CLINICAL RESEARCH PROTOCOL

PROTOCOL PTl-125-02

A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multiple Dose, Biomarker and Safety Study of PTl-125 in Mild-to-moderate Alzheimer's Disease Patients

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Protocol Date:	June 28, 2019

This clinical trial is funded by NIH grant AG060878.

Confidentiality

Cassava Sciences, Inc.

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A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multiple Dose, Biomarker and Safety Study of PTI-125 in Mild-to-moderate AD patients

Approvals:

28 Jun 2019

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Date

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Signature of Agreement for Protocol PTI-125-02

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
ALP	alkaline phosphatase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CRO	contract research organization
CSF	cerebrospinal fluid
CSI	Cassava Sciences, Inc.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DSMB/DMC	Data Safety Monitoring Board/Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
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
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
PK	pharmacokinetics
PTI-125	small molecule drug candidate to treat AD
PTI-125Dx	blood-based diagnostic/biomarker candidate
RBC	red blood cell
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

Cassava Sciences Inc. (CSI) 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 persistently 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 mg/kg/day (equivalent to 60 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 toxicity studies in rats and dogs. In a 28-day repeat dose oral toxicity study followed by a 28-day drug-free recovery period in rats (PTI-125-NC-040) 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. 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). Safety margins based on this study are shown in **Table 1**.

Table 1. Safety Margin for a 100 mg b.i.d. Human Dose Based on the 4-week Rat Tox

NOAEL (mg/kg)	C_{max} (ng/mL)		AUC_{last} (hr*ng/mL)		Rat-to-Human Ratio (Safety Margin)	
	Rat[a]	Human[b]	Rat[a]	Human[b]	C_{max}	AUC_{0-24}
500	44,900	1,104	249,000	8,483	40.7	29.4

[a] Mean exposure for male and female rats combined on last day of study

[b] Mean exposure for patients after 100 mg b.i.d. dose of PTI-125 on Day 28 (CSR PTI-125-03)

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). Safety margins based on this study are shown in **Table 2**.

Table 2. Safety Margin for a 100 mg b.i.d. Human Dose Based on the 4-week Dog Tox

NOAEL (mg/kg)	C_{max} (ng/mL)		AUC_{last} (hr*ng/mL)		Dog-to-Human Ratio (Safety Margin)	
	Dog[a]	Human[b]	Dog[a]	Human[b]	C_{max}	AUC_{0-24}
100	49,000	1,104	214,000	8,483	44.4	25.2

[a] Mean exposure for male and female dogs combined on last day of study

[b] Mean exposure for patients after 100 mg b.i.d. dose of PTI-125 on Day 28 (CSR PTI-125-03)

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. Safety

margins based on this study are shown in **Table 3**.

Table 3. Safety Margin for a 100 mg b.i.d. Human Dose Based on the 13-week Dog Tox

NOAEL (mg/kg)	C_{max} (ng/mL)		AUC_{last} (hr*ng/mL)		Dog-to-Human Ratio (Safety Margin)	
	Dog[a]	Human[b]	Dog[a]	Human[b]	C_{max}	AUC_{0-24}
150	71,100	1,104	447,000	8,483	64.3	52.7

[a] Mean exposure for male and female dogs combined on last day of study

[b] Mean exposure for patients after 100 mg b.i.d. dose of PTI-125 on Day 28 (CSR PTI-125-03)

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. None of the six 1000 mg/kg animals exhibited convulsions. On Day 4, the mid (300 mg/kg) and high (1000 mg/kg) doses were reduced to 150 and 200 mg/kg/day, respectively.

