Pain Therapeutics, Inc.
7801 N. Capital of Texas Hwy, Ste. 260
Austin, TX 78731

CLINICAL RESEARCH PROTOCOL

PROTOCOL PTI-125-01

A Phase I, Single Center, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose, Pharmacokinetic and Safety Study of PTI-125 in Healthy Volunteers

Sponsor: Pain Therapeutics, Inc.

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Protocol Date: 15 June 2017

Confidentiality

Pain Therapeutics, Inc.

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Approvals:

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SVP, Regulatory Affairs
Pain Therapeutics, Inc.

16 June 2017
Date

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Chief Operating and Medical Officer
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Date

Pain Therapeutics, Inc.

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Signature of Agreement for Protocol PTI-125-01

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practice (GCP) and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 312.

Principal Investigator Signature

06/16/2017

Date

George T. Atiee M.D.

Print Principal Investigator Name and Title

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1. LIST OF ABBREVIATIONS

α7nAChR	α7 nicotinic acetylcholine receptor
$A\beta_{42}$	amyloid beta$_{1-42}$
AD	Alzheimer's disease
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CRF	case report form
CRO	contract research organization
DSMB/DMC	Data Safety Monitoring Board/Data Monitoring Committee
EC	ethics committee
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
FDA	Federal Drug Association
FLNA	filamin A
GCP	good clinical practics
GGT	gamma glutamyl transpeptidase
GLP	good laboratory practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hERG	human ether-a-go-go-related gene
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	insulin receptor
IRB	independent review board
LDH	lactose dehydrogenase
LOQ	limit of quantitation
NMDA	N-methyl D-aspartate
NOAEL	no observable adverse effect level
OTC	over-the-counter
PHCG	placental human chorionic gonadotropin
PK	pharmacokinetics
PTI	Pain Therapeutics, Inc.
QS	quantity sufficient
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
Tmax	time to Cmax
WBC	white blood cell

2. INTRODUCTION

Pain Therapeutics Inc. (PTI) is developing PTI-125, a novel drug candidate designed to treat and slow the progression of Alzheimer's disease (AD). PTI-125 binds with femtomolar affinity to filamin A (FLNA), a scaffolding protein we recently demonstrated is critical to beta amyloid's toxicity. Beta amyloid$_{1-42}$ (Aβ_{42}) exerts its toxic effects by hijacking the α7-nicotinic acetylcholine receptor (α7nAChR) and signaling via this receptor to hyperphosphorylate tau. In addition to disrupting the normal functions of α7nAChR and tau protein, this toxic signaling leads to the signature tangles and plaques found in brains of AD patients. In two animal models and in postmortem human AD brain tissue, PTI-125 restored function of three receptors that are impaired in AD: the α7 nicotinic acetylcholine receptor (α7nAChR); the NMDA receptor; and the insulin receptor (IR).[1] PTI-125 also reduced tau hyperphosphorylation, amyloid deposits, neurofibrillary tangles and inflammatory cytokine release.[1] We therefore expect PTI-125 to improve memory and slow or halt AD progression, which are clear improvements over existing therapeutics. Both mouse models used a single efficacious dose equivalent to 20-22 mg/kg/day PTI-125 free base. The first mouse study administered twice daily i.p. injections of 10 mg/kg (equivalent to 60 mg/m^2) PTI-125. The second study delivered 22 mg/kg/day (equivalent to 66 mg/m^2) via drinking water.

A robust nonclinical ADME, safety pharmacology, and general and genetic toxicology program has been carried out with PTI-125. In vitro metabolic profiling showed minimal metabolism across several species and in man. PTI-125 was rapidly absorbed and eliminated in in vivo studies in rat and dog with nearly 100% oral bioavailability, a 2.67-h half-life in dog, dose proportional PK and no accumulation. Safety pharmacology studies showed no adverse effects on gross behavioral and physiological parameters in the Irwin test of CNS toxicity in rats, no adverse effects on respiratory rate, tidal volume or minute volume in the rat respiratory test, and no adverse effects on arterial blood pressure, heart rate and ECG parameters in the dog cardiovascular study. The in vitro hERG test for cardiotoxicity also indicated no adverse effect. A full battery of genotoxicity studies was conducted (in vitro bacterial Ames, in vitro chromosomal aberration, and in vivo rat micronucleus test) and were all negative. An in vitro specificity screen showed no significant activation or inhibition of a panel of 67 receptors, channels and transporters.

PTI-125 was tested in single dose and repeat dose oral general toxicity studies in rats and dogs. In a 28-day repeat dose oral general toxicity study followed by a 28-day drug-free recovery period in rats, with PTI-125 dose levels up to and including 1000 mg/kg/day (equivalent to 6,000 mg/m^2), toxicity was mainly characterized at 1000 mg/kg/day by a decrease in mean body weight which continued during the recovery period. A diffuse cellular hypertrophy of the liver was seen at 1000 mg/kg/day in males and females and was interpreted as an adaptive response to the test article. There were no other adverse effects and all biologically significant findings noted during the dosing period were resolved at the end of the 28-day recovery period. A no-observed-effect-level (NOEL) could not be determined and the no-observed-adverse-effect-level (NOAEL) was determined to be 500 mg/kg/day (equivalent to 3,000 mg/m^2).

A 28-day repeat dose oral general toxicity study in dogs, followed by a 28-day drug-free recovery period, with PTI-125 dose levels up to and including 200 mg/kg/day (equivalent

to 4,000 mg/m^2). Findings included slight muscle fasciculations in some animals at the high dose only, an increase in blood pressure in high dose females, and sporadic alterations in clinical chemistry profiles at the high dose. All observations resolved during the recovery period. An NOEL could not be determined and the NOAEL was determined to be 100 mg/kg/day (equivalent to 2,000 mg/m^2).

It should be noted that in a 7-day non-GLP dose-range finding study in dogs, convulsions (rated "slight") were observed in one of six animals administered 300 mg/kg/day on Day 2 and Day 3. On Day 4, this dose was reduced to 150 mg/kg/day, and the high dose, 1000 mg/kg/day, was reduced to 200 mg/kg/day. Convulsions were not observed in the 1000/200 mg/kg/day animals.

FDA Guidance[1] for estimating the maximum safe starting dose in initial clinical trials was followed in determining the dose levels for this clinical trial. A safe human starting dose of 1/10th the human dose equivalent of the NOAEL in the most sensitive species (dog) was calculated as 330 mg. This first in human Phase I Single Ascending Dose (SAD) study will assess the safety and pharmacokinetics of PTI-125 solution at three single oral doses (50, 100 and 200 mg, equivalent to 31, 62, and 123 mg/m^2, respectively) in healthy normal volunteers.

