A Phased Clinical Trial of a Dietary Supplement Kava: Biomarker Changes and Anxiolytic Effects Phase 1: Kava Pharmacokinetics

Unique Protocol Identification Number: PAR-18-829

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[IND/IDE] Sponsor:

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
3	Exploratory objectives	Plasma cortisol changes in the already collected plasma samples will support kava-induced pharmacodynamics
9.4.9.	Changes of plasma cortisol levels as an exploratory endpoint	To analyze the already collected plasma samples that will not impose any foreseeable risk to the participants. Plasma cortisol level is a biomarker candidate in the biomarker phase of this study. The changes of the plasma cortisol level from the already collected pk plasma sample therefore will support the biomarker phase evaluations, including method validation and potential pharmacodynamics of kava on cortisol.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC) [Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Phased Clinical Trial of a Dietary Supplement Kava: Biomarker Changes and Anxiolytic Effects	
Study Description:		
Objectives:	Primary Objective:	To characterize pharmacokinetics of flavokavain A/B free kava.
	Secondary Objectives:	None
Endpoints:	Primary Endpoint:	Examining the half life of each of the six major kavalactones.
	Secondary Endpoints:	None
Study Population:	We will recruit 10 healthy participants. There are no restrictions on ethnicity, social background, or gender. All subjects must meet the following criteria at baseline to be eligible for participation in the pharmacokinetic study (a) be between the ages of 18 and 50 years (b) Females of potential childbearing status must use adequate contraceptive precautions.	
Phase:	1	
Description of Sites/Facilities Enrolling Participants:	The University of Florida Clinical Research Center will be used to enroll participants and conduct research procedures. This facility is designed for clinical research.	
Description of Study Intervention:	Ten subjects will be recruited and enrolled into the pilot pharmacokinetic study. Each subject will stay in the out-patient Clinical Research Center (CRC) at the CTSI during the 8-h study period. Participants will be asked to refrain from food, liquids other than water, and medications for 12 hours prior to entering the Clinical Research Center of the UF CTSI. They will have an indwelling venous catheter placed in the lower arm to facilitate the multiple blood collections during the study. Each subject will take three 75 mg kava capsules and ten blood draws (2 mL EDTA vacutainer) will be collected corresponding to the absorption, distribution, metabolism and excretion phase of the pharmacokinetic curve. Specifically, blood will be withdrawn at baseline and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after kava ingestion. The blood samples will be processed and then stored at -80ºC till analysis. The period of follow up for any delayed adverse effects (e.g, monitoring of liver function) will be extended such that all participants will be followed for a full 12 weeks after their last kava ingestion.	

Study Duration: 24 weeks
Participant Duration: 12 weeks

1.2 SCHEMA

Week/Day (-14 to -1) Screening

- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain medical history
- Height and weight
- Concomitant medication review
- Lab testing (CMP, PT/INR, Indirect bilirubin, CYP2D6)
- Urine Drug Screen
- Urine Pregnancy test (for women on child bearing potential)
- C-SSRS
- HAM-A

Visit1 /Day Baseline assessments/Study intervention

- Concomitant medication review
- Adverse event review and evaluation
- Administer study medication
- Urine drug screen
- Urine pregnancy test (for women of child bearing potential)
- PK sampling (pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours post dose)
- Lab testing (CMP)

Visit 2/Week 1

- Lab testing (CMP)
- Adverse event review and evaluation
- Concomitant medication review

Visit 3/Week 4

- Lab testing (CMP)
- Adverse event review and evaluation
- Concomitant medication review

Visit 4/Week 8

- Lab testing (CMP)
- Adverse event review and evaluation
- Concomitant medication review

Visit 5/Week 12 Final assessments

- Lab testing (CMP, PT/INR)
- Adverse event review and evaluation
- Concomitant medication review

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Phone Screen	Screening Day -14 to -1	Baseline Visit 1, Day 1	Week 1 Study Visit 2 Day 7 +/- 1 day	Week 4 Study Visit 3 Day 28 +/- 1 day	Week 8 Study Visit 4 Day 56 +/-1 day	Week 12/Final Visit Study Visit 5 Day 84 +/- 1 day
Informed consent		X					
Demographics		X					
Inclusion/exclusion review	X	X					
Medical History		X					
Administer study intervention			X				
Concomitant medication review		X	X				
Height and weight		X					
Vital signs		X					
CYP2D6 testing		X					
Comprehensive Metabolic Panel testing		X	X [b]	X	X	X	X
PT/INR		X					X
Urine pregnancy test [a]		X	X				
Urine drug screen		X	X				
Adverse event review and evaluation			X				
Pharmacokinetic sampling			X				
HAM-A		X					
C-SSRS		X					
Complete Case Report Forms (CRFs)		X	X	X	X	X	X

a: for women of child bearing potential
b: test will be performed at 12 hours post initial kava ingestion

2 INTRODUCTION

2.1 STUDY RATIONALE

To determine the pharmacokinetics of flavokavain A/B-free kava in order to determine optimal dosing for a planned study of biomarkers of anxiolysis following kava administration.