A subsequent 6-month repeat dose oral toxicity study in rat (PTI-125-NC-049) used the same doses as the 28-day study (50, 500 and 1000 mg/kg/day). The toxicological response was characterized by decreased body weights and adverse structural and functional alterations in the liver of 500 and 1000 mg/kg animals, including increased weight, hepatocellular hypertrophy and vacuolation, single/multiple basophilic/ eosinophilic/clear cell focus, hepatocellular degeneration, pigmentation, and oval cell hyperplasia. The presence of bile pigment was consistent with cholestasis. These findings correlated with changes to the clinical chemistry profile, including increased ALP and total/direct bilirubin. Over the 1-month recovery period, there was complete recovery of the hepatocellular degeneration and partial recovery of hepatocellular hypertrophy. The NOAEL from this 6-month study was 50 mg/kg/day (equivalent to 300 mg/m^2). Safety margins based on this study are shown in **Table 4**.

Table 4. Safety Margin for a 100 mg b.i.d. Human Dose Based on the 6-month Rat Tox

NOAEL (mg/kg)	C_{max} (ng/mL)		AUC_{last} (hr*ng/mL)		Rat-to-Human Ratio (Safety Margin)	
	Rat[a]	Human[b]	Rat[a]	Human[b]	C_{max}	AUC_{0-24}
50	6,240	1,104	21,200	8,483	5.7	2.5

[a] Mean exposure for male and female rats combined on last day of study

[b] Mean exposure for patients after 100 mg b.i.d. dose of PTI-125 on Day 28 (CSR PTI-125-03)

A second 6-month repeat dose oral toxicity study in rat has been initiated with the goal of determining a more accurate NOAEL. Doses are vehicle and 125 and 250 mg/kg/day.

A 9-month toxicity study in dog has been completed and is awaiting pathology. This study started with 200 mg/kg/day as the high dose, which was reduced after 1 month to 150 mg/kg/day due to a decrease in body weight that was considered unsustainable for 9 months. Based on clinical signs, clinical chemistry, body weights and food consumption, the 150 mg/kg/day dose is estimated to be the NOAEL for this study until pathology is complete.

A first-in-human (FIH) double-blind, Single Ascending Dose clinical trial was conducted in healthy normal volunteers, age 18-45 with oral dosing solution. Doses were placebo, 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).

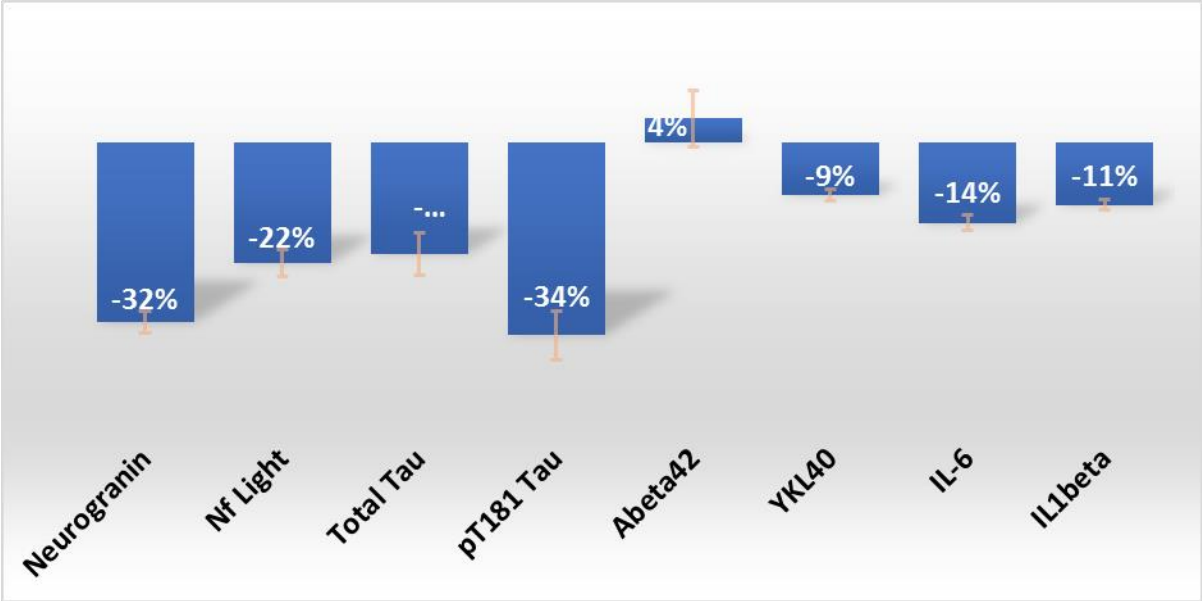
A 28-day study was conducted with mild-to-moderate AD patients, receiving PTI-125 100 mg b.i.d. as oral tablets. Key inclusion criteria were MMSE $\geq$ 16 and $\leq$ 24, age 50-85, and a CSF total tau/Aβ_{42} ratio $\geq$ 0.30. CSF samples were collected at screening and Day 28. Nine CSF biomarkers were analyzed using commercially available ELISA kits. PTI-125 was safe and well tolerated in all patients. All 8 biomarkers that are elevated in AD were significantly reduced (**Table 5 and Figure 1**). Aβ_{42}, which is low in AD, was increased slightly but non-significantly. Reduced neuroinflammation was indicated by reductions in inflammatory cytokines and YKL-40. A reduced neurodegenerative drive was suggested by reductions in neurogranin, neurofilament light chain, and total tau. Finally, the robust reduction in phospho-tau (pT181) confirms the mechanism of action of PTI-125.

