TITLE: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential Cohort, Dose-Ranging Study of the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of TPI-287 in Patients with Mild to Moderate Alzheimer's Disease

PROTOCOL NO.: TPI287-AD-001

INVESTIGATIONAL DRUG: TPI 287

DOSAGE FORM: Injection, solution

INVESTIGATOR & IND SPONSOR:

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PROTOCOL SIGNATURE SHEET

The undersigned has reviewed the format and content of this protocol and has approved Protocol No. TPI287-AD-001 for issuance.

6/26/15

Adam Boxer, M.D., Ph.D.
Investigator & Investigational New Drug application (IND) Sponsor
University of California, San Francisco (UCSF)
Memory and Aging Center

Date

INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and of the preclinical and clinical information on the investigational drug to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the investigational drug and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), I will not modify this protocol without obtaining the prior approval of the IRB/IEC, except when necessary to protect the safety, rights, or welfare of subjects. I will submit the protocol modifications and/or any informed consent form (ICF) modifications to the IRB/IEC, and approval will be obtained before any modifications are implemented. Further, any such protocol modifications will be submitted to the Food and Drug Administration (FDA) prior to implementation.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (GCP) [current International Conference of Harmonisation (ICH) guidelines], and the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision.

Adam Boxer, M.D., Ph.D. Investigator & IND Sponsor UCSF Memory and Aging Center	Date

LIST OF ABBREVIATIONS

β-hCG	beta-chorionic gonadotropin
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ASL	arterial spin labeling
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero extrapolated to infinity
AUC_t	area under the concentration-time curve from time zero to time of last measurable concentration
BSA	body surface area
CBC	complete blood count
CFR	Code of Federal Regulations
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CT	computer tomography
CV	cardiovascular
CYP2C8	cytochrome P450 2C8
CYP3A4	cytochrome P450 3A4
DEHP	di(2-ethylhexyl)phthalate
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery

GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GRE	gradient-recalled echo
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug application
INR	International Normalized Ratio
IP	intraperitoneal
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
K_2	di-potassium
LC/MS-MS	liquid chromatography/tandem mass spectrometry
MDR	multidrug resistance
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemic Scale
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MRT	mean residence time
MTD	maximum tolerated dose
MW	molecular weight
NCI	National Cancer Institute
NF	National Formulary
NFT	neurofibrillary tangle
NOAEL	no-observed-adverse-effect-level
PD	pharmacodynamic
PHI	Protected Health Information
PK	pharmacokinetic
PT	prothrombin time
PTT	partial thromboplastin time
PVC	polyvinyl chloride
rsfMRI	resting state functional magnetic resonance imaging
SAE	serious adverse event
$t_{1/2}$	apparent terminal phase half- life
T_{max}	time to maximum concentration
UCSF	University of California, San Francisco
ULN	upper limit of normal
USP	United States Pharmacopeia
Vd	apparent volume of distribution

w/v	weight/volume
WCBP	women of childbearing potential

PROTOCOL SYNOPSIS

Name of Sponsor:	Adam Boxer, M.D., Ph.D. (Investigator-Sponsored IND)
Name of Finished Product:	TPI 287 Injection
Name of Active Ingredient:	TPI 287
Title of Study:	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential Cohort, Dose-Ranging Study of the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of TPI-287 in Patients with Mild to Moderate Alzheimer's Disease
Protocol No.:	TPI287-AD-001
Number of Study Centers:	Single-center (UCSF Memory and Aging Center, San Francisco, CA)
Phase of Development:	Phase 1
Study Period:	21 months (first subject enrolled to last subject completed)
Objectives:	**Primary Objectives** To determine the safety and tolerability [maximum tolerated dose (MTD) within planned dosing range] of intravenous (IV) infusions of TPI 287 administered once every 3 weeks for 9 weeks (for a total of 4 infusions) in patients with mild to moderate dementia of the Alzheimer's type (Alzheimer's disease, AD). **Secondary Objectives** To determine the pharmacokinetic (PK) profile of TPI 287 in plasma after a single IV infusion of TPI 287 and the steady-state cerebrospinal (CSF) concentration of TPI 287 1 week after completion of the fourth infusion. **Exploratory Objectives** 1. To explore the effects of TPI 287 on changes in the concentration of CSF biomarkers of AD [beta amyloid (1-42), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides] 1 week after completion of the fourth infusion of TPI 287 compared to Screening; 2. To explore the effects of TPI 287 on changes in brain network functional and structural connectivity and perfusion [connectivity between hippocampus and posterior cingulate as measured by resting state functional magnetic resonance imaging (rsfMRI), white matter fractional anisotropy within cortical tracts as measured by diffusion tensor imaging (DTI), and medial temporal lobe and regional cortical perfusion as measured by arterial spin labeling (ASL) perfusion MRI] 2 weeks after completion of the fourth infusion of TPI 287 compared to Screening; 3. To explore the effects of TPI 287 on changes in cognition, degree of disability, and behavior [Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), Alzheimer's Disease Cooperative Study-Activities

	of Daily Living Scale (ADCS-ADL), and Geriatric Depression Scale (GDS)] 1 week after completion of the fourth infusion of TPI 287 compared to Baseline (Day 1; for ADAS-cog and ADCS-ADL) or Screening (for MMSE and GDS); 4. To explore the safety of an optional additional 6 weeks of TPI 287 administered once every 3 weeks in an open-label extension phase (for a total of 7 infusions overall).
Methodology:	This is a phase 1, single-center, randomized, double-blind, placebo-controlled, sequential cohort, dose-ranging study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of TPI-287 in up to 33 patients with mild to moderate AD. All subjects will be administered study drug (placebo or active) as an IV infusion (target duration of 1 hour) once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase. The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For each dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. The dose escalation rules are as follows: If ≤1 of the 8 active subjects per cohort experiences dose limiting toxicity (DLT, as defined below) during the first 4 weeks (first 2 infusions and 1 week follow-up), the dose of TPI 287 for the next cohort will be escalated to the next higher planned dose level. If 2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to be the MTD and there will be no further dose escalation. If >2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to have exceeded the MTD and there will be no further dose escalation. Pending consultation with an independent, non-blinded Data Safety Monitoring Board (DSMB), the next cohort may be de-escalated to a lower dose to refine the MTD determination. No more than 3 cohorts will be enrolled in this trial. A DLT is defined as: 1) any Grade 3 or higher adverse event (AE) per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for which there is reasonable possibility that TPI 287 caused the event, 2) any Grade 2 AE in the CTCAE system organ class of nervous system disorders that is considered clinically significant and for which there is reasonable possibility that TPI 287 caused the event, or 3) any infusion-related toxicities (e.g., allergic reaction/hypersensitivity) occurring during the infusion of TPI 287 or within 24 hours after completing the infusion that do not resolve promptly with a reduced infusion rate and/or supportive care. Subjects that complete the placebo-controlled (dose-ranging) phase of this study, including the follow-up assessments 1 and 2 weeks after the last infusion with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension (for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the

	placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized. **Screening:** Each subject will be provided with an informed consent form (ICF) describing the study and will have any questions answered. Subjects that consent to participate in the study will undergo the following eligibility assessments: medical and surgical history, physical examination (including neurological examination), height and weight, vital signs (blood pressure, pulse rate, respiration rate, and temperature), 12-lead electrocardiogram (ECG), MMSE, GDS, Modified Hachinski Ischemic Scale (MHIS), safety labs [complete blood count (CBC) with differential, comprehensive metabolic panel, and urinalysis], coagulation tests [prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR)], serum pregnancy test for women of childbearing potential (WCBP), and recording of medications taken within 2 months of Screening visit, including those that are known to be inhibitors or enhancers of cytochrome P450 isoforms. Subjects who meet eligibility criteria after the initial screening assessments will have the following MRI procedures: rsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and gradient-recalled echo (GRE) sequences. Subjects who continue to meet eligibility criteria after the MRI screening assessments will have CSF collected via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of AD, and pre-dose assessment of TPI 287 concentration. Blood samples will also be collected for the purpose of banking deoxyribonucleic acid (DNA) and plasma for future research (approximately 10 and 5 mL, respectively). For subjects enrolled before banking was added to the protocol (and thus that missed the blood collections at Screening), collection of a blood sample for DNA banking will be allowed at a later time point up to and including the final study visit. Collection of the pre-dose plasma banking sample will not be allowed at a later time point; however, the scheduled post-dose draws will still be allowed (regardless of whether a pre-dose sample is available). **Study Day 1:** Subjects will return to the clinic on the morning of Day 1. Blood and urine will be collected for safety labs. The following baseline procedures will be completed **prior to enrollment** to confirm that the subject continues to meet eligibility criteria: updated medical history, physical examination (including neurological examination), weight [and calculation of body surface area (BSA) for the purpose of determining dose], vital signs, 12-lead ECG, ADAS-cog, ADCS-ADL, urine pregnancy test for WCBP, and recording of medications taken since initial Screening visit. Subjects that continue to meet all eligibility requirements after the above baseline assessments will be enrolled in the study and randomized to treatment. The study drug (placebo or active) will be administered in either an inpatient or outpatient facility. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions.

	Monitoring for treatment emergent AEs will begin immediately following the initiation of the study drug infusion and will continue throughout the study. Subjects will be given a diary to record any AEs or concomitant medications taken between visits. Subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Vital signs will be monitored at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion. For time points that include both vital signs and PK analysis, the vital signs will be taken first. Blood samples for the determination of TPI 287 plasma levels will be collected within an hour prior to the start of study drug infusion, at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion. To minimize discomfort, an indwelling cannula rather than repeated venipunctures will be used for the PK blood sampling. Topical anesthesia will be allowed to place the cannula. **Study Day 2:** Subjects will return to the clinic on the morning of Day 2 for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, collection of blood for determination of TPI 287 plasma levels (24 hours post-infusion), and safety labs. **Study Days 8 and 15:** Subjects will return to the clinic on the morning of Days 8 and 15 (-1 Day/+2 Days) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, and safety labs. **Study Days 22, 43, and 64:** Subjects will return to clinic on the morning of Days 22, 43, and 64 for the administration of study drug. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. **Prior to study drug administration**, the following procedures will be performed: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (calculation of BSA for dose determination), vital signs, 12-lead ECG, safety labs, coagulation tests (Day 64 only), and collection of blood for determination of trough levels of TPI 287 in plasma. The subjects will remain in the clinic for 1 hour after completion of the study drug infusion. Vital signs will be monitored at 0.25, 0.5, 1, and 2 hours after initiation of the infusion. **Final Study Visits for Placebo-Controlled Phase:** The final study visit for the placebo-controlled phase of the trial will occur during 2-3 visits, depending on whether the subject is eligible and opts to proceed with the open-label extension. All subjects will return to the clinic 1 week ± 3 days after the fourth study drug infusion for the following procedures: review of diary for any AEs or concomitant medications taken, vital signs, safety labs, collection of blood for determination of TPI 287 plasma level (for comparison with TPI 287 CSF level), collection of CSF via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of AD, and TPI 287 concentration, and collection of a blood sample (5 mL) for the banking of plasma for future research.

	A week later (2 weeks ± 3 days after the fourth study drug infusion), all subjects will return to the clinic for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, ADAS-cog, MMSE, ADCS-ADL, GDS, MRIs (rsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences), and safety labs. Following the above assessments, those subjects found to be ineligible for the open-label extension or that do not opt to participate in the open-label extension will return to the clinic 4 weeks ± 7 days after the fourth study drug infusion for the following final study procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, safety labs, and collection of a blood sample (5 mL) for the banking of plasma for future research. If a subject is discontinued from study drug treatment early during the placebo-controlled phase, all evaluations described for the above final study visits will be performed if feasible. Any subject with a suspected study drug-related AE at either final study visit will be followed until resolution or stabilization of the event. **Optional Open-Label Extension:** Subjects who are eligible and opt to proceed with the open-label extension will return to the clinic 3 weeks after their last dose of study drug in the placebo-controlled phase of the trial. The following procedures will be performed **prior to study drug administration**: subject signature and date on ICF consenting to optional procedures, review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (and calculation of BSA for dose determination), vital signs, 12-lead ECG, safety labs, and urine pregnancy test for WCBP. Study drug (active) will be administered following the completion of the above assessments. The subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Vital signs will be monitored at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion. Subjects will return to the clinic the following morning (24 hours post-infusion) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, and safety labs. Subjects will return to the clinic on the morning of Days 8 and 15 (-1 Day/+2 Days) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, and safety labs. Subjects will return to the clinic on the morning of Days 22 and 43. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. **Prior to study drug administration**, the following procedures will be performed: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (and calculation of BSA for dose

	determination), vital signs, 12-lead ECG (for second dose of open-label phase only), and safety labs. The subjects will remain in the clinic for 1 hour after completion of the study drug infusion. Vital signs will be monitored at 0.25, 0.5, 1, and 2 hours after initiation of the infusion. **Final Study Visit for Open-Label Phase:** Subjects will return to the clinic 4 weeks ± 7 days after the third study drug infusion of the open-label phase for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, ADAS-cog, ADCS-ADL, GDS, safety labs, and collection of a blood sample (5 mL) for the banking of plasma for future research. If a subject is discontinued from study drug treatment early during the open-label phase, all evaluations described for the above final study visit will be performed if feasible. Any subject with a suspected study drug-related AE at the final study visit will be followed until resolution or stabilization of the event. Any subject that experiences a DLT (as defined above) will be discontinued from further TPI 287 treatment. Dose escalation will only proceed per the criteria outlined above. Further, the trial as a whole, including enrollment of new subjects and dosing of ongoing subjects, will be temporarily stopped if either of the criteria listed below are met: 1. A death within 30 days after study drug administration where there is a reasonable possibility that the drug caused the event; 2. Two Grade 4 AEs where there is a reasonable possibility that the drug caused the events. The Investigator and DSMB will discuss whether a lower dose or any additional treatment guidelines should be implemented, or if the trial should be permanently stopped. Any proposed changes to the protocol to address such findings will be submitted for review and approval by the IRB and Food and Drug Administration (FDA) prior to re-starting the trial.
Number of Subjects (planned):	Up to 33 subjects, depending on the dose level at which toxicity is observed
Diagnosis and Main Criteria for Inclusion:	**Inclusion Criteria:** Subjects must meet **all** of the following inclusion criteria to be enrolled in this trial: 1. Between 50 and 82 years of age (inclusive); 2. Meets National Institute on Aging-Alzheimer's Association Workgroups criteria for probable AD dementia (McKhann et al. 2011); 3. MRI at Screening is consistent with AD (≤ 4 microhemorrhages, and no large strokes or severe white matter disease); 4. MHIS at Screening is ≤ 4; 5. MMSE at Screening is between 14 and 26 (inclusive); 6. FDA-approved AD medications are allowed as long as the dose is stable for 2 months prior to Screening. Other medications (except those listed under exclusion criteria) are

	allowed as long as the dose is stable for 30 days prior to Screening; 7. Has a reliable study partner who agrees to accompany the subject to visits, and spends at least 5 hours per week with the subject; 8. Agrees to 2 lumbar punctures; 9. Signed and dated written informed consent obtained from the subject and the subject's caregiver in accordance with local IRB regulations; 10. Males and all WCBP agree to abstain from sex or use an adequate method of contraception for the duration of the study and for 30 days after the last dose of study drug. **Exclusion Criteria:** Subjects meeting **any** of the following exclusion criteria will be excluded from the trial: 1. Any medical condition other than AD that could account for cognitive deficits (e.g., active seizure disorder, stroke, vascular dementia); 2. History of significant cardiovascular, hematologic, renal, or hepatic disease (or laboratory evidence thereof); 3. History of significant peripheral neuropathy; 4. History of major psychiatric illness or untreated depression; 5. Neutrophil count <1,500/mm^3, platelets <100,000/mm^3, serum creatinine >1.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN, alanine aminotransferase (ALT) >3 x ULN, aspartate aminotransferase (AST) >3 x ULN, or INR >1.2 at Screening; 6. Evidence of any clinically significant findings on Screening or baseline evaluations which, in the opinion of the Investigator would pose a safety risk or interfere with appropriate interpretation of study data; 7. Current or recent history (within four weeks prior to Screening) of a clinically significant bacterial, fungal, or mycobacterial infection; 8. Current clinically significant viral infection; 9. Major surgery within four weeks prior to Screening; 10. Unable to tolerate MRI scan at Screening; 11. Any contraindication to or unable to tolerate lumbar puncture at Screening, including use of anti-coagulant medications such as warfarin. Daily administration of 81 mg aspirin will be allowed as long as the dose is stable for 30 days prior to Screening; 12. Subjects who, in the opinion of the Investigator, are unable or unlikely to comply with the dosing schedule or study evaluations; 13. Previous exposure to microtubule inhibitors (including TPI 287) within 5 years of Screening; 14. Participation in another AD clinical trial within 3 months of Screening; 15. Treatment with another investigational drug within 30 days of Screening; 16. Known hypersensitivity to the inactive ingredients in the study drug; 17. Pregnant or lactating; 18. Positive pregnancy test at Screening or Baseline (Day 1); 19. Cancer within 5 years of Screening, except for non-metastatic skin cancer or non-metastatic prostate cancer not expected to cause significant morbidity or mortality within one year of Baseline.

Test Product, Dose and Mode of Administration:	**Active Pharmaceutical Ingredient** The investigational drug is TPI 287. TPI 287 is a microtubule inhibitor belonging to the taxane diterpenoid (taxoid) family, and specifically to the abeotaxane class. The chemical name of TPI 287 is (2'R,3'S)-2'-hydroxy-N-carboxy-3'-amino-5'-methyl-hexanoic,N-*tert*-butyl ester, 13 ester 5β-20-epoxy-1β,2α,4α,7β,9α,10α,13α-heptahydroxy-4,10-diacetate-2-benzoate-(1"S)-7,9-acrolein acetal-11(15 →1)-abeotaxane. TPI 287 has a molecular weight (MW) of 869.99 Da and a molecular formula of $C_{46}H_{63}NO_{15}$. **Drug Products** The dosage form of the investigational drug product is a sterile parenteral solution for IV infusion (TPI 287 Injection). The inactive ingredients are polyoxyl 35 castor oil [Kolliphor® ELP, previously named Cremophor® EL-P, National Formulary (NF)] and dehydrated alcohol, United States Pharmacopeia (USP). A single strength (10 mg/mL) of TPI 287 Injection will be used for this trial. Each single-use vial contains 10 mL of drug product with 100 mg of TPI 287 in a 15:85 mixture (weight/volume, w/v) of Kolliphor® ELP and dehydrated alcohol (1.58 g Kolliphor in quantity sufficient ethanol to 10 mL). TPI 287 Injection must be diluted prior to administration. The Investigational Site pharmacist will dilute the required volume of 10 mg/mL TPI 287 Injection in a di(2-ethylhexyl)phthalate- (DEHP-) free, non-polyvinyl chloride (non-PVC), 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP for administration. Based on the proposed doses (2, 6.3, and 20 mg/m^2) and assuming a 1.62 m^2 individual, the dilution of TPI 287 Injection will range from approximately 1,544- to 155.3-fold. The placebo to be used in this trial will be a DEHP-free, non-PVC, 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP. The final volume for administration will be approximately 500 mL. **Dose and Mode of Administration** All doses of study drug (placebo and active) will be administered in an inpatient or outpatient facility. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. An administration set comparable to those used for paclitaxel administration (i.e., a DEHP-free and/or polyethylene-lined IV administration set with an in-line 0.2 micron filter) must be used for study drug administration. The following administration sets or their equivalent may be used: Baxter Product Codes 2C7557, 2C8857, 2C8858, or 2C7558, B. Braun Product Code V9902F, CareFusion Product Code 10010454, CareFusion Product Code 28053 with 20350E extension, or Hospira Product Code 14248-28 with 20668-28 extension. TPI 287 must be administered as an IV infusion only (i.e., it should not be administered as an IV push or bolus). All doses of study drug will be administered as an IV infusion (target duration of 1 hour). The entire IV bag content will be administered, minus the volume that remains in the administration set (priming volume). A 0.9% Sodium Chloride for Injection, USP flush will then be used to ensure that the remainder of the TPI 287 dose in the line is administered to the subject.

	If a mild-to-moderate (Grade 1 to 2) hypersensitivity reaction is observed, the TPI 287 infusion rate may be reduced to half that of the initial attempt at the discretion of the Investigator. Further, this reduced rate may be used at subsequent infusions at the discretion of the Investigator. All subjects in this trial will be administered study drug (placebo or active) once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase. The dose of TPI 287 will be escalated in sequential cohorts. For each dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. Subjects that complete the placebo-controlled (dose-ranging) phase with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension (for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized.
Duration of Treatment:	9 weeks (for a total of 4 infusions) under the placebo-controlled (dose-ranging) phase, or 15 weeks (for a total of 7 infusions) if the subject is eligible and opts to participate in the open-label extension
Criteria for Evaluation:	**Primary Endpoints** Safety and tolerability (MTD within planned range) of IV infusions of TPI 287 administered once every 3 weeks for 9 weeks (for a total of 4 infusions) in patients with mild to moderate AD are the primary endpoints for this trial. Safety and tolerability will be assessed based on AEs, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PT/PTT/INR, CSF cell count with differential, glucose, and total protein, ADAS-cog, ADCS-ADL, GDS, and MRI (standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences). **Secondary Endpoints** The PK profile of TPI 287 in plasma after a single TPI 287 IV infusion (Day 1) and the steady-state CSF concentration of TPI 287 1 week after completion of the fourth TPI 287 infusion are the secondary endpoints for this trial. The plasma PK assessments will be based on maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from time zero to time of last measurable concentration (AUC_t), area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal phase half- life ($t_{1/2}$), clearance (CL), apparent volume of distribution (Vd), mean residence time (MRT), and trough concentrations (at Days 22, 43, and 64). **Exploratory Endpoints** 1. Changes in the concentration of CSF biomarkers of AD [beta amyloid (1-42), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides] 1 week after completion of the fourth infusion of TPI 287 compared to Screening;

	2. Changes in brain network functional and structural connectivity and perfusion (connectivity between hippocampus and posterior cingulate as measured by rsfMRI, white matter fractional anisotropy within cortical tracts as measured by DTI, and medial temporal lobe and regional cortical perfusion as measured by ASL perfusion MRI) 2 weeks after completion of the fourth infusion of TPI 287 compared to Screening; 3. Changes in cognition, degree of disability, and behavior (ADAS-cog, MMSE, ADCS-ADL, and GDS) 1 week after completion of the fourth infusion of TPI 287 compared to Baseline (Day 1; for ADAS-cog and ADCS-ADL) or Screening (for MMSE and GDS). 4. Safety of an optional additional 6 weeks of TPI 287 administered once every 3 weeks in an open-label extension phase(for a total of 7 infusions overall). Safety will be assessed based on AEs, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, ADAS-cog, ADCS-ADL, and GDS.
Statistical Methods:	**Safety** Data from all subjects who receive at least one dose of study drug (placebo or active) will be included in the safety analysis. AEs will be tabulated by body system and preferred term [per Medical Dictionary for Regulatory Activities (MedDRA)], and will be further categorized by treatment group, phase of trial [i.e., placebo-controlled (dose-ranging) phase versus open-label extension], severity, and assigned relationship to study drug. The incidence for each AE will be provided as the total number of subjects that experienced the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables. AEs will also be listed for individual subjects, along with information regarding onset, duration, severity, relationship to study drug, and outcome. AEs that lead to withdrawal from the study will be listed and summarized. A separate tabulation and listing of serious adverse events (SAEs) will also be generated. Other safety assessments, including physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PT/PTT/INR, CSF cell count with differential, glucose, and total protein, ADAS-cog, ADCS-ADL, GDS, and MRI (standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences) will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Inferential statistical analysis comparing the safety data among treatment groups or phases of the trial is not planned. The MTD of TPI 287 in patients with mild to moderate AD will be defined as the highest dose level achieved (within planned dosing range) at which no more than 2 of 8 active subjects experienced a DLT during the first 4 weeks (2 infusions and 1 week follow-up).

	Pharmacokinetics The concentration of TPI 287 in plasma and CSF will be measured using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methods. Individual and mean (standard deviation) plasma and CSF TPI 287 concentration data will be tabulated and plotted by dose level. Plasma TPI 287 concentration-time data will be analyzed by non-compartmental methods using WinNonlin (Pharsight Corporation, CA). PK parameters will be calculated according to standard equations. Individual PK parameters will be summarized by descriptive statistics for each dose group. The descriptive statistics will include arithmetic mean, standard deviation, median, minimum, maximum, and geometric mean (log-transformed). Inferential statistical analysis comparing PK data among treatment groups is not planned. **Exploratory Pharmacodynamics and Efficacy** CSF concentrations of beta amyloid (1-42), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides at Screening and 1 week after completion of the fourth study drug infusion, as well as the calculated changes in these measurements will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation). Inferential statistical analysis comparing data among treatment groups is not planned. Connectivity between hippocampus and posterior cingulate as measured by rsfMRI, white matter fractional anisotropy within cortical tracts as measured by DTI, and medial temporal lobe and regional cortical perfusion as measured by ASL perfusion MRI at Screening and 2 weeks after completion of the fourth study drug infusion, as well as the calculated changes in these measurements will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation). Inferential statistical analysis comparing data among treatment groups is not planned. ADAS-cog, MMSE, ADCS-ADL, and GDS assessments at Screening or Baseline and 1 week after completion of the fourth study drug infusion, as well as the calculated change in these assessments will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Analysis of variance (ANOVA) will be used to compare the changes in these assessments across treatment groups.

1. BACKGROUND

1.1 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition hallmarked by early short term memory loss, problems with word finding, and navigational deficits (Perry and Hodges 1999). The incidence of AD doubles every 5 years after age 65 (Mayeux 2003). Disease duration varies from 2-20 years (Mayeux 2003). It is estimated that 30% or more of all persons 85 and older suffer from this disease, making AD the most common cause of dementia in the world (Matthews 2010).

Pathologically, AD is characterized by the accumulation of extracellular neuritic plaques composed of beta amyloid and intracellular neurofibrillary tangles (NFTs) composed of abnormal (hyperphosphorylated) tau (Reitz et al. 2011). The amyloid plaques deposit diffusely in the cortex and the pattern of amyloid deposition does not appear to directly correlate with the severity or pattern of disease. On the other hand, the NFTs collect in a progressive pattern of brain tissue that correlates directly with symptomatic disease progression.

NFT deposition begins in the brainstem, moves to the entorhinal cortex, to the hippocampal regions and amygdala, and finally to the neocortex (Braak and Braak 1991; Jack et al. 2010). Recently, several studies have shown that abnormal forms of tau may spread from cell to cell in a trans-synaptic manner similar to that of prion disease, making tau a newly appreciated and desirable target for drug development (Liu et al. 2012; Nussbaum et al. 2012).

Brain atrophy patterns associated with AD include atrophy of the hippocampus, precuneus, and bilateral parietal lobes – the pattern of which in asymptomatic or mildly symptomatic patients may accurately predict underlying pathology (Rabinovici et al. 2007). Further, resting state analysis reveals a pattern of dysregulation in the salience network that may also contain predictive potential (Seeley et al. 2009). Lastly, current cerebrospinal (CSF) biomarkers beta amyloid, tau, and phosphorylated tau are able to accurately predict disease pathology and can present with changes that predate clinical symptoms by up to 20 years (Jack et al. 2010).

1.2 TPI 287

TPI 287 is being developed for the treatment of mild to moderate dementia of the Alzheimer's type (i.e., AD) under an Investigator-Sponsored IND (Adam Boxer, M.D., Ph.D., UCSF Memory and Aging Center).

This trial is a phase 1, single-center, randomized, double-blind, placebo-controlled, sequential cohort, dose-ranging study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of TPI-287 in up to 33 patients with mild to moderate AD.

All subjects will be administered study drug (placebo or active) as a 1-hour intravenous (IV) infusion once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase. TPI 287 will be formulated in 15:85 Kolliphor ELP:dehydrated alcohol and diluted approximately 155- to 1,544-fold with 0.9% Sodium Chloride for Injection prior to administration.

The dose of TPI 287 will be escalated in sequential cohorts. For each dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. Dose escalation will only be allowed if no more than 1 of the 8 active subjects per cohort experiences dose limiting toxicity (DLT) during the first 4 weeks (first two infusions and one week of follow-up).

Subjects that complete the placebo-controlled (dose-ranging) phase with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension (for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized.

The proposed clinical trial is the first trial of TPI 287 for AD, and thus there is no previous human experience with TPI 287 in patients with AD. However, TPI 287 has been in clinical development for the treatment of advanced recurrent or refractory cancers for over eight years under INDs 69,967 and 119,041 sponsored by Cortice Biosciences, Inc. (Cortice; previously known as Archer Biosciences, Inc.), as well as an Investigator-Sponsored IND (104,512) and MD Anderson Cancer Center-sponsored INDs (106,771 and 115,287) for which Cortice has provided study drug. Cortice will provide study drug (TPI 287 Injection) for the proposed clinical trial for AD.

TPI 287 is a microtubule inhibitor belonging to the taxane diterpenoid (taxoid) family, and specifically to the abeotaxane class. It is manufactured by a semi-synthetic process beginning from 10-deacetylbaccatin III extracted from yew (*Taxus baccata*). The synthesis involves modifications of the side chain to make the drug more lipophilic, and modifications of the baccatin ring structure with the intent of circumventing resistance associated with the expression of the multidrug resistance- (MDR-) 1 gene or mutations of β-tubulin.

The pharmacological rationale for developing TPI 287 for the treatment of AD is based on the proposed role that abnormal tau function plays in AD pathology and TPI 287's pharmacological

classification as a microtubule inhibitor. As reviewed by Yoshiyama et al. 2012, under normal physiological conditions, tau binds to microtubules and promotes assembly and stabilization of microtubules for axonal transport. The balance of phosphorylation and dephosphorylation of tau coordinates tau attachment to and from the microtubules, regulating microtubule stability and trafficking of cargo along the axon.

There is increasing evidence that loss of tau function in AD leads to insoluble tau deposits and destabilization and disassembly of microtubules, with a variety of deleterious effects on neurons including impaired axonal transport (Yoshiyama et al. 2012). Hyperphosphorylation of tau decreases the ability of tau to bind microtubules, leading to an abnormal increase in the levels of unbound tau that likely promotes its aggregation into filaments. These filaments are sequestered into NFTs, thereby depleting functional tau.

TPI 287 binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This inhibition of microtubule dynamics leads to stabilization of the microtubules, which in the context of AD patients is hypothesized to compensate for the loss in tau function and decrease insoluble hyperphosphorylated tau deposition, resulting in restoration of axonal transport, improved cognitive function, and decreased neurodegeneration.

This hypothesis is supported by an *in vitro* tubulin polymerization assay that showed TPI 287 promoted the assembly of microtubules with a potency similar to or exceeding that of paclitaxel, docetaxel, and epothilone B (Section 8 of IND). Further, tau transgenic mouse model studies of other drugs in the same pharmacological class (i.e., microtubule inhibitors) showed that the stabilization of microtubules by such drugs can compensate for loss of tau function and decrease tau pathology, resulting in restoration of axonal transport, improved cognitive function, and decreased neurodegeneration, and thus such microtubule inhibitors may have therapeutic potential for treating AD (Zhang et al. 2005, Brunden et al. 2010, Barten et al. 2012, and Zhang et al. 2012).

The initial steps in the mechanism of action for TPI 287 for the treatment of cancer are conceptually similar to those for the treatment of AD. The difference is that the level of stabilization of microtubules at high TPI 287 doses results in the inhibition of mitotic and interphase cellular functions and cell death. Thus, unlike for AD patients (with a loss in tau function) where low dose TPI 287 microtubule stabilization is hypothesized to lead to restoration of function, in cancer cells, high dose TPI 287 leads to higher levels of microtubule stabilization resulting in inhibition of cellular function and cell death.

The pharmacologically active dose of TPI 287 for the AD indication (i.e., for restoration of function) is hypothesized to be lower than that for the cancer indication (i.e., for inhibition of cell function and cell death). This is based on tau transgenic mouse model studies of paclitaxel and epothilone D that showed efficacy at weekly intraperitoneal (IP) dose levels 10 mg/kg

(30 mg/m^2) and 1 mg/kg (3 mg/m^2), respectively, the *in vitro* tubulin polymerization assay showing that TPI 287 had a potency similar to or exceeding that of paclitaxel and epothilone B, and a pharmacokinetic (PK) study in mice and rats demonstrating that TPI 287 is able to effectively cross the blood brain barrier. The planned dose levels for the proposed trial are significantly lower than those used for the same schedule for the cancer indication (i.e., 160 mg/m^2), yet are anticipated to be pharmacologically active.

Five clinical trials of TPI 287 for the treatment of cancer have been conducted under Cortice IND 69,967, including three phase 1 trials and two phase 2 trials (all single agent), and two clinical trials of TPI 287 for the treatment of cancer have been initiated under Cortice IND 119,041, including two phase 2 trials (both combination agent). In addition, seven clinical trials of TPI 287 for the treatment of cancer have been initiated under an Investigator-Sponsored IND (104,512) or MDACC-sponsored INDs (106,771 and 115,287), including one phase 1 trial (single and combination agent), three phase 1/2 trials (one single agent, one combination agent, and one with single and combination agent components), and three phase 2 trials (one single agent and two with single and combination agent components). Four of the seven trials are ongoing.

