CSF

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

CLINICAL RESEARCH PROTOCOL

PROTOCOL PTl-125-03

A Phase 2a, Open-label, Multiple Dose, Safety, Pharmacokinetic and Biomarker Study of PTl-125 in Mild-to-moderate Alzheimer's Disease Patients

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Protocol Date:	October 12, 2018
Amendment #1:	October 30, 2018
Amendment #2:	February 5, 2019

This clinical trial is funded by NIH grant AG060878.

Confidentiality

Pain Therapeutics, Inc.
CLINICAL RESEARCH PROTOCOL

A Phase 2a, Open-label, Multiple Dose, Safety, Pharmacokinetic and Biomarker Study of PTl-125 in Mild-to-moderate AD patients

SUMMARY OF PROTOCOL AMENDMENT #2

The purpose of protocol amendment #2 is:

- to reduce the amount of CSF withdrawn during lumbar puncture at Screening and on Day 28

Section 7.1.1 – Screening Period
Changed from:
If meeting all other criteria:

- CSF sample collection (10 mL)
- BEHAVE-AD test

Changed to:
If meeting all other criteria:

- CSF sample collection (**5 mL**)
- BEHAVE-AD test

Section 7.1.5 Day 28 Follow-up Visit
Changed from: CSF sample collection (10 mL) on Study Day 28 will occur 1-2 h after dosing, and the nearest plasma PK sample collection will be noted. The CSF samples will be tested for PTI-125 levels as well as the Aβ/tau Index, YKL40, inflammatory cytokines and other biomarkers.

Changed to: CSF sample collection (**5 mL**) on Study Day 28 will occur 1-2 h after dosing, and the nearest plasma PK sample collection will be noted. The CSF samples will be tested for PTI-125 levels as well as the Aβ/tau Index, YKL40, inflammatory cytokines and other biomarkers.

Section 7.2.4 CSF Assays
Changed from: CSF samples should be split, with 5 mL of all samples shipped to Dr. Wang at CUNY and, for Day 28 only, an additional 1 mL shipped to Worldwide Clinical Trials. The remaining 4-5 mL will be retained at the study site at -20°C until otherwise informed by the Sponsor. All samples will be shipped frozen on dry ice.

CSF samples (1.0 mL) from Study Day 28 will be shipped to Worldwide Clinical Trials Bioanalytical Sciences (8609 Cross Park Drive, Austin, TX 78754) to be assayed for the PTI-125 analyte using a qualified assay.

Changed to: CSF samples should be split, with **2.5 mL** of all samples shipped to Dr. Wang at CUNY and, for Day 28 only, an additional **0.5** mL shipped to Worldwide Clinical Trials. The remaining **2.0** mL will be retained at the study site at -20°C until otherwise informed by the Sponsor. All samples will be shipped frozen on dry ice.

CSF samples (**0.5 mL**) from Study Day 28 will be shipped to Worldwide Clinical Trials Bioanalytical Sciences (8609 Cross Park Drive, Austin, TX 78754) to be assayed for the PTI-125 analyte using a qualified assay.

Pain Therapeutics, Inc.

CLINICAL RESEARCH PROTOCOL

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SUMMARY OF PROTOCOL AMENDMENT #1

The purpose of protocol amendment #1 is:

- to require FSH testing at screening for certain females
- to add possible FSH test, caregiver information and a caregiver signature to the consent form

Section 5.2 – Inclusion Criteria, Number 5
Changed from:
If female, postmenopausal for at least 1 year
Changed to:
Females should be of non-childbearing potential. Non-childbearing potential is defined as postmenopausal (last natural menses > 24 months) or surgically sterile by a documented bilateral tubal ligation or hysterectomy. If last menses < 24 months or uncertain, post-menopausal status should be confirmed by serum FSH.

Section 7.1.1 Screening Period
Changed to add: If female and last natural menses < 24 months or uncertain, post-menopausal status should be confirmed by serum FSH.

Section 7.1.1 Screening Period

1. **Changed to add:** NOTE: For patients determined by C-SSRS to have suicidality tendencies, inform the patient's primary care physician and refer the patient for follow-up.

Appendix A– Events Schedule
Changed to add: Possible FSH test at screening

Appendix B – Informed Consent Document, Page 35
Changed to add:
CAREGIVER PARTICIPATION

As required by the study, every patient must have a caregiver/study partner to participate with them in the study. A caregiver/study partner is a person who spends sufficient time with the study subject so that you can provide certain information. The caregiver/study partner must

have the ability to:

- Observe the subject for any changes in health/possible side effects or cognitive function throughout the study
- Report and assist with the subject's compliance with study procedures and medications.
- Accompany the subject to all study visits and procedures (e.g. lumbar puncture).
- Reliably answer interview questions regarding the subject's medical condition, medication use, daily functioning, behaviors, and how he or she feels.

The caregiver/study partner may be compensated for time and travel as per the compensation table. As a caregiver/study partner, you will not receive any direct benefit by taking part in this study. Information from this study may also help researchers come up with new tests or medicines in the future to help people with Alzheimer's disease.

