by mouth).

You may be given a placebo (inactive dummy substance that looks like kratom without any active drug) instead of kratom.

This is a “double-blind” study. This means that neither you, nor study staff, will know if you are taking kratom or placebo. The pharmacy staff at the research site will know whether you are receiving kratom or placebo. In an emergency and if it is necessary for your medical care, the study staff can find out if you have been given kratom.

The intent of this research study is to evaluate the safety and tolerability of a single, escalating oral dose of kratom in healthy, non-dependent (someone who has no physical dependence on a substance or drug) recreational drug users with experience with the use of opioid drugs. Another objective of the study is to evaluate the pharmacokinetics and pharmacodynamics of kratom. Pharmacokinetics is the study of how a drug is absorbed into the blood, circulated, broken down, and eventually eliminated by the body. Pharmacodynamics is the study of the drug’s effects on the body. Blood samples will be drawn throughout the study for pharmacokinetic analysis. Various procedures will be done throughout the study for pharmacodynamic analysis, including taking measurements of the size of your pupil and completing study questionnaires and scales.

It is important that you understand how often you will need to come to the research site for the visits, how long the in-house stay is, and that you are able to keep to the study schedule and follow the rules of the research site.

The duration of your participation in this study will be approximately 37 days including the screening visit and follow-up visit. Screening will occur within 28 days prior to you taking the study treatment. You will stay at the research site for 4 days and 3 nights. The follow-up visit will occur 4 days after your discharge from the research site.

If you qualify and decide to participate, you will be one of approximately 40 male or female subjects, between the ages of 18 and 59, inclusive, participating in this research study. Additional subjects in each group may also be admitted to the research site the day before dosing for each group and may serve as back-up study subjects.

You may be selected to participate in this research study as either a study subject or a back-up study subject. Back-up study subjects must follow all the study restrictions and be ready to participate in the study just as all other eligible subjects. Backup study subjects will replace subjects who are not eligible to receive the study treatment or who do not show up for the study treatment period. If you are selected as an overnight backup, you will be asked to stay in the research site until the subjects are given the study treatment. If you are not given study treatment, the study staff will let you know if your participation in the study is complete, or they may ask you to return for a different study treatment period.

This is the only research site participating in this study.

DOSING AND PROCEDURES

There will be 5 cohorts (dose groups) of 8 subjects each participating in this study. In each dose group, 6 subjects will be given kratom and 2 subjects will be given placebo. Additional cohorts may be added. You will be randomly assigned to receive either kratom or placebo. Randomly means by chance, like flipping a coin. You will have a 3 in 4 (75%) chance of receiving kratom and a 1 in 4 (25%) chance of receiving placebo.

You will only be participating in one cohort. The planned doses range from 1 g to 8 g of kratom. These doses are approximations and may be increased or decreased; the highest dose level may exceed 8 mg if deemed safe. **You will not be informed of the dose level to be used in your cohort.**

You will only receive one dose of kratom or placebo in the morning on Day 1 of the study.

All doses will be given in the fed (no food or drink other than water for a minimum of 10 hours prior to receiving a high-fat breakfast) and will be taken with approximately 240 mL (8 ounces, or 1 cup) of water.

The decision to decrease/increase the dose level will be made by the study staff after they review all laboratory tests, vital signs, ECG data, reported side effects, and pharmacokinetic/pharmacodynamic data from previous cohort(s). This is to be sure that the dose level in the previous cohort was well tolerated. Depending on the overall results of this review, the dose for your cohort could be higher, lower, the same, or the study could be stopped. The highest dose may be higher than 8 g if deemed safe by the study staff.

Screening

Before the study starts, you will be asked to sign this consent form. The informed consent will be reviewed with you by a member of the study staff. If you agree to participate, you will be asked to sign the informed consent form. You will be given the chance to have your questions answered so that you have a good understanding of the study. A member of the study staff may ask you some questions to make sure you understand what you need to know about the study. You will be asked to give personal information about yourself such as date of birth, race, etc. You will be asked about your medical and medication history. You will be asked if you take any over-the-counter or prescription medicines, vitamins, herbal products, or nutritional supplements. It is very important that you be honest with the study staff about your health and medication history, or it may not be safe for you to be in this study. You will also be asked about prior caffeine, alcohol, tobacco, and illicit drug use.