Table 5 Reductions in CSF biomarkers after 28 days PTI-125 (100 mg, b.i.d.)

	Neurogranin	**Neurofilament Light Chain**	**Total Tau**	**P-Tau (T181)**	**Aβ_{42}**	**YKL40**	**IL-6**	**IL-1β**	**TNF-α**
Percent Change	-32.1%	-21.5%	-19.8%	-34.4%	4.3%	-9.4%	-14.3%	-11.1%	-5.1%
P value*	$p < 0.00001$	$p < 0.00001$	$p < 0.00001$	$p < 0.00001$	N.S.	$p = 0.043$	$p < 0.00001$	$p < 0.00001$	$p < 0.001$

*Screening vs. Day 28, *paired t test*

Fig. 1 Mean Change from Baseline to Day 28 in CSF biomarkers (±SEM)



3. STUDY OBJECTIVES

The objectives of this study are to investigate the safety and effect on biomarkers and cognition of PTI-125 following 1-month, repeat-dose oral administration in mild-to-moderate AD patients, 50-85 years of age, with MMSE $\geq$ 16 and $\leq$ 26. A second objective is to replicate the effects on biomarkers shown in the previous open-label 1-month study (PTI-125-03). A third objective is to investigate a dose-response of PTI-125.

4. SUMMARY OF STUDY DESIGN

This is a Phase 2b, multi-center, randomized, double-blind, placebo-controlled, study of PTI-125 in mild-to-moderate AD patients, 50-85 years of age. Approximately sixty (60) patients will be enrolled into the study and randomized to one of three cohorts. Cohorts will receive placebo or PTI-125 at 50 or 100 mg b.i.d. (n=20 per group). Placebo or PTI-125 will be administered as coated tablets.

There will be two screening visits within 30 days of start of the study. Patients meeting initial screening criteria, including a Mini-Mental State Examination (MMSE) score $\geq$ 16 and $\leq$ 26 will return for 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. Cambridge Cognition testing will be conducted at the second screening visit, Day 1, and at the end of the study. Patients will be assessed for suicidality via the Columbia Suicide Severity Scale (C-SSRS) during the first and last visits.

Patients will report to clinic the morning of Day 1. The following will be conducted prior to dosing: Cambridge Cognition testing, a full physical exam, an ECG and a blood draw for clinical labs and biomarkers (PTI-125Dx and mTOR). After dosing, patients will be monitored for adverse events and vital signs will be taken through 4 h. Patients will return to the clinic on Days 7, 14 and 28.