Entering a research study is completely voluntary. Although a caregiver/study partner is required for participation, a caregiver/study partner can decide to stop at any time and a replacement will need to be identified. If the caregiver/study partner withdraws from the study, you will only be paid for the study visits completed.

If you have any questions about being a caregiver/study partner in this study, you should ask the study doctor or study staff.

Appendix B – Informed Consent Document, Screening Page 36
Changed to add: If female and last natural menses < 24 months or uncertain, post-menopausal status will be confirmed by serum FSH.

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Appendix B – Informed Consent Document, Page 46
Changed to add:
Printed Name of Caregiver/Study Partner

Signature of Caregiver/Study Partner	Date	Time (24-hour clock)

Printed Name of Person Explaining Consent Form

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

Pain Therapeutics, Inc.

CLINICAL RESEARCH PROTOCOL

A Phase 2a, Open-label, Multiple Dose, Safety, Pharmacokinetic and Biomarker Study of PTI-125 in Mild-to-moderate AD patients

Approvals:

Michael Marsman, Pharm D — Date

Regulatory Affairs and QA

Pain Therapeutics, Inc.

Lindsay Burns, PhD. — Date

VP, Neuroscience

Pain Therapeutics, Inc.

Nadav Friedmann, PhD, MD — Date

Chief Operating and Medical Officer

Pain Therapeutics, Inc.

Pain Therapeutics, Inc.

CLINICAL RESEARCH PROTOCOL

A Phase 2a, Open-label, Multiple Dose, Safety, Pharmacokinetic and Biomarker Study of PTl-125 in Mild-to-moderate AD patients

Signature of Agreement for Protocol PTI-125-03

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 Date

_____

Print Principal Investigator Name and Title

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1. LIST OF ABBREVIATIONS

α7nAChR	α7 nicotinic acetylcholine receptor
$A\beta_{42}$	amyloid $beta_{1-42}$
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
BEHAVE-AD	behavioral pathology in Alzheimer's disease rating scale
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DSMB/DMC	Data Safety Monitoring Board/Data Monitoring Committee
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
FDA	Federal Drug Association
FIH	first in human
FLNA	filamin A
GCP	good clinical practice
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
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	insulin receptor
IRB	independent review board
ISLT	International Shopping List Test
LDH	lactose dehydrogenase
LOQ	limit of quantitation

MATE1	multidrug and toxin extrusion protein 1
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NMDAR	N-methyl D-aspartate receptor
NOAEL	no observable adverse effect level
NOEL	no observable effect level
OTC	over-the-counter
PK	pharmacokinetics
PTI	Pain Therapeutics, Inc.
PTI-125	small molecule drug candidate to treat AD
PTI-125DX	blood-based diagnostic/biomarker
QS	quantity sufficient
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SOP	standard operating procedure
Tmax	time to Cmax
ULN	upper limit of normal
WBC	white blood cell
YKL40	chitinase-like protein 1, a secreted glycoprotein associated with inflammation and tissue remodeling

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 an altered conformation of filamin A (FLNA) that is induced by beta amyloid$_{1-42}$ (Aβ_{42}), present in AD brain and critical to the toxicity of Aβ_{42}.[1-3] PTI-125 binding reverses the altered FLNA conformation and restores FLNA's native shape, preventing two toxic signaling cascades of Aβ_{42}. Aβ_{42}, in monomer or small oligomer form, hijacks the α7-nicotinic acetylcholine receptor (α7nAChR) and signals via this receptor to hyperphosphorylate tau, and this signaling requires the recruitment of altered FLNA to this receptor. Second, altered FLNA associates with toll-like receptor 4 (TLR4) to allow Aβ_{42} to aberrantly activate this receptor. Normal FLNA does not associate with either α7nAChR or TLR4. In addition to disrupting the normal functions of α7nAChR and tau protein, Aβ_{42}'s toxic signaling to hyperphosphorylate tau leads to the signature tangles and plaques found in brains of AD patients. In two AD mouse models and in postmortem human AD brain tissue, PTI-125 restored function of three receptors that are impaired in AD: the α7nAChR, the N-methyl-D-aspartate receptor (NMDAR), and the insulin receptor (IR).[2,3] PTI-125 also reduced tau hyperphosphorylation, amyloid deposits, neurofibrillary tangles and inflammatory cytokine release.[2,3] We therefore expect PTI-125 to improve memory and to slow or halt AD progression. Both mouse models used a dose of 20-22 mg/kg/day (equivalent to 60 and 66 mg/m^2/day).

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 including humans. 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 68 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 toxicity study in dogs that included a 28-day drug-free recovery period used 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. A NOEL could not be determined, and the NOAEL was determined to be 100 mg/kg/day (equivalent to 2,000 mg/m^2).

