THE LANCET Neurology

## Supplementary webappendix

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# Supplemental Methods for Davunetide for Progressive Supranuclear Palsy: a multicenter, randomized, double-blind, placebo controlled trial.

## *A. Methods for automated volume estimation by label propagation on T1 weighted Magnetic Resonance Images:* Application to Midbrain and Superior Cerebellar Peduncle

### 1. Custom template and atlas label creation

#### 1.1 Mayo Clinic Patients for custom template creation

We identified a set of 55 subjects with probable Alzheimer's Disease (AD), and 55 PIB-negative cognitively normal (CN) patients who had undergone a standardized Magnetic Resonance Imaging (MRI) exam as participants in the Mayo Clinic Alzheimer's Disease Research Center (ADRC) and the Mayo Clinic Study of Aging (MCSA). The 55 AD and 55 CN subjects were matched on age, gender and education. The PIB-negative status of the CN subjects was defined as global PIB scaled uptake value ratio less than 1.4. We applied this PIB-negative criterion in order to exclude CN subjects who have indication of early AD pathology. We included AD patients in the custom MRI template to account for potential cortical atrophy that can occur in PSP. We did not have sufficient numbers of PSP patients prior to this study to create a PSP-specific template.

#### 1.2 Unbiased average template creation

In order to create an average template from the 110 Mayo subjects, we first used an iterative rigid body co-registration routine using the co-registration algorithm in SPM5 [1]. For each iteration of the rigid body registration, we registered all 110 images to their mean, in order to produce an unbiased mean image. We did this for 10 iterations, recomputing the mean after each iteration, allowing for 6 degrees of freedom (DOF) in the registration parameters, followed by 10 iterations allowing 9DOF. We concatenated and applied all these linear registration parameters to the original images, then resliced all 110 co-registered images to uniform voxel dimensions of 1mm by 1mm by 1mm. Next, in order to create a crisp nonlinearly aligned group average, we used the ANTS software package [2], which provides a method for iterative nonlinear diffeomorphic registration between all input images. Proceeding iteratively, we used the greedy version of the Symmetric Normalization (greedy-SyN) warping algorithm, driven by a cross-correlation similarity metric, to spatially align all 110 images to their unbiased mean. We then computed a new unbiased mean and repeated the process for a total of four iterations, to arrive at the final custom template.

#### 1.3 Midbrain and Superior Cerebellar Peduncle atlas label creation

Using our unbiased custom template described above as an anatomical reference, one rater traced the superior cerebellar peduncle and midbrain volume using previously published guidelines [3,4] in Analyze software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). All three orientations were viewed to guide the tracing. The final traced masks are shown overlaid on the custom unbiased template in figure 1. The midbrain is shown in blue and the right and left superior cerebellar peduncles in red.

#### 1.4 Image Preprocessing for the unbiased template image

We processed the unbiased image through the following steps in a fully automated pipeline. First, using SPM5 unified segmentation, and a set of custom tissue priors and template [5], we obtained grey matter (GM) white matter (WM) and cerebrospinal fluid (CSF) probability images,, and discrete cosine transformation (DCT) normalization parameters required to spatially normalize the image to the SPM5 template space.