The study staff will do some tests to find out if you can be in the study. These tests include the following:

- You will be asked how you are feeling and if you have taken any medications (prescription or over-the-counter) and if so, when you have taken the medications

- Complete physical examination
- Vital signs (blood pressure, heart rate, breathing rate, and oral body temperature)
- Measurement of the amount of oxygen in your blood using a small device which will be placed on your fingertips
- Height and weight
- Calculate Body Mass Index (BMI - a measure of your weight in relation to your height)
- Electrocardiogram (ECG) - a test to monitor the electrical activity of your heart (male subjects may be required to have their chest shaved for the ECG; female subjects may not be allowed to wear a bra for the ECG)
- Blood and urine samples for safety laboratory testing
- Urine drug screen test
- Blood test for human immunodeficiency virus (HIV) and Hepatitis B and C*
- Blood pregnancy test for female subjects*
- Blood test to confirm menopausal status for female subjects
- Alcohol urine test
- You will be asked questions about whether you have had any thoughts about suicide or any acts to attempt suicide. This is done as part of a questionnaire called the Columbia Suicide Severity Rating Scale (C-SSRS)

*These tests must be negative in order to continue in the study

Prior to the above tests, you will need to fast (no food or drink other than water) for at least 8 hours.

HIV Antibody and Hepatitis Testing

As required for participation in this research study, you must have your blood tested for the hepatitis viruses and for HIV. HIV is the virus that causes AIDS. If you have a positive HIV or hepatitis test, you cannot be in the study. It may take weeks or months after being infected with HIV for the test to be positive.

If either of these tests is positive, a confirmation test will be done by the laboratory.

If the HIV or hepatitis test are positive, you will be notified by the research site and given information on how to follow up for further medical care. As required by law, positive test results must be reported by the research site to the State Department of Health. If you have any questions about what information is required to be reported, please ask the study staff.

Your test results are kept private under a Certificate of Confidentiality, so that only study personnel can see them. This means that your health or study records cannot be released outside of the study unless a court of law orders it.

STUDY PROCEDURES

Research Site Admission - Day -1

You will report to the research site. You will be confined (inpatient) to the research site for 3 nights and 4 days. You will be assigned to a hospital-like bed within one of our male or female subject dormitories. You will be provided with a locker to securely store your personal belongings. You will have access to the internet, television, movie room, and gaming machines during appropriate times while you stay at the research site. Private bathrooms with showers will be accessible to you as well. Standard meals and drinks will be provided during your stay. You will eat only the food and drinks provided at the scheduled meal times.

Upon admission to the research site, the following procedures will take place:

- You will be asked how you are feeling and if you have taken any medications since your screening visit
- Symptom-oriented physical examination
- ECG
- Vital signs (blood pressure, heart rate, and oral body temperature)
- Blood and urine samples for safety laboratory testing
- Urine drug screen test*
- Urine pregnancy test for female subjects*
- Alcohol urine test*
- C-SSRS questionnaire
- Training session: you will be trained on how to complete the questionnaires which will be administered throughout the study

*These tests must be negative in order to continue in the study.

After completion of these procedures, it will be determined by the study staff if you meet the eligibility criteria and if you may continue in the study.

You will begin fasting (no food or drink other than water) in the evening to ensure a minimum of 10 hours without food before breakfast.

Day 1

Before you receive the study treatment (kratom or placebo), the following procedures will take place:

- Vital signs (blood pressure, heart rate, breathing rate, and oral body temperature)
- Measurement of the amount of oxygen in your blood using a small device which will be placed on your fingertips
- Continuous monitoring of the amount of oxygen in your blood starting 1 hour before study treatment administration
- Blood sample for pharmacokinetic analysis
- Measurement of the size of your pupil

- You will complete the study questionnaires in electronic format (for example, on a computer or tablet)
- You will be asked how you are feeling and if you have taken any medications

Thirty minutes before you receive the assigned study treatment, you will be asked to start your high fat, high-calorie breakfast that consist of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 240 mL (8 ounces, or 1 cup) of whole milk. You should eat the whole content of your meal in 30 minutes or less. If you eat less than 75% of this meal, you will be removed from the study.

The study treatment will then be administered with approximately 240 mL (8 ounces, or 1 cup) of water. If needed, an additional 240 mL of water will be allowed as needed.

After receiving the study treatment, the following procedures will take place:

- Vital signs (blood pressure, heart rate, and breathing rate) will be taken 4 times
- ECG will be done 2 times
- Blood samples for pharmacokinetic analysis will be collected 12 times
- Measurement of the size of your pupil done 11 times
- Continuous monitoring of the amount of oxygen in your blood for 6 hours after study treatment administration
- Measurement of the amount of oxygen in your blood using a small device which will be placed on your fingertips will be done 9 times
- You will complete the study questionnaires 12 times

You will continue to fast (no food or drink) for approximately 4 hours after dosing. You will be able to drink a limited amount of water during this time.