Over 190 cancer patients have been treated with TPI 287 in the above referenced trials at dose levels ranging from 7 to 185 mg/m^2 and for durations ranging from 1 day to 10 months. The dosing regimens used for the cancer indication include 1-hour IV infusions once every week for three weeks with the fourth week off (4-week cycle), once every week for three weeks without the fourth week off (condensed weekly regimen), or once every three weeks (21-day cycle). The latter is the proposed dosing regimen for this trial of TPI 287 in AD patients.

The maximum tolerated dose (MTD) for the once every three week dosing regimen in cancer patients was determined to be 160 mg/m^2. The proposed starting dose for the trial in AD patients is 80-fold lower than this MTD. Further, the maximum planned dose level for the proposed dose-escalation trial is 8-fold lower. There were no trials of the once every three week dosing regimen at dose levels as low as those proposed for the AD trial (i.e., 2-20 mg/m^2). At the lowest dose level tested for this schedule in cancer patients (56 mg/m^2), there were no adverse events (AEs) considered possibly, probably, or definitely related to TPI 287, except for Grade 1 nausea.

Dose levels within the proposed range for the trial in AD patients (i.e., 2-20 mg/m^2) were tested for the more frequent dosing schedule (i.e., once weekly for three weeks with the fourth week off). At 7 or 14 mg/m^2 TPI 287, AEs considered possibly, probably, or definitely related to TPI 287 included diarrhoea, nausea, vomiting, fatigue, anorexia, back pain, balance disorder, dizziness, headache, dyspnoea, alopecia, and flushing. All of these occurred at severities no greater than Grade 1 or 2, except for the back pain, dizziness, dyspnoea, and flushing that

occurred at Grade 3 at 14 mg/m^2. The MTD for the once weekly for three weeks with fourth week off dosing regimen in cancer patients was determined to be 127.5 mg/m^2.

Nonclinical safety pharmacology studies of single IV injections of TPI 287 formulated in Kolliphor ELP and diluted 10-fold in 0.9% sodium chloride resulted in no central nervous system (CNS) or respiratory adverse findings in rats and no cardiovascular (CV) adverse findings in dogs. The human equivalent doses for the highest doses tested in the rat and dog safety pharmacology studies were 148 mg/m^2 and 207.2 mg/m^2, respectively. The proposed starting dose for this trial is 74- and 103.6-fold lower, respectively, than these dose levels associated with no adverse findings.

The proposed starting dose is also 43-fold below the human equivalent dose of the no-observed-adverse-effect-level (NOAEL) determined for the rat (most sensitive species) single dose IV injection toxicity study. It is 20-fold below the human equivalent dose of the lowest dose tested in the rat once a week for three week IV injection toxicity study; the NOAEL could not be determined from the dose levels tested in the study.

In summary, the previous human experience with TPI 287 in cancer patients indicates that the proposed dosing regimen will be well tolerated in patients with AD. This coupled with the preclinical rationale for efficacy, the supporting nonclinical toxicology studies, and the planned safety monitoring/precautions indicate that the proposed clinical trial of TPI 287 in patients with AD, for which there is no known curative therapy appears reasonably safe to initiate.

For further details regarding the nonclinical and clinical studies of TPI 287 please refer to the most current application (Sections 8 and 9).

This study will be performed in compliance with the current ICH guidelines for GCP and all applicable regulatory requirements.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this trial are to determine the safety and tolerability (MTD within planned dosing range) of IV infusions of TPI 287 administered once every 3 weeks for 9 weeks (for a total of 4 infusions) in patients with mild to moderate dementia of the Alzheimer's type (AD).

2.2 Secondary Objectives

The secondary objectives of this trial are to determine the PK profile of TPI 287 in plasma after a single IV infusion of TPI 287 and the steady-state CSF concentration of TPI 287 1 week after completion of the fourth infusion.

2.3 Exploratory Objectives

The exploratory objectives of this trial are as follows:

1. To explore the effects of TPI 287 on changes in the concentration of CSF biomarkers of AD [beta amyloid (1-42), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides] 1 week after completion of the fourth infusion of TPI 287 compared to Screening;

2. To explore the effects of TPI 287 on changes in brain network functional and structural connectivity and perfusion [connectivity between hippocampus and posterior cingulate as measured by resting state functional magnetic resonance imaging (rsfMRI), white matter fractional anisotropy within cortical tracts as measured by diffusion tensor imaging (DTI), and medial temporal lobe and regional cortical perfusion as measured by arterial spin labeling (ASL) perfusion MRI] 2 weeks after completion of the fourth infusion of TPI 287 compared to Screening;

3. To explore the effects of TPI 287 on changes in cognition, degree of disability, and behavior [Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), Alzheimer’s Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL), and Geriatric Depression Scale (GDS)] 1 week after completion of the fourth infusion of TPI 287 compared to Baseline (Day 1; for ADAS-cog and ADCS-ADL) or Screening (for MMSE and GDS);

4. To explore the safety of an optional additional 6 weeks of TPI 287 administered once every 3 weeks in an open-label extension phase (for a total of 7 infusions overall).

3. STUDY DESIGN

This is a phase 1, single-center, randomized, double-blind, placebo-controlled, sequential cohort, dose-ranging study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of TPI-287 in up to 33 patients with mild to moderate AD. All subjects will be administered study drug (placebo or active) as an IV infusion (target duration of 1 hour) once

every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase.

The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For each dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. The dose escalation rules are as follows:

If ≤1 of the 8 active subjects per cohort experiences DLT (as defined below) during the first 4 weeks (first 2 infusions and 1 week follow-up), the dose of TPI 287 for the next cohort will be escalated to the next higher planned dose level.

If 2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to be the MTD and there will be no further dose escalation.

If >2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to have exceeded the MTD and there will be no further dose escalation. Pending consultation with an independent, non-blinded Data Safety Monitoring Board (DSMB), the next cohort may be de-escalated to a lower dose to refine the MTD determination. No more than 3 dose cohorts will be enrolled in this trial.

A DLT is defined as: 1) any Grade 3 or higher AE per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for which there is reasonable possibility that TPI 287 caused the event, 2) any Grade 2 AE in the CTCAE system organ class of nervous system disorders that is considered clinically significant and for which there is reasonable possibility that TPI 287 caused the event, or 3) any infusion-related toxicities (e.g., allergic reaction/hypersensitivity) occurring during the infusion of TPI 287 or within 24 hours after completing the infusion that do not resolve promptly with a reduced infusion rate and/or supportive care.

Subjects that complete the placebo-controlled (dose-ranging) phase of this study, including the follow-up assessments 1 and 2 weeks after the last infusion with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension(for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized.

Screening: Each subject will be provided with an ICF describing the study and will have any questions answered. Subjects that consent to participate in the study will undergo the following eligibility assessments: medical and surgical history, physical examination (including

neurological examination), height and weight, vital signs (blood pressure, pulse rate, respiration rate, and temperature), 12-lead electrocardiogram (ECG), MMSE, GDS, Modified Hachinski Ischemic Scale (MHIS), safety labs [complete blood count (CBC) with differential, comprehensive metabolic panel, and urinalysis], coagulation tests [prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR)], serum pregnancy test for women of childbearing potential (WCBP), and recording of medications taken within 2 months of Screening visit, including those that are known to be inhibitors or enhancers of cytochrome P450 isoforms.

Subjects who meet eligibility criteria after the initial screening assessments will have the following MRI procedures: rsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and gradient-recalled echo (GRE) sequences.

Subjects who continue to meet eligibility criteria after the MRI screening assessments will have CSF collected via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of AD, and pre-dose assessment of TPI 287 concentration.

Blood samples will also be collected for the purpose of banking deoxyribonucleic acid (DNA) and plasma for future research (approximately 10 and 5 mL, respectively). For subjects enrolled before banking was added to the protocol (and thus that missed the blood collections at Screening), collection of a blood sample for DNA banking will be allowed at a later time point up to and including the final study visit. Collection of the pre-dose plasma banking sample will not be allowed at a later time point; however, the scheduled post-dose draws will still be allowed (regardless of whether a pre-dose sample is available).

Study Day 1: Subjects will return to the clinic on the morning of Day 1. Blood and urine will be collected for safety labs. The following baseline procedures will be completed **prior to enrollment** to confirm that the subject continues to meet eligibility criteria: updated medical history, physical examination (including neurological examination), weight [and calculation of body surface area (BSA) for the purpose of determining dose], vital signs, 12-lead ECG, ADAS-cog, ADCS-ADL, urine pregnancy test for WCBP, and recording of medications taken since initial Screening visit.

Subjects that continue to meet all eligibility requirements after the above baseline assessments will be enrolled in the study and randomized to treatment. The study drug (placebo or active) will be administered in either an inpatient or outpatient facility. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions.

Monitoring for treatment emergent AEs will begin immediately following the initiation of the study drug infusion and will continue throughout the study. Subjects will be given a diary to record any AEs or concomitant medications taken between visits.

Subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Vital signs will be monitored at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion. For time points that include both vital signs and PK analysis, the vital signs will be taken first.

Blood samples for the determination of TPI 287 plasma levels will be collected within an hour prior to the start of study drug infusion, at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion. To minimize discomfort, an indwelling cannula rather than repeated venipunctures will be used for the PK blood sampling. Topical anesthesia will be allowed to place the cannula.

Study Day 2: Subjects will return to the clinic on the morning of Day 2 for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, collection of blood for determination of TPI 287 plasma levels (24 hours post-infusion), and safety labs.

Study Days 8 and 15: Subjects will return to the clinic on the morning of Days 8 and 15 (-1 Day/+2 Days) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, and safety labs.

Study Days 22, 43, and 64: Subjects will return to clinic on the morning of Days 22, 43, and 64 for the administration of study drug. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. **Prior to study drug administration**, the following procedures will be performed: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (calculation of BSA for dose determination), vital signs, 12-lead ECG, safety labs, coagulation tests (Day 64 only), and collection of blood for determination of trough levels of TPI 287 in plasma. The subjects will remain in the clinic for 1 hour after completion of the study drug infusion. Vital signs will be monitored at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Final Study Visits for Placebo-Controlled Phase: The final study visit for the placebo-controlled phase of the trial will occur during 2-3 visits, depending on whether the subject is eligible and opts to proceed with the open-label extension. All subjects will return to the clinic 1 week ± 3 days after the fourth study drug infusion for the following procedures: review of diary for any AEs or concomitant medications taken, vital signs, safety labs, collection of blood

for determination of TPI 287 plasma level (for comparison with TPI 287 CSF level), collection of CSF via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of AD, and TPI 287 concentration, and collection of a blood sample (5 mL) for the banking of plasma for future research.

A week later (2 weeks ± 3 days after the fourth study drug infusion), all subjects will return to the clinic for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, ADAS-cog, MMSE, ADCS-ADL, GDS, MRIs (rsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences), and safety labs.

Following the above assessments, those subjects found to be ineligible for the open-label extension or that do not opt to participate in the open-label extension will return to the clinic 4 weeks ± 7 days after the fourth study drug infusion for the following final study procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, safety labs, and collection of a blood sample (5 mL) for the banking of plasma for future research.

If a subject is discontinued from study drug treatment early during the placebo-controlled phase, all evaluations described for the above final study visits will be performed if feasible. Any subject with a possible study drug-related AE at either final study visit will be followed until resolution or stabilization of the event.

Optional Open-Label Extension: Subjects who are eligible and opt to proceed with the open-label extension will return to the clinic 3 weeks after their last dose of study drug in the placebo-controlled phase of the trial. The following procedures will be performed **prior to study drug administration**: subject signature and date on ICF consenting to optional procedures, review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (and calculation of BSA for dose determination), vital signs, 12-lead ECG, safety labs, and urine pregnancy test for WCBP.

Study drug (active) will be administered following the completion of the above assessments. The subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Vital signs will be monitored at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion.

Subjects will return to the clinic the following morning (24 hours post-infusion) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, and safety labs.

Subjects will return to the clinic on the morning of Days 8 and 15 (-1 Day/+2 Days) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, and safety labs.

Subjects will return to the clinic on the morning of Days 22 and 43. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. **Prior to study drug administration**, the following procedures will be performed: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (and calculation of BSA for dose determination), vital signs, 12-lead ECG (for second dose of open-label phase only), and safety labs. The subjects will remain in the clinic for 1 hour after completion of the study drug infusion. Vital signs will be monitored at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Final Study Visit for Open-Label Phase: Subjects will return to the clinic 4 weeks ± 7 days after the third study drug infusion of the open-label phase for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, ADAS-cog, ADCS-ADL, GDS, safety labs, and collection of a blood sample (5 mL) for the banking of plasma for future research.

If a subject is discontinued from study drug treatment early during the open-label phase, all evaluations described for the above final study visit will be performed if feasible. Any subject with a possible study drug-related AE at the final study visit will be followed until resolution or stabilization of the event.

4. ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

A subject may be included in this study if he or she meets **all** of the following criteria:

1. Between 50 and 82 years of age (inclusive);

2. Meets National Institute on Aging-Alzheimer's Association Workgroups criteria for probable AD dementia (McKhann et al. 2011; Appendix 1);

3. MRI at Screening is consistent with AD (≤ 4 microhemorrhages, and no large strokes or severe white matter disease);

4. MHIS at Screening is ≤ 4;

5. MMSE at Screening is between 14 and 26 (inclusive);

6. FDA-approved AD medications are allowed as long as the dose is stable for 2 months prior to Screening. Other medications (except those listed under exclusion criteria) are allowed as long as the dose is stable for 30 days prior to Screening;

7. Has a reliable study partner who agrees to accompany the subject to visits, and spends at least 5 hours per week with the subject;

8. Agrees to 2 lumbar punctures;

9. Signed and dated written informed consent obtained from the subject and the subject's caregiver in accordance with local IRB regulations;

10. Males and all WCBP agree to abstain from sex or use an adequate method of contraception for the duration of the study and for 30 days after the last dose of study drug.

    Adequate contraceptive methods include those with a low failure rate, i.e., less than 1% per year, when used consistently and correctly, such as complete abstinence from sexual intercourse with a potentially fertile partner, and some double barrier methods (condom with spermicide) in conjunction with use by the partner of an intrauterine device (IUD), diaphragm with spermicide, oral contraceptives, birth control patch or vaginal ring, oral, or injectable or implanted contraceptives.

    For this study, a woman who has been surgically sterilized or who has been in a state of amenorrhea for more than two years will be deemed not to be of childbearing potential;

4.2 Exclusion Criteria

A subject will be excluded from this study if he or she meets **any** of the following criteria:

1. Any medical condition other than AD that could account for cognitive deficits (e.g., active seizure disorder, stroke, vascular dementia);

2. History of significant cardiovascular, hematologic, renal, or hepatic disease (or laboratory evidence thereof);

3. History of significant peripheral neuropathy;

4. History of major psychiatric illness or untreated depression;

5. Neutrophil count <1,500/mm^3, platelets <100,000/mm^3, serum creatinine >1.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN, alanine aminotransferase (ALT) >3 x ULN, aspartate aminotransferase (AST) >3 x ULN, or INR >1.2 at Screening;

6. Evidence of any clinically significant findings on Screening or baseline evaluations which, in the opinion of the Investigator would pose a safety risk or interfere with appropriate interpretation of study data;

7. Current or recent history (within four weeks prior to Screening) of a clinically significant bacterial, fungal, or mycobacterial infection;

8. Current clinically significant viral infection;

9. Major surgery within four weeks prior to Screening;

10. Unable to tolerate MRI scan at Screening;

11. Any contraindication to or unable to tolerate lumbar puncture at Screening, including use of anti-coagulant medications such as warfarin. Daily administration of 81 mg aspirin will be allowed as long as the dose is stable for 30 days prior to Screening;

12. Subjects who, in the opinion of the Investigator, are unable or unlikely to comply with the dosing schedule or study evaluations;

13. Previous exposure to microtubule inhibitors (including TPI 287) within 5 years of Screening. Treatment with microtubule inhibitors other than TPI 287 while on study will not be allowed;

14. Participation in another AD clinical trial within 3 months of Screening;

15. Treatment with another investigational drug within 30 days of Screening. Treatment with investigational drugs other than TPI 287 while on study will not be allowed;

16. Known hypersensitivity to the inactive ingredients in the study drug;

17. Pregnant or lactating;

18. Positive pregnancy test at Screening or Baseline (Day 1);

19. Cancer within 5 years of Screening, except for non-metastatic skin cancer or non-metastatic prostate cancer not expected to cause significant morbidity or mortality within one year of Baseline.

4.3 Withdrawal of Subjects

A subject may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

A subject will be withdrawn from this study if one or more of the following events occur:

1. Subject requests to be withdrawn from study;

2. DLT (as defined in Section 3);

3. AE that in the judgment of the Investigator poses unacceptable risk to the subject;

4. Intercurrent illness that requires treatment that is not consistent with the protocol requirements, or intercurrent illness or the associated treatment that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study;

5. Pregnant or suspected of being pregnant;

6. Use of prohibited medication (listed in Section 5.7) that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study or that will interfere with the interpretation of the results of this study;

7. Significant protocol violation or noncompliance on the part of the subject or the Investigator;

8. Investigator terminates the study;

9. Any other reason that in the judgment of Investigator poses unacceptable risk to the subject.

If a subject is withdrawn from the study, the date and reason will be recorded in the source documents and the case report form (CRF), and final study visit evaluations will be performed if feasible. Any subject withdrawn due to a suspected study drug-related AE will be followed until resolution or stabilization of the event.

If subject becomes pregnant or is suspected of being pregnant, study drug will be discontinued immediately, and the subject will be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The subject will be followed until delivery or other termination of pregnancy for outcome.

Subjects may choose to withdraw authorization to use and disclose their Protected Health Information (PHI) as defined by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 or foreign equivalent where appropriate. Such withdrawal of authorization must be made to the Investigator in writing. Any PHI collected by the Investigator prior to the date of such withdrawal will continue to be used and disclosed.

4.4 Replacement of Subjects

Subjects who are withdrawn from the study for reasons other than DLTs may be replaced at the Investigator's discretion.

4.5 Termination of Trial

The Investigator has the right to terminate this study at any time. The Investigator will notify the IRB/IEC in writing of a premature termination of the study.

Events that may trigger premature termination of the study include, but are not limited to, a new toxicity finding, a request to discontinue the trial from a regulatory authority, non-compliance with the protocol, slow recruitment, or change in development plans for the study drug.

The trial as a whole, including enrollment of new subjects and dosing of ongoing subjects, will be temporarily stopped if **either** of the criteria listed below are met:

1. A death within 30 days after study drug administration where there is a reasonable possibility that the drug caused the event;

2. Two Grade 4 AEs where there is a reasonable possibility that the drug caused the events.

The Investigator and DSMB will discuss whether a lower dose or any additional treatment guidelines should be implemented, or if the trial should be permanently stopped. Any proposed changes to the protocol to address such findings will be submitted for review and approval by the IRB and FDA prior to re-starting the trial.

5. STUDY DRUG

5.1 Description of Investigational Drug

5.1.1 Active Pharmaceutical Ingredient

The investigational drug is TPI 287. TPI 287 is a microtubule inhibitor belonging to the taxane diterpenoid (taxoid) family, and specifically to the abeotaxane class. The chemical name of TPI 287 is (2'R,3'S)-2'-hydroxy-N-carboxy-3'-amino-5'-methyl-hexanoic,N-*tert*-butyl ester, 13 ester 5β-20-epoxy-1β,2α,4α,7β,9α,10α,13α-heptahydroxy-4,10-diacetate-2-benzoate-(1"S)-7,9-acrolein acetal-11(15→1)-abeotaxane. TPI 287 has a molecular weight (MW) of 869.99 and a molecular formula of $C_{46}H_{63}NO_{15}$.

5.1.2 Drug Product

The dosage form of the investigational drug product, TPI 287 Injection, is a sterile parenteral solution for IV infusion. The inactive ingredients are polyoxyl 35 castor oil [Kolliphor® ELP, previously named Cremophor® EL-P, National Formulary (NF)] and dehydrated alcohol, United States Pharmacopeia (USP).

A single strength (10 mg/mL) of TPI 287 Injection will be used for this study. Each single-use vial contains 10 mL of drug product with 100 mg of TPI 287 in a 15:85 mixture (weight/volume, w/v) of Kolliphor® ELP and dehydrated alcohol (1.58 g Kolliphor in quantity sufficient ethanol to 10 mL).

5.1.3 Packaging and Labeling

Cortice will supply the study drug (TPI 287 Injection) for this trial. TPI 287 Injection, 10 mg/mL (15:85 Kolliphor® ELP:dehydrated alcohol) will be provided as 10-mL single-use vials (Type I USP flint glass) with Teflon-coated butyl stoppers, and aluminum flip-off caps.

The study drug vial will be labeled according to the requirements of local law and legislation. A copy of the label will be provided by Cortice for inclusion in the study files.

The Investigational Site pharmacist will not be blinded to the study drug, and thus the labeling of the vials will not be blinded for this study.

5.1.4 Storage and Handling

At the Investigational Site, all investigational study drug will be stored in a locked, secure area to prevent unauthorized access. TPI 287 Injection will be stored in the provided packaging (vial) in the upright position out of direct sunlight and at controlled room temperature (68 to 77°F; 20 to 25°C). Excursions between 59 to 86°F (15 to 30°C) are permitted. The diluted TPI 287 will be stored at room temperature and must be used within 12 hours of preparation.

Appropriate care should be exercised when handling the investigational drug product, as TPI 287 is a cytotoxic agent. Unused investigational drug product should be disposed of using proper procedures as defined by investigational site standard operating procedures.

5.2 Randomization

This is a randomized, double-blind, placebo-controlled study. The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For each dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2.

Only subjects that meet all eligibility criteria at Screening and subsequent baseline evaluations will be randomized to treatment. Randomization will take place on Day 1 after completion of the following baseline evaluations: updated medical history, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, ADAS-cog, ADCS-ADL, urine pregnancy test for WCBP, and recording of medications taken since initial Screening visit.

A computer-generated randomization schedule will be used for assigning the sequence in which subjects are assigned to placebo and active treatment. The Investigational Site pharmacist will be responsible for generating and maintaining the randomization schedule, and will assign a randomization code to each subject upon enrollment.

This study will continue to be double-blinded during the open-label extension (i.e., although the investigator and subjects will know they are receiving TPI 287 during the open-label extension, they will not know what the subject received during the placebo-controlled phase).

5.3 Preparation and Administration of Study Drug

TPI 287 Injection **must be diluted prior to administration**. The Investigational Site pharmacist will dilute the required volume of 10 mg/mL TPI 287 Injection drug product in a di(2-ethylhexyl)phthalate- (DEHP-) free, non-polyvinyl chloride (non-PVC), 500 mL IV bag of

0.9% Sodium Chloride for Injection, USP. Appropriate aseptic technique will be used. The volume of drug product required to deliver the protocol-specified dose will be removed from the single-use TPI 287 Injection vial via a sterile, pyrogen-free needle and added to the 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP. The solution will be mixed thoroughly for 10 to 15 seconds by carefully squeezing and shaking the IV bag.

If particulate matter or discoloration is observed on visual inspection of the single-use vial of TPI 287 Injection or the resulting diluted product, the study drug should not be used for administration.

The planned dose levels of TPI 287 are 2, 6.3, and 20 mg/m^2, and will be based on BSA determinations made prior to each study drug administration. Assuming an average BSA of 1.62 mg/m^2, the planned dose levels correspond to 3.24, 10.21, and 32.4 mg TPI 287 and 0.32, 1.02, and 3.24 mL of the 10 mg/mL TPI 287 Injection drug product, respectively. Dilution of these amounts of TPI 287 Injection drug product into 500 mL IV bags of 0.9% Sodium Chloride for Injection, USP will result in approximate final concentrations of 0.006, 0.02, and 0.064 mg/mL, respectively. Per USP, the IV bags are filled with sufficient excess (i.e., more than 500 mL), and thus these are approximations of the maximum concentrations for this particular BSA.

The placebo to be used in this trial will be a DEHP-free, non-PVC, 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP. The final volume for placebo administration will be approximately 500 mL (see further details regarding administration below).

All doses of study drug (placebo and active) will be administered in either an inpatient or outpatient facility. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions.

An administration set comparable to those used for paclitaxel administration (i.e., a DEHP-free and/or polyethylene-lined IV administration set with an in-line 0.2 micron filter) must be used for study drug administration. The following administration sets or their equivalent may be used: Baxter Product Codes 2C7557, 2C8857, 2C8858, or 2C7558, B. Braun Product Code V9902F, CareFusion Product Code 10010454, CareFusion Product Code 28053 with 20350E extension, or Hospira Product Code 14248-28 with 20668-28 extension. If an administration set with a vent is used, the vent should be closed.

All doses of study drug will be administered as an IV infusion with a targeted duration of 1 hour. A window of ± 15 minutes will be permitted (and will not be considered a protocol deviation). If a mild-to-moderate (Grade 1 to 2) hypersensitivity reaction is observed, the TPI 287 infusion rate may be reduced to half that of the initial attempt at the discretion of the Investigator. Further, this reduced rate may be used at subsequent infusions at the discretion of the Investigator.

An infusion pump must be used for administration of the study drug. The target duration (1 hour) and nominal study drug volume (500 mL + the mL of 10 mg/mL TPI 287 Injection added to the bag) should be used as the pump entries to determine the rate of infusion. However, the pump should not automatically be turned off at 1 hour. Instead, the bag should be monitored closely as the infusion duration nears 1 hour to **ensure that the entire IV bag content, minus the volume that remains in the administration set (priming volume) is administered. A 0.9% Sodium Chloride for Injection, USP flush should then be used to ensure that the remainder of the TPI 287 dose in the line is administered to the subject.**

All subjects will be administered study drug (placebo or active) once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase. The dose of TPI 287 will be escalated in sequential cohorts. For each dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. See Section 3 for dose cohort escalation rules.

Subjects that complete the placebo-controlled (dose-ranging) phase with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension (for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized.

5.4 Premedication

The TPI 287 formulation to be used in this trial contains Kolliphor® ELP at a concentration of 158 mg/mL. At the proposed TPI 287 dose range (and assuming a 1.62 m^2 individual), the corresponding dose of Kolliphor will range from 51 to 512 mg. This will be diluted approximately 1,544- to 155.3-fold in a 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP prior to administration, yielding approximate final concentrations of Kolliphor of 0.1023 to 1.017 mg/mL, respectively. Per USP, the IV bags are filled with sufficient excess (i.e., more than 500 mL), and thus these are approximations of the maximum concentrations for this particular BSA. The diluted study drug/Kolliphor will be administered as a one hour IV infusion.

These doses of Kolliphor are 80- to 8-fold lower, respectively, than the dose of Kolliphor administered at the 160 mg/m^2 TPI 287 MTD dose administered to cancer subjects under the same dosing schedule (i.e. 1-hour infusion once every 3 weeks). Further, the concentrations of Kolliphor to be administered are 145- to 15-fold lower, respectively, than the concentration of Kolliphor administered at the 160 mg/m^2 TPI 287 dose in cancer subjects.

Given the above, the risk of anaphylaxis or severe hypersensitivity reactions to the Kolliphor component of the TPI 287 formulation is anticipated to be relatively low in this trial. However, as a precaution, the study drug will be administered in an inpatient or outpatient facility with experience in treating such reactions. Specifically, a crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions.

In the clinical trials of TPI 287 in cancer subjects, where the dose and concentration of Kolliphor are significantly higher, all subjects are premedicated prior to TPI 287 administration to prevent any potential hypersensitivity reactions. The premedications used include a corticosteroid, an antihistamine, and an H2 blocker. Under Versions 1-2 of this protocol for Alzheimer's subjects, premedication was not used given the planned lower dose and concentration of Kolliphor.

The addition of an antihistamine premedication requirement was added to this protocol under Version 3 as a result of 2 of 6 subjects experiencing reactions during or after a study drug (placebo or active) infusion. Each of these events is summarized briefly below.

- Subject No. 005-04: 55-year-old female Japanese-American experienced Grade 1 hypertension (182 mmHg/74 mmHg) and Grade 1 flushing 2-3 minutes after the start of her second study drug infusion (placebo or 2 mg/m^2 TPI 287). These events resolved spontaneously. About an hour later, she developed a Grade 1 unilateral, rash in the left antecubital fossa in the same arm where the infusion had been delivered into a vein on the dorsal aspect of the hand. The subject was administered 50 mg of IV diphenhydramine and the rash completely resolved in less than one hour.

- Subject No. 006-05: 56-year-old female Caucasian experienced a Grade 1 papular rash on her forearms and legs that was noted by her caregiver approximately 2 to 3 days after the first study drug infusion (placebo or 2 mg/m^2 TPI 287). The appearance of this rash was distinct from that observed for Subject No. 005-04. No treatment was given and the rash slowly resolved over the course of 3-4 weeks. The investigator decided to discontinue the subject from the study (early termination) given the possible relationship of the rash to study drug infusion.

Due to the double-blind, placebo-controlled design of this trial, it is currently unknown as to whether these two subjects received TPI 287 or placebo. Neither of the above events met the protocol-specified definition of a DLT. Given this and the mild severity and complete recovery of these events, breaking of the blind was not deemed necessary.

A meeting between the Investigator and the DSMB was held regarding the above events, and it was unanimously agreed that all subjects enrolled in this trial would be administered 25 mg of

diphenhydramine IV within 30 minutes to one hour prior to each dose of study drug (placebo or active). No other changes to the protocol were recommended by the DSMB.

On October 6, 2014, the 10th subject enrolled in this trial experienced a likely anaphylactoid reaction. The event is summarized below.

> Subject No. 013-10: 51-year-old female Caucasian female diagnosed with Alzheimer's disease in April 2013 with a Screening MMSE of 24. The subject had a history of allergy to benzoin, and was taking the following concomitant medications: lexapro 10 mg orally once a day, donepezil 10 mg orally once a day, curcumin (unknown dose) orally once a day, omega 3 1000 mcg orally once a day, and vitamin E 1000 IU orally once a day.
>
> On Study Day 22, the subject was premedicated with 25 mg of IV diphenhydramine 30 minutes prior to infusion of her second dose of study drug. Within one minute of initiating the study drug infusion, the subject experienced chest tightness, shortness of breath, and a deep flush covering her face and upper body. The subject indicated that her throat was tightening and that she was having great difficulties breathing.
>
> The study drug infusion was stopped (at approximately 3 minutes after initiation) and normal saline was started. The subject's vital signs were taken and reported as follows: blood pressure of 150/80 mmHg (compared to 96/55 mmHg pre-infusion), heart rate of 80 bpm (compared to 44 bpm pre-infusion), and respiratory rate of 14 breaths per minute (compared to 16 breaths per minute pre-infusion). The O_2 saturation was 97%.
>
> The subject was administered two puffs of albuterol inhaler (90 mcg/puff) approximately 2 minutes after stopping the study drug infusion. The subject's coloring began to improve and she reported feeling much relief, but still had trouble breathing, was anxious appearing with chest heaving, and continued to experience some chest tightness.
>
> Approximately 5 minutes after stopping the study drug infusion, the subject was administered 0.3 mg epinephrine (1 mg/mL) via IV push. Her coloring completely resolved followed by turning very pale with complaints of very rapid heart rate and chest tightness. Three minutes after administering the epinephrine, the subject's vital signs were as follows: blood pressure of 83/54 mmHg, heart rate of 53 bpm, and respiratory rate of 20 breaths per minute. Of note, the subject's baseline blood pressure typically runs in the 80s-90s systolic and 50s diastolic.
>
> The subject was laid flat in the reclining infusion chair and provided with supplemental oxygen via nasal cannula (O_2 saturation at 100%). Two additional puffs of albuterol inhaler were administered. The subject stabilized and her coloring returned to baseline, though she still complained of rapid heart rate. Upon suggestion from the Rapid

Response Team (RRT), the subject was transferred to the Emergency Department (ED) for observation.

Within 52 minutes of stopping the study drug infusion, the subject's vital signs had returned to baseline levels and the subject was reportedly feeling better. A half hour later, the ED physician ordered 60 mg oral prednisone, and removed the nasal cannula. The subject was discharged from the ED approximately 2 hours after stopping study drug infusion. The subject was prescribed 20 mg prednisone three times a day for three days along with an EpiPen to keep on her person in case of any unexpected sudden tightness of her chest or difficulty breathing. Phone follow-up the next day and 48 hours later indicated the subject was doing well without any sequelae of the event.

This event was assigned a severity grade of 3 based on the criteria outlined in NCI CTCAE version 4.0. The event was considered serious, based on the outcome definitions provided in Section 7.1.1.2 of this protocol; specifically, the study physician viewed the event as life-threatening. The principal investigator considered this event related to study drug, and in particular assigned a relationship of "adverse reaction". The blind was broken for this subject, and it was confirmed that the subject was randomized to the 2 mg/m^2 TPI 287 cohort. As a Grade 4 anaphylactic reaction was previously reported in a cancer trial of TPI 287 (Protocol No. TPI 287-02), this event was not considered unexpected. Therefore an expedited IND Safety Report was not required and was not filed.

Per Version 3 of the protocol, if anaphylaxis or a severe hypersensitivity reaction was observed, the Investigator and DSMB would discuss whether further premedication or any additional treatment guidelines should be implemented. Further, any proposed changes to the protocol to address such findings would be submitted for review and approval by the IRB and FDA prior to re-starting the trial. As such, the trial was put on temporary hold following the above anaphylactoid reaction.