A subsequent 13-week repeat dose oral toxicity study with a 28-day recovery in dogs used doses of 25, 75 and 150 mg/kg/day. The toxicological response was characterized primarily by increased incidence of emesis and salivation (sometimes extreme), and decreased food consumption in 150 mg/kg animals (reversible). There were occasional incidences of muscle fasciculations, and a few isolated incidences of tremors, lying down, reluctance to stand, and hypoactivity (generally slight). Based the severity and time course of these observations, the NOAEL was established at 150 mg/kg/day. The Day 90 C_{max} at this dose was 70.3 and 71.8 µg/mL in males and females, respectively, and the Day 90 AUC_{last} was 456 and 439 h• µg/mL in males and females, respectively.

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 Days 2 and 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.

A first-in-human (FIH) Single Ascending Dose (SAD) clinical trial was conducted in healthy normal volunteers, age 18-45 with oral dosing solution. Doses were 50, 100 and 200 mg (equivalent to 31, 62, and 123 mg/m^2, respectively) administered to three different groups of volunteers. The study showed dose proportional PK, and there were no drug-related adverse events (AEs).

This study in mild-to-moderate AD patients will use a 100 mg b.i.d. dose, based on dog-to-human dose exposure scaling between both 28-day and 13-week repeat dose oral toxicity studies in dog and the exposure levels from the SAD study in volunteers. Safety margins of the human exposure levels from 50, 100 and 200 mg by C_{max} over the NOAEL in the 13-week dog study were 55-fold for the 200 mg dose and ≥125-fold for the 100 mg dose by C_{max} or $AUC_{0\text{-}last}$. Additionally, an accumulation ratio using elimination rate constants from the SAD study predicted minimal accumulation with b.i.d. dosing.

3. STUDY OBJECTIVES

The objectives of this study are to investigate the safety, pharmacokinetics and effect on biomarkers of PTI-125 following 28-day repeat-dose oral administration in mild-to-moderate AD patients, 50-85 years of age, within an MMSE range of ≥ 16 and ≤ 24.

4. SUMMARY OF STUDY DESIGN

This is a Phase 2a, multi-center, open-label study of PTI-125 in mild-to-moderate AD patients, 50-85 years of age. A total of twelve (12) patients will be enrolled into the study. Patients will receive 100 mg b.i.d. of PTI-125.

The study includes a screening period (Day -30 to Day -1). Patients meeting initial screening criteria, including a Mini-Mental State Examination (MMSE) score ≥ 16 and ≤ 24 will subsequently undergo a CSF draw at a second screening visit to confirm that the Aβ/tau Index is indicative of AD (final inclusion criterion). This CSF sample will also serve as baseline measurement for the YKL40 neuroinflammation and other potential CSF biomarker assays. The BEHAVE-AD psychological test and the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered during this second screening visit, and on Day 28 (and for BEHAVE-AD, also on Day 14).

Patients will report to clinic on Study Day 1 and will return for visits on Days 7, 14, 28 and 29.

PK blood samples will be obtained prior to the first and last doses (Day 1 and Day 28) and at timepoints through 24 h after the first and last dose. Additional PK blood samples will be obtained prior to the first dose on Days 7 and 14 for C_{min} values. PK parameters will be calculated using non-compartmental analysis.

Clinical laboratory testing (blood and urine) will be performed at screening, prior to dosing on Day 1, and on Days 7, 14 and 29. Safety assessments of vital signs and listening to heart and lungs and ECGs will also be conducted on Days 7 and 14. Baseline and final ECGs will be conducted on Day 1 (pre-dose) and on Day 29, respectively.

Blood samples for testing in PTI-125DX, the companion diagnostic/biomarker, mTOR activation and other potential blood-based biomarkers will be drawn on Day 1 (pre-dose), Day 14 and Day 28. A CSF sample collection will be performed on Day 28 for Aβ/tau, YKL40 and other potential CSF biomarker assays as well as bioanalysis of PTI-125.

An independent Data Safety Monitoring Board/Data Monitoring Committee (DSMB/DMC) will be established and will meet periodically to review patient safety assessments and determine if dosing may continue.

5. SUBJECT SELECTION

5.1. STUDY POPULATION

A total of twelve (12) patients will be enrolled in the study (male and female).

5.2. INCLUSION CRITERIA

Each patient must comply with the following Inclusion Criteria:

1. Ages ≥ 50 and ≤ 85 years
2. Informed consent form (ICF) signed by the subject or legally acceptable representative. If a legally acceptable representative signs the ICF, a notation of capacity of the subject must be noted.
3. Clinical diagnosis of dementia due to possible or probable AD consistent with criteria established by a workgroup of the National Institute on Aging and the Alzheimer's Disease Association.
4. MMSE score ≥ 16 and ≤ 24 at screening
5. If female and last natural menses < 24 months or uncertain, post-menopausal status should be confirmed by serum FSH.
6. Patient living at home, senior residential setting, or an institutional setting without the need for continuous (i.e. 24-h) nursing care
7. General health status acceptable for participation in the study
8. Fluency (oral and written) in English or Spanish
9. If receiving memantine, rivastigmine, galantamine or an AChEI, receiving a stable dose for at least 3 months (90 days) before screening and with continuous dosing for at least 3 months. If receiving donepezil, receiving any dose lower than 23 mg once daily.
10. The patient is a non-smoker for at least 12 months.
11. The patient or legal representative must agree to comply with the drawing of blood samples for the PK assessments, laboratory assessments and PTI-125DX and with a lumbar puncture and the drawing of CSF samples for biomarker assessments.
12. The patient has an Aβ/tau Index in CSF that indicates AD. This value (total tau/$A\beta_{42}$) will be ≥ 0.30.
13. Patient has a caregiver or legal representative responsible for administering the drug and recording the time.