2.2 BACKGROUND

There is a critical need for new anxiolytics with novel mechanisms for GAD treatment. GAD is a common, chronic, and impairing psychiatric disorder that affects more than 16 million American adults annually (1). Evidence-based treatments for GAD include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRI's), serotonin type 1A partial agonists, and benzodiazepines (BZD) (47). Unfortunately, many patients with GAD report only a partial response with these treatments or cannot tolerate their side effects. These patients continue to suffer with high levels of anxiety and impairment throughout their lives. BZDs are of particular concern because they often become the only treatment option for patients with GAD but carry a risk of chemical dependency, tolerance to the therapeutic effects, cognitive impairment, and in the long term, dementia and even death (3). Specifically, there is an unmet clinical need for new anxiolytics with a mechanism different from BZDs and free of the associated adverse effects (4). **Kava is a promising candidate as a mechanistically novel anxiolytic.** Kava is derived from *Piper methysticum,* a shrub that grows in the South Pacific islands. Extracts from the roots of this shrub (kava) are traditionally consumed as a daily beverage to help people relax, socialize, and improve sleep quality. Kava was used to treat anxiety in Europe in the 1990s (7-13). Clinical studies have shown that kava is effective for anxiolysis across a variety of patient groups (7-13). A recent meta-analysis of four randomized placebo-controlled trials that examined kava use for GAD favored improvement of anxiety symptoms with kava over placebo, although the results were not statistically significant (standardized mean difference = -0.99, CI -2.12 to 0.14) (14, 15). *Importantly, current studies demonstrate no signs of addiction or withdrawal from kava, a clear advantage over the BZDs (23).* These results not only suggest that kava is a promising candidate for treatment of GAD, but also clearly indicate that more research is needed to confirm its utility. The mechanisms behind kava's anxiolytic activity are far from established. Several targets have been proposed based on biochemical or cellular results at human irrelevant concentrations without *in vivo* validation, including $GABA_A$ (17-19), dopamine receptors (18), opioid receptors (18), histamine receptors (18), MAO-B (20), or ion channels (21). A few *in vivo* studies indicate that kava's anxiolytic effect is not mediated through $GABA_A$ (24, 25), consistent with its lack of addiction or withdrawal in clinic. Given that most of currently available treatments for GAD work via serotonin reuptake or $GABA_A$, this study has the potential to identify an anxiolytic with a unique mechanism of action. **Kava use as a dietary supplement is increasing.** Kava has long been available as a dietary supplement in the US market with a resurgence recently – the amount of kava exported from Vanuatu, Fiji and Tonga (the major kava producing countries) increased by ~25% annually between 2008 – 2013 and the U.S.A. is a major destination of kava export (30). Quality control and standardization, however, are lacking – we have analyzed the composition of 25 commercial kava products by LC-MS/MS. The abundance of the major kavalactones

varied by 10 – 30 fold (30) despite the fact that these kavalactones have been recommended for standardization (48). These products therefore likely vary significantly in their anxiolytic efficacies. The abundance of the hepatotoxic compounds, flavokavains A and B (32), varies even more (30), such that some products may impose higher risk of hepatotoxicity than others. Rigorous research therefore is needed to characterize kava's pharmacology in conjunction with accurate characterization of its chemical compositions, essential to maximize kava's benefit and to minimize its potential adverse risk.

Kava is safe for use in clinical populations, especially when properly prepared. Kava was banned for clinical use in Europe from 2001 – 2014 because of concerns about potential hepatotoxicity (26). However, the purported incidence rate of kava-induced hepatotoxicity is extremely low (0.3 – 1 cases per one million daily doses) (48-56), much lower than BZD-based anxiolytics (57, 58). In addition, the WHO found that kava-related hepatotoxicity was likely due to quality problems, adulteration of the root with other parts of the plant, use of ethanol- rather than water-based extraction, and in some cases, interactions between kava and other drugs/herb preparations or chronic alcohol use (5, 49, 50, 59). As a result of these assessments, the ban on kava use was lifted in 2014, and kava is again available for use in Europe (26). We have closely monitored the safety of kava and its ingredients in all of our studies. We detected no signs of hepatotoxicity when kava was evaluated alone, even at elevated dosages and extended exposures (27-29, 32, 36, 60, 61). This was further supported by the results of our recent study, demonstrating that kava was safe unless co-administered with acetaminophen, due to flavokavains A and B (32), two lipophilic chemicals low in aqueous extracts (30). This finding suggests that the already low rate of potential hepatotoxicity with kava can be further mitigated by the use of preparations that have low (or no) levels of flavokavains A and B, and by excluding patients who are taking medications known to have potential hepatotoxicity. The risk of observing an instance of hepatotoxicity according to the WHO is less than 0.03% in the R61 phase and less than 0.9% in the R33 phase of this study; this risk is further mitigated by our use of flavokavain A/B-free kava.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks of participating in this project include those incurred during the administration of rating scales, blood drawing, and the administration of study medication (kava).