Based on review of the above event (anaphylactoid reaction), the Investigator and DSMB unanimously agreed that moving forward, **a pre-medication regimen that includes a corticosteroid, an antihistamine, and an H2 blocker will be required prior to each study drug (placebo or active) infusion**. This combination has been well established as a prophylaxis for hypersensitivity reactions for other taxanes, such as paclitaxel (Bookman et al. 1997 and Quock et al. 2002), and is being used successfully in ongoing cancer trials of TPI 287. Listed below is the specific pre-medication regimen **required** for this trial:

- 10 mg IV dexamethasone (or methylprednisone equivalent, if dexamethasone not available) one hour prior to infusion, **and**
- 25 mg IV diphenhydramine within 30 minutes to one hour prior to infusion, **and**

- IV H2 blocker such as ranitidine (50 mg) or famotidine (20 mg) within 30 minutes to one hour prior to infusion.

5.5 Measuring Subject Compliance

The study drug will be administered via IV infusion in the clinic. Compliance will be ascertained by Investigational Site staff by monitoring of the IV bag and administration set. The following infusion details will be recorded as part of monitoring compliance: infusion start and stop times, confirmation that the entire IV bag content was administered, and approximate flush volume.

5.6 Drug Accountability

In accordance with current GCP, the Investigational Site will account for all study drug supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the Investigational Site. Copies of the study drug accountability record will be provided to the supplier of the study drug (Cortice).

Study drug will only be dispensed to subjects randomized to treatment under this protocol, and only as directed by this protocol. Administration of study drug will be accurately recorded in each subject's source documents and CRF.

5.7 Concomitant Medications

All medications (or treatments) other than study drug taken or received by the subject at any time during the study from the first dose of study drug through the final study visit assessment will be considered concomitant medications. Use of all concomitant medications, including any change in therapy, must be recorded and updated in the source documentation and on the CRF.

Subjects with previous exposure to microtubule inhibitors (including TPI 287) within 5 years of Screening are not eligible to participate in this trial. Treatment with microtubule inhibitors (other than TPI 287) while on study is prohibited.

Subjects are also not to take any other investigational drugs beginning 30 days prior to the first dose of study drug and continuing until completion of the study (final study visit).

FDA-approved AD medications are allowed as long as the dose is stable for 2 months prior to Screening. Other medications (except those listed above) are allowed as long as the dose is stable for 30 days prior to Screening. All drugs taken during the two months prior to Screening, as well as between Screening and baseline (Day 1) should be recorded.

All intercurrent medical conditions will be treated at the discretion of the Investigator according to acceptable community standards of medical care.

TPI 287 was shown to be rapidly metabolized by pooled human S-9 liver fractions, and seven putative phase 1 (modification) metabolites were detected. Based on this and the well-established metabolism of other taxanes such as paclitaxel by cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2C8 (CYP2C8), the concomitant use of CYP3A4 and CYP2C8 substrates, inhibitors, and inducers are strongly discouraged. Caution and careful monitoring must be exercised when TPI 287 is concomitantly administered with such drugs, including but not limited to midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam, repaglinide, rosiglitazone, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, gemfibrozil, rifampin, carbamazepine, St. John‘s Wort, warfarin, and other coumarin-derivative anti-coagulants.

Subjects receiving warfarin or other coumarin-derivative anti-coagulants are not eligible for enrollment in this trial due to the contraindication with the lumbar puncture (i.e., this is an exclusion criterion).

6. SCHEDULE OF EVENTS

The schedule of events is provided in tabular format in Appendix B [placebo-controlled (dose-ranging) phase] and Appendix C (optional open-label extension), and is summarized below by study visit.

6.1 Screening

The Investigator is responsible for keeping a record of all subjects screened for entry into the study and subsequently excluded. The reason(s) for exclusion will be recorded in the source documents.

Each subject will be provided with oral and written information (ICF) describing the study and will have any questions answered. Written informed consent must be obtained prior to performing any screening evaluations.

Subjects that consent to participate in the study will undergo the eligibility assessments listed below. All procedures must be completed within 28 days of the first dose of study drug (Day 1):

1. Record demographic data (date of birth/age at Screening, gender, and race);
2. Complete medical and surgical history, including baseline concurrent illness assessment;
3. Review and record medications taken within 2 months prior to initial Screening visit;
4. Height and body weight;
5. Comprehensive physical examination, including neurological examination;
6. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
7. 12-lead ECG;
8. MMSE;
9. GDS;
10. MHIS;
11. Safety labs (see Appendix D for list of tests);
12. Coagulation tests (PT, PTT, and INR). The coagulation tests must be performed before the lumbar puncture;
13. Serum pregnancy test [beta-chorionic gonadotropin (β-hCG)] for WCBP only;
14. MRI procedures, including RsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences. These procedures will only be performed if the subject meets all other eligibility criteria after completion of the above listed Screening procedures.
15. Collection of CSF via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of AD, and pre-dose assessment of TPI 287 concentration. The lumbar puncture must be performed after the MRI procedures, and will only be performed if the subject continues to meet eligibility criteria after completion of the MRI procedures.

16. Collection of blood samples for the purpose of banking DNA and plasma for future research (approximately 10 and 5 mL, respectively). For subjects enrolled before banking was added to the protocol (and thus that missed the blood collections at Screening), collection of a blood sample for DNA banking will be allowed at a later time point up to and including the final study visit. Collection of the pre-dose plasma banking sample will not be allowed at a later time point; however, the scheduled post-dose draws will still be allowed (regardless of whether a pre-dose sample is available).

17. Assessment of inclusion and exclusion criteria.

Subjects who meet eligibility criteria based on the completion of the above Screening assessments will be instructed as follows:

1. Do not take any microtubule inhibitor (other than the study drug) for the duration of the study (through final follow-up visit);

2. Do not take any investigational drug (other than the study drug) for the duration of the study (through final follow-up visit);

3. Do not take any AD medications (other than the study drug) for the duration of the study (through final follow-up visit), except for those for which the dose is expected to be stable for 2 months prior to Screening;

4. Do not take any other medications for the duration of the study (through final follow-up visit), except for those for which the dose is expected to be stable for 30 days prior to Screening;

5. For males and WCBP: Abstain from sex or use an adequate method of contraception for the duration of the study and through 30 days after the last dose of study drug.

6. Return to the clinic on Day 1 for baseline procedures.

6.2 Treatment Period – Placebo-Controlled (Dose-Ranging) Phase

6.2.1 Study Day 1

Subjects who meet eligibility criteria after completing all Screening evaluations will return to clinic the morning of Day 1. Blood and urine will be collected for baseline safety labs (see Appendix D for list of tests). The following baseline procedures will be completed **prior to enrollment** to confirm that the subject continues to meet eligibility criteria:

1. Update of medical history (intercurrent illness assessment);
2. Review and record medications taken since initial Screening visit;
3. Physical examination, including neurological examination;
4. Weight and calculation of BSA for the purpose of determining study drug dose;
5. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
6. 12-lead ECG;
7. ADAS-cog;
8. ADCS-ADL;
9. Urine pregnancy test (β-hCG) for WCBP only;
10. Review of inclusion/exclusion criteria.

Subjects that continue to meet all eligibility requirements after the completion of the above specified baseline assessments will be enrolled in the study and randomized to treatment. An indwelling cannula will be placed for PK assessments, and a blood sample will be collected within an hour prior to starting study drug infusion for the pre-dose assessment of TPI 287 concentration. Topical anesthesia will be allowed to place the cannula.

The study drug (placebo or active) will be administered in either an inpatient or outpatient facility on the morning of Day 1. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 1 after the start of study drug infusion:

1. Monitor for treatment emergent AEs beginning immediately following the initiation of the first study drug infusion;
2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion. For time points that include both vital signs and PK assessments, the vital signs will be taken first;

3. Collection of blood samples for PK assessments at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion;

4. Subjects will be provided with a diary and instructed to record any AEs or concomitant medications taken between visits, and to bring the completed diary to each visit for review.

Subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Following the above procedures, the subjects will be instructed to return to the clinic the following day (Day 2).

6.2.2 Study Day 2

Subjects will return to clinic on the morning of Day 2 for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

4. Collection of blood for PK assessment (24-hour post-infusion);

5. Safety labs (see Appendix D for list of tests).

Pending no safety issues, subjects will be instructed to return to the clinic in 6 days (Day 8).

6.2.3 Study Day 8

Subjects will return to clinic on the morning of Day 8 (-1 day/+ 2 days) for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. Safety labs (see Appendix D for list of tests).

Pending no safety issues, subjects will be instructed to return to the clinic in 7 days (Day 15).

6.2.4 Study Day 15

Subjects will return to clinic on the morning of Day 15 (-1 day/+ 2 days) for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. Safety labs (see Appendix D for list of tests).

Pending no safety issues, subjects will be instructed to return to the clinic in 7 days (Day 22).

6.2.5 Study Day 22

Subjects will return to clinic on the morning of Day 22 (-1 day/+ 2 days). The following procedures will be performed **prior to administering the second study drug infusion**:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight and calculation of BSA for the purpose of determining study drug dose;
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. 12-lead ECG;
6. Safety labs (see Appendix D for list of tests);

7. Collection of blood for PK assessment (trough level).

Pending no safety issues, the second dose of study drug (placebo or active) will be administered in either an inpatient or outpatient facility on the morning of Day 22. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 22 after the start of study drug infusion:

1. Monitor for AEs;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in three weeks (Day 43).

6.2.6 Study Day 43

Subjects will return to clinic on the morning of Day 43. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. The following procedures will be performed **prior to administering the third study drug infusion**:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight and calculation of BSA for the purpose of determining study drug dose;

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. 12-lead ECG;

6. Safety labs (see Appendix D for list of tests);

7. Collection of blood for PK assessment (trough level).

Pending no safety issues, the third dose of study drug (placebo or active) will be administered in either an inpatient or outpatient facility on the morning of Day 43. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 43 after the start of study drug infusion:

1. Monitor for AEs;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in three weeks (Day 64).

6.2.7 Study Day 64

Subjects will return to clinic on the morning of Day 64. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. The following procedures will be performed **prior to administering the fourth study drug infusion**:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight and calculation of BSA for the purpose of determining study drug dose;

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. 12-lead ECG;

6. Safety labs (see Appendix D for list of tests);

7. Collection of blood for PK assessment (trough level);

8. Coagulation tests (PT, PTT, and INR).

Pending no safety issues, the fourth and final dose of study drug (placebo or active) for the dose-ranging phase of the trial will be administered in either an inpatient or outpatient facility on the morning of Day 64. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 64 after the start of study drug infusion:

1. Monitor for AEs;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in one week.

6.3 Final Study Visits for Placebo-Controlled (Dose-Ranging) Phase

The final study visit for the placebo-controlled (dose-ranging) phase of the trial will occur during 2-3 visits, depending on whether the subject is eligible and opts to proceed with the open-label extension. The procedures that will be performed at each visit are described below.

6.3.1 One Week after Fourth Study Drug Infusion

All subjects will return to the clinic 1 week ± 3 days after the fourth study drug infusion for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

3. Safety labs (see Appendix D for list of tests);

4. Collection of blood for determination of TPI 287 plasma level for comparison with TPI 287 CSF level;

5. Collection of CSF via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of AD, and TPI 287 concentration;

6. Collection of blood sample (5 mL) for the purpose of banking plasma for future research.

6.3.2 Two Weeks after Fourth Study Drug Infusion

All subjects will return to the clinic 2 weeks ± 3 days after the fourth study drug infusion for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. Safety labs (see Appendix D for list of tests);

6. ADAS-cog;

7. MMSE;

8. ADCS-ADL;

9. GDS;

10. RsfMRI;

11. DTI;

12. ASL perfusion MRI;

13. Standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences.

Following completion of the above assessments, subjects who are eligible and opt to proceed with the open-label extension phase of the trial will be instructed to return to the clinic three weeks from their last dose of study drug for initiation of the open-label phase. Subjects found to

be ineligible or that opt not to participate in the open-label extension will be instructed to return to the clinic four weeks from their last dose of study drug for their final study visit.

6.3.3 Four Weeks after Fourth Study Drug Infusion

Subjects found to be ineligible for the open-label extension or that opt not to participate in the open-label extension will return to the clinic 4 weeks ± 7 days after their last dose of study drug for the following final procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
4. Safety labs (see Appendix D for list of tests);
5. Collection of blood sample (5 mL) for the purpose of banking plasma for future research.

If a subject is discontinued from study drug treatment early during the placebo-controlled (dose-ranging) phase, all evaluations described for the above three final study visits will be performed if feasible. Any subject with a possible study drug-related AE at either final study visit will be followed until resolution or stabilization of the event.

6.4 Treatment Period – Open-Label Extension Phase

6.4.1 Study Day 1

Subjects who are eligible and opt to proceed with the open-label extension phase of the trial will return to clinic three weeks after their last dose of study drug in the placebo-controlled (dose-ranging) phase. This will be defined as Day 1 of the open-label extension.

Written informed consent must be obtained prior to performing any evaluations under this optional phase of the trial. Subjects that consent to participate in the optional phase (i.e., sign and date ICF for optional procedures) will undergo the following procedures **prior to administering the first study drug infusion of the open-label extension phase**:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight and calculation of BSA for the purpose of determining study drug dose;

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. 12-lead ECG;

6. Safety labs (see Appendix D for list of tests);

7. Urine pregnancy test (β-hCG) for WCBP only.

Subjects that continue to meet all eligibility requirements after the completion of the above assessments will be administered TPI 287 in either an inpatient or outpatient facility on the morning of Day 1 of the open-label extension. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 1 of the open-label extension after the start of study drug infusion:

1. Monitor for AEs;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion.

Subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Following the above procedures, the subjects will be instructed to return to the clinic the following day (Day 2 of the open-label extension).

6.4.2 Study Day 2

Subjects will return to clinic on the morning of Day 2 of the open-label extension for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

4. Safety labs (see Appendix D for list of tests).

Pending no safety issues, subjects will be instructed to return to the clinic in 6 days (Day 8).

6.4.3 Study Day 8

Subjects will return to the clinic on the morning of Day 8 (-1 day/+ 2 days) of the open-label extension for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. Safety labs (see Appendix D for list of tests).

Pending no safety issues, the subjects will be instructed to return to the clinic in 7 days (Day 15).

6.4.4 Study Day 15

Subjects will return to clinic on the morning of Day 15 (-1 day/+ 2 days) of the open-label extension for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. Safety labs (see Appendix D for list of tests).

Pending no safety issues, the subjects will be instructed to return to the clinic in 7 days (Day 22).

6.4.5 Study Day 22

Subjects will return to clinic on the morning of Day 22 (-1 day/+ 2 days). The following procedures will be performed **prior to administering the second study drug infusion of the open-label extension**:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight and calculation of BSA for the purpose of determining study drug dose;
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. 12-lead ECG;
6. Safety labs (see Appendix D for list of tests).

Pending no safety issues, the second infusion of TPI 287 of the open-label extension will be administered in either an inpatient or outpatient facility on the morning of Day 22. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 22 after the start of study drug infusion:

1. Monitor for AEs;
2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in three weeks (Day 43).

6.4.6 Study Day 43

Subjects will return to clinic on the morning of Day 43. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. The following

procedures will be performed **prior to administering the third study drug infusion of the open-label extension**:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight and calculation of BSA for the purpose of determining study drug dose;
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. Safety labs (see Appendix D for list of tests).

Pending no safety issues, the third infusion of TPI 287 of the open-label extension will be administered in either an inpatient or outpatient facility on the morning of Day 43. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 43 after the start of study drug infusion:

1. Monitor for AEs;
2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in five weeks.

6.5 Final Study Visit for Open-Label Extension Phase

Subjects will return to the clinic 4 weeks ± 7 days after the third study drug infusion of the open-label extension for the following final study visit procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;

3. Weight
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. 12-lead ECG;
6. Safety labs (see Appendix D for list of tests);
7. ADAS-cog;
8. ADCS-ADL;
9. GDS;
10. Collection of blood sample (5 mL) for the purpose of banking plasma for future research.

If a subject is discontinued from study drug treatment early during the open-label extension phase, all evaluations described for the above final study visit will be performed if feasible. Any subject with a possible study drug-related AE at the final study visit will be followed until resolution or stabilization of the event.

6.6 Duration of Participation

The total duration of participation for subjects in this study will be up to 17 weeks (first Screening visit through final follow-up visit) for the placebo-controlled (dose-range finding) phase of the study. If a subject is eligible and opts to continue treatment under the open-label extension phase of the study, the subject will participate for an additional 12 weeks, for a total duration of up to 29 weeks.

7. ASSESSMENT OF SAFETY

Safety will be assessed primarily based on AEs. Secondary safety assessments will include physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PT/PTT/INR, CSF cell count with differential, glucose, and total protein, ADAS-cog, ADCS-ADL, GDS, and MRI (standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences). Refer to Appendices B and C for a tabular summary of the timing of the safety assessments.

7.1 Safety Reporting and Adverse Events

7.1.1 Definitions

7.1.1.1 Adverse Event

An AE is defined in 21 Code of Federal Regulations (CFR) 312.32(a) as follows:

> Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
>
> An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

7.1.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined in 21 CFR 312.32(a) as follows:

> An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
>
> - death
> - a life-threatening AE
> - inpatient hospitalization or prolongation of existing hospitalization
> - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
> - a congenital anomaly/birth defect
>
> Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.1.2 Severity of Adverse Events

The severity of AEs will be graded according to NCI CTCAE version 4.0. A copy of CTCAE version 4.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

The severity of AEs not classified by the above referenced toxicity grading scale will be categorized using the following definitions:

Mild (Grade 1):	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2):	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Severe (Grade 3):	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Life-threatening (Grade 4):	Life-threatening consequences; urgent intervention indicated
Death (Grade 5):	Death related to AE

7.1.3 Relationship of Adverse Events to the Study Drug

The relationship of AEs to the study drug will be classified as one of the following:

1. **Adverse reaction**: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

2. **Suspected adverse reaction**: Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.
   Examples of the types of evidence that would suggest a causal relationship between the drug and the AE are as follows:

   - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

   - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

   - An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

3. **Unrelated**: AE for which there is evidence that the AE definitely has an etiology other than the drug.

7.1.4 Expectedness of Adverse Events

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.1.5 Monitoring of Adverse Events

AEs will be monitored continuously during the study starting immediately after the start of the first infusion of study drug. Subjects will be instructed to report all AEs experienced during the

study, and subjects will be assessed for the occurrence of AEs throughout the study. Subjects will be given a diary to record any AEs between visits.

In order to avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?"

All AEs will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests.

7.1.6 Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded in the source documents and on the AE form of the CRF.

The information to be entered in the CRF will include:

1. Time of onset of any new AE or the worsening of a previously observed AE;
2. Specific type of reaction in standard medical terminology;
3. Duration of AE (start and stop dates);
4. Severity/grade of AE according to criteria in Section 7.1.2;
5. Assessment of the relationship of the AE to the study drug according to the definitions in Section 7.1.3;
6. Description of action taken in treating the AE and/or change in study drug administration or dose.

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the AE.

7.1.7 Reporting of Serious Adverse Events, Including Death

SAEs, including death due to any cause, which occur during this study or within 30 days following the last dose of the study drugs, whether or not related to the administration of study drugs, will be recorded in the source documents, on the AE form of the CRF, and on an SAE report. The SAE report will include the following information:

1. Subject identification including subject number, initials, and date of birth;
2. Randomization number;
3. Date of first dose of study drug and details of administration, including study drug name (including labeled strength and manufacturer), lot number, expiration date, and dose;
4. Date of last dose of study drug (i.e., prior to onset of SAE) and details of administration, including study drug name (including labeled strength and manufacturer), lot number, expiration date, and dose;
5. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event);
6. Date of onset of the event;
7. Date of resolution of the event (or confirmation ongoing);
8. Severity of the event according to criteria in Section 7.1.2;
9. Assessment of the attributability of the event to the study drug according to the definitions in Section 7.1.3;
10. Why event is considered serious per the definition in Section 7.1.1.2;
11. Whether the event is expected per the definition in Section 7.1.4;
12. Action taken in treating the event and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the subject was discontinued from the study);
13. All concomitant medications (including doses, routes, regimens, and indications);
14. Pertinent laboratory data;
15. Medical history.

The Investigator will review each SAE report and evaluate the relationship of the adverse experience to study drug and to underlying disease. Based on the Investigator's assessment of the adverse experience, a decision will be made concerning the need for further action. The

primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Investigator will take immediate steps to notify the regulatory authorities.
Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol;

2. Discontinuation or suspension of the study;

3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings;

4. Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study drug-related.

Any SAE that is determined by the Investigator/IND Sponsor to be reportable to FDA as an IND Safety Report (as defined in 21 CFR 312.32 and as further clarified in Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012) will be reported to FDA by the Investigator/IND Sponsor within the specified time frame. All IND Safety Reports will also be promptly submitted to the IRB/IEC.

7.2 Physical Examination (Including Neurologic Examination)

The scheduled physical examinations for assessment of safety will include the following organ or body system assessments: skin; head, eyes, ears, nose, throat, thyroid, lungs, cardiovascular, liver, spleen, lymph nodes, extremities, and neurologic examination.

7.3 Weight

The scheduled weight measurements for assessment of safety and calculation of TPI 287 dose will use a calibrated digital scale with the subject wearing light clothes and no shoes.

Height will be measured using a calibrated stadiometer with the subject wearing no shoes. Height will only be measured at the Screening visit, and will be used in combination with each current weight measurement to calculate current BSA using standard operating procedures in place at the UCSF Investigational Pharmacy.

7.5 Vital Signs

The scheduled vital sign measurements for assessment of safety will include the following: blood pressure, pulse rate, respiratory rate, and temperature. Vital signs will be taken with the subject in the sitting position after 5 minutes of rest.

7.6 ECG

Twelve-lead ECGs will be performed with the subject in the recumbent position after 5 minutes of rest. ECGs will be read for QT and QTc intervals.

7.7 Safety Labs

Blood and urine for clinical safety laboratory assessments will be collected and processed using standard procedures. A local laboratory will perform the safety laboratory tests.

The safety labs will include CBC with differential, comprehensive metabolic panel, and urinalysis. Refer to Appendix D for a listing of each test to be performed.

7.8 PT/PTT/INR

Blood for coagulation assessments (PT, PTT, and INR) will be collected and processed using standard procedures. These coagulation assessments will be done within 1 month prior to each lumbar puncture to meet the modified Alzheimer's Disease Neuroimaging Initiative (ADNI) lumbar puncture protocol provided in Appendix E. Specifically, the blood for coagulation assessments will be collected at Screening (prior to the first lumbar puncture) and at Day 64 (one week prior to the second lumbar puncture). A local laboratory will perform the coagulation tests.

7.9 CSF Cell Count with Differential, Glucose, and Total Protein

CSF samples for measuring cell count with differential, glucose, and total protein will be collected via lumbar puncture at Screening and at the first final study visit of the dose escalation phase (1 week after the fourth dose of study drug).

The CSF samples will be collected and processed per the modified ADNI lumbar puncture protocol provided in Appendix E.

7.10 ADAS-cog

The ADAS-cog rating instrument (Rosen et al. 1984) will be used to evaluate the severity of cognitive dysfunctions, and thus AD severity. The ADAS-cog will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the ADAS-cog.

7.11 ADCS-ADL

The ADCS-ADL rating instrument (Galasko et al. 1997) will be used to evaluate function, and in particular the degree of disability. The ADCS-ADL will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the ADCS-ADL.

7.12 GDS

The GDS rating instrument (Yesavage et al. 1983) will be used to evaluate depression in elderly subjects. The GDS will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the GDS.

7.13 MRI

MRI for the purpose of safety assessments will be performed on a Siemens 3T TrioTim Scanner using sequences based on the ADNI 2 standard protocol including T1-weighted volumetric structural, FLAIR, DWI and GRE sequences (http://adni.loni.ucla.edu/methods/documents/mri-protocols/).

7.14 Definition of DLT

A DLT for this trial is defined as: 1) any Grade 3 or higher AE per NCI CTCAE severity criteria for which there is reasonable possibility that TPI 287 caused the event, 2) any Grade 2 AE in the CTCAE system organ class of nervous system disorders that is considered clinically significant and for which there is reasonable possibility that TPI 287 caused the event, or 3) any infusion-related toxicities (e.g., allergic reaction/hypersensitivity) occurring during the infusion of TPI 287 or within 24 hours after completing the infusion that do not resolve promptly with a reduced infusion rate and/or supportive care.

7.15 MTD Determination

The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For each dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. The dose escalation rules are as follows:

If ≤1 of the 8 active subjects per cohort experiences DLT (as defined in Section 7.14) during the first 4 weeks (first 2 infusions and 1 week follow-up), the dose of TPI 287 for the next cohort will be escalated to the next higher planned dose level.

If 2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to be the MTD and there will be no further dose escalation.

If >2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to have exceeded the MTD and there will be no further dose escalation. Pending consultation with an independent, non-blinded DSMB, the next cohort may be de-escalated to a lower dose to refine the MTD determination. No more than 3 dose cohorts will be enrolled in this trial.

Enrollment of subjects into the cohort at the next higher planned dose level will not commence until all eight subjects have completed the first 4 weeks (first 2 infusions and 1 week follow-up) and the criteria for escalation are met. Enrollment in a cohort will be terminated early if >2 active subjects experiences DLT during the first 4 weeks.

Subjects who are withdrawn from the study for reasons other than DLTs before completion of the first 4 weeks may be replaced at the Investigator's discretion, and will not be counted towards the 8 subjects defined above.

The MTD determination for this study will be limited to the planned dosing range of 2 to 20 mg/m^2 TPI 287 (i.e., the objective is not to identify the highest possible dose that AD subjects can tolerate). For this study, the MTD in subjects with mild to moderate dementia of the Alzheimer's type will be defined as the highest dose level achieved at which no more than 2 out of 8 active subjects experienced a DLT during the first 4 weeks (first 2 infusions and 1 week follow-up).

8. ASSESSMENT OF PHARMACOKINETICS

The PK profile of TPI 287 in plasma after a single IV infusion and the steady-state CSF concentration of TPI 287 one week after completion of the fourth TPI 287 infusion are secondary

endpoints for this trial. Refer to Appendix B for a tabular summary of the timing of the PK blood and CSF draws.

8.1 Blood Collection

Blood samples for PK assessments on Day 1 will be taken by an indwelling cannula inserted in a forearm vein to minimize discomfort associated with repeated venipunctures. Topical anesthesia will be allowed to place the cannula. Blood samples for PK assessments on other days will be taken by direct venipuncture.

The planned time points for PK blood collections are Day 1 [within an hour prior to the start of study drug infusion, at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion], Day 2 (24-hour post-infusion), Days 22, 43, and 64 (trough levels; single point prior to dosing), and at the first final study visit of the dose-ranging phase (one week after fourth study drug infusion; single point for comparison with TPI 287 CSF level). No PK blood samples will be collected during the open-label extension phase of this trial.

A window of ± 5 minutes will be allowed for each time point on Day 1, except for the 5, 15, and 30 minute time points which will have an allowed window of ± 2 minutes. A window of ± 20 minutes will be allowed for the 24-hour post-infusion collection on Day 2. The actual time of blood collections will be recorded in the source documents and CRFs. All deviations outside the allowed ranges will be documented as protocol deviations.

The blood sample volume at each collection time point will be 5 mL. The sample will be collected in di-potassium ethylenediaminetetraacetic acid- (K_2EDTA-) containing tubes.

8.2 Blood Processing, Labeling, and Shipment

Blood samples collected for PK assessments will be processed to plasma. Each plasma sample will be split into two cryo vials (1mL/vial) to serve as primary and back-up samples. The plasma samples will be stored at approximately -80°C until analyzed. The primary samples will be shipped on dry-ice to a designated contract research organization (CRO)/bioanalytical laboratory for analysis of TPI 287 concentration. The back-up samples will be reserved for retesting if required. Detailed processing, labeling, and shipping instructions will be specified in a PK lab manual provided by the bioanalytical laboratory.

8.3 CSF Collection

CSF samples for the determination of TPI 287 concentration will be collected via lumbar puncture at Screening and at the first final study visit of the dose escalation phase (1 week after the fourth dose of study drug).

The CSF samples will be collected per the modified ADNI lumbar puncture protocol provided in Appendix E.

8.4 CSF Processing, Labeling, and Shipment

The CSF samples collected for PK assessments will be processed per the modified ADNI lumbar puncture protocol provided in Appendix E. A portion of each CSF sample will be transferred to two cryo vials (1mL/vial) to serve as primary and back-up PK samples. The CSF samples will be stored at approximately -80°C until analyzed. The primary samples will be shipped on dry-ice to a designated CRO/bioanalytical laboratory for analysis of TPI 287 concentration. The back-up samples will be reserved for retesting if required.

8.5 Bioanalytical Methods

The concentration of TPI 287 in plasma and CSF will be measured using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methods.

9. ASSESSMENT OF EFFICACY AND PHARMACODYNAMICS

The efficacy endpoints for this trial include changes in cognition, degree of disability, and behavior (ADAS-cog, MMSE, ADCS-ADL, and GDS). The exploratory pharmacodynamic (PD) endpoints for this trial include changes in the concentration of CSF biomarkers of AD [beta amyloid (1-42), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides] and changes in brain network functional and structural connectivity and perfusion (rsfMRI, DTI, and ASL perfusion MRI). Refer to Appendix B for a tabular summary of the timing of the efficacy and PD evaluations.

9.1 ADAS-cog

The ADAS-cog rating instrument (Rosen et al. 1984) will be used to evaluate the severity of cognitive dysfunctions, and thus AD severity. The ADAS-cog will serve a dual function as both

a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the ADAS-cog.

9.2 MMSE

The MMSE (Folstein et al. 1975) will be used to evaluate the cognitive function of subjects. Refer to the referenced publication for details regarding the exam.

9.3 ADCS-ADL

The ADCS-ADL rating instrument (Galasko et al. 1997) will be used to evaluate function, and in particular the degree of disability. Refer to the referenced publication for details regarding the administration and scoring of the ADCS-ADL.

9.4 GDS

The GDS rating instrument (Yesavage et al. 1983) will be used to evaluate depression in elderly subjects. The GDS will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the GDS.

9.5 CSF Biomarkers of AD

CSF samples for measuring the concentration of biomarkers of AD [beta amyloid (1-42), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides] will be collected via lumbar puncture at Screening and at the first final study visit of the dose escalation phase (1 week after the fourth dose of study drug).

The CSF samples will be collected and processed per the modified ADNI lumbar puncture protocol provided in Appendix E.

The CSF concentration of beta amyloid (1-42), total tau, and phosphorylated tau will be determined by the INNO-BIA AlzBio3 method described by Fagan et al. 2011. The CSF samples will be shipped to Dr. Anne Fagan's lab at Washington University, St. Louis, MO for this purpose.

Quantification of the stoichiometry of different tau isoforms and fragments, as well as novel CSF tau phosphopeptides will be performed using FLEXI-Tau mass spectrometry similar to the method described by Singh et al. 2012. The CSF samples will be shipped to Dr. Judith Steen's lab at Boston Children's Hospital, Boston, MA for this purpose.

9.6 Brain Imaging

The connectivity between hippocampus and posterior cingulate will be measured via rsfMRI. White matter fractional anisotropy within cortical tracts will be measured by DTI. Medial temporal lobe and regional cortical perfusion will be measured by ASL perfusion MRI.

MRI acquisition will take place on a 3T Siemens Trim Trio Scanner at the UCSF Neuroscience Imaging center using protocols based on ADNI 2 (http://adni.loni.ucla.edu/) which are already implemented on this scanner. RsfMRI and DTI scan protocols will be similar to ADNI 2 as designed by Dr. Norbert Schuff for multiple studies at UCSF, including Dr. Boxer's 4 Repeat Tauopathy Neuroimaging Initiative (Gardner et al. 2013).

10. STATISTICS

10.1 Sample Size Considerations

The primary outcome measures of this phase 1 trial are the safety and tolerability of TPI 287 in AD patients. As such, the sample size considerations were based on a standard phase 1 dose escalation scheme.

The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For each dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. No more than 3 dose cohorts will be enrolled in this trial. The MTD determination for this study will be limited to the planned dosing range of 2 to 20 mg/m^2 TPI 287 (i.e., the objective is not to identify the highest possible dose that AD subjects can tolerate). The sample size is anticipated to be up to 33 subjects, depending on the dose level at which toxicity is observed.

10.2 Statistical Analysis of Safety Data

Data from all subjects who receive at least one dose of study drug (placebo or active) will be included in the safety analysis.

AEs will be tabulated by body system and preferred term [per Medical Dictionary for Regulatory Activities (MedDRA)], and will be further categorized by treatment group, phase of trial [i.e., placebo-controlled (dose-ranging) phase versus open-label extension], severity, and assigned relationship to study drug. The incidence for each AE will be provided as the total number of subjects that experienced the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables.

AEs will also be listed for individual subjects, along with information regarding onset, duration, severity, relationship to study drug, and outcome. AEs that lead to withdrawal from the study will be listed and summarized. A separate tabulation and listing of SAEs will also be generated.

Other safety assessments, including physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PT/PTT/INR, CSF cell count with differential, glucose, and total protein, ADAS-cog, ADCS-ADL, GDS, and MRI (standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences) will be listed and summarized.

Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Inferential statistical analysis comparing the safety data among treatment groups or phases of the trial is not planned.

The MTD of TPI 287 in patients with mild to moderate AD will be defined as the highest dose level achieved (within planned dosing range) at which no more than 2 of 8 active subjects experienced a DLT during the first 4 weeks (first 2 study drug infusions and 1 week follow-up).

