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Sodium selenate as a disease-modifying treatment for progressive supranuclear palsy: protocol for a phase 2, randomised, double-blind, placebo-controlled trial

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ABSTRACT

Introduction Progressive supranuclear palsy (PSP) is a neurodegenerative disorder for which there are currently no disease-modifying therapies. The neuropathology of PSP is associated with the accumulation of hyperphosphorylated tau in the brain. We have previously shown that protein phosphatase 2 activity in the brain is upregulated by sodium selenate, which enhances dephosphorylation. Therefore, the objective of this study is to evaluate the efficacy and safety of sodium selenate as a disease-modifying therapy for PSP.

Methods and analysis This will be a multi-site, phase 2b, double-blind, placebo-controlled trial of sodium selenate. 70 patients will be recruited at six Australian academic hospitals and research institutes. Following the confirmation of eligibility at screening, participants will be randomised (1:1) to receive 52 weeks of active treatment (sodium selenate; 15 mg three times a day) or matching placebo. Regular safety and efficacy visits will be completed throughout the study period. The primary study outcome is change in an MRI volume composite (frontal lobe+midbrain–3rd ventricle) over the treatment period. Analysis will be with a general linear model (GLM) with the MRI composite at 52 weeks as the dependent variable, treatment group as an independent variable and baseline MRI composite as a covariate. Secondary outcomes are change in PSP rating scale, clinical global impression of change (clinician) and change in midbrain mean diffusivity. These outcomes will also be analysed with a GLM as above, with the corresponding baseline measure entered as a covariate. Secondary safety and tolerability outcomes are frequency of serious adverse events, frequency of down-titration occurrences and frequency of study discontinuation. Additional, as yet unplanned, exploratory outcomes will include analyses of other imaging, cognitive and biospecimen measures.

Ethics and dissemination The study was approved by the Alfred Health Ethics Committee (594/20). Each participant or their legally authorised representative and their study partner will provide written informed consent at trial commencement. The results of the study will be presented at national and international conferences and published in peer-reviewed journals.

Trial registration number Australian New Zealand Clinical Trials Registry (ACTRN12620001254987).

Strengths and limitations of this study

- A large placebo-controlled, double-blind randomised controlled trial of a new drug treatment for progressive supranuclear palsy.
- The collection of a large body of clinical, cognitive and imaging data will result in a highly characterised prospective patient cohort, which will inform the field for future selection of clinical trial outcome measures.
- The use of both established and novel diagnostic methods may result in the validation of new diagnostic and prognostic approaches for future application in both clinical and research settings.
- The long treatment duration could impact participant completion due to disease progression.

INTRODUCTION

Progressive supranuclear palsy (PSP) is a rare, rapidly progressing, neurodegenerative movement disorder. Richardson's syndrome (PSP-RS) is the classical and most common form of PSP. It is a Parkinsonian disorder, characterised by vertical oculomotor (OM) dysfunction, frontal dysexecutive dysfunction and postural instability and falls. The prevalence rate is approximately 6 per 100 000 people,[1] with typical survival being 7–8 years from symptoms onset.[2] There are currently

no approved disease-modifying treatments for PSP, and none of the limited number of international clinical trials that have been conducted to date have been successful.[3 4] Therefore there is a major unmet clinical need for the treatment of PSP.

PSP is considered pathologically in the group of diseases termed 'tauopathies' which are characterised by the accumulation of hyperphosphorylated inclusions of the microtubule-associated protein *tau*, which in patients with PSP initially accumulates in the basal ganglia and deep nuclei of the cerebellum, before spreading to other cortical and subcortical brain regions.[5] Thus, hyperphosphorylated tau is a potential target for the treatment of PSP that warrants exploration in randomised clinical trials.

Pharmacological reduction of tau hyperphosphorylation may be achieved by two broad approaches: (1) inhibition of tau phosphorylation through action on serine/threonine kinases, the group of enzymes responsible for phosphorylation, or (2) increasing dephosphorylation of hyperphosphorylated tau by activating tau serine/threonine phosphatases, the group of enzymes that dephosphorylate proteins. Protein phosphatase 2 (PP2A) is the major tau phosphatase in the brain accounting for more than 70% of brain phosphatase activity, and thus stimulation of its activity presents a compelling strategy for reducing hyperphosphorylated tau.[6] PP2A is colocalised with tau, and in many neurodegenerative diseases, reduced PP2A activity is observed alongside reductions in tau dephosphorylation.[7–9]

The trace metal selenium is an essential element in humans. It is present in low concentrations in the environment and in foods such as Brazil nuts. Previously, dietary supplementation with selenium has been reported to have potential chemopreventive benefits,[10] however, this has been limited to selenium, with the potential therapeutic benefits of other selenium compounds yet to be comprehensively investigated. Work by our team and others is amassing a large growing body of preclinical, and emerging clinical data, demonstrating that sodium selenate, a selenium salt, may have potential as a therapeutic agent. Our work has demonstrated that through the activation of PP2A increasing rates of dephosphorylation, sodium selenate has potential as a disease-modifying treatment in neurodegenerative diseases associated with hyperphosphorylated tau, as well as epilepsy and traumatic brain injury.[11–21] We have reported sodium selenate provides benefits in a range of animal models of disease including Alzheimer's disease (AD),[13 22] cancer,[12] traumatic brain injury[11 18 19] and epilepsy.[15 16 18 21] Moreover, these benefits were specific to sodium selenate, with no benefits observed with other selenium species, and were only observed when supranutritional doses were administered.[17 23]

Three clinical trials completed by our team have demonstrated the safety and tolerability of chronic dosing with sodium selenate in clinical populations other than PSP. The first study was a phase 1 safety and tolerability study in patients with castration-resistant prostate cancer. Safety and tolerability was good, with doses up to 60 mg per day being well-tolerated, and dose-limiting toxicity observed at 90 mg per day.[12] A phase 2a trial in patients with mild-moderate AD (n=40), confirmed the safety and tolerability of sodium selenate (30 mg/day) at this dose over 6 months.[17 23] In exploratory efficacy analyses, diffusion tensor imaging (DTI) measures indicated relatively less neurodegeneration in the treatment group compared with the combined placebo/nutritional dose group. Widespread neurodegeneration was observed on DTI, with the corpus callosum showing the most severe degeneration.[17] Increased selenium levels in serum and cerebrospinal fluid (CSF) of the treatment group demonstrated that the sodium selenate was able to cross the blood-brain barrier and enter the central nervous system.[23] The degree of cognitive decline (measured on the Mini-Mental State Examination) over the 24 weeks of treatment inversely correlated with selenium levels in the CSF, suggesting neuroprotective efficacy may be dependent on greater drug exposure levels.[23] Long-term safety and tolerability were demonstrated in an open-label extension study, where patients with AD received sodium selenate (30 mg/day) for up to 23 months.[24] Furthermore, cognitive decline measured on the Alzheimer's Disease Assessment Scale Cognitive Subscale and other psychometric scales showed substantially less decline than would be predicted based on the natural progression of AD.[24]

Most recently we completed a small phase 1b open-label study of sodium selenate treatment at doses up to 45 mg per day in patients with possible behavioural variant frontotemporal dementia (bvFTD), another neurodegenerative disease characterised by hyperphosphorylated tau (ACTRN12617001218381). Safety and tolerability were again excellent, with all patients (n=12) completing the study. Adverse events were mild and similar to those reported in previous studies, the most common being nail changes (58%) and hair loss (42%). Exploratory efficacy measures (MRI, cognition, behaviour) suggested slowing of disease progression in a subgroup of participants (n=7), with the other subgroup (n=4) showing substantial disease progression. This division of 'responders' and 'non-responders' is in keeping with the known incidence of tau and non-tau pathology in bvFTD.[25] Informed by these results we have recently commenced recruitment of a phase 2b placebo-controlled randomised controlled trial of sodium selenate as a treatment for bvFTD (ACTRN12620000236998[26]).

These prior experiences in neurodegenerative diseases defined by aggregation of hyperphosphorylated tau have informed this current study, a multi-centred placebo-controlled, double-blind randomised controlled trial of sodium selenate as a treatment for PSP. The present study closely mirrors our phase 2b trial in bvFTD in overall trial design, schedule of assessments (including safety assessments and outcomes, cognitive measures and exploratory biomarkers) and numerous exclusion criteria.[26]

METHODS AND ANALYSIS

This is a multi-site, phase 2, double-blind, randomised, placebo-controlled trial to assess the safety and efficacy of sodium selenate as a treatment for PSP (RS). Participants will receive either sodium selenate (15 mg, three times a day) or placebo for 52 weeks. Seventy patients will be recruited in to this study. The study will be conducted at six centres in Melbourne, Sydney, Brisbane and Adelaide. The study is funded by the Australian Medical Research Future Fund (GNT1200254). Ethics approval was granted by Alfred Health Human Research Ethics Committee, Melbourne (594/20). The trial is registered with the ANZCTR (ACTRN12620001254987). The study commenced recruitment in July 2021 and is anticipated to complete (last patient last visit) in March 2025.

Outcomes

The primary outcome measure will be a change in MRI composite volume (frontal lobe+midbrain–3rd ventricle) over the 52-week treatment period.