You will be served a standard meal and drink at approximately 4 and 9 hours after dosing.

Day 2
The following procedures will take place:

- You will be asked how you are feeling and if you have taken any medications
- Vital signs (blood pressure and heart rate) will be taken 1 time
- ECG will be done 1 time
- A blood sample for pharmacokinetic analysis will be collected
- Measurement of the size of your pupil will be done 1 time
- You will complete the study questionnaires 1 time

Day 3
The following procedures will take place:

- You will be asked how you are feeling and if you have taken any medications

- Symptom-oriented physical examination
- C-SSRS questionnaire done 1 time
- Vital signs (blood pressure and heart rate) will be taken 1 time
- ECG will be done 1 time
- A blood sample for pharmacokinetic analysis will be collected
- Blood and urine samples for laboratory tests will be collected 1 time
- Urine pregnancy test for female subjects will be done 1 time

Following the procedures on Day 3, you will be discharged from the research site if the study staff determines it is medically acceptable for you to leave. You will be instructed on when to return to the research site for your Follow-Up Visit.

Follow-Up Visit (Day 7) or Early Termination

You will be asked to return to the research site for a follow-up visit. The procedures below will take place. These procedures will also be performed should you stop your participation in the study early.

- You will be asked how you are feeling and if you have taken any medications since your last visit
- Vital signs (blood pressure and heart rate)
- ECG
- Complete physical examination including weight and BMI
- Blood and urine samples for laboratory tests
- Urine pregnancy test for female subjects
- C-SSRS questionnaire

How long procedures may take and the length of time for research site restrictions can vary each time depending on other procedures and study activities scheduled during your stay.

Additional assessments or procedures may be performed if the study doctor feels they are necessary to ensure your safety.

After these procedures, your participation in the study will end.

Unscheduled Visits

You may be asked to report to the research site for an unscheduled visit if the study staff feels it is necessary for your safety. This may occur if you have experienced any side effects. In the event that you are asked to return to the research site for an unscheduled visit, some or all of the assessments and procedures outlined above may be performed. The study staff may also request to have procedures performed that are not listed above to ensure your safety throughout the study.

ADDITIONAL DRUG AND ALCOHOL SCREENS

Random urine drug and alcohol screens may be repeated at any time during the study if the study staff suspects alcohol or drug use. If you test positive for drug or alcohol use, at any time after the first dose of study treatment, you will be discontinued from the study.

CONTROLLED SEARCH

Designated study staff reserves the right to do a controlled search by having you put on a gown in order to have your clothes and person checked for disallowed items (for example, medications, food, etc) that may have been brought into the research site. This search involves removing all undergarments as well as putting on a gown so that there is no place the disallowed items could be kept.

RESTRICTIONS

Throughout your entire participation in the research study, the following restrictions will apply:

- Do not participate in any heavy exercise or strenuous activities during your stay at the clinic
- Refrain from drinking alcohol for at least 48 hours before dosing with study treatment
- Do not consume any grapefruit and/or pomelo (a large citrus fruit closely related to grapefruit), or any grapefruit/pomelo-containing foods or beverages for at least 7 days before dosing with study treatment
- Do not consume any caffeine/xanthine-containing foods or beverages (for example coffee, tea, cola, chocolate, caffeine-containing soda (Mountain Dew, Dr. Pepper, etc.), caffeine/xanthine-containing “energy drinks” (Red Bull, Extreme Energy Shot, etc.) for at least 48 hours before dosing with study treatment
- Refrain from use of any non-prescription medications and products (including over-the-counter herbal supplements, vitamins, and dietary supplements) for 7 days before dosing with study treatment
- Refrain from consuming all recreational drugs (including cannabis) from the time of screening and for the duration of the study
- If you are a smoker
    - Refrain from smoking more than 20 cigarettes per day
    - Refrain from smoking from 1 hour before study drug administration until 8 hours after study drug administration
    - Refrain from use of other nicotine-containing products (for example, vaping or smokeless tobacco) until 8 hours after study drug administration
- You must not have used any investigational drug within 28 days before study treatment administration
- You must not have used kratom within 14 days before study treatment administration
- You must not have been in a previous group for this clinical study

- You must not have used St. John's wort within 28 days before study treatment administration
- You must not have donated plasma in the 7 days before dosing with study treatment
- You must not have donated 500 mL (2 cups) or more of blood in the 56 days before dosing with study treatment
- You will be asked to refrain from driving, operating machinery, or engaging in hazardous activities (activities that are considered highly risky) until you and the study doctor are certain that the study treatment is not impairing your ability to perform these tasks safely
- Refrain from use of any prescription drugs for 28 days before dosing with study treatment*

*Female subjects can continue taking systemic contraceptives or hormone replacement therapy.