3. STUDY OBJECTIVES

The objective of this study is to determine the safety and pharmacokinetics of PTI-125 following single-dose oral administration in healthy male and female normal volunteers, age 18 - 45.

4. SUMMARY OF STUDY DESIGN

This is a Phase I, single center, randomized, double-blind, placebo-controlled, SAD study of three escalating doses of PTI-125 in healthy male and female volunteers, 18-45 years of age. A total of twenty-four (24) subjects will be enrolled into the study in one of three dose cohorts. Each cohort will contain 8 subjects; six (6) subjects will receive PTI-125 and two (2) will receive placebo in each cohort. Three single ascending doses of PTI-125 oral solution (50, 100, and 200 mg) or placebo solution will be administered to respective cohorts.

The study includes a screening period (Day -28 to Day -1) and an inpatient treatment period (Day 0 through Day 4) and a follow-up visit (Day 7). Subjects will report to clinic the day before dosing and will be randomized to receive either a single dose of orally administered PTI-125 or placebo. Each dose will be administered following an overnight fast of 10 h.

For each dose level, dosing will be staggered such that 2 subjects (one active and one placebo) will be dosed prior to the rest of the group. After a minimum of 24 h and review of all 24-h safety assessments (ECG, brief physical, vital signs and laboratory

[1] Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. FDA, CDER, July 2005.

assessments) an independent Data Safety Monitoring Board/Data Monitoring Committee (DSMB/DMC) will determine whether the remaining 6 subjects will be dosed. If safety concerns are raised, 2 additional subjects (randomized according to the Rand schedule to maintain blinding) will be dosed followed by collection and review of the 24-hour safety assessments. The DSMB/DMC will determine after review if dosing will proceed for the remaining 4 subjects.

PK blood samples will be obtained prior to dosing and at specified intervals during the study (0-72 h post-dose). PK parameters will be calculated using non-compartmental analysis.

Blood draws for laboratory testing will be performed prior to dosing and at 24 h post-dose. After safety assessments of ECG, vital signs and a brief physical exam at 72 h, subjects will be discharged from the clinic and will return 7 days post-dose for a final safety assessment.

4.1 STOPPING CRITERIA

Dose escalation will be suspended or stopped if any of the following occur and are potentially related to administration of the study drug:

- Clinical signs or symptoms of moderate intensity or greater in two or more subjects
- A single clinical sign or symptom of severe intensity
- AST/ALT elevation greater than 3x upper limit of normal
- Bilirubin elevation greater than 2x upper limit of normal
- Creatinine elevation greater than 1.5x upper limit of normal
- Any significant laboratory finding, confirmed by repeat laboratory testing

The DSMB/DMC may subsequently recommend a second sentinel group to proceed with planned protocol dosing, or termination of the study.

5. SUBJECT SELECTION

5.1. STUDY POPULATION

A total of 24 male and female subjects will be enrolled in the study.

5.2. INCLUSION CRITERIA

Each subject must comply with the following criteria:

1. Male or female subjects between 18 and 45 years of age, inclusive.
2. The subject has a body mass index (BMI) within 18-30 kg/m^2 (inclusive).
3. The subject is in good health as determined by medical history and physical examination and clinical laboratory parameters.
4. The subject is willing and able to speak, read, and understand English and provide written informed consent.
5. The subject is a non-smoker for at least 12 months. If a former smoker, the reason for stopping must be evaluated.
6. Females who are physically incapable of childbearing defined as postmenopausal, or surgically sterile (hysterectomy, bilateral tubal ligation, bilateral oophorectomy or an Essure procedure). Appropriate documentation (ex; medical record) of the surgical sterilization procedure to be obtained and held within the subject's study file.
7. The subject must agree to comply with the drawing of blood samples for the PK assessments.
8. The subject is willing and able to comply with all testing and requirements defined in the protocol.
9. The subject is willing and able to remain at the study site unit for the duration of the confinement period and return for the outpatient visit.

5.3. EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study.

1. The subject has any relevant deviations from normal in physical examination, electrocardiogram (ECG), or clinical laboratory tests, as evaluated by the investigator.
2. The subject has had a clinically significant illness within 30 days of Check-in.
3. The subject has a history of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease.
4. The subject has used any prescription medication within 14 days of dosing or over-the-counter (OTC) medication within 48 h of dosing or intends to use any prescription medication or OTC medication during the study that may interfere with the evaluation of study medication.
5. The subject has used alcohol, caffeine or xanthine-containing products 48 h before dosing or intends to use any of these products during the study.
6. The subject has used grapefruit, grapefruit juice, or grapefruit-containing products 7 days before dosing or intends to use any of these products during the study.
7. The subject has a history of substance abuse or a positive ethanol breath test, urine cotinine, or urine drug screen at screening or at check-in.

8. The subject has a positive serum hepatitis B surface antigen or positive HCV antibody test at the Screening Visit.
9. The subject has a positive HIV test at the Screening Visit.
10. Female subject is pregnant or breastfeeding.
11. The subject has received an investigational drug within 30 days of Check-in.
12. The subject has donated or lost a significant volume of blood (>450 mL) within 4 weeks prior to the study.
13. The subject is unwilling to reside in the study unit for the duration of the study or to cooperate fully with the investigator or site personnel.
14. The subject has an AST/ALT or total bilirubin greater than the ULN. One repeat test will be allowed.

6. STUDY DRUG

6.1. PTI-125 PHYSICAL DESCRIPTION AND PREPARATION

Investigational PTI-125 will be supplied by PTI as the bis-HCl monohydrate salt solid form and buffer components. An on-site pharmacist will mix a 50 mg/ml solution (free base equivalent) in pH 5.2, 0.3 M citric acid / citrate buffer following the study-specific pharmacy manual, PTI-125 Clinical Dosing Instructions. To achieve 50 mg, 100 mg, and 200 mg dosing solutions, 1, 2 or 4 ml drawn into a 5-ml syringe will be mixed with 15 ml of ORA-sweet SF drawn into a 20-ml syringe using a syringe connector as specified in the manual. After mixing, each dose will be contained in the 20-ml syringe and appropriately labeled. Further details on dose preparation and administration are found in PTI-125 Clinical Dosing Instructions. Placebo will be 15 ml ORA-sweet SF mixed with 1, 2 or 4 ml pH 5.2, 0.3 M citric acid / citrate buffer.

All containers, syringes or bottles of PTI-125, used or unused, will be saved for final disposition by the sponsor or designee.

6.1.1. Storage

The bottles and syringes of PTI-125 prior to dissolving and as a solution must be stored at refrigerated conditions (2° C – 8° C). PTI-125 in solution can be kept at room temperature prior to dosing up to 4 h.