Drawing blood requires venipuncture and is associated with the momentary discomfort of the needle stick. The risks of venipuncture include discomfort at the site of puncture, possible bruising and swelling around the puncture site, rarely an infection and uncommonly faintness.

Potential side effects from the administration of Kava include: excessive sedation if combined with alcohol, rare allergic reactions and rare liver toxicity. The frequency of liver injury in Kava is not known. Based upon reported cases, liver injury due to kava is less than 1:1,000,000 daily doses, and is likely due to the presence of flavokavains A and B in the kava preparation. A few cases of clinically apparent liver injury have been published in the literature. One of the potential risks with kava is an acute liver injury with severe hepatitis ending in fulminant hepatic failure, requiring liver transplantation, or even leading to death. Preliminary data from a previous human study by our group did not identify any adverse events due to the consumption of kava supplementation. In addition, we

are using a kava preparation that has been rigorously tested for the removal of flavokavains A and B, which are thought to cause the rare cases of liver toxicity that have been observed.

2.3.2 KNOWN POTENTIAL BENEFITS

None

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

All study personnel are accustomed to maintaining and ensuring patient confidentiality in the course of their work. In addition, all study personnel are highly trained in research procedures and in issues regarding protection of participants' rights and privacy. All members of the research team, including the PIs, coinvestigators, study coordinator, data collectors, research assistants, data manager, and all students associated with the project will complete UF-mandated human subject training prior to study commencement. Participants' identities will be protected through the following measures: consent forms will be stored behind a locked door and in a locked filing cabinet accessible only by the PI, and all identifying information will be stored in a separate, secured location from data that is collected during the study. Access to locked files will be restricted to essential personnel only. In addition to consent and identification files that are secured, all data files will be coded in a manner that makes identification of the participants extremely unlikely. Indeed, participants will be given a numerical ID code to ensure that inadvertent or unauthorized identification does not occur. Data will receive additional layers of security because the whole building, floor, and office in which locked records are maintained have restricted, keyed access. The anonymous codes assigned to participants will be verified and maintained throughout the study, and codes with names will be provided only to meet federal guidelines applicable to the facility. Data will be entered into a REDCap data base developed for the project. REDCap (Research Electronic Data Capture) is a secure, HIPAA-aligned web-based application designed to support traditional case report form data capture. REDCap's automated export procedure will be utilized to export data into a SAS data set for analysis.

The study coordinator for the proposed project has 6 years of experience and will be trained in all study procedures. She will coordinate the screening of potential participants and will meet with Dr. Mathews weekly to discuss study progress. Dr. Firpi-Morell, a gastroenterologist with expertise in hepatology and liver transplantation, will be responsible for overseeing the medical safety monitoring for this trial. He has extensive experience as a medical monitor for national clinical trials of multiple medications. He will communicate with Dr. Mathews on a regular basis, and will also communicate any and all adverse events to the data safety monitoring board. He will interpret the results of the liver biochemistries (all results will be blinded to treatment condition) and will be responsible for referring participants to appropriate additional clinical evaluation and intervention if needed.

Effective screening will rule out active medical or psychiatric conditions, including supplement or medication use, chronic alcohol use, and evidence of pre-existing liver disease that may prevent someone from participating in the studies. Once the subject enters the study, an experienced research team will closely follow him or her. The research team has developed considerable expertise in monitoring the safety of subjects participating in research studies. An experienced research psychiatrist and the hepatologist is available 24 hours a day, 7 days a week. If at any point in the procedures