10.3 Statistical Analysis of Pharmacokinetic Data

The PK profile of TPI 287 in plasma after a single TPI 287 IV infusion (Day 1) and the steady-state CSF concentration of TPI 287 1 week after completion of the fourth TPI 287 infusion are the secondary endpoints for this trial.

The concentration of TPI 287 in plasma and CSF will be measured using validated LC/MS-MS methods. Individual and mean (standard deviation) plasma and CSF TPI 287 concentration data will be tabulated and plotted by dose level. The plasma data will include the serial blood collections following the Day 1 infusion, as well as trough concentrations at Days 22, 43, and 64, and 1 week after the fourth infusion for comparison with the post-dose CSF level.

Plasma TPI 287 concentration-time data will be analyzed by non-compartmental methods using WinNonlin (Pharsight Corporation, CA). PK parameters will be calculated according to standard

equations, and will include maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from time zero to time of last measurable concentration (AUC_t), area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal phase half- life ($t_{1/2}$), clearance (CL), apparent volume of distribution (Vd), and mean residence time (MRT).

Individual PK parameters will be summarized by descriptive statistics for each dose group. The descriptive statistics will include arithmetic mean, standard deviation, median, minimum, maximum, and geometric mean (log-transformed). Inferential statistical analysis comparing PK data among treatment groups is not planned.

10.4 Statistical Analysis of Efficacy and Exploratory Pharmacodynamic Data

CSF concentrations of beta amyloid (1-42), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides at Screening and 1 week after completion of the fourth study drug infusion, as well as the calculated changes in these measurements will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation). Inferential statistical analysis comparing data among treatment groups is not planned.

Connectivity between hippocampus and posterior cingulate as measured by rsfMRI, white matter fractional anisotropy within cortical tracts as measured by DTI, and medial temporal lobe and regional cortical perfusion as measured by ASL perfusion MRI at Screening and 2 weeks after completion of the fourth study drug infusion, as well as the calculated changes in these measurements will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation). Inferential statistical analysis comparing data among treatment groups is not planned.

ADAS-cog, MMSE, ADCS-ADL, and GDS assessments at Screening or Baseline and 1 week after completion of the fourth study drug infusion, as well as the calculated change in these assessments will be listed and summarized. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Analysis of variance (ANOVA) will be used to compare the changes in these assessments across treatment groups.

11. ACCESS TO SOURCE DOCUMENTS AND RETENTION OF RECORDS

The Investigator will make the source documents for this trial available for monitoring by regulatory authorities or health authority inspectors.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, and the IRB/IEC.

The information developed in this clinical study will be used by the Investigator/IND Sponsor in the clinical development of the study drug and therefore may be disclosed by the Investigator/IND Sponsor to other clinical investigators, to pharmaceutical companies, to the FDA or other government agencies.

The Investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least 2 years after the Investigation is discontinued and regulatory authorities have been notified.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Data Collection

All data required by the study protocol will be entered onto CRFs and must be verifiable against source documents. CRFs will be completed for every subject who is enrolled in the trial.

Only authorized Investigational Site personnel will enter data on the CRFs. Any corrections to data entered into the CRF will be made in such a way that the original entry is not obscured. The date of the correction and the initials of the person making the correction will be documented.

The CRFs will be kept up-to-date by the Investigator and the research staff at the Investigational Site. The Investigator will be responsible for reviewing all data and CRF entries and will sign and date each subject's CRF, verifying that the information is true and correct.

12.2 Data Management

After the CRFs have been reviewed by the Investigator and all identified discrepancies have been addressed, the Investigator signed copy of the CRFs will be forwarded to Data Management.

Queries generated by Data Management will be sent to the clinical team for resolution. The Investigator is responsible for the review and approval of all responses.

All CRF data will be entered into a validated database and an electronic audit trial of edits maintained. Data may be imported to the database electronically.
The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

12.3 Inspection by Regulatory Authorities

At some point during the study, a regulatory authority may visit the Investigator to conduct an inspection of the study. The Investigator and staff will cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents.

13. ETHICS

13.1 Declaration of Helsinki

This study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision, as described in Appendix F.

13.2 Good Clinical Practice and Regulatory Compliance

This study will be conducted in accordance with the principles of GCP (current ICH guideline) and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

13.3 Institutional Review Board/Independent Ethics Committee

The protocol, ICF, and any materials (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/IEC.

The Investigator will ensure that all aspects of the IRB/IEC review are conducted in accordance with current institutional, local, and national regulations. The study will not be initiated until the Investigator receives a letter documenting IRB/IEC approval.

Amendments to the protocol will be subject to the same requirements as the original protocol. Implementation of the changes described in the protocol amendment will not be initiated until the Investigator receives a letter documenting IRB/IEC approval.

Revisions to the ICF will be reviewed and approved by the IRB/IEC prior to use in the study. The Investigator will inform the IRB/IEC of all reportable AEs. IND Safety Reports will be promptly forwarded to the IRB/IEC by the Investigator.

The Investigator will submit all periodic reports and updates that the IRB/IEC may require. After completion or termination of the study, the Investigator will submit a final report to the IRB/IEC. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995).

13.4 Informed Consent

No study related procedures, including screening evaluations, will be performed until the subject has given written informed consent.

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the subject understands. Further, the ICF will identify the Sponsor, the Principal Investigator and institutional affiliation, potential conflicts of interest, provisions for treating subjects who are harmed as a consequence of participation in the study, and provisions for post-trial access.

The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and any additional elements required by the Investigator's institution or local regulatory authorities. The Investigator will submit the ICF to the IRB/IEC for review, and will not proceed with initiation of the study until the IRB/IEC provides a letter documenting approval.

The IRB/IEC approved ICF will be given to each prospective participant. The subjects will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each subject who agrees to participate in the trial and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The Investigator will also obtain authorization from the subject to use and/or disclose PHI in compliance with HIPAA or equivalent. Written HIPAA authorization may be obtained as part of the informed consent process.

If a protocol amendment substantially alters the study design or increases the potential risk to the subject, or the known risks of the study drug change over the course of the study, the ICF will be revised and submitted to the IRB/IEC for review and approval. The revised approved ICF must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment and to obtain consent from new subjects prior to enrollment.

13.5 Emergency Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Investigator/IND Sponsor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was effected) is to continue in the study. The CRF and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

14. PUBLICATION POLICY

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

This trial will be registered in a publicly accessible database (clinicaltrials.gov) not later than 21 days after enrollment of the first subject. Results of this trial, including negative and inconclusive, as well as positive results, will be made publicly available.

15. PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will not modify the protocol without first receiving IRB/IEC authorization to do so, except in those cases intended to reduce immediate risk of the subjects. The Investigator/IND Sponsor is responsible for submitting protocol amendments to the appropriate IRB/IEC and government regulatory authorities.

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APPENDIX A: NATIONAL INSTITUTE ON AGING-ALZHEIMER'S ASSOCIATION WORKGROUPS RECOMMENDATIONS ON DIAGNOSTIC GUIDELINES FOR ALZHEIMER'S DISEASE (MCKHANN ET AL. 2011)

Subjects enrolled in this trial must be diagnosed with probable AD dementia per the criteria recommended by the National Institute on Aging-Alzheimer's Association Workgroups (McKhann et al. 2011) as outlined below.

Criteria for all-cause dementia: Core clinical criteria

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and

2. Represent a decline from previous levels of functioning and performing; and

3. Are not explained by delirium or major psychiatric disorder;

4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

5. The cognitive or behavioral impairment involves a minimum of two of the following domains:

    a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

    b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

    c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

Probable AD dementia: Core clinical criteria

Probable AD dementia is diagnosed when the patient:

1. Meets criteria for dementia described above (i.e., criteria for all-cause dementia), and in addition, has the following characteristics:

   A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

   B. Clear-cut history of worsening of cognition by report or observation; and

   C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

      a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

      b. Nonamnestic presentations:

         - Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.

         - Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia ***should not*** be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

APPENDIX B: SCHEDULE OF EVENTS FOR PLACEBO-CONTROLLED (DOSE-RANGING) PHASE

	Screening	Treatment Period – Placebo-Controlled (Dose-Ranging) Phase							Final Study Visits[b]		
	28 Days Prior to Day 1	Day 1	Day 2	Day 8[a]	Day 15[a]	Day 22[a]	Day 43[a]	Day 64[a]	1 Week After Last Dose	2 Weeks After Last Dose	4 Weeks After Last Dose
Informed consent form	x[c]										
Record demographic data	x										
Medical and surgical history	x	x[d]									
Physical & neurological exam	x	x[c]	x	x	x	x[e]	x[e]	x[e]		x	x
Height	x										
Weight	x	x[d]		x	x	x[e]	x[e]	x[e]		x	
Calculate body surface area for dosing		x[c]				x[e]	x[e]	x[e]			
Vital signs[f]	x	x[d,g]	x	x	x	x[e,h]	x[e,h]	x[e,h]	x	x	x
12-lead electrocardiogram	x	x[d]				x[e]	x[e]	x[e]			
ADAS-cog		x[d]								x	
MMSE	x									x	
ADCS-ADL		x[d]								x	
GDS	x									x	
MHIS	x										
Safety labs[i]	x	x[d]	x	x	x	x[e]	x[e]	x[e]	x	x	x
Coagulation tests[j]	x							x[e]			
Serum β-hCG (WCBP only)	x										
Urine β-hCG (WCBP only)		x[d]									
Recording of medications[k]	x	x[d]	x	x	x	x[e]	x[e]	x[e]	x	x	
MRI procedures[l]	x[o]									x	
Collection of CSF via lumbar puncture[m]	x[o]								x		
Randomize to treatment		x									
Pre-medication & study drug infusion		x				x	x	x			

	Screening	Treatment Period – Placebo-Controlled (Dose-Ranging) Phase							Final Study Visits[b]		
	28 Days Prior to Day 1	Day 1	Day 2	Day 8[a]	Day 15[a]	Day 22[a]	Day 43[a]	Day 64[a]	1 Week After Last Dose	2 Weeks After Last Dose	4 Weeks After Last Dose
Monitor of adverse events		x	x	x	x	x[e]	x[e]	x[e]	x	x	x
Diary[n]		x	x	x	x	x[e]	x[e]	x[e]	x	x	x
Collection of blood for PK assessments		x[d,p]	x			x[e]	x[e]	x[e]	x		
Collection of blood for DNA banking for future research	x[q]										
Collection of blood for plasma banking for future research	x[q]								x		x

β-hCG = beta-chorionic gonadotropin; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale; CSF = cerebrospinal; DNA = deoxyribonucleic acid; GDS = Geriatric Depression Scale; MHIS = Modified Hachinski Ischemic Scale; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PK = pharmacokinetic; WCBP = women of childbearing potential

a. A -1 day/+2 day window will be allowed for the Day 8, 15, 22, 43, and 64 visits, as long as the duration between TPI 287 infusions is at least 20 days
b. Final study visits for the placebo-controlled phase of the trial will occur during 2-3 visits, depending on whether the subject is eligible and opts to proceed with the open-label extension. The allowed visit window is ± 3 days for the first two visits and ± 7 days for the third visit. Subjects that are eligible and opt to proceed with the open-label extension phase will not undergo the third final visit and will instead return to the clinic three weeks from their last dose of study drug to start the open-label extension (see Appendix C). If a subject is discontinued from treatment early, all evaluations listed for the three final study visits will be performed if feasible. Any subject with a possible study drug-related AE will be followed until resolution or stabilization of the event.
c. ICF must be signed prior to performing any other Screening evaluations
d. Each of these baseline evaluations must be completed before randomizing the subject to treatment
e. Each of these evaluations must be completed prior to study drug administration that visit
f. Blood pressure, pulse rate, respiration rate, and temperature
g. Prior to initiating study drug, and then at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of infusion. For time points that include both vital signs and PK blood collections, the vital signs will be taken first.
h. Prior to initiating study drug, and then at 0.25, 0.5, 1, and 2 hours following the initiation of infusion
i. Complete blood count with differential, comprehensive metabolic panel, and urinalysis
j. Prothrombin time, partial thromboplastin time, and International Normalized Ratio. These tests must be done before the lumbar punctures.
k. Record all medications taken within 2 months of the first Screening visit through the final study visit

l. Resting state functional MRI, diffusion tensor imaging, arterial spin labeling perfusion MRI, and standard T1-weighted volumetric structural, fluid-attenuated inversion recovery, diffusion-weighted imaging, and gradient-recalled echo sequences
m. For measurement of cell count with differential, glucose, and total protein, CSF biomarkers of AD [beta amyloid (1-42), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides], and TPI 287 concentration
n. Subjects will be given a diary to record any adverse events or concomitant medications taken between visits. The diary will be reviewed at each visit.
o. Screening MRI procedures should only be performed if the subject meets all other eligibility criteria after completion of the initial Screening assessments. The lumbar puncture must be performed after the MRI procedures, and should only be performed if the subject continues to meet eligibility criteria after the completion of the MRI procedures.
p. Blood samples for the determination of TPI 287 plasma levels will be collected within an hour prior to the start of study drug infusion, at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion. To minimize discomfort, an indwelling cannula rather than repeated venipunctures will be used for the PK blood sampling on Day 1.
q. For subjects enrolled before banking was added to the protocol (and thus that missed the blood collections at Screening), collection of a blood sample for DNA banking will be allowed at a later time point up to and including the final study visit. Collection of the pre-dose plasma banking sample will not be allowed at a later time point; however, the scheduled post-dose draws will still be allowed (regardless of whether a pre-dose sample is available).

APPENDIX C: SCHEDULE OF EVENTS FOR OPTIONAL OPEN-LABEL EXTENSION PHASE

	Treatment Period – Open-Label Extension[a]						Final Study Visit[b]
	Day 1	Day 2	Day 8[k]	Day 15[k]	Day 22[k]	Day 43[k]	4 Weeks After Last Dose
Informed consent form for optional phase[c]	x						
Physical & neurological exam	x[d]	x	x	x	x[d]	x[d]	x
Weight	x[d]		x	x	x[d]	x[d]	x
Calculate body surface area for dosing	x[d]				x[d]	x[d]	
Vital signs[e]	x[d,f]	x	x	x	x[d,g]	x[d,g]	x
12-lead electrocardiogram	x[d]				x[d]		x
ADAS-cog							x
ADCS-ADL							x
GDS							x
Safety labs[h]	x[d]	x	x	x	x[d]	x[d]	x
Urine β-hCG (WCBP only)	x[d]						
Recording of medications[i]	x[d]	x	x	x	x[d]	x[d]	x
Premedication & study drug infusion	x				x	x	
Monitor of adverse events	x[d]	x	x	x	x[d]	x[d]	x
Diary[j]	x[d]	x	x	x	x[d]	x[d]	x
Collection of blood for plasma banking for future research							x

β-hCG = beta-chorionic gonadotropin; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale; GDS = Geriatric Depression Scale; WCBP = women of childbearing potential

a. Subjects that are eligible and opt to proceed with the open-label extension phase will return to the clinic one week after the second final study visit of the placebo-controlled (dose-ranging) phase (i.e., 3 weeks after their last dose of study drug) to start the open-label extension (see Appendix B).
b. The allowed visit window is ± 7 days. If a subject is discontinued from treatment early, all evaluations listed for the final study visit will be performed if feasible. Any subject with a possible study drug-related AE will be followed until resolution or stabilization of the event.
c. ICF must be signed prior to performing any other extension study evaluations
d. Each of these evaluations must be completed prior to study drug administration that visit
e. Blood pressure, pulse rate, respiration rate, and temperature
f. Prior to initiating study drug, and then at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of infusion.

g. Prior to initiating study drug, and then at 0.25, 0.5, 1, and 2 hours following the initiation of infusion
h. Complete blood count with differential, comprehensive metabolic panel, and urinalysis
i. Record all medications taken since the second final study visit of the dose-ranging phase through the final study visit of the extension phase
j. Subjects will continue to record any adverse events or concomitant medications taken between visits in their diary. The diary will be reviewed at each visit.
k. A -1 day/+2 day window will be allowed for the Day 8, 15, 22, and 43 visits, as long as the duration between TPI 287 infusions is at least 20 days

APPENDIX D: SAFETY LABORATORY TESTS

The tests listed below will be performed at each visit where "safety labs" are specified, except where noted. Pregnancy tests, coagulation tests, and CSF cell count with differential, glucose, and total protein are performed **in addition** to the safety labs listed below when specified in Section 6 and the Schedule of Events tables in Appendices B and C.

CBC with Differential	**Comprehensive Metabolic Panel**	**Urinalysis**
Hematocrit		Color and appearance
Hemoglobin	Alkaline phosphatase	pH and specific gravity
Mean corpuscular hemoglobin	Alanine aminotransferase	Bilirubin
Mean corpuscular hemoglobin conc.	Aspartate aminotransferase	Glucose
Mean corpuscular volume	Bicarbonate	Ketones
Mean platelet volume	Blood urea nitrogen	Leukocytes
Platelet count	Calcium	Nitrite
Red blood cell distribution width	Chloride	Occult blood
Red blood cell count		Protein
White blood cell count	Creatinine	Urobilinogen
White blood cell differential	Potassium	Microscopic analysis
(% & absolute):	Sodium	
Basophils	Glucose	
Eosinophils	Total/direct bilirubin	
Lymphocytes	Total protein (Screening only)	
Monocytes		
Neutrophils		

CBC = complete blood count

APPENDIX E: MODIFIED ADNI LUMBAR PUNCTURE PROTOCOL

The CSF samples for the measurement of cell count with differential, glucose, and total protein, biomarkers of AD, and TPI 287 concentration will be collected per the modified ADNI lumbar puncture protocol outlined below.

Modified ADNI Lumbar Puncture Protocol

Collection procedure:

I. General issues:

- Verify that PT/PTT and platelet count done within 1 month prior to lumbar puncture.

II. All samples will be collected:

- At a standard time of day (8am or preferably sometime in the morning)
- Same position each time for each patient (laying down, or upright)
- After any scan for that time point. If this is not possible, ensure that there is at least a 3 day window between the lumbar puncture and an MRI appointment.
- Emphasis on consistency: method of collection, position, and time of day collected should be consistent across all subjects.

III. The UCSF (ADNI–preferred) method for obtaining CSF by lumbar puncture:

1. Use of a smallest feasible caliber traumatic or atraumatic needle.
2. Discard first 1-2 mL of CSF to clear any blood from minor trauma associated with needle insertion
3. Reserve next 2-3 mL for standard tests such as cell counts, glucose, and total protein with determinations to be done at UCSF clinical lab.
4. Do not use manometer or extension tube for any CSF to be used for research
5. Collect at least 20 mL of CSF directly into polypropylene collection tube. If possible, collect all CSF into a single polypropylene collection tube, if it is at least 20 mL in volume. If collection tube larger than 20 mL is not available, collect CSF into smaller polypropylene collection tubes until at least 20 mL has been collected.
6. When LP complete, have patient relax in bed for at least 20 minutes. They can eat at this time.

NOTE: Computer tomography (CT)-guided lumbar puncture is allowed if necessary (e.g., failed attempt using method above or subjects who are obese or have anatomical issues).

Sample processing:

1. Transfer all CSF (except that described in steps III2 and III3 above) into one 50 mL polypropylene centrifuge tube and invert two to three times to mix gently and place on ice.
2. Aliquot CSF into several polypropylene tubes (1 mL/tube). Put these tubes on dry ice as soon as possible in the upright position. For the CSF samples to be used for PK analysis, use the cryo vials and labels provided by the designated CRO/bioanalytical lab for this step. Two cryo vials (1mL/vial) per CSF sample will be set up to serve as primary and back-up PK samples.
3. CSF is frozen upright on dry ice for at least 20 minutes before being stored.
4. Store CSF samples at approximately -80°C until analyzed.
5. CSF aliquots will be shipped on dry ice in batch at end of study to:
   a. A designated CRO/bioanalytical lab for determination of TPI 287 concentration via a validated LC/MS-MS method;
   b. Washington University, St. Louis, MO (Dr. Anne Fagan's lab) for beta amyloid (1-42), total tau, and phosphorylated tau measurements;
   c. Boston Children's Hospital, Boston, MA (Dr. Judith Steen's lab) for quantification of the stoichiometry of different tau isoforms and fragments, as well as novel CSF tau phosphopeptides.

Lumbar Puncture Supplies (ADNI recommended – comes with the ADNI LP kits)

I. LP materials:

- Lumbar puncture tray
- 22G Sprotte Atraumatic Spinal Needle with Introducer, or 22G standard needle (tray comes with 24G Sprotte needle)
- Polypropylene collection tubes, preferably single tube at least 30 mL volume
- 2 x 13 mL transfer tubes, if large (>20 mL) polypropylene tube unavailable
- Betadine solution (not Betadine scrub)
- Sterile gloves in correct size for person performing the LP (one plus extras for back up)
- Blue "chux" pad, plus extras
- Extra bottle 1% lidocaine (useful, not mandatory)
- Tegaderm adhesive covering for LP site after procedure
- Clean washcloths and towels
- Sharps container
- Extra sterile 4x4 gauze pads
- Extra adhesive bandages

II. LP tray (ADNI provided)

- 2 Sprotte Spinal Needles (24G x 90mm)
- 22G recommended, but not provided in kit

- 2 Introducer Needles (1mm x 30mm)
- 1 22G x 1 ½ in. Needle
- 1 Plastic Syringe (3mL, Luer Slip) with 25G x 5/8 in. Needle (Attached)
- 1 Needle Stick Pad
- 3 Sponge Applicators
- 3 Gauze Sponges
- 1 Fenestrated Drape with 2 Tabs
- Prep Well
- Lidocaine hydrochloride USP, 1%, 2mL ampule
- Adhesive bandage

APPENDIX F: DECLARATION OF HELSINKI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

TITLE: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential Cohort, Dose-Ranging Study of the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of TPI 287 in Patients with Primary Four Repeat Tauopathies: Corticobasal Syndrome or Progressive Supranuclear Palsy

PROTOCOL NO.: TPI287-4RT-001

INVESTIGATIONAL DRUG: TPI 287

DOSAGE FORM: Injection, solution

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DATE OF VERSION: March 23, 2015

VERSION: 5

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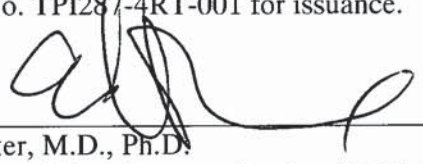
PROTOCOL SIGNATURE SHEET

The undersigned has reviewed the format and content of this protocol and has approved Protocol No. TPI287-4RT-001 for issuance.



7/23/15

Adam Boxer, M.D., Ph.D. Date
Investigational New Drug application (IND) Sponsor
University of California, San Francisco (UCSF)
Memory and Aging Center

INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and of the preclinical and clinical information on the investigational drug to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the investigational drug and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), I will not modify this protocol without obtaining the prior approval of the IRB/IEC, except when necessary to protect the safety, rights, or welfare of subjects. I will submit the protocol modifications and/or any informed consent form (ICF) modifications to the IRB/IEC, and approval will be obtained before any modifications are implemented. Further, any such protocol modifications will be submitted to the Food and Drug Administration (FDA) prior to implementation.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (GCP) [current International Conference of Harmonisation (ICH) guidelines], and the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision.

Investigator's Signature	Date
Investigator's Printed Name	
Investigational Site Name	

LIST OF ABBREVIATIONS

4RT	four repeat tauopathies
β-hCG	beta-chorionic gonadotropin
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ASL	arterial spin labeling
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero extrapolated to infinity
AUC_t	area under the concentration-time curve from time zero to time of last measurable concentration
BSA	body surface area
C9ORF72	chromosome 9 open reading frame 72
CBC	complete blood count
CBD	corticobasal degeneration
CBS	corticobasal syndrome
CDR-SB-FTLD	clinical dementia rating scale sum of boxes with added frontotemporal lobar degeneration scales
CFR	Code of Federal Regulations
CHMPB2	chromatin modifying protein 2B
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV	cardiovascular
CYP2C8	cytochrome P450 2C8
CYP3A4	cytochrome P450 3A4
DEHP	di(2-ethylhexyl)phthalate
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging

ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
FTDP	frontotemporal dementia with parkinsonism linked to chromosome 17
FTLD	frontotemporal lobar degeneration
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GRE	gradient-recalled echo
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug application
INR	International Normalized Ratio
IP	intraperitoneal
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
K_2	di-potassium
LC/MS-MS	liquid chromatography/tandem mass spectrometry
MDR	multidrug resistance
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MRT	mean residence time
MTD	maximum tolerated dose
MW	molecular weight
NCI	National Cancer Institute
NF	National Formulary
NfL	neurofilament light chain
NFT	neurofibrillary tangle
NINDS-SPSP	National Institute of Neurological Disorders and Stroke – Society for Progressive Supranuclear Palsy
NNIPPS	Neuroprotection and Natural History in Parkinson Plus Syndromes
NOAEL	no-observed-adverse-effect-level
PD	pharmacodynamic
PET	positron emission tomography
PHI	Protected Health Information
PK	pharmacokinetic

PSP	progressive supranuclear palsy
PSPRS	Progressive Supranuclear Palsy Rating Scale
PT	prothrombin time
PTT	partial thromboplastin time
PVC	polyvinyl chloride
PVF	phonemic verbal fluency
rsfMRI	resting state functional magnetic resonance imaging
SAE	serious adverse event
SEADL	Schwab and England Activities of Daily Living scale
$t_{1/2}$	apparent terminal phase half- life
TDP-43	transactive response deoxyribonucleic acid binding protein 43 kDa
T_{max}	time to maximum concentration
UCSF	University of California, San Francisco
ULN	upper limit of normal
USP	United States Pharmacopeia
VCP	valosin containing protein
Vd	apparent volume of distribution
w/v	weight/volume
WCBP	women of childbearing potential

PROTOCOL SYNOPSIS

Name of Sponsor:	Adam Boxer, M.D., Ph.D. (Investigator-Sponsored IND)
Name of Finished Product:	TPI 287 Injection
Name of Active Ingredient:	TPI 287
Title of Study:	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential Cohort, Dose-Ranging Study of the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of TPI 287 in Patients with Primary Four Repeat Tauopathies: Corticobasal Syndrome or Progressive Supranuclear Palsy
Protocol No.:	TPI287-4RT-001
Number of Study Centers:	Multi-center
Phase of Development:	Phase 1
Study Period:	21 months (first subject enrolled to last subject completed)
Objectives:	**Primary Objectives** To determine the safety and tolerability [maximum tolerated dose (MTD) within planned dosing range] of intravenous (IV) infusions of TPI 287 administered once every 3 weeks for 9 weeks (for a total of 4 infusions) in patients with primary four repeat tauopathies (4RT), corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP). **Secondary Objectives** To determine the pharmacokinetic (PK) profile of TPI 287 in plasma after a single IV infusion of TPI 287 and the steady-state cerebrospinal (CSF) concentration of TPI 287 1 week after completion of the fourth infusion. **Exploratory Objectives** 1. To explore the effects of TPI 287 on changes in the concentration of CSF biomarkers of neurodegeneration [neurofilament light chain (NfL), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides] 1 week after completion of the fourth infusion of TPI 287 compared to Screening; 2. To explore the effects of TPI 287 on changes in brain network functional and structural connectivity and perfusion [connectivity between midbrain tegmentum and pre-supplementary motor area as measured by resting state functional magnetic resonance imaging (rsfMRI), white matter fractional anisotropy within cortical oculomotor tracts as measured by diffusion tensor imaging (DTI), and medial temporal lobe and regional cortical perfusion as measured by arterial spin labeling (ASL) perfusion MRI] 2 weeks after completion of the fourth infusion of TPI 287 compared to Screening; 3. To explore the effects of TPI 287 on changes in motor function, cognition, activities of daily living, and behavior [Progressive Supranuclear Palsy Rating Scale (PSPRS),

	Schwab and England Activities of Daily Living scale (SEADL), clinical dementia rating scale sum of boxes with added frontotemporal lobar degeneration scales (CDR-SB-FTLD), one-minute phonemic verbal fluency (PVF) test for words starting in "F", "A" and "S", Mini-Mental State Examination (MMSE), and Geriatric Depression Scale (GDS)] 1 week after completion of the fourth infusion of TPI 287 compared to Baseline (Day 1; for PSPRS, SEADL, CDR-SB-FTLD, and PVF) or Screening (for MMSE and GDS); 4. To explore the safety of an optional additional 6 weeks of TPI 287 administered once every 3 weeks in an open-label extension phase (for a total of 7 infusions overall).
Methodology:	This is a phase 1, multi-center, randomized, double-blind, placebo-controlled, sequential cohort, dose-ranging study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of TPI 287 in up to 44 patients with primary 4RT (CBS or PSP). All subjects will be administered study drug (placebo or active) as an IV infusion (target duration of 1 hour) once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase. The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For the initial dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively, for each diagnosis (i.e., 11 for CBS and 11 for PSP). For the remaining dose cohorts, 11 subjects with primary 4RT (i.e., a mix of CBS and PSP subjects with no required ratio of the two) will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. The dose escalation rules are as follows: If ≤1 of the 8 active subjects per cohort experiences dose limiting toxicity (DLT, as defined below) during the first 4 weeks (first 2 infusions and 1 week follow-up), the dose of TPI 287 for the next cohort will be escalated to the next higher planned dose level. If 2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to be the MTD and there will be no further dose escalation. If >2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to have exceeded the MTD and there will be no further dose escalation. Pending consultation with an independent, non-blinded Data Safety Monitoring Board (DSMB), the next cohort may be de-escalated to a lower dose to refine the MTD determination. No more than 3 dose cohorts will be enrolled in this trial. Screening for the second dose cohort (mixed population) may begin as soon as the first dose cohort assessment for one of the two diagnoses (CBS or PSP) is completed and indicates it is safe to proceed. However, the screening will be limited to that diagnosis until such time that the first dose cohort assessment for the other diagnosis is completed and indicates that it is safe to proceed.

	A DLT is defined as: 1) any Grade 3 or higher adverse event (AE) per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for which there is reasonable possibility that TPI 287 caused the event, 2) any Grade 2 AE in the CTCAE system organ class of nervous system disorders that is considered clinically significant and for which there is reasonable possibility that TPI 287 caused the event, or 3) any infusion-related toxicities (e.g., allergic reaction/hypersensitivity) occurring during the infusion of TPI 287 or within 24 hours after completing the infusion that do not resolve promptly with a reduced infusion rate and/or supportive care. Subjects that complete the placebo-controlled (dose-ranging) phase of this study, including the follow-up assessments 1 and 2 weeks after the last infusion with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension (for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized. **Screening:** Each subject will be provided with an informed consent form (ICF) describing the study and will have any questions answered. Subjects that consent to participate in the study will undergo the following eligibility assessments: medical and surgical history, physical examination (including neurological examination), height and weight, vital signs (blood pressure, pulse rate, respiration rate, and temperature), 12-lead electrocardiogram (ECG), MMSE, GDS, safety labs [complete blood count (CBC) with differential, comprehensive metabolic panel, and urinalysis], coagulation tests [prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR)], serum pregnancy test for women of childbearing potential (WCBP), and recording of medications taken within 2 months of Screening visit, including those that are known to be inhibitors or enhancers of cytochrome P450 isoforms. In addition, CBS subjects who meet eligibility criteria after the initial screening assessments will undergo ^{18}F florbetapir positron emission tomography (PET) scanning to rule out the presence of amyloid that would suggest CBS due to Alzheimer's pathology. CBS subjects will also undergo screening for mutations in the progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9ORF72*) genes to rule out CBS due to transactive response deoxyribonucleic acid binding protein 43 kDa (TDP-43) pathology. Subjects who meet eligibility criteria after the initial screening assessments will have the following MRI procedures: rsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and gradient-recalled echo (GRE) sequences. Subjects who continue to meet eligibility criteria after the MRI screening assessments will have CSF collected via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of neurodegeneration, and pre-dose assessment of TPI 287 concentration. Blood samples will also be collected for the purpose of banking deoxyribonucleic acid (DNA) and plasma for future research (approximately 10 and 5 mL, respectively). For

	subjects enrolled before banking was added to the protocol (and thus that missed the blood collections at Screening), collection of a blood sample for DNA banking will be allowed at a later time point up to and including the final study visit. Collection of the pre-dose plasma banking sample will not be allowed at a later time point; however, the scheduled post-dose draws will still be allowed (regardless of whether a pre-dose sample is available). All screening assessments must be completed within 28 days of the first dose of study drug (Day 1). **Study Day 1:** Subjects will return to the clinic on the morning of Day 1 and baseline safety labs will be performed. The following baseline procedures will be performed **prior to enrollment** to confirm that the subject continues to meet eligibility criteria: updated medical history, physical examination (including neurological examination), weight [and calculation of body surface area (BSA) for the purpose of determining dose], vital signs, 12-lead ECG, PSPRS, SEADL, CDR-SB-FTLD, PVF, urine pregnancy test for WCBP, and recording of medications taken since initial Screening visit. Subjects that continue to meet all eligibility requirements will be enrolled in the study and randomized to treatment. The study drug (placebo or active) will be administered in either an inpatient or outpatient facility. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. Monitoring for treatment emergent AEs will begin immediately following the initiation of the study drug infusion and will continue throughout the study. Subjects will be given a diary to record any AEs or concomitant medications taken between visits. Subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Vital signs will be monitored at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion. For time points that include both vital signs and PK analysis, the vital signs will be taken first. Blood samples for the determination of TPI 287 plasma levels will be collected within an hour prior to the start of study drug infusion, at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion. To minimize discomfort, an indwelling cannula rather than repeated venipunctures will be used for the PK blood sampling. Topical anesthesia will be allowed to place the cannula. **Study Day 2:** Subjects will return to the clinic on the morning of Day 2 for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, collection of blood for determination of TPI 287 plasma levels (24 hours post-infusion), and safety labs. **Study Days 8 and 15:** Subjects will return to the clinic on the morning of Days 8 and 15 (-1 Day/+2 Days) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, and safety labs.