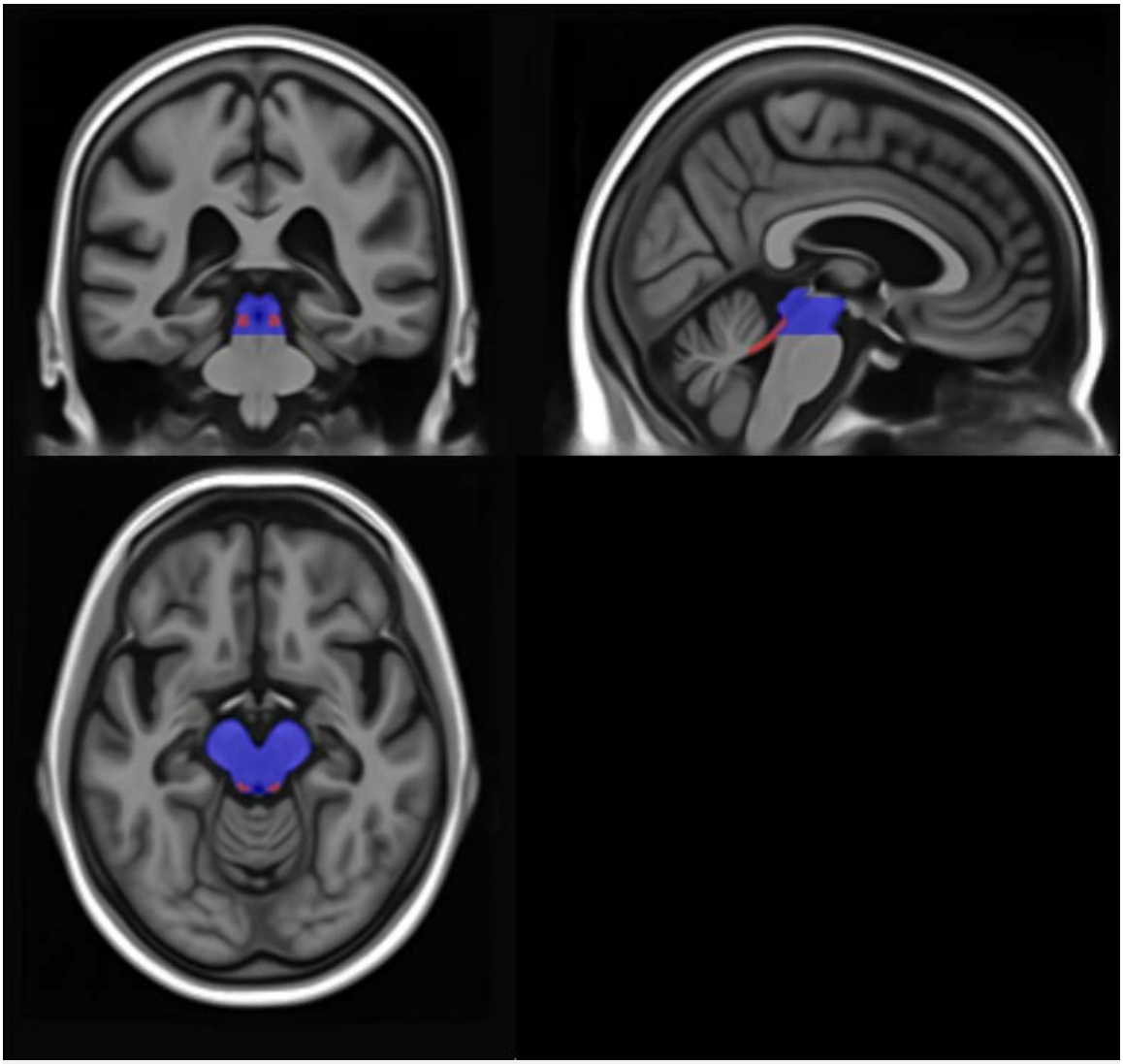

Figure 1: The custom unbiased template with the hand-traced midbrain (blue) and right and left superior cerebellar peduncles (red).

2. Automated mask propagation

### 2.1 Data Processed

We processed all available T1 weighted MRI exams from the AL-108-231 study.

### 2.2 Image Preprocessing for each individual image

We processed each incoming image through the following steps in a fully automated pipeline. For each image, first, using SPM5 unified segmentation, and a set of custom tissue priors and template [5], we obtained grey matter (GM) white matter (WM) and cerebrospinal fluid (CSF) probability images, which we used to create an approximate intra-cranial mask, for inclusion in initial inhomogeneity correction via N3 [6]. We then re-run SPM5 unified segmentation on the N3 corrected image to yield a bias corrected image, updated GM, WM, and CSF probabilities, and discrete cosine transformation (DCT) normalization parameters required to spatially normalize the image to the SPM5 template space, as well as the inverse DCT parameters which can be used to propagate images from the SPM5 template space back to the subject's native space. Combining the unbiased template's DCT parameters from section 1.4 with the inverse DCT parameters for each subject, we propagate the midbrain and SCP masks from the unbiased template to the subject's native space, using the SPM5 template space as a pass through space. The DCT parameters are combined and applied at once, to avoid interpolation artifacts on the final output masks in subject space.

