

## RESEARCH ARTICLE

# A phase 1b open-label study of sodium selenate as a disease-modifying treatment for possible behavioral variant frontotemporal dementia

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## Abstract

**Introduction:** Sodium selenate increases tau dephosphorylation through protein phosphatase 2 activation. Here we report an open-label Phase 1b study of sodium selenate as a disease-modifying treatment for behavioral variant frontotemporal dementia (bvFTD).

**Methods:** Twelve participants with bvFTD received sodium selenate (15 mg, three times a day) for 52 weeks. Safety assessments were carried out throughout the trial. Primary outcomes were frequency of adverse events (AEs), serious adverse events (SAEs), and discontinuations. Secondary outcomes of potential efficacy included cognitive and behavioral assessments, magnetic resonance imaging (MRI) whole brain volume, and cerebrospinal fluid (CSF) and blood total tau (t-tau), phosphorylated tau (p-tau), and neurofilament light (NfL) levels, which were measured at baseline and at week 52.

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**Results:** Sodium selenate was safe and well tolerated. All participants completed the study, and the majority (64.7%) of reported AEs were mild. One SAE occurred, which was not treatment related. Small declines in MRI and cognitive and behavioral measures were observed over the treatment period. There was no evidence for change in CSF protein levels (t-tau, p-tau, or NfL). Further analysis showed two distinct groups when measuring disease progression markers over the course of the study—one (n = 4) with substantial brain atrophy (2.5% to 6.5% reduction) and cognitive and behavioral decline over the 12-month treatment period, and the second group (n = 7) with no detectable change in cognitive and behavioral measures and less brain atrophy (0.3% to 1.7% reduction).

**Conclusion:** Sodium selenate is safe and well tolerated in patients with bvFTD. Randomized-controlled trials are warranted to investigate potential efficacy.

#### KEYWORDS

anti-tau treatment, behavioral variant frontotemporal dementia (bvFTD), clinical trial, fluid biomarkers, frontotemporal lobar degeneration (FTLD), magnetic resonance imaging (MRI), phosphorylated tau, safety and tolerability, tau, therapeutic trial

## 1 | INTRODUCTION

Behavioral variant frontotemporal dementia (bvFTD) is one of the clinical syndromes seen in patients with frontotemporal lobar degeneration (FTLD), and is the second most common form of dementia in younger patients.<sup>1</sup> Tau-based pathology underlies ≈45% of bvFTD cases, with an excess of hyperphosphorylated tau disassociating from microtubules disrupting axonal transport and neuronal integrity, leading to neurodegeneration.<sup>2</sup> Hyperphosphorylated tau represents a potential target for disease-modifying therapies for the subgroup of bvFTD patients with a tau-based pathology. Protein phosphatase 2 (PP2A) accounts for ≈70% of the phosphatase activity in the brain, and is the primary phosphatase catalyzing the dephosphorylation of tau,<sup>3</sup> and both the levels and activity of this enzyme are reduced in neurodegenerative disease. Therefore, stabilization and upregulation of this enzyme may reduce levels of hyperphosphorylated tau.<sup>4</sup>

Sodium selenate has been shown to specifically upregulate brain PP2A activity and reduce hyperphosphorylated tau levels in animal models of FTD and epilepsy.<sup>4,5</sup> We have previously reported a Phase 2 double-blind placebo-controlled randomized-controlled trial (RCT) of 6 months of treatment with sodium selenate,<sup>6</sup> and a subsequent open-label extension study of sodium selenate in mild-moderate Alzheimer's disease (AD).<sup>7</sup> These studies found that sodium selenate was safe and well tolerated at a dose of 30 mg per day in participants with AD for up to 23 months of treatment. The RCT did not find any differences in cognitive measures between groups over the treatment period (24 weeks)<sup>6</sup>; however, there was evidence of less neurodegeneration on diffusion-tensor magnetic resonance imaging (MRI) measures in the sodium selenate group compared to controls.<sup>6</sup> Subsequent post hoc analysis found that participants who had higher levels of selenium (a

metabolite of sodium selenate) in their blood and cerebrospinal fluid (CSF) showed less cognitive decline than those with lower selenium levels.<sup>8</sup>

The aim of this current study was to investigate the safety and tolerability of treatment with sodium selenate in patients with bvFTD, and to evaluate measures of efficacy to inform future RCTs of sodium selenate in patients with bvFTD.

## 2 | METHODS

### 2.1 | Study design

This was an open-label, Phase 1b trial of sodium selenate as a disease-modifying treatment for patients with bvFTD. The study was conducted at a single center in Melbourne, Australia, from August 2017 to Jan 2021.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was approved by the local institutional human research ethics committee (2017.090, Melbourne Health, Melbourne, Victoria, Australia), prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12617001218381), and the protocol compliant with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.<sup>9</sup> Written informed consent was obtained from the participant or their legally authorized representative (as required by local laws and regulations), and the participant's career.

Eligible patients were older than 35 years of age with a diagnosis of possible bvFTD,<sup>10</sup> a negative amyloid positron emission tomography (PET), and living in the community. Participants with genetic forms of bvFTD that are not considered primary tauopathies were excluded.

The full inclusion/exclusion criteria are detailed in the study protocol (Supplement 1).

## 2.2 | Procedures and treatment

The duration of the study was up to 64 weeks (up to 8 weeks of screening, 52 weeks of treatment, 4 weeks of follow-up). Participants received sodium selenate, initially at a dosage of 10 mg three times a day (t.i.d.), uptitrating to 15 mg t.i.d. at week 4, which was maintained for the duration of the treatment period (unless down-titrated for tolerability reasons). The schedule of clinical visits was as follows: screening; baseline; and weeks 4, 8, 16, 26, 39, 52 (end of treatment), and 56 (end of study). Safety telephone calls were completed at weeks 2 and 6 to ensure participant safety and treatment compliance.

## 2.3 | Outcomes

The primary outcomes were safety and tolerability, defined as the frequency of adverse events (AEs), serious adverse events (SAEs), and frequency of early discontinuations. Secondary outcomes investigated potential efficacy measures between baseline and week 52. CSF total-tau (t-tau) and phosphorylated tau (p-tau), whole brain volume, and cognitive and behavioral measures including the National Institutes of Health (NIH) toolbox,<sup>11</sup> mini Social and Emotional Assessment (mini-SEA),<sup>12</sup> California Verbal Learning Test II (CVLT-II),<sup>13</sup> Neuropsychiatry Unit Cognitive Screening Tool (NUCOG),<sup>14</sup> Cambridge Behavioural Inventory (CBI) Revised,<sup>15</sup> Revised Self-Monitoring Scale (RSMS),<sup>16</sup> and Zarit Burden Index (ZBI)<sup>17</sup> were investigated.

Additional exploratory outcomes included change between baseline and week 52 in CSF neurofilament light chain (NfL) and serum t-tau and p-tau. Exploratory sub-analyses further investigated all cognitive, behavioral, and protein biomarkers in a sub-group of participants deemed “non-progressors” based on their relative lack of progression of whole brain volume change (see section 2.6 Statistical Analysis).

## 2.4 | MRI analysis

MRI brains were acquired at baseline and week 52 using a clinical whole-body scanner (3T Prisma, Siemens); the study protocol included volumetric T1 (1 mm<sup>3</sup>, field of view [FOV] 22 × 22 cm, matrix 256 × 256 × 208) and T2 space (0.7 mm<sup>3</sup>, matrix 320 × 320 × 240). The SIENA pipeline within FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA>) was used to generate percentage whole brain volume change (PBVC) from baseline to week 52 for each participant.<sup>18</sup>

## 2.5 | Biofluid analysis

Quantification of t-tau and p-tau 181 levels in serum and CSF was performed using Simoa Tau Advantage and pTau 181 V2 Advantage

## RESEARCH IN CONTEXT

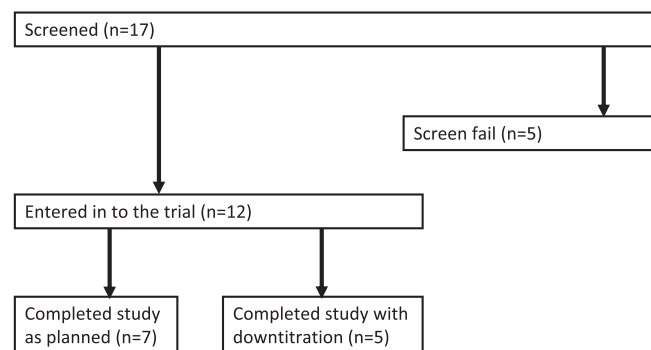
- 1. Systematic Review:** We searched and reviewed the literature using PubMed. Eleven studies have reported clinical trials of treatments for behavioral variant frontotemporal dementia (bvFTD). None of the seven randomized controlled trials met their efficacy outcomes. The only study of a potentially disease-modifying therapy for sporadic bvFTD showed a worsening in the active treatment group compared to placebo in the primary and secondary efficacy end points.
- 2. Interpretation:** This is the second study investigating a potentially disease-modifying therapy in sporadic bvFTD, demonstrating that long-term sodium selenate treatment is safe and well tolerated in patients with bvFTD. Exploratory biomarkers of disease progression distinguished two groups, progressors and non-progressors, which could indicate treatment response in subset of patients.
- 3. Future Directions:** Our current findings show that sodium selenate is safe and well tolerated in patients with bvFTD. The results of this study further suggest randomized, placebo-controlled trials of sodium selenate for bvFTD are warranted to investigate the potential efficacy of this treatment.

kits run on a Simoa HD-X Analyzer (Quanterix, Billerica, MA, USA) at Monash University, Department of Neuroscience. Assays were performed in a temperature-controlled laboratory by an experimenter blinded to the clinical information. All samples were tested in duplicate and measured above the lower limit of detection for t-tau (0.019 pg/mL) and p-tau 181 (0.028 pg/mL). The average inter-plate coefficient of variation (CV) for t-tau and p-tau was 14% and 4%, respectively. The average intra-plate CV for t-tau and p-tau was 6% and 6%, respectively.

CSF NfL levels were analyzed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (UmanDiagnostics, Umea, Sweden) at National Dementia Diagnostics Laboratory (Parkville, Melbourne Australia). The intra-assay CV was 11%.

## 2.6 | Statistical analyses

Analysis of safety data was performed on the intention-to-treat population. Efficacy analyses were performed on all participants who had data for those measures. Exploratory analyses were performed on “non-progressors”—defined as a PBVC of less than −1.81% (ie, a 50% reduction rate in annualized brain atrophy rates observed in patients with bvFTD, corrected for atrophy rates in healthy aging [−0.47%/year]).<sup>19</sup>



**FIGURE 1** Consort-style diagram of participant flow through the study

**TABLE 1** Baseline characteristics of patients (continuous variables are presented as median and range)

Age	60.5 (48.7-71.6 years)
Sex	4F:8M
Time from diagnosis	13.5 (1.5-19.25 months)
NUCOG total score	79.5 (47.5-93)
Presence of genetic mutations	10 UNK, 1 MAPT, 1 C9orf72 <sup>a</sup>
TOPF	102 (56-123)
WASI-II	72 (64-109)

<sup>a</sup>C9orf72 status disclosed after the week 52 visit. NUCOG, neuropsychiatry unit cognitive screening tool; TOPF, test of premorbid function; WASI-II, Wechsler abbreviated scale of intelligence version 2; UNK, unknown; MAPT, microtubule associated protein tau; C9