Single Ascending Dose Phase I Clinical Trial of PTI-125 in Healthy Volunteers

Lindsay H. Burns, PhD,[1] George J. Atiee, MD,[2] Michael Marsman, PharmD[1] and Nadav Friedmann, PhD, MD[1]

1. Pain Therapeutics, Inc., Austin, TX 2. Worldwide Clinical Trials, San Antonio, TX

ABSTRACT

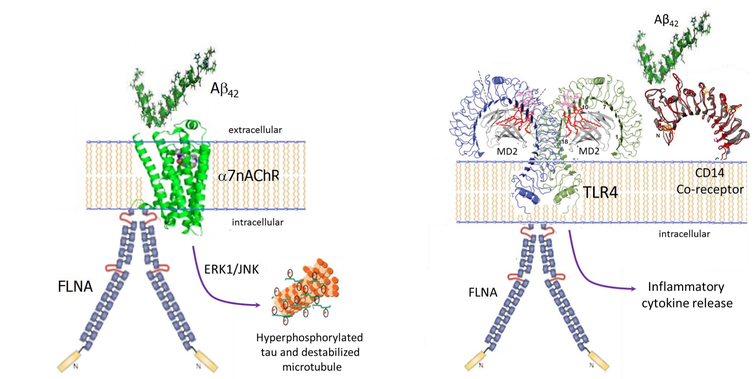
Background: PTI-125 is a novel small molecule drug candidate to treat Alzheimer's disease (AD). PTI-125 preferentially binds and reverses an altered conformation of the scaffolding protein filamin A (FLNA) that is present in AD brain (Wang et al., 2017). PTI-125 binds *altered* FLNA in AD brain with femtomolar affinity and control FLNA with a 100-fold lower, picomolar affinity. Altered FLNA links to both the α7 nicotinic acetylcholine receptor (α7nAChR) and toll-like receptor 4 (TLR4) to enable α7nAChR-mediated $A\beta_{42}$-induced tau phosphorylation and TLR4-mediated inflammatory cytokine release (**Fig. 1**). PTI-125's restoration of FLNA's normal conformation prevents the aberrant FLNA linkages to both receptors and the resultant tau hyperphosphorylation and neuroinflammation. In triple transgenic AD mice (22 mg/kg/day, equivalent to 105 mg for a 60-Kg person) and in postmortem human AD brain (1 nM), beneficial effects included (1) reduced tau hyperphosphorylation, (2) reduced TNFα, IL-1β and IL-6 brain levels, (3) reduced $A\beta_{42}$ – α7nAChR complexes (4) improved function of α7nAChR, NMDAR and insulin receptors, (5) improved synaptic plasticity, evidenced by activity-dependent expression of Arc, the master synaptic plasticity regulator, (6) reduced $A\beta_{42}$ deposits and neurofibrillary lesions, and (7) improved cognitive/behavioral assessments. No-observable-adverse-effect-levels (NOAELs) in 28-day toxicity studies were 500 mg/kg/day in rat and 100 mg/kg/day in dog. These preclinical data suggest that PTI-125 will provide some cognitive recovery as well as slow disease progression.

Methods: Following IRB approval, we conducted a double-blind, placebo-controlled Single Ascending Dose (SAD) Phase I clinical trial in 24 healthy volunteers, age 18-45. PTI-125 was administered orally at doses of 50, 100 and 200 mg. Each dose cohort consisted of 6 active and 2 placebo subjects. PTI-125 was administered as an oral dosing solution in an ORA Sweet SF vehicle for taste-masking to maintain blinding. The study followed a sentinel design, with one active and one placebo subject dosed first, followed by the full dose cohort after Data and Safety Monitoring Board (DSMB) review of 24-h safety assessments. Blood draws for laboratory testing were conducted pre-dose and 24 h post-dose. PK blood draws occurred at 13 timepoints from 20 min through 72 h. Orthostatic vital signs were taken pre-dose and at 12 timepoints from 10 min through 72 h. Electrocardiograms (ECGs) were conducted at all vital sign timepoints except 10 min. A physical exam was conducted at 72 h prior to discharge. All safety assessments were repeated at a 7-day follow-up visit.

Results: PTI-125 was well tolerated in healthy volunteers at 50, 100 and 200 mg. PK showed PTI-125 oral solution was rapidly absorbed with a T_{max} of 1 - 1.56 h and $T_{1/2}$ of 4.45 - 6.05 h. C_{max} and AUC_{last} values showed dose proportionality.

Conclusions: PTI-125 is orally bioavailable, safe and well tolerated in this study in the anticipated therapeutic dose range.

Fig. 1 Altered FLNA enables Aβ signaling via α7nAChR and TLR4



STUDY DESIGN

This SAD trial of PTI-125 oral solution was in 24 male and female healthy volunteers, age 18-45. Females were of non-childbearing potential. Separate dose cohorts of 6 active and 2 placebo received 50, 100 or 200 mg. A sentinel dose group of 1 active and 1 placebo preceded each full dose cohort. Blood draws for laboratory tests were pre-dose and 24 h and 7 days post-dose. PK timepoints were 0, 20 and 40 min and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h. Orthostatic vital signs were conducted at 0, 10 and 30 min and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h, with ECGs performed at all vital sign timepoints except 10 min. Physical exams were conducted at 24 and 72 h and at 7 days. Adverse events were monitored.