	Study Days 22, 43, and 64: Subjects will return to clinic on the morning of Days 22, 43, and 64 for the administration of study drug. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. **Prior to study drug administration**, the following procedures will be performed: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (calculation of BSA for dose determination), vital signs, 12-lead ECG, safety labs, coagulation tests (Day 64 only), and collection of blood for determination of trough levels of TPI 287 in plasma. The subjects will remain in the clinic for 1 hour after completion of the study drug infusion. Vital signs will be monitored at 0.25, 0.5, 1, and 2 hours after initiation of the infusion. **Final Study Visits for Placebo-Controlled Phase:** The final study visit for the placebo-controlled phase of the trial will occur during 2-3 visits, depending on whether the subject is eligible and opts to proceed with the open-label extension. All subjects will return to the clinic 1 week ± 3 days after the fourth study drug infusion for the following procedures: review of diary for any AEs or concomitant medications taken, vital signs, safety labs, collection of blood for determination of TPI 287 plasma level (for comparison with TPI 287 CSF level), collection of CSF via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of neurodegeneration, and TPI 287 concentration, and collection of a blood sample (5 mL) for the banking of plasma for future research. A week later (2 weeks ± 3 days after the fourth study drug infusion), all subjects will return to the clinic for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, PSPRS, SEADL, CDR-SB-FTLD, PVF, MMSE, GDS, MRIs (rsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences), and safety labs. Following the above assessments, those subjects found to be ineligible for the open-label extension or that do not opt to participate in the open-label extension will return to the clinic 4 weeks ± 7 days after the fourth study drug infusion for the following final study procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, safety labs, and collection of a blood sample (5 mL) for the banking of plasma for future research. If a subject is discontinued from study drug treatment early during the placebo-controlled phase, all evaluations described for the above final study visits will be performed if feasible. Any subject with a suspected study drug-related AE at either final study visit will be followed until resolution or stabilization of the event. **Optional Open-Label Extension:** Subjects who are eligible and opt to proceed with the open-label extension will return to the clinic 3 weeks after their last dose of study drug in the placebo-controlled phase of the trial. The following procedures will be performed **prior to study drug administration**: subject signature and date on ICF consenting to optional procedures, review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (and calculation of BSA for dose determination), vital signs, 12-lead ECG, safety labs, and urine pregnancy test for WCBP.

	Study drug (active) will be administered following the completion of the above assessments. The subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Vital signs will be monitored at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion. Subjects will return to the clinic the following morning (24 hours post-infusion) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, and safety labs. Subjects will return to the clinic on the morning of Days 8 and 15 (-1 Day/+2 Days) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, and safety labs. Subjects will return to the clinic on the morning of Days 22 and 43. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. **Prior to study drug administration**, the following procedures will be performed: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (and calculation of BSA for dose determination), vital signs, 12-lead ECG (for second dose of open-label phase only), and safety labs. The subjects will remain in the clinic for 1 hour after completion of the study drug infusion. Vital signs will be monitored at 0.25, 0.5, 1, and 2 hours after initiation of the infusion. **Final Study Visit for Open-Label Phase:** Subjects will return to the clinic 4 weeks ± 7 days after the third study drug infusion of the open-label phase for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, PSPRS, SEADL, CDR-SB-FTLD, PVF, GDS, safety labs, and collection of a blood sample (5 mL) for the banking of plasma for future research. If a subject is discontinued from study drug treatment early during the open-label phase, all evaluations described for the above final study visit will be performed if feasible. Any subject with a suspected study drug-related AE at the final study visit will be followed until resolution or stabilization of the event. Any subject that experiences a DLT (as defined above) will be discontinued from further TPI 287 treatment. Dose escalation will only proceed per the criteria outlined above. Further, the trial as a whole, including enrollment of new subjects and dosing of ongoing subjects, will be temporarily stopped if either of the criteria listed below are met: 1. A death within 30 days after study drug administration where there is a reasonable possibility that the drug caused the event; 2. Two Grade 4 AEs where there is a reasonable possibility that the drug caused the events.

	The IND Sponsor and DSMB will discuss whether a lower dose or any additional treatment guidelines should be implemented, or if the trial should be permanently stopped. Any proposed changes to the protocol to address such findings will be submitted for review and approval by the IRB and Food and Drug Administration (FDA) prior to re-starting the trial.
Number of Subjects (planned):	Up to 44 primary 4RT subjects (CBS or PSP), depending on the dose level at which toxicity is observed
Diagnosis and Main Criteria for Inclusion:	**Inclusion Criteria:** The inclusion criteria for CBS and PSP subjects are listed below, and are the same, except where noted. Subjects must meet **all** of the specified inclusion criteria for CBS to be enrolled in the CBS dose escalation portion of the trial. Subjects must meet **all** of the specified inclusion criteria for PSP to be enrolled in the PSP dose escalation portion of the trial. 1. Between 50 and 85 years of age (inclusive); 2. Able to walk 5 steps with minimal assistance (stabilization of one arm or use of cane/walker); 3. MRI at Screening is consistent with CBS or PSP ($\leq$ 4 microhemorrhages, and no large strokes or severe white matter disease); 4. MMSE at Screening is between 14 and 30 (inclusive); 5. FDA-approved Alzheimer's disease (AD) medications are sometimes prescribed for CBS and PSP subjects, and are allowed as long as the dose is stable for 2 months prior to Screening. Other medications (except those listed under exclusion criteria) are allowed as long as the dose is stable for 30 days prior to Screening; 6. FDA-approved Parkinson's medications are allowed as long as the dose is stable for 2 months prior to Screening; 7. Has a reliable study partner who agrees to accompany the subject to visits, and spends at least 5 hours per week with the subject; 8. Agrees to 2 lumbar punctures; 9. Signed and dated written informed consent obtained from the subject and the subject's caregiver in accordance with local IRB regulations; 10. Males and all WCBP agree to abstain from sex or use an adequate method of contraception for the duration of the study and for 30 days after the last dose of study drug; **For PSP Only** 11. Meets National Institute of Neurological Disorders and Stroke – Society for Progressive Supranuclear Palsy (NINDS-SPSP) probable or possible PSP criteria (Litvan et al. 1996a), as modified for the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) clinical trial (Bensimon et al. 2009). **For CBS Only** 11. Meets 2013 consensus criteria for possible or probable corticobasal degeneration, CBS subtype (Armstrong et al. 2013). **Exclusion Criteria:** The exclusion criteria for CBS and PSP are listed below, and are the same, except where noted. Subjects meeting **any** of the specified exclusion criteria for CBS will be excluded from the CBS dose escalation portion of the trial. Subjects meeting **any** of

	the specified exclusion criteria for PSP will be excluded from the PSP dose escalation portion of the trial. 1. Meets National Institute on Aging-Alzheimer's Association Workgroups criteria for probable AD (McKhann et al. 2011); 2. Any medical condition other than CBS or PSP that could account for cognitive deficits (e.g., active seizure disorder, stroke, vascular dementia); 3. A prominent and sustained response to levodopa therapy; 4. History of significant cardiovascular, hematologic, renal, or hepatic disease (or laboratory evidence thereof); 5. History of significant peripheral neuropathy; 6. History of major psychiatric illness or untreated depression; 7. Neutrophil count <1,500/mm^3, platelets <100,000/mm^3, serum creatinine >1.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN, alanine aminotransferase (ALT) >3 x ULN, aspartate aminotransferase (AST) >3 x ULN, or INR >1.2 at Screening evaluations; 8. Evidence of any clinically significant findings on Screening or baseline evaluations which, in the opinion of the Investigator would pose a safety risk or interfere with appropriate interpretation of study data; 9. Current or recent history (within four weeks prior to Screening) of a clinically significant bacterial, fungal, or mycobacterial infection; 10. Current clinically significant viral infection; 11. Major surgery within four weeks prior to Screening; 12. Unable to tolerate MRI scan at Screening; 13. Any contraindication to or unable to tolerate lumbar puncture at Screening, including use of anti-coagulant medications such as warfarin. Daily administration of 81 mg aspirin will be allowed as long as the dose is stable for 30 days prior to Screening; 14. Subjects who, in the opinion of the Investigator, are unable or unlikely to comply with the dosing schedule or study evaluations; 15. Previous exposure to microtubule inhibitors (including TPI 287) within 5 years of Screening. Treatment with microtubule inhibitors other than TPI 287 while on study will not be allowed; 16. Participation in another interventional clinical trial within 3 months of Screening; 17. Treatment with another investigational drug within 30 days of Screening. Treatment with investigational drugs other than TPI 287 while on study will not be allowed; 18. Known hypersensitivity to the inactive ingredients in the study drug; 19. Pregnant or lactating; 20. Positive pregnancy test at Screening or Baseline (Day 1); 21. Cancer within 5 years of Screening, except for non-metastatic skin cancer or non-metastatic prostate cancer not expected to cause significant morbidity or mortality within one year of Baseline; **For CBS Only** 22. History or evidence at Screening of cortical amyloid levels on ^{18}F florbetapir PET scans consistent with underlying AD;

	23. History of serum or plasma progranulin level less than one standard deviation below the normal subject mean for the laboratory performing the assay; 24. History or evidence at Screening of known disease-associated mutations in *GRN* or *C9ORF72* genes to rule out CBS due to TDP-43 pathology; 25. History of known disease-associated mutations in ribosomal protein L3 ([TDP-43 gene (*TARBP*)], chromatin modifying protein 2B (*CHMPB2*) or valosin containing protein (*VCP*) genes or any other frontotemporal lobar degeneration (FTLD) causative genes discovered during the course of the trial and not associated with underlying tau pathology.
Test Product, Dose and Mode of Administration:	**Active Pharmaceutical Ingredient** The investigational drug is TPI 287. TPI 287 is a microtubule inhibitor belonging to the taxane diterpenoid (taxoid) family, and specifically to the abeotaxane class. The chemical name of TPI 287 is (2'R,3'S)-2'-hydroxy-N-carboxy-3'-amino-5'-methyl-hexanoic,N-*tert*-butyl ester, 13 ester 5β-20-epoxy-1β,2α,4α,7β,9α,10α,13α-heptahydroxy-4,10-diacetate-2-benzoate-(1"S)-7,9-acrolein acetal-11(15 →1)-abeotaxane. TPI 287 has a molecular weight (MW) of 869.99 Da and a molecular formula of $C_{46}H_{63}NO_{15}$. **Drug Products** The dosage form of the investigational drug product is a sterile parenteral solution for IV infusion (TPI 287 Injection). The inactive ingredients are polyoxyl 35 castor oil [Kolliphor® ELP, previously named Cremophor® EL-P, National Formulary (NF)] and dehydrated alcohol, United States Pharmacopeia (USP). A single strength (10 mg/mL) of TPI 287 Injection will be used for this trial. Each single-use vial contains 10 mL of drug product with 100 mg of TPI 287 in a 15:85 mixture (weight/volume, w/v) of Kolliphor® ELP and dehydrated alcohol (1.58 g Kolliphor in quantity sufficient ethanol to 10 mL). TPI 287 Injection must be diluted prior to administration. The Investigational Site pharmacist will dilute the required volume of 10 mg/mL TPI 287 Injection in a di(2-ethylhexyl)phthalate- (DEHP-) free, non-polyvinyl chloride (non-PVC), 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP for administration. Based on the proposed doses (2, 6.3, and 20 mg/m^2) and assuming a 1.62 m^2 individual, the dilution of TPI 287 Injection will range from approximately 1,544- to 155.3-fold. The placebo to be used in this trial will be a DEHP-free, non-PVC, 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP. The final volume for administration will be approximately 500 mL. **Dose and Mode of Administration** All doses of study drug (placebo and active) will be administered in an inpatient or outpatient facility. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. An administration set comparable to those used for paclitaxel administration (i.e., a DEHP-free and/or polyethylene-lined IV administration set with an in-line 0.2 micron filter) must be used for study drug administration. The following administration sets or their equivalent

	may be used: Baxter Product Codes 2C7557, 2C8857, 2C8858, or 2C7558, B. Braun Product Code V9902F, CareFusion Product Code 10010454, CareFusion Product Code 28053 with 20350E extension, or Hospira Product Code 14248-28 with 20668-28 extension. TPI 287 must be administered as an IV infusion only (i.e., it should not be administered as an IV push or bolus). All doses of study drug will be administered as an IV infusion (target duration of 1 hour). The entire IV bag content will be administered, minus the volume that remains in the administration set (priming volume). A 0.9% Sodium Chloride for Injection, USP flush will then be used to ensure that the remainder of the TPI 287 dose in the line is administered to the subject. If a mild-to-moderate (Grade 1 to 2) hypersensitivity reaction is observed, the TPI 287 infusion rate may be reduced to half that of the initial attempt at the discretion of the Investigator. Further, this reduced rate may be used at subsequent infusions at the discretion of the Investigator. All subjects in this trial will be administered study drug (placebo or active) once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase. The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For the initial dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively, for each diagnosis (i.e., 11 for CBS and 11 for PSP). For the remaining dose cohorts, 11 subjects with primary 4RT (i.e., a mix of CBS and PSP subjects with no required ratio of the two) will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. Subjects that complete the placebo-controlled (dose-ranging) phase with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension (for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized.
Duration of Treatment:	9 weeks (for a total of 4 infusions) under the placebo-controlled (dose-ranging) phase, or 15 weeks (for a total of 7 infusions) if the subject is eligible and opts to participate in the open-label extension
Criteria for Evaluation:	**Primary Endpoints** Safety and tolerability (MTD within planned range) of IV infusions of TPI 287 administered once every 3 weeks for 9 weeks (for a total of 4 infusions) in patients with primary 4RT, CBS or PSP, are the primary endpoints for this trial. Safety and tolerability will be assessed based on AEs, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PT/PTT/INR, CSF cell count with differential, glucose, and total protein, PSPRS, SEADL, CDR-SB-FTLD, PVF, MMSE, GDS, MRI (standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences).

	Secondary Endpoints The PK profile of TPI 287 in plasma after a single TPI 287 IV infusion (Day 1) and the steady-state CSF concentration of TPI 287 1 week after completion of the fourth TPI 287 infusion are the secondary endpoints for this trial. The plasma PK assessments will be based on maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from time zero to time of last measurable concentration (AUC_t), area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal phase half- life ($t_{1/2}$), clearance (CL), apparent volume of distribution (Vd), mean residence time (MRT), and trough concentrations (at Days 22, 43, and 64). **Exploratory Endpoints** The endpoints listed below are the exploratory endpoints for the trial. 1. Changes in the concentration of CSF biomarkers of neurodegeneration (NfL, total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides) 1 week after completion of the fourth infusion of TPI 287 compared to Screening; 2. Changes in brain network functional and structural connectivity and perfusion (connectivity between midbrain tegmentum and pre-supplementary motor area as measured by rsfMRI, white matter fractional anisotropy within cortical oculomotor tracts as measured by DTI, and medial temporal lobe and regional cortical perfusion as measured by ASL perfusion MRI) 2 weeks after completion of the fourth infusion of TPI 287 compared to Screening; 3. Changes in motor function, cognition, activities of daily living, and behavior (PSPRS, SEADL, CDR-SB-FTLD, PVF, MMSE, and GDS) 1 week after completion of the fourth infusion of TPI 287 compared to Baseline (Day 1; for PSPRS, SEADL, CDR-SB-FTLD and PVF) or Screening (for MMSE and GDS). 4. Safety of an optional additional 6 weeks of TPI 287 administered once every 3 weeks in an open-label extension phase(for a total of 7 infusions overall). Safety will be assessed based on AEs, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PSPRS, SEADL, CDR-SB-FTLD, PVF and GDS.
Statistical Methods:	**Safety** Data from all subjects who receive at least one dose of study drug (placebo or active) will be included in the safety analysis. AEs will be tabulated by body system and preferred term [per Medical Dictionary for Regulatory Activities (MedDRA)], and will be further categorized by treatment group, phase of trial [i.e., placebo-controlled (dose-ranging) phase versus open-label extension], severity, and assigned relationship to study drug. The incidence for each AE will be provided as the total number of subjects that experienced the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment

	for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables. AEs will also be listed for individual subjects, along with information regarding onset, duration, severity, relationship to study drug, and outcome. AEs that lead to withdrawal from the study will be listed and summarized. A separate tabulation and listing of serious adverse events (SAEs) will also be generated. Other safety assessments, including physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PT/PTT/INR, CSF cell count with differential, glucose, and total protein, PSPRS, SEADL, PVF, CDR-SB-FTLD, MMSE, GDS, and MRI (standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences) will be listed and summarized by treatment group and phase of trial [i.e., placebo-controlled (dose-ranging) phase versus open-label extension]. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Inferential statistical analyses comparing the safety data among treatment groups or phases of the trial are not planned. The MTD of TPI 287 in patients with primary 4RT will be defined as the highest dose level achieved (within planned dosing range) at which no more than 2 of 8 active subjects experienced a DLT during the first 4 weeks (2 infusions and 1 week follow-up). **Pharmacokinetics** The concentration of TPI 287 in plasma and CSF will be measured using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methods. Individual and mean (standard deviation) plasma and CSF TPI 287 concentration data will be tabulated and plotted by dose level. Plasma TPI 287 concentration-time data will be analyzed by non-compartmental methods using WinNonlin (Pharsight Corporation, CA). PK parameters will be calculated according to standard equations. Individual PK parameters will be summarized by descriptive statistics for each dose group. The descriptive statistics will include arithmetic mean, standard deviation, median, minimum, maximum, and geometric mean (log-transformed). Inferential statistical analyses comparing PK data among treatment groups are not planned. **Exploratory Pharmacodynamics and Efficacy** CSF concentrations of NfL, total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides at Screening and 1 week after completion of the fourth study drug infusion, as well as the calculated changes in these measurements will be listed and summarized by treatment group. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation). Inferential statistical analyses comparing data among treatment groups are not planned.

	Connectivity between midbrain tegmentum and pre-supplementary motor area as measured by rsfMRI, white matter fractional anisotropy within cortical oculomotor tracts as measured by DTI, and medial temporal lobe and regional cortical perfusion as measured by ASL perfusion MRI at Screening and 2 weeks after completion of the fourth study drug infusion, as well as the calculated changes in these measurements will be listed and summarized by treatment group. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation). Inferential statistical analyses comparing data among treatment groups are not planned. PSPRS, SEADL, CDR-SB-FTLD, PVF, MMSE, and GDS assessments at Screening or Baseline and 1 week after completion of the fourth study drug infusion, as well as the calculated change in these assessments will be listed and summarized by treatment group and phase of trial [i.e., placebo-controlled (dose-ranging) phase versus open-label extension]. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Analysis of variance (ANOVA) will be used to compare the changes in these assessments across treatment groups.

1. BACKGROUND

1.1 Primary Four Repeat Tauopathies: Corticobasal Syndrome and Progressive Supranuclear Palsy

Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are the neuropathological terms for well-defined neurodegenerative disorders that are associated with pathogenic accumulation in the brain of hyperphosphorylated tau protein in different anatomical patterns. They are considered to be tauopathies because of the central role of tau in their pathology and the lack of other associated pathogenic proteins. Both disorders were originally described in the 1960's as atypical movement disorders associated with unique patterns of neuropathology at autopsy (Steele et al. 1964, Rebeiz et al. 1968). As classically described, both CBD and PSP generally begin in the 50's, 60's or 70's and are slowly progressive, leading to death on average 5-7 years from diagnosis (Wenning et al. 1998, Golbe and Ohman-Strickland 2007). The prevalence of PSP based on clinical diagnoses is estimated to be 1.9 - 6.4 cases per 100,000 (Golbe et al. 1988, Schrag et al. 1999). There are no published studies of CBD prevalence; however, clinical experience suggests the prevalence is similar to that of PSP.

Consensus research criteria have been developed for PSP and have excellent predictive power for underlying PSP pathology (Litvan et al. 1996a, Litvan et al. 1996b, Bensimon et al. 2009). PSP is named for its characteristic eye movement abnormalities, and a diagnosis of probable PSP requires a slowly progressive disorder with onset after age 40, a vertical supranuclear gaze palsy of eye movements and falls within the first year of diagnosis. Other supportive criteria include prominent axial rigidity, early dysphagia and dysarthria, apathy, and cognitive impairments (in abstraction or verbal fluency).

Consensus research criteria have also been developed for CBD (Armstrong et al. 2013). The most common clinical presentation for CBD is a progressive, asymmetric, akinetic-rigid syndrome that does not respond to levodopa treatment, called **corticobasal syndrome (CBS)**. Individuals have a combination of deficits attributable to cortical dysfunction, such as apraxia, language difficulties, cortical sensory loss or neglect as well as symptoms attributable to basal ganglia dysfunction such as rigidity or dystonia. Other features classically associated with CBS include stimulus sensitive myoclonus and alien limb phenomenon. Most commonly, the first symptom is apraxia or dystonia involving one limb that gradually worsens and spreads to the contralateral side (Riley et al. 1990). Eye movements are impaired in CBS, and progressively worsen with disease progression (Rivaud-Pechoux et al. 2000, Garbutt et al. 2008). Cognitively, planning and other aspects of executive function are impaired in CBS (Murray et al. 2007).

Over time, it has been increasingly recognized that both PSP and CBD, when defined by their neuropathological findings at autopsy, can present clinically with cognitive or behavioral impairments that would be classified as frontotemporal lobar degeneration (FTLD), or other

neurodegenerative syndromes resembling idiopathic Parkinson's disease or Alzheimer's disease (AD) (Feany et al. 1996, Litvan et al. 1997, Schneider et al. 1997, Boeve et al. 1999, Kertesz et al. 2000, Hughes et al. 2002, Morris et al. 2002, Belfor et al. 2005, Josephs et al. 2006a, Josephs et al. 2006b, Williams et al. 2009). Conversely, some clinically-defined CBS cases are found to have non-CBD pathology at autopsy, most commonly PSP, but sometimes AD (Schneider et al. 1997, Boeve et al. 1999). Despite this dissociation between clinical syndrome and autopsy findings, clinically defined cases that display the classic PSP (now called Richardson's syndrome by some investigators (Williams et al. 2005) or CBS movement disorder are highly likely to have either PSP or CBD pathology at autopsy (Josephs et al. 2006b), and often have more severe tau pathology than cases with atypical clinical presentations (Litvan et al. 1996b, Litvan et al. 1997, Morris et al. 2002, Williams et al. 2007).

Thus, by recruiting both typical CBS and PSP cases, and excluding atypical forms of AD using biomarkers such as amyloid imaging [^{18}F florbetapir positron emission tomography (PET)], one can have a high degree of confidence that the underlying molecular pathology will be purely tau-related, even if the neuropathological diagnosis does not correspond to the clinical diagnosis.

1.2 Tau Biochemistry in CBD and PSP

Tau is a protein that binds to and stabilizes microtubules, subcellular structures necessary for maintaining neuronal shape and for transport of cellular cargo (reviewed in Brunden et al. 2009). Humans express six isoforms of tau protein due to alternative splicing of the tau (*MAPT*) gene. One of the alternatively spliced exons, exon 10, contains a microtubule binding domain. The absence or presence of exon 10 determines whether tau with 3 microtubule binding domain repeats (3R tau) or 4 microtubule binding domain repeats (4R tau) is present. 4R tau binds to microtubule domains more strongly than 3R tau, and most normal human brains have roughly equal ratios of 3R to 4R tau.

A variety of mutations have been identified in *MAPT* that lead to an autosomal dominantly-inherited human neurodegenerative disease, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) (Clark et al. 1998, Hutton et al. 1998, Reed et al. 2001). Interestingly, many of these mutations affect the splicing of exon 10, and alter the ability of tau to bind to microtubules or to form insoluble aggregates (Hong et al. 1998). A number of FTDP-17 mutations lead to clinical phenotypes consistent with CBS or PSP (Morris et al. 2003, Rossi et al. 2008, Skoglund et al. 2008). The hyperphosphorylated tau that accumulates in both CBD and PSP brains at autopsy is predominantly 4R tau, leading to the designation of both CBD and PSP as 4R tauopathies (Brunden et al., 2009).

1.3 TPI 287

TPI 287 is being developed for the treatment of the primary four repeat tauopathies (4RT), CBS and PSP, under an Investigator-Sponsored IND (Adam Boxer, M.D., Ph.D., UCSF Memory and Aging Center).

This trial is a phase 1, multi-center, randomized, double-blind, placebo-controlled, sequential cohort, dose-ranging study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of TPI 287 in up to 44 patients with primary 4RT (CBS or PSP).

All subjects will be administered study drug (placebo or active) as an intravenous (IV) infusion (target duration of 1 hour) once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase. TPI 287 will be formulated in 15:85 Kolliphor ELP:dehydrated alcohol and diluted approximately 155- to 1,544-fold with 0.9% Sodium Chloride for Injection prior to administration.

The dose of TPI 287 will be escalated in sequential cohorts. For the initial dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively, for each diagnosis (i.e., 11 for CBS and 11 for PSP). For the remaining dose cohorts, 11 subjects with primary 4RT (i.e., a mix of CBS and PSP subjects with no required ratio of the two) will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. Dose escalation will only be allowed if no more than 1 of the 8 active subjects per cohort experiences dose limiting toxicity (DLT) during the first 4 weeks (first two infusions and one week of follow-up).

Subjects that complete the placebo-controlled (dose-ranging) phase with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension (for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized.

The proposed clinical trial is the first trial of TPI 287 for primary 4RT (CBS and PSP), and thus there is no previous human experience with TPI 287 in patients with primary 4RT. TPI 287 is being studied in patients with AD (under IND 118,790 sponsored by Adam Boxer, M.D., Ph.D., UCSF Memory and Aging Center) using a protocol that is nearly identical to this one (Protocol No. TPI287-AD-001, Version 2). Protocol No. TPI287-AD-001 is open for enrollment, and as of May 9, 2014, six subjects have been enrolled and no DLTs have occurred.

TPI 287 has been in clinical development for the treatment of various advanced recurrent or refractory cancers for over eight years under Cortice Biosciences, Inc. (Cortice) INDs 69,967 and

119,041, as well as an Investigator-Sponsored IND (104,512) and MD Anderson Cancer Center-sponsored INDs (106,771 and 115,287) for which Cortice has provided study drug. Cortice is also providing study drug for the above-referenced AD trial, and will provide study drug (TPI 287 Injection) for the proposed clinical trial for 4RT.

TPI 287 is a microtubule inhibitor belonging to the taxane diterpenoid (taxoid) family, and specifically to the abeotaxane class. It is manufactured by a semi-synthetic process beginning from 10-deacetylbaccatin III extracted from yew (*Taxus baccata*). The synthesis involves modifications of the side chain to make the drug more lipophilic, and modifications of the baccatin ring structure with the intent of circumventing resistance associated with the expression of the multidrug resistance- (MDR-) 1 gene or mutations of β-tubulin.

The pharmacological rationale for developing TPI 287 for the treatment of primary 4RT (CBS and PSP) is based on the proposed role that abnormal tau function plays in 4RT pathology and TPI 287's pharmacological classification as a microtubule inhibitor. As reviewed by Yoshiyama et al. 2012, under normal physiological conditions, tau binds to microtubules and promotes assembly and stabilization of microtubules for axonal transport. The balance of phosphorylation and dephosphorylation of tau coordinates tau attachment to and from the microtubules, regulating microtubule stability and trafficking of cargo along the axon.

There is increasing evidence that loss of tau function in tauopathies such as 4RT leads to insoluble tau deposits and destabilization and disassembly of microtubules, with a variety of deleterious effects on neurons including impaired axonal transport (Yoshiyama et al. 2012). Hyperphosphorylation of tau decreases the ability of tau to bind microtubules, leading to an abnormal increase in the levels of unbound tau that likely promotes its aggregation into filaments. These filaments are sequestered into neurofibrillary tangles (NFTs), thereby depleting functional tau.

TPI 287 binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This inhibition of microtubule dynamics leads to stabilization of the microtubules, which in the context of 4RT patients is hypothesized to compensate for the loss in tau function and decrease insoluble hyperphosphorylated tau deposition, resulting in restoration of axonal transport, improved cognitive function, and decreased neurodegeneration.

This hypothesis is supported by an *in vitro* tubulin polymerization assay that showed TPI 287 promoted the assembly of microtubules with a potency similar to or exceeding that of paclitaxel, docetaxel, and epothilone B (Section 8 of IND). Further, tau transgenic mouse model studies of other drugs in the same pharmacological class (i.e., microtubule inhibitors) showed that the stabilization of microtubules by such drugs can compensate for loss of tau function and decrease tau pathology, resulting in restoration of axonal transport, improved cognitive function, and decreased neurodegeneration, and thus such microtubule inhibitors may have therapeutic

potential for treating tauopathies, in particular primary 4RT, since 4RT are biochemically more similar to transgenic mouse tauopathy models than are other clinical disorders such as AD (Zhang et al. 2005, Brunden et al. 2010, Barten et al. 2012, and Zhang et al. 2012).

The initial steps in the mechanism of action for TPI 287 for the treatment of cancer are conceptually similar to those for the treatment of primary 4RT. The difference is that the level of stabilization of microtubules at high TPI 287 doses results in the inhibition of mitotic and interphase cellular functions and cell death. Thus, unlike for 4RT patients (with a loss in tau function) where low dose TPI 287 microtubule stabilization is hypothesized to lead to restoration of function, in cancer cells, high dose TPI 287 leads to higher levels of microtubule stabilization resulting in inhibition of cellular function and cell death.

The pharmacologically active dose of TPI 287 for the primary 4RT indication (i.e., for restoration of function) is hypothesized to be lower than that for the cancer indication (i.e., for inhibition of cell function and cell death). This is based on tau transgenic mouse model studies of paclitaxel and epothilone D that showed efficacy at weekly intraperitoneal (IP) dose levels 10 mg/kg (30 mg/m^2) and 1 mg/kg (3 mg/m^2), respectively, the *in vitro* tubulin polymerization assay showing that TPI 287 had a potency similar to or exceeding that of paclitaxel and epothilone B, and a pharmacokinetic (PK) study in mice and rats demonstrating that TPI 287 is able to effectively cross the blood brain barrier. The tau transgenic mice overexpress 4R tau and have accumulation of hyperphosphorylated 4R tau similar to patients with CBD and PSP. The planned dose levels for the proposed trial are significantly lower than those used for the same schedule for the cancer indication (i.e., 160 mg/m^2), yet are anticipated to be pharmacologically active.

Five clinical trials of TPI 287 for the treatment of cancer have been conducted under Cortice IND 69,967, including three phase 1 trials and two phase 2 trials (all single agent), and two clinical trials of TPI 287 for the treatment of cancer have been initiated under Cortice IND 119,041, including two phase 2 trials (both combination agent). In addition, seven clinical trials of TPI 287 for the treatment of cancer have been initiated under an Investigator-Sponsored IND (104,512) or MDACC-sponsored INDs (106,771 and 115,287), including one phase 1 trial (single and combination agent), three phase 1/2 trials (one single agent, one combination agent, and one with single and combination agent components), and three phase 2 trials (one single agent and two with single and combination agent components). Four of the seven trials are ongoing.

Over 190 cancer patients have been treated with TPI 287 in the above referenced trials at dose levels ranging from 7 to 185 mg/m^2 and for durations ranging from 1 day to 10 months. The dosing regimens used for the cancer indication include 1-hour IV infusions once every week for three weeks with the fourth week off (4-week cycle), once every week for three weeks without the fourth week off (condensed weekly regimen), or once every three weeks (21-day cycle). The

latter is the proposed dosing regimen for this trial of TPI 287 in primary 4RT patients, and is the same dosing regimen in the approved protocol for AD patients.

The maximum tolerated dose (MTD) for the once every three week dosing regimen in cancer patients was determined to be 160 mg/m^2. The proposed starting dose for the trial in primary 4RT patients is 80-fold lower than this MTD. Further, the maximum planned dose level for the proposed dose-escalation trial is 8-fold lower. There were no trials of the once every three week dosing regimen at dose levels as low as those proposed for the 4RT trial (i.e., 2-20 mg/m^2). At the lowest dose level tested for this schedule in cancer patients (56 mg/m^2), there were no adverse events (AEs) considered possibly, probably, or definitely related to TPI 287, except for Grade 1 nausea. The proposed starting dose and maximum planned dose level for this trial are the same as for the approved protocol for AD patients.

Dose levels within the proposed range for the trial in primary 4RT patients (i.e., 2-20 mg/m^2) were tested for the more frequent dosing schedule (i.e., once weekly for three weeks with the fourth week off). At 7 or 14 mg/m^2 TPI 287, AEs considered possibly, probably, or definitely related to TPI 287 included diarrhoea, nausea, vomiting, fatigue, anorexia, back pain, balance disorder, dizziness, headache, dyspnoea, alopecia, and flushing. All of these occurred at severities no greater than Grade 1 or 2, except for the back pain, dizziness, dyspnoea, and flushing that occurred at Grade 3 at 14 mg/m^2. The MTD for the once weekly for three weeks with fourth week off dosing regimen in cancer patients was determined to be 127.5 mg/m^2.