The secondary outcome measures (safety) will be the rate and severity of adverse events and the rate of study withdrawal. Secondary efficacy outcome variables will be the change in PSP symptoms as measured by the PSP rating scale total score, change in disease severity as measured by the clinical global impression of change (CGI-C) total score and change in mean diffusivity (MD) in the midbrain calculated from diffusion-weighted MRI over the 52 weeks of treatment.

Numerous exploratory outcomes will also be measured including changes in protein biomarkers (total-tau, phospho-tau and neurofilament light chain (NfL)) in CSF, plasma and serum, changes in cognitive measures, changes in OM functioning (including measures of motor and cognitive functioning), changes in other structural and functional neuroimaging metrics including regional volumes and cortical thickness, advanced MRI (diffusion imaging, quantitative susceptibility mapping, resting state functional MRI) and tau-binding positron emission tomography (PET) and pharmacokinetic modelling. Advanced statistical modelling will be investigated to identify baseline predictors of treatment response and non-response. Finally, correlation analyses will be used to investigate the relationships between objective biomarkers and the presence and progression of symptoms.

Eligibility criteria

Inclusion criteria

Participants will be aged over 40, have a diagnosis of probable PSP-RS[27] and symptoms present for <5 years at the time of screening. The participant must live in the community and have at least 10 contact hours per week with a responsible carer. The carer should be capable of ensuring the participant's compliance with the medication and study, and complete questionnaires about the participant's symptoms throughout the study. Participants must be using effective contraception for the duration of the trial. Participants must have a lumbar puncture (LP) and MRI performed during screening. The structural brain MRI must be not inconsistent with a diagnosis of PSP-RS with no other gross structural abnormalities indicating another neurological disorder. Written informed consent must be obtained from the participant or their legally authorised representative (as required by local laws and regulations), and the participant's carer.

Exclusion criteria

Participants will be excluded based on: history of substance use disorder (including alcohol and cannabis); previous participation in an interventional clinical trial (within 3 months of screening), with the exception of prior exposure to sodium selenate; known sensitivity to selenium, sodium selenate, any medicine or vitamin containing sodium selenate, similar agents or any of the excipients (including microcrystalline cellulose) used; likely non-compliance with the trial visit schedule or trial medication; evidence or history of neurological, psychiatric or other illness that could contribute to PSP-like symptoms; known history of familial AD or genetic variant that confers likelihood of another neurodegenerative condition (eg, *PRNP, SYNJ1, PSEN1, C9ORF72* expansion); significant comorbid medical (including unstable diabetes) or neurological disease, with the exception of PSP, that is not adequately controlled by therapy and may interfere with the patient's ability to complete the study or affect the patient's cognitive performance; contraindication to MRI or LP; significant impairment of renal, hepatic or haematological function; participant is or has (within 6 weeks of the screening visit) taken any of the following: N-methyl-D-aspartate (NMDA) receptor antagonists, oral and/or injectable steroids, digoxin, phenobarbitone or warfarin; commencement or titration of other medications known to have an effect on mood or cognition within the 4 weeks prior to screening, including anticholinergics, hypnotics, sedatives, anxiolytics, antidepressants, antiepileptics, antipsychotics, memory-enhancing drugs, nutraceuticals and other supplements which contain selenium and dopaminergic drugs.[26]

Intervention, randomisation and blinding

Once consent has been obtained, each participant will be provided a unique screening number. On completion of all screening assessments and confirmation of eligibility, a sequential randomisation number will be generated from within the redcap electronic Case Report Form ((eCRF) subject to entry of key data into the eCRF). Once the randomisation number has been provided to the unblinded site pharmacist, the unblinded pharmacist will dispense the drug/placebo in accordance with the randomisation schedule. Participants will be allocated at a ratio of 1:1 either sodium selenate or placebo for 52 weeks. Each tablet will contain 5 mg of drug or placebo. Participants will titrate from an initial dose of two tablets (10 mg) three times a day, increasing to three tablets (15 mg) three times a day at week 4, subject to tolerability. If an adverse event occurs that is potentially related to the

study drug administration, treatment may be temporarily interrupted, at the discretion of the investigator, a single within-subject dose reduction, to 10 mg three times a day will also be allowed. A further down-titration to 5 mg three times a day will require consultation with and approval by the medical monitor.

Throughout the course of the study, the participant, their study partner and all site staff (with the exception of the pharmacy team) will remain blinded to treatment allocation. Emergency unblinding of individual participants may performed by site pharmacy staff or by accessing individual unblinding envelopes kept on site. The data safety monitoring board (DSMB) will remain blinded to treatment allocation when reviewing safety data. Unblinding of data may be requested by the DSMB in the event of unexpected adverse events for which unblinding is deemed necessary for the assessment of potential causality.[26]

Procedures and assessments

Table 1 outlines the testing and procedures that participants will undergo which is based on our other phase 2 trial in bvFTD.[26] Briefly, at screening, the participant will be reviewed to ensure they meet all the inclusion criteria and none of the exclusion criteria. Neuroimaging (MRI) will follow to corroborate the PSP-RS diagnosis. At baseline, the participant's eligibility will be confirmed by repeated review of the inclusion and exclusion criteria. Baseline tau-PET, CSF sampling and cognitive and symptomatic assessment will be completed. OM testing will be performed in participants who consent to the OM substudy. Finally, the participant will receive their first dose of the study drug (10 mg) in the clinic and multiple blood draws taken for pharmacokinetic analysis.

Safety phone calls to monitor for adverse events will be completed. Subject to tolerability, participants will be uptitrated to three tablets (15 mg three times a day) at week 4. Both solicited and unsolicited adverse events that occur between clinic visits will be recorded in diary cards given to participants.

As detailed in table 1, regular study visits will occur to assess participant safety and well-being, and to ensure treatment compliance and continued supply of the study medication. Additionally at weeks 26 and 52, the cognitive and symptomatic assessment (as well as OM testing for those in the substudy) will be repeated. Repeated neuroimaging (MRI and tau-PET) and CSF sampling for biomarker analyses will occur in the 2 weeks prior to the week 52 clinical visit. A final safety visit will be completed 4 weeks after the end of treatment (week 52) visit.

Measures

Neuroimaging

MRIs will be acquired during the screening period and week 52. The following sequences are included in the MRI protocol: whole-brain volumetric 3D T1-weighted (0.8 mm isotropic voxels), T2-weighted (0.8 mm isotropic) and T2-weighted fluid-attenuated inversion recovery (FLAIR; 0.8 mm isotropic) images; multi-echo T2*-weighted images (0.8 mm isotropic) for susceptibility mapping; multi-shell diffusion-weighted imaging (DWI; 2 mm isotropic) and multi-band resting state functional MRI (2.4 mm isotropic).

The primary study outcome will be the change in MRI composite (frontal lobe+midbrain–3rd ventricle) volume, measured using T1-weighted structural MRI, from baseline to 52 weeks. Change in composite volume will be measured using the method described by Höglinger *et al*.[28] Volumes will be corrected for intracranial volume (ICV), and normalised to the mean ICV for the whole study population.

Tau PET using the second-generation specific tau-binding radiotracer [^{18}F]-PI2620 (Life Molecular Imaging, Berlin, Germany) will be performed at baseline and in the 2 weeks prior to week 52. A dynamic 3D acquisition (10×30 s, 5×60 s, 10×300 s) will begin on intravenous injection of 185MBq (±10%) of the tracer.

Cognitive and symptomatic battery

The cognitive and symptomatic battery, consisting of the following scales will be administered at three timepoints throughout the study, baseline, week 26 and week 52.

PSP rating scale

The PSP rating scale is a clinician-administered quantitative measure of disability in participants with PSP.[29] The PSP rating scale comprises 28 items in 6 areas. The available total score ranges from 0 (normal) to 100. The six areas assessed are: daily activities, mentation, bulbar, ocular motor, limb and gait.

Clinical global impression of change

The CGI-C scale is a clinician-administered scale which measures the change in the patient's clinical status from a specific point in time.[30] Using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change.

Trail Making Test A and B

The Trail Making Test is a test of visual attention, processing speed and task switching. There are two parts to the test, A and B, where the participant is asked to draw lines to connect 25 targets as quickly as possible without making any mistakes. In the first part of the test, the participant is asked to connect sequential numbers in order (1–25). In the second part the targets alternate between numbers and letters (1, A, 2, B, etc). Part A is a measure of processing speed, while part B measures executive function. The number of seconds taken to complete each path are the scores for this assessment.[31]

Frontal assessment battery

The frontal assessment battery is a battery of six short tests which examines executive function.[32] The tests consist of (1) similarities, whereby the participant must identify in what way two objects are similar (eg, banana and orange), (2) verbal fluency, whereby the participant must