6.1.2. Drug Accountability

The Investigator will be responsible for monitoring the receipt, storage, dispensing and accounting of all study medications according to site SOPs. All invoices of study medication shipments must be retained in the site study file. Accurate, original site records must be maintained of drug inventory and dispensing. All

records must be made available to the sponsor (or designee) and appropriate regulatory agencies upon request.

6.2. ADMINISTRATION AND DOSING REGIMEN

All subjects in each cohort (8 subjects) will be randomized to receive PTI-125 (6 subjects) or placebo (2 subjects). Following an overnight fast of at least 10 h, subjects will receive a single oral dose of PTI-125 oral solution or placebo followed by approximately 240 mls of room temperature water. No food will be allowed until 4 h post-dose. Water will be allowed as desired except for 1 h before and 1 h after dosing.

6.3. CONCOMITANT MEDICATIONS

Use of prescription medications will be prohibited for 14 days before initial drug administration and during the study. Non-prescription medications will be prohibited for 48 h before initial drug administration and during the study.

Use of alcohol and caffeine- or xanthine-containing products is prohibited for all subjects 48 h before dosing and during the study.

Use of grapefruit, grapefruit juice, and grapefruit-containing products is prohibited for all subjects 7 days before dosing and during the study.

7. STUDY PROCEDURES

Appendix A presents the Schedule of Activities.

Prior to any study-related activities, the Informed Consent Form must be signed and dated by the subject. The format and content of the Informed Consent Form must be agreed upon by the Principal Investigator(s), the appropriate IRB and the Sponsor (or designee). Appendix B contains a sample Informed Consent for this study. The signed and dated Informed Consent Form must be retained by the Investigator in the subject's file.

7.1. EVALUATIONS BY VISIT

7.1.1. Screening Period

The following will be completed within 29 days prior to administration of the study medication:

- Informed Consent (written consent must be obtained prior to conducting any screening activities)
- Review of Inclusion and Exclusion Criteria

- Medical history
- Review of concomitant medications
- Physical examination, including measurement of orthostatic vital signs (blood pressure, temperature, pulse and respiratory rate after a 3-min sitting period followed by blood pressure and pulse after a 2-min stand period), height, weight and calculated BMI.
- A 12-lead ECG (5-minute supine)
- Laboratory assessments, including serum chemistry, hematology, and urinalysis; ethanol breath test, urine drug screen, urine cotinine, HIV test, HBsAg and HCV Antibody.
- FSH test for female subjects claiming post-menopausal status

7.1.2. In-patient Period - Study Days 0-4

Note: Study Day 1 is defined as the day of dosing for each dose cohort.

Subjects will check into the clinic at the designated time on Day 0, and will remain confined to the clinic until Study Day 4. Upon check-in, the following assessments will be conducted:

- Confirmation of inclusion/exclusion criteria
- Ethanol breath test
- Urine drug screen
- Urine Cotinine test
- Review of concomitant medications
- Orthostatic vital signs (blood pressure, temperature, pulse and respiratory rate after a 3-min sitting period followed by blood pressure and pulse after a 2-min stand period).
- Brief physical examination

Following a supervised fast for at least 10 h, subjects will be administered a single oral dose of study drug (or placebo) on Study Day 1.

The appropriate dosing syringe of PTI-125 or placebo (15 ml ORA-sweet SF mixed with 1, 2 or 4 ml pH 5.2, 0.3 M citric acid / citrate buffer) mixed with ORA-sweet SF for taste masking will be administered. Subjects will also consume water provided as a rinse of the dosing syringe, to ensure complete consumption of study drug.

No food will be allowed for 4 h post-dose. Water will be allowed as desired except for 1 h before and 1 h after dosing. At 4 h post-dose, subjects will be provided a standard lunch.

On the morning of Study Day 1, within 30 min prior to dosing, the following assessments will be conducted:

- Orthostatic vital signs (blood pressure, temperature, pulse and respiratory rate after a 3-min sitting period followed by blood pressure and pulse after a 2-min stand period).
- Review of concomitant medications
- Blood sample collection for baseline PK assessment (Sample Time=0)
- On Day 1, blood sample collection for laboratory testing prior to dosing (Time=0)
- ECG (Time=0)

After dose, the following assessments will be conducted:

- Orthostatic vital signs (blood pressure, temperature, pulse and respiratory rate after a 3-min sitting period followed by blood pressure and pulse after a 2-min stand period) at approximately 10 and 30 minutes, and 1, 2, 3, 4, 8, 12, 24, 36, 48 and 72 h post-dose.
- Blood samples will be drawn at 20, 40, and 60 min following dosing and at 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h for PK assessments
- Adverse event monitoring
- Clinical laboratory tests at approximately 24 h post-dose
- Brief physical examination at approximately 24 and 72 h post-dose
- ECG at approximately 30 min, and 1, 2, 3, 4, 8, 12, 24, 36, 48 and 72 h post-dose.

Should procedures occur at the same nominal timepoint collection of the PK assessment will take priority. All other procedures will be performed within a sufficient +/- window for logistical purposes.

All subjects will receive a standardized lunch 4 h post-dose. All subsequent meals will be served at standard meal times.

Clinic personnel will monitor the subjects for the occurrence of any adverse events until subjects are discharged from the clinic. Subjects will be discharged from the clinic upon investigator judgment after results of all safety assessments following the last dose have been reviewed.

7.1.3. Follow-up Visit – Study Day 7

At the Day 7 follow up visit, the following assessments will be conducted:

- Orthostatic vital signs (blood pressure, temperature, pulse and

respiratory rate after a 3-min sitting period followed by blood pressure and pulse after a 2-min stand period)

- ECG
- Adverse event monitoring
- Physical examination
- Clinical laboratory tests

7.2. LABORATORY ASSESSMENTS

7.2.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed at screening, Day 1 pre-dose, at 24 h post-dose, and at the Day 7 follow-up visit:

- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.
- Serum Chemistry: glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, uric acid, phosphorus, calcium, total protein, albumin, globulin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), total bilirubin, lactose dehydrogenase (LDH).
- Urinalysis: color, specific gravity, pH, protein, sugar, ketones, occult blood, creatinine clearance calculation by Cockcroft-Gault equation.
- At screen only: FSH will be performed on all females claiming to be of post-menopausal status.

The following tests will be performed at screening and at check-in to the clinic:

- Urine drug screen: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, and cannabinoids
- Urine Cotinine
- Ethanol breath test
- HIV test (screening only)
- HBsAg, HCV Antibody tests (screening only)

7.2.2. Preparation of Plasma Samples for Pharmacokinetic Determination

At each blood collection, blood samples (4 mL) will be drawn into a Vacutainer® tube containing K_2EDTA. The tubes will be placed on ice. Within 30 minutes of collection, the blood will be centrifuged at approximately 1000 X G for 15 minutes between 4-5°C. Within 30 minutes of centrifuging, plasma (at least 1.5 mL) will be split evenly into two aliquots, transferred to polypropylene tubes and stored at

approximately -70°C or below until analysis. The time from sample collection to storage should not exceed 60 minutes.