### 2.3 Computation of Midbrain and SCP volumes

After propagating the atlas masks to each individual subject image in its native space, we applied a brain mask to the image to eliminate any spurious CSF voxels that may have been included in the warped mask. Finally, we summed up the number of voxels in each mask, and multiplied by the voxel dimensions in millimeters, to arrive at the fnal

volumes for the midbrain and SCP masks on each subject image.

### 3. References


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## B. Methods for plasma phosphorylated neurofilament heavy chain (pNFH) measurements

Phosphorylated neurofilament heavy chain was detected using a kit (EMD Millipore Corporation, Billerica, MA) based on two polyclonal antisera against high molecular weight bovine pNfH. CPCA-NF-H (chicken anti-pNfH) is used as the capture antibody in this sandwich ELISA while RCA-NF-H (rabbit anti-pNfH) is used as the secondary. The immune complex is detected with commercial goat anti-rabbit detection antibodies. Both anti-pNfH antisera are specific for pNfH, recognizing some lower molecular weight phosphoforms but they do no recognize dephosphorylated species. The ELISA method was originally published by Shaw et al 2005, and has been used in a number of studies looking at pNfH in disease.

### Reference


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## C. AL-108-231 Ocular Motor Substudy Protocol

### 1. Introduction

Progressive Supranuclear Palsy (PSP) is named for its characteristic oculomotor impairments (1). A variety of oculomotor impairments have been described in PSP including impairments in saccades (both reflexive and voluntary), pursuit and eyelid function (2-5). Clinically, individuals with PSP are known to show progressive worsening of their oculomotor function over time (6) (7), particularly reductions in the velocity and gain of saccades. These impairments most prominently affect saccades in the vertical plane, but most individuals will eventually experience impaired horizontal eye movements as well. Vertical eye movement abnormalities are correlated with dorsal midbrain atrophy in PSP and related disorders suggesting they are good measures of brainstem damage. (8)

### 2. Rationale

These findings suggest that measurements of vertical and horizontal saccades in PSP may be sensitive biomarkers of disease progression that could potentially reveal treatment effects in clinical trials. Since there are few longitudinal studies of saccade function in PSP over the course of one year, the rates of change of saccade variables and their test-retest reliability are not known. This exploratory substudy will take place at a small number of sites who have the necessary equipment and expertise to perform quantitative saccade measurements in PSP.

Saccade impairments associated with PSP (Richardson's Syndrome) include increased latency of initiation, decreased velocity and decreased gain. (2) These parameters will be measured as part of this substudy.

Additionally, oculomotor impairments in PSP often include difficulty in suppressing reflexive visually-guided saccades on antisaccade tasks where the instruction is to look in the opposite direction from a target. Thus, the percentage correct on an antisaccade task will be used as an additional outcome measure.

### 3. Objectives

The objectives of this substudy are to assess whether davunetide treatment leads to changes in:

- The dynamic properties of saccades in individuals with PSP; and
- The rate of progression of horizontal and vertical saccade abnormalities in PSP.