Table 1 Schedule of assessments

	Screening	Baseline										
Visit #	**1a**	**2a**	**2b**	**TC1**	**TC2**	**TC3**	**3**	**4**	**5**	**6**	**7**	**8**
Week	**−8 to 0**	**−2**	**0**	**2**	**4**	**6**	**8**	**16**	**26**	**39**	**52**	**56**
Written informed consent	X											
Assess eligibility	X											
Confirmation of eligibility			X									
Medical history	X											
Confirmation of Dx of PSP	X											
MRI scan	X										X	
tau PET scan		X									X	
Lumbar puncture		X									X	
Physical examination	X		X				X	X	X	X	X	X
Vital signs	X		X				X	X	X	X	X	X
12-lead ECG	X		X				X	X	X	X	X	X
Neurological examination	X		X						X		X	
Oculomotor testing (optional)			X						X		X	
PSP rating scale			X						X		X	
CGI-C			X						X		X	
Frontal assessment battery			X						X		X	
Trails A and B			X						X		X	
Digit span (forward and reverse)			X						X		X	
COWAT and CFT			X						X		X	
Victoria Stroop			X						X		X	
Hayling Sentence			X						X		X	
NIH toolbox			X						X		X	
EQ-5D			X						X		X	
BRIEF-A			X						X		X	
C-SSRS	X		X				X	X	X	X	X	X
Haematology	X		X				X		X	X	X	X
Biochemistry	X		X				X		X	X	X	X
Coagulation	X									X		
Blood collected for future exploratory assessments		X					X		X		X	
Blood collected for pharmacokinetic analysis			X				X				X	
Urinalysis (dipstick)	X		X				X		X	X	X	X
Urine pregnancy test			X				X	X	X	X	X	X
Plasma hCG pregnancy test	X											
Dispense drug			X					X	X	X		
Redispense drug							X					
Study drug administration in clinic			X				X					
Dispense diary card			X				X	X	X	X	X	
Review of diary card				X	X	X	X	X	X	X	X	X
Review of AEs/SAEs			X	X	X	X	X	X	X	X	X	X
Review of concomitant medications	X		X	X	X	X	X	X	X	X	X	X

BRIEF-A, Behaviour Rating Inventory of Executive Function A; CFT, Category Fluency Test; CGI-C, clinical global impression of change; COWAT, Controlled Oral Word Association Test; C-SSRS, Colombia Suicide Severity Rating Scale; EQ-5D, European Quality of Life, 5 Dimensions; hCG, human chorionic gonadotropin; PET, positron emission tomography; PSP, progressive supranuclear palsy; SAE, serious adverse event.

name as many words as they can that begin with a particular letter in 60 s, (3) programming, whereby patients are asked to copy then repeat a series of motor acts, (4) conflicting instructions, whereby the participant is asked to tap the table once when the examiner taps it twice, and tap the table twice when the examiner taps it once. After a practice, the trial consists of a series of 10, (5) go/no–go, whereby the participant is instructed to tap the table once if the examiner does so, but do nothing if the examiner taps twice, (6) prehension behaviour, the examiner places the participants hands palms up on their knees and instructs them to do nothing, the examiner then places their hands on the participant's palms and scores according to the participant's response. The score is computed from summing each of the task scores (range 0–18).

Category Fluency Test

The Category Fluency Test is a test of verbal fluency that measures the participant's ability to spontaneously produce words that belong to a specific category (animals). The participant scored on the number of words they can correctly name in 1 min that belong to that category.

Controlled Oral Word Association Test

The Controlled Oral Word Association Test is another test of verbal fluency that also measures executive function. Participants are given a letter of the alphabet and asked to name as many words, within the bounds of test rules (no proper nouns, no repetitions, no identical stem words), that begin with that letter as they can in 1 min. The test is administered three times with three different letters. They are scored on the number of correct responses over the three trials. The whole examination usually takes up to 5 min.[33]

Digit span

The digit span test measures both attention and working memory. A sequence of digits is read to the participant, which the participant must then repeat back to the examiner. The length of the digit sequences becoming increasing longer over the test. The test is administered both forwards and backwards, with two trials presented at each string length. The score is the sum of correct trials repeated under the two conditions.[34]

Victoria Stroop Test

Executive function is measured by the Victoria Stroop Test. Three test conditions are used whereby the participant must name the colour of the ink of the stimulus presented. In the first condition they are presented with dots, in the second neutral words and the third incongruent colours. There are 24 items for each condition.[35]

Hayling Sentence Test

The Hayling Sentence Completion test measures both response initiation and response suppression. The test is entirely verbal, meaning it can be administered to patients who have impairments in reading or visual perception such as those with PSP. The test involves two series of 15 sentences which are missing the final word. For the first part the examiner reads each sentence aloud which the participant must complete as quickly as they can, thus generating a measure of the speed of response initiation. In the second half of the test, the participant must again complete the sentence read to them, but this time with a non-sensical ending, which measures the ability to suppress responses as well as thinking time. The test administration takes approximately 5 min. The test produces three measures of executive function that can be used alone or in combination.[36]

NIH toolbox

The NIH toolbox cognitive battery consists of a number of cognitive tests that can be used alone or in combination to assess global cognitive function. It has been designed for longitudinal measurement of participants' function and is thus validated for repeated administration. The cognitive battery takes approximately 30 min to complete.[37]

European Quality of Life, 5 Dimensions, 5 Levels

The European Quality of Life, 5 Dimensions, 5 Levels is a quality of life scale that comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems, expressed as a single digit (range 1-5).[38] The participant's health state is the combination of these digits in to a 5-digit number. The participant is also asked to mark their health on a visual analogue scale (range 0–100).

Behaviour Rating Inventory of Executive Function A

The Behaviour Rating Inventory of Executive Function A is a participant-administered and informant-administered scale which assesses executive function.[39] In instances where the participant is unable or has limited awareness of their own difficulties, the informant-only report may be used.

The assessment covers nine areas of executive functioning: inhibition, self-monitoring, planning and organisation, attention shifting, initiative task monitoring, emotional control, working memory and organisation of materials. These areas form two broad indices: behavioural regulation and metacognition, as well as an overall global executive composite.

OM testing

In participants who consent to the OM substudy, testing will be carried out at baseline, week 26 and week 52. Horizontal and vertical displacement of both eyes will be recorded using the Saccadometer Research Advanced (Ober Consulting) or the Eyelink 1000 plus dark pupil video-oculography system at a sample frequency of 1000 Hz. These systems incorporate built-in visual targets using miniature laser projectors mounted on a sensor forehead plate, and records average movement of both eyes in response to a number of pre-programmed trials. Participants will be seated 50 cm from

a blank wall. Experimental trials will include: Horizontal saccades (test of basic OM function)—participants will generate saccades to targets that step from centre fixation to either 5° or 10° left or right of centre; vertical saccades (test of basic OM function)—participants will generate saccades to targets that step from centre fixation to either 5° or 10° directly above or below centre; antisaccades (test of inhibitory/executive control)—participants will generate saccades in the mirror-opposite location of targets that step from centre fixation to either 5° or 10° left or right of centre; memory-guided saccades (test of working memory)—participants will generate saccades to the remembered location of a previously presented target that appeared at either 5° or 10° left or right of centre; fixation (test of basic OM function)—participants will maintain fixation on a stationary target that appears at centre or 5° or 10° left or right of centre.

For each task the measures of interest will include: saccade latency, saccade velocity, saccade accuracy and task error. Test results will be stored in the device's memory, downloaded and transferred to the central laboratory to be collated and analysed.

Safety assessments

Each clinic visit will include the following safety assessments: physical examination, 12-lead ECG and haematology, chemistry and urinalysis (all visits except week 16). Neurological examinations will also be completed at screening, baseline, week 26 and 52. The results of these investigations will be reviewed and clinically significant abnormalities will be documented as adverse events. At each clinic visit the participant and their study partner will be asked about any adverse events or concomitant medications, and any adverse events recorded on the diary cards confirmed and recorded.[26]

Blood biomarkers

Pharmacokinetic, biomarker and exploratory blood samples will be collected as detailed in table 1. Blood samples (6 mL/sample) for pharmacokinetics will be taken predose (~1 hour), then 0.5, 1, 2 and 4 hours after dosing at the baseline, week 8, and week 52 visits. Plasma will be stored at −80°C until measurement of sodium selenate levels for establishing the pharmacokinetic profile.

Plasma and serum samples will be taken at baseline, week 8, week 26 and week 52 for exploratory analyses. Additional samples for DNA and RNA will be taken only at baseline. Biomarkers of neurodegeneration including total-tau, phospho-tau, neurofilament light, as well as testing for genes associated with PSP (*MAPT, LRRK2*) will be included in the exploratory analyses. Additional hypothesis driven testing may be performed.[26]

CSF biomarkers

Sampling of CSF will be performed at baseline (pretreatment) and week 52. Approximately 20 mL of CSF will be collected using atraumatic needles (20G) and polypropylene tubes (10 mL) cooled on ice. Samples will remain on ice until they are aliquoted in to 500 µL polypropylene aliquots. Samples will be stored at −80°C until analysis. Planned analyses will measure the proteins total-tau, phospho-tau and NfL. Additional testing of CSF will be performed as new research questions emerge.

Power and sample size

The study is powered to detect a difference in the primary outcome and will therefore be declared positive or negative on the primary outcome measure. The sample size has been determined on the primary outcome variable (MRI composite volume). The annual rate of change of this composite in PSP-RS is −12.9% (SD=7.1).[28] The mean atrophy rate in controls is 3.76%.[40] A sample size of 46 patients (randomised 1:1 into two groups) would be sufficient to detect a medium effect size (Cohen's d=0.50, alpha=5%, power=80%). This equates to detecting a 7% rate of atrophy, which is a 46% reduction in atrophy rate compared with the natural history, which will represent a clinically meaningful treatment effect.

Trials in PSP have high withdrawal rates. Recruitment of 70 participants will allow for up to 30% attrition while ensuring the study remains adequately powered. Previous studies have demonstrated the safety and tolerability of sodium selenate, for this reason there will be no interim safety, efficacy or futility analyses.