BLOOD SAMPLES

Blood samples will be drawn by single needle-sticks or intravenous (IV) catheter. An IV catheter is a small plastic tube inserted into your arm vein by a needle, as determined by the study staff. The total amount of blood drawn will be up to about 134 mL (approximately 1/2 cup). For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 2 cups (500 mL) of blood.

Additional blood samples may be drawn during the study, if the study staff considers it necessary for monitoring your health.

The study doctor may decide that placing an IV catheter (a small plastic tube) into one of your veins for drawing blood may be helpful to decrease the number of needle sticks and minimize discomfort. A catheter is a flexible tube inserted into the vein that allows taking several blood samples without repeated needle insertion into the skin. At each blood collection time point, the first 1 mL (approximate) of blood will be drawn and discarded as waste; then the blood sample will be collected. After each blood collection, very small amount of saline (salt water) will be injected into this needle for flushing to prevent clogging.

SUBJECT RESPONSIBILITIES

As a subject in this study, you have certain responsibilities to help ensure your safety. These responsibilities are listed below.

- Complete all required visits
- Comply with all study restrictions
- Follow all instructions from study staff
- Report all possible side effects and medical problems to the study staff
- Inform the study staff if you decide to discontinue your participation in the study

- You may be asked to complete the early termination visit procedures as described in this consent form

POTENTIAL RISKS AND DISCOMFORTS

The following side effects were the most commonly reported in people using kratom (10% or more). These side effects may have been reported in chronic (long-term) users of kratom, in people using kratom in combination with other drugs, or in people using different doses of kratom than what will be used during this study. Therefore, you may or may not experience the same side effects.

- Kidney injury
- Agitation
- Altered consciousness (a state in which your perception of yourself or of the world changes)
- Anxiety
- Lack of emotion
- Loss of appetite
- Blood pressure increased or decreased
- Feeling confused
- Constipation
- Feeling hot
- Dizziness
- Drowsiness, feeling tired
- Difficulty breathing
- Hallucinations
- Headache
- Heart rate increased
- Difficulty sleeping
- Feeling drunk or like you are under the influence of drugs (intoxicated)
- Feeling irritable
- Elevated cholesterol
- Decrease of sexual desire/sexual performance
- Shrinking or dilation of the pupils
- Decreased motivation
- Nausea
- Irregular heartbeat
- Physical pain
- Respiratory failure
- Stomachache or abdominal pain
- Tongue numbness
- Shaking
- Weight loss
- Vomiting
- Depression

The following serious side effects were reported in less than 4% of people using kratom:

- Respiratory depression or arrest (breathing disorder characterized by
- Rhabdomyolysis (destruction or degeneration of muscle tissue)
- Coma
- Kidney failure
- Blue/purple discoloration of

slow and ineffective breathing)
- Cardiac arrest (condition in which the heart stops beating)
- Decreased heart rate
- Increased levels of bilirubin in the blood (bilirubin is a yellowish pigment that is made during the normal breakdown of red blood cells)
- the skin (usually the lips, mouth, earlobes and fingernails)

The following serious side effects were also reported in some people using kratom alone (not in combination with other drugs); the frequency of these side effects is unknown:

- Seizure
- Serious liver conditions and injuries
- Bleeding in the brain
- Inflammation and death of the tissues of the intestines
- Involuntary muscle twitches or spasms
- Catatonic state (a state in which someone is awake but does not seem to respond to other people and their environment)

In the United States, some deaths were reported that **may** have been associated with the use of kratom. **However, in these cases, other causes of death could not be completely ruled out, such as the use of other substances in combination with kratom or pre-existing medical conditions.**

There may be risks or side effects that are related to the study treatment and that are unknown at this time. It is also possible to experience a serious allergic reaction, which could become life-threatening or fatal. Symptoms of an allergic reaction include rash, hives, itching, swelling of the mouth, face, lips or tongue, dizziness, tightness in the chest or trouble breathing.