Nonclinical safety pharmacology studies of single IV injections of TPI 287 formulated in Kolliphor ELP and diluted 10-fold in 0.9% sodium chloride resulted in no central nervous system (CNS) or respiratory adverse findings in rats and no cardiovascular (CV) adverse findings in dogs. The human equivalent doses for the highest doses tested in the rat and dog safety pharmacology studies were 148 mg/m^2 and 207.2 mg/m^2, respectively. The proposed starting dose for this trial is 74- and 103.6-fold lower, respectively, than these dose levels associated with no adverse findings.

The proposed starting dose is also 43-fold below the human equivalent dose of the no-observed-adverse-effect-level (NOAEL) determined for the rat (most sensitive species) single dose IV injection toxicity study. It is 20-fold below the human equivalent dose of the lowest dose tested in the rat once a week for three week IV injection toxicity study; the NOAEL could not be determined from the dose levels tested in the study.

In summary, the previous human experience with TPI 287 in cancer patients indicates that the proposed dosing regimen will be well tolerated in patients with primary 4RT. This coupled with the preclinical rationale for efficacy, the supporting nonclinical toxicology studies, and the planned safety monitoring/precautions indicate that the proposed clinical trial of TPI 287 in

patients with primary 4RT, for which there is no known curative therapy appears reasonably safe to initiate.

For further details regarding the nonclinical and clinical studies of TPI 287 please refer to the most current Investigator's Brochure.

This study will be performed in compliance with the current ICH guidelines for GCP and all applicable regulatory requirements.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this trial are to determine the safety and tolerability (MTD within planned dosing range) of IV infusions of TPI 287 administered once every 3 weeks for 9 weeks (for a total of 4 infusions) in patients with primary 4RT, CBS or PSP.

2.2 Secondary Objectives

The secondary objectives of this trial are to determine the PK profile of TPI 287 in plasma after a single IV infusion of TPI 287 and the steady-state cerebrospinal fluid (CSF) concentration of TPI 287 1 week after completion of the fourth infusion.

2.3 Exploratory Objectives

The exploratory objectives of this trial are as follows:

1. To explore the effects of TPI 287 on changes in the concentration of CSF biomarkers of neurodegeneration [neurofilament light chain (NfL), total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides] 1 week after completion of the fourth infusion of TPI 287 compared to Screening;

2. To explore the effects of TPI 287 on changes in brain network functional and structural connectivity and perfusion [connectivity between midbrain tegmentum and pre-supplementary motor area as measured by resting state functional magnetic resonance imaging (rsfMRI), white matter fractional anisotropy within cortical oculomotor tracts as measured by diffusion tensor imaging (DTI), and regional cortical perfusion as measured

by arterial spin labeling (ASL) perfusion MRI] 2 weeks after completion of the fourth infusion of TPI 287 compared to Screening;

3. To explore the effects of TPI 287 on changes in motor function, cognition, activities of daily living, and behavior [Progressive Supranuclear Palsy Rating Scale (PSPRS), Schwab and England Activities of Daily Living scale (SEADL), clinical dementia rating scale sum of boxes with added frontotemporal lobar degeneration scales (CDR-SB-FTLD), one-minute phonemic verbal fluency (PVF) test for words starting in "F", "A" and "S", Mini-Mental State Examination (MMSE), and Geriatric Depression Scale (GDS)] 1 week after completion of the fourth infusion of TPI 287 compared to Baseline (Day 1; for PSPRS, SEADL, CDR-SB-FTLD, and PVF) or Screening (for MMSE and GDS);

4. To explore the safety of an optional additional 6 weeks of TPI 287 administered once every 3 weeks in an open-label extension phase (for a total of 7 infusions overall).

3. STUDY DESIGN

This is a phase 1, multi-center, randomized, double-blind, placebo-controlled, sequential cohort, dose-ranging study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of TPI 287 in up to 44 patients with primary 4RT (CBS or PSP). All subjects will be administered study drug (placebo or active) as an IV infusion (target duration of 1 hour) once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase.

The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For the initial dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively, for each diagnosis (i.e., 11 for CBS and 11 for PSP). For the remaining dose cohorts, 11 subjects with primary 4RT (i.e., a mix of CBS and PSP subjects with no required ratio of the two) will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. The dose escalation rules are as follows:

If ≤1 of the 8 active subjects per cohort experiences DLT (as defined below) during the first 4 weeks (first 2 infusions and 1 week follow-up), the dose of TPI 287 for the next cohort will be escalated to the next higher planned dose level.

If 2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to be the MTD and there will be no further dose escalation.

If >2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to have exceeded the MTD and there will be no further dose escalation. Pending consultation with an independent, non-blinded Data Safety Monitoring Board (DSMB), the next cohort may be de-escalated to a lower dose to refine the MTD determination. No more than 3 dose cohorts will be enrolled in this trial.

Screening for the second dose cohort (mixed population) may begin as soon as the first dose cohort assessment for one of the two diagnoses (CBS or PSP) is completed and indicates it is safe to proceed. However, the screening will be limited to that diagnosis until such time that the first dose cohort assessment for the other diagnosis is completed and indicates that it is safe to proceed.

A DLT is defined as: 1) any Grade 3 or higher AE per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for which there is reasonable possibility that TPI 287 caused the event, 2) any Grade 2 AE in the CTCAE system organ class of nervous system disorders that is considered clinically significant and for which there is reasonable possibility that TPI 287 caused the event, or 3) any infusion-related toxicities (e.g., allergic reaction/hypersensitivity) occurring during the infusion of TPI 287 or within 24 hours after completing the infusion that do not resolve promptly with a reduced infusion rate and/or supportive care.

Subjects that complete the placebo-controlled (dose-ranging) phase of this study, including the follow-up assessments 1 and 2 weeks after the last infusion with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension(for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized.

Screening: Each subject will be provided with an ICF describing the study and will have any questions answered. Subjects that consent to participate in the study will undergo the following eligibility assessments: medical and surgical history, physical examination (including neurological examination), height and weight, vital signs (blood pressure, pulse rate, respiration rate, and temperature), 12-lead electrocardiogram (ECG), MMSE, GDS, safety labs [complete blood count (CBC) with differential, comprehensive metabolic panel, and urinalysis], coagulation tests [prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR)], serum pregnancy test for women of childbearing potential (WCBP), and recording of medications taken within 2 months of Screening visit, including those that are known to be inhibitors or enhancers of cytochrome P450 isoforms.

In addition, CBS subjects who meet eligibility criteria after the initial screening assessments will undergo ^{18}F florbetapir PET scanning to rule out the presence of amyloid that would suggest CBS due to Alzheimer's pathology. CBS subjects will also undergo screening for mutations in the progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9ORF72*) genes to rule out CBS due to transactive response deoxyribonucleic acid binding protein 43 kDa (TDP-43) pathology.

Subjects who meet eligibility criteria after the initial screening assessments will have the following MRI procedures: rsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and gradient-recalled echo (GRE) sequences.

Subjects who continue to meet eligibility criteria after the MRI screening assessments will have CSF collected via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of neurodegeneration, and pre-dose assessment of TPI 287 concentration.

Blood samples will also be collected for the purpose of banking deoxyribonucleic acid (DNA) and plasma for future research (approximately 10 and 5 mL, respectively). For subjects enrolled before banking was added to the protocol (and thus that missed the blood collections at Screening), collection of a blood sample for DNA banking will be allowed at a later time point up to and including the final study visit. Collection of the pre-dose plasma banking sample will not be allowed at a later time point; however, the scheduled post-dose draws will still be allowed (regardless of whether a pre-dose sample is available).

All screening assessments must be completed within 28 days of the first dose of study drug (Day 1).

Study Day 1: Subjects will return to the clinic on the morning of Day 1 and baseline safety labs will be performed. The following baseline procedures will be performed **prior to enrollment** to confirm that the subject continues to meet eligibility criteria: updated medical history, physical examination (including neurological examination), weight [and calculation of body surface area (BSA) for the purpose of determining dose], vital signs, 12-lead ECG, PSPRS, SEADL, CDR-SB-FTLD, PVF, urine pregnancy test for WCBP, and recording of medications taken since initial Screening visit.

Subjects that continue to meet all eligibility requirements will be enrolled in the study and randomized to treatment. The study drug (placebo or active) will be administered in either an inpatient or outpatient facility. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions.

Monitoring for treatment emergent AEs will begin immediately following the initiation of the study drug infusion and will continue throughout the study. Subjects will be given a diary to record any AEs or concomitant medications taken between visits.

Subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Vital signs will be monitored at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion. For time points that include both vital signs and PK analysis, the vital signs will be taken first.

Blood samples for the determination of TPI 287 plasma levels will be collected within an hour prior to the start of study drug infusion, at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion. To minimize discomfort, an indwelling cannula rather than repeated venipunctures will be used for the PK blood sampling. Topical anesthesia will be allowed to place the cannula.

Study Day 2: Subjects will return to the clinic on the morning of Day 2 for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, collection of blood for determination of TPI 287 plasma levels (24 hours post-infusion), and safety labs.

Study Days 8 and 15: Subjects will return to the clinic on the morning of Days 8 and 15 (-1 Day/+2 Days) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, and safety labs.

Study Days 22, 43, and 64: Subjects will return to clinic on the morning of Days 22, 43, and 64 for the administration of study drug. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. **Prior to study drug administration**, the following procedures will be performed: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (calculation of BSA for dose determination), vital signs, 12-lead ECG, safety labs, coagulation tests (Day 64 only), and collection of blood for determination of trough levels of TPI 287 in plasma. The subjects will remain in the clinic for 1 hour after completion of the study drug infusion. Vital signs will be monitored at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Final Study Visits for Placebo-Controlled Phase: The final study visit for the placebo-controlled phase of the trial will occur during 2-3 visits, depending on whether the subject is eligible and opts to proceed with the open-label extension. All subjects will return to the clinic 1 week ± 3 days after the fourth study drug infusion for the following procedures: review of diary for any AEs or concomitant medications taken, vital signs, safety labs, collection of blood

for determination of TPI 287 plasma level (for comparison with TPI 287 CSF level), collection of CSF via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of neurodegeneration, and TPI 287 concentration, and collection of a blood sample (5 mL) for the banking of plasma for future research.

A week later (2 weeks ± 3 days after the fourth study drug infusion), all subjects will return to the clinic for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, PSPRS, SEADL, CDR-SB-FTLD, PVF, MMSE, GDS, MRIs (rsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences), and safety labs.

Following the above assessments, those subjects found to be ineligible for the open-label extension or that do not opt to participate in the open-label extension will return to the clinic 4 weeks ± 7 days after the fourth study drug infusion for the following final study procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, safety labs, and collection of a blood sample (5 mL) for the banking of plasma for future research.

If a subject is discontinued from study drug treatment early during the placebo-controlled phase, all evaluations described for the above final study visits will be performed if feasible. Any subject with a possible study drug-related AE at either final study visit will be followed until resolution or stabilization of the event.

Optional Open-Label Extension: Subjects who are eligible and opt to proceed with the open-label extension will return to the clinic 3 weeks after their last dose of study drug in the placebo-controlled phase of the trial. The following procedures will be performed **prior to study drug administration**: subject signature and date on ICF consenting to optional procedures, review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (and calculation of BSA for dose determination), vital signs, 12-lead ECG, safety labs, and urine pregnancy test for WCBP.

Study drug (active) will be administered following the completion of the above assessments. The subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Vital signs will be monitored at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion.

Subjects will return to the clinic the following morning (24 hours post-infusion) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), vital signs, and safety labs.

Subjects will return to the clinic on the morning of Days 8 and 15 (-1 Day/+2 Days) for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, and safety labs.

Subjects will return to the clinic on the morning of Days 22 and 43. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. **Prior to study drug administration**, the following procedures will be performed: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight (and calculation of BSA for dose determination), vital signs, 12-lead ECG (for second dose of open-label phase only), and safety labs. The subjects will remain in the clinic for 1 hour after completion of the study drug infusion. Vital signs will be monitored at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Final Study Visit for Open-Label Phase: Subjects will return to the clinic 4 weeks ± 7 days after the third study drug infusion of the open-label phase for the following procedures: review of diary for any AEs or concomitant medications taken, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, PSPRS, SEADL, CDR-SB-FTLD, PVF, GDS, safety labs, and collection of a blood sample (5 mL) for the banking of plasma for future research.

If a subject is discontinued from study drug treatment early during the open-label phase, all evaluations described for the above final study visit will be performed if feasible. Any subject with a possible study drug-related AE at the final study visit will be followed until resolution or stabilization of the event.

4. ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

The inclusion criteria for CBS and PSP subjects are listed below, and are the same, except where noted. Subjects must meet **all** of the specified inclusion criteria for CBS to be enrolled in the CBS dose escalation portion of the trial. Subjects must meet **all** of the specified inclusion criteria for PSP to be enrolled in the PSP dose escalation portion of the trial.

1. Between 50 and 85 years of age (inclusive);

2. Able to walk 5 steps with minimal assistance (stabilization of one arm or use of cane/walker);

3. MRI at Screening is consistent with CBS or PSP (≤ 4 microhemorrhages, and no large strokes or severe white matter disease);

4. MMSE at Screening is between 14 and 30 (inclusive);

5. FDA-approved AD medications are sometimes prescribed for CBS and PSP subjects, and are allowed as long as the dose is stable for 2 months prior to Screening. Other medications (except those listed under exclusion criteria) are allowed as long as the dose is stable for 30 days prior to Screening;

6. FDA-approved Parkinson's medications are allowed as long as the dose is stable for 2 months prior to Screening;

7. Has a reliable study partner who agrees to accompany the subject to visits, and spends at least 5 hours per week with the subject;

8. Agrees to 2 lumbar punctures;

9. Signed and dated written informed consent obtained from the subject and the subject's caregiver in accordance with local IRB regulations;

10. Males and all WCBP agree to abstain from sex or use an adequate method of contraception for the duration of the study and for 30 days after the last dose of study drug.

    Adequate contraceptive methods include those with a low failure rate, i.e., less than 1% per year, when used consistently and correctly, such as complete abstinence from sexual intercourse with a potentially fertile partner, and some double barrier methods (condom with spermicide) in conjunction with use by the partner of an intrauterine device (IUD), diaphragm with spermicide, oral contraceptives, birth control patch or vaginal ring, oral, or injectable or implanted contraceptives.

    For this study, a woman who has been surgically sterilized or who has been in a state of amenorrhea for more than two years will be deemed not to be of childbearing potential;

For PSP Only

11. Meets National Institute of Neurological Disorders and Stroke – Society for Progressive Supranuclear Palsy (NINDS-SPSP) probable or possible PSP criteria (Litvan et al. 1996a), as modified for the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) clinical trial (Bensimon et al. 2009).

For CBS Only

11. Meets 2013 consensus criteria for possible or probable corticobasal degeneration, CBS subtype (Armstrong et al. 2013).

4.2 Exclusion Criteria

The exclusion criteria for CBS and PSP are listed below, and are the same, except where noted. Subjects meeting **any** of the specified exclusion criteria for CBS will be excluded from the CBS dose escalation portion of the trial. Subjects meeting **any** of the specified exclusion criteria for PSP will be excluded from the PSP dose escalation portion of the trial.

1. Meets National Institute on Aging-Alzheimer's Association Workgroups criteria for probable AD (McKhann et al. 2011);

2. Any medical condition other than CBS or PSP that could account for cognitive deficits (e.g., active seizure disorder, stroke, vascular dementia);

3. A prominent and sustained response to levodopa therapy;

4. History of significant cardiovascular, hematologic, renal, or hepatic disease (or laboratory evidence thereof);

5. History of significant peripheral neuropathy;

6. History of major psychiatric illness or untreated depression;

7. Neutrophil count <1,500/mm^3, platelets <100,000/mm^3, serum creatinine >1.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN, alanine aminotransferase (ALT) >3 x ULN, aspartate aminotransferase (AST) >3 x ULN, or INR >1.2 at Screening evaluations;

8. Evidence of any clinically significant findings on Screening or baseline evaluations which, in the opinion of the Investigator would pose a safety risk or interfere with appropriate interpretation of study data;

9. Current or recent history (within four weeks prior to Screening) of a clinically significant bacterial, fungal, or mycobacterial infection;

10. Current clinically significant viral infection;

11. Major surgery within four weeks prior to Screening;

12. Unable to tolerate MRI scan at Screening;

13. Any contraindication to or unable to tolerate lumbar puncture at Screening, including use of anti-coagulant medications such as warfarin. Daily administration of 81 mg aspirin will be allowed as long as the dose is stable for 30 days prior to Screening;

14. Subjects who, in the opinion of the Investigator, are unable or unlikely to comply with the dosing schedule or study evaluations;

15. Previous exposure to microtubule inhibitors (including TPI 287) within 5 years of Screening. Treatment with microtubule inhibitors other than TPI 287 while on study will not be allowed;

16. Participation in another interventional clinical trial within 3 months of Screening;

17. Treatment with another investigational drug within 30 days of Screening. Treatment with investigational drugs other than TPI 287 while on study will not be allowed;

18. Known hypersensitivity to the inactive ingredients in the study drug;

19. Pregnant or lactating;

20. Positive pregnancy test at Screening or Baseline (Day 1);

21. Cancer within 5 years of Screening, except for non-metastatic skin cancer or non-metastatic prostate cancer not expected to cause significant morbidity or mortality within one year of Baseline;

For CBS Only

22. History or evidence at Screening of cortical amyloid levels on ^{18}F florbetapir PET scans consistent with underlying AD;

23. History of serum or plasma progranulin level less than one standard deviation below the normal subject mean for the laboratory performing the assay;

24. History or evidence at Screening of known disease-associated mutations in *GRN* or *C9ORF72* genes to rule out CBS due to TDP-43 pathology;

25. History of known disease-associated mutations in ribosomal protein L3 [TDP-43 gene (*TARBP*)], chromatin modifying protein 2B (*CHMPB2*) or valosin containing protein

(*VCP*) genes or any other frontotemporal lobar degeneration (FTLD) causative genes discovered during the course of the trial and not associated with underlying tau pathology.

4.3 Withdrawal of Subjects

A subject may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

A subject will be withdrawn from this study if one or more of the following events occur:

1. Subject requests to be withdrawn from study;
2. DLT (as defined in Section 3);
3. AE that in the judgment of the Investigator poses unacceptable risk to the subject;
4. Intercurrent illness that requires treatment that is not consistent with the protocol requirements, or intercurrent illness or the associated treatment that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study;
5. Pregnant or suspected of being pregnant;
6. Use of prohibited medication (listed in Section 5.7) that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study or that will interfere with the interpretation of the results of this study;
7. Significant protocol violation or noncompliance on the part of the subject or the Investigator;
8. Investigator terminates the study;
9. Any other reason that in the judgment of Investigator poses unacceptable risk to the subject.

If a subject is withdrawn from the study, the date and reason will be recorded in the source documents and the case report form (CRF), and final study visit evaluations will be performed if feasible. Any subject withdrawn due to a suspected study drug-related AE will be followed until resolution or stabilization of the event.

If subject becomes pregnant or is suspected of being pregnant, study drug will be discontinued immediately, and the subject will be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The subject will be followed until delivery or other termination of pregnancy for outcome.

Subjects may choose to withdraw authorization to use and disclose their Protected Health Information (PHI) as defined by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 or foreign equivalent where appropriate. Such withdrawal of authorization must be made to the Investigator in writing. Any PHI collected by the Investigator prior to the date of such withdrawal will continue to be used and disclosed.

4.4 Replacement of Subjects

Subjects who are withdrawn from the study for reasons other than DLTs may be replaced at the Investigator's discretion.

4.5 Termination of Trial

The Investigator has the right to terminate this study at any time. The Investigator will notify the IRB/IEC in writing of a premature termination of the study.

Events that may trigger premature termination of the study include, but are not limited to, a new toxicity finding, a request to discontinue the trial from a regulatory authority, non-compliance with the protocol, slow recruitment, or change in development plans for the study drug.

The trial as a whole, including enrollment of new subjects and dosing of ongoing subjects, will be temporarily stopped if **either** of the criteria listed below are met:

1. A death within 30 days after study drug administration where there is a reasonable possibility that the drug caused the event;

2. Two Grade 4 AEs where there is a reasonable possibility that the drug caused the events.

The IND Sponsor and DSMB will discuss whether a lower dose or any additional treatment guidelines should be implemented, or if the trial should be permanently stopped. Any proposed changes to the protocol to address such findings will be submitted for review and approval by the IRB and FDA prior to re-starting the trial.

5. STUDY DRUG

5.1 Description of Investigational Drug

5.1.1 Active Pharmaceutical Ingredient

The investigational drug is TPI 287. TPI 287 is a microtubule inhibitor belonging to the taxane diterpenoid (taxoid) family, and specifically to the abeotaxane class. The chemical name of TPI 287 is (2'R,3'S)-2'-hydroxy-N-carboxy-3'-amino-5'-methyl-hexanoic,N-*tert*-butyl ester, 13 ester 5β-20-epoxy-1β,2α,4α,7β,9α,10α,13α-heptahydroxy-4,10-diacetate-2-benzoate-(1"S)-7,9-acrolein acetal-11(15→1)-abeotaxane. TPI 287 has a molecular weight (MW) of 869.99 and a molecular formula of $C_{46}H_{63}NO_{15}$.

5.1.2 Drug Product

The dosage form of the investigational drug product, TPI 287 Injection, is a sterile parenteral solution for IV infusion. The inactive ingredients are polyoxyl 35 castor oil [Kolliphor® ELP, previously named Cremophor® EL-P, National Formulary (NF)] and dehydrated alcohol, United States Pharmacopeia (USP).

A single strength (10 mg/mL) of TPI 287 Injection will be used for this study. Each single-use vial contains 10 mL of drug product with 100 mg of TPI 287 in a 15:85 mixture (weight/volume, w/v) of Kolliphor® ELP and dehydrated alcohol (1.58 g Kolliphor in quantity sufficient ethanol to 10 mL).

5.1.3 Packaging and Labeling

Cortice will supply the study drug (TPI 287 Injection) for this trial. TPI 287 Injection, 10 mg/mL (15:85 Kolliphor® ELP:dehydrated alcohol) will be provided as 10-mL single-use vials (Type I USP flint glass) with Teflon-coated butyl stoppers, and aluminum flip-off caps.

The study drug vial will be labeled according to the requirements of local law and legislation. A copy of the label will be provided by Cortice for inclusion in the study files.

The Investigational Site pharmacist will not be blinded to the study drug, and thus the labeling of the vials will not be blinded for this study.

5.1.4 Storage and Handling

At the Investigational Site, all investigational study drug will be stored in a locked, secure area to prevent unauthorized access. TPI 287 Injection will be stored in the provided packaging (vial) in the upright position out of direct sunlight and at controlled room temperature (68 to 77°F; 20 to 25°C). Excursions between 59 to 86°F (15 to 30°C) are permitted. The diluted TPI 287 will be stored at room temperature and must be used within 12 hours of preparation.

Appropriate care should be exercised when handling the investigational drug product, as TPI 287 is a cytotoxic agent. Unused investigational drug product should be disposed of using proper procedures as defined by investigational site standard operating procedures.

5.2 Randomization

This is a randomized, double-blind, placebo-controlled study. The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For the initial dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively, for each diagnosis (i.e., 11 for CBS and 11 for PSP). For the remaining dose cohorts, 11 subjects with primary 4RT (i.e., a mix of CBS and PSP subjects with no required ratio of the two) will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2.

Only subjects that meet all eligibility criteria at Screening and subsequent specified baseline evaluations will be randomized to treatment. Randomization will take place on Day 1 after completion of the following baseline evaluations: updated medical history, physical examination (including neurological examination), weight, vital signs, 12-lead ECG, PSPRS, SEADL, CDR-SB-FTLD, PVF, urine pregnancy test for WCBP, and recording of medications taken since initial Screening visit.

A computer-generated randomization schedule will be used for assigning the sequence in which subjects are assigned to placebo and active treatment. The UCSF Investigational Site pharmacist will be responsible for generating and maintaining the randomization schedule, and will assign a randomization code to each subject upon enrollment.

This study will continue to be double-blinded during the open-label extension (i.e., although the investigator and subjects will know they are receiving TPI 287 during the open-label extension, they will not know what the subject received during the placebo-controlled phase).

5.3 Preparation and Administration of Study Drug

TPI 287 Injection **must be diluted prior to administration**. The Investigational Site pharmacist will dilute the required volume of 10 mg/mL TPI 287 Injection drug product in a di(2-ethylhexyl)phthalate- (DEHP-) free, non-polyvinyl chloride (non-PVC), 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP. Appropriate aseptic technique will be used. The volume of drug product required to deliver the protocol-specified dose will be removed from the single-use TPI 287 Injection vial via a sterile, pyrogen-free needle and added to the 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP. The solution will be mixed thoroughly for 10 to 15 seconds by carefully squeezing and shaking the IV bag.

If particulate matter or discoloration is observed on visual inspection of the single-use vial of TPI 287 Injection or the resulting diluted product, the study drug should not be used for administration.

The planned dose levels of TPI 287 are 2, 6.3, and 20 mg/m^2, and will be based on BSA determinations made prior to each study drug administration. Assuming an average BSA of 1.62 mg/m^2, the planned dose levels correspond to 3.24, 10.21, and 32.4 mg TPI 287 and 0.32, 1.02, and 3.24 mL of the 10 mg/mL TPI 287 Injection drug product, respectively. Dilution of these amounts of TPI 287 Injection drug product into 500 mL IV bags of 0.9% Sodium Chloride for Injection, USP will result in approximate final concentrations of 0.006, 0.02, and 0.064 mg/mL, respectively. Per USP, the IV bags are filled with sufficient excess (i.e., more than 500 mL), and thus these are approximations of the maximum concentrations for this particular BSA.

The placebo to be used in this trial will be a DEHP-free, non-PVC, 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP. The final volume for placebo administration will be approximately 500 mL (see further details regarding administration below).

All doses of study drug (placebo and active) will be administered in either an inpatient or outpatient facility. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions.

An administration set comparable to those used for paclitaxel administration (i.e., a DEHP-free and/or polyethylene-lined IV administration set with an in-line 0.2 micron filter) must be used for study drug administration. The following administration sets or their equivalent may be used: Baxter Product Codes 2C7557, 2C8857, 2C8858, or 2C7558, B. Braun Product Code V9902F, CareFusion Product Code 10010454, CareFusion Product Code 28053 with 20350E extension, or Hospira Product Code 14248-28 with 20668-28 extension. If an administration set with a vent is used, the vent should be closed.

All doses of study drug will be administered as an IV infusion with a targeted duration of 1 hour. A window of ± 15 minutes will be permitted (and will not be considered a protocol deviation). If a mild-to-moderate (Grade 1 to 2) hypersensitivity reaction is observed, the TPI 287 infusion rate may be reduced to half that of the initial attempt at the discretion of the Investigator. Further, this reduced rate may be used at subsequent infusions at the discretion of the Investigator.

An infusion pump must be used for administration of the study drug. The target duration (1 hour) and nominal study drug volume (500 mL + the mL of 10 mg/mL TPI 287 Injection added to the bag) should be used as the pump entries to determine the rate of infusion. However, the pump should not automatically be turned off at 1 hour. Instead, the bag should be monitored closely as the infusion duration nears 1 hour to **ensure that the entire IV bag content, minus the volume that remains in the administration set (priming volume) is administered. A 0.9% Sodium Chloride for Injection, USP flush should then be used to ensure that the remainder of the TPI 287 dose in the line is administered to the subject.**

All subjects will be administered study drug (placebo or active) once every 3 weeks for 9 weeks (for a total of 4 infusions) as part of the placebo-controlled (dose-ranging) phase. The dose of TPI 287 will be escalated in sequential cohorts. For the initial dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively, for each diagnosis (i.e., 11 for CBS and 11 for PSP). For the remaining dose cohorts, 11 subjects with primary 4RT (i.e., a mix of CBS and PSP subjects with no required ratio of the two) will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. See Section 3 for dose cohort escalation rules.

Subjects that complete the placebo-controlled (dose-ranging) phase with no DLTs will be eligible to receive an optional additional 6 weeks of study drug as part of an open-label extension (for a total of 7 infusions overall). All subjects that participate in the open-label extension will be administered TPI 287 (i.e., those administered placebo during the placebo-controlled phase will crossover to TPI 287). The dose of TPI 287 will be the same dose used in the cohort from which the subject was randomized.

5.4 Premedication

The TPI 287 formulation to be used in this trial contains Kolliphor® ELP at a concentration of 158 mg/mL. At the proposed TPI 287 dose range (and assuming a 1.62 m^2 individual), the corresponding dose of Kolliphor will range from 51 to 512 mg. This will be diluted approximately 1,544- to 155.3-fold in a 500 mL IV bag of 0.9% Sodium Chloride for Injection, USP prior to administration, yielding approximate final concentrations of Kolliphor of 0.1023 to 1.017 mg/mL, respectively. Per USP, the IV bags are filled with sufficient excess (i.e., more than 500 mL), and thus these are approximations of the maximum concentrations for this

particular BSA. The diluted study drug/Kolliphor will be administered as a one hour IV infusion.

These doses of Kolliphor are 80- to 8-fold lower, respectively, than the dose of Kolliphor administered at the 160 mg/m^2 TPI 287 MTD dose administered to cancer subjects under the same dosing schedule (i.e. 1-hour infusion once every 3 weeks). Further, the concentrations of Kolliphor to be administered are 145- to 15-fold lower, respectively, than the concentration of Kolliphor administered at the 160 mg/m^2 TPI 287 dose in cancer subjects.

Given the above, the risk of anaphylaxis or severe hypersensitivity reactions to the Kolliphor component of the TPI 287 formulation is anticipated to be relatively low in this trial. However, as a precaution, the study drug will be administered in an inpatient our outpatient facility with experience in treating such reactions. Specifically, a crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions.

In the clinical trials of TPI 287 in cancer subjects, where the dose and concentration of Kolliphor are significantly higher, all subjects are premedicated prior to TPI 287 administration to prevent any potential hypersensitivity reactions. The premedications used include a corticosteroid, an antihistamine, and an H2 blocker. Under Version 1 of this protocol for primary 4RT subjects, premedication was not used given the planned lower dose and concentration of Kolliphor.

The addition of an antihistamine premedication requirement was added to this protocol under Version 2 as a precautionary measure based on reactions reported in Protocol No. TPI287-AD-001, a protocol that is nearly identical to this one, but in subjects with AD. Specifically, 2 of the 6 subjects enrolled in Protocol No. TPI287-AD-001 as of May 9, 2014 had experienced reactions during or after a study drug (placebo or active) infusion. Each of these events is summarized briefly below.

- Subject No. 005-04: 55-year-old female Japanese-American experienced Grade 1 hypertension (182 mmHg/74 mmHg) and Grade 1 flushing 2-3 minutes after the start of her second study drug infusion (placebo or 2 mg/m^2 TPI 287). These events resolved spontaneously. About an hour later, she developed a Grade 1 unilateral, rash in the left antecubital fossa in the same arm where the infusion had been delivered into a vein on the dorsal aspect of the hand. The subject was administered 50 mg of IV diphenhydramine and the rash completely resolved in less than one hour.

- Subject No. 006-05: 56-year-old female Caucasian experienced a Grade 1 papular rash on her forearms and legs that was noted by her caregiver approximately 2 to 3 days after the first study drug infusion (placebo or 2 mg/m^2 TPI 287). The appearance of this rash was distinct from that observed for Subject No. 005-04. No treatment was given and the

rash slowly resolved over the course of 3-4 weeks. The investigator decided to discontinue the subject from the study (early termination) given the possible relationship of the rash to study drug infusion.

Due to the double-blind, placebo-controlled design of the trial, it is currently unknown as to whether these two subjects received TPI 287 or placebo. Neither of the above events met the protocol-specified definition of a DLT. Given this and the mild severity and complete recovery of these events, breaking of the blind was not deemed necessary.

A meeting between the Investigator and the DSMB for the AD trial was held regarding the above events, and they unanimously agreed that as a precautionary measure, moving forward, all subjects enrolled Protocol No. TPI287-AD-001 would be administered 25 mg of diphenhydramine IV within 30 minutes to one hour prior to each dose of study drug (placebo or active). Due to the similarity of the 4RT and AD study designs and patient populations, the same precautionary measure was applied to this 4RT trial (Version 2).

On October 6, 2014, the 10th subject enrolled in Protocol No. TPI287-AD-001 (AD trial) experienced a likely anaphylactoid reaction. The event is summarized below.

Subject No. 013-10: 51-year-old female Caucasian female diagnosed with Alzheimer's disease in April 2013 with a Screening MMSE of 24. The subject had a history of allergy to benzoin, and was taking the following concomitant medications: lexapro 10 mg orally once a day, donepezil 10 mg orally once a day, curcumin (unknown dose) orally once a day, omega 3 1000 mcg orally once a day, and vitamin E 1000 IU orally once a day.

On Study Day 22, the subject was premedicated with 25 mg of IV diphenhydramine 30 minutes prior to infusion of her second dose of study drug. Within one minute of initiating the study drug infusion, the subject experienced chest tightness, shortness of breath, and a deep flush covering her face and upper body. The subject indicated that her throat was tightening and that she was having great difficulties breathing.

The study drug infusion was stopped (at approximately 3 minutes after initiation) and normal saline was started. The subject's vital signs were taken and reported as follows: blood pressure of 150/80 mmHg (compared to 96/55 mmHg pre-infusion), heart rate of 80 bpm (compared to 44 bpm pre-infusion), and respiratory rate of 14 breaths per minute (compared to 16 breaths per minute pre-infusion). The O_2 saturation was 97%.