Outcomes and statistical overview

Primary endpoint

The primary endpoint measure is the change in MRI volume composite (frontal lobe+midbrain–3rd ventricle) from baseline to week 52 between treatment and placebo groups. The primary analysis will include all participants with a post-baseline MRI. Statistical analysis will use a GLM, with the MRI composite at week 52 as the dependent variable, treatment group as an independent variable, and baseline MRI composite as the covariate.

Secondary endpoints

Descriptive statistics (mean, median, minimum, maximum, SD) by visit will report all continuous secondary efficacy endpoints. Data transformations (such as change and percentage change) will be summarised similarly.

The change from baseline to week 52 in PSPRS, CGI-C and midbrain MD (measured on DWI) will be analysed using a GLM which includes the respective baseline measure as a covariate in the model. The model will estimate the adjusted mean change (with 95% confidence limits) as a marker of treatment.

Safety and tolerability

Safety and tolerability measures will be presented as frequency tables of categorical outcomes by visit (number of participants and percentage). Tables will demonstrate both the number of participants affected (N) and the number of incidences (n).

Determination of safety and tolerability will be by the frequency of serious adverse events ((SAEs), Common Terminology Criteria for Adverse Events score ≥3),

frequency of down-titration events and frequency of study discontinuation.[26]

Monitoring and data quality

In accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, source data verification will be completed by the project manager at regular intervals throughout the study to ensure the eCRF remains up to date, accurate and reliable. The rate of subject recruitment will determine monitoring visit frequency.[26]

Safety oversight will be provided by an independent medical monitor, who will oversee the study conduct and regularly (every 3 months) review all safety-related events.

The DSMB will be made up of an independent clinician, an independent biostatistician and the medical monitor. The DSMB meetings will begin within 2 weeks of the week 8 visit for the third randomised patient or within 1 week of the second SAE occurring, whichever is first. Subsequently meetings will be at 6 monthly intervals. The medical monitor or site principal investigator may request additional DSMB meetings should there be urgent safety concerns. The medical monitor will make recommendations to the principal investigator based on the safety and tolerability issues after each DSMB review.[26]

Patient and public involvement

Study conception and design did not involve patients. As is required by Australian ethics committees and stated in the study consent forms, a plain English summary of the study will be provided to all study participants (and their person responsible/study partner) at the conclusion of the study. Wider dissemination of the results of the study to the community will be done via the media, patient support groups such as Parkinson's Australia and PSP Australia, and open events at our hospitals and research institutes.

ETHICS AND DISSEMINATION

Ethics approval for the study has been granted by the Alfred Hospital Ethics Committee (HREC, 594/20). All participants or their legally authorised representative and their study partner will provide written informed consent prior to commencement of any study assessments. An example form is available as online supplemental file 1. The study results will be disseminated through presentations at national and international conferences and published in peer-reviewed journals. Any protocol amendments will be approved by the HREC prior to implementation and subsequently updated on ANZCTR.

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REFERENCES

1 Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. *Lancet* 1999;354:1771–5.
2 O'Sullivan SS, Massey LA, Williams DR, *et al*. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain* 2008;131:1362–72.
3 Höglinger GU, Litvan I, Mendonca N, *et al*. Safety and efficacy of tilavonemab in progressive supranuclear palsy: a phase 2, randomised, placebo-controlled trial. *Lancet Neurol* 2021;20:182–92.

4 Bensimon G, Ludolph A, Agid Y, *et al*. Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. *Brain* 2009;132:156–71.
5 Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol* 2009;8:270–9.
6 Goedert M, Jakes R, Qi Z, *et al*. Protein phosphatase 2A is the major enzyme in brain that dephosphorylates tau protein phosphorylated by proline-directed protein kinases or cyclic AMP-dependent protein kinase. *J Neurochem* 1995;65:2804–7.
7 Arnold SE, Hyman BT, Flory J, *et al*. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cereb Cortex* 1991;1:103–16.
8 Hyman BT, Van Hoesen GW, Damasio AR, *et al*. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science* 1984;225:1168–70.
9 Gong CX, Lidsky T, Wegiel J, *et al*. Phosphorylation of microtubule-associated protein tau is regulated by protein phosphatase 2A in mammalian brain. Implications for neurofibrillary degeneration in Alzheimer's disease. *J Biol Chem* 2000;275:5535–44.
10 Corcoran NM, Najdovska M, Costello AJ. Inorganic selenium retards progression of experimental hormone refractory prostate cancer. *J Urol* 2004;171:907–10.
11 Brady RD, Grills BL, Romano T, *et al*. Sodium selenate treatment mitigates reduction of bone volume following traumatic brain injury in rats. *J Musculoskelet Neuronal Interact* 2016;16:369.
12 Corcoran NM, Hovens CM, Michael M, *et al*. Open-Label, phase I dose-escalation study of sodium selenate, a novel activator of PP2A, in patients with castration-resistant prostate cancer. *Br J Cancer* 2010;103:462–8.
13 Corcoran NM, Martin D, Hutter-Paier B, *et al*. Sodium selenate specifically activates PP2A phosphatase, dephosphorylates tau and reverses memory deficits in an Alzheimer's disease model. *J Clin Neurosci* 2010;17:1025–33.
14 Iqbal K, Alonso AdelC, Chen S, *et al*. Tau pathology in Alzheimer disease and other tauopathies. *Biochim Biophys Acta* 2005;1739:198–210.
15 Jones NC, Nguyen T, Corcoran NM, *et al*. Targeting hyperphosphorylated tau with sodium selenate suppresses seizures in rodent models. *Neurobiol Dis* 2012;45:897–901.
16 Liu S-J, Zheng P, Wright DK, *et al*. Sodium selenate retards epileptogenesis in acquired epilepsy models reversing changes in protein phosphatase 2A and hyperphosphorylated tau. *Brain* 2016;139:1919–38.
17 Malpas CB, Vivash L, Genc S, *et al*. A phase IIa randomized control trial of VEL015 (Sodium Selenate) in mild-moderate Alzheimer's disease. *J Alzheimers Dis* 2016;54:223–32.
18 Shultz SR, Wright DK, Zheng P, *et al*. Sodium selenate reduces hyperphosphorylated tau and improves outcomes after traumatic brain injury. *Brain* 2015;138:1297–313.
19 Tan XL, Wright DK, Liu S, *et al*. Sodium selenate, a protein phosphatase 2A activator, mitigates hyperphosphorylated tau and improves repeated mild traumatic brain injury outcomes. *Neuropharmacology* 2016;108:382–93.
20 Whitehouse PJ, Price DL, Struble RG, *et al*. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* 1982;215:1237–9.
21 Zheng P, Shultz SR, Hovens CM, *et al*. Hyperphosphorylated tau is implicated in acquired epilepsy and neuropsychiatric comorbidities. *Mol Neurobiol* 2014;49:1532–9.
22 van Eersel J, Ke YD, Liu X, *et al*. Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. *Proc Natl Acad Sci U S A* 2010;107:13888–93.
23 Cardoso BR, Roberts BR, Malpas CB, *et al*. Supranutritional sodium selenate supplementation delivers selenium to the central nervous system: results from a randomized controlled pilot trial in Alzheimer's disease. *Neurotherapeutics* 2019;16:192–202.
24 Vivash L, Malpas C, Hovens A, *et al*. Sodium selenate as a disease modifying treatment for mild-moderate Alzheimer's Disease: an open label extension study. *BMJ Neurology Open*;In press.
25 Chare L, Hodges JR, Leyton CE, *et al*. New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications. *J Neurol Neurosurg Psychiatry* 2014;85:865–70.
26 Vivash L, Malpas CB, Churilov L, *et al*. A study protocol for a phase II randomised, double-blind, placebo-controlled trial of sodium selenate as a disease-modifying treatment for behavioural variant frontotemporal dementia. *BMJ Open* 2020;10:e040100.
27 Höglinger GU, Respondek G, Stamelou M, *et al*. Clinical diagnosis of progressive supranuclear palsy: the movement disorder Society criteria. *Mov Disord* 2017;32:853–64.
28 Höglinger GU, Schöpe J, Stamelou M, *et al*. Longitudinal magnetic resonance imaging in progressive supranuclear palsy: a new combined score for clinical trials. *Mov Disord* 2017;32:842–52.
29 Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. *Brain* 2007;130:1552–65.
30 Guy W. Clinical Global Impressions. In: *ECDEU assessment manual for psychopharmacology*. Rockville MD: US Department of Health, Education and Welfare, 1976: 218–22.
31 Tombaugh TN. Trail making test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol* 2004;19:203–14.
32 Dubois B, Slachevsky A, Litvan I, *et al*. The Fab: a frontal assessment battery at bedside. *Neurology* 2000;55:1621–6.
33 Benton AL, Hamsher KdeS. *Multilingual aphasia examination: Mnaul of instruction*. Iowa City: University of Iowa, 1976.
34 Wechsler D. *Wechsler adult intelligence scale*. Vol. 22. *Fourth Edition (WAIS–IV)*. San Antonio, TX: NCS Pearson, 2008.
35 Spreen O, Strauss E. *A compendium of neuropsychological tests: Administration, norms and commentary*. 2 ed. New York: Oxford University Press, 1998.
36 Burgess PaS. T. *Hayling and Brixton tests*. Pearson, 1997.
37 Weintraub S, Dikmen SS, Heaton RK, *et al*. Cognition assessment using the NIH Toolbox. *Neurology* 2013;80:S54–64.
38 Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
39 Roth RM*et al*. Development of the behavior rating inventory of executive Function-Adult version. *Arch Clin Neuropsychol* 2005;20:906.
40 Takao H, Hayashi N, Ohtomo K. A longitudinal study of brain volume changes in normal aging. *Eur J Radiol* 2012;81:2801–4.