If you experience an injury, bad effect, or any other unusual health experience during this study, you must immediately contact the study doctor or the study staff listed on page 1 of this consent form. In the event of a medical emergency, please visit your nearest hospital's emergency room or call 9-1-1.

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

ECG risks
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 of ECG patches.

Blood Sample risks (taken by single needle-sticks or by intravenous [IV] catheter)
Local pain, bruising, bleeding, inflammation or infection might occur at the site of the needle stick where blood is drawn with the needle-sticks. There is a possibility of dizziness or fainting while your blood is being drawn. Infection, redness, pain, bruising or swelling, vein irritation from the fluids being given, local swelling due to IV fluid accidentally entering the tissue rather than the vein, and blood clots, which may cause inflammation, swelling and pain, might occur at the site where the catheter is inserted. Precautions will be taken to minimize the above complications.

Pupillometry risks
During the study, the size of your pupil will be measured several times. This will be done using a technique called pupillometry, with a device called a pupillometer. A pupillometer is a handheld scanner. This procedure will be done in a dark room. The study staff will wait for your eyes to acclimate to the dark prior to taking the measurement. Then, the study staff will place the pupillometer in front of one of your eyes in order to measure the size of your pupil. You will need to keep your eye open (no blinking) while the measurement is being taken. This is a safe and painless procedure.

Discomfort With Questionnaires
Some people feel uncomfortable when answering questions about the quality of their life. Though it is always better to have fully completed questionnaires, you do not need to answer any questions that make you feel uncomfortable, however, this may impact your eligibility to participate in the study.

If you are having suicidal thoughts or feel in crisis, call the study doctor at the telephone number listed on the first page of this form. You can also call or text the National Suicide & Crisis Lifeline at 9-8-8 or 1-800-273-TALK (8255). The Lifeline numbers are answered 24 hours a day every day of the year by a skilled, trained counselor. You can also present to a healthcare provider, your local emergency room, or call 9-1-1 to be connected to local emergency services.

Unknown/Unforeseeable Risks
In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of this study treatment, including allergic reaction or interaction with another medication. You must notify the study staff immediately if you experience an allergic reaction such as rash, hives, or itching. If you experience any of the above symptoms, you must call the study staff at the phone number(s) listed on the first page of this form.

PREGNANCY/BIRTH CONTROL

Female subjects

It is not known whether study treatment with kratom may cause injury or harm to an embryo or fetus (unborn child) if taken during pregnancy, or if it may cause harm to a breastfeeding infant. For this reason, pregnant or breastfeeding women are not allowed to take part in the study. It is important that women avoid getting pregnant during the study.

Women capable of having children include all women except those whose menstrual periods have not occurred for more than 1 year after menopause (change of life), or those who have had sterilization surgery (tubal ligation [tubes tied] or a hysterectomy [removal of the uterus or womb] and/or removal of both ovaries). Women who are not capable of bearing children are exempt from contraception requirements. Menopause will be confirmed by a blood test at the Screening visit.

Abstinence from the Screening visit, during the study and for at least 30 days after the last study treatment administration is surely the most effective way to prevent pregnancy. If you have heterosexual intercourse that could result in pregnancy during that period, you are required to use contraception (birth control). Below is a list of acceptable methods of birth control for women capable of having children while participating in this study.

A. One of the following effective contraceptive methods from at least 28 days prior to the Screening visit, during the study and for at least 30 days after study treatment administration:

   - Systemic contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)
   - Intrauterine device (with or without hormones)
   - Your partner had a vasectomy at least 6 months prior to the Screening visit

Or

B. The following double-barrier contraceptive method from the Screening visit, during the study and for at least 30 days after study treatment administration:

   - Male condom with spermicide
   - Diaphragm with spermicide
   - Cervical cap with spermicide

Male subjects

The effect of kratom on the embryo, fetus, or nursing infant is unknown at this time. The effect of the study treatment on the male reproductive system is unknown.

Abstinence is surely the most effective way to avoid getting your partner pregnant from the study treatment administration and for a period of 90 days following study treatment

administration. If you have heterosexual intercourse that could result in getting your partner pregnant, you are required to use a double-barrier method such as condoms with spermicide or condoms with an intra-vaginally applied spermicide (gel, foam, or suppository) from the study treatment administration and for a period of 90 days following study treatment administration.

If you do not use any of the acceptable methods of contraception listed above, you must be sterile due to a vasectomy (at least 6 months prior to administration of the study treatment).