5.3. EXCLUSION CRITERIA

Patients meeting any of the following criteria will be excluded from the study:

1. Exposure to an experimental drug, experimental biologic or experimental medical device within the longer of 5 half-lives or 3 months before screening
2. Residence in a skilled nursing facility
3. Clinically significant laboratory test results
4. Clinically significant untreated hypothyroidism (if treated, thyroid-stimulating hormone level and thyroid supplementation dose must be stable for at least 6 months before screening)
5. Insufficiently controlled diabetes mellitus or requiring insulin
6. Renal insufficiency (serum creatinine >2.0 mg/dL)
7. Malignant tumor within 3 years before screening (except squamous and basal cell carcinoma or cervical carcinoma in situ or localized prostate cancer or localized stage 1 bladder cancer)
8. History of ischemic colitis or ischemic enterocolitis
9. Unstable medical condition that is clinically significant in the judgment of the investigator
10. Alanine transaminase (ALT) or aspartate transaminase (AST) >2 times the upper limit of normal or total bilirubin greater than the ULN.
11. History of myocardial infarction or unstable angina within 6 months before screening
12. History of more than 1 myocardial infarction within 5 years before screening
13. Clinically significant cardiac arrhythmia (including atrial fibrillation), cardiomyopathy, or cardiac conduction defect (patients with a pacemaker are acceptable)
14. Symptomatic hypotension, or uncontrolled hypertension
15. Clinically significant abnormality on screening electrocardiogram (ECG), including but not necessarily limited to a confirmed QTc value ≥ 450 msec for males or ≥ 470 msec for females.
16. Stroke within 18 months before screening, or history of a stroke concomitant with onset of dementia
17. History of brain tumor or other clinically significant space-occupying lesion on CT or MRI

18. Head trauma with clinically significant loss of consciousness within 12 months before screening or concurrent with the onset of dementia
19. Onset of dementia secondary to cardiac arrest, surgery with general anesthesia, or resuscitation
20. Specific degenerative CNS disease diagnosis other than AD (eg, Huntington's disease, Creutzfeld-Jacob disease, Down's syndrome, Frontotemporal Dementia, Parkinson's disease)
21. Wernicke's encephalopathy
22. Active acute or chronic CNS infection
23. Donepezil 23 mg or greater QD currently or within 3 months prior to enrollment in the study
24. Discontinued AChEI < 30 days prior to enrollment in the study
25. Antipsychotics; low doses are allowed only if given for sleep disturbances, agitation and/or aggression, and only if the subject has received a stable dose for at least 3 months before enrollment in the study
26. Tricyclic antidepressants and monoamine oxidase inhibitors; all other antidepressants are allowed only if the subject has received a stable dose for at least 3 months before enrollment in the study
27. Anxiolytics or sedative-hypnotics, including barbiturates (unless given in low doses for benign tremor); low doses of benzodiazepines and zolpidem are allowed only if given for insomnia/sleep disturbance, and only if the subject has received a stable dose for at least 3 months before enrollment in the study
28. Peripherally acting drugs with effects on cholinergic transmission
29. Immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses (Steroid use for allergy or other inflammation is permitted.)
30. Antiepileptic medications if taken for control of seizures
31. Chronic intake of opioid-containing analgesics
32. Sedating H1 antihistamines
33. Nicotine therapy (all dosage forms including a patch), varenicline (Chantix), or similar therapeutic agent within 30 days before screening
34. Clinically significant illness within 30 days of enrollment
35. History of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease

36. Positive serum hepatitis B surface antigen (HBsAg) or positive hepatitis C virus HCV antibody test at screening
37. Positive HIV test at screening
38. Loss of a significant volume of blood (> 450 mL) within 4 weeks prior to the study
39. Metformin or cimetidine. PTI-125 is a marginal/weak inhibitor of the multidrug and toxin extrusion protein 1 (MATE1) transporter.

6. STUDY DRUG

6.1. PTI-125 PHYSICAL DESCRIPTION AND PREPARATION

Investigational PTI-125 will be supplied by PTI as coated tablets in 20-count bottles.

All remaining PTI-125 study drug will be returned to the sponsor or designee.

6.1.1. Storage

Bottles of PTI-125 tablets should be stored at controlled room temperature, 20-25º C (68-77º F) and protected from light and moisture.

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

Patients will receive 100 mg PTI-125 b.i.d. Study drug should be taken 1-2 h before or after a meal.