The subject was administered two puffs of albuterol inhaler (90 mcg/puff) approximately 2 minutes after stopping the study drug infusion. The subject's coloring began to improve and she reported feeling much relief, but still had trouble breathing, was anxious appearing with chest heaving, and continued to experience some chest tightness.

Approximately 5 minutes after stopping the study drug infusion, the subject was administered 0.3 mg epinephrine (1 mg/mL) via IV push. Her coloring completely resolved followed by turning very pale with complaints of very rapid heart rate and chest tightness. Three minutes after administering the epinephrine, the subject's vital signs were as follows: blood pressure of 83/54 mmHg, heart rate of 53 bpm, and respiratory rate of 20 breaths per minute. Of note, the subject's baseline blood pressure typically runs in the 80s-90s systolic and 50s diastolic.

The subject was laid flat in the reclining infusion chair and provided with supplemental oxygen via nasal cannula (O_2 saturation at 100%). Two additional puffs of albuterol inhaler were administered. The subject stabilized and her coloring returned to baseline, though she still complained of rapid heart rate. Upon suggestion from the Rapid Response Team (RRT), the subject was transferred to the Emergency Department (ED) for observation.

Within 52 minutes of stopping the study drug infusion, the subject's vital signs had returned to baseline levels and the subject was reportedly feeling better. A half hour later, the ED physician ordered 60 mg oral prednisone, and removed the nasal cannula. The subject was discharged from the ED approximately 2 hours after stopping study drug infusion. The subject was prescribed 20 mg prednisone three times a day for three days along with an EpiPen to keep on her person in case of any unexpected sudden tightness of her chest or difficulty breathing. Phone follow-up the next day and 48 hours later indicated the subject was doing well without any sequelae of the event.

This event was assigned a severity grade of 3 based on the criteria outlined in NCI CTCAE version 4.0. The study physician viewed the event as life-threatening, and therefore the event was designated as a serious adverse event. The principal investigator considered the event related to study drug, and in particular assigned a relationship of "adverse reaction". The blind was broken for this subject, and it was confirmed that the subject was randomized to the 2 mg/m^2 TPI 287 cohort. As a Grade 4 anaphylactic reaction was previously reported in a cancer trial of TPI 287 (Protocol No. TPI 287-02), this event was not considered unexpected. Therefore an expedited IND Safety Report was not required and was not filed.

Under the AD trial protocol, if anaphylaxis or a severe hypersensitivity reaction was observed, the Investigator (IND Sponsor) and DSMB would discuss whether further premedication or any additional treatment guidelines should be implemented. Further, any proposed changes to the protocol to address such findings would be submitted for review and approval by the IRB and FDA prior to re-starting the trial. As such, the AD trial was put on temporary hold following the above anaphylactoid reaction.

Based on review of the above event (anaphylactoid reaction), the Investigator and DSMB unanimously agreed that moving forward with the AD trial, **a pre-medication regimen that includes a corticosteroid, an antihistamine, and an H2 blocker will be required prior to each study drug (placebo or active) infusion**. This combination has been well established as a prophylaxis for hypersensitivity reactions for other taxanes, such as paclitaxel (Bookman et al. 1997 and Quock et al. 2002), and is being used successfully in ongoing cancer trials of TPI 287. Listed below is the specific pre-medication regimen **required** for the AD trial:

- 10 mg IV dexamethasone (or methylprednisone equivalent, if dexamethasone not available) one hour prior to infusion, **and**
- 25 mg IV diphenhydramine within 30 minutes to one hour prior to infusion, **and**
- IV H2 blocker such as ranitidine (50 mg) or famotidine (20 mg) within 30 minutes to one hour prior to infusion.

Due to the similarity of the 4RT and AD study designs and patient populations, the same precautionary measure is being applied to this 4RT trial. Thus, moving forward with the 4RT trial, the above listed (3 bullet point) pre-medication regimen will be required prior to each study drug (placebo or active) infusion.

5.5 Measuring Subject Compliance

The study drug will be administered via IV infusion in the clinic. Compliance will be ascertained by Investigational Site staff by monitoring of the IV bag and administration set. The following infusion details will be recorded as part of monitoring compliance: infusion start and stop times, confirmation that the entire IV bag content was administered, and approximate flush volume.

5.6 Drug Accountability

In accordance with current GCP, the Investigational Site will account for all study drug supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the Investigational Site. Copies of the study drug accountability record will be provided to the supplier of the study drug (Cortice).

Study drug will only be dispensed to subjects randomized to treatment under this protocol, and only as directed by this protocol. Administration of study drug will be accurately recorded in each subject's source documents and CRF.

5.7 Concomitant Medications

All medications (or treatments) other than study drug taken or received by the subject at any time during the study from the first dose of study drug through the final study visit assessment will be considered concomitant medications. Use of all concomitant medications, including any change in therapy, must be recorded and updated in the source documentation and on the CRF.

Subjects with previous exposure to microtubule inhibitors (including TPI 287) within 5 years of Screening are not eligible to participate in this trial. Treatment with microtubule inhibitors (other than TPI 287) while on study is prohibited.

Subjects are also not to take any other investigational drugs beginning 30 days prior to the first dose of study drug and continuing until completion of the study (final study visit).

FDA-approved AD and Parkinson's medications are allowed as long as the dose is stable for 2 months prior to Screening. Other medications (except those listed above) are allowed as long as the dose is stable for 30 days prior to Screening. All drugs taken during the two months prior to Screening, as well as between Screening and baseline (Day 1) should be recorded.

All intercurrent medical conditions will be treated at the discretion of the Investigator according to acceptable community standards of medical care.

TPI 287 was shown to be rapidly metabolized by pooled human S-9 liver fractions, and seven putative phase 1 (modification) metabolites were detected. Based on this and the well-established metabolism of other taxanes such as paclitaxel by cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2C8 (CYP2C8), the concomitant use of CYP3A4 and CYP2C8 substrates, inhibitors, and inducers are strongly discouraged. Caution and careful monitoring must be exercised when TPI 287 is concomitantly administered with such drugs, including but not limited to midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam, repaglinide, rosiglitazone, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, gemfibrozil, rifampin, carbamazepine, St. John's Wort, warfarin, and other coumarin-derivative anti-coagulants.

Subjects receiving warfarin or other coumarin-derivative anti-coagulants are not eligible for enrollment in this trial due to the contraindication with the lumbar puncture (i.e., this is an exclusion criterion).

6. SCHEDULE OF EVENTS

The schedule of events is provided in tabular format in Appendix C [placebo-controlled (dose-ranging) phase] and Appendix D (optional open-label extension), and is summarized below by study visit.

6.1 Screening

The Investigator is responsible for keeping a record of all subjects screened for entry into the study and subsequently excluded. The reason(s) for exclusion will be recorded in the source documents.

Each subject will be provided with oral and written information (ICF) describing the study and will have any questions answered. Written informed consent must be obtained prior to performing any screening evaluations.

Subjects that consent to participate in the study will undergo the eligibility assessments listed below. All procedures must be completed within 28 days of the first dose of study drug (Day 1):

1. Record demographic data (date of birth/age at Screening, gender, and race);
2. Complete medical and surgical history, including baseline concurrent illness assessment;
3. Review and record medications taken within 2 months prior to initial Screening visit;
4. Height and body weight;
5. Comprehensive physical examination, including neurological examination;
6. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
7. 12-lead ECG;
8. MMSE;
9. GDS;
10. Safety labs (see Appendix E for list of tests);

11. Coagulation tests (PT, PTT, and INR). The coagulation tests must be performed before the lumbar puncture;

12. Serum pregnancy test [beta-chorionic gonadotropin (β-hCG)] for WCBP only;

13. For CBS subjects only: If subject meets eligibility criteria after the initial screening assessments above (items 1-12), the subject will undergo ^{18}F florbetapir PET scanning to rule out the presence of amyloid that would suggest CBS due to Alzheimer's pathology;

14. For CBS subjects only: If subject meets eligibility criteria after the initial screening assessments above (items 1-12), the subject will undergo screening for mutations in the progranulin (*GRN*) and *C9ORF72* genes to rule out CBS due to TDP-43 pathology;

15. MRI procedures, including RsfMRI, DTI, ASL perfusion MRI, and standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences. These procedures will only be performed if the subject meets all other eligibility criteria after completion of the above listed Screening procedures.

16. Collection of CSF via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of neurodegeneration, and pre-dose assessment of TPI 287 concentration. The lumbar puncture must be performed after the MRI procedures, and will only be performed if the subject continues to meet eligibility criteria after completion of the MRI procedures.

17. Collection of blood samples for the purpose of banking DNA and plasma for future research (approximately 10 and 5 mL, respectively). For subjects enrolled before banking was added to the protocol (and thus that missed the blood collections at Screening), collection of a blood sample for DNA banking will be allowed at a later time point up to and including the final study visit. Collection of the pre-dose plasma banking sample will not be allowed at a later time point; however, the scheduled post-dose draws will still be allowed (regardless of whether a pre-dose sample is available).

18. Assessment of inclusion and exclusion criteria.

Subjects who meet eligibility criteria based on the completion of the above Screening assessments will be instructed as follows:

1. Do not take any microtubule inhibitor (other than the study drug) for the duration of the study (through final follow-up visit);

2. Do not take any investigational drug (other than the study drug) for the duration of the study (through final follow-up visit);

3. Do not take any AD or Parkinson's medications (other than the study drug) for the duration of the study (through final follow-up visit), except for those for which the dose is expected to be stable for 2 months prior to Screening;

4. Do not take any other medications for the duration of the study (through final follow-up visit), except for those for which the dose is expected to be stable for 30 days prior to Screening;

5. For males and WCBP: Abstain from sex or use an adequate method of contraception for the duration of the study and through 30 days after the last dose of study drug.

6. Return to the clinic on Day 1 for baseline procedures.

6.2 Treatment Period – Placebo-Controlled (Dose-Ranging) Phase

6.2.1 Study Day 1

Subjects who meet eligibility criteria after completing all Screening evaluations will return to clinic the morning of Day 1. Baseline safety labs (see Appendix E for list of tests) will be performed. The following baseline procedures will be performed **prior to enrollment** to confirm that the subject continues to meet eligibility criteria:

1. Update of medical history (intercurrent illness assessment);

2. Review and record medications taken since initial Screening visit;

3. Physical examination, including neurological examination;

4. Weight and calculation of BSA for the purpose of determining study drug dose;

5. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

6. 12-lead ECG;

7. PSPRS;

8. SEADL;

9. CDR-SB-FTLD;

10. PVF;

11. Urine pregnancy test (β-hCG) for WCBP only;

12. Review of inclusion/exclusion criteria.

Subjects that continue to meet all eligibility requirements will be enrolled in the study and randomized to treatment. An indwelling cannula will be placed for PK assessments, and a blood sample will be collected within an hour prior to starting study drug infusion for the pre-dose assessment of TPI 287 concentration. Topical anesthesia will be allowed to place the cannula.

The study drug (placebo or active) will be administered in either an inpatient or outpatient facility on the morning of Day 1. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 1 after the start of study drug infusion:

1. Monitor for treatment emergent AEs beginning immediately following the initiation of the first study drug infusion;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion. For time points that include both vital signs and PK assessments, the vital signs will be taken first;

3. Collection of blood samples for PK assessments at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion;

4. Subjects will be provided with a diary and instructed to record any AEs or concomitant medications taken between visits, and to bring the completed diary to each visit for review.

Subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Following the above procedures, the subjects will be instructed to return to the clinic the following day (Day 2).

6.2.2 Study Day 2

Subjects will return to clinic on the morning of Day 2 for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
4. Collection of blood for PK assessment (24-hour post-infusion);
5. Safety labs (see Appendix E for list of tests).

Pending no safety issues, subjects will be instructed to return to the clinic in 6 days (Day 8).

6.2.3 Study Day 8

Subjects will return to clinic on the morning of Day 8 (-1 day/+ 2 days) for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. Safety labs (see Appendix E for list of tests).

Pending no safety issues, subjects will be instructed to return to the clinic in 7 days (Day 15).

6.2.4 Study Day 15

Subjects will return to clinic on the morning of Day 15 (-1 day/+ 2 days) for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;
3. Weight
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. Safety labs (see Appendix E for list of tests).

Pending no safety issues, subjects will be instructed to return to the clinic in 7 days (Day 22).

6.2.5 Study Day 22

Subjects will return to clinic on the morning of Day 22 (-1 day/+ 2 days). The following procedures will be performed **prior to administering the second study drug infusion**:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight and calculation of BSA for the purpose of determining study drug dose;
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. 12-lead ECG;
6. Safety labs (see Appendix E for list of tests);
7. Collection of blood for PK assessment (trough level).

Pending no safety issues, the second dose of study drug (placebo or active) will be administered in either an inpatient our outpatient facility on the morning of Day 22. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 22 after the start of study drug infusion:

1. Monitor for AEs;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in three weeks (Day 43).

6.2.6 Study Day 43

Subjects will return to clinic on the morning of Day 43. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. The following procedures will be performed **prior to administering the third study drug infusion**:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight and calculation of BSA for the purpose of determining study drug dose;
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. 12-lead ECG;
6. Safety labs (see Appendix E for list of tests);
7. Collection of blood for PK assessment (trough level).

Pending no safety issues, the third dose of study drug (placebo or active) will be administered in either an inpatient or outpatient facility on the morning of Day 43. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 43 after the start of study drug infusion:

1. Monitor for AEs;
2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in three weeks (Day 64).

6.2.7 Study Day 64

Subjects will return to clinic on the morning of Day 64. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. The following procedures will be performed **prior to administering the fourth study drug infusion**:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight and calculation of BSA for the purpose of determining study drug dose;
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. 12-lead ECG;
6. Safety labs (see Appendix E for list of tests);
7. Collection of blood for PK assessment (trough level);
8. Coagulation tests (PT, PTT, and INR).

Pending no safety issues, the fourth and final dose of study drug (placebo or active) for the dose-ranging phase of the trial will be administered in either an inpatient or outpatient facility on the morning of Day 64. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 64 after the start of study drug infusion:

1. Monitor for AEs;
2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in one week.

6.3 Final Study Visits for Placebo-Controlled (Dose-Ranging) Phase

The final study visit for the placebo-controlled (dose-ranging) phase of the trial will occur during 2-3 visits, depending on whether the subject is eligible and opts to proceed with the open-label extension. The procedures that will be performed at each visit are described below.

6.3.1 One Week after Fourth Study Drug Infusion

All subjects will return to the clinic 1 week ± 3 days after the fourth study drug infusion for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
3. Safety labs (see Appendix E for list of tests);
4. Collection of blood for determination of TPI 287 plasma level for comparison with TPI 287 CSF level;
5. Collection of CSF via lumbar puncture for measurement of cell count with differential, glucose, total protein, CSF biomarkers of neurodegeneration, and TPI 287 concentration;
6. Collection of blood sample (5 mL) for the purpose of banking plasma for future research.

6.3.2 Two Weeks after Fourth Study Drug Infusion

All subjects will return to the clinic 2 weeks ± 3 days after the fourth study drug infusion for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;

3. Weight
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. Safety labs (see Appendix E for list of tests);
6. PSPRS;
7. SEADL;
8. CDR-SB-FTLD;
9. PVF;
10. MMSE;
11. GDS;
12. rsfMRI;
13. DTI;
14. ASL perfusion MRI;
15. Standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences.

Following completion of the above assessments, subjects who are eligible and opt to proceed with the open-label extension phase of the trial will be instructed to return to the clinic three weeks from their last dose of study drug for initiation of the open-label phase. Subjects found to be ineligible or that opt not to participate in the open-label extension will be instructed to return to the clinic four weeks from their last dose of study drug for their final study visit.

6.3.3 Four Weeks after Fourth Study Drug Infusion

Subjects found to be ineligible for the open-label extension or that opt not to participate in the open-label extension will return to the clinic 4 weeks ± 7 days after their last dose of study drug for the following final procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

4. Safety labs (see Appendix E for list of tests);

5. Collection of blood sample (5 mL) for the purpose of banking plasma for future research.

If a subject is discontinued from study drug treatment early during the placebo-controlled (dose-ranging) phase, all evaluations described for the above three final study visits will be performed if feasible. Any subject with a possible study drug-related AE at either final study visit will be followed until resolution or stabilization of the event.

6.4 Treatment Period – Open-Label Extension Phase

6.4.1 Study Day 1

Subjects who are eligible and opt to proceed with the open-label extension phase of the trial will return to clinic three weeks after their last dose of study drug in the placebo-controlled (dose-ranging) phase. This will be defined as Day 1 of the open-label extension.

Written informed consent must be obtained prior to performing any evaluations under this optional phase of the trial. Subjects that consent to participate in the optional phase (i.e., sign and date ICF for optional procedures) will undergo the following procedures **prior to administering the first study drug infusion of the open-label extension phase**:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight and calculation of BSA for the purpose of determining study drug dose;

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. 12-lead ECG;

6. Safety labs (see Appendix E for list of tests);

7. Urine pregnancy test (β-hCG) for WCBP only.

Subjects that continue to meet all eligibility requirements after the completion of the above assessments will be administered TPI 287 in either an inpatient or outpatient facility on the morning of Day 1 of the open-label extension. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 1 of the open-label extension after the start of study drug infusion:

1. Monitor for AEs;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of the infusion.

Subjects will remain in the clinic under observation for 9 hours after initiation of the infusion. Following the above procedures, the subjects will be instructed to return to the clinic the following day (Day 2 of the open-label extension).

6.4.2 Study Day 2

Subjects will return to clinic on the morning of Day 2 of the open-label extension for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

4. Safety labs (see Appendix E for list of tests).

Pending no safety issues, subjects will be instructed to return to the clinic in 6 days (Day 8).

6.4.3 Study Day 8

Subjects will return to the clinic on the morning of Day 8 (-1 day/+ 2 days) of the open-label extension for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. Safety labs (see Appendix E for list of tests).

Pending no safety issues, the subjects will be instructed to return to the clinic in 7 days (Day 15).

6.4.4 Study Day 15

Subjects will return to clinic on the morning of Day 15 (-1 day/+ 2 days) of the open-label extension for the following procedures:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;
3. Weight
4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);
5. Safety labs (see Appendix E for list of tests).

Pending no safety issues, the subjects will be instructed to return to the clinic in 7 days (Day 22).

6.4.5 Study Day 22

Subjects will return to clinic on the morning of Day 22 (-1 day/+ 2 days). The following procedures will be performed **prior to administering the second study drug infusion of the open-label extension**:

1. Review of diary for any AEs or concomitant medications taken;
2. Physical examination, including neurological examination;

3. Weight and calculation of BSA for the purpose of determining study drug dose;

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. 12-lead ECG;

6. Safety labs (see Appendix E for list of tests).

Pending no safety issues, the second infusion of TPI 287 of the open-label extension will be administered in either an inpatient or outpatient facility on the morning of Day 22. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 22 after the start of study drug infusion:

1. Monitor for AEs;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in three weeks (Day 43).

6.4.6 Study Day 43

Subjects will return to clinic on the morning of Day 43. A -1 day/+2 day visit window will be allowed, as long as it has been at least 20 days since the last TPI 287 infusion. The following procedures will be performed **prior to administering the third study drug infusion of the open-label extension**:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight and calculation of BSA for the purpose of determining study drug dose;

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. Safety labs (see Appendix E for list of tests).

Pending no safety issues, the third infusion of TPI 287 of the open-label extension will be administered in either an inpatient or outpatient facility on the morning of Day 43. A crash cart and appropriate medications to treat anaphylaxis or severe hypersensitivity reactions will be available nearby and there will be medical personnel and a physician present to treat such reactions. **All subjects will be pre-medicated as described in Section 5.4 prior to initiation of infusion.**

The following procedures will be performed on Day 43 after the start of study drug infusion:

1. Monitor for AEs;

2. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) at 0.25, 0.5, 1, and 2 hours after initiation of the infusion.

Subjects will remain in the clinic under observation for 1 hour after completion of the study drug infusion. Following the above procedures, the subjects will be instructed to return to the clinic in five weeks.

6.5 Final Study Visit for Open-Label Extension Phase

Subjects will return to the clinic 4 weeks ± 7 days after the third study drug infusion of the open-label extension for the following final study visit procedures:

1. Review of diary for any AEs or concomitant medications taken;

2. Physical examination, including neurological examination;

3. Weight

4. Vital signs (blood pressure, pulse rate, respiration rate, and temperature);

5. 12-lead ECG;

6. Safety labs (see Appendix E for list of tests);

7. PSPRS;

8. SEADL;

9. CDR-SB-FTLD;

10. PVF;

11. GDS;

12. Collection of blood sample (5 mL) for the purpose of banking plasma for future research.

If a subject is discontinued from study drug treatment early during the open-label extension phase, all evaluations described for the above final study visit will be performed if feasible. Any subject with a possible study drug-related AE at the final study visit will be followed until resolution or stabilization of the event.

6.6 Duration of Participation

The total duration of participation for subjects in this study will be up to 17 weeks (first Screening visit through final follow-up visit) for the placebo-controlled (dose-range finding) phase of the study. If a subject is eligible and opts to continue treatment under the open-label extension phase of the study, the subject will participate for an additional 12 weeks, for a total duration of up to 29 weeks.

7. ASSESSMENT OF SAFETY

Safety will be assessed primarily based on AEs. Secondary safety assessments will include physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PT/PTT/INR, CSF cell count with differential, glucose, and total protein, PSPRS, SEADL, CDR-SB-FTLD, PVF, MMSE, GDS, and MRI (standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences). Refer to Appendices C and D for a tabular summary of the timing of the safety assessments.

7.1 Safety Reporting and Adverse Events

7.1.1 Definitions

7.1.1.1 Adverse Event

An AE is defined in 21 Code of Federal Regulations (CFR) 312.32(a) as follows:

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

7.1.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined in 21 CFR 312.32(a) as follows:

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.1.2 Severity of Adverse Events

The severity of AEs will be graded according to NCI CTCAE version 4.0. A copy of CTCAE version 4.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

The severity of AEs not classified by the above referenced toxicity grading scale will be categorized using the following definitions:

Mild (Grade 1):	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2):	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Severe (Grade 3):	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Life-threatening (Grade 4):	Life-threatening consequences; urgent intervention indicated
Death (Grade 5):	Death related to AE

7.1.3 Relationship of Adverse Events to the Study Drug

The relationship of AEs to the study drug will be classified as one of the following:

1. **Adverse reaction**: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

2. **Suspected adverse reaction**: Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Examples of the types of evidence that would suggest a causal relationship between the drug and the AE are as follows:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

3. **Unrelated**: AE for which there is evidence that the AE definitely has an etiology other than the drug.

7.1.4 Expectedness of Adverse Events

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.1.5 Monitoring of Adverse Events

AEs will be monitored continuously during the study starting immediately after the start of the first infusion of study drug. Subjects will be instructed to report all AEs experienced during the study, and subjects will be assessed for the occurrence of AEs throughout the study. Subjects will be given a diary to record any AEs between visits.

In order to avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?"

All AEs will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests.

7.1.6 Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded in the source documents and on the AE form of the CRF.

The information to be entered in the CRF will include:

1. Time of onset of any new AE or the worsening of a previously observed AE;
2. Specific type of reaction in standard medical terminology;
3. Duration of AE (start and stop dates);
4. Severity/grade of AE according to criteria in Section 7.1.2;
5. Assessment of the relationship of the AE to the study drug according to the definitions in Section 7.1.3;
6. Description of action taken in treating the AE and/or change in study drug administration or dose.

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the AE.

7.1.7 Reporting of Serious Adverse Events, Including Death

SAEs, including death due to any cause, which occur during this study or within 30 days following the last dose of the study drugs, whether or not related to the administration of study drugs, must be reported to the Medical Monitor by telephone or fax **within 24 hours of learning of the event**. The contact information for the Medical Monitor is provided below.

Medical Monitor: **Adam Boxer, MD, PhD**
Mobile: **(650) 468-5445**
Fax: **(415) 476-0679**

SAE Forms will be provided by the IND Sponsor or designee. The study site should call prior to faxing the SAE Form to the Medical Monitor so that the tracking procedure can begin immediately upon receipt of the telephone call. If the Medical Monitor is informed of a SAE via a telephone call, preliminary information will be obtained, and the study site will be instructed to fax an SAE Form.

If all information is not known at the time of initial reporting, an initial report should still be made. In the event there is a question as to whether the experience is serious, the information should be forwarded to the Medical Monitor for review. The Investigator is responsible for following up on completion of the SAE Form. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Medical Monitor. In the case of fatality, autopsy reports will be furnished to the Medical Monitor as soon as available.

During the initial telephone call, the Medical Monitor will require the following information about the subject and the reported SAE:

1. Subject identification including subject number, initials, and date of birth;

2. Randomization number;

3. Date of first dose of study drug and details of administration, including study drug name (including labeled strength and manufacturer), lot number, expiration date, and dose;

4. Date of last dose of study drug (i.e., prior to onset of SAE) and details of administration, including study drug name (including labeled strength and manufacturer), lot number, expiration date, and dose;

5. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event);

6. Date of onset of the event;

7. Date of resolution of the event (or confirmation ongoing);

8. Severity of the event according to criteria in Section 7.1.2;

9. Assessment of the attributability of the event to the study drug according to the definitions in Section 7.1.3;

10. Why event is considered serious per the definition in Section 7.1.1.2;

11. Whether the event is expected per the definition in Section 7.1.4;

12. Action taken in treating the event and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the subject was discontinued from the study);

13. All concomitant medications (including doses, routes, regimens, and indications);

14. Pertinent laboratory data;

15. Medical history.

The Investigator and Medical Monitor will review each SAE report and evaluate the relationship of the adverse experience to study drug and to underlying disease. Based on the Investigator's and Medical Monitor's assessment of the adverse experience, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the IND Sponsor will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol;

2. Discontinuation or suspension of the study;

3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings;

4. Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study drug-related.

Any SAE that is determined by the IND Sponsor to be reportable to FDA as an IND Safety Report (as defined in 21 CFR 312.32 and as further clarified in Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012) will be reported to FDA by the IND Sponsor within the specified time frame. All IND Safety Reports will also be promptly provided to the Investigator for submission to his or her IRB/IEC.

7.2 Physical Examination (Including Neurologic Examination)

The scheduled physical examinations for assessment of safety will include the following organ or body system assessments: skin; head, eyes, ears, nose, throat, thyroid, lungs, cardiovascular, liver, spleen, lymph nodes, extremities, and neurologic examination.

7.3 Weight

The scheduled weight measurements for assessment of safety and calculation of TPI 287 dose will use a calibrated digital scale with the subject wearing light clothes and no shoes.

Height will be measured using a calibrated stadiometer with the subject wearing no shoes. Height will only be measured at the Screening visit, and will be used in combination with each current weight measurement to calculate current BSA. BSA will be calculated per standard operating procedures in place at the UCSF Investigational Pharmacy (Mosteller formula):

BSA (m^2) = square root of ([height (cm) x weight (kg)]/3600)

Mosteller RD. 1987. Simplified calculation of body-surface area. N Engl J Med. 317(17):1098.

7.4 Vital Signs

The scheduled vital sign measurements for assessment of safety will include the following: blood pressure, pulse rate, respiratory rate, and temperature. Vital signs will be taken with the subject in the sitting position after 5 minutes of rest.

7.5 ECG

Twelve-lead ECGs will be performed with the subject in the recumbent position after 5 minutes of rest. ECGs will be read for QT and QTc intervals.

7.6 Safety Labs

Blood and urine for clinical safety laboratory assessments will be collected and processed using standard procedures. A local laboratory will perform the safety laboratory tests.

The safety labs will include CBC with differential, comprehensive metabolic panel, and urinalysis. Refer to Appendix E for a listing of each test to be performed.

7.7 PT/PTT/INR

Blood for coagulation assessments (PT, PTT, and INR) will be collected and processed using standard procedures. These coagulation assessments will be done within 1 month prior to each lumbar puncture to meet the modified Alzheimer's Disease Neuroimaging Initiative (ADNI) lumbar puncture protocol provided in Appendix F. Specifically, the blood for coagulation assessments will be collected at Screening (prior to the first lumbar puncture) and at Day 64 (one week prior to the second lumbar puncture). A local laboratory will perform the coagulation tests.

7.8 CSF Cell Count with Differential, Glucose, and Total Protein

CSF samples for measuring cell count with differential, glucose, and total protein will be collected via lumbar puncture at Screening and at the first final study visit of the dose escalation phase (1 week after the fourth dose of study drug).

The CSF samples will be collected and processed per the modified ADNI lumbar puncture protocol provided in Appendix F.

7.9 PSPRS

The PSPRS (Golbe and Ohman-Strickland 2007) will be used as a global measure of clinical disability and its progression. The PSPRS will serve a dual function as both a safety endpoint and an efficacy endpoint. The PSPRS consists of 28 items in six categories: daily activities, behavior, bulbar, ocular motor, limb motor, and gait/midline. Refer to the referenced publication for details regarding the administration and scoring of the PSPRS.

7.10 SEADL

The SEADL scale (Schwab and England 1969) will be used to evaluate activities of daily living. The SEADL scale will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administrating and scoring of the SEADL scale.

7.11 CDR-SB-FTLD

The CDR-SB-FTLD (Knopman et al. 2008) will be used to evaluate dementia. The CDR-SB-FTLD will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administrating and scoring of the CDR-SB-FTLD.

7.12 PVF

The one-minute PVF test for words starting in "F", "A", and "S" (Strauss et al. 2006) will be used to evaluate cognitive function. The PVF test will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administrating and scoring of the PVF test.

7.13 MMSE

The MMSE (Folstein et al. 1975) will be used to evaluate the cognitive function of subjects. The MMSE will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the exam.

7.14 GDS

The GDS rating instrument (Yesavage et al. 1983) will be used to evaluate depression in elderly subjects. The GDS will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the GDS.

7.15 MRI

MRI for the purpose of safety assessments will be performed on either a Siemens 3T TrioTim Scanner or a Phillips 3T MRI Scanner using sequences based on the ADNI 2 standard protocol including T1-weighted volumetric structural, FLAIR, DWI and GRE sequences (http://adni.loni.ucla.edu/methods/documents/mri-protocols/).

7.16 Definition of DLT

A DLT for this trial is defined as: 1) any Grade 3 or higher AE per NCI CTCAE severity criteria for which there is reasonable possibility that TPI 287 caused the event, 2) any Grade 2 AE in the CTCAE system organ class of nervous system disorders that is considered clinically significant and for which there is reasonable possibility that TPI 287 caused the event, or 3) any infusion-related toxicities (e.g., allergic reaction/hypersensitivity) occurring during the infusion of TPI 287 or within 24 hours after completing the infusion that do not resolve promptly with a reduced infusion rate and/or supportive care.

7.17 MTD Determination

The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For the initial dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively, for each diagnosis (i.e., 11 for CBS and 11 for PSP). For the remaining dose cohorts, 11 subjects with primary 4RT (i.e., a mix of CBS and PSP subjects with no required ratio of the two) will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. The dose escalation rules are as follows:

If ≤1 of the 8 active subjects per cohort experiences DLT (as defined in Section 7.14) during the first 4 weeks (first 2 infusions and 1 week follow-up), the dose of TPI 287 for the next cohort will be escalated to the next higher planned dose level.

If 2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to be the MTD and there will be no further dose escalation.

If >2 of the 8 active subjects per cohort experiences DLT during the first 4 weeks, this dose of TPI 287 will be determined to have exceeded the MTD and there will be no further dose escalation. Pending consultation with an independent, non-blinded DSMB, the next cohort may be de-escalated to a lower dose to refine the MTD determination. No more than 3 dose cohorts will be enrolled in this trial.

Screening for the second dose cohort (mixed population) may begin as soon as all eight active subjects for one of the two diagnoses (CBS or PSP) in the first dose cohort have completed the first 4 weeks (first 2 infusions and 1 week follow-up) and the criteria for escalation are met. However, the screening will be limited to that diagnosis until such time that all eight active subjects for the other diagnosis have completed the first 4 weeks (first 2 infusions and 1 week follow-up) and the criteria for escalation are met.

Screening for the third dose cohort (mixed population) may begin once all eight active subjects for the second dose cohort have completed the first 4 weeks (first 2 infusions and 1 week follow-up) and the criteria for escalation are met.

Enrollment in a cohort will be terminated early if >2 active subjects experiences DLT during the first 4 weeks.

Subjects who are withdrawn from the study for reasons other than DLTs before completion of the first 4 weeks may be replaced at the Investigator's discretion, and will not be counted towards the 8 subjects defined above.

The MTD determination for this study will be limited to the planned dosing range of 2 to 20 mg/m^2 TPI 287 (i.e., the objective is not to identify the highest possible dose that primary 4RT subjects can tolerate).

The MTD will be defined as the highest dose level achieved at which no more than 2 out of 8 active subjects experienced a DLT during the first 4 weeks (first 2 infusions and 1 week follow-up).

8. ASSESSMENT OF PHARMACOKINETICS

The PK profile of TPI 287 in plasma after a single IV infusion and the steady-state CSF concentration of TPI 287 one week after completion of the fourth TPI 287 infusion are secondary endpoints for this trial. Refer to Appendix C for a tabular summary of the timing of the PK blood and CSF draws.

8.1 Blood Collection

Blood samples for PK assessments on Day 1 will be taken by an indwelling cannula inserted in a forearm vein to minimize discomfort associated with repeated venipunctures. Topical anesthesia will be allowed to place the cannula. Blood samples for PK assessments on other days will be taken by direct venipuncture.