You may NOT donate sperm at any time through the entire study and for at least 90 days following study treatment administration.

Pregnancy Reporting

If you are a female subject and you think you may be pregnant during the study or during the 30 days following the last dose of the study treatment, you must immediately contact the study staff. You will be monitored until the completion of pregnancy and the outcomes of the birth and health of the infant will be reported to the study sponsor. Any pregnancy complications will also be reported.

If you are a male subject and you think your female partner may be pregnant during the study or during the 90 days following study treatment administration, you must immediately contact the study staff. Your partner will be asked to sign a separate consent form in order to be monitored until the completion of pregnancy. The outcomes of the birth and the health of the infant and any pregnancy complications will be reported to the sponsor.

NEW INFORMATION

You will be informed 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.

POTENTIAL BENEFITS

Since the study drug is not being given to treat any symptoms or illness, there will be no medical benefit. Your participation will provide information about the study treatment. This might benefit others in the future.

ALTERNATIVE TREATMENTS

Your only alternative would be to not take part in the study.

COSTS

There is no charge to you for participating in this research study.

COMPENSATION

For your participation in this study, you may be compensated as follows:

Visit 1	Screening	$150
Visit 2 - 4	Day -1 to 2: Inpatient	$1,125
Visit 5	Day 3: Discharge	$375
Visit 6	Day 7: Follow-Up Visit	$400
	Completion Amount	$450
	Total up to	$2,500

Visit 1 will be compensated in the amount of $150 at the completion of the visit.

Visits 2 through 5 will be compensated in the amount of $1,500 upon discharge at Visit 5.

Visit 6 will be compensated in the amount of $400 at the completion of the visit.

For any outpatient visit that occurs on a weekend, the associated compensation will be paid on the next business day.

Compensation will be issued in the form of a check, pre-loaded MasterCard, or cash. The form of compensation will be determined by the study staff. If a pre-loaded card is used, payment will be loaded on your card within 1 to 3 business days following the completion of the visit. This includes Screening, Admission, Discharge and Follow-up visits. Please do not contact the site prior to this if your payment is not loaded on your card.

Unscheduled visits may be compensated up to $50 as determined by the study staff.

All visits must be completed within the scheduled timeframe in order to receive the end of study completion amount of $450 on Visit 6. Failure to complete all visits within the allowable timeframe will make you ineligible to receive the completion amount.

Money may be deducted from your study compensation if you do not follow the in-house rules or other reasonable instructions given by the study staff. Non-compliance with the study rules includes, but is not limited to, improper conduct, taking alcohol and/or any drugs (including recreational drugs), or consuming any foods/beverages that are not allowed in the study.

If you withdraw or are withdrawn from the study early, you will only be compensated for the visits that you complete.

If you discontinue from the inpatient portion of the study early for any reason, you will only be compensated one night's earned stipend. The remainder of your earned in-house stipend will be compensated to you on the originally scheduled study day/date of discharge from the in-house portion of the study.

You may be required to report the compensation received for this study to the Internal Revenue Service as taxable income. According to the IRS (Internal Revenue Service) guidelines, you will be responsible for paying taxes on any compensation that you receive from your study participation. Altasciences Clinical Kansas, Inc. will send you a 1099-form for this purpose. Altasciences Clinical Kansas, Inc. will also report to the IRS any compensation that you receive that totals $600.00 or more for the calendar year. You must tell Altasciences Clinical Kansas, Inc. of your new mailing address if you move after your participation in a study. This is to make sure you receive your 1099 for your year-end tax reporting.

If you are a back-up subject who completed check-in procedures, stayed overnight at the site, and you did not receive the study drug, the compensation for your participation will be $375. There will be no delay before you can participate in another clinical study.

If you are a back-up subject, did not dose, or are a roll-over subject, meaning you are not a back-up subject but will be scheduled for the next group or cohort, you may be asked to remain at the site and check-in for a subsequent cohort of the study, if you qualify. You will have all check-in procedures performed again at this next check-in. The study staff will inform you if staying additional nights is applicable. You will be compensated $100 per night for any additional nights you stay at the site in between the check-ins.

RESEARCH-RELATED INJURIES

If you have any side effects to the study treatment or changes in your physical or mental condition during the course of the study, you must immediately notify the study staff at the research site or, if you are not at the research site anymore, notify the study staff by calling the phone number(s) listed on the first page of this form.

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. Altasciences Research 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.

Further information regarding medical treatment for research-related injuries can be obtained from the study staff. You must notify the study staff immediately of any possible research-related injury.

