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A study protocol for a phase II randomized, double-blind, placebo-controlled trial of sodium selenate as a disease-modifying treatment for behavioural variant frontotemporal dementia

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Abstract

Introduction: Behavioural variant frontotemporal dementia (bvFTD) is a neurodegenerative disorder often neuropathologically associated with the accumulation of abnormally hyperphosphorylated tau, for which there is currently no disease modifying treatment. Previous work by our group has shown sodium selenate upregulates the activity of PP2A in the brain, increasing the rate of tau dephosphorylation.

Objective: To evaluate the efficacy and safety of sodium selenate as a disease-modifying treatment for bvFTD.

Trial design: A multi-site, phase 2b, double-blind, randomised placebo-controlled trial.

Setting: Four Australian academic hospitals that are centres of expertise for patients with bvFTD.

Participants and intervention: 120 participants will be enrolled in the study. Following screening, participants will be randomised (1:1) to blinded treatment with either sodium selenate (15 mg three times a day) or matching placebo.

Main outcome measure and analysis: The primary study outcome will be percentage brain volume change (PBVC) as measured on MRI over 52 weeks of treatment. This will be analysed with a general linear model (ANCOVA) with the PBVC as an output, the treatment as an input, and the baseline brain volume as covariate for adjustment purposes. Secondary outcomes include safety and tolerability measures, and efficacy measures; change in CSF total-tau, Addenbrooke's Cognitive Examination-III and Cambridge Behavioural Inventory-Revised scores over the 52 weeks of treatment. These will also be analysed with analysis of covariance (ANCOVA) where the corresponding baseline measure will be incorporated in the model. Additional exploratory outcomes will include other imaging, cognitive and biospecimen analyses.

Ethics and dissemination: The study was approved by the Human Research & Ethics Committee of the lead site as part of the Australian Multisite Ethics approval system. The results of the study will be presented at national and international conferences and published in peer-reviewed journals.

Trial registration number: ACTRN12620000236998

Strengths and Limitations

- A large placebo-controlled RCT of a new drug for behavioural variant frontotemporal dementia (bvFTD)
- Extensive clinical, cognitive and imaging data will be collected producing a highly characterised prospective patient cohort which will be of huge significance to the field
- A mixture of established and novel diagnostic methods will be used, potentially validating new diagnostic approaches for future use
- Due to difficulty identifying pathology of bvFTD in life, some participants may not have the pathology targeted by this drug

Background

Behavioural-variant frontotemporal dementia (bvFTD) is the most common clinical syndrome caused by frontotemporal lobar degeneration (FTLD). It is a neurodegenerative disease characterised by the development of progressive behavioural features including disinhibition, apathy, loss of empathy, perseveration and stereotyped behaviour. bvFTD is a devastating condition for both patients and their families, and is invariably fatal. Prevalence rates of bvFTD range from 15-50 cases per 100,000 people [1-3]. No approved disease-modifying treatments currently exist for bvFTD, and the few international clinical trials that have been carried out have been unsuccessful [4]. A major unmet need therefore exists in the treatment of this condition. Approximately 45% of bvFTD cases are classified as 'tauopathies', neuropathologically characterised by abnormally hyperphosphorylated inclusions of the microtubule-associated protein *tau* [5]. Hyperphosphorylated tau dissociates from microtubules and aggregates in to filamentous tau deposits, disrupting axonal structure and transport leading to neurodegeneration. Targeting this hyperphosphorylated tau is a promising treatment strategy for these patients that requires validation with randomised clinical trials [6].

Targeting hyperphosphorylated tau

Two broad approaches are possible to pharmacologically reduce tau hyperphosphorylation in the brain: 1) *inhibition* of tau serine/threonine kinases, or 2) *activation* of tau serine/threonine phosphatases. Multiple kinases have been implicated in the phosphorylation of tau, hence a more feasible strategy is the upregulation of protein phosphatase 2 (PP2A), the major tau serine/threonine phosphatase present in the brain, which accounts for over 70% of phosphatase activity [7]. PP2A is co-localised with tau [8-10] , and reductions in PP2A activity, and therefore reduced tau dephosphorylation are observed in many neurodegenerative diseases. Further, PP2A activity negatively correlates with tau levels in human tissue [10].

Selenium is an essential trace element in humans and is present in low concentrations in food and the environment. Whilst numerous studies have reported potential chemopreventive benefits associated with selenium dietary supplementation, the therapeutic potential of other selenium compounds has not been widely explored. A large body of pre-clinical, and emerging clinical data, have provided evidence for the potential of sodium selenate, an oxidised salt of selenium, as a disease-modifying treatment for hyperphosphorylated tau-based neurodegenerative diseases, traumatic brain injury, and epilepsy [11-21]. Our research has not only demonstrated significant therapeutic benefits in preclinical models of cancer [12], Alzheimer's disease [13, 22], epilepsy [15, 16, 18, 21] and traumatic brain injury [11, 18, 19], but also has showed that these benefits were restricted to the administration of the single selenium species, sodium selenate, and were only beneficial in a therapeutic setting when administered in supranutritional doses [17, 23].

Clinical Trials of Sodium Selenate for Other Conditions

Two clinical trials have demonstrated the safety and tolerability of sodium selenate in patients with diseases other than FTD. First, a Phase I study in patients with castration-resistant prostate cancer demonstrated a favourable safety profile of VEL015 (sodium selenate) [12]. This study demonstrated that doses up to 60mg per day were tolerable in chronic dosing, with dose-limiting toxicity observed at 90mg per day.

More recently, our group completed and published a Phase IIa trial of sodium selenate (30mg/day) in 40 patients with mild-moderate Alzheimer's disease (AD), which confirmed the safety and tolerability of the agent [17, 23]. This AD study was designed to evaluate

safety and tolerability and not treatment efficacy, however MR diffusion tensor imaging (DTI) measures were exploratory outcome measures in this study. Voxel-wise analysis of DTI metrics showed relatively less degeneration in the treatment group compared to placebo, which was widespread, but most prominent in the corpus callosum [17]. Selenium levels in patients' serum and CSF were higher in the treatment group, which is evidence of penetration of the agent across the blood-brain barrier and into the CNS [23]. In addition, selenium levels were inversely correlated with the degree of decline in cognitive measures over the 6-month treatment period, indicating a relationship between drug exposure and neuroprotective efficacy [23].