The planned time points for PK blood collections are Day 1 [within an hour prior to the start of study drug infusion, at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion], Day 2 (24-hour post-infusion), Days 22, 43, and 64 (trough levels; single point prior to dosing), and at the first final study visit of the dose-ranging phase (one week after fourth study drug infusion; single point for comparison with

TPI 287 CSF level). No PK blood samples will be collected during the open-label extension phase of this trial.

A window of ± 5 minutes will be allowed for each time point on Day 1, except for the 5, 15, and 30 minute time points which will have an allowed window of ± 2 minutes. A window of ± 20 minutes will be allowed for the 24-hour post-infusion collection on Day 2. The actual time of blood collections will be recorded in the source documents and CRFs. All deviations outside the allowed ranges will be documented as protocol deviations.

The blood sample volume at each collection time point will be 5 mL. The sample will be collected in di-potassium ethylenediaminetetraacetic acid- (K_2EDTA-) containing tubes.

8.2 Blood Processing, Labeling, and Shipment

Blood samples collected for PK assessments will be processed to plasma. Each plasma sample will be split into two cryo vials (1mL/vial) to serve as primary and back-up samples. The plasma samples will be stored at approximately -80°C until analyzed. The primary samples will be shipped on dry-ice to a designated contract research organization (CRO)/bioanalytical laboratory for analysis of TPI 287 concentration. The back-up samples will be reserved for retesting if required. Detailed processing, labeling, and shipping instructions will be specified in a PK lab manual provided by the bioanalytical laboratory.

8.3 CSF Collection

CSF samples for the determination of TPI 287 concentration will be collected via lumbar puncture at Screening and at the first final study visit of the dose escalation phase (1 week after the fourth dose of study drug).

The CSF samples will be collected per the modified ADNI lumbar puncture protocol provided in Appendix F.

8.4 CSF Processing, Labeling, and Shipment

The CSF samples collected for PK assessments will be processed per the modified ADNI lumbar puncture protocol provided in Appendix F. A portion of each CSF sample will be transferred to two cryo vials (1mL/vial) to serve as primary and back-up PK samples. The CSF samples will be stored at approximately -80°C until analyzed. The primary samples will be shipped on dry-

ice to a designated CRO/bioanalytical laboratory for analysis of TPI 287 concentration. The back-up samples will be reserved for retesting if required.

8.5 Bioanalytical Methods

The concentration of TPI 287 in plasma and CSF will be measured using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methods.

9. ASSESSMENT OF EFFICACY AND PHARMACODYNAMICS

The exploratory efficacy endpoints for this trial include changes in motor function, cognition, activities of daily living, and behavior (PSPRS, SEADL, CDR-SB-FTLD, PVF, MMSE, and GDS). The exploratory pharmacodynamic (PD) endpoints for this trial include changes in the concentration of CSF biomarkers of neurodegeneration (NfL, total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides) and changes in brain network functional and structural connectivity and perfusion (rsfMRI, DTI, and ASL perfusion MRI). Refer to Appendix C for a tabular summary of the timing of the efficacy and PD evaluations.

9.1 PSPRS

The PSPRS (Golbe and Ohman-Strickland 2007) will be used as a global measure of clinical disability and its progression. The PSPRS will serve a dual function as both a safety endpoint and an efficacy endpoint. The PSPRS consists of 28 items in six categories: daily activities, behavior, bulbar, ocular motor, limb motor, and gait/midline. Refer to the referenced publication for details regarding the administration and scoring of the PSPRS.

9.2 SEADL

The SEADL scale (Schwab and England 1969) will be used to evaluate activities of daily living. The SEADL scale will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administrating and scoring of the SEADL scale.

9.3 CDR-SB-FTLD

The CDR-SB-FTLD (Knopman et al. 2008) will be used to evaluate dementia. The CDR-SB-FTLD will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administrating and scoring of the CDR-SB-FTLD.

9.4 PVF

The one-minute PVF test for words starting in "F", "A", and "S" (Strauss et al. 2006) will be used to evaluate cognitive function. The PVF test will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administrating and scoring of the PVF test.

9.5 MMSE

The MMSE (Folstein et al. 1975) will be used to evaluate the cognitive function of subjects. The MMSE will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the exam.

9.6 GDS

The GDS rating instrument (Yesavage et al. 1983) will be used to evaluate depression in elderly subjects. The GDS will serve a dual function as both a safety endpoint and an efficacy endpoint. Refer to the referenced publication for details regarding the administration and scoring of the GDS.

9.7 CSF Biomarkers of Neurodegeneration

CSF samples for measuring the concentration of biomarkers of neurodegeneration (NfL, total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides) will be collected via lumbar puncture at Screening and at the first final study visit of the dose escalation phase (1 week after the fourth dose of study drug).

The CSF samples will be collected and processed per the modified ADNI lumbar puncture protocol provided in Appendix F.

The CSF concentration of NfL, total tau, and phosphorylated tau will be determined by the INNO-BIA AlzBio3 method described by Fagan et al. 2011. The CSF samples will be shipped to Dr. Anne Fagan's lab at Washington University, St. Louis, MO for this purpose.

Quantification of the stoichiometry of different tau isoforms and fragments, as well as novel CSF tau phosphopeptides will be performed using FLEXI-Tau mass spectrometry similar to the method described by Singh et al. 2012. The CSF samples will be shipped to Dr. Judith Steen's lab at Boston Children's Hospital, Boston, MA for this purpose.

9.8 Brain Imaging

The connectivity between midbrain tegmentum and pre-supplementary motor area will be measured via rsfMRI. White matter fractional anisotropy within cortical oculomotor tracts will be measured by DTI. Medial temporal lobe and regional cortical perfusion will be measured by ASL perfusion MRI.

MRI acquisition will take place on a 3T Siemens Trim Trio Scanner or a Phillips 3T MRI Scanner using protocols based on ADNI 2 (http://adni.loni.ucla.edu/). RsfMRI and DTI scan protocols will be similar to ADNI 2 as designed by Dr. Norbert Schuff for multiple studies at UCSF, including Dr. Boxer's 4 Repeat Tauopathy Neuroimaging Initiative (Gardner et al. 2013).

10. STATISTICS

10.1 Sample Size Considerations

The primary outcome measures of this phase 1 trial are the safety and tolerability of TPI 287 in patients with primary 4RT, CBS or PSP. As such, the sample size considerations were based on a standard phase 1 dose escalation scheme.

The dose of TPI 287 will be escalated in sequential cohorts. Subjects will be assigned to cohorts in the order of study entry. For the initial dose cohort, 11 subjects will be randomized 3:8 to placebo or active, respectively, for each diagnosis (i.e., 11 for CBS and 11 for PSP). For the remaining dose cohorts, 11 subjects with primary 4RT (i.e., a mix of CBS and PSP subjects with no required ratio of the two) will be randomized 3:8 to placebo or active, respectively. The planned dose levels of TPI 287 are: 2, 6.3, and 20 mg/m^2. No more than 3 dose cohorts will be enrolled in this trial.

The MTD determination for this study will be limited to the planned dosing range of 2 to 20 mg/m^2 TPI 287 (i.e., the objective is not to identify the highest possible dose that primary

4RT subjects can tolerate). The sample size is anticipated to be up to 44 subjects (CBS or PSP), depending on the dose level at which toxicity is observed.

10.2 Statistical Analysis of Safety Data

Data from all subjects who receive at least one dose of study drug (placebo or active) will be included in the safety analysis.

AEs will be tabulated by body system and preferred term [per Medical Dictionary for Regulatory Activities (MedDRA)], and will be further categorized by treatment group, phase of trial [i.e., placebo-controlled (dose-ranging) phase versus open-label extension], severity, and assigned relationship to study drug. The incidence for each AE will be provided as the total number of subjects that experienced the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables.

AEs will also be listed for individual subjects, along with information regarding onset, duration, severity, relationship to study drug, and outcome. AEs that lead to withdrawal from the study will be listed and summarized. A separate tabulation and listing of SAEs will also be generated.

Other safety assessments, including physical examination (including neurological examination), weight, vital signs, 12-lead ECG, CBC with differential, comprehensive metabolic panel, urinalysis, PT/PTT/INR, CSF cell count with differential, glucose, and total protein, PSPRS, SEADL, PVF, CDR-SB-FTLD, MMSE, GDS, and MRI (standard T1-weighted volumetric structural, FLAIR, DWI, and GRE sequences) will be listed and summarized by treatment group and phase of trial [i.e., placebo-controlled (dose-ranging) phase versus open-label extension].

Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Inferential statistical analyses comparing the safety data among treatment groups or phases of the trial are not planned.

The MTD will be defined as the highest dose level achieved (within planned dosing range) at which no more than 2 of 8 active subjects experienced a DLT during the first 4 weeks (first 2 study drug infusions and 1 week follow-up).

10.3 Statistical Analysis of Pharmacokinetic Data

The PK profile of TPI 287 in plasma after a single TPI 287 IV infusion (Day 1) and the steady-state CSF concentration of TPI 287 1 week after completion of the fourth TPI 287 infusion are the secondary endpoints for this trial.

The concentration of TPI 287 in plasma and CSF will be measured using validated LC/MS-MS methods. Individual and mean (standard deviation) plasma and CSF TPI 287 concentration data will be tabulated and plotted by dose level. The plasma data will include the serial blood collections following the Day 1 infusion, as well as trough concentrations at Days 22, 43, and 64, and 1 week after the fourth infusion for comparison with the post-dose CSF level.

Plasma TPI 287 concentration-time data will be analyzed by non-compartmental methods using WinNonlin (Pharsight Corporation, CA). PK parameters will be calculated according to standard equations, and will include maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from time zero to time of last measurable concentration (AUC_t), area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal phase half- life ($t_{1/2}$), clearance (CL), apparent volume of distribution (Vd), and mean residence time (MRT).

Individual PK parameters will be summarized by descriptive statistics for each dose group. The descriptive statistics will include arithmetic mean, standard deviation, median, minimum, maximum, and geometric mean (log-transformed). Inferential statistical analyses comparing PK data among treatment groups are not planned.

10.4 Statistical Analysis of Efficacy and Exploratory Pharmacodynamic Data

CSF concentrations of NfL, total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides at Screening and 1 week after completion of the fourth study drug infusion, as well as the calculated changes in these measurements will be listed and summarized by treatment group. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation). Inferential statistical analyses comparing data among treatment groups are not planned.

Connectivity between midbrain tegmentum and pre-supplementary motor area as measured by rsfMRI, white matter fractional anisotropy within cortical oculomotor tracts as measured by DTI, and medial temporal lobe and regional cortical perfusion as measured by ASL perfusion MRI at Screening and 2 weeks after completion of the fourth study drug infusion, as well as the calculated changes in these measurements will be listed and summarized by treatment group. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard

deviation). Inferential statistical analyses comparing data among treatment groups is not planned.

PSPRS, SEADL, CDR-SB-FTLD, PVF, MMSE and GDS assessments at Screening or Baseline and 1 week after completion of the fourth study drug infusion, as well as the calculated change in these assessments will be listed and summarized by treatment group and phase of trial [i.e., placebo-controlled (dose-ranging) phase versus open-label extension]. Descriptive statistics will be generated as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Analysis of variance (ANOVA) will be used to compare the changes in these assessments across treatment groups.

11. ACCESS TO SOURCE DOCUMENTS AND RETENTION OF RECORDS

The Investigator will make the source documents for this trial available for monitoring by the IND Sponsor or its representatives, regulatory authorities or health authority inspectors.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their subject number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the IND Sponsor (or designee), and the IRB/IEC.

The information developed in this clinical study will be used by the IND Sponsor in the clinical development of the study drug and therefore may be disclosed by the IND Sponsor to other clinical investigators, to pharmaceutical companies, to the FDA or other government agencies.

The Investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least 2 years after the Investigation is discontinued and regulatory authorities have been notified.

The Investigator will notify the IND Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the IND Sponsor must be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the Investigator and the IND Sponsor for storage. If source documents are required for continued care of the subject, appropriate copies for storage off-site will be made.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Data Collection

All data required by the study protocol will be entered onto CRFs and must be verifiable against source documents. CRFs will be completed for every subject who is enrolled in the trial. Only authorized Investigational Site personnel will enter data on the CRFs. Any corrections to data entered into the CRF will be made in such a way that the original entry is not obscured. The date of the correction and the initials of the person making the correction will be documented.

The CRFs will be kept up-to-date by the Investigator and the research staff at the Investigational Site. The Investigator will be responsible for reviewing all data and CRF entries and will sign and date each subject's CRF, verifying that the information is true and correct.

12.2 Data Management

After the CRFs have been reviewed by the IND Sponsor and all identified discrepancies have been addressed, the Investigator signed copy of the CRFs will be forwarded to Data Management. Queries generated by Data Management will be sent to the clinical team for resolution. The Investigator is responsible for the review and approval of all responses.

All CRF data will be entered into a validated database and an electronic audit trial of edits maintained. Data may be imported to the database electronically.

The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

12.3 Inspection by Regulatory Authorities

At some point during the study, a regulatory authority may visit the Investigator to conduct an inspection of the study. The Investigator and staff will cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The

Investigator will immediately notify the IND Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

13. ETHICS

13.1 Declaration of Helsinki

This study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision, as described in Appendix G.

13.2 Good Clinical Practice and Regulatory Compliance

This study will be conducted in accordance with the principles of GCP (current ICH guideline) and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

13.3 Institutional Review Board/Independent Ethics Committee

The protocol, ICF, and any materials (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/IEC.

The Investigator will ensure that all aspects of the IRB/IEC review are conducted in accordance with current institutional, local, and national regulations. The study will not be initiated until the Investigator receives a letter documenting IRB/IEC approval. A letter documenting the IRB/IEC approval will be provided to the IND Sponsor prior to initiation of the study.

Amendments to the protocol will be subject to the same requirements as the original protocol. Implementation of the changes described in the protocol amendment will not be initiated until the Investigator receives a letter documenting IRB/IEC approval. A letter documenting the IRB/IEC approval will be provided to the IND Sponsor prior to implementation of the changes described in the protocol amendment.

Revisions to the ICF will be reviewed and approved by the IRB/IEC prior to use in the study. The Investigator will inform the IRB/IEC of all reportable AEs. IND Safety Reports provided by the IND Sponsor will be promptly forwarded to the IRB/IEC by the Investigator. Updates to the IB provided by the Sponsor to the Investigator will be submitted to the IRB/IEC by the Investigator.

The Investigator will submit all periodic reports and updates that the IRB/IEC may require. After completion or termination of the study, the Investigator will submit a final report to the IRB/IEC. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995). The final report will be prepared by the IND Sponsor (or designee) and will include data from all Investigational Sites.

13.4 Informed Consent

No study related procedures, including screening evaluations, will be performed until the subject has given written informed consent.

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the subject understands. Further, the ICF will identify the Sponsor, the Principal Investigator and institutional affiliation, potential conflicts of interest, provisions for treating subjects who are harmed as a consequence of participation in the study, and provisions for post-trial access.

The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and any additional elements required by the Investigator's institution or local regulatory authorities. The Investigator will submit the ICF to the IRB/IEC for review, and will provide the IND Sponsor with a letter documenting the IRB/IEC approval prior to initiation of the study.

The IRB/IEC approved ICF will be given to each prospective participant. The subjects will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each subject who agrees to participate in the trial and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The Investigator will also obtain authorization from the subject to use and/or disclose PHI in compliance with HIPAA or equivalent. Written HIPAA authorization may be obtained as part of the informed consent process.

If a protocol amendment substantially alters the study design or increases the potential risk to the subject, or the known risks of the study drug change over the course of the study, the ICF will be revised and submitted to the IRB/IEC for review and approval. The revised approved ICF must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment and to obtain consent from new subjects prior to enrollment.

13.5 Emergency Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the IND Sponsor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was effected) is to continue in the study. The CRF and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

14. PUBLICATION POLICY

All information and data obtained in the course of the study are the property of the IND Sponsor and are considered confidential. To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the clinical trial agreement.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

This trial will be registered in a publicly accessible database (clinicaltrials.gov) not later than 21 days after enrollment of the first subject. Results of this trial, including negative and inconclusive, as well as positive results, will be made publicly available.

15. PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will not modify the protocol without first receiving IND Sponsor authorization to do so, except in those cases intended to reduce immediate risk of the subjects. The IND Sponsor is responsible for submitting protocol amendments to the appropriate government regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB/IEC. Approval by the IRB/IEC will be obtained before protocol modifications are implemented, except in those cases intended to reduce immediate risk to subjects.

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APPENDIX A: MODIFIED NINDS-SPSP PSP CRITERIA BASED ON NNIPPS STUDY (LITVAN ET AL. 1996A AND BENSIMON ET AL. 2009)

PSP subjects enrolled in this trial must be diagnosed with probable or possible PSP per NINDS-SPSP criteria (Litvan et al. 1996a), as modified for the NNIPPS clinical trial (Bensimon et al. 2009). The modified criteria for probable or possible PSP are as follows:

a) at least a 12-month history of postural instability or falls during the first 3 years that symptoms are present; and
b) at screening, a decreased downward saccade velocity defined as observable eye movement (deviation from the "main sequence" linear relationship between saccade amplitude and saccade velocity), or supranuclear ophthalmoplegia defined as 50% reduction in upward gaze or 30% reduction in downward gaze; and
c) age at symptom onset of 40 to 85 years by history; and
d) an akinetic-rigid syndrome with prominent axial rigidity.

APPENDIX B: POSSIBLE OR PROBABLE CBS CRITERIA (ARMSTRONG ET AL. 2013)

CBS subjects enrolled in this trial must be diagnosed with possible or probable corticobasal degeneration, CBS subtype per 2013 consensus criteria (Armstrong et al. 2013). The criteria for possible or probable CBS are as follows:

> Symmetric or asymmetric presentation of: a) limb rigidity or akinesia, b) limb dystonia, or c) limb myoclonus;
>
> plus one of: d) orobuccal or limb apraxia, e) cortical sensory deficit, or f) alien limb phenomena (more than simple levitation).

APPENDIXC: SCHEDULE OF EVENTS FOR PLACEBO-CONTROLLED (DOSE-RANGING) PHASE

	Screening	Treatment Period – Placebo-Controlled (Dose-Ranging) Phase							Final Study Visits[b]		
	Within 28 Days Prior to Day 1	Day 1	Day 2	Day 8[a]	Day 15[a]	Day 22[a]	Day 43[a]	Day 64[a]	1 Week After Last Dose	2 Weeks After Last Dose	4 Weeks After Last Dose
Informed consent form	x[c]										
Record demographic data	x										
Medical and surgical history	x	x[d]									
Physical & neurological exam	x	x[d]	x	x	x	x[e]	x[e]	x[e]		x	x
Height	x										
Weight	x	x[d]		x	x	x[e]	x[e]	x[e]		x	
Calculate body surface area for dosing		x[d]				x[e]	x[e]	x[e]			
Vital signs[f]	x	x[d,g]	x	x	x	x[e,h]	x[e,h]	x[e,h]	x	x	x
12-lead electrocardiogram	x	x[d]				x[e]	x[e]	x[e]			
PSPRS		x[d]								x	
MMSE	x									x	
SEADL		x[d]								x	
CDR-SB-FTLD		x[d]								x	
PVF		x[d]								x	
GDS	x									x	
Safety labs[i]	x	x[d]	x	x	x	x[e]	x[e]	x[e]	x	x	x
Coagulation tests[j]	x							x[e]			
Serum β-hCG (WCBP only)	x										
Urine β-hCG (WCBP only)		x[d]									
Recording of medications[k]	x	x[d]	x	x	x	x[e]	x[e]	x[e]	x	x	
^{18}F florbetapir PET (CBS subjects only)		x[d,o]									
Screening for mutations in *GRN* and *C9ORF72* genes (CBS subjects only)		x[d,p]									
MRI procedures[l]	x[q]									x	

	Screening	Treatment Period – Placebo-Controlled (Dose-Ranging) Phase							Final Study Visits[b]		
	Within 28 Days Prior to Day 1	Day 1	Day 2	Day 8[a]	Day 15[a]	Day 22[a]	Day 43[a]	Day 64[a]	1 Week After Last Dose	2 Weeks After Last Dose	4 Weeks After Last Dose
Collection of CSF via lumbar puncture[m]	x[q]								x		
Randomize to treatment		x									
Pre-medication & study drug infusion		x				x	x	x			
Monitor of adverse events		x	x	x	x	x[e]	x[e]	x[e]	x	x	x
Diary[n]		x	x	x	x	x[e]	x[e]	x[e]	x	x	x
Collection of blood for PK assessments		x[d,r]	x			x[e]	x[e]	x[e]	x		
Collection of blood for DNA banking for future research	x[s]										
Collection of blood for plasma banking for future research	x[s]								x		x

β-hCG = beta-chorionic gonadotropin; CDR-SB-FTLD = clinical dementia rating scale sum of boxes with added frontotemporal lobar degeneration scales; CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; PSPRS = Progressive Supranuclear Palsy Rating Scale; PVF = phonemic verbal fluency; SEADL = Schwab and England Activities of Daily Living scale; WCBP = women of childbearing potential

a. A -1 day/+2 day window will be allowed for the Day 8, 15, 22, 43, and 64 visits, as long as the duration between TPI 287 infusions is at least 20 days
b. Final study visits for the placebo-controlled phase of the trial will occur during 2-3 visits, depending on whether the subject is eligible and opts to proceed with the open-label extension. The allowed visit window is ± 3 days for the first two visits and ± 7 days for the third visit. Subjects that are eligible and opt to proceed with the open-label extension phase will not undergo the third final visit and will instead return to the clinic three weeks from their last dose of study drug to start the open-label extension (see Appendix D). If a subject is discontinued from treatment early, all evaluations listed for the three final study visits will be performed if feasible. Any subject with a possible study drug-related AE will be followed until resolution or stabilization of the event.
c. ICF must be signed prior to performing any other Screening evaluations
d. Each of these baseline evaluations must be completed before randomizing the subject to treatment, except for baseline safety labs that will be collected prior to randomization, but for which randomization will not be delayed to wait for results
e. Each of these evaluations must be completed prior to study drug administration that visit
f. Blood pressure, pulse rate, respiration rate, and temperature
g. Prior to initiating study drug, and then at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of infusion. For time points that include both vital signs and PK blood collections, the vital signs will be taken first.

h. Prior to initiating study drug, and then at 0.25, 0.5, 1, and 2 hours following the initiation of infusion
i. Complete blood count with differential, comprehensive metabolic panel, and urinalysis
j. Prothrombin time, partial thromboplastin time, and International Normalized Ratio. These tests must be done before the lumbar punctures.
k. Record all medications taken within 2 months of the first Screening visit through the final study visit
l. Resting state functional MRI, diffusion tensor imaging, arterial spin labeling perfusion MRI, and standard T1-weighted volumetric structural, fluid-attenuated inversion recovery, diffusion-weighted imaging, and gradient-recalled echo sequences
m. For measurement of cell count with differential, glucose, and total protein, CSF biomarkers of neurodegeneration (NfL, total tau, phosphorylated tau, tau isoforms and fragments, and tau phosphopeptides), and TPI 287 concentration
n. Subjects will be given a diary to record any adverse events or concomitant medications taken between visits. The diary will be reviewed at each visit.
o. For CBS subjects only. If subject meets eligibility criteria after the initial screening assessments (all tests before the MRI and CSF), the subject will undergo ^{18}F florbetapir PET scanning to rule out the presence of amyloid that would suggest CBS due to Alzheimer's pathology.
p. For CBS subjects only. If subject meets eligibility criteria after the initial screening assessments (all tests before the MRI and CSF), the subject will undergo screening for mutations in the progranulin (*GRN*) and *C9ORF72* genes to rule out CBS due to TDP-43 pathology.
q. Screening MRI procedures should only be performed if the subject meets all other eligibility criteria after completion of the initial Screening assessments. The lumbar puncture must be performed after the MRI procedures, and should only be performed if the subject continues to meet eligibility criteria after the completion of the MRI procedures.
r. Blood samples for the determination of TPI 287 plasma levels will be collected within an hour prior to the start of study drug infusion, at 5, 15, 30, and 60 minutes following the initiation of the infusion (with the 60 minute time point just prior to the end of the infusion), and at 5, 15, 30, and 60 minutes and 2, 4, and 8 hours following completion of the infusion. To minimize discomfort, an indwelling cannula rather than repeated venipunctures will be used for the PK blood sampling on Day 1.
s. For subjects enrolled before banking was added to the protocol (and thus that missed the blood collections at Screening), collection of a blood sample for DNA banking will be allowed at a later time point up to and including the final study visit. Collection of the pre-dose plasma banking sample will not be allowed at a later time point; however, the scheduled post-dose draws will still be allowed (regardless of whether a pre-dose sample is available).

APPENDIX D: SCHEDULE OF EVENTS FOR OPTIONAL OPEN-LABEL EXTENSION PHASE

	Treatment Period – Open-Label Extension[a]						Final Study Visit[b]
	Day 1	**Day 2**	**Day 8[k]**	**Day 15[k]**	**Day 22[k]**	**Day 43[k]**	**4 Weeks After Last Dose**
Informed consent form for optional phase[c]	x						
Physical & neurological exam	x[d]	x	x	x	x[d]	x[d]	x
Weight	x[d]		x	x	x[d]	x[d]	x
Calculate body surface area for dosing	x[d]				x[d]	x[d]	
Vital signs[e]	x[d,f]	x	x	x	x[d,g]	x[d,g]	x
12-lead electrocardiogram	x[d]				x[d]		x
PSPRS							x
SEADL							x
CDR-SB-FTLD							x
PVF							x
GDS							x
Safety labs[h]	x[d]	x	x	x	x[d]	x[d]	x
Urine β-hCG (WCBP only)	x[d]						
Recording of medications[i]	x[d]	x	x	x	x[d]	x[d]	x
Pre-medication & study drug infusion	x				x	x	
Monitor of adverse events	x[d]	x	x	x	x[d]	x[d]	x
Diary[j]	x[d]	x	x	x	x[d]	x[d]	x
Collection of blood for plasma banking for future research							x

β-hCG = beta-chorionic gonadotropin; CDR-SB-FTLD = clinical dementia rating scale sum of boxes with added frontotemporal lobar degeneration scales; GDS = Geriatric Depression Scale; PSPRS = Progressive Supranuclear Palsy Rating Scale; PVF = phonemic verbal fluency; SEADL = Schwab and England Activities of Daily Living scale; WCBP = women of childbearing potential

a. Subjects that are eligible and opt to proceed with the open-label extension phase will return to the clinic one week after the second final study visit of the placebo-controlled (dose-ranging) phase (i.e., 3 weeks after their last dose of study drug; see Appendix C) to start the open-label extension.
b. The allowed visit window is ± 7 days. If a subject is discontinued from treatment early, all evaluations listed for the final study visit will be performed if feasible. Any subject with a possible study drug-related AE will be followed until resolution or stabilization of the event.
c. ICF must be signed prior to performing any other extension study evaluations
d. Each of these evaluations must be completed prior to study drug administration that visit
e. Blood pressure, pulse rate, respiration rate, and temperature

f. Prior to initiating study drug, and then at 15, 30, and 60 minutes following the initiation of infusion, and at 1, 2, 4, and 8 hours following completion of infusion.
g. Prior to initiating study drug, and then at 0.25, 0.5, 1, and 2 hours following the initiation of infusion
h. Complete blood count with differential, comprehensive metabolic panel, and urinalysis
i. Record all medications taken since the second final study visit of the dose-ranging phase through the final study visit of the extension phase
j. Subjects will continue to record any adverse events or concomitant medications taken between visits in their diary. The diary will be reviewed at each visit.
k. A -1 day/+2 day window will be allowed for the Day 8, 15, 22, and 43 visits, as long as the duration between TPI 287 infusions is at least 20 days

APPENDIX E: SAFETY LABORATORY TESTS

The tests listed below will be performed at each visit where "safety labs" are specified, except where noted. Pregnancy tests, coagulation tests, and CSF cell count with differential, glucose, and total protein are performed **in addition** to the safety labs listed below when specified in Section 6 and the Schedule of Events tables in Appendices C and D.

CBC with Differential	**Comprehensive Metabolic Panel**	**Urinalysis**
Hematocrit		Color and appearance
Hemoglobin	Alkaline phosphatase	pH and specific gravity
Mean corpuscular hemoglobin	Alanine aminotransferase	Bilirubin
Mean corpuscular hemoglobin conc.	Aspartate aminotransferase	Glucose
Mean corpuscular volume	Bicarbonate	Ketones
Mean platelet volume	Blood urea nitrogen	Leukocytes
Platelet count	Calcium	Nitrite
Red blood cell distribution width	Chloride	Occult blood
Red blood cell count		Protein
White blood cell count	Creatinine	Urobilinogen
White blood cell differential	Potassium	Microscopic analysis
(% & absolute):	Sodium	
Basophils	Glucose	
Eosinophils	Total/direct bilirubin	
Lymphocytes	Total protein (Screening only)	
Monocytes		
Neutrophils		

CBC = complete blood count

APPENDIX F: MODIFIED ADNI LUMBAR PUNCTURE PROTOCOL

The CSF samples for the measurement of cell count with differential, glucose, and total protein, biomarkers of neurodegeneration, and TPI 287 concentration will be collected per the modified ADNI lumbar puncture protocol outlined below.

Modified ADNI Lumbar Puncture Protocol

Collection procedure:

I. General issues:

- Verify that PT/PTT and platelet count done within 1 month prior to lumbar puncture.

II. All samples will be collected:

- At a standard time of day (8am or preferably sometime in the morning)
- Same position each time for each patient (laying down, or upright)
- After any scan for that time point. If this is not possible, ensure that there is at least a 3 day window between the lumbar puncture and an MRI appointment.
- Emphasis on consistency: method of collection, position, and time of day collected should be consistent across all subjects.

III. The ADNI–preferred method for obtaining CSF by lumbar puncture:

1. Use of a smallest feasible caliber traumatic or atraumatic needle.
2. Discard first 1-2 mL of CSF to clear any blood from minor trauma associated with needle insertion
3. Reserve next 2-3 mL for standard tests such as cell counts, glucose, and total protein with determinations to be done at local clinical lab.
4. Do not use manometer or extension tube for any CSF to be used for research
5. Collect at least 20 mL of CSF directly into polypropylene collection tube. If possible, collect all CSF into a single polypropylene collection tube, if it is at least 20 mL in volume. If collection tube larger than 20 mL is not available, collect CSF into smaller polypropylene collection tubes until at least 20 mL has been collected.
6. When LP complete, have patient relax in bed for at least 20 minutes. They can eat at this time.

NOTE: Computer tomography (CT)-guided lumbar puncture is allowed if necessary (e.g., failed attempt using method above or subjects who are obese or have anatomical issues).

Sample processing:

1. Transfer all CSF (except that described in steps III2 and III3 above) into one 50 mL polypropylene centrifuge tube and invert two to three times to mix gently and place on ice.
2. Aliquot CSF into several polypropylene tubes (1 mL/tube). Put these tubes on dry ice as soon as possible in the upright position. For the CSF samples to be used for PK analysis, use the cryo vials and labels provided by the designated CRO/bioanalytical lab for this step. Two cryo vials (1mL/vial) per CSF sample will be set up to serve as primary and back-up PK samples.
3. CSF is frozen upright on dry ice for at least 20 minutes before being stored.
4. Store CSF samples at approximately -80°C until analyzed.
5. CSF aliquots will be shipped on dry ice in batch at end of study to:
   a. A designated CRO/bioanalytical lab for determination of TPI 287 concentration via a validated LC/MS-MS method;
   b. Washington University, St. Louis, MO (Dr. Anne Fagan's lab) for NfL, total tau, and phosphorylated tau measurements;
   c. Boston Children's Hospital, Boston, MA (Dr. Judith Steen's lab) for quantification of the stoichiometry of different tau isoforms and fragments, as well as novel CSF tau phosphopeptides.

Lumbar Puncture Supplies (ADNI recommended – comes with the ADNI LP kits)

I. LP materials:

- Lumbar puncture tray
- 22G Sprotte Atraumatic Spinal Needle with Introducer, or 22G standard needle (tray comes with 24G Sprotte needle)
- Polypropylene collection tubes, preferably single tube at least 30 mL volume
- 2 x 13 mL transfer tubes, if large (>20 mL) polypropylene tube unavailable
- Betadine solution (not Betadine scrub)
- Sterile gloves in correct size for person performing the LP (one plus extras for back up)
- Blue "chux" pad, plus extras
- Extra bottle 1% lidocaine (useful, not mandatory)
- Tegaderm adhesive covering for LP site after procedure
- Clean washcloths and towels
- Sharps container
- Extra sterile 4x4 gauze pads
- Extra adhesive bandages

II. LP tray (ADNI provided)

- 2 Sprotte Spinal Needles (24G x 90mm)
- 22G recommended, but not provided in kit

- 2 Introducer Needles (1mm x 30mm)
- 1 22G x 1 ½ in. Needle
- 1 Plastic Syringe (3mL, Luer Slip) with 25G x 5/8 in. Needle (Attached)
- 1 Needle Stick Pad
- 3 Sponge Applicators
- 3 Gauze Sponges
- 1 Fenestrated Drape with 2 Tabs
- Prep Well
- Lidocaine hydrochloride USP, 1%, 2mL ampule
- Adhesive bandage

APPENDIX G: DECLARATION OF HELSINKI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.