The study site will not be responsible for any dental care expenses related to fillings, crowns, broken teeth, etc. unless directly related to the study treatment at the discretion of the study doctor. If you have pre-existing dental issues, you may not be allowed to participate in the study at the discretion of the study doctor.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

You are free to withdraw from this study at any time. You should inform the study staff immediately if you intend to withdraw. Your decision not to participate in this study or to withdraw early will involve no penalty or loss of benefits to which you are otherwise entitled.

The study doctor or study staff in charge of the study can remove you from this study, without your consent, for any reason, including, but not limited to:

- The study doctor's or study staff's judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Failure on your part to follow the instructions of the study staff
- Discontinuation of the study by study staff participating in the study prior to completion.
- The study is cancelled by the FDA.

If you withdraw or are withdrawn from the study after having taken the study treatment, you will be asked to come back to the research site for an early termination visit. At this visit, you will have discharge procedures performed and blood tests to ensure that there are no changes to your current health status. You will be asked about any changes in your health and about any medications you are taking.

CONFIDENTIALITY

Your study information may be used to prepare reports or publications about the study. If the results of this study are published or presented in a meeting, your name will not be used and no one will be able to tell that you were in the study from the publication or presentation.

The study information will be kept confidential within the limits of the law. The U.S. Food and Drug Administration may keep study samples and data collected for future research. Identifiers might be removed from your identifiable private information or identifiable biospecimens collected during this study and could then be used for future research studies or distributed to another investigator for future research studies without additional informed consent. You will not be contacted about each of these future uses for additional informed consent. Although future research that uses your samples may lead to the development of new products, you will not receive any payments for these new products.

The study information will be stored both as hard copies as well as computer records. All persons using the study information will make efforts to keep your personal information confidential.

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

If you sign this form, you are giving permission for the use and disclosure of your information for purposes of this research study to the people/groups listed below. You do not have to give this permission. However, if you do not, you will not be able to participate in the study.

The study staff will record your medical and medication history, and the results of examinations and tests done during the study on study forms. Your name will not appear on the study forms. You will be assigned a unique identification number. Study forms may include your subject identification number and your initials. Your name that is linked to your unique identification number is stored in a secure location, only accessible to the study doctor and the study staff.

The study doctor will retain the list that links your personal medical records, your name, and code number for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years after the formal discontinuation of clinical development of the study treatment.

Your blood samples, collected during the study, may be used to perform additional tests (to meet the objectives of the study) after the study is completed.

Unless required by law, your name and study information 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;
- The Institutional Review Board (IRB) that reviewed this study and any other committees responsible for overseeing the research;
- Health authority inspectors, such as the U.S. Food & Drug Administration;
- Study monitors and auditors;
- 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.

Representatives from these groups may receive information from your study forms and/or your medical records. Your medical records may include other health information about you and may include documents that directly identify you. Representatives from the groups identified above may need to look at your medical records to make sure that the information on the study forms is correct or that the study was conducted properly. Therefore, your total privacy cannot be guaranteed. Reviews of your study forms and/or your medical records will take place at the research site or where the study data or medical records are stored and can take place after the study is over.

Some individuals may be provided these records remotely (from a distance, without physical contact) in a secure fashion, in order to monitor the research and verify the accuracy of the study data. Where applicable, the study may be remotely monitored via access to limited and secure internet portals, which prohibit duplication.

For example, regulators and/or Contract Research Organization may be personally present during all study procedures, including study drug administration, as part of their monitoring and review process. Alternatively, they may perform a virtual monitoring and view the study procedures via access to limited live stream video in which you may appear. The live stream video will not permit recording of any kind.

If you stop participating in the study early, for any reason, the study staff will inform the sponsor why. All information collected about you may continue to be used and disclosed.

The study staff may need to correct or provide missing information about you even after your study participation is over. The review of your medical records may also take place after the study is over.

You have a right to view your information, make copies of your medical records, and request to correct errors. However, to ensure the validity of the study, you may need to wait to see your study records until the study is completed. If you decide to withdraw from the study, there is a possibility that your information that was collected up to the point you left the study will continue to be used as long as it is permitted by law.

The research site contains open areas and semi-private sleeping rooms. In this environment, it is possible that someone might recognize you or could overhear your response to medical questions during study procedures. The study staff will always be concerned about protecting your privacy and will take precautions to protect it.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be

disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the agency which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of, for instance, child abuse or neglect, harm to self or others, and communicable diseases.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

PERSONS TO CONTACT FOR QUESTIONS, CONCERNS, OR COMPLAINTS

If you have questions, concerns or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number(s) listed above on the first page.