6.3. CONCOMITANT MEDICATIONS

Use of prescription or non-prescription medications will be recorded during the study. Chronic medications must be stable for 3 months.

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 patient or legal representative. 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 30 days prior to administration of the study medication:

- Informed Consent. If Informed Consent is signed by a legally authorized representative, patient capacity must be noted.
- Review of Inclusion and Exclusion Criteria
- Medical history
- Review of concomitant medications
- Physical examination, including measurement of vital signs (blood pressure, temperature, pulse and respiratory rate), height, weight.
- A 12-lead ECG (5-min supine).
- Laboratory assessments, including serum chemistry, hematology, urinalysis, and screens for HCV, HIV and HBsAg.
- MMSE evaluation
- If female, negative FSH test if >60 years and last natural menses was < 24 months prior to screening

If meeting all other criteria:

- CSF sample collection (5 mL)
- BEHAVE-AD test

2. Columbia Suicide Severity Rating Scale (C-SSRS) **NOTE:** For patients determined by C-SSRS to have suicidality tendencies, inform the patient's primary care physician and refer the patient for follow-up.

7.1.2. Study Days 1-2 (In-patient)

Note: Study Day 1 is defined as the day of dosing initiation. Clinic visits on Study days 7, 14 and 28 can occur +/- 2 days of the designated day. The clinic visit on Day 29 will immediately follow the Day 28 visit.

Patients will come to the clinic the morning of Study Day 1. Within 1 h prior to dosing, the following assessments will be conducted:

- Confirmation of inclusion/exclusion criteria
- Review of concomitant medications
- Brief physical examination
- ECG
- Blood drawn for PTI-125DX and mTOR assessments (8 mL whole blood)
- Blood sample collection for baseline PK assessment (Sample Time=0)
- Clinical laboratory tests (blood and urine)

Patients will be administered 100 mg PTI-125 b.i.d. 1-2 h before breakfast.

After the first dose on Study Day 1, the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate) at approximately 10 and 30 min, and 1, 2, 4, 8 and 12 h post-dose.
- Blood samples will be drawn at 20, 40, and 60 min and at 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h after the first dose for PK assessments. *Please note that the 12 h PK samples will be collected prior to the second dose.*
- Adverse event monitoring

After the second dose on Study Day 1 (administered 12 h after the first), the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate) at 30 min, 1 and 2 h after this second dose.

On the morning of Study Day 2, within 30 min prior to dosing, the following assessments will be conducted:

- Blood sample collection for PK assessment (for C_{min})
- Clinical laboratory tests (blood and urine)

After dose on Study Day 2, the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate)
- Listen to heart and lungs
- Adverse event monitoring
- ECG

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.

Clinic personnel will monitor the patients for the occurrence of any adverse events until patients are discharged from the clinic. Patients will be discharged from the clinic on Day 2 upon investigator judgment. They will leave with their bottle of Study Drug and be instructed to take one tablet each morning and evening, 1-2 h before or after a meal.

For follow-up visits, patients will come to the clinic in the morning and will be instructed NOT to take their morning dose prior to coming to the clinic. They will be instructed to bring their bottle of Study Drug for each visit and will receive a new bottle on Day 7 and two new bottles on Day 14.

7.1.3. Day 7 Follow-up Visit

On the morning of Study Day 7, within 30 min prior to dosing, the following assessments will be conducted:

- Blood sample collection for PK assessment (for C_{min})
- Clinical laboratory tests (blood and urine)

After dose, the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate)
- Listen to heart and lungs
- ECG
- Adverse event monitoring

7.1.4. Day 14 Follow-up Visit

Patients will return to clinic the morning of Study Day 14 for the assessments listed below.

On the morning of Study Day 14, within 30 min prior to dosing, the following assessments will be conducted:

- Blood sample collection for PK assessment (for C_{min})
- Blood sample collection for PTI-125DX, mTOR and other biomarkers
- Clinical laboratory tests (blood and urine)

After dose, the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate)
- Listen to heart and lungs
- Adverse event monitoring
- ECG
- BEHAVE-AD test

7.1.5. Day 28 Follow-up Visit

Patients will return to the clinic on Study Day 28, prior to the morning dose, which will be the LAST dose of the study.

On the morning of Study Day 28, within 30 min prior to dosing, the following assessments will be conducted:

- Blood sample collection for PK assessment (Sample Time=0)
- Blood sample collection for PTI-125DX, mTOR and other biomarkers

After dose on Study Day 28, the following assessments will also be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate)
- Blood samples will be drawn at 20, 40, and 60 min and 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h after the single dose on Day 28 for PK assessments.
- CSF draw
- Adverse event monitoring
- BEHAVE-AD test

Columbia Suicide Severity Rating Scale (C-SSRS) **NOTE:** For patients determined by C-SSRS to have suicidality tendencies, inform the patient's primary care physician and refer the patient for follow-up.

CSF sample collection (5 mL) on Study Day 28 will occur 1-2 h after dosing, and the nearest plasma PK sample collection will be noted. The CSF samples will be tested for PTI-125 levels as well as the Aβ/tau Index, YKL40, inflammatory cytokines and other biomarkers.

