Supplementary Online Content

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eMethods. Inclusion/Exclusion Criteria, Quantification Methods, and Imaging Acquisition and Processing

A. Inclusion/Exclusion Criteria for TPI-287 AD trial

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[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;

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/mm3, platelets <100,000/mm3, 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.

B. Inclusion/Exclusion Criteria for TPI-287 4RT trial

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 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 as modified for the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) clinical trial.[2,3]

For CBS Only

11. Meets 2013 consensus criteria for possible or probable corticobasal degeneration, CBS subtype.[4]

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[1]
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/mm3, platelets <100,000/mm3, 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.

C. Methods for quantification of TPI-287 in human plasma and cerebrospinal fluid (CSF) using liquid chromatography-mass spectrometry (LC/ESI-MS/MS).
Proteins in human plasma samples and CSF were precipitated with D_9-TPI-287 internal standard solution in acetonitrile and were removed by centrifugation. RP-HPLC was used to concentrate and chromatograph prepared samples. TPI-287 and internal standard were detected via ESI-MS/MS using a specific multiple-reaction-monitoring method. The peak areas of TPI-287 and internal standards were integrated in their respective MS-chromatograms and the ratios of these peak areas were used for quantification. Concentrations of TPI-287 in unknown samples were interpolated from a calibration curve of standards of known concentrations and are reported as ng/mL in plasma and ug/mL in CSF.

D. Methods for structural MRI scan acquisition, longitudinal T1 processing and diffusion image processing
Subjects were scanned at the UCSF Neuroscience Imaging Center on a Siemens Trio or a Siemens Prisma Fit 3T scanner equipped with a 64-channel head coil. A magnetization prepared rapid gradient echo (MPRAGE) sequence

was used to acquire T1-weighted images of the entire brain (Sagittal slice orientation; slice thickness = 1.0 mm; slices per slab = 160; in-plane resolution = 1.0x1.0 mm; matrix = 240X256; TR = 2,300 ms; TE = 2.9 ms; TI = 900 ms; flip angle = 9°). Diffusion-weighted images were acquired using single-short spin-echo sequence with the following parameters: repetition time = 5300 ms; echo time = 88 ms; inversion time = 2500 ms; flip angle = 90; field of view = 256*256 mm; 2 diffusion values of b = 0 and 1000 s/mm; 12 diffusion directions; 4 repeats; 40 slices; matrix size = 128*128; voxel size = 2 mm*2 mm; slice thickness = 3 mm; and generalized autocalibrating partial parallel acquisition = 2.

Before any prepossessing of the images, all T1-weighted images were visually inspected for quality control. Images with excessive motion or image artifact were excluded. Only subjects with all timepoints collected on a single scanner were included. T1-weighted images underwent bias field correction using N3 algorithm, and segmentation was performed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK, http://www. fil.ion.ucl.ac.uk/spm) unified segmentation.[5] An intra-subject template was created by non-linear diffeomorphic and rigid-body registration proposed by the symmetric diffeomorphic registration for longitudinal MRI framework.[6] The intra-subject template was segmented also using SPM12's unified segmentation. A group template was generated from the within-subject average gray and white matter tissues by non-linear and rigid-body registration template generation using *Diffeomorphic Anatomical Registration using Exponentiated Lie algebra* (DARTEL).[7] Subjects' native space gray and white matter were normalized, modulated and smoothed in the group template using intra-subject and inter-subject transformations. The applied smoothing used a Gaussian kernel with 4~mm full width half maximum. For statistical purposes, linear and non-linear transformations between DARTEL's space and International Consortium of Brain Mapping (ICBM) were applied. Each subject and average subject's segmentation was carefully inspected to ensure robustness of the process. In the intra-subject template, we capture the volume variation between two timepoints by subtracting the timepoint's jacobian. We estimate how quickly the change occurs by dividing the variation with respect to the time difference between the two timepoints. This velocity, modulating the intra-subject gray matter, is registered to the group template.

Cross-sectional baseline T1 processing (for control VBM)

Following bias correction and segmentation as described, subjects' baselineT1-weighted images and images from 44 age and sex matched, β-amyliod negative healthy comparison subjects were also warped to create a study-specific group template using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL).[7] In this group template, gray matter and white matter tissues were modulated and smoothed using a Gaussian kernel with 4~mm FWHM. Each subject's segmentation was carefully inspected to ensure robustness of the process.

Diffusion Tensor imaging processing

We reconstructed the diffusion tensor images following the principals from Basser and Pierpaoli, 1996.[8] Diffusion imaging processing began with denoising.[9] Then images were realigned to the primary volume of the sequence, using FSL MCFLIRT algorithm.[10] Data reflecting absolute displacement parameters beyond 1mm were screened out and removed if necessary. Background voxels not considered as brain tissue were then masked out of the DWI volumes by applying a median otsu function. This function utilized the B0 acquisitions to provide a mask using otsu thresholding with a 4mm radius and 4 iterations to minimize intra-class variance.[11] We used the re-aligned diffusion images, the mask, and the b-vectors and b-values in the eddy current-induced distortions correction process.[12] Angular parameters, output of the previous step, are used to correct the b-vectors directions. Diffusion tensors were then fitted using Dipy with a non-linear least-squares approach.[11] Diffusion metrics, fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD), derived from the fitted tensor are reconstructed in the native space for quality control.