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Alfred Hospital

Title	A Phase 2 Randomised Controlled Trial of Sodium Selenate as a Disease Modifying Treatment for Probable Progressive Supranuclear Palsy
Short Title	Sodium Selenate for PSP
Protocol Number	SEL 003
Project Sponsor	Alfred Health
Coordinating Principal Investigator/Principal Inestigator	Prof Terence O'Brien
HREC Reference	HREC/ 69184/Alfred-2020
Local Project Number	594/20
Location	*The Alfred Hospital, 55 Commercial Rd, Melbourne VIC 3004*

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have Progressive Supranuclear Palsy. The research project is testing a new drug for the potential treatment of Progressive Supranuclear Palsy. The new treatment is called sodium selenate.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Due to the nature of your disease your condition may worsen during the period of the study which may impact your capacity to provide consent during the study. If, due to your disease progression, you lose the ability to provide consent to participate during the trial, you, or your caregiver, have the option to discontinue participation at any time. You will be able to indicate your preference by checking the appropriate box on page 19 of the Consent form.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

Vivash L, *et al. BMJ Open* 2021; 11:e055019. doi: 10.1136/bmjopen-2021-055019

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Currently there are no approved treatments for Progressive Supranuclear Palsy. The main purpose of this research project is to look at whether the trial drug, sodium selenate, when given at 10 milligrams three times a day, increasing to 15mg after 4 weeks, decreases the rate of brain shrinkage in patients with Progressive Supranuclear Palsy. The research project will also look into the effect of sodium selenate on your brain function, symptoms and markers of disease measured on brain scans, in blood, and in the fluid around your brain and spine to see if you are responding to the treatment.

Everyone has a naturally occurring protein called tau in the brain and the fluid around their brain and spine (cerebrospinal fluid). There is a link between Progressive Supranuclear Palsy and a reaction involving tau where too much phosphate is attached to the tau. This may cause brain cells to not work properly or die. The enzyme, protein phosphatase 2A (PP2A), breaks down the phosphate attached to tau. Sodium selenate works by increasing the activity of PP2A and therefore decreasing the available phosphate in the brain. Studies in animals have shown that sodium selenate helps to prevent this reaction between tau and phosphate. We now want to find out if it will help to treat Progressive Supranuclear Palsy in humans.

Sodium selenate is a form of selenium. In a healthy balanced diet, everyone consumes a small amount of selenium. Selenium is found in foods such as nuts, cereals, meat, fish and eggs, and some people also take nutritional supplements that contain low doses of selenium. However, sodium selenate is equivalent to a much higher dose of selenium than people normally ingest.

Sodium selenate has previously been studied in patients with fronto-temporal dementia, Alzheimer's disease and prostate cancer.

Up to 70 participants in Melbourne, Sydney, Brisbane and Adelaide, will take part in this research project overall.

Medications, drugs and devices have to be approved for use by the Australian Federal Government through the Therapeutic Goods Administration (TGA). Sodium selenate is an experimental treatment. This means that it is not an approved treatment for progressive supranuclear palsy in Australia.

This research has been initiated by the principal study doctor, Professor Terence O'Brien of the Alfred Hospital and Monash University, and is being funded by the Medical Research Future Fund.

3 What does participation in this research involve?

You will be participating in a randomised, controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random).

There will be two groups in this study, one group will receive the active treatment, sodium selenate, and the other group will receive the placebo. A placebo is a medication with no active ingredients or a procedure without any medical benefit. It looks like the real thing but is not. You will have a one in two (50%) chance of receiving the active treatment.

You will be participating in a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way.

If you decide to participate in this research project, the study doctor will inform your local doctor.

Participation in this study will involve coming to the study doctor's clinic up to 9 times over 64 weeks (15 months).

The dose of the study drug (or placebo) will be 10 milligrams three times a day, increasing to 15mg three times a day after 4 weeks. Below is an outline of what will happen at each of the study visits. Table 1 (below) gives a summary of which assessments will occur at each visit.

Screening (Visit 1):

You will be asked to sign this Participant Information Sheet and Consent Form before any screening tests are done as part of this study.

Before you can enrol in the study and receive study drug, you will need to come into the clinic for screening tests to see if the study is suitable for you. The screening visit may occur up to 8 weeks before you have your first dose of study drug.

If you decide to take part in this study, the first step will be for the study doctor to find out if you are suitable for it. To do this the following assessments will be performed:

- The study doctor will ask you about your disease, your medical history and demographics (sex, age, years of education).
- The study doctor will ask you about the medications you have been taking, including any over-the-counter or prescription medications, vitamins or herbal supplements.
- The study doctor will ask you about any birth control method (if you are able to get pregnant or make someone pregnant).
- A physical exam and neurological exam will be completed by the study doctor.
- Your height and weight will be recorded.
- Your vital signs (heart rate, temperature and blood pressure) will be measured.
- An Electrocardiogram (ECG) will be performed to check the electrical activity of your heart.
- A blood sample (approximately 10 ml or 2 teaspoons) for routine blood tests (haematology (cell counts) and blood chemistry) will be collected to check on your health. At this visit the blood tests will also include coagulation (blood clotting), and a pregnancy test if you are a woman.
- A urine sample will be collected to check your general health.
- A questionnaire will be used to assess your mental well-being and thoughts about death and suicide. This questionnaire will take approximately 10 minutes to complete.

If you are having significant thoughts about death and suicide, you will not be able to continue in the study and you will be referred to your family doctor for follow-up care. Independent counselling will be offered to those having significant thoughts about death and suicide.

- A member of the study team will give you a test that measures the status of your disease, memory and brain function. This test will take approximately 30 minutes to complete.
- An MRI (Magnetic Resonance imaging) scan of your brain will be conducted.
- **This will be performed at the Baker Heart and Diabetes Institute on the Alfred Hospital campus in Prahran.**

Pre-baseline Visit (Visit 2a):

If the results of all these tests fit the research requirements, you will be asked to return to have a baseline lumbar puncture to collect a 20mL (4 teaspoons) sample of fluid from your spine, known as cerebrospinal fluid (CSF).

This will be done to measure the levels of proteins associated with progressive supranuclear palsy in your CSF. The CSF will also be stored for future exploratory analyses.

A lumbar puncture is performed in the lower back, in the lumbar region. During the lumbar puncture, a needle is inserted between two lumbar bones (vertebrae) to remove a sample of CSF. Local anaesthetic will be injected into the back before the procedure to help numb the area.

A blood sample (approximately 31mL or just over 6 teaspoons of blood) will be taken for exploratory biomarkers, which may include genetic testing. Biomarkers are indicators in your blood, which may show how the study drug works or give us new information about PSP.

A tau PET scan of your brain will also be performed. This is a brain scan that will look at the amount of the tau protein in different parts of your brain.

This will be performed at the Alfred Hospital, Prahran.

Baseline Visit (Visit 2b)
If you are eligible to take part in the study you will come back to the study site for the Baseline Visit This visit will last approximately 6 hours. Your support person/caregiver will need to attend this visit with you. You will receive the study treatment or placebo at this visit and then take this 3 times a day.

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The following tests and procedures will be performed at this visit:

- You will be asked how you are feeling.
- You will be asked if you have been in the hospital or have been seriously ill.
- You will be asked about the medications you have been taking since your last visit, including any over-the-counter or prescription medicines, vitamins or herbal supplements.
- A physical exam and neurological exam will be completed by the study doctor. Your weight will be recorded.
- Your vital signs (heart rate, temperature and blood pressure) will be measured before you take your dose of study drug.
    - These will be measured again at 15 minutes and then 2 hours after you take your dose of study drug.

- An electrocardiogram (ECG) will be performed to check the electrical activity of your heart.
- A blood sample (approximately 7mL or just over 1 teaspoon of blood) will be collected for routine blood tests (haematology and blood chemistry) to check on your health.
- A urine sample will be collected to check your health including a pregnancy test (if you are able to become pregnant).
- The status of your disease, symptoms, memory and brain function will be tested using a combination of interviews, questionnaires, and tests which assess thinking.
- You will receive your first dose of study drug or placebo in the clinic.
- Five blood samples (approximately 6ml or 1 teaspoon of blood each) will be taken (at 1 hour before and 30 minutes, 1 hour, 2 hours and 4 hours after dosing with the study drug) to measure the amount of drug that is in your blood at each of these timepoints (known as pharmacokinetic analysis).
- Before your dose of the study drug and 1 hour after your dose of study drug you will be given a questionnaire which will be used to assess your mental well-being and thoughts about death and suicide.

  If you are having significant thoughts about death and suicide, you will not be able to continue in the study and you will be referred to your family doctor for follow-up care. Independent counselling will be offered to those having significant thoughts about death and suicide.
- You will be given a diary card and instructed how to fill it out.