PK blood samples will be obtained prior to the first dose on Day 14 for C_{min} values. On Day 28, there will be a CSF draw after the last dose, and an additional PK blood sample will be obtained after this CSF draw for calculation of CSF/plasma ratio.

Blood draws for clinical laboratory testing will be performed at screening and on Days 1, 7, 14 and 28. Safety assessments of vital signs and listening to heart and lungs will be conducted at all visits. ECGs will be conducted on Days 7, 14 and 28.

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 and Day 28. The Day 28 blood sample will also be used for APOE genotyping. A CSF sample collection will be performed on Day 28 for neurogranin, neurofilament light chain, total tau, pTau (T181), $A\beta_{42}$, $A\beta_{40}$, YKL40, IL-6, IL-1β, TNFα and other potential CSF biomarker assays as well as bioanalysis of PTI-125.

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

5. SUBJECT SELECTION

5.1. STUDY POPULATION

Approximately sixty (60) patients will be enrolled in the study (male and female). Dropouts may be replaced at the discretion of Sponsor.

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 ≤ 26 at screening, OR if > 26, a prior CSF total tau/Aβ_{42} ratio ≥ 0.28. (A new CSF draw would be required for analysis of pre-dose biomarkers.)
5. If female, postmenopausal for at least 1 year
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. Multiple medications are allowed.
10. The patient is a non-smoker for at least 3 years.
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 a ratio of total tau/Aβ_{42} in CSF that indicates AD. This value (total tau/Aβ_{42}) will be ≥ 0.28.
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. Enrollment in the previous PTI-125 trial
3. A medical condition that would interfere with a lumbar puncture
4. Residence in a skilled nursing facility and requiring 24 h care.
5. Clinically significant laboratory test results

6. Clinically significant untreated hypothyroidism (if treated, thyroid-stimulating hormone level and thyroid supplementation dose must be stable for at least 6 months before screening)
7. Insufficiently controlled diabetes mellitus
8. Renal insufficiency (serum creatinine > ULN)
9. 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)
10. History of ischemic colitis or ischemic enterocolitis
11. Unstable medical condition that is clinically significant in the judgment of the investigator
12. Alanine transaminase (ALT) or aspartate transaminase (AST) > ULN or total bilirubin > ULN.
13. History of myocardial infarction or unstable angina within 6 months before screening
14. History of more than 1 myocardial infarction within 5 years before screening
15. Clinically significant cardiac arrhythmia (including atrial fibrillation), cardiomyopathy, or cardiac conduction defect (patients with a pacemaker are acceptable)
16. Symptomatic hypotension, or uncontrolled hypertension
17. 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.
18. Stroke within 18 months before screening, or history of a stroke concomitant with onset of dementia
19. History of brain tumor or other clinically significant space-occupying lesion on CT or MRI
20. Head trauma with clinically significant loss of consciousness within 12 months before screening or concurrent with the onset of dementia
21. Onset of dementia secondary to cardiac arrest, surgery with general anesthesia, or resuscitation
22. Specific degenerative CNS disease diagnosis other than AD (eg, Huntington's disease, Creutzfeld-Jacob disease, Down's syndrome, Frontotemporal Dementia, Parkinson's disease)
23. Wernicke's encephalopathy

24. Active acute or chronic CNS infection
25. Donepezil 23 mg or greater QD currently or within 3 months prior to randomization
26. Discontinued AChEI < 30 days prior to randomization
27. 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 randomization
28. 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 randomization
29. 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 randomization
30. Immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses (Steroid use for allergy or other inflammation is permitted.)
31. Antiepileptic medications if taken for control of seizures
32. Chronic intake of opioid-containing analgesics
33. Sedating H1 antihistamines
34. Nicotine therapy (all dosage forms including a patch), varenicline (Chantix), or similar therapeutic agent within 30 days before screening
35. Clinically significant illness within 30 days of enrollment
36. History of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease
37. Positive serum hepatitis B surface antigen (HBsAg) or positive hepatitis C virus HCV antibody test at screening
38. Positive HIV test at screening
39. Positive urine drug test at screening
40. Loss of a significant volume of blood (> 450 mL) within 4 weeks prior to the study
41. Suicidality on C-SSRS at screening