Phase 1 Open-label Trial of Sodium Selenate for bvFTD

We are currently undertaking a single site, exploratory, Phase Ib open labelled study of sodium selenate as a treatment for patients with bvFTD (ACTRN12617001218381, https://anzctr.org.au). The primary objective is to assess the safety and tolerability of a supranutritional dose of sodium selenate in patients with possible bvFTD. Twelve patients have been recruited, and eight patients have completed the 12-month treatment phase so far. There have been no withdrawals, and adverse effects have been relatively mild and similar to those experienced in the Phase IIa AD trial [17].

Informed by this experience, we will now conduct a multi-centred placebo-controlled randomised controlled trial of sodium selenate as a treatment for bvFTD.

Aims/Outcomes

The aim of this study is to investigate the efficacy and safety of sodium selenate (15 mg, three times a day) as a disease-modifying treatment of probable bvFTD.

The primary outcome variable is change in whole brain volume over 52 weeks of treatment.

The secondary outcome variables (safety) will be rate and severity of adverse events and rate of study withdrawal. Secondary efficacy outcome variables are change in cerebrospinal fluid (CSF) total-tau, change in cognition as measured by the Addenbrooke's Cognitive Examination-III (ACE-III) total score and change in behaviour as measured by the Cambridge Behavioural Inventory-Revised (CBI) total score over 52 weeks.

Additional exploratory outcomes will investigate changes in CSF, serum and plasma protein biomarkers (total-tau, phospho-tau and neurofilament light chain (NfL)), changes in other measures of cognition and behaviour (memory, language, executive function, attention), and changes in additional neuroimaging measures, including cortical thickness, volumetrics, advanced MRI (diffusion, quantitative susceptibility mapping (QSM), resting state) and fluoro-deoxy glucose (FDG) and tau-binding positron emission tomography (PET). The study will also use advanced statistical modelling to identify predictors of treatment response and non-response, and correlations between biomarkers and cognitive function and behaviour.

Methods/Design

This is a multi-site, phase 2b double-blind, randomised, placebo-controlled trial of sodium selenate as a treatment for probable bvFTD. Patients will receive 52 weeks of treatment with either sodium selenate (15 mg tds) or placebo. 120 patients will be recruited in to this study. The study will be conducted at 4 centres in Melbourne and Sydney. The study is funded by the Australian National Health and Medical Research Council (NHMRC; APP1170276).

Ethics approval was granted by the Alfred Health Human Research Ethics Committee, Melbourne (609/19). The trial is registered with ANZCTR (ACTRN12620000236998)

Eligibility Criteria

Inclusion criteria*:* Participants will be aged over 35, have a diagnosis of probable bvFTD [24] and a modified Hachinski score <5 [25]. Participants must be using effective contraception for the duration of the trial. Participants must have a lumbar puncture and MRI performed during screening. The structural brain MRI must be consistent with a bvFTD diagnosis with no other gross structural abnormalities indicating another neurological disorder. The participant must have a negative amyloid-PET scan (either as part of screening assessments or historical). 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 behaviour throughout the study. 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; known history of familial Alzheimer's disease or genetic form of FTD that is not considered a primary tauopathy (e.g., *GRN* mutation or *C9ORF72* expansion); lifelong primary psychiatric disorder; significant traumatic brain injury with loss of consciousness >5 mins; significant medical or neurological disease, with the exception of bvFTD 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: 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.

Intervention, Randomisation and Blinding

Each participant will be provided a unique screening number upon signing the consent form. Once all screening assessments have been completed and the participant is eligible to continue, the participant will be assigned a sequential randomisation number generated within the redcap eCRF (subject to entry of key data into the eCRF). This randomisation number will be provided to the unblinded site pharmacist who will dispense the drug/placebo in accordance with the randomisation schedule.

Participants will receive either sodium selenate or placebo (1:1) for 52 weeks. Each capsule will contain 5 mg of drug or placebo. The initial dose will be two capsules (10 mg) three times a day (tds), increasing to three capsules (15mg) tds at week 4, subject to tolerability. In the event of adverse events potentially related to the study drug administration, treatment may be temporarily interrupted and a single within-subject dose reduction, to 10 mg tds will,

at the investigator's discretion, be allowed. An additional down-titration to 5 mg tds will only be allowed after consultation with the medical monitor.

The study participant, their study partner and all site staff (with the exception of the pharmacy team) will remain blinded throughout the course of the study. Individual unblinding envelopes for emergency unblinding of individual patients will be kept at the study sites. The data safety monitoring board (DSMB) will also be blind to study treatment when reviewing safety data. In the event of unexpected adverse events the DSMB may request unblinding of data to assess potential causality.

Procedures and Assessments

Participants will undergo study testing and procedures as outlined in Table 1. Briefly, at the screening assessment, the participant will be reviewed to ensure they meet all the inclusion criteria and none of the exclusion criteria. Neuroimaging (MRI, and amyloid-PET) will follow to strengthen the bvFTD diagnosis (and exclude Alzheimer's disease). At the baseline visit, the inclusion and exclusion criteria will be reviewed to ensure the participant remains eligible for the study. The participant will undergo an FDG-PET, baseline CSF sampling and a cognitive and behavioural assessment. Lastly the participant will be administered the study drug (10mg) in the clinic and multiple blood draws taken for pharmacokinetic analysis.

Follow-up phone calls will be made to monitor for adverse events. If participants are tolerating the study drug, they will be instructed to increase to 3 capsules (15mg tds) at week 4. Diary cards will be given to participants to record adverse events that occur between clinic visits.

Participants will attend regular in-clinic study visits to assess their safety and well-being, and to resupply the study medication. The cognitive and behavioural assessment will be repeated at weeks 26 and 52. Prior to their week 52 clinical visit participants will undergo repeat neuroimaging (MRI, FDG-PET) and CSF sampling for biomarker analyses. Participants will attend a final safety follow up visit 4 weeks following the cessation of the study drug.

Measures

Neuroimaging

MRIs will be acquired during the screening period and week 52. The MRI protocol includes the following sequences; volumetric T1 (1mm^3), T2-space (0.8 x 1.1 x 4mm), volumetric T1 (1mm^3), multi-band DWI (2.5mm^3), resting state fMRI (4.5mm^3), multi-echo QSM (3.5mm^3).

The primary outcome measure will be the change in whole-brain volume (percentage brain volume change; PBVC) from baseline to 52 weeks. Whole-brain volume will be measured using T1-weighted structural MRI acquired at baseline and after 52 weeks of treatment. Change in whole-brain volume will be computed using the *SIENA* module within the FSL software [26]. Briefly, *SIENA* performs brain extraction, halfway-space registration, and tissue segmentation. Perpendicular edge displacement is then computed between the brain/non-brain edge points of the two images. The accuracy of this method is very high, with longitudinal error reported at 0.15% [27].