Telephone Calls (Weeks 2, 4 and 6):

Two weeks after your first dose of the study drug (or placebo) you will be contacted by the study staff to see how you are doing. The staff member will ask whether you have had any side effects or been unwell and whether you have taken any other medications. They will also ask about whether you have been taking the study drug properly. The staff member will also remind you about completing your study diary. This phone call will take approximately 15 minutes.

Four weeks after your first dose the study staff will contact you again. You will be asked the same questions as the previous telephone call. As long as you are not having any bad side effects from the medication you will then be instructed to increase your dose of the study drug (or placebo) to three capsules three times a day. This phone call will take approximately 15 minutes.

Six weeks after the first dose you will again be contacted by site staff. You will be asked the same questions as the previous telephone calls, will be reminded of your next visit to the clinic, and reminded to bring your diary card and study medication with you. This phone call will take approximately 15 minutes.

Visit 3 (Week 8):

This visit to the study site will last approximately 6 hours. Your support person/caregiver will need to attend this visit with you.

The following tests and procedures will be performed:

- We will review your diary card.
- We will count the number of capsules of the study medication you have taken then give the bottles back to you.
- You will be asked how you are feeling.

- You will be asked if you have been in the hospital or have been seriously ill.
- You will be asked about the medications you have been taking since your last visit, including any over-the-counter or prescription medicines, vitamins or herbal supplements.
- A physical exam will be completed by the study doctor. Your weight will be recorded.
- Your vital signs (heart rate, temperature and blood pressure) will be measured before you take your dose of study drug and again 15 minutes and 2 hours after you take your dose of study drug.
- An electrocardiogram (ECG) will be performed to check the electrical activity of your heart.
- A blood sample (approximately 7mL or just over 1 teaspoon of blood) will be collected for routine blood tests (haematology and blood chemistry) to check on your health.
- A blood sample (approximately 20mL or 4 teaspoons of blood) will be collected for analysis of exploratory biomarkers, indicators in your blood which may show how the study drug works.
- You will take your dose of the study medication in the clinic
- Five blood samples (approximately 6mL or 1 teaspoon of blood each) will be taken 1 hour before and 30 minutes, 1 hour, 2 hours and 4 hours after dosing with the study drug for pharmacokinetic analysis
- Collect a urine sample to check your health including a pregnancy test (if you are able to become pregnant).
- Before your dose of the study drug and 1 hour after your dose of study drug you will be given a questionnaire which will be used to assess your mental well-being and thoughts about death and suicide.

  If you are having significant thoughts about death and suicide, you will not be able to continue in the study and you will be referred to your family doctor for follow-up care. Independent counselling will be offered to those having significant thoughts about death and suicide.
- You will be given a new diary card and reminded how to fill it out

Visit 4 (Week 16)

This visit to the study site will last approximately 1 hour. Your support person/caregiver will need to attend this visit with you.

The following tests and procedures will be performed:

- We will review your diary card.
- We will count the number of capsules of the study medication you have taken.
- You will be asked how you are feeling.
- You will be asked if you have been in the hospital or have been seriously ill.
- You will be asked about the medications you have been taking since your last visit, including any over-the-counter or prescription medicines, vitamins or herbal supplements.
- A physical exam will be completed by the study doctor. Your weight will be recorded.
- Your vital signs (heart rate, temperature and blood pressure) will be measured.

- An electrocardiogram (ECG) will be performed to check the electrical activity of your heart.
- A urine pregnancy test will be performed (if you are able to become pregnant).
- You will be given a questionnaire will be used to assess your mental well-being and thoughts about death and suicide.

  If you are having significant thoughts about death and suicide, you will not be able to continue in the study and you will be referred to your family doctor for follow-up care. Independent counselling will be offered to those having significant thoughts about death and suicide.
- You will be given a new diary card and reminded how to fill it out
- You will be given a new supply of study medication

Visit 5 (week 26)

This visit to the study site will last approximately 4 hours. Your support person/caregiver will need to attend this visit with you.

The following tests and procedures will be performed:

- We will review your diary card.
- We will count the number of capsules of the study medication you have taken
- You will be asked how you are feeling.
- You will be asked if you have been in the hospital or have been seriously ill.
- You will be asked about the medications you have been taking since your last visit, including any over-the-counter or prescription medicines, vitamins or herbal supplements.
- A physical exam and neurological exam will be completed by the study doctor. Your weight will be recorded.
- Your vital signs (heart rate, temperature and blood pressure) will be measured.
- An Electrocardiogram (ECG) will be performed to check the electrical activity of your heart.
- A blood sample (approximately 7mL or just over 1 teaspoon of blood) will be collected for routine blood tests (haematology and blood chemistry) to check on your health.
- A blood sample (approximately 20mL or 4 teaspoons of blood) will be collected for analysis of exploratory biomarkers, indicators in your blood which may show how the study drug works will be taken
- Collect a urine sample to check your health including a pregnancy test (if you are able to become pregnant).
- The status of your disease, symptoms, memory and brain function will be tested using a combination of interviews, questionnaires, and tests which assess thinking.
- You will be given a questionnaire which will be used to assess your mental well-being and thoughts about death and suicide.

  If you are having significant thoughts about death and suicide, you will not be able to continue in the study and you will be referred to your family doctor for follow-up care. Independent counselling will be offered to those having significant thoughts about death and suicide.
- You will be given a new diary card and reminded how to fill it out

- You will be given a new supply of study medication.

Visit 6 (Week 39)

This visit to the study site will last approximately 1 hour. Your support person/caregiver will need to attend this visit with you.

The following tests and procedures will be performed:

- We will review your diary card.
- We will count the number of capsules of the study medication you have taken
- You will be asked how you are feeling.
- You will be asked if you have been in the hospital or have been seriously ill.
- You will be asked about the medications you have been taking since your last visit, including any over-the-counter or prescription medicines, vitamins or herbal supplements.
- A physical exam will be completed by the study doctor. Your weight will be recorded.
- Your vital signs (heart rate, temperature and blood pressure) will be measured.
- An electrocardiogram (ECG) will be performed to check the electrical activity of your heart.
- A blood sample (approximately 10mL or 2 teaspoons of blood) will be collected for routine blood tests (haematology and blood chemistry) to check on your health and an additional test to look at coagulation (blood clotting).
- Collect a urine sample to check your health including a pregnancy test (if you are able to become pregnant).
- You will be given a questionnaire which will be used to assess your mental well-being and thoughts about death and suicide.

  If you are having significant thoughts about death and suicide, you will not be able to continue in the study and you will be referred to your family doctor for follow-up care. Independent counselling will be offered to those having significant thoughts about death and suicide.
- You will be given a new diary card and reminded how to fill it out
- You will be given a new supply of study medication.

Visit 7 (Week 52, End of Treatment Visit)

This visit to the study site will be performed across 2 to 4 days in the 2 weeks up to week 52. Your support person/caregiver will need to attend these visits with you. The following assessments will be done prior to your final clinic visit:

- A magnetic resonance imaging (MRI) scan of your brain will be conducted.
- **This will be performed at the Baker Heart and Diabetes Institute on the Alfred Hospital campus in Prahran.**

- Lumbar puncture to collect a 20mL (4 teaspoon) sample of fluid from your spine, known as cerebrospinal fluid (CSF). This will be done to measure the levels of proteins associated with progressive supranuclear palsy in your cerebrospinal fluid.

    - A lumbar puncture is performed in the lower back, in the lumbar region. During the lumbar puncture, a needle is inserted between two lumbar bones (vertebrae)

to remove a sample of CSF. Local anaesthetic will be injected into the back before the procedure to help numb the area.

- A blood sample will be taken (approximately 20mL or 4 teaspoons of blood) for analysis of exploratory biomarkers, indicators in your blood which may show how the study drug works.
- A tau PET scan of your brain will also be performed. This is a brain scan that will look at the amount of the tau protein in different parts of your brain.
- **This will be performed at the Alfred Hospital, Prahran.**

At your End of Treatment clinic visit the following tests and procedures will be performed:

- We will review your diary card.
- We will count the number of capsules of the study medication you have returned
- You will be asked how you are feeling.
- You will be asked if you have been in the hospital or have been seriously ill.
- You will be asked about the medications you have been taking since your last visit, including any over-the-counter or prescription medicines, vitamins or herbal supplements.
- A physical exam and neurological exam will be completed by the study doctor. Your weight will be recorded.
- Your vital signs (heart rate, temperature and blood pressure) will be measured.
- An Electrocardiogram (ECG) will be performed to check the electrical activity of your heart.
- A blood sample (approximately 7mL or just over 1 teaspoon of blood) for routine blood tests (haematology and blood chemistry) to check on your health.
- Five blood samples (approximately 6ml or 1 teaspoon of blood) will be taken 1 hour before and 30 minutes, 1 hour, 2 hours and 4 hours after dosing with the study drug for pharmacokinetic analysis
- Collect a urine sample to check your health including a pregnancy test (if you are able to become pregnant).
- The status of your disease, symptoms, memory and brain function will be tested using a combination of interviews, questionnaires, and tests which assess thinking.
- You will be given a questionnaire which will be used to assess your mental well-being and thoughts about death and suicide.

  If you are having significant thoughts about death and suicide, you will not be able to continue in the study and you will be referred to your family doctor for follow-up care. Independent counselling will be offered to those having significant thoughts about death and suicide.
- You will be given a new diary card and reminded how to fill it out

Visit 8 (Week 56)

This visit to the study site will take approximately 1 hour. The following tests and procedures will be performed:

- We will review your diary card.