symptoms become distressing or dangerous, subjects will be withdrawn from the study and, if necessary, treatment instituted.
This project will be conducted in compliance with research statutes outlined in the Health Insurance Portability and Accountability Act. Each participant will be assigned a unique identification number, and this number will be used to link all subsequent information collected. This file will be secured with password access, since it represents a direct link between the name and identification number of a participant. All paper files and data are kept in locked file cabinets to ensure confidentiality. The other procedures to ensure confidentiality follow the regulations and policies of the University of Florida and UF Health. Data file archival and back-up will be performed on a regular basis. The routine monitoring, maintenance, and quality control of the databases will be the responsibility of Dr. Mathews.
Participant distress during evaluations: All evaluations have been designed to minimize burden on patients with respect to fatigue, stress and/or discomfort. Only trained individuals will administer study tests and questionnaires. These individuals will be trained to be sensitive to signs of patient fatigue, stress or discomfort. Breaks during testing will be scheduled, and can be initiated by the patient if they desire. Participants may choose whether or not to receive the results of their clinical interviews. Participants who are assessed as suffering from an untreated psychiatric disorder and choose to obtain the results of their interview will be offered referrals to treatment locally if they choose. Participants will be free to discontinue their participation at any time if they feel that it is causing unacceptable distress or discomfort.
Loss of Confidentiality: All research material will be treated in a confidential manner, and only research staff will have access to the data. Confidentiality will be maintained by assigning identification numbers for all aspects of the project; all data entered into computer databases will use only this identifier. Data are kept in separate coded REDCap data sets and in locked cabinets in locked rooms at UF with access limited to a small number of study personnel. All clinical and other records have identifying names of participants and relatives removed. Electronic data will be password protected and stored in a database on a secure server that is also password protected, with no patient identifying information. No identifiable individual data are presented in scientific publications. Only research personnel will have access to this data.
Risks of Treatments of Unknown Efficacy: Participants will be informed by the investigators and through the written consent that few studies exist for kava treatment, and kava for GAD in particular has not been adequately tested.
Emergence of Depressive or other Psychiatric Symptoms or Suicidality: The research team will receive training in the rapid assessment and management of distress or emergence of psychiatric symptoms that may arise during the PK protocol. If a participant's status raises concern, Dr. Mathews will offer a clinical evaluation and, when appropriate, the study is discontinued, and the participant is referred for treatment according to clinical indication (hospitalization, partial hospitalization, other psychosocial interventions, pharmacotherapy, etc.). If a participant's psychiatric state worsens at any point such that they are no longer able to participate in the treatment, the participant will be withdrawn from the research protocol and referred for the appropriate treatment according to clinical indication. The same procedures apply to any participant who reports suicidal intent or plan or makes a suicide attempt at any point in the study. Dr. Mathews is a licensed psychiatrist and will provide clinical oversight over assessments of suicidal ideation and safety.

Management of psychiatric emergencies: We believe that the risk of psychiatric emergencies occurring during the execution of this study is low, based on the pilot data and because participants are healthy volunteers who have been pre-screened for psychiatric stability. However, should such an emergency arise (such as an acute decompensation, statement or demonstration of active suicidal ideation, violence, etc), we have procedures in place to ensure the safety of the participant and the staff.

Liver function abnormalities: We will use a kava product that has removed the potentially liver toxic elements, flavokavain A and B, and has been rigorously tested for quality. However, we will nevertheless closely monitor serum liver biochemistries (AST, ALT, ALP, bilirubin and albumin) at screening, at hour 12 post-kava ingestion, and at weeks 1, 4, 8 and 12. Although the timing of any potential liver toxicity with kava is not known, the timing of the few reported cases in the NIH liver tox database suggests that the onset of symptoms related to hepatotoxicity (including nausea, fatigue) is likely to be between 2 weeks and 12 weeks following initial ingestion. We will also encourage participants to contact the study team for any concerning symptoms that they may have for up to 6 months post-treatment to ensure that no delayed reactions, no matter how unlikely, are missed. We will carefully educate participants about symptoms to watch for throughout the study and following treatment.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To characterize pharmacokinetics of flavokavain A/B-free kava	Examining the half-life of each of the six major kavalactones	This is a standard marker for pharmacokinetics studies
Secondary		
None	None	N/A
Tertiary/Exploratory		
To characterize plasma cortisol level upon A/B-free kava use	Validate the method and provide pharmacodynamic knowledge of kava on plasma cortisol, which is a biomarker candidate for the biomarker phase of this study	The results will support the studies proposed in the biomarker phase of this study.

4 STUDY DESIGN

4.1 OVERALL DESIGN

- To develop a pharmacokinetic model to identify the best dose and dosage regimens of flavokavain A/B free kava for its further development as a drug for the treatment of GAD
- Phase 1 Single site study
- Open-label
- An equal number of male and female subjects will be enrolled in study. All races and ethnicities will be included. A dose of supplement kava 225 mg will be administered at baseline either in a single dose or dosed at three times during the study visit. Study group-Pharmacokinetics is a single day intervention with 12 week follow up post study drug ingestion. Ten subjects will be recruited and enrolled into the pilot pharmacokinetic study. Each subject will stay in the out-patient Clinical Research Center (CRC) at the CTSI during the 12 hour study period. Participants will be asked to refrain from food, liquids other than water, and medications for 12 hours prior to entering the Clinical Research Center of the UF CTSI. They will have an indwelling venous catheter placed in the lower arm to facilitate the multiple blood collections during the study. Each subject will take three 75 mg kava capsules and ten blood draws (2 mL EDTA vacutainer) will be collected corresponding to the absorption, distribution, metabolism and excretion phase of the pharmacokinetic curve. Specifically, blood will be withdrawn at baseline and 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours after kava ingestion. The blood samples will be processed and then stored at -80ºC till analysis. The period of follow up for any delayed adverse effects (e.g, monitoring of liver function) will be extended such that all participants will be followed for a full 12 weeks after their last kava ingestion. CYP2D6 testing will be conducted to determine if the genotype affects the pharmacokinetics of kava.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Determining the clearance (Cl/F) and volume of distribution (V_d/F) of each of the major kavalactones will allow us to determine the optimal dosing regimen to maximize the pharmacodynamics and optimize compliance.