### 4. Endpoints

- Mean latency of 10 degree horizontal saccades*
- Mean first gain of 10 degree vertical saccades*
- Mean latency of 10 degree vertical saccades
- Mean peak velocity of 10 degree horizontal saccades
- Mean peak velocity of 10 degree vertical saccades
- Mean first gain of 10 degree horizontal saccades
- Mean end gain of 10 degree vertical saccades
- Mean end gain of 10 degree horizontal saccades
- Mean percentage of correct antisaccade responses

* reported in manuscript; other data not shown

### 5. Participating Sites

The following sites have agreed to participate in the Ocular Motor substudy: University of California, San Francisco: UCSF Memory and Aging Center; The Alfred Hospital (Melbourne, Australia); University of Munich: Klinikum Grosshadern (Germany); Hopital de la Pitie-Salpetriere (Paris, France); University of Chicago Medical Center; Johns Hopkins University Hospital (Baltimore, MD); and Case Western University Medical Center (Cleveland, OH).

## 6. Procedures

Vertical (up or down) and horizontal (left or right) visually-guided saccades will be recorded using the standard high-speed infrared oculography procedures available in each investigator's laboratory.

Subjects should be seated in a darkened room with head stabilized on a chin rest or equivalent device. Information regarding experimental apparatus, equipment and analysis tools will be recorded at the beginning of the study for each site. Any alterations to these parameters must be reported to the Sponsor.

### 6.1. Stimuli and Stimulus Presentation

Targets should consist of bright spots that subtend 0.1-0.3deg of visual angle and should be presented against a dark background. Targets should be high-contrast, and the luminance of target and background should be recorded at the beginning of the study for each site.

Three types of tasks will be presented: fixation, prosaccades, and antisaccades.

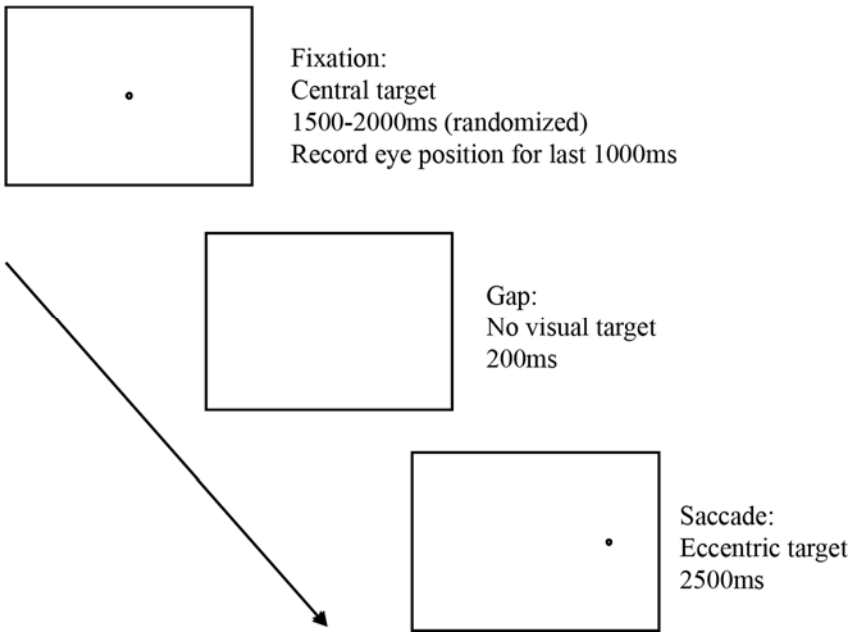
- Fixation. Fixation trials will be used to assess and monitor square-wave jerks and other abnormalities in gaze stability. Fixation trials will consist of a central target illuminated for 10 s. Two fixation trials should be measured before the prosaccade trials. An additional two fixation trials should be presented after the prosaccade trials, and a final set of two trials should be presented following the antisaccade trial block.