Florbetaben PET will be conducted at screening to exclude Alzheimer's disease. 300MBq (±10%) will be injected intravenously, 90 minutes post-injection a dynamic 3D scan (4x300 sec frames) will be acquired. This will not be required for participants who have a historical negative amyloid PET that is available for review by the site principal investigator.

FDG PET will be conducted at baseline and week 52 to assess disease progression. 185 MBq (±10%) will be injected intravenously, the patient will rest in a quiet room for 20 minutes, and a dynamic 3D acquisition will begin 30 minutes post-injection (6x300sec frames).
An optional sub-study investigating tau PET as a marker of disease progression will also be conducted. Participants who consent will have two tau PET scans, at baseline and in the two weeks prior to week 52. A dynamic 3D acquisition (12x150 s frames) will begin 45 minutes after the intravenous injection of 185MBq (±10%) of PI-2620.

Cognitive and Behavioural Battery

The following cognitive and behavioural scales will be administered at baseline, week 26 and week 52 of the study.

Addenbrooke's Cognitive Examination III: The Addenbrooke's Cognitive Examination is a broad cognitive screening test of 5 cognitive domains; attention/orientation, memory, language, verbal fluency and visuospatial skills, producing a score out of 100 (normal scores ≥ 88/100). Administration takes about 15 minutes and three different versions are available [28]. This will be analysed as one of the secondary efficacy endpoints.

NIH Toolbox: The NIH Toolbox is a multidimensional battery of measures used to assess cognitive, sensory, motor and emotional function in people. The NIH Toolbox has been validated for ages 3-85 years and is designed such that repeated assessments can be completed for longitudinal monitoring of disease progression. The NIH Toolbox takes approximately 30 minutes to administer [29, 30].

Hayling Sentence Test: The Hayling Sentence Completion test is a measure of response initiation and response suppression. It is entirely verbal, and therefore can be administered to patients with problems with reading and visual perception. It consists of two sets of 15 sentences each having the last word missing. In the first section the examiner reads each sentence aloud and the participant has to simply complete the sentences as quickly as possible, yielding a simple measure of response initiation speed. The second part of the Hayling requires participants to complete a sentence with a nonsense ending word, giving measures of response suppression ability and thinking time. It takes approximately 5 minutes to administer and yields three different measures of executive functioning which can be considered separately or combined into an overall score [30].

Victoria Stroop Test: The Victoria Stroop Test is a measure of executive function commonly used in neuropsychological evaluation. The test uses three conditions that consist in naming the color of dots, of neutral words, and of color words printed in incongruent colors. Each condition contains 24 items. Because of its short administration time, approximately 5 minutes, it is appropriate for use in geriatric populations and with those suffering from dementia [31].

Controlled Oral Word Association Test (COWAT): Controlled Oral Word Association Test, is a verbal fluency test that measures executive function. The participant is asked to name words beginning with a designated letter for one minute under certain conditions (e.g., no repetitions, no proper nouns, no identical stem words) and this procedure is repeated with three different letters. The whole examination usually takes 5–10 minutes [32].

Trail Making Test A and B: The Trail Making Test is a test of visual attention and task switching. It consists of two parts in which the subject is instructed to connect a set of 25 targets as quickly as possible while still maintaining accuracy. There are two parts to the test: in the

first, the targets are all numbers (1, 2, 3, etc.) which the participant must connect sequentially; in the second part, the subject alternates between numbers and letters (1, A, 2, B, etc.). The first part of the test is used to primarily measure processing speed, whilst the second part is a test of executive function. The time to complete the paths are the scores for this assessment [33].

Digit Span: The digit span test is a measure of attention and working memory. Participants are told a sequence of digits (which become progressively longer) which they must repeat back to the examiner. This test is performed forwards and backwards. The score is the maximum length of digits they correctly repeated under the two conditions [34].

Sydney Language Battery: The Sydney Language Battery is a test of language at a single word level, which measures naming, repetition, comprehension, and semantic association. The same set of 30 multisyllabic nouns (3 or more syllables) are used across the four tasks. Words are ordered with decreasing frequency and are graded into three broad levels of difficulty [35].

Mini Social Emotional Assessment (mini-SEA): The Mini Social Emotional Assessment (mini-SEA) is a cognitive battery designed to assess social and emotional function. The battery contains two components: (a) a faux-pas test assessing theory of mind, and (b) a facial emotional recognition test. The neural correlates of the mini-SEA have been established in bvFTD, with significant relationships reported with the medial prefrontal cortex (mPFC). The mini-SEA takes approximately 30 minutes to administer [36].

Cambridge Behavioural Inventory - Revised: The Cambridge Behavioural Inventory – Revised (CBI-R) is an informant questionnaire that assesses neuropsychiatric and neurobehavioral symptoms in patients with neurodegenerative disease [18]. The instrument contains 45 questions assessing the following domains: (a) memory and orientation, (b) everyday skills, (c) self-care, (d) abnormal behaviour, (e) mood, (f) beliefs, (g) eating habits, (h) sleep, (i) stereotypic and motor behaviours, and (j) motivation. The instrument takes approximately 10 minutes to complete. A total score is generated that will be used for this study [37]. This will be analysed as one of the secondary efficacy endpoints.

Caregiver Burden Scale: The Caregiver Burden Scale (CBS) is a caregiver-completed instrument that assesses the experience of burden in people who care for those with cognitive disorders [38]. The instrument contains 22 questions and takes approximately 5 minutes to complete. A total score is generated that will be used for the present study [38].

Safety Assessments

A 12-ECG and a physical examination will be performed at each clinic visit, haematology, chemistry and urinalysis will be performed at each clinic visit except week 16. Neurological examinations will be carried out at screening, baseline, week 26 and 52. Any clinically significant abnormalities in any of these investigations will be considered adverse events. The diary cards will be reviewed to ascertain any adverse events that occurred between visits, and the participant and their study partner interviewed to confirm adverse events and concomitant therapies.

Blood biomarkers

Additional blood samples will be collected for pharmacokinetic, biomarker and exploratory analyses. Pharmacokinetic sampling (6ml/sample) will be performed at baseline, week 8 and

week 52. A pre-dose (1 hour) sample will be taken, then 4 additional samples, 0.5, 1, 2, 4 hours after dosing. Sodium selenate levels in plasma will subsequently be measured in these samples for determination of the pharmacokinetic profile.