At the end of the study the samples will be shipped frozen on dry ice to: Worldwide Clinical Trials Bioanalytical Sciences, 8609 Cross Park Drive, Austin, TX 78754 for bioanalytical analysis of PTI-125 with a validated assay. Remaining samples following the analysis of PTI-125 are to be retained until directed for disposition by PTI. All samples from PTI-125 subjects will be analyzed. One sample around the Cmax from each placebo subject will be analyzed, such as 40 min, 1 or 2 h. All secondary samples will be shipped to Worldwide Clinical Trials Bioanalytical Sciences upon confirmation of receipt of the primary samples.

8. EARLY DISCONTINUATION

Subjects may choose to discontinue study drug or study participation at any time, for any reason, and without prejudice.

The following must be completed and documented in the source documents and CRFs for all subjects who discontinue the study early:

- The reason for early study discontinuation.
- Safety data should be obtained and will include the following:
    - Orthostatic vital signs (blood pressure, temperature, pulse and respiratory rate after a 3-min sitting period followed by blood pressure and pulse after a 2-min stand period), brief physical examination, clinical laboratory tests, ECG, use of concomitant medications, and adverse events.

9. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

9.1. ADVERSE EVENTS - DEFINITION

An adverse event (AE) is any undesirable event that occurs to a subject during a study, whether or not that event is considered study drug-related. Monitoring for AEs will start at dosing. Examples include:

- Any treatment-emergent signs and symptoms (events that are marked by a change from the subject's baseline/entry status [e.g., an increase in severity or frequency of pre-existing abnormality or disorder])
- All reactions from study drug, an overdose, abuse of drug, withdrawal phenomena, sensitivity or toxicity to study drug
- Apparently unrelated illnesses
- Injury or accidents (Note: if a medical condition is known to have caused the

injury or accident, the medical condition and the accident should be reported as two separate medical events [e.g., for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately])

- Extensions or exacerbations of symptoms, subjective subject-reported events, new clinically significant abnormalities in clinical laboratory, physiological testing or physical examination

All AEs, whether or not related to the study drug, must be fully and completely documented on the AE page of the Case Report Form (CRF) and in the subject's clinical chart.

In the event that a subject is withdrawn from the study because of an AE, it must be recorded on the CRF as such. The subject should be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

The Investigator must report all directly observed AEs and all spontaneously reported AEs. The Investigator will ask the subject a non-specific question (e.g., "Have you noticed anything different since your dose of the study medication?") to assess whether any AEs have been experienced since the last assessment. AEs will be identified and documented on the AE CRF in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported on the CRF (see below).

9.2. ADVERSE EVENTS - SEVERITY RATING

The severity of each AE should be characterized and then classified into one of three clearly defined categories as follows:

- Mild - the AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.
- Moderate - the AE produces some impairment of functioning, but is not hazardous to health. It is uncomfortable or an embarrassment.
- Severe - the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report, and the physician's observations. The severity of the AE should be recorded in the appropriate section of the Adverse Event CRF.

9.3. ADVERSE EVENTS - RELATIONSHIP TO STUDY DRUG

The relationship of each AE to the study drug will be classified into one of three defined categories as follows:

- Unlikely – a causal relationship between the AE and the study drug is

unlikely.

- Possible — a causal relationship between the AE and the study drug is possible.
- Probable – a causal relationship between the AE and the study drug is probable. For example, the AE is a common adverse event known to occur with the pharmacological class the study drug belongs to; or the AE abated on study drug discontinuation and reappeared upon rechallenge with the study drug

These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report, the timing of the AE in relationship to study drug administration/discontinuation, the physician's observations and the physician's prior experience. The relationship of the AE to the study drug will be recorded in the appropriate section of the Adverse Event CRF.

9.4. SERIOUS ADVERSE EVENTS AND UNEXPECTED ADVERSE EVENTS - DEFINITIONS

Any AE that suggests a significant hazard, contraindication, side effect or precaution is defined as a Serious Adverse Event (SAE). An SAE includes (but is not limited to) an experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., the subject is at immediate risk of death from the reaction as it occurs). "Life-threatening" does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
- In-patient hospitalization (hospital admission, not an emergency room visit) or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity (i.e., a substantial disruption of the subject's ability to carry out normal life functions).
- A congenital anomaly/birth defect.

In addition, medical and scientific judgment should be exercised in deciding whether other situations should be considered an SAE (i.e., important medical events that may not be immediately life-threatening or result in death, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above). Examples of such medical events include (but are not limited to): allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

An **unexpected** AE is one for which the specificity or severity is not consistent with the current Investigator's Brochure. For example, hepatic necrosis would be

unexpected (by virtue of greater severity) if the Investigator's Brochure only listed elevated hepatic enzymes or hepatitis.

Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure only listed cerebral vascular accidents.

9.5. SERIOUS ADVERSE EVENTS REPORTING

The reporting of SAEs by the Sponsor to Regulatory Authorities (e.g., FDA) is a regulatory requirement. Each Regulatory Agency has established a timetable for reporting SAEs based upon established criteria. Likewise, it is the responsibility of the Principal Investigator to report SAEs to their EC/IRB.

All SAEs must be reported immediately **(within 24 h of learning of the event)** by telephone to:

Nadav Friedmann, PhD, MD

Pain Therapeutics, Inc.

Email: nfriedmann@paintrials.com

Phone: 925-788-4585

Do not delay reporting a suspected SAE to obtain additional information. Any additional information, if collected, can be reported to the Sponsor as a follow-up to the initial report.

A completed SAE report form must be faxed within five working days to the medical monitor. SAEs must also be reported to the responsible EC/IRB immediately.

In the case of a death or other SAE that has occurred within 30 days after receiving study drug, the Principal Investigator must also report such an event within 24 hours of being notified. Your local EC/IRB may also require these reports.

In the event of any SAE (other than death), the subject will be instructed to contact the study physician (Principal Investigator or designee) using the phone number provided in the Informed Consent Form. All subjects experiencing an SAE will be seen by a Principal Investigator or designee as soon as feasible following the report of an SAE.

10. STATISTICAL CONSIDERATIONS

10.1. RANDOMIZATION

Subjects will be assigned to PTI-125 or placebo based on a computer-generated randomization schedule prepared prior to the study. Pain Therapeutics, Inc. (PTI) will interact with the pharmacy to have study drug for each subject labeled according to this randomization code. Randomization Numbers will be used as subject code numbers and will be assigned when qualified subjects are randomized.