4.3 JUSTIFICATION FOR DOSE

We have isolated the major chemicals in kava and determined their benefits (66) and risks (32) in vivo. With such knowledge, we screened twenty-five commercially available kava products and quantified the major beneficial kavalactones, including kavain, dihydrokavain, methysticin, and dihydromethysticin (DHM, the chemopreventive ingredient), and the hepatotoxic compounds – flavokavains A and B (30). We identified one dietary kava product from Gaia Herbs (Kava Root) for our pilot human trial that has a high DHM content and low flavokavain A and B content. To ensure consistency, we characterized the content of three batches of this product by HPLC and NMR. Each capsule contained 75 ± 3 mg of kavalactones (the anxiolytic ingredients), consistent with the labeled 75 mg kavalactone per capsule. Each capsule also contained ~20 mg DHM. With three capsules per day, the human daily dose of kava is within the proposed anxiolytic range (120-280 mg daily (14)); the amount of DHM would be comparable

to its in vivo chemopreventive dose. This kava product also contained minimal flavokavains A and B (<1.0 mg/capsule).

4.4 END OF STUDY DEFINITION

The study will come to an end when the data for 10 healthy subjects has been collected and analyzed.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

All subjects must meet the following criteria at baseline to be eligible for participation in the pharmacokinetic study:

- Be between the ages of 18 and 50 years
- Females of potential childbearing status must use adequate contraceptive precautions.

5.2 EXCLUSION CRITERIA

Subjects will be excluded if they meet any of the following criteria at the time of screening or at their baseline visit:

- Currently taking any medication or supplement other than vitamins
- Inability to refrain from acetaminophen, alcohol, or other potentially hepatotoxic substances during the study
- Have a history of liver disease or currently have liver disease. (d) Elevation in serum ALT, AST, ALP or total bilirubin that reaches clinical significance (as determined by the PI) at screening. Have an unstable medical, psychiatric, or neurological condition determined by history taken during the screening visit and a physical examination at the baseline visit.
- Have a positive urine drug screen for substances of abuse.
- Current tobacco users will be excluded.

5.3 LIFESTYLE CONSIDERATIONS

This study will exclude any individual who is a current tobacco smoker and anyone who is not able to abstain from alcohol consumption for the duration of the study.

5.4 SCREEN FAILURES

Subjects who do not meet inclusion and/or meets criteria for any of the exclusion criteria will be deemed a screen fail.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We will recruit and screen potential participants until we are able to randomize and enroll 10 healthy individuals in the R61 pk phase trial. We will recruit males and females of all races/ethnicities ages 18-50 from the following locations.

Recruitment sites will include:
Gainesville and the surrounding community: Gainesville has a population of approximately 100,000 people, not including the student population. Alachua County, which includes Gainesville and the surrounding towns and rural areas, has a population of over 250,000 residents

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Participants will be asked to refrain from food, liquids other than water, and medications for 12 hours prior to entering the Clinical Research Center of the UF CTSI. They will have an indwelling venous catheter placed in the lower arm to facilitate the multiple blood collections during the study (Support Letter from CTSI and its quote of estimated cost attached in Appendix). Each subject will take three 75 mg kava capsules and ten blood draws (2 mL EDTA vacutainer) will be collected corresponding to the absorption, distribution, metabolism and excretion phase of the pharmacokinetic curve. Specifically, blood will be withdrawn at baseline and 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours after kava ingestion, based on our mouse pharmacokinetic knowledge of kava. The blood samples will be processed and then stored at -80ºC till analysis. The period of follow up for any delayed adverse effects (e.g, monitoring of liver function) will be extended such that all participants will be followed for a full 12 weeks after their last kava ingestion.