Exploratory sampling will occur at baseline, week 8, week 26 and week 52. Samples will be taken for plasma, serum and PMBC isolation at each of these visits. Blood for DNA and RNA will be taken only at baseline. Exploratory analyses will include measurement of proteins associated with neurodegeneration (total-tau, phospho-tau, beta-amyloid$_{42}$, neurofilament light) in serum and plasma, testing for genetic mutations associated with bvFTD (*MAPT*, *GRN*, *C9ORF72* expansion). As yet undetermined additional testing may be performed.

CSF biomarkers

CSF sampling will take place at baseline (pre-treatment) and week 52. Samples will be analysed for beta-amyloid$_{42}$, total-tau, phospho-tau and NfL protein levels. Additional as yet undetermined testing may also be performed. Change in total-tau will be used as a secondary efficacy outcome measure.

Power and Sample Size

All outcomes are predefined prospectively in hierarchical order, meaning that the trial will be declared positive or negative based on primary outcome. Statistical power has thus been determined on the primary outcome variable (PBVC). Previous studies indicate that the mean annual rate of PBVC in FTD is 3.15% (*SD* = 2.08)[39]. The mean atrophy rate in controls is 0.47%. Slowing the rate of atrophy by 50% (half-way between the FTD rate and the control rate = 1.81%) would represent a clinically meaningful treatment effect. Assuming the standard deviation of the FTD group holds across treatment and placebo arms, this would correspond to a medium effect size (Cohen's d = 0.64). Given a critical two-tailed alpha of 0.05, recruiting 80 participants (randomised 1:1 into two groups) would yield power of 0.80, to observe such or larger difference. Participant attrition rates are high (10-40%) in similar trials in FTDs [40-43], therefore a sample size of 120 will allow for adequate power. Given the previously demonstrated safety and tolerability, no interim analyses of efficacy, futility or safety are planned.

Outcomes and statistical overview

Primary endpoint

The primary outcome measure will be the PBVC from baseline to 52 weeks between the treatment and placebo groups. All participants with a post-baseline MRI will be included in the primary analysis. This will be analysed with a general linear model (ANCOVA) with the PBVC as an output, the treatment as an input, and the baseline brain volume as covariate for adjustment purposes.

Secondary endpoints

All continuous secondary efficacy endpoints will be reported using descriptive statistics (mean, median, minimum, maximum, standard deviation) by visit. Transformations of these endpoints (such as change and percentage change) will be summarised similarly.
The analysis of change from Baseline to Week 52 in CSF total-tau, ACE-III and CBI-R will be performed using a general linear model (ANCOVA) where the corresponding baseline

measure will be incorporated as a covariate in the model. Estimates will be obtained from the model of the adjusted mean change (with 95% confidence limits) in marker for treatment.

Safety and tolerability

For all categorical outcomes frequency tables (number of subjects and percentage) will be presented by visit, these tables will indicate both the number of subjects in the cohort (N) and the number of observations (n).
Safety and tolerability will be determined by frequency of adverse events (CTCAE score ≥3), frequency of down-titration events and frequency of study discontinuation.

Monitoring and Data Quality

In accordance with GCP and ICH guidelines, the project manager will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment.

An independent medical monitor has been appointed to provide safety oversight during the conduct of the study, and to review all safety-related events at three-month intervals.

The DSMB will consist of the medical monitor, an independent clinician and independent biostatistician. The first DSMB review will be conducted within two weeks of the third randomised patient reaching their week 8 visit or within one week of two SAEs occurring, whichever is first. Subsequent DSMB reviews will occur every six months. Additional DSMB meetings may be called at the request of the medical monitor or site principal investigators in the event of urgent safety concerns. After each review the medical monitor will make recommendations to the principal investigator based on the safety and tolerability issues.

Ethics and Dissemination

The study has been approved by the Alfred Hospital Human Research Ethics Committee (HREC, 609/19). Results of this study will be disseminated through presentations at national and international conferences and published in peer-reviewed journals. Any amendments to the protocol will be approved by the HREC prior to implementation and subsequently updated on ANZCTR.

Patient and Public Involvement Statement

Patients were not involved in the study conception or design. All study participants will be provided with a plain English summary of the results of the study at its conclusion (a requirement of Australian ethics committees and stated in the study consent form).
Dissemination of results to the wider community will be through open events at our hospitals and Dementia Australia as well as media reports.

Conclusions

To date there have been few clinical trials in bvFTD, with such trials complicated by different underlying pathologies such as hyperphosphorylated tau and TDP43. This study represents the first to target hyperphosphorylated tau pathology, which accounts for approximately 50% of cases. Sodium selenate has been shown to activate PP2A, increasing dephosphorylation of hyperphosphorylated tau. Therefore, this double blind randomised controlled trial will

investigate sodium selenate as a potential disease-modifying treatment for bvFTD. The main outcome will be efficacy of sodium selenate as measured by PBVC over 52 weeks of treatment. In addition to testing a potential new treatment for bvFTD, the study will also generate considerable longitudinal multimodal data which will lead to a greater understanding of disease progression and potentially identify new biomarkers of treatment response that can be used in future clinical trials in bvFTD. The statistical modelling of factors influencing treatment (non-)response will enable a "precision medicine" approach for the future development of sodium selenate as a treatment. This will allow the identification of patients most likely to respond to the treatment, increasing the chances of success of future studies, whilst minimising the resources needed to continue development and avoiding treating patients who will not benefit from the treatment.

Table 1: Schedule of Assessments

	Screening		Baseline										
Visit #	**1a**	**1b**	**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 bvFTD	X												
MRI scan	X											X	
Amyloid PET scan		X											
FDG PET scan			X									X	
tau PET scan (optional)			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	
Modified HIS	X												
ACE	X			X						X		X	
Cognitive and Behavioural Battery				X						X		X	
C-SSRS	X			X				X	X	X	X	X	X
Haematology and 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
Plasma HCG pregnancy test	X												
Urine pregnancy test				X				X	X	X	X	X	X
Dispense IP				X					X	X	X		
Redispense IP								X					
IMP Administration				X				X					
Dispense Diary Card				X				X	X	X	X	X	
Review 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

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A study protocol for a phase II randomized, double-blind, placebo-controlled trial of sodium selenate as a disease-modifying treatment for behavioural variant frontotemporal dementia

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Abstract

Introduction: Behavioural variant frontotemporal dementia (bvFTD) is a neurodegenerative disorder often neuropathologically associated with the accumulation of abnormally hyperphosphorylated tau, for which there is currently no disease modifying treatment. Previous work by our group has shown sodium selenate upregulates the activity of PP2A in the brain, increasing the rate of tau dephosphorylation. The objective of this study is to evaluate the efficacy and safety of sodium selenate as a disease-modifying treatment for bvFTD.

Methods and analysis: This will be a multi-site, phase 2b, double-blind placebo-controlled trial of sodium selenate. One hundred and twenty participants will be enrolled across 4 Australian academic hospitals. Following screening eligible participants will be randomised (1:1) to sodium selenate (15mg three times a day) or placebo for 52 weeks. Participants will have regular safety and efficacy visits throughout the study period. The primary study outcome will be percentage brain volume change (PBVC) as measured on MRI over 52 weeks of treatment. This will be analysed with a general linear model (ANCOVA) with the PBVC as an output, the treatment as an input, and the baseline brain volume as covariate for adjustment purposes. Secondary outcomes include safety and tolerability measures, and efficacy measures; change in CSF total-tau, Addenbrooke's Cognitive Examination-III and Cambridge Behavioural Inventory-Revised scores over the 52 weeks of treatment. These will also be analysed with analysis of covariance (ANCOVA) where the corresponding baseline measure will be incorporated in the model. Additional exploratory outcomes will include other imaging, cognitive and biospecimen analyses.

Ethics and dissemination: The study was approved by the Human Research & Ethics Committee of the lead site as part of the Australian Multisite Ethics approval system. The results of the study will be presented at national and international conferences and published in peer-reviewed journals.

Trial registration number: ACTRN12620000236998

Strengths and Limitations

- A large placebo-controlled RCT of a new drug for behavioural variant frontotemporal dementia (bvFTD)
- Extensive clinical, cognitive and imaging data will be collected producing a highly characterised prospective patient cohort which will be of huge significance to the field
- A mixture of established and novel diagnostic methods will be used, potentially validating new diagnostic approaches for future use
- Due to difficulty identifying pathology of bvFTD in life, some participants may not have the pathology targeted by this drug

Background

Behavioural-variant frontotemporal dementia (bvFTD) is the most common clinical syndrome caused by frontotemporal lobar degeneration (FTLD). It is a neurodegenerative disease characterised by the development of progressive behavioural features including disinhibition, apathy, loss of empathy, perseveration and stereotyped behaviour. bvFTD is a devastating condition for both patients and their families, and is invariably fatal. Prevalence rates of bvFTD range from 15-50 cases per 100,000 people [1-3]. No approved disease-modifying treatments currently exist for bvFTD, and the few international clinical trials that have been carried out have been unsuccessful [4]. A major unmet need therefore exists in the treatment of this condition. Approximately 45% of bvFTD cases are classified as 'tauopathies', neuropathologically characterised by abnormally hyperphosphorylated inclusions of the microtubule-associated protein *tau* [5]. Hyperphosphorylated tau dissociates from microtubules and aggregates in to filamentous tau deposits, disrupting axonal structure and transport leading to neurodegeneration. Targeting this hyperphosphorylated tau is a promising treatment strategy for these patients that requires validation with randomised clinical trials [6].

Targeting hyperphosphorylated tau

Two broad approaches are possible to pharmacologically reduce tau hyperphosphorylation in the brain: 1) *inhibition* of tau serine/threonine kinases, or 2) *activation* of tau serine/threonine phosphatases. Multiple kinases have been implicated in the phosphorylation of tau, hence a more feasible strategy is the upregulation of protein phosphatase 2 (PP2A), the major tau serine/threonine phosphatase present in the brain, which accounts for over 70% of phosphatase activity [7]. PP2A is co-localised with tau [8-10] , and reductions in PP2A activity, and therefore reduced tau dephosphorylation are observed in many neurodegenerative diseases. Further, PP2A activity negatively correlates with tau levels in human tissue [10].

Selenium is an essential trace element in humans and is present in low concentrations in food and the environment. Whilst numerous studies have reported potential chemopreventive benefits associated with selenium dietary supplementation, the therapeutic potential of other selenium compounds has not been widely explored. A large body of pre-clinical, and emerging clinical data, have provided evidence for the potential of sodium selenate, an oxidised salt of selenium, as a disease-modifying treatment for hyperphosphorylated tau-based neurodegenerative diseases, traumatic brain injury, and epilepsy [11-21]. Our research has not only demonstrated significant therapeutic benefits in preclinical models of cancer [12], Alzheimer's disease [13, 22], epilepsy [15, 16, 18, 21] and traumatic brain injury [11, 18, 19], but also has showed that these benefits were restricted to the administration of the single selenium species, sodium selenate, and were only beneficial in a therapeutic setting when administered in supranutritional doses [17, 23].

Clinical Trials of Sodium Selenate for Other Conditions

Two clinical trials have demonstrated the safety and tolerability of sodium selenate in patients with diseases other than FTD. First, a Phase I study in patients with castration-resistant prostate cancer demonstrated a favourable safety profile of VEL015 (sodium selenate) [12]. This study demonstrated that doses up to 60mg per day were tolerable in chronic dosing, with dose-limiting toxicity observed at 90mg per day.

More recently, our group completed and published a Phase IIa trial of sodium selenate (30mg/day) in 40 patients with mild-moderate Alzheimer's disease (AD), which confirmed

the safety and tolerability of the agent [17, 23]. This AD study was designed to evaluate safety and tolerability and not treatment efficacy, however MR diffusion tensor imaging (DTI) measures were exploratory outcome measures in this study. Voxel-wise analysis of DTI metrics showed relatively less degeneration in the treatment group compared to placebo, which was widespread, but most prominent in the corpus callosum [17]. Selenium levels in patients' serum and CSF were higher in the treatment group, which is evidence of penetration of the agent across the blood-brain barrier and into the CNS [23]. In patients treated with 10mg tds of sodium selenate, serum selenium levels increased from 145.4±28.8 µg/L at baseline to 858.3±446.1 µg/L at week 24, and CSF selenium levels increased from 1.4 ± 0.5 µg/L to 20.2 ± 9.1 µg/L, no change in serum or CSF levels was observed in the placebo-treated patients [23]. In addition, selenium levels were inversely correlated with the degree of decline in cognitive measures over the 6-month treatment period, indicating a relationship between drug exposure and neuroprotective efficacy [23].

Phase 1 Open-label Trial of Sodium Selenate for bvFTD

We are currently undertaking a single site, exploratory, Phase Ib open labelled study of sodium selenate as a treatment for patients with bvFTD (ACTRN12617001218381, https://anzctr.org.au). The primary objective is to assess the safety and tolerability of a supranutritional dose of sodium selenate in patients with possible bvFTD. Twelve patients have been recruited, and eight patients have completed the 12-month treatment phase so far. There have been no withdrawals, and adverse effects have been relatively mild and similar to those experienced in the Phase IIa AD trial [17].

Informed by this experience, we will now conduct a multi-centred placebo-controlled randomised controlled trial of sodium selenate as a treatment for bvFTD.

Aims/Outcomes

The aim of this study is to investigate the efficacy and safety of sodium selenate (15 mg, three times a day) as a disease-modifying treatment of probable bvFTD.

The primary outcome variable is change in whole brain volume over 52 weeks of treatment.

The secondary outcome variables (safety) will be rate and severity of adverse events and rate of study withdrawal. Secondary efficacy outcome variables are change in cerebrospinal fluid (CSF) total-tau, change in cognition as measured by the Addenbrooke's Cognitive Examination-III (ACE-III) total score and change in behaviour as measured by the Cambridge Behavioural Inventory-Revised (CBI) total score over 52 weeks.

Additional exploratory outcomes will investigate changes in CSF, serum and plasma protein biomarkers (total-tau, phospho-tau and neurofilament light chain (NfL)), changes in other measures of cognition and behaviour (memory, language, executive function, attention), and changes in additional neuroimaging measures, including cortical thickness, volumetrics, advanced MRI (diffusion, quantitative susceptibility mapping (QSM), resting state) and fluoro-deoxy glucose (FDG) and tau-binding positron emission tomography (PET). The study will also use advanced statistical modelling to identify predictors of treatment response and non-response, and correlations between biomarkers and cognitive function and behaviour.

Methods/Design

This is a multi-site, phase 2b double-blind, randomised, placebo-controlled trial of sodium selenate as a treatment for probable bvFTD. Patients will receive 52 weeks of treatment with

either sodium selenate (15 mg tds) or placebo. 120 patients will be recruited in to this study. The study will be conducted at 4 centres in Melbourne and Sydney. The study is funded by the Australian National Health and Medical Research Council (NHMRC; APP1170276). Ethics approval was granted by the Alfred Health Human Research Ethics Committee, Melbourne (609/19). The trial is registered with ANZCTR (ACTRN12620000236998)

Eligibility Criteria

Inclusion criteria*:* Participants will be aged over 35, have a diagnosis of probable bvFTD [24] and a modified Hachinski score <5 [25]. Participants must be using effective contraception for the duration of the trial. Participants must have a lumbar puncture and MRI performed during screening. The structural brain MRI must be consistent with a bvFTD diagnosis with no other gross structural abnormalities indicating another neurological disorder. The participant must have a negative amyloid-PET scan (either as part of screening assessments or historical). 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 behaviour throughout the study. 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; known history of familial Alzheimer's disease or genetic form of FTD that is not considered a primary tauopathy (e.g., *GRN* mutation or *C9ORF72* expansion); lifelong primary psychiatric disorder; significant traumatic brain injury with loss of consciousness >5 mins; significant medical or neurological disease, with the exception of bvFTD 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: 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.

Intervention, Randomisation and Blinding

Each participant will be provided a unique screening number upon signing the consent form. Once all screening assessments have been completed and the participant is eligible to continue, the participant will be assigned a sequential randomisation number generated within the redcap eCRF (subject to entry of key data into the eCRF). This randomisation number will be provided to the unblinded site pharmacist who will dispense the drug/placebo in accordance with the randomisation schedule.
Participants will receive either sodium selenate or placebo (1:1) for 52 weeks. Each capsule will contain 5 mg of drug or placebo. The initial dose will be two capsules (10 mg) three

times a day (tds), increasing to three capsules (15mg) tds at week 4, subject to tolerability. In the event of adverse events potentially related to the study drug administration, treatment may be temporarily interrupted and a single within-subject dose reduction, to 10 mg tds will, at the investigator's discretion, be allowed. An additional down-titration to 5 mg tds will only be allowed after consultation with the medical monitor.

The study participant, their study partner and all site staff (with the exception of the pharmacy team) will remain blinded throughout the course of the study. Individual unblinding envelopes for emergency unblinding of individual patients will be kept at the study sites. The data safety monitoring board (DSMB) will also be blind to study treatment when reviewing safety data. In the event of unexpected adverse events the DSMB may request unblinding of data to assess potential causality.

Procedures and Assessments

Participants will undergo study testing and procedures as outlined in Table 1. Briefly, at the screening assessment, the participant will be reviewed to ensure they meet all the inclusion criteria and none of the exclusion criteria. Neuroimaging (MRI, and amyloid-PET) will follow to strengthen the bvFTD diagnosis (and exclude Alzheimer's disease). At the baseline visit, the inclusion and exclusion criteria will be reviewed to ensure the participant remains eligible for the study. The participant will undergo an FDG-PET, baseline CSF sampling and a cognitive and behavioural assessment. Lastly the participant will be administered the study drug (10mg) in the clinic and multiple blood draws taken for pharmacokinetic analysis.

Follow-up phone calls will be made to monitor for adverse events. If participants are tolerating the study drug, they will be instructed to increase to 3 capsules (15mg tds) at week 4. Diary cards will be given to participants to record adverse events that occur between clinic visits.

Participants will attend regular in-clinic study visits to assess their safety and well-being, and to resupply the study medication. The cognitive and behavioural assessment will be repeated at weeks 26 and 52. Prior to their week 52 clinical visit participants will undergo repeat neuroimaging (MRI, FDG-PET) and CSF sampling for biomarker analyses. Participants will attend a final safety follow up visit 4 weeks following the cessation of the study drug.

Measures

Neuroimaging

MRIs will be acquired during the screening period and week 52. The MRI protocol includes the following sequences; volumetric T1 (1mm^3), T2-space (0.8 x 1.1 x 4mm), volumetric T1 (1mm^3), multi-band DWI (2.5mm^3), resting state fMRI (4.5mm^3), multi-echo QSM (3.5mm^3).

The primary outcome measure will be the change in whole-brain volume (percentage brain volume change; PBVC) from baseline to 52 weeks. Whole-brain volume will be measured using T1-weighted structural MRI acquired at baseline and after 52 weeks of treatment. Change in whole-brain volume will be computed using the *SIENA* module within the FSL software [26]. Briefly, *SIENA* performs brain extraction, halfway-space registration, and tissue segmentation. Perpendicular edge displacement is then computed between the brain/non-brain edge points of the two images. The accuracy of this method is very high, with longitudinal error reported at 0.15% [27].

Florbetaben PET will be conducted at screening to exclude Alzheimer's disease. 300MBq (±10%) will be injected intravenously, 90 minutes post-injection a dynamic 3D scan (4x300 sec frames) will be acquired. This will not be required for participants who have a historical negative amyloid PET that is available for review by the site principal investigator.

FDG PET will be conducted at baseline and week 52 to assess disease progression. 185 MBq (±10%) will be injected intravenously, the patient will rest in a quiet room for 20 minutes, and a dynamic 3D acquisition will begin 30 minutes post-injection (6x300sec frames).
An optional sub-study investigating tau PET as a marker of disease progression will also be conducted. Participants who consent will have two tau PET scans, at baseline and in the two weeks prior to week 52. A dynamic 3D acquisition (12x150 s frames) will begin 45 minutes after the intravenous injection of 185MBq (±10%) of PI-2620.

Cognitive and Behavioural Battery

The following cognitive and behavioural scales will be administered at baseline, week 26 and week 52 of the study.

Addenbrooke's Cognitive Examination III: The Addenbrooke's Cognitive Examination is a broad cognitive screening test of 5 cognitive domains; attention/orientation, memory, language, verbal fluency and visuospatial skills, producing a score out of 100 (normal scores ≥ 88/100). Administration takes about 15 minutes and three different versions are available [28]. This will be analysed as one of the secondary efficacy endpoints.

NIH Toolbox: The NIH Toolbox is a multidimensional battery of measures used to assess cognitive, sensory, motor and emotional function in people. The NIH Toolbox has been validated for ages 3-85 years and is designed such that repeated assessments can be completed for longitudinal monitoring of disease progression. The NIH Toolbox takes approximately 30 minutes to administer [29, 30].

Hayling Sentence Test: The Hayling Sentence Completion test is a measure of response initiation and response suppression. It is entirely verbal, and therefore can be administered to patients with problems with reading and visual perception. It consists of two sets of 15 sentences each having the last word missing. In the first section the examiner reads each sentence aloud and the participant has to simply complete the sentences as quickly as possible, yielding a simple measure of response initiation speed. The second part of the Hayling requires participants to complete a sentence with a nonsense ending word, giving measures of response suppression ability and thinking time. It takes approximately 5 minutes to administer and yields three different measures of executive functioning which can be considered separately or combined into an overall score [30].

Victoria Stroop Test: The Victoria Stroop Test is a measure of executive function commonly used in neuropsychological evaluation. The test uses three conditions that consist in naming the color of dots, of neutral words, and of color words printed in incongruent colors. Each condition contains 24 items. Because of its short administration time, approximately 5 minutes, it is appropriate for use in geriatric populations and with those suffering from dementia [31].

Controlled Oral Word Association Test (COWAT): Controlled Oral Word Association Test, is a verbal fluency test that measures executive function. The participant is asked to name words beginning with a designated letter for one minute under certain conditions (e.g., no repetitions, no proper nouns, no identical stem words) and this procedure is repeated with three different letters. The whole examination usually takes 5–10 minutes [32].

Trail Making Test A and B: The Trail Making Test is a test of visual attention and task switching. It consists of two parts in which the subject is instructed to connect a set of 25 targets as quickly as possible while still maintaining accuracy. There are two parts to the test: in the first, the targets are all numbers (1, 2, 3, etc.) which the participant must connect sequentially; in the second part, the subject alternates between numbers and letters (1, A, 2, B, etc.). The first part of the test is used to primarily measure processing speed, whilst the second part is a test of executive function. The time to complete the paths are the scores for this assessment [33].

Digit Span: The digit span test is a measure of attention and working memory. Participants are told a sequence of digits (which become progressively longer) which they must repeat back to the examiner. This test is performed forwards and backwards. The score is the maximum length of digits they correctly repeated under the two conditions [34].

Sydney Language Battery: The Sydney Language Battery is a test of language at a single word level, which measures naming, repetition, comprehension, and semantic association. The same set of 30 multisyllabic nouns (3 or more syllables) are used across the four tasks. Words are ordered with decreasing frequency and are graded into three broad levels of difficulty [35].

Mini Social Emotional Assessment (mini-SEA): The Mini Social Emotional Assessment (mini-SEA) is a cognitive battery designed to assess social and emotional function. The battery contains two components: (a) a faux-pas test assessing theory of mind, and (b) a facial emotional recognition test. The neural correlates of the mini-SEA have been established in bvFTD, with significant relationships reported with the medial prefrontal cortex (mPFC). The mini-SEA takes approximately 30 minutes to administer [36].

Cambridge Behavioural Inventory - Revised: The Cambridge Behavioural Inventory – Revised (CBI-R) is an informant questionnaire that assesses neuropsychiatric and neurobehavioral symptoms in patients with neurodegenerative disease [18]. The instrument contains 45 questions assessing the following domains: (a) memory and orientation, (b) everyday skills, (c) self-care, (d) abnormal behaviour, (e) mood, (f) beliefs, (g) eating habits, (h) sleep, (i) stereotypic and motor behaviours, and (j) motivation. The instrument takes approximately 10 minutes to complete. A total score is generated that will be used for this study [37]. This will be analysed as one of the secondary efficacy endpoints.

Caregiver Burden Scale: The Caregiver Burden Scale (CBS) is a caregiver-completed instrument that assesses the experience of burden in people who care for those with cognitive disorders [38]. The instrument contains 22 questions and takes approximately 5 minutes to complete. A total score is generated that will be used for the present study [38].

Safety Assessments

A 12-ECG and a physical examination will be performed at each clinic visit, haematology, chemistry and urinalysis will be performed at each clinic visit except week 16. Neurological examinations will be carried out at screening, baseline, week 26 and 52. Any clinically significant abnormalities in any of these investigations will be considered adverse events. The diary cards will be reviewed to ascertain any adverse events that occurred between visits, and the participant and their study partner interviewed to confirm adverse events and concomitant therapies.

Blood biomarkers

Additional blood samples will be collected for pharmacokinetic, biomarker and exploratory analyses. Pharmacokinetic sampling (6ml/sample) will be performed at baseline, week 8 and week 52. A pre-dose (1 hour) sample will be taken, then 4 additional samples, 0.5, 1, 2, 4 hours after dosing. Sodium selenate levels in plasma will subsequently be measured in these samples for determination of the pharmacokinetic profile.

Exploratory sampling will occur at baseline, week 8, week 26 and week 52. Samples will be taken for plasma, serum and PMBC isolation at each of these visits. Blood for DNA and RNA will be taken only at baseline. Exploratory analyses will include measurement of proteins associated with neurodegeneration (total-tau, phospho-tau, beta-amyloid$_{42}$, neurofilament light) in serum and plasma, testing for genetic mutations associated with bvFTD (*MAPT*, *GRN*, *C9ORF72* expansion). As yet undetermined additional testing may be performed.

CSF biomarkers

CSF sampling will take place at baseline (pre-treatment) and week 52. Atraumatic needles (20G) will be used for sampling. CSF (~20 mL) will be collected in polypropylene tubes (10 mL) cooled on ice. Samples will be kept on ice until processing, aliquoted in to 500 µL polypropylene aliquots and stored at -80 ºC. Samples will be analysed for beta-amyloid$_{42}$, total-tau, phospho-tau and NfL protein levels. Additional as yet undetermined testing may also be performed. Change in total-tau will be used as a secondary efficacy outcome measure.

Power and Sample Size

All outcomes are predefined prospectively in hierarchical order, meaning that the trial will be declared positive or negative based on primary outcome. Statistical power has thus been determined on the primary outcome variable (PBVC). Previous studies indicate that the mean annual rate of PBVC in FTD is 3.15% (*SD* = 2.08)[39]. The mean atrophy rate in controls is 0.47%. Slowing the rate of atrophy by 50% (half-way between the FTD rate and the control rate = 1.81%) would represent a clinically meaningful treatment effect. Assuming the standard deviation of the FTD group holds across treatment and placebo arms, this would correspond to a medium effect size (Cohen's d = 0.64). Given a critical two-tailed alpha of 0.05, recruiting 80 participants (randomised 1:1 into two groups) would yield power of 0.80, to observe such or larger difference. As a proportion of participants will have a non-tau-based pathology (estimated ~30% based on previous experience), therefore we anticipate a sample size of 120 will allow for adequate power. Due to the previously demonstrated safety and tolerability, no interim analyses of efficacy, futility or safety are planned.

Outcomes and statistical overview

Primary endpoint

The primary outcome measure will be the PBVC from baseline to 52 weeks between the treatment and placebo groups. All participants with a post-baseline MRI will be included in the primary analysis. This will be analysed with a general linear model (ANCOVA) with the PBVC as an output, the treatment as an input, and the baseline brain volume as covariate for adjustment purposes.

Secondary endpoints

All continuous secondary efficacy endpoints will be reported using descriptive statistics (mean, median, minimum, maximum, standard deviation) by visit. Transformations of these endpoints (such as change and percentage change) will be summarised similarly.
The analysis of change from Baseline to Week 52 in CSF total-tau, ACE-III and CBI-R will be performed using a general linear model (ANCOVA) where the corresponding baseline measure will be incorporated as a covariate in the model. Estimates will be obtained from the model of the adjusted mean change (with 95% confidence limits) in marker for treatment.

Safety and tolerability

For all categorical outcomes frequency tables (number of subjects and percentage) will be presented by visit, these tables will indicate both the number of subjects in the cohort (N) and the number of observations (n).
Safety and tolerability will be determined by frequency of adverse events (CTCAE score ≥3), frequency of down-titration events and frequency of study discontinuation.

Monitoring and Data Quality

In accordance with GCP and ICH guidelines, the project manager will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment.

An independent medical monitor has been appointed to provide safety oversight during the conduct of the study, and to review all safety-related events at three-month intervals.

The DSMB will consist of the medical monitor, an independent clinician and independent biostatistician. The first DSMB review will be conducted within two weeks of the third randomised patient reaching their week 8 visit or within one week of two SAEs occurring, whichever is first. Subsequent DSMB reviews will occur every six months. Additional DSMB meetings may be called at the request of the medical monitor or site principal investigators in the event of urgent safety concerns. After each review the medical monitor will make recommendations to the principal investigator based on the safety and tolerability issues.

Ethics and Dissemination

The study has been approved by the Alfred Hospital Human Research Ethics Committee (HREC, 609/19). Results of this study will be disseminated through presentations at national and international conferences and published in peer-reviewed journals. Any amendments to the protocol will be approved by the HREC prior to implementation and subsequently updated on ANZCTR.

Patient and Public Involvement Statement

Patients were not involved in the study conception or design. All study participants will be provided with a plain English summary of the results of the study at its conclusion (a requirement of Australian ethics committees and stated in the study consent form).
Dissemination of results to the wider community will be through open events at our hospitals and Dementia Australia as well as media reports.

Table 1: Schedule of Assessments

	Screening		Baseline										
Visit #	**1a**	**1b**	**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 bvFTD	X												
MRI scan	X											X	
Amyloid PET scan		X											
FDG PET scan			X									X	
tau PET scan (optional)			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	
Modified HIS	X												
ACE	X			X						X		X	
Cognitive and Behavioural Battery				X						X		X	
C-SSRS	X			X				X	X	X	X	X	X
Haematology and 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
Plasma HCG pregnancy test	X												
Urine pregnancy test				X				X	X	X	X	X	X
Dispense IP				X					X	X	X		
Redispense IP								X					
IMP Administration				X				X					
Dispense Diary Card				X				X	X	X	X	X	
Review 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

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	PageNo	Description
Administrative information			
Title	1	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	6	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	6	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	n/a	Date and version identifier
Funding	4	6	Sources and types of financial, material, and other support
Roles and responsibilities	5a	1	Names, affiliations, and roles of protocol contributors
	5b	n/a	Name and contact information for the trial sponsor
	5c	n/a	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	n/a	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction			
Background and rationale	6a	4	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

	6b	n/a	Explanation for choice of comparators
Objectives	7	5	Specific objectives or hypotheses
Trial design	8	5	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
			Methods: Participants, interventions, and outcomes
Study setting	9	6	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	6	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	6	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	7	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	7	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	6	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	5, 7-10	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	7, 13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size	14	10	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	10	Strategies for achieving adequate participant enrolment to reach target sample size
			Methods: Assignment of interventions (for controlled trials)
Allocation:			
Sequence generation	16a	11	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	11	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	11	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	12	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	12	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
			Methods: Data collection, management, and analysis
Data collection methods	18a	7-10	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

	18b	n/a	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	11	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	10-11	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	n/a	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	10	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
			Methods: Monitoring
Data monitoring	21a	11	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	10-11	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	7	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	n/a	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
			Ethics and dissemination

Research ethics approval	24	6	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	11	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	6	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	n/a	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	6	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	1	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	n/a	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	n/a	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	11	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	n/a	Authorship eligibility guidelines and any intended use of professional writers
	31c	n/a	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices			
Informed consent materials	32	n/a	Model consent form and other related documentation given to participants and authorised surrogates

Biological specimens	33	4-5	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.