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

All meals will be served at standard meal times. Patients can leave the clinic after the 12-h blood draw and will return prior to the 24-h blood draw on Day 29.

7.1.6. Day 29 Follow-up Visit

On Study Day 29, patients will return to the clinic for the following assessments:

- Blood sample collection for PK assessment (24 h after the last dose)
- Clinical laboratory tests (blood and urine)
- ECG
- Full physical exam

7.2. LABORATORY ASSESSMENTS

7.2.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed at screening, Day 1 pre-dose, Day 2 and at follow-up visits on Day 7, 14 and 29:

- 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.

7.2.2. Preparation of Whole Blood Samples for PTI-125DX and mTOR

Blood samples to be assessed in the PTI-125DX assay and the mTOR assay (**8 mL total**) will be drawn into a Vacutainer® tube containing K_2EDTA. Collection will occur on Days 1 (pre-dose), 14 and 28. The tubes will be placed immediately on ice and shipped AS WHOLE BLOOD at 2-8°C within 24-48 h to: Dr. Hoau-Yan Wang, CUNY School of Medicine, SOM CDI 3370, 85 St. Nicolas Terrace, New York, NY 10031.

7.2.3. Preparation of Plasma Samples for Pharmacokinetic Determination

At each blood collection for PK, blood samples (4 mL) will be drawn into a Vacutainer® tube containing K_2EDTA. The tubes will be placed on ice. Within 30 min 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 into two aliquots, transferred to polypropylene tubes and stored at approximately -20°C or below until analysis.

At the end of the study, PK 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. The second set of samples will be shipped separately once receipt of the first set is confirmed.

7.2.4. CSF assays

CSF samples should be split, with 2.5 mL of all samples shipped to Dr. Wang at CUNY and, for Day 28 only, an additional 0.5 mL shipped to Worldwide Clinical Trials. The remaining 2.0 mL will be retained at the study site at -20°C until otherwise informed by the Sponsor. All samples will be shipped frozen on dry ice.

The samples will be collected using polypropylene screw-cap tubes (e.g. Sarstedt® 13 ml, 101 x 16.5 mm tubes) at the second screening visit and on Study Day 28. Samples shipped to Dr. Hoau-Yan Wang, (CUNY School of Medicine, SOM CDI 3370, 85 St. Nicolas Terrace, New York, NY 10031) will be tested in several biomarker assays including:

- Abeta
- Tau, ptau
- YKL40
- IL-6, TNFα and IL-1β

CSF samples (0.5 mL) from Study Day 28 will be shipped to Worldwide Clinical Trials Bioanalytical Sciences (8609 Cross Park Drive, Austin, TX 78754) to be assayed for the PTI-125 analyte using a qualified assay.

8. EARLY DISCONTINUATION

Patients may choose to discontinue study drug or study participation at any time, for any reason, and without prejudice. Patients who discontinue will not be replaced.

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

- The reason for early study discontinuation.
- Full physical examination
- Clinical laboratory tests (blood and urine)
- ECG
- Adverse events
- Blood draw for PTI-125DX and other biomarkers
- BEHAVE-AD
- CSF draw for biomarkers

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

A Serious Adverse Event (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)** 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 patients 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. ANALYSIS POPULATIONS

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

10.2. PHARMACOKINETIC PARAMETERS

Plasma 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. Accumulation will be estimated based by the ratios of the AUC on the last day of dosing to the corresponding AUC the

first day of dosing. Time to steady state may be estimated, if possible, based on C_{min} blood samples taken on Days 7, 14, and 28, prior to the first dose of the day.
In the PK analysis, below limit of quantitation (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.

CSF concentrations of PTI-125 will be measured using a qualified assay. A CSF to plasma ratio will be determined if possible, using the nearest plasma timepoint.

10.3. STATISTICAL ANALYSIS

Comparison of the PK parameters C_{max}, AUC_{last}, and AUC_{inf} (if possible) for PTI-125 between the first and last Day of dosing will be done using an analysis of variance (ANOVA) model with factors for subject and day as the classification variables, using the natural logarithms of the data. Confidence intervals (90%) will be constructed for the ratios of the last Day and first Day of dosing for both parameters using the log-transformed data and the two-one-sided t-tests procedure. The point estimates and confidence intervals will be exponentiated back to the original scale. The point estimate for C_{max} will provide an estimate of the extent of accumulation between the first and last Day of dosing.

Biomarker endpoints to be analyzed include: 1) the CSF Aβ/tau Index, 2) CSF ptau/tau, 3) CSF YKL40 4) CSF IL-6, TNFα and IL-1β 5) PTI-125DX lymphocyte assay, and 6) PTI-125DX plasma assay, and 7) a lymphocyte mTOR assay. These data will be analyzed by repeated measures ANOVA.

Although not powered for efficacy, cognitive/behavioral endpoint to be analyzed will be the BEHAVE-AD to assess behavioral/psychological symptoms of dementia. These data will also be analyzed by repeated measures ANOVA.