The randomization code will not be revealed to study subjects, investigators, clinical staff or study monitors until all subjects have completed therapy and the database has been finalized and closed.

Under normal circumstances, the blind should not be broken. The blind may be broken only if specific emergency treatment is indicated. The date, time and reason for the unblinding must be documented on the case report form, and the medical monitor must be informed as soon as possible.

10.2. ANALYSIS POPULATIONS

All subjects who receive study medication will be included in safety analyses. All subjects who have sufficient data for PK analysis will be included in the PK analysis population.

10.3. PHARMACOKINETIC PARAMETERS

PK parameters for PTI-125 will be calculated using non-compartmental methods in WinNonlin. The peak drug concentration (C_{max}), the time to peak drug concentration (T_{max}), T_{last} and C_{last}, the time to and concentration of the last quantifiable drug concentration, will be obtained directly from the data without interpolation. The following parameters will be calculated: the elimination rate constant (λ_z), the terminal elimination half-life ($T_{1/2}$), the AUC from time zero to the time of the last quantifiable concentration (AUC_{last}), the AUC from time zero extrapolated to infinity (AUC_{inf}), and the percentage of AUC_{inf} based on extrapolation (AUC_{extrap}(%)), Cl/F, the apparent oral clearance, and Vz/F, apparent volume of distribution.

In the pharmacokinetic analysis, BLQ concentrations will be treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations will be treated as “missing”. Full precision concentration data (not rounded to three significant figures) and actual sample times will be used for all pharmacokinetic and statistical analyses. Nominal sampling times will be used to prepare concentration versus time profiles.

10.4. STATISTICAL ANALYSIS

Comparison of the PK parameters C_{max}, AUC_{last}, and AUC_{inf} for PTI-125 between treatments will be done using an analysis of variance (ANOVA) model with factors for period and treatment. T_{max} will be compared among groups using a non-parametric analysis (Wilcoxon Rank Sum or Signed Ranks tests).

10.5. SAFETY ANALYSIS

Adverse events reported on case report forms will be mapped to preferred terms and organ systems using the MedDRA mapping system. Vital signs and clinical laboratory results will be descriptively summarized in terms of change from screening values.

10.6. SAMPLE SIZE

2 4 subjects will be enrolled in this study. Sample size was determined by estimating the intrasubject variability for log-transformed data from previous studies of new chemical entities (NCEs).

11. STUDY TERMINATION

The study will be terminated following completion of the study or at any time at the discretion of the Sponsor.

12. DATA COLLECTION, RETENTION AND MONITORING

12.1. CASE REPORT FORMS

Case report forms (CRFs) will be provided for each subject. The subjects in the study will not be identified by name on any study documents to be collected by the Sponsor (or CRO designee), but will be identified by a Screening Number and Randomization Number.

All clinical information requested in this protocol will be recorded in electronic CRFs.

CRFs must be reviewed and verified for accuracy by the Principal Investigator and signed-off before collection by the Sponsor (or CRO designee). A copy of the CRF will remain at the Investigator's site at the completion of the study.

12.2. AVAILABILITY AND RETENTION OF INVESTIGATIONAL RECORDS

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee) and Regulatory Agency

(e.g., FDA) inspectors upon request. To assure accuracy of data collected in the CRFs, it is mandatory that Sponsor representatives have access to original source documents (e.g., subject records, subject charts, and laboratory reports). During review of these documents, the subject's anonymity will be maintained with adherence to professional standards of confidentiality and applicable laws. A file for each subject must be maintained that includes the signed Informed Consent Form and all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

Investigators are required to maintain all study documentation until notification by PTI that any records may be discarded.

The Investigator is responsible for maintaining adequate case histories in each subject's source records. The Sponsor reserves the right to terminate the study for the Investigator's refusal to supply source documentation of work performed in this clinical trial.

12.3. SUBJECT CONFIDENTIALITY

All reports and subject samples will be identified only by Study Identification Number and initials to maintain subject confidentiality. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

12.4. LIABILITY

In the event of a side effect or injury, appropriate medical care as determined by the Investigator or his/her designated alternate will be provided.

If a bodily injury is sustained, resulting directly from the use of the study drug, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and his/her staff. No other compensation of any type will be provided by the study Sponsor. Financial compensation for lost wages, disability or discomfort due to the study is not available.

12.5. ETHICAL AND LEGAL ISSUES

The Investigator and site personnel are responsible for conducting this study in accordance with the ICH, GCP, and all other applicable laws and regulations.

12.5.1. Ethics Committee/Institutional Review Board

The protocol and Informed Consent Form must be approved by an EC/IRB before the study is initiated. The EC/IRB must comply with U.S. CFR 21 Part 56 and local regulations.

Documentation of EC/IRB approval must be provided to the Sponsor. Investigators are responsible for the following:

- Obtaining EC/IRB approval of the protocol, Informed Consent Form, and any advertisements to recruit subjects and EC/IRB approval of any protocol amendments and Informed Consent Form revisions before implementing the changes.
- Providing the EC/IRB with any required information before or during the study.
- Submitting progress reports to the EC/IRB, as required, requesting additional review and approval, as needed; and providing copies of all relevant EC/IRB communications to the Sponsor.
- Notifying the EC/IRB within 15 calendar days of all SAEs and unexpected AEs related to study medications reported by the Sponsor to the Investigator.

12.6. INFORMED CONSENT FORM

The Sponsor (or designee) must review the Investigator's proposed Informed Consent Form prior to EC/IRB submission for approval. An EC/IRB-approved copy of the Informed Consent Form is forwarded to the Sponsor.

The Informed Consent Form documents study-specific information the Investigator provides to the subject and the subject's agreement to participate. The Investigator explains in plain terms the nature of the study along with the aims, methods, anticipated benefits, potential risks, and any discomfort that participation may entail. The Informed Consent Form must be signed and dated before the subject enters the study. The original Informed Consent Form and any amended Informed Consent Form, signed and dated, must be retained in the subject's file at the study site and a copy must be given to the subject.