- Vertical and horizontal, visually-guided (pro-) saccades. Prosaccade trials consist of randomly interleaved 5 and 10 degree saccade targets presented up, down, left, or right of center (a total of 8 possible positions). For simplicity's sake, a saccade towards a 10-degree eccentric target will be referred to as a "10 degree saccade", although for many patients, the amplitude of the initial saccade to the target will not reach 10 degrees. Each trial will begin with illumination of a central fixation spot for 1500-2000 ms. This initial fixation period should be randomized to avoid anticipation effects; randomization is left to the individual investigator. Eye position should be recorded for the final 1000ms of fixation and for the remainder of the trial. At the end of the fixation period, a "gap" of 200ms will occur where no target or fixation is illuminated. After the blank screen gap, a target will appear at one of the 8 possible eccentric positions, and remain illuminated for 2500 ms. Subjects are instructed to look at the central fixation point while it is illuminated, then to look as quickly and as accurately as possible at the eccentric target. Trial timing is indicated below in this schematic example of a 10 degree rightward saccade.

  A minimum of seven responses should be recorded for each stimulus location. Analysis will focus only on the 10 degree trials.

- Horizontal antisaccades. Visually, these trials are identical to horizontal proscaccade trials; however, the instructed response is different. Only targets located 10 degrees left or right of center are used. Antisaccade trials begin with the illumination of the central fixation point for 1500-2000 ms (randomized). Eye position should be recorded for the final 1000 ms of fixation and for the duration of the trial. After a 200 ms gap with a blank screen, a target appears 10 degrees to the right or left and remains illuminated for 2500 ms. Subjects are given instructions to "Look at the target when it is in the center. When the target moves, look away from the target that appears on the side, and instead at the corresponding spot in the opposite direction. If you make a mistake try to correct yourself." Subjects should verbally confirm their understanding of the task, and be given a total of 10 practice trials prior to recording responses. At least ten responses (preferably 20) should be recorded in each direction for a total of 20-40 responses.

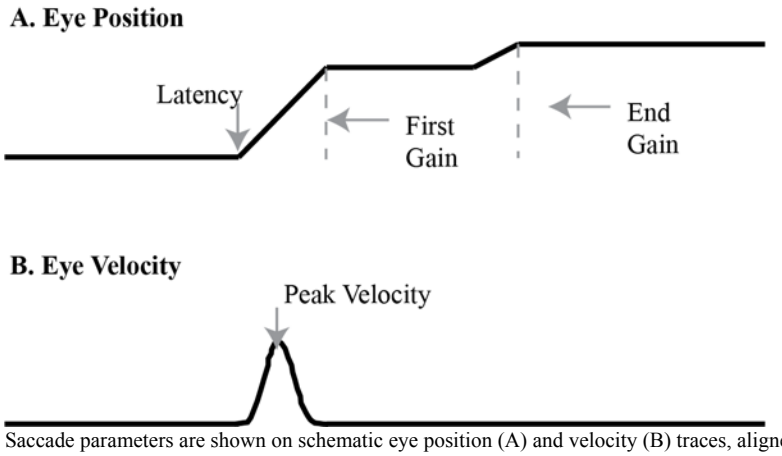
**Figure 1. Time course of saccade trials.**




### 6.2. Analysis

- General considerations. Eye position and velocity traces from each trial should be visually inspected for tracking quality. Velocity should be calculated as the derivative of position. The velocity threshold for determination of saccade onset is 10 degrees/second. Although most investigators will be able to generate digital output files corresponding to raw or analyzed data, for regulatory reasons, paper Case Report Forms (CRFs) will be used to record data for this substudy.

**Figure 2. Saccade Parameters**




Saccade parameters are shown on schematic eye position (A) and velocity (B) traces, aligned in time (x-axis, ms) on the onset of the eccentric saccade target.

- Prosaccades. For both horizontal and vertical prosaccades, the primary outcome measures are latency, peak velocity and gain. (Section 2). Latency from target onset (ms), saccade gain (amplitude in degrees), and

peak saccade velocity (degrees/second) should be determined for the initial saccade in each trial and recorded. Peak velocity is the maximal value during the initial saccade. Because many subjects will not be able to make a full 10 degree saccade, we are primarily interested in the initial saccade gain (First gain). However, as an exploratory measure that might potentially display a treatment effect, the final gain attained during each trial (End gain) will also be recorded.