6. STUDY DRUG

6.1. PTI-125 PHYSICAL DESCRIPTION AND PREPARATION

Investigational PTI-125 and matching placebo will be supplied by CSI 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 be randomized to receive placebo (20 patients) or 50 mg PTI-125 b.i.d. (20 patients) or 100 mg PTI-125 b.i.d. (20 patients). 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 and the caregiver. 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). The signed and dated Informed Consent Form must be retained by the Investigator in the subject's file.

7.1. LIVER CHEMISTRY STOPPING CRITERIA

Liver chemistry threshold stopping criteria have been designed to assure patient safety and to evaluate liver event etiology during administration of Study Drug. Administration of Study Drug will be discontinued if any of the following liver chemistry stopping criteria occurs:

- ALT or AST ≥ 2.5 x ULN.
- ALT or AST ≥ 2 x ULN and total bilirubin ≥ 2 x ULN. Note: Serum bilirubin fractionation should be performed if total bilirubin is ≥ 2 x ULN.
- ALT or AST ≥ 2 x ULN if associated with appearance or worsening of a rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia).
- ALP or GGT ≥ 2.5 x ULN.

In the event of discontinuation due to liver abnormalities, the patient will be appropriately investigated to determine the potential cause.

7.2. EVALUATIONS BY VISIT

Follow-up visits can be scheduled +/- two (2) days from the actual Study Day number. Please notify Sponsor of changes so that the biomarker lab is aware of whole blood sample shipments.

7.2.1. Screening Visit 1 (No longer than 30 days prior to Day 1)

The following will be completed in the first screening visit:

- Informed Consent.
- Review of Inclusion and Exclusion Criteria
- Medical history
- Review of concomitant medications
- MMSE evaluation
- Columbia Suicide Severity Rating Scale (C-SSRS)
- 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.
- Urine drug screen.

7.2.2. Screening Visit 2 (If all Screening Visit 1 criteria are met)

- Cambridge Cognition testing (conducted prior to CSF collection)
- CSF sample collection (5 mL)

CSF total tau/Aβ_{42} criterion (~1-week turnaround) must be met prior to Day 1.

7.2.3. Study Day 1 (Dosing Initiation)

Patients will come to the clinic in the morning. Prior to dosing, the following assessments will be conducted:

- Confirmation of inclusion/exclusion criteria
- Review of concomitant medications
- Vital signs (blood pressure, temperature, pulse and respiratory rate).
- Listen to heart and lungs
- Cambridge Cognition testing; the average of this result and that of the second screening visit will be taken as the baseline value.
- Blood sample collection for clinical laboratory tests
- Blood sample collection for PTI-125Dx and mTOR assessments (8 mL total)
- ECG

Patients will be administered Study Drug at least 1 h before or after a meal. The patient will be discharged 2 h later with their supply of Study Drug.

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

- Vital signs (blood pressure, temperature, pulse and respiratory rate) at approximately 30 min, and 1 and 2 h post-dose.
- Adverse event monitoring

Clinic personnel will monitor the patients for the occurrence of any adverse events until patients are discharged from the clinic. Upon investigator judgment, patients will be discharged from the clinic with their supply of study drug until the next visit. The caregiver will be instructed to administer study drug twice daily at least 1 h before or after a meal. A dose can be up to 4 h late, but if a dose is missed, the next dose should NOT be doubled.

For all 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.

7.2.4. Day 7 Follow-up Visit

Patients will return to clinic on Study Day 7 before taking their morning dose.