Post processing steps included construction of a group template and normalization of diffusion tensors into standard tensor space. Tensor Based Registration was completed trough using DTI-TK.[13] DTI-TK implements a tensor-based registration paradigm, maximizing the alignment of white matter structures and minimizing interpolation of DTI images. Intra-subject templates were created through iterative linear and non-linear registration of baseline and follow-up diffusion tensor images. A similar process was repeated at the inter-subject level using the intra-subject templates to create a study specific template. Deformations from native space to intra-subject space and from individual subject to group space were concatenated and applied to individual timepoint images bringing them to group space. Once in group space, diffusion tensor images were diagonalized to extract the diffusion metrics like fractional anisotropy and mean diffusivity. Regions of Interest were extracted from the ICBM-DTI-81 white matter labels and tract atlas.[14]

E. Methods for functional MRI scan acquisition, processing and head motion exclusion criteria

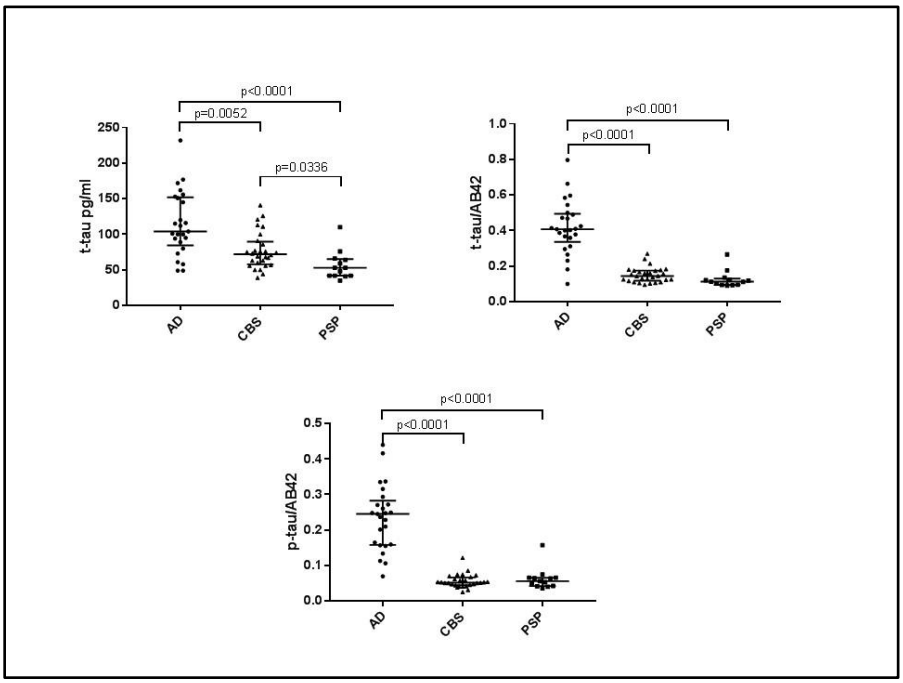
Resting state functional MRI scans were obtained as previously described.[15] Publications after the study was completed suggested that stronger functional connectivity maps would be achieved with the following new seed regions chosen: right angular gyrus for AD, left paracingulate gyrus for PSP and right postcentral gyrus for CBS.[15-17] Functional MRI images were obtained over 8 minutes, during which participants were instructed to relax with their eyes closed, using a T2*-weighted gradient echo planar imaging sequence (repetition time = 2000 ms; 240 volumes; echo time = 27 ms; flip angle = 80°; field of view = 230 x 230 mm2; inplane voxel size = 2.5 mm2; matrix size = 92 x 92). The sequence was acquired with an online gradient adjustment to compensate for head motion.
Functional imaging data were analyzed using Statistical Parametric Mapping (SPM)12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the FMRIB Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl/). After discarding the first 5 volumes to allow for magnetic field stabilization, functional images were slice-time corrected, spatially realigned, co-registered to each participant's structural T1-weighted image, normalized to the Montreal Neurological Institute (MNI) T1 template using SPM segment, re-sampled to a voxel resolution of 2 mm3, and smoothed with a 6 mm full-width at half-maximum Gaussian kernel. To reduce the effect of low frequency drift and high-frequency noise, a band pass filter ranging between 0.0083-0.15Hz was applied.

Because head motion can induce spurious correlations in fMRI signals,[18] only participants who fulfilled all of the following criteria were included into the study: maximum translational movement ≤3 mm, maximum rotational movement ≤3°, and maximum displacement ≤3 mm between functional volumes, and spikes (=max displacement > 1 mm) occurring in less than 10% of all 235 volumes.