6.1.2 DOSING AND ADMINISTRATION

Each subject will take three 75 mg kava capsules and 10 blood draws (2 mL EDTA vacutainer) will be collected corresponding to the absorption, distribution, metabolism and excretion phase of the pharmacokinetic curve

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Subjects will be provided with either a onetime dosage or a three time dose of kava (each capsule being 75mgs for a total of 225 mgs for a daily total dose) at the baseline visit. Ingestion of kava will be monitored by the research coordinator and documented on a study drug accountability log.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Bottles of flavokavain AB-free kava (75 mg kavalactones/capsule) with the same lot number will be directly purchased from Thorne Research Inc. This product will be used because of its lack of flavokavains A and B (<0.2 mg/capsule) and consistent content of total kavalactones. For ongoing quality control, three capsules from each bottle will be analyzed via our established method to ensure adequate and constant content of total kavalactones and no flavokavains A and B. The Investigational Drug Service (IDS) pharmacy will package the investigational kava. Supplies with the appropriate number of capsules for each subject will be prepared and bottled for administration.

6.2.3 PRODUCT STORAGE AND STABILITY

Product will be stored according to manufacturer recommendations. All unused supplement will be returned to IDS via study personnel and destroyed by IDS.

6.2.4 PREPARATION

Bottles of flavokavain AB-free kava (75 mg kavalactones/capsule) with the same lot number will be directly purchased from Thorne Research Inc. This product will be used because of its lack of flavokavains A and B (<0.2 mg/capsule) and consistent content of total kavalactones.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

There is no randomization process in this study. All qualified and consented study participants will receive the same total daily dose of kava and will follow through will all follow up procedures.

6.4 STUDY INTERVENTION COMPLIANCE

Study subjects will have one day screening and one day of study intervention therefore compliance is highly achievable.

6.5 CONCOMITANT THERAPY

No concomitant medications will be allowed during this study with the exception of multi vitamins and contraception.

6.5.1 RESCUE MEDICINE

Diphenhydramine will be available for use in the case of any allergic response for subjects who have ingested the study drug.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial. If at any time during the study the participants are found to be at excessive risk, the study will be terminated. All key research personnel have completed the required human subjects training course. Key personnel include all individuals responsible for the design and conduct of the study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Study subjects will be informed that they are welcome to withdrawal or discontinue the study at any time should they feel this is not their best interest, does not meet their time availability, or for any other reason they see fit. Subjects will be asked to speak with the study coordinator or the investigator to indicate their request for withdrawal and all study related activity will stop.

7.3 LOST TO FOLLOW-UP

NCCIH considers lost to follow-up as a research subject who was participating in the study at a certain point in time and subsequently missed two consecutive study visits and is unresponsive to study contact, or is no longer participating in study activities. The anticipated lost to follow-up rate for this study will be 20% of total enrolment (e.g., N=2).

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

There is no intention of determining efficacy during this phase of the study.

8.2 SAFETY AND OTHER ASSESSMENTS

All subjects will undergo lab testing at various time points. Before ingestion of kava and at weeks 1, 4, 8, and 12 to monitor for safety.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value), or any combination of these regardless of relationship to participation in the study.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

Any undesirable and unintended (although not necessarily unexpected) effect occurring as a result of interventions, interactions, or collection of identifiable private information in research. In medical research, any untoward physical or psychological occurrence in research, including abnormal laboratory finding, symptom, or disease temporally associated with the use of (although not necessarily related to) a medical treatment or procedure. Adverse events involving drugs are also referred to as adverse drug experiences. The PI will review and access for any adverse event classification in this study.

8.3.3.1 SEVERITY OF EVENT

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    1. The event is known to occur with the study intervention.
    2. There is a temporal relationship between the intervention and event onset.
    3. The event abates when the intervention is discontinued.
    4. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    1. There is no temporal relationship between the intervention and event onset.
    2. An alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The Study PI and Independent Monitoring Committee will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Unanticipated problems will be recorded in the data collection system throughout the study.
The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitors(s), IRB, FDA, and NCCIH in accordance with requirements. For the IND:

- 7-day IND Safety Report (unexpected fatal or life-threatening AEs related to the intervention); a copy of the report sent to the FDA will be submitted to the NCCIH Program Officer and Independent Safety Monitor(s) within 24 hours of FDA notification.
- 15-day IND Safety Report (any other serious and unexpected AE related to the intervention); a copy of the report submitted to the FDA will be submitted to the NCCIH Program Officer and Independent Safety Monitor(s) within 24 hours of FDA notification.

All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed

8.3.7 REPORTING EVENTS TO PARTICIPANTS

In the case of abnormal lab values (liver functions), the PI will address these findings with the study subjects and provide the subject with a copy of the result for their current physician.

8.3.8 EVENTS OF SPECIAL INTEREST

None

8.3.9 REPORTING OF PREGNANCY

All individuals of child bearing age range will be required to provide a urine sample for pregnancy testing at the screening PK visit. If they are determined to be pregnant they will be excluded from the study. The pharmacokinetics phase of the study is a one day visit.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the investigator becoming aware of the problem.