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 will be conducted:

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

7.2.5. Day 14 Follow-up Visit

Patients will return to clinic on Study Day 14 before taking their morning dose.

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})
- Clinical laboratory tests (blood and urine)

After dose, the following will be conducted:

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

7.2.6. Day 28 Follow-up Visit

Patients will return to the clinic in the morning on Study Day 28 and take their morning dose upon arrival.

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

- Vital signs (blood pressure, temperature, pulse and respiratory rate)
- Adverse event monitoring

- Cambridge Cognition testing
- MMSE
- Columbia Suicide Severity Rating Scale (C-SSRS)
- ECG
- CSF sample collection (time post-dose to be recorded)
- Blood sample collection for PK (time post-dose to be recorded)
- Clinical laboratory tests (blood and urine)
- Blood sample collection for PTI-125Dx, mTOR and other biomarkers (8 mL total)

CSF sample collection (5 mL) on Study Day 28 will occur 1-2 h after dosing and after the MMSE and Cambridge Cognition testing have been completed. These samples will be tested for PTI-125 levels as well as the Aβ/tau Index, YKL40, inflammatory cytokines and other biomarkers.

Blood sample collection for PK assessment on Study Day 28 should be taken **as soon after the CSF draw as possible** to allow CSF to plasma ratio to be calculated.

7.2.7. End-of-study Follow-up

Patient will receive a follow-up phone call 7-14 days after the last dose. If needed, a follow-up clinic visit will be scheduled.

7.2.8. Unscheduled Visits and Discontinuation due to AEs

For unscheduled visits due to AEs, any assessments conducted will be at the discretion of the investigator and pertinent to the AE. If a decision is made to discontinue the patient from study drug, the Sponsor will be notified immediately. Restarting the patient on study drug will be a mutual decision by the investigator and the Sponsor.

7.3. LABORATORY ASSESSMENTS

7.3.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed at screening, Day 1 pre-dose, and at follow-up visits on Day 7, 14, and 28:

- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.

- Serum Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), total bilirubin, creatinine, cholesterol, triglycerides, albumin, globulin, total protein, uric acid, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), lactose dehydrogenase (LDH).
- Urinalysis: color, specific gravity, pH, protein, glucose, ketones and occult blood.

7.3.2. Preparation of Whole Blood Samples for biomarkers and APOE genotyping

Blood samples to be assessed in blood-based (lymphocytes or plasma) biomarkers, e.g. PTI-125Dx and mTOR, or genotyping (**8 mL total**) will be drawn into a Vacutainer® tube containing K_2EDTA. Collection will occur on Days 1 and 28. The tubes will be placed immediately on wet ice or in a refrigerator and shipped **as whole blood, unfrozen**, with **cold gel packs** (2-8°C) within 24 h to: Dr. Hoau-Yan Wang, CUNY School of Medicine, SOM CDI 3370, 85 St. Nicolas Terrace, New York, NY 10027. **Do not freeze, do not ship with dry ice, and do not ship whole blood samples on Friday**.

7.3.3. 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 min, preferably at 4-5°C. Within 30 min 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 or when advised by Sponsor, 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. One sample from each placebo subject will be analyzed. The timepoint will be selected to be near the C_{max}.

7.3.4. CSF assays

CSF samples should be split, with 2.5 mL shipped to Dr. Wang at CUNY and, for Day 28 only, an additional 0.5 mL shipped to Worldwide Clinical Trials (WCT). This 0.5 mL sample will be assayed for the PTI-125 analyte at WCT using a qualified assay. The remaining 2.5 or 2 mL will be retained at the study site frozen at -20°C or below until informed by the Sponsor.

CSF will be collected into **5 ml Screw-Cap LoBind Eppendorf® tubes (# 0030122356).** When dividing into aliquots, the same tubes can be used or a **2 ml Sarstedt® Screw Cap Micro Tube Protein Low Binding (#72.694.600).** CSF samples will be collected at the second screening visit and on Study Day 28.