F. Methods for arterial spin label (ASL) perfusion MRI processing.

ASL data was processed to obtain partial volume corrected maps of gray matter perfusion as previously described .[19-21] Frames of the ASL acquisition were corrected for motion, co-registered with the first frame (M0) using FSL,[22] and differential perfusion images were created by subtracting unlabeled from adjacent labeled frames and averaging these subtraction images.[23] Susceptibility artifacts along the phase-encoding direction were corrected in the M0 frame and perfusion map using ANTs-SyN restricted to the coronal axis.[24] An automatic quality control process removed tagged/untagged pair of frames when the relative root mean square (RMS) distance value between two consecutive frames was higher than 0.5 mm. The subject was dropped if this RMS value was higher than 1 mm. Cerebral Blood Flow (CBF) was calculated by applying the Buxton kinetic model to the perfusion map.[25,26] Partial volume correction was based on the tissue segmentation maps from MPRAGE using the transformation matrix from T1 to M0.[20,27] Analyses of partial volume corrected mean perfusion were performed for the same regions used in the structural analysis. All CBF images were visually inspected in the native and MNI spaces. Poor quality images out of the field of view, with large susceptibility or motion artifacts were removed from the study.

eFigure. Baseline CSF tau, p-tau/Aβ42, and t-tau/Aβ42 Differences



Differences are shown between Alzheimer's disease (AD), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) diagnostic groups.

eTable. TPI-287 Concentration in Plasma (ng/mL) and CSF (ng/mL) in Selected Time Points

	Dose panel	Screening	Pre-infusion	Time after infusion start		Time after infusion end		End of study	
		CSF	plasma 0m	plasma 30m*	Plasma 60m*	plasma 5m	plasma 60m	plasma 1 week post last infusion	CSF
AD	Placebo	0	0	0	0	0	0	0	0
	2 mg/m^2	0	0	21 (6·4)	24·1 (8·8)	14·6 (2·9)	5·1 (2·5)	0	0
	6.3 mg/m^2	0	0	104·3 (34·7)	112·9 (47·2)	77·1 (20·8)	27 (4·9)	0	0
	20 mg/m^2	0	0	NA	NA	199·7 (15·4)	75·4 (17·3)	0	0
4RT	Placebo	0	0	0	0	0	0	0	0
	2 mg/m^2	0	0	27 (7·7)	31·4 (8·9)	22·6 (7·3)	15·4 (27·8)	0	0
	6.3 mg/m^2	0	0	74·5 (38·1)	67·8 (31·8)	61·9 (23·4)	21·2 (5·2)	0	0
	20 mg/m^2	0	0	NA	NA	165·3 (57)	59·5 (15·5)	1·1 (2·1)	0

Data are mean (SD). m minutes, NA data not available

*PK tested in 10 AD (8 in 2 mg/m^2 cohort, 2 in 6.3 mg/m^2 cohort) and 19 4RT (15 in 2 mg/m^2 cohort with 8 PSP patients, 4 in 6.3 mg/m^2 cohort with 4 CBS patients

eResults. Supplement Narratives for Serious Adverse Events

One participant in the low dose AD cohort received the second study drug infusion at 14:35. Pre-infusion vitals at 1430 were 96/55 mmHg, 44 bpm, 16 bpm and 36.8℃. Within one minute of infusion, participant declared chest tightness, shortness of breath and was observed to have developed a deep flush covering face and upper body. At 14:38, study drug infusion was stopped, normal saline infusion starred and vitals were 150/80 mmHg, 80 bpm, 14 bpm, O2 saturation was 97%. Albuterol inhaler and epinephrine injection as administered and participant transferred to emergency room for observation. Vital signs and participant symptoms returned to baseline levels at 1530. 60mg prednisone and 20mg prednisone x 3 days was ordered by emergency room physician at 16:00 and participant returned home without further incidents at 21:40.

One participant in the high dose AD cohort received the second study drug infusion at 12:05. Pre-infusion vitals were 144/74 mmHg, 47bpm, 16 bpm, 36.1℃. At 1209, participant experienced chest pain, pressure, dyspnea and flushing of face and trunk. The infusion was stopped at 12:11. Symptoms improved after infusion was stopped, and serum CK/troponins and EKG were within normal limits. Vitals recorded at 12:27 were 135/78 mmHg, 53 bpm, 16 bpm, 36.2℃. No further symptoms were reported.

One participant in the high dose AD cohort received the second study drug infusion at 11:00. Pre-infusion vitals were 116/63 mmHg, 58 bpm, 18 bpm, 36.4℃. At 11:07 participant complained of chest tightness, shortness of breath, nasal congestion and nausea. Flushing and perspiration was observed. Albuterol inhaler and diphenhydramine were administered. EKG was within normal limits. The participant’s symptoms resolved rapidly and participant was transferred to emergency room for observation at 11:46 and discharged at 13:54 with 8 day prednisone taper. No further symptoms were reported.

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