- Antisaccades. An antisaccade trial is scored as correct if the first saccade after fixation offset has an amplitude > 3 degrees and is in the opposite direction from the target. Saccades within the first 100 msec of eccentric target illumination are excluded as these are likely to be express saccades. Antisaccade self-corrected errors are recorded as correct antisaccades that occur within 500 ms after the initial erroneous prosaccade. Self-corrected errors should also be recorded. The primary outcome measure will be a simple percentage of correct responses for each subject at each timepoint.

**Table 1: Timeline**

Laboratory measurement of saccades will occur at baseline (Visit 2), Visit 5, and at endpoint (Visit 7).

## 7. References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**D. Complete Study Inclusion and Exclusion Criteria**

**Inclusion Criteria:**
Subjects may be included in the study only if they meet all of the following criteria:

1. Probable or possible progressive supranuclear palsy defined as:
   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.
2. Aged 41 to 85 years at the time of screening (Visit 1).
3. Judged by investigator to be able to comply with neuropsychological evaluation at baseline and throughout the study.
4. Must have reliable caregiver accompany subject to all study visits. Caregiver must read, understand, and speak local language fluently to ensure comprehension of informed consent form and informant-based assessments of subject. Caregiver must also have frequent contact with subject (at least 3 hours per week at one time or at different times) and be willing to monitor study medication compliance and the subject's health and concomitant medications throughout the study.
5. Modified Hachinski score ≤ 3. This modified Hachinski will not include the focal neurological signs, symptoms or pseudobulbar affect questions, given the prominence of all 3 in PSP.
6. Score ≥ 15 on the Mini-Mental State Examination (MMSE) at screening (Visit 1).
7. Written informed consent provided by subject (or legally-appointed representative, as appropriate) and caregiver (if not the legally-appointed representative) who are both fluent local language speakers.
8. Subject resides outside a skilled nursing facility or dementia care facility at the time of screening (Visit 1), and admission to such a facility is not planned. Residence in an assisted living facility is allowed.
9. If the subject is receiving CoQ10, levodopa/carbidopa, levodopa/benserazide, a dopamine agonist, catechol-o-methyltransferase (COMT) inhibitor, or other Parkinson's medication, the dose must have been stable for at least 90 days prior to the screening visit (Visit 1) and must remain stable for the duration of the study. No such medication can be initiated during the study.
10. Able to tolerate the MRI scan during screening.
11. Able to ambulate independently or with assistance defined as the ability to take at least 5 steps with a walker (guarding is allowed provided there is no contact) or the ability to take at least 5 steps with the assistance of another person who can only have contact with one upper extremity.
12. Presence of symptoms for less than 5 years or the presence of symptoms for more than 5 years with a PSPRS baseline score ≥ 40.
13. Stable on other chronic medications for at least 30 days prior to screening.

**Exclusion Criteria**
Subjects will be excluded from the study for any of the following reasons:

1. Insufficient fluency in local language to complete neuropsychological and functional assessments.
2. A diagnosis of Amyotrophic Lateral Sclerosis (ALS) or other motor neuron disease.
3. Any of the following:
   a. Abrupt onset of symptoms defined in inclusion criteria 1 associated with ictal events,
   b. Head trauma related to onset of symptoms defined in inclusion criteria 1,
   c. Severe amnesia within 6 months of the symptoms defined in inclusion criteria 1,
   d. Cerebellar ataxia,
   e. Choreoathetosis,
   f. Early, symptomatic autonomic dysfunction, or
   g. Tremor while at rest.
4. Presence of other significant neurological or psychiatric disorders including (but not limited to) Alzheimer's disease; dementia with Lewy bodies; prion disease; Parkinson's disease (which has not subsequently been revised to PSP), any psychotic disorder; severe bipolar or unipolar depression; seizure

disorder; tumor or other space-occupying lesion; or history of stroke or head injury with loss of consciousness for at least 15 minutes within the past 20 years.