- You will be asked how you are feeling.
- You will be asked if you have been in the hospital or have been seriously ill.
- You will be asked about the medications you have been taking since your last visit, including any over-the-counter or prescription medicines, vitamins or herbal supplements.
- A physical exam will be completed by the study doctor. Your weight will be recorded.
- Your vital signs (heart rate, temperature and blood pressure) will be measured.
- An Electrocardiogram (ECG) will be performed to check the electrical activity of your heart.
- A blood sample (approximately 7mL or over 1 teaspoon of blood) will be collected for routine blood tests (haematology and blood chemistry) to check on your health.
- Collect a urine sample to check your health including a pregnancy test (if you are able to become pregnant).
- You will be given a questionnaire which will be used to assess your mental well-being and thoughts about death and suicide.

  If you are having significant thoughts about death and suicide you will be referred to your family doctor for follow-up care. Independent counselling will be offered to those having significant thoughts about death and suicide.

Table 1 - Summary of study assessments

	Screening	Baseline										
Visit #	**1a**	**2a**	**2b**	**TC1**	**TC2**	**TC3**	**3**	**4**	**5**	**6**	**7**	**8**
Week	**-8 to 0**	**-2**	**0**	**2**	**4**	**6**	**8**	**16**	**26**	**39**	**52**	**56**
Written informed consent	X											
Assess eligibility	X											
Confirmation of eligibility			X									
Medical history	X											
Confirmation of diagnosis of PSP	X											
MRI scan – Baker Heart & Diabetes Institute	X										X	
tau PET scan - Alfred Hospital		X									X	
Lumbar puncture		X									X	
Physical examination	X		X				X	X	X	X	X	X
Vital signs	X		X				X	X	X	X	X	X
12-Lead ECG	X		X				X	X	X	X	X	X
Neurological exam	X		X						X		X	
Oculomotor testing (optional)			X						X		X	
Scales of disease progression and cognitive testing			X						X		X	
C-SSRS	X		X				X	X	X	X	X	X
Haematology	X		X				X		X	X	X	X
Biochemistry	X		X				X		X	X	X	X

Coagulation	X									X		
Blood collected for future exploratory assessments		X					X		X		X	
Blood collected for pharmacokinetic analysis			X				X				X	
Urinalysis (dipstick)	X		X				X		X	X	X	X
Urine pregnancy test			X				X	X	X	X	X	X
Plasma HCG pregnancy test	X											
Dispense study drug			X					X	X	X		
Redispense study drug							X					
Study drug Administration			X				X					
Dispense Diary Card			X				X	X	X	X	X	
Review and completion of Diary Card				X	X	X	X	X	X	X	X	X
Review of AEs/SAEs			X	X	X	X	X	X	X	X	X	X
Review of concomitant medications.	X		X	X	X	X	X	X	X	X	X	X

If you decide to take part in this research project, the study doctor will inform your local doctor.

Reimbursement

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You may be reimbursed for any reasonable travel and parking. Meal vouchers will be given to participants for study visits over 4 hours.

4 What do I have to do?

Participation in any research project is voluntary. If you decide to take part you will have to keep your study appointments and complete all study assessments. If you cannot attend an appointment, please tell the study staff (such as the study doctor or research staff) as soon as possible. They will then set a new appointment.

Tell study staff about any symptoms you have immediately, do not wait until your next scheduled visit. Side effects commonly observed can be found in section 9. Also tell them about changes in medications, doctor or nurse appointments, or any hospital admissions.

You should take your medication as instructed by the study staff. You or your partner should not become pregnant whilst participating in this study.

As a precaution it is advisable for you to limit eating foods that are known to have a high selenium content, particularly Brazil nuts, and you must not take any dietary supplements containing more than 26 micrograms of selenium at any time during the study.
Dehydration is a possible side effect, so you should drink at least 2 litres of fluid every day, which is about 8 large glasses.

5 Other relevant information about the research project

This study will be conducted at six hospitals in Melbourne, Sydney, Brisbane and Adelaide and will recruit up to 70 patients with progressive supranuclear palsy.

This study follows on from an earlier smaller study in 15 patients with behavioural variant fronto-temporal dementia that was conducted at the Royal Melbourne Hospital.

This project is a collaborative project between doctors and researchers at Hospitals and Universities in Melbourne, Sydney, Brisbane and Adelaide.

Monash University are storing the biospecimens and imaging data and will conduct the data analysis for the study.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Alfred Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital/facility. Your study doctor will discuss alternatives to participation with you; and you will continue to receive appropriate medical care for your disease. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include access to a potential treatment for progressive supranuclear palsy. The study may also provide a better understanding of progressive supranuclear palsy to improve future treatment of the disease.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study

doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Study Drug (sodium selenate)
Selenium compounds have been reported to be toxic (able to cause harm) at high dose. The general signs and symptoms of selenium toxicity are loss of hair and nails, thickening of the flesh under the toenails and fingernails, skin changes (redness, swelling, blisters and sores), and tooth decay. In a report about people consuming extremely high amounts of a different selenium compound as part of their diet during a famine, it was reported that neurological symptoms of tingling, pain, paralysis and convulsions (fits) were reported. All of these symptoms resolved when their diet was corrected. In our earlier study of sodium selenate no participants experienced paralysis or convulsions (fits).

You must not take any dietary supplements containing more than 26 micrograms of selenium at any time during the study. As a precaution it is advisable for you to limit eating foods that are known to have a high selenium content, particularly Brazil nuts.

In a previous study with sodium selenate in patients with Alzheimer's disease the following side effects were experienced:
- 35% (7 out of 20) of patients experienced fatigue and headache
- 30% (6 out of 20) experienced lethargy and nausea
- 20% (4 out of 20) experienced muscle spasms and dizziness
- 10% (2 out of 20) experienced changes to their nails, decreased appetite and muscle pain

In a previous study in patients with frontotemporal dementia, at the same dose of the drug as used in this study the following side effects were experienced:
- 64% (7 out of 11) of patients experienced changes to their nails
- 36% (4 out of 11) of patients experienced fatigue
- 27% (3 out of 11) of patients experienced hair loss and muscle pain
- 18% (2 out of 11) of patients experienced headache and diarrhoea

Some side effects, such as hair loss and nail changes, will not go away straight away after you stop taking sodium selenate. Problems with your nails may go away over a period of time, but we do not know that for sure. If you lose your hair, it may grow back over time when you stop taking sodium selenate, but again we do not know that for sure.

Dehydration is also a possible side effect of sodium selenate, although nobody who took part in the previous study experienced this side effect. In order to prevent dehydration, it is important that you drink plenty of fluid every day during this study. You should drink at least 2 litres of fluid every day, which is about 8 large glasses.

Pregnancy

The effects of sodium selenate on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project.

You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least twelve weeks after the last dose of study medication.

Vivash L, *et al. BMJ Open* 2021; 11:e055019. doi: 10.1136/bmjopen-2021-055019

Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of twelve weeks after the last dose of the study drug. You should discuss methods of effective contraception with your study doctor.

For female participants
If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

For male participants
You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

Blood Draw
Having blood taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

Lumbar Puncture
The most common risks associated with having a lumbar puncture include:

- Pain and discomfort when the needle is inserted and the cerebrospinal fluid (CSF) is taken. The CSF is clear fluid that surrounds your brain and spinal cord in your back. There may be a bruise and some bleeding where the needle is put in. This is usually minor and short-lasting. Some people experience leg pain at the time of the procedure.

- Headache after the CSF collection which can last several days. Pain killers may help relieve the pain. It is reported by as many as half of the people who have the procedure. The headache may be more severe when you are upright (e.g. standing). If the headache does not go away after 1 or 2 days, it may be due to a leak of the cerebrospinal fluid. A leak can be treated with bed rest, hydration and steroids. If these measures do not heal the leak, the leak can be treated with a blood “patch”. This is when your blood is injected into the area of the back where the leak is occurring.

- Pain or tenderness in your lower back after the procedure.

- An allergic reaction to the local anaesthetic. An allergic reaction can be mild to moderate (e.g. hives or welts on the skin, itching, pain), or severe, known as an anaphylactic reaction (difficulty breathing, swelling of the tongue, coughing, etc). An anaphylactic reaction to local anaesthetic is rare.

There are also risks, which are rare, such as bleeding into the spinal canal or an infection of the spinal fluid (known as meningitis). These rare complications may be serious. They could require hospitalisation for urgent care, such as antibiotic therapy, brain surgery, or a breathing machine (known as a ventilator).

MRI – at the Baker Heart and Diabetes Institute
MRI stands for magnetic resonance imaging. A MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. The pictures taken by the machine are called MRI scans. The MRI will take

approximately 30 minutes, and will be performed at the Baker Heart and Diabetes Institute on the Alfred Hospital campus in Prahran.

We will ask you to lie on a table inside the MRI scanner. The scanner will record information about your brain. It is very important that you keep very still during the scanning. When you lie on the table, we will make sure you are in a comfortable position so that you can keep still. The scanner is very noisy and we can give you some earphones to reduce the noise. Some people may experience symptoms of claustrophobia from lying in a confined space. If you do experience discomfort at any time during the scan, you will be able to alert staff by pressing on a call button provided to you.