10.4. 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.

10.5. SAMPLE SIZE

Twelve (12) patients 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 patients 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 unique patient number.

All clinical information requested in this protocol will be recorded in the CRFs provided by PTI. In case of error, the correction will be noted, initialed and dated.

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 for the CRF.

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.

12.3. SUBJECT CONFIDENTIALITY

All reports and subject samples will be identified only by the assigned patient 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. 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. Institutional Review Board

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

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

- Obtaining IRB approval of the protocol, Informed Consent Form, and any advertisements to recruit patients and IRB approval of any protocol amendments and Informed Consent Form revisions before implementing the changes.
- Providing the IRB with any required information before or during the study.
- Submitting progress reports to the IRB, as required, requesting additional review and approval, as needed; and providing copies of all relevant IRB communications to the Sponsor.
- Notifying the 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 IRB submission for approval. An 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, except to protect the safety, rights, or welfare of patients.
- Personally conduct or supervise the study.
- Ensure that requirements for 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 patients 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. REFERENCES

1. Burns LH, Wang H-Y. Altered filamin A enables amyloid beta-induced tau hyperphosphorylation and neuroinflammation in Alzheimer's disease. Neuroimmunol Neuroinflammation 2017;4:263-71.

2. Wang H-Y, Lee K-C, Pei Z, Khan A, Bakshi K, Burns L. PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis. Neurobiol Aging 2017;55:99-114.

3. Wang H-Y, Bakshi K, Frankfurt M, et al. Reducing amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting filamin A. J Neurosci 2012;32:9773-84.

15. APPENDIX A

Events Schedule

PROCEDURE	SCREENING (Days -29 to Day 0)	DAY 1	DAY 2	DAY 7	DAY 14	DAY 28	DAY 29
Informed consent	X						
Medical and medication histories	X						
ECG	X	X	X	X	X		X
Vital signs	X	X	X	X	X	X	
Physical examination	X	Brief	*	*	*		X
FSH Test **	X						
Biochemistry, hematology, urinalysis	X	X	X	X	X		X
MMSE	X						
HCV, HBsAg & HIV screen	X						
Drug administration		X	X	X	X	X	
Blood sample collection for PK analysis		X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Discharge			X				
Blood draw PTI-125DX, mTOR		X			X	X	
Behave AD	X				X	X	
C-SSRS	X					X	
CSF draw	X					X	

* Listen to heart and lungs

**If female and last natural menses < 24 months or uncertain, post-menopausal status should be confirmed by serum FSH.

16. 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-125-02:
"A Phase 2a, Open-label, Multiple Dose,
Safety, Pharmacokinetic and Biomarker Study
of PTI-125 in Mild-to-Moderate AD patients"

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

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

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.

The study drug has previously been given to healthy volunteers as ONE SINGLE DOSE. There were no drug-related side effects. **THIS IS THE FIRST STUDY IN WHICH THE STUDY DRUG IS BEING GIVEN AS A REPEATED, DAILY DOSE.**

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 when taken daily for a month. 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 PTI-125 (investigational product). You will receive your dose twice a day for 28 days.

This is an open-label study, which means that all patient participants will be taking PTI-125.

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

The study will last about 28 days, excluding the screening period, and involve 1 night at the facility. You will also be required to make follow-up visits to the facility at least four times during the 28 days. About 12 men and women who have been diagnosed with mild-to-moderate Alzheimer's disease, ages 50 through 85, 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 3 months of your screening visit.
- 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 patients 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.

CAREGIVER PARTICIPATION

As required by the study, every patient must have a caregiver/study partner to participate with them in the study. A caregiver/study partner is a person who spends sufficient time with the study subject so that you can provide certain information. The caregiver/study partner must have the ability to:

- Observe the subject for any changes in health/possible side effects or cognitive function throughout the study
- Report and assist with the subject's compliance with study procedures and medications.
- Accompany the subject to all study visits and procedures (e.g. lumbar puncture).
- Reliably answer interview questions regarding the subject's medical condition, medication use, daily functioning, behaviors, and how he or she feels.

The caregiver/study partner may be compensated for time and travel. As a caregiver/study partner, you will not receive any direct benefit by taking part in this study. Information from this study may also help researchers come up with new tests or medicines in the future to help people with Alzheimer's disease.

Entering a research study is completely voluntary. Although a caregiver/study partner is required for participation, a caregiver/study partner can decide to stop at any time and a replacement will need to be identified. If the caregiver/study partner withdraws from the study, you will only be paid for the study visits completed.

If you have any questions about being a caregiver/study partner in this study, you should ask the study doctor or study staff.

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
- Memory testing – Mini Mental State Exam
- If female and last natural menses < 24 months or uncertain, post-menopausal status should be confirmed by serum FSH.

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

- If you meet the criteria above, you will come back for a lumbar puncture for more tests to confirm your diagnosis of Alzheimer's disease. The lumbar puncture sample will also be tested for a neuroinflammation marker and possibly other cerebrospinal fluid biomarkers.