This research is being overseen by an Institutional Review Board (“IRB”). An IRB is a group of people who perform independent review of research studies. The goal of the IRB is to protect the rights and welfare of the study 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
6100 Merriweather Dr., Suite 600
Columbia, MD 21044
Or by phone: 1-877-992-4724 (toll-free)
Or by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00072762.

LEGAL RIGHTS

You will not lose any of your legal rights to which you are otherwise entitled by signing this consent form.

CONSENT

- You have read (or someone has read to you) this Informed Consent Document.
- This document describes the purpose and nature of this study.
- You have had time to review this information.
- You have been offered a chance to ask questions.
- You received satisfactory answers to your questions.
- If you do not take part in the study, you will not lose any benefits.
- If you leave the study, you will not lose any benefits.
- If you leave the study, you will not lose any legal rights.
- Your participation in this study is completely voluntary.

You will receive a copy of this signed and dated Informed Consent Document for your records.

You agree to participate in this study.

_____
Printed Name of Subject

_____
Subject Signature

__ __/__ __ __/__ __ __ __ _____
D D M M M Y Y Y Y Time

_____
Person Conducting Consent Name (Print)

_____
Person Conducting Consent Signature

__ __/__ __ __/__ __ __ __ _____
D D M M M Y Y Y Y Time

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

A privacy rule has been issued to protect the privacy rights of subjects. This rule (the "Privacy Rule") was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule is designed to protect the confidentiality of your health information and requires your written permission for your health information to be used in this study. This section, called an "Authorization," explains how your health information will be used and disclosed (shared) during this study and describes your rights, including the right to see your health information.

By signing this consent form, you allow the study doctor to use your Personal Health Information and samples to carry out this study. Your "Personal Health Information" is information about you that could be used to identify you, such as your name, address, telephone number, photograph, date of birth, social security number, new and existing medical records, DNA samples, or the types, dates, and results of various tests and procedures. This may include information in your medical record and information created or collected during the study.

By signing this consent form, you also allow the study doctor to disclose your Personal Health Information to other parties in other countries for clinical research and safety reporting purposes, including to the following: (1) sponsor, its affiliates and licensing partners; (2) business partners assisting sponsor, its affiliates and licensing partners; and (4) institutional review boards/ethics committees.

Your Personal Health Information may no longer be protected by the Privacy Rule once it is disclosed by the study doctor, although other confidentiality safeguards apply. The people who receive your Personal Health Information could use it in ways not discussed in this form and could disclose it to others. However, these groups are committed to keeping your health information confidential. If you have questions about how your Personal Health Information will be protected, you can also ask the study doctor. You have the right to see and copy your Personal Health Information related to the study for as long as this information is held by the study doctor. However, to ensure the scientific integrity of the study, you agree that you may not be able to review some of your records related to the study until after the study has been completed. The sponsor may

conduct additional future research with your coded study related information and/or samples without your additional consent. For example, the sponsor may reanalyze the study data at a later date or combine your information with information from other studies for research purposes not directly related to this study. When using the information in these ways, the sponsor may share it with other researchers, its business partners, or companies it hires to provide research-related services. However, your name will never appear in any sponsor forms, reports, databases, or publications, or in any future disclosures by the sponsor. You will not know the results of any future study-related research performed with your personal health information or samples and such information will not be placed in your medical records.

You may cancel this Authorization at any time by sending a written notice to the study doctor at his/her address listed on the first page. If you cancel this Authorization, the study doctor will no longer use or disclose your Personal Health Information under this Authorization for this study, unless the study doctor needs to use or disclose some of your Personal Health Information to preserve the scientific integrity of the study. The study staff will no longer collect any new health information about you unless you have a side effect related to the study. Information given to sponsor before you cancel this Authorization may still be used by sponsor.

Your decision to withdraw your Authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are otherwise entitled.

If you do not sign this consent form, you cannot participate in the study. If you cancel this Authorization in the future, you will no longer be able to participate in the study. For further information regarding cancellation, see the “Voluntary Participation Statement” and the “Right To Withdraw Or Removal From Study” sections above.

This Authorization will expire 50 years from the date you sign it unless you revoke (cancel or withdraw) it sooner. By signing below, you allow the study doctor to use or disclose your Personal Health Information as described above.

_____
Printed Name of Subject

_____ _____
Subject Signature Date