All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

During this study we will follow the NIH and UF IRB guidelines on reporting unanticipated problems to study participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Not applicable as this is not an efficacy study.

- Secondary Efficacy Endpoint(s):

N/A

9.2 SAMPLE SIZE DETERMINATION

We will recruit and screen potential participants until we are able to randomize 10 healthy individuals into the pharmacokinetics phase of this study. As kava pharmacokinetics have never been characterized in humans, this is a pilot study such that, with 10 participants, these results will provide preliminary data of kava pharmacokinetics in humans. The data will be the foundation for future systematic characterization of kava pk in humans.

9.3 POPULATIONS FOR ANALYSES

Healthy adults ages 18-50

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Plasma concentration-time data of individual kava lactone in will be subjected to non-linear mixed effect modeling (NONMEM). Compartmental modeling approach will be applied to achieve the best fit model on the basis of residual sum of squared error, Akaike's Information Criterion and objective function value. Chi-squared distribution will be assessed to evaluate the significance; e.g. an objective function change (OBJ) of 3.84 is significant at alpha=0.05.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Pharmacokinetic parameters will be derived from this study and these parameters will be used to design future efficacy studies

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Not applicable

9.4.4 SAFETY ANALYSES

At several time points in the study we will be collecting blood to access the study subjects liver functions pre and post kava ingestion. In the event that serum liver enzymes become elevated, (e.g., greater than 3 times the upper limits or normal for two repeated measures, or greater than 5 times the upper limits of normal once) the medical monitor will be notified and results will be communicated with the subject along with recommendations for follow up by a hepatologist.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Gender, age, percentage of subjects on oral contraceptive, percentage of subjects who take multi vitamins.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable

9.4.7 SUB-GROUP ANALYSES

None

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Plasma concentration-time of all the volunteers will be tabulated in a csv file to do pharmacokinetic modeling and simulation.

9.4.9 EXPLORATORY ANALYSES

Plasma concentration-time of cortisol levels of all the volunteers will be quantified and tabulated in a csv file to explore the potential effects of kava on the plasma cortisol.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

To complete the informed consent process at the end of study participation, study staff will inform the subject when his/her participation has come to an end and will document the discussion in the study record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

All consented subjects will be provided a copy of their fully executed informed consent document.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Each subject will review the informed consent document with the study coordinator and will be provided time to ask and receive answers to any questions. The name of the person obtaining consent will be documented along with date and time consent was obtained.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial."

If at any time during the study the participants are found to be at excessive risk, the study will be terminated. All key research personnel have completed the required human subjects training course. Key personnel include all individuals responsible for the design and conduct of the study.

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records. All research material will be treated in a confidential manner, and only research staff will have access to the data. Confidentiality will be maintained by assigning identification numbers for all aspects of the project; all data entered into computer databases will use only this identifier. Data are kept in separate coded REDCap data sets and in locked cabinets in locked rooms at UF with access limited to a small number of study personnel. All clinical and other records have identifying names of participants and relatives removed. Electronic data will be password protected and stored in a database on a secure server that is also password protected, with no patient identifying information. No identifiable individual data are presented in scientific publications. Only research personnel will have access to this data.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Chengguo Xing	Roberto Firpi
Carol Mathews	

10.1.6 SAFETY OVERSIGHT

The Data and Safety Monitoring Plan for this project will also include monitoring by an independent Data Safety Monitoring Board (DSMB), consisting of an anxiety disorders expert (Dr. Carr), a hepatologist (Dr. Morelli), a statistician (Dr. Wu), and a pharmacologist (Dr. Law). These individuals will have no affiliation to the proposed study. The DSMB will review any serious adverse event that is reported within 48 hours. They will also convene annually and at the end of the study to review all adverse events. Adverse events that are serious and unexpected will be immediately reported to the IRB, NIH, and FDA (if warranted). Non-serious unanticipated problems shall be described in annual reports to the IRB and NIH. The DSMB will review the adverse events and discuss any concerns regarding them with the Principal Investigators.

Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitor(s) semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor(s) and will be forwarded to the IRB and NCCIH, FDA, and sponsoring industry collaborator. The IRB and other applicable recipients will review progress of this study on an annual basis

10.1.7 CLINICAL MONITORING

The study team will generate Study Reports for the Independent Monitor and will provide information on the following study parameters: liver function, serious adverse events, and pharmacokinetic data.

Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The site SC will ensure that all study personnel have completed all required institution-specific and protocol-specific trainings and that these trainings are documented appropriately on the Training Log. The site SC will also ensure that new personnel are appropriately documented on the Delegation of Responsibilities Log (DOR). While training should be completed and documented in real time, the Lead SC will verify that all training is current and appropriately documented. All study staff will complete CITI or NIH Human Subjects training prior to commencement of study.