    - You will have a needle placed in your spine to collect a small amount of cerebrospinal fluid (Lumbar Puncture).

If you qualify for the study, you will return to the clinic to start the study. You will need to stay in the clinic the first night after receiving study drug (active or placebo) and part of the following day before being discharged from the clinic. During this time, you will have blood draws, vital signs, and an ECG. You will continue to take study drug each day at home, morning and evening. You will need to return to the clinic on the 7th and 14th days of the study for up to 2 hours. During these two hours the following testing may be performed: ECG, vital signs, listening to your heart and lungs, blood draws and some memory testing. You will return to the clinic once more in the morning of the 28th (last) day of taking the study drug for the same testing along with another lumbar puncture. You will also have and a blood draw 12 hours after your last dose. You will return the next morning for one final blood draw, 24 hours after your last dose, an ECG and a physical examination.

Study Procedures

In-clinic Periods (Days 1-2) and clinic visits

<u>The following will be done before taking the first dose:</u>

- 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
- You will have a brief physical exam including vital signs (blood pressure, heart rate, breathing rate and temperature)
- You will have a behavioral/psychological test and a test for suicidal thoughts
- You will have a blood draw for an experimental test to confirm your diagnosis and to measure other biomarkers such as mTOR.
- You will have a blood draw for clinical laboratory tests.

After your first dose of Study Drug:

- Standard meals will be given at scheduled times during your stay in the clinic
- The level of study drug in your blood will be measured. About 3/4 teaspoon (4 mL) of blood will be taken during your stay in the study clinic at different timepoints during the days.
- Vital Signs (temperature, blood pressure, heart rate and breathing rate) will be performed at multiple time points during the study.
- A doctor or nurse will listen to your heart and lungs prior to discharge on Day 2 and at every subsequent clinic visit.
- An electrocardiogram (ECG; a recording of the electrical activity of your heart) will be conducted on Day 1 prior to dosing, on Day 2 prior to discharge and at subsequent clinic visits on Days 14 and 29.
- Lab tests will be conducted (blood and urine).
- A blood draw to repeat the experimental test to confirm your diagnosis and to measure other blood-based biomarkers such as mTOR (Days 14 and 28).
- A blood draw to determine your APOE genotype will be performed. You can choose not to know the results of this test.
- You will be monitored for any side effects.
- You will have a behavioral/psychological test and a test for suicidal thoughts.

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)
- Memory testing
- CSF draw

Blood Samples:

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 36 blood draws not including 3 blood draws during screening. The total amount of blood drawn in the study will be about 154 mL, or about 2/3 of a 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.
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

Spinal Tap or Lumbar Puncture:

Lumbar puncture (spinal tap) is performed in the lower back, in the lumbar region. During lumbar puncture, a needle is inserted between two lumbar bones (vertebrae) to remove a sample of cerebrospinal fluid — the fluid that surrounds your brain and spinal cord to protect them from injury. Side effects may include:

- headache
- nausea
- vomiting dizziness
- back pain or discomfort
- bleeding at puncture site or rarely into epidural space

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.

Reproductive Risks

Women

Women in this study will not be of childbearing potential.

Men

It is unknown if the drug used in this study may harm an unborn child. You should not have sexual intercourse or you or your partner should use a method of birth control that is acceptable to you, the study doctor, and the sponsor during the study. If you think that you have gotten a woman pregnant, you must tell the study doctor at once. If your partner gets pregnant during the study, she will be asked to sign a release of information form to allow your study doctor to contact her obstetrician to collect updates on the progress of the pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study doctor or study staff right away if you have any problems.

POSSIBLE BENEFITS OF THE STUDY

This study is not intended to provide medical benefit to the participants. The results of this research study will help guide the development of the study drug and may help others.

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

- Advarra IRB

The Institutional Review Board (IRB), Advarra IRB, 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:

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 Advarra. Advarra's policy indicates that all concerns/complaints are to be submitted in writing for review at a convened IRB meeting to:

Mailing Address:	OR Website:
Chairperson Advarra IRB 6940 Columbia Gateway Drive, Suite 110 Columbia, MD 21046	https://www.advarra.com/contact-us/

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

410-884-2900

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

Advarra has approved the information in this consent form and has given approval for the investigator to do the study. This does not mean Advarra 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 $XXXX.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 the clinic. 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 the clinic. If you take study drug, you will be paid as listed below, for each completed visit:

- $XXX.00 for each overnight stay (up to 3 total)

If you successfully complete the entire study, you will receive up to an additional $XXX.00:

- $XXX.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.

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.

The investigator, the sponsor company, Advarra, 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 patients participating in research studies.

Advarra, the IRB for this study

Advarra is an IRB whose board members provide IRB services worldwide.

To meet requirements of the law, the Advarra 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 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.

You and your caregiver 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)

_____
Printed Name of Caregiver/Study Partner

_____
Signature of Caregiver/Study Partner Date Time (24-hour clock)

_____
Printed Name of Person Explaining Consent Form

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