5. Within 4 weeks of screening (Visit 1) or during the course of the study, concurrent treatment with memantine; acetylcholinesterase inhibitors; antipsychotic agents (other than quetiapine) or mood stabilizers (e.g., valproate, lithium); or benzodiazepines (except as below).
    a. Low dose lorazepam may be used for sedation prior to MRI scans for those subjects requiring sedation. At the discretion of the investigator, 0.5 – 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. No more than a total of 2 mg lorazepam may be used for any MRI scan. Neuropsychological testing may not be performed on the same day of lorazepam administration. Subject and study partner must be informed of risks of lorazepam use prior to administration.
    b. Subjects who take short acting benzodiazepines (only temazepam or zolpidem are allowed) for sleep may continue to do so if they have been on a stable dose for 30 days prior to screening.
    c. Clonazepam may be used for treatment of dystonia or painful rigidity associated with PSP if the dose has been stable for 90 days prior to screening and is not expected to change during the course of the study.
6. Treatment with lithium, methylene blue, tramiprosate, ketone bodies, latrepirdine, or any putative disease-modifying agent directed at tau within 90 days of screening (Visit 1).
7. A history of alcohol or substance abuse within 1 year prior to screening (Visit 1) and deemed to be clinically significant by the site investigator.
8. Any malignancy (other than non-metastatic dermatological condisitons) within 5 years of the screening visit (Visit 1) or current clinically significant hematological, endocrine, cardiovascular, renal, hepatic, gastrointestinal, or neurological disease. For the non-cancer conditions, if the condition has been stable for at least the one year before the screening visit (Visit 1) and is judged by the site investigator not to interfere with the subject's participation in the study, the subject may be included.
9. Clinically significant laboratory abnormalities at screening(Visit 1), including creatinine $\geq$ 2.5 mg/dL, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 3 times the upper limit of the normal reference range, vitamin B12 below the laboratory normal reference range, or thyroid stimulating hormone (TSH) above the laboratory normal reference range.
10. The systolic blood pressure measurement is > 190 or < 85 mm Hg. The diastolic blood pressure measurement is > 105 or < 50 mm Hg at screening (Visit 1).
11. Abnormal ECG tracing at screening (Visit 1) and judged to be clinically significant by the site investigator.
12. Treatment with any investigational drugs or device within 90 days of screening (Visit 1).
13. Known history of serum or plasma progranulin level less than one standard deviation below the normal subject mean for the laboratory performing the assay.
14. Known presence of known disease-associated mutation in TDP-43, PGRN, CHMPB2 or VCP genes or any other frontotemporal lobar degeneration (FTLD) causative genes not associated with underlying tau pathology (e.g., Chromosome 9 associated FTD).
15. History of deep brain stimulator surgery other than sham surgery for deep brain stimulation (DBS) clinical trial.
16. History of early, prominent rapid eye movement (REM) sleep behavior disorder.
17. Women who are pregnant or lactating and women of childbearing potential who are not using at least two different forms of medically recognized and highly effective methods of birth control, resulting in a low failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.
18. An employee or relative of an employee of the Sponsor, a clinical site, or contract research organization (CRO) participating in the study.
19. Significant anatomical nasal abnormality (e.g., septal deviation obstructing airflow to at least one nostril or septal perforation) or history of nasal turbinate surgery.
20. History of a clinically significant medical condition that would interfere with the subject's ability to comply with study instructions, would place the subject at increased risk, or might confound the interpretation of the study results.
21. Contraindication to the MRI examination for any reason (e.g., severe claustrophobia, ferromagnetic metal in body).
22. Structural abnormality on the MRI that precludes diagnosis of PSP, such as cortical infarct in brain region that might account for subject's symptoms.

23. In subjects receiving anti-Parkinson's Disease medication at the time of screening (Visit 1), in the opinion of the investigator substantial worsening of motor signs or symptoms compared with normal functioning following overnight withdrawal of the anti-Parkinson medication.
24. Known hypersensitivity to davunetide or any ingredient of the formulation.