10.1.9 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.
All data will be entered into a REDCap (Research Electronic Data Capture) database developed for this project. REDCap is a secure, HIPAA-compliant web-based application designed to support traditional case report form data capture. Data will be exported into a SAS data set for analysis. Data integrity will be evaluated using descriptive statistics (e.g., means, standard deviations, frequencies, percent, range) appropriate for measurement levels. Checks for implausible or out-of-range values, distributional forms, and missingness will be performed. Data transformations (e.g., Box-Cox family of transforms) and/or crossproduct terms will be incorporated, if required, based on evaluation of tenability of statistical model assumptions and model fit to the data. All analyses will be conducted using SAS version 9.4 or later.

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

10.1.9.2 STUDY RECORDS RETENTION

During this study we will follow NIH, UF IRB, and FDA regulations on study record retention. Should the retention durations differ, we will recognize the longer duration for record retention.

10.1.10 PROTOCOL DEVIATIONS

All protocol deviation reporting will follow NIH and UF IRB guidelines.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Sharing of data generated by this project is an essential part of our proposed activities and will be carried out in several different ways. We will publish the results of our work in appropriate psychiatric and pharmacological journals. After the publication of the results of the study, clinical data (without identifiers) will be made available to other investigators, if requested. As required by the IRB at UF, participants in our study have the option to choose whether or not they agree to allow their data to be shared with other investigators. In our experience, the vast majority of participants agree to have their information shared with other investigators who are interested in studying neuropsychiatric disorders. We also welcome collaboration with others to further explore kava's clinical potential, its active ingredient(s) and detailed mechanism of action.

Our plan includes the following:

- Presentations at scientific meetings
    - From the projects, it is expected that approximately two to three presentations at scientific meetings would be appropriate in the field of anxiety, biomarker or pharmacokinetics.
- Peer-reviewed publications
    - The research results will be prepared for peer-reviewed publication. It is expected that the results from the proposed studies will be the basis for 2 – 4 manuscripts in the R61 phase, including 1) pharmacokinetic characterization of kava and its major ingredients; 2) biomarker changes in response to kava treatment and other clinical results.
- Protocol sharing
    - We agree to share our experimental protocols and data with other researchers who are PIs and co-PIs of NIH grants. The sharing can be arranged through the following approaches: 1) on-line data base with a password that can be released to other researchers through the discussion with

the program director; and 2) teleconference with other researchers through the arrangement of the program director.

- Department websites
    - Both multi-PI's department maintain departmental websites that have "News" section and websites for individual faculty. The general clinical trial information will be posted both at the "News" site and the multi-PI's individual faculty website that further detailed information may be requested from the multi-PI.
- Clinicaltrials.gov
    - The trial will be registered at clinicaltrials.gov and will be updated as the trial proceeds.

10.1.12 CONFLICT OF INTEREST POLICY

During this study we will follow the NIH policy pertaining to any current or possible conflicts of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices

GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
4.0	23Nov2020	Change to include 10 timepoints of blood collection during PK visit	This additional time point at 12 hours post does was added to capture the elimination phase of the study drug

4.0	23Nov2020	Update to the schema to include changes in procedures which includes CYP2D6 testing	Adding the CYP2D6 testing will help to determine if genotype affects the pharmacokinetics of kava
4.0	23Nov2020	Addition of indirect bilirubin to screening labs	Adding the indirect bilirubin will allow the medical monitor and the PI to determine if a subject is eligible to move forward in the study from a safety perspective.
4.0	23Nov2020	Change from single dosing only to allow for single dosing for the first 5 participants and three times a day dosing for second 5 participants	This change is implemented based on preliminary analysis of data from participants. This change will be implemented to evaluate the pk results of the three times a day dosing vs single dosing. It will help determine dosing regimen for 2nd phase of the study.
1.1		Change to include a 12-hour post dosing blood draw during pk visit	This timepoint will allow researchers to capture the elimination phase of the study drug
1.2		Update to schema to include the CYP2D6 at the screening visit	CYP2D6 testing is being done to determine if genotype affects the pharmacokinetics of kava
1.2		Update to schema to include indirect bilirubin testing at the screening visit	Adding the indirect bilirubin will allow the medical monitor and PI more information in order to determine eligibility from a safety perspective
1.3		Update to correct the study visit windows	Number of days that corresponded with days listed on previous version were noted to be incorrect
4.1	23Nov2020	Change from single dose only to single dose for first five subjects and three times a day dose for second five subjects	Based on preliminary analysis, adding in the three times a day dosage will allow for the evaluation of optimal dosing regimen for phase 2 of the study.

11 REFERENCES