Dose Selection

Doses of PTI-125 were based on the efficacious daily dose in preclinical mouse studies. Mouse studies used total daily doses of 20 mg/kg i.p. for the first study[1] and 22 mg/kg orally via drinking water in the second.[2] By body surface area conversion, the human dose equivalent of 22 mg/kg in a mouse is 105 mg for a 60-Kg person. Additionally, based on the 100 mg/kg NOAEL dose in dog, the more sensitive tox species, and using a 10x safety factor, a safe human starting dose was determined to be 330 mg.

RESULTS

Adverse Events

There were no adverse events (AEs) in the 50 mg cohort. One incident of lightheadedness upon standing was reported for a subject in the 100 mg group at 1 h post-dose. A subject in the 200 mg group reported transient musculoskeletal chest wall pain and acne.

Adverse Event	Number of Subjects	Dose group	Severity	Time of onset	Duration	Causality
Lightheadedness	1	100 mg	Mild	1 h post-dose	1 min	Possibly related
Musculoskeletal chest wall pain	1	200 mg	Mild	56 h post-dose	15 min	Unlikely related
Acneiform eruptions	1	200 mg	Mild	87 h post-dose	3 days	Unlikely related

Laboratory Tests

There were no significant findings in clinical chemistry or urinalysis.

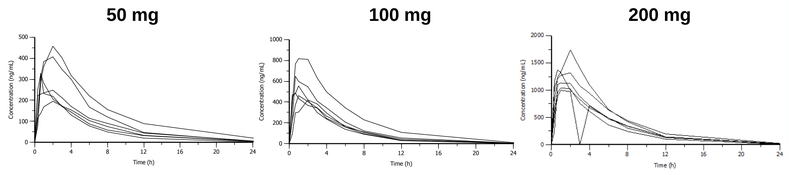
Vital Signs, ECGs and Physical Exams

There were no notable findings in vital signs, ECGs or physical exams.

Pharmacokinetics

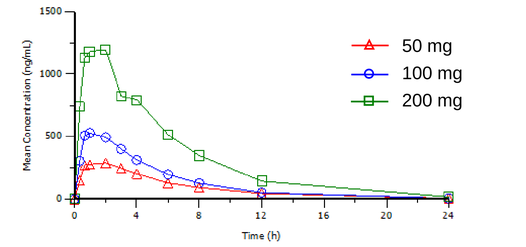
PTI-125 was rapidly absorbed and eliminated. Plasma concentration time plots for each subject in each dose group (Fig. 2) and means for each group (Fig. 3) are shown below.

Fig. 2 Individual Subject PTI-125 Plasma Concentrations



(Note: Missing value for one subject at 3 h)

Fig. 3 Mean PTI-125 plasma concentrations



PK Parameters

PTI-125 was rapidly absorbed and eliminated. T_{max} was 1 – 1.56 h, $T_{1/2}$ was 4.5 – 6 h and clearance was 0.14 – 0.16/h. PTI-125 showed dose proportional PK, with a C_{max} of 327, 565 and 1270 ng/mL for 50, 100 and 200 mg doses, respectively.

Dose	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{Extrap} (%)	λ_z (1/h)	$T_{1/2}$	T_{last}	C_{last}	CL/F	Vz/F
50 mg	1.56 ± 0.689	327 ± 96.7	2170 ± 893	0.411 ± 0.187	0.141 ± 0.0539	6.05 ± 3.88	44.0 ± 16.4	1.04 ± 0.497	25.7 ± 8.41	199 ± 64.9
100 mg	1.06 ± 0.491	565 ± 147	3260 ± 1150	0.151 ± 0.0366	0.157 ± 0.0154	4.45 ± 0.388	46.0 ± 4.90	0.760 ± 0.295	33.0 ± 8.16	215 ± 64.7
200 mg	1.28 ± 0.574	1270 ± 275	8100 ± 1650	0.0899 ± 0.0713	0.144 ± 0.0516	5.93 ± 3.87	50.0 ± 11.8	0.805 ± 0.291	25.5 ± 4.99	226 ± 182

CONCLUSIONS

PTI-125 was safe and well tolerated in this First-in-Human Phase I clinical trial in healthy volunteers. PTI-125 oral solution was rapidly absorbed and eliminated, with a 4.5 – 6 h half-life. PK was dose-proportional and consistent with preclinical studies. The 100 mg human dose is equivalent to the efficacious daily dose in 3xTg AD mice (22 mg/kg/day). By preferentially binding and reversing an altered conformation of FLNA in AD brain, PTI-125 blocks (1) $A\beta_{42}$'s toxic signaling via α7nAChR, which hyperphosphorylates tau, and (2) $A\beta_{42}$'s aberrant activation of TLR4, which promotes neuroinflammation. PTI-125 is a new drug candidate that has demonstrated a reduction in multiple AD-related neuropathologies in preclinical mouse models and in human postmortem AD brain tissue. PTI-125 was shown to be safe, well tolerated and dose-proportional in this First-in-Human study. These data support clinical evaluation of PTI-125 in Alzheimer's disease patients.

ACKNOWLEGEMENTS

This study was funded by NIA grant 1R44 AG056166.

PTI-125 Publications

1. Wang H-Y, Bakshi K, Frankfurt M, Stucky A, Goberdhan M, Shah SM, Burns LH. Reducing amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting filamin A. *J Neurosci* 2012;32:9773-84.

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

3. Burns LH and Wang HY. Altered filamin A enables Aβ-induced tau hyperphosphorylation and neuroinflammation in Alzheimer's disease. *Neuroimmunol Neuroinflamm, in press.*