13. INVESTIGATOR RESPONSIBILITIES

The Investigator agrees to:

- Conduct the study in accordance with the protocol and only make changes

after notifying the Sponsor, except to protect the safety, rights, or welfare of subjects

- Personally conduct or supervise the study
- Inform any subjects or individuals used as controls that the drug is being used for investigational purposes
- Ensure that requirements related to obtaining informed consent and EC/IRB review and approval comply with ICH, CFR 21 Parts 50 and 56, and local laws.
- Report to the Sponsor any AEs that occur during the study in accordance with ICH, CFR 21 Part 312.64 and local laws
- Read and understand the Investigator's Brochure including potential risks and side effects of the drug.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate records in accordance with ICH, 21 CFR Part 312.62, and local laws and have records available for inspection by the Sponsor, FDA, or other authorized agency.
- Ensure that EC/IRB complies with requirements of ICH, 21 CFR Part 56, and local laws and will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the EC/IRB and the Sponsor all changes in research activity and unanticipated problems involving risks to subjects or others (including amendments and expedited safety reports).
- Comply with all other requirements regarding obligations of Clinical Investigators and all other pertinent requirements listed in ICH, 21 CFR Part 312 and local laws.

14. APPENDIX A

Events Schedule

PROCEDURE	SCREENING (Day -28 to Day -1)	CHECK-IN (Day 0)	DAY 1 Time=0	DAYS 2 & 3	DAY 4 (72 Hours)	DAY 7
Informed consent	X					
Medical and medication histories	X	X				
ECG	X		X	X	X	X
Vital signs	X	X	X	X	X	X
Physical examination	X	Brief		Brief [b]	Brief	X
Biochemistry, hematology, urinalysis	X		X	X[b]		X
FSH (female participants claiming post-menopausal status only)	X					
Urine cotinine screen	X	X				
Urine drug screen[a]	X	X				
Ethanol breath test	X	X				
HIV test	X					
HBsAg and HCV Antibody	X					
Drug administration			X			
Blood sample collection for PK analysis			X	X	X	
Adverse events			X	X	X	X
Discharge					X	

a. amphetamines, barbituates, benzodiazepines, cocaine, opiates and cannabinoids
b. 24 h post dose

15. APPENDIX B

INFORMED CONSENT DOCUMENT

AGREEMENT TO BE IN A RESEARCH STUDY

NAME OF SPONSOR COMPANY: Pain Therapeutics, Inc.

PROTOCOL NUMBER AND TITLE OF STUDY: **PTI-125-01: "A Phase I, Single Center, Randomized, Double-blind, Placebo-controlled, Three-Period Single Ascending Dose, Pharmacokinetic and Safety Study of PTI-125 in Healthy Volunteers"**

NAME OF PERSON IN CHARGE OF THE RESEARCH STUDY (STUDY DOCTOR/INVESTIGATOR): George J. Atiee, M.D.

TELEPHONE NUMBER(S), DAYTIME: (210) 635-1500 (Monday-Friday, 8:00 a.m.-5:00 p.m.)
AFTER HOURS: (210) 426-5342

INTRODUCTION

You are being invited to volunteer for a medical research study. You must read and sign this form before you agree to take part in this study. This form will give you more information about this study. Please ask as many questions as you need to before you decide if you want to be in the study. You should not sign this form if you have any questions that have not been answered.

The investigator is being paid by the sponsor (the company paying for this study) to conduct this research study.

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

THIS IS THE FIRST STUDY IN WHICH THE STUDY DRUG IS BEING GIVEN TO HUMANS.

PURPOSE OF THE STUDY

In this document, you may see the terms "medication", "treatment", and "treatment period"; these are terms used in research studies as mentioned above. This does not mean that you will be receiving

medical treatment for any condition. These terms apply to the investigational study drug and parts of the study where you will be receiving this investigational product.

The purpose of this study is to measure the blood levels of Pain Therapeutics, Inc.'s new investigational drug PTI-125, and to determine if there are any side effects associated with the drug. PTI-125 is intended to slow the progression of Alzheimer's disease as well as provide some cognitive recovery.

"Investigational" means the study drug being tested is not approved by the United States Food and Drug Administration (FDA).

If you qualify for the study, you will receive three doses of PTI-125 (investigational product), listed below, or three doses of placebo. Each dose (active or placebo) will be separated by a 3-day drug-free (washout) period. The first two subjects (sentinel group) in the group will receive the first dose of study drug or placebo and the rest of the group will receive their assigned dose at least 24 hours later unless it is determined that an additional sentinel group is necessary.

- A single 50 mg dose of oral solution of PTI-125 or placebo oral solution
- A single 100 mg dose of oral solution of PTI-125 or placebo oral solution
- A single 200 mg dose of oral solution of PTI-125 or placebo oral solution

Placebo contains no active ingredient.

This is a double-blind study, which means that neither you nor the investigator will know whether you are taking PTI-125 or placebo. The study staff can get this information if needed.

Whether you receive PTI-125 or placebo will be assigned by chance, like the flip of a coin.

HOW LONG THE STUDY WILL LAST AND HOW MANY PEOPLE WILL BE IN THE STUDY

The study will last about 11 days, excluding the screening period, and involve up to 10 nights at the facility. About 16 healthy men and women, ages 18 through 45, are expected to be in this study.

TO BE IN THIS STUDY

You cannot be in this study if you:

- Are in another research study or if you have been in any other research study in which you received study drug within 30 days before the first dose of study formulation
- Are taking any drugs of abuse (illegal and/or prescription). A urine test will be performed to check for the use of these drugs. You may be observed during any urine sample collection process.
- Have donated blood within 4 weeks before the first dose of study formulation

Subject Responsibilities:

While participating in this research study, you will need to:

- Be willing and able to follow the study directions and procedures
- Tell the study staff about any side effects or problems
- Ask questions as you think of them
- Tell the investigator or the study staff if you change your mind about staying in the study.

This study involves testing an investigational drug developed by the sponsor. We ask subjects to keep information as confidential as possible. This would include not sharing details of the study, including requirements for participation, information received on the risks and benefits of dosing with this study drug, and symptoms or reactions to study drug dosing while enrolled in the study, with persons other than the clinic staff, your family and your healthcare provider. This would also include not disclosing such information on social media sites or webpages.

WHAT WILL HAPPEN DURING THE STUDY

Screening

Before the study starts, you will be asked to sign this consent form, give your health and social history, and tell study staff if you take any over-the-counter or prescription medicines, vitamins, or herbs.

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

- Physical exam, including vital signs (blood pressure, temperature, heart and breathing rates), height and weight
- An electrocardiogram (ECG) will be taken - this is a recording of the electrical activity of your heart
- Lab tests (blood and urine)
- Blood test for HIV and hepatitis B and C
- Urine test for drugs of abuse (illegal and/or prescription) and cotinine (tobacco)
- Alcohol breath test will be done
- Urine pregnancy tests for female participants of childbearing potential

The Screening Visit may take up to 2 hours and 30 minutes of your time.

If you qualify for the study, you will return to the clinic for the three Treatment Periods. If you are more than 1 hour late to your study check in, you may be placed in alternate/backup status.