There are no proven long-term risks related to MRI scans as used in this research project. MRI is considered to be safe when performed at a centre with appropriate procedures. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room.

We will thoroughly examine you to make sure there is no reason for you not to have the scan. You must tell us if you have metal implanted in your body, such as a pacemaker or metal pins.

The scans we are taking are for research purposes. They are not intended to be used like scans taken for a full clinical examination. The scans will not be used to help diagnose, treat or manage a particular condition. A specialist will look at your MRI scans for features relevant to the research project. On rare occasions, the specialist may find an unusual feature that could have a significant risk to your health. If this happens, we will contact you to talk about the findings. We cannot guarantee that we will find any/all unusual features.

Tau-PET scan – at the Alfred
PET stands for positron emission tomography. To conduct the PET scan, it is necessary to use a radioactive imaging agent known as PET radiotracers. The scan will take approximately 60 minutes, and will be performed at the Alfred Hospital, Prahran.

You will be asked to lie on a table inside the PET scanner, and a small amount of the PET radiotracer (PI2620) will be injected in to a vein in your hand or arm. PI2620 is not currently approved by the TGA in Australia and therefore its use in this study is considered experimental.

This research study involves exposure to a small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 12 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be low.
Have you been involved in any other research studies that involve radiation? If so, please tell us. Please keep information contained within the Participant Information and Consent Form about your exposure to radiation in this study, including the radiation dose, for at least five years. You will be required to provide this information to researchers of any future research projects involving exposure to radiation.

10 What will happen to my test samples?

By consenting to take part in this study, you also consent to the collection, storage and use of tissue samples and imaging data as specified below. All samples collected will be labelled with your unique study code (your name will not be recorded on the labels).

- Routine blood, urine and CSF samples will be processed and tested by the local laboratory, the Department of [insert site information] Hospital. These samples are taken for routine testing to ensure your safety in participating in the trial and will be destroyed after testing.

- The pharmacokinetic and exploratory biomarker blood and CSF samples will be stored on site within the Department of [insert site information] Hospital for analysis at a later time. They will then be transferred to Monash University, Victoria for storage and testing for this study. Samples will be kept for up to 15 years
    - You may choose to consent to the leftover portions of these samples being used for future research that is (a) closely related to this research project or (b) any future research. This is **optional** and not agreeing to this will not affect your participation in this study or your relationship with those treating your or your relationship with the Alfred Hospital
    - You can indicate your preference on the Consent form at the end of this document.
    - If you consent to your leftover samples being kept for future research, they will be kept for up to 15 years. After samples have been tested they will be destroyed.
- MRI and PET imaging data will be transferred to Monash University for analysis and long-term storage. Images and associated data will be kept indefinitely.
    - You may choose to consent to the use of your MRI and PET images and data for future research that is (a) closely related to this research project or (b) any future research. This is **optional** and not agreeing to this will not affect your participation in this study or your relationship with those treating your or your relationship with the Alfred Hospital.
    - You can indicate your preference on the Consent form at the end of this document.

Other genuine researchers may request access to these de-identified samples/data in the future. This will require approval from the original research team, and be subject to you having given extended consent (for closely related research) or unspecified consent (for any future research) for the use of these samples (see Consent form), which is **optional.**

If you withdraw your consent to participate in this study, you have the right to request that your research samples be destroyed. The data generated prior to your request to destroy your research samples will not be destroyed and may still be used.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies,

acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

It may also be necessary for you to take medication during or after the research project to address side effects or symptoms that you may have. You may need to pay for these medications and so it is important that you ask your doctor about this possibility.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• The drug being shown not to be effective
• The drug being shown to work and not need further testing

15 What happens when the research project ends?

When the treatment phase of the research project is over you will not have access to the study drug.

At the end of the study you will need to discuss your options for treatment with your doctor.

A final report will be provided to the Principal Investigator who will share the results with you or your medical treatment decision maker/Person Responsible and/or caregiver when requested. It is usual for a number of years to elapse before definitive results of this type of study are available. These may be published in medical journals that are available to the public. You, your medical treatment decision maker/Person Responsible and/or caregiver should feel free to ask the study staff about this.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. The information collected in relation to this study will be identified by your study number. All identifiable information will be treated as confidential, and stored on site in a locked office, only accessible to site staff directly involved in this research project. Data related to this project will be kept indefinitely.

Your information will only be used for the purpose of this research project unless you consent for its use in (a) other closely related research and/or (b) any future research, which is **optional.** Your information will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the sponsor, Alfred Health, the institution relevant to this Participant Information Sheet, the Alfred Hospital, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Each participant will be assigned a study number, you will only be identified by this study number in recording of study data and subsequent analysis and presentation of this data. The code linking you to your study number will be kept at the study site and only accessible to study staff directly related to the conduct of this study.

Information about participation in this research project may be recorded in your health records.

Following the publication of this study de-identified data will be archived in the Australian Data Archive (ADA). The ADA is data repository hosted by Australian National University. Deidentified data will be publicly available from the ADA. Any personal information that could identify you will be removed before the files are made public.

Stricter controls will be placed on your biological samples and imaging data. If you have given extended or unspecified consent, other genuine researchers may request access to these de-identified samples/data in the future. This will require approval from the original research team, a human research ethics committee, and be subject to you having given extended consent (for closely related research) or unspecified consent (for any future research) for the use of these samples (see Consent form), which is **optional.**

Any information obtained for the purpose of this research project and for the future research described in Section 10 that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

Your data may be transferred within Australia.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

If you are not satisfied with how your personal information has been handled (as laid out in the Privacy Act, 1988), then you can make a complaint to the Office of the Australian Information Commissioner (OAIC). Please refer to http://www.oaic.gov.au/privacy/privacy-complaints for more information.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by Professor Terence O'Brien and collaborators.

Alfred Health and Monash University may benefit financially from this research project if, for example, the project assists Alfred Health and Monash University to obtain approval for a new drug.

By taking part in this research project you agree that samples of your blood or tissue (or data generated from analysis of these materials) may be provided to Monash University. Monash University may directly or indirectly benefit financially from your samples or from knowledge acquired through analysis of these samples.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to Monash University.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Monash University, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Monash University will receive a payment from the Medical Research Future Fund for undertaking this research project. The study sites will receive payment from Monash University to cover the costs of conducting the project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Alfred Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on XXXXXXXX or any of the following people:

Site Clinical contact person

Name	*Prof Terence O'Brien*
Position	*Principal Investigator*
Telephone	*XXXXXXXX*
Email	*XXXXXXXX*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Site Complaints contact person

Position	*Complaints Officer*
Telephone	*03 9076 3619*
Email	*research@alfred.org.au*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Alfred Hospital Ethics Committee
Position	HREC Executive Officer
Telephone	03 9076 3619
Email	research@alfred.org.au

Local HREC Office contact (Single Site - Research Governance Officer)

Reviewing HREC name	Alfred Hospital Ethics Committee
Position	Governance Officer
Telephone	03 9076 3619
Email	research@alfred.org.au

Consent Form - *Adult providing own consent*

Title	A Phase 2 Randomised Controlled Trial of Sodium Selenate as a Disease Modifying Treatment for Probable Progressive Supranuclear Palsy
Short Title	Sodium Selenate for PSP
Protocol Number	SEL 003
Project Sponsor	Alfred Health
Coordinating Principal Investigator/Principal Investigator	Prof Terence O'Brien
HREC Reference	HREC/ 69184/Alfred-2020
Local Project Number	594/20
Location	*Alfred Hospital, 55 Commercial Rd, Melbourne VIC 3004*

Consent Agreement

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to the Alfred Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

If my condition progresses and at any time during the study my doctor considers that I no longer have capacity to give ongoing informed consent I would like to:

☐ be withdrawn from the study

☐ continue participating in the study

I understand that if I have indicated that I would like to continue participating in the study, the investigators will ask my medical treatment decision maker (MTDM)/person responsible to make a decision about whether I will continue to participate in the study.

I understand that I will be given a signed copy of this document to keep.

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

Declaration - for participants unable to read the information and consent form

See Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 Section 4.8.9. The subject's legally acceptable representative may be a witness*.

Witness to the informed consent process

Name (please print) _____

Signature _____ Date _____

* Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Optional Use of Samples and Images for Future Research

I consent to the storage and use of blood and tissue (CSF) samples and MRI and PET imaging data taken from me, as well as personal and health information, for use, as described in the relevant sections of the Participant Information Sheet (Section 10 and Section 16), for:

☐ Other research that is closely related to this research project

☐ Any future research

Name of Participant (please print) _____

Signature _____ Date _____

For participants unable to read the information and consent form

See Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 Section 4.8.9. The subject's legally acceptable representative may be a witness*.

Witness to the informed consent process

Name (please print) _____

Signature _____ Date _____

*Witness must be 18 years or older.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	A Phase 2 Randomised Controlled Trial of Sodium Selenate as a Disease Modifying Treatment for Probable Progressive Supranuclear Palsy
Short Title	Sodium Selenate for PSP
Protocol Number	SEL 003
Project Sponsor	Alfred Health
Coordinating Principal Investigator/Principal Investigator	Prof Terry O'Brien
HREC Reference	HREC/ 69184/Alfred-2020
Local Project Number	594/20
Location	*Alfred Hospital, 55 Commercial Rd, Melbourne VIC 3004*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with the Alfred Hospital.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.