The samples collected at screening and on Study Day 28 will be shipped **frozen on dry ice** (Monday – Wednesday) to Dr. Hoau-Yan Wang, CUNY School of Medicine, SOM CDI 3370, 85 St. Nicolas Terrace, New York, NY 10027 to be tested in biomarker assays including:

- Abeta
- Tau, ptau
- YKL40
- IL-6, TNFα and IL-1β
- Neurogranin
- Neurofilament light chain

CSF samples collected at screening should be shipped to Dr. Wang upon collection; all Day 28 CSF samples can be held until end of study and shipped together per Sponsor instructions (2 mL samples), or for the 0.5 mL samples, to WCT along with plasma PK samples in one shipment.

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 may be replaced at the discretion of Sponsor.

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.
- Vital signs (blood pressure, temperature, pulse and respiratory rate), full physical examination, clinical laboratory tests, ECG, use of concomitant medications, and adverse events) should be obtained at discharge prior to release.
- Blood draw for PTI-125Dx, mTOR and other biomarkers
- MMSE
- Cambridge Cognition testing if not performed within the last 3 days

- 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 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 eCRF.

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)** by telephone to:

Nadav Friedmann, PhD, MD
Cassava Sciences, Inc.
Email: nfriedmann@cassavasciences.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. RANDOMIZATION

Randomized treatments will be assigned by patient numbers in a randomly generated numeric sequence.

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

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 patients who receive study medication will be included in analyses for safety, biomarkers and cognition.

10.3. PHARMACOKINETIC PARAMETERS

The only plasma PK parameters to be collected from this study are the C_{min} values from blood samples taken prior to dosing on Days 7 and 14 and the sample on Day 28

collected just after the CSF draw.

A CSF to plasma ratio will be determined using the Day 28 CSF and plasma samples.

10.4. STATISTICAL ANALYSIS

CSF biomarker endpoints to be analyzed include: 1) neurogranin, 2) neurofilament light chain, 3) total tau, 4) pTau (T181), 5) $A\beta_{42}$, 6) YKL40, 7) IL-6, 8) TNFα, and 9) IL-1β. Plasma and lymphocyte assays include 1) PTI-125Dx lymphocyte assay, 2) PTI-125Dx plasma assay and 3) mTOR assay. CSF biomarkers may also be measured in plasma. All biomarker data will be analyzed by a two-tailed paired t test or other appropriate statistics.

Although not powered for efficacy, the Cambridge Cognition tests will be analyzed by repeated measures ANOVA or other appropriate statistics.

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

Sixty (60) 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

Electronic case report forms (eCRFs) will be used 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 eCRFs provided by CSI. Case report forms must be completed within 48 hours of a patient's visit. In case of error, the correction will be noted, initialed and dated.

eCRFs must be reviewed and verified for accuracy and signed-off by the Principal Investigator before collection by the Sponsor (or CRO designee). Paper source documents, if used, 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 eCRFs, 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 eCRF.

Investigators are required to maintain all study documentation until notification by CSI 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 Trial 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 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 will be 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 – SCHEDULE OF ACTIVITIES

PROCEDURE	SCREEN 1 (Days -29 to Day -1)	SCREEN 2 (Days -28 to Day 0)	DAY 1 Time=0	DAY 7	DAY 14	DAY 28
Informed consent	X					
Medical and medication histories	X		X			
ECG	X		X		X	X
Vital signs	X		X	X	X	X
Physical examination	X		*	*	*	X
FSH Test**	X					
Biochemistry, hematology, urinalysis	X		X	X	X	X
MMSE	X					X
HCV, HBsAg & HIV screen	X					
Urine drug screen	X					
Drug administration			X	X	X	X
Blood sample collection for PK analysis				X	X	X
Adverse Events			X	X	X	X
Blood draw for biomarkers and one time only, APOE genotyping			X			X
Cambridge Cognition testing		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