Study Procedures

Prior to Treatment Period 1

The following will be done prior to the first of three Treatment Periods (each of three doses will be separated by 3 days):

- You will be asked questions to be sure that you still qualify for this study
- You will be asked about any changes in your health or drugs you have taken since your last visit
- Vital signs (blood pressure, heart rate, breathing rate and temperature) will be taken prior to receiving each dose of study drug
- If you are female of childbearing potential, a urine pregnancy test will be performed at check in
- A urine sample will be taken at check in – the urine tests will include finding out if you have used any cotinine or drugs of abuse (illegal and prescription). You may be observed during any urine sample collection process.
- An alcohol breath test will be done at check-in to ensure you have not recently consumed alcohol
- An optional snack will be given the evening of check-in at the clinic

Treatment Periods 1, 2 and 3

- Standard meals will be given at scheduled times during each stay in the clinic
- You will have to fast (nothing to eat or drink except water) for at least 10 hours before taking study drug and for 4 hours after dosing
- You will be randomly assigned, like the flip of a coin, to take PTI-125 or placebo.
- You will take an oral solution of the assigned study drug or placebo. The study staff will perform a mouth check to ensure that the solution is swallowed completely.
- Aside from the oral solution and two rinses of the dosing syringe with water, you may not drink any other water from 1 hour before dosing through 1 hour after dosing. At other times during the study, you can drink water.
- After taking the study drug you will not be allowed to lie down for the first 1-2 hours and must stay seated during that time
- The level of study drug in your blood will be measured. About 3/4 teaspoon (4 mL) of blood will be taken at multiple time-points during your stay in the study clinic
- Vital Signs (temperature, blood pressure, heart rate and breathing rate) will be performed at multiple time points during the study
- A physical exam will be conducted at 48 hours after each dose of study drug or placebo
- An electrocardiogram (ECG; a recording of the electrical activity of your heart) will be conducted at 48 hours after each dose of study drug or placebo.
- Lab tests (blood and urine)
- You will be monitored for any side effects

If you leave the study early or are withdrawn the following procedures will be performed:
- Vital Signs (temperature, blood pressure, heart and breathing rates)
- Physical examination
- Lab tests (blood and urine)
- Electrocardiogram (ECG)

<u>Blood Samples</u>:

Blood samples will be taken by single needle-sticks or by a tube that is left in your arm. You cannot choose how the blood is taken.
There will be about 41 blood draws. The total amount of blood drawn will be about 227 mL, or about 1 cup. For comparison, the standard blood donation is about 480 mL (two cups). Additional blood may be drawn and additional tests performed for your safety.

HIV AND HEPATITIS TESTING

As required by the study and if any person is exposed to your blood, 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. The HIV test is not always right.

We are required to report positive HIV test results to the San Antonio Metro Health District. We may also be required to report positive hepatitis test results to the San Antonio Metro Health District. Positive test results may be required to be reported to the State Department of Health. If you have any questions about what information is required to be reported please ask the investigator or study staff.

Although this testing is supposed to be private, this cannot be guaranteed. For example, it is possible for a court of law to get health or study records without your permission.

Additionally, in the unlikely event that a study employee has been exposed to your blood or other body fluid either through a needle stick injury, splash incident or contact with broken skin (i.e., cut, bite), additional samples may be collected to determine and confirm whether or not you have a certain infection. Your de-identified results will be released to the injured employee, and to the health care provider evaluating and treating that employee, to aid the injured employee and the medical provider make decisions regarding his/her medical treatment and follow-up care as a result of this on-the-job exposure.

POSSIBLE SIDE EFFECTS AND RISKS

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

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

In pre-clinical (animal studies) the following side effects were seen:

- Vomiting
- Increased salvation
- Increased blood pressure
- Weight loss
- Changes to the size of the liver cells

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

All drugs may cause allergic reactions in some people. Below is a list of symptoms of an allergic reaction:

- Swelling of the face, lips, throat, and other areas of the skin
- Difficulty swallowing or breathing
- Raised, red areas on your skin
- Skin rash, itching, flaking, or peeling

If you have a side effect of the drug, such as a skin rash or other visible injury, it might be useful to take a digital picture of the affected area to send to the sponsor. By signing this consent, you authorize the study doctor or study staff to take such a picture and provide it to the sponsor. Every effort will be made to protect your identity if a photograph is necessary.

ADDITIONAL RISKS OR DISCOMFORTS

Blood Samples (taken by single needle-sticks or by a tube that is left in your arm):

There may be side effects of having blood drawn such as:

- Fainting
- Redness
- Pain
- Bruising
- Bleeding
- Infection
- Blood clots, which may cause inflammation, swelling and pain
- Nerve damage

If you feel faint tell the study staff right away.

Risks of Using an Intravenous (IV) Catheter for blood draws:

- Infection
- Pain
- Redness
- Bruising
- Vein irritation from the fluids or medication being given
- Local swelling due to IV fluid (saline) accidentally entering the tissue rather than the vein
- Blood clots, which may cause inflammation, swelling and pain

Electrocardiogram (ECG):

The ECG test is a recording of the electrical activity of your heart. The sticky pads used may be cold when applied and sometimes cause some discomfort such as redness or itching. If the hair under the patches needs to be shaved, irritation from shaving also could occur.

Fasting

Fasting could cause dizziness, headaches, stomach discomfort or fainting

Pregnancy/Birth Control

Participation in this study may involve unforeseen risks to you or your baby if you become pregnant during the study. Females must not be able to physically have children or must use an appropriate method of birth control, as described below.

If you are a man, it is suggested that you use birth control if you choose to have sex with women while in this study.

Methods of birth control for this study include:

- Postmenopausal (at least 1 years before dosing)
- Surgical sterilization (bilateral tubal ligation – tubes tied, hysterectomy – removal of the uterus, bilateral oophorectomy – removal of both ovaries) at least 6 months before dosing
- Double barrier (diaphragm with spermicide; condoms with spermicide)
- Intrauterine device (IUD)
- Implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months before study dosing and throughout the study duration
- Oral, patch, or injected contraceptives, or vaginal hormonal device (i.e. NuvaRing®), in use for at least 3 consecutive months before study dosing and throughout the study duration

If you are a woman and have discontinued the use of implanted, intrauterine, or injected hormonal contraceptives, you must not have used any within 6 months before the first dose of study drug.

If you are a woman and have discontinued the use of oral, patch, or vaginal hormonal contraceptives, you must not have used any within 3 months before the first dose of study drug.

Even if you use birth control during the study, there is a chance you could become pregnant. You cannot be in the study if you are pregnant. If you are pregnant or become pregnant during the study, the study drug may involve unforeseeable risks to the unborn baby.

A pregnancy test can be wrong, especially if it is early in the pregnancy. If you become pregnant during the study, inform the investigator at once.

You cannot be in the study if you are breastfeeding. It is not known whether the study drug is safe for breast fed babies.

POSSIBLE BENEFITS OF THE STUDY

You will get no medical benefit from this study. You may receive a chance to be in a research study that may help others.

16. ALTERNATIVES TO PARTICIPATING IN THE STUDY

Since this study is for research only, the only other choice would be not to be in the study.

CONFIDENTIALITY

Your records of being in this study will be kept private except when ordered by law. The following people will have access to your study records:

- The investigator
- Sponsor company or research institution [including monitor(s) and auditor(s)]
- The United States Food and Drug Administration (FDA)
- Other state or federal regulatory agencies
- IntegReview IRB

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

IN CASE OF STUDY RELATED INJURY

If you are injured while in this study, you should contact the study investigator as soon as possible in person or at the telephone number listed on page one of this consent form. Medical care may be obtained in the same way you would ordinarily obtain other medical treatment. If you suffer a study-related injury, the reasonable costs of necessary medical treatment of the injury will be reimbursed by the study sponsor to the extent these costs are not covered by your insurance or other third party coverage. **No other form of compensation is offered**. A study-related injury is a physical injury that is directly caused by the study drug given as described in the study protocol or by medical procedures that are required by the study and that are not standard of care.

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

LEGAL RIGHTS

You will not lose any of your legal rights by signing this consent form.

CONTACT INFORMATION

If you have questions, concerns, or complaints about this study or to report a study related injury, contact:

George J. Atiee, M.D., or a member of the study staff at
(210) 635-1500, Monday-Friday between 8:00 am-5:00 pm
(210) 426-5342 after hours

If you feel this emergency may be life-threatening, call 911.

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

If you do not want to talk to the investigator or study staff, if you have concerns or complaints about the research, or to ask questions about your rights as a study subject you may contact IntegReview. IntegReview's policy indicates that all concerns/complaints are to be submitted in writing for review at a convened IRB meeting to:

Mailing Address:	OR	Email Address:
Chairperson IntegReview IRB 3815 S. Capital of Texas Highway Suite 320 Austin, Texas 78704		integreview@integreview.com

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

512-326-3001 or

toll free at 1-877-562-1589

between 8 a.m. and 5 p.m. Central Time

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

PAYMENT FOR BEING IN THE STUDY

You may receive up to $2000.00 for being in this study. This money covers the costs for time spent at the clinic and is to help cover travel expenses to and from Worldwide Clinical Trials. If you choose to leave or are withdrawn by the study staff before finishing all study procedures, you will be paid a lesser amount that is based on the completed visits made to Worldwide Clinical Trials. If you take study drug, you will be paid as listed below, for each completed visit:

- $150.00 for each overnight stay (10 total)

If you successfully complete the entire study, you will receive up to an additional $500.00:

- $500.00 for completion of entire study (all visits)

You will not be paid for the screening visit.

Should you be required to stay additional time in the research unit for safety follow up you will be compensated for your time based on the overnight compensation of $150.00 per overnight.

No other payment will be offered to you. You will receive your payment within two weeks of your final study visit.

If you are a backup subject who has to stay the night in the clinic, you will be paid $75.00. If you do not have to stay the night, you will be paid $25.00.

You must follow the Worldwide Clinical Trials inpatient clinic rules of conduct while you are taking part in this study. If you do not follow the rules, part of your payment (not to exceed the amount of the additional payment) may be taken away. You may not be able to take part in other studies at Worldwide Clinical Trials. These rules will be reviewed with you at the screening visit and are available on the Worldwide Clinical Trials website.

You may be required to report the payment received for this study to the Internal Revenue Service as taxable income.

VOLUNTEERING TO BE IN THE STUDY

It is your choice if you want to be in the study. No one can force you to be in the study. You may not want to be in this study or you may leave the study at any time without penalty or loss of benefits to which you are otherwise entitled. If you break the study rules you may be discontinued from this study. If you break the study rules leaving the impression you may not be a compliant participant you may not be allowed to participate in Worldwide Clinical Trials studies for a period of time or in some cases you may not be allowed to participate in any future Worldwide Clinical Trials studies. All participants are considered a back-up until told otherwise. No one can be sure they will be in a study.

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

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

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

ADDITIONAL COSTS

There is no cost to you during the study for any of the following:

- Any study test or procedure, including physical exam and blood tests
- Study drug

NEW FINDINGS

If there is new information or any significant new findings that could relate to your willingness to continue participation we will tell you. You can then decide if you still want to be in the study.

THE REASON FOR INSTITUTIONAL REVIEW BOARDS AND INFORMED CONSENT

What is a consent form?
The informed consent document contains information required by federal regulations. The informed consent document must be approved by an Institutional Review Board (IRB).

What is an Institutional Review Board (IRB)?
An Institutional Review Board (IRB) is a group of people that reviews research studies. The main goal of this review is to protect the rights and well-being of the human subjects participating in research studies.

IntegReview, the IRB for this study
IntegReview is an IRB whose board members provide IRB services across the United States, Canada, Latin America, and Japan.

To meet requirements of the law, the IntegReview Boards currently include:

- Doctors
- Pharmacists
- Nurses
- Toxicologists (people who study the harmful effects of chemicals)
- Other specialists
- Others who do not have a background in science/medicine

AGREEMENT TO BE IN THE STUDY

This consent form contains important information to help you decide if you want to be in the study. If you have any questions that are not answered in this consent form, ask one of the study staff.

Please answer **YES** or **NO** to the following questions:

A. Is this document in a language you understand? _____

B. Do you understand the information in this consent form? _____

C. Have you been given enough time to ask questions and talk about the study? _____

D. Have all of your questions been answered to your satisfaction? _____

E. Do you think you received enough information about the study? _____

F. Do you volunteer to be in this study of your own free will and without being pressured by the investigator or study staff? _____

G. Do you know that you can leave the study at any time without giving a reason and without affecting your health care? _____

H. Do you know that your health records from this study may be reviewed by the sponsor company and by government authorities? _____

I. Do you know that you cannot be in another study while you are in this study? _____

IF YOU ANSWERED "NO" TO ANY OF THE ABOVE QUESTIONS,
OR YOU ARE UNABLE TO ANSWER ANY OF THE ABOVE QUESTIONS,
YOU SHOULD NOT SIGN THIS CONSENT FORM.

You will be given a signed and dated copy of this consent form to keep.

_____
Printed Name of Adult Study Subject

_____
Signature of Adult Study Subject Date Time (24-hour clock)

_____
Printed Name of Person Explaining Consent Form

_____
Signature of Person Explaining Consent Form Date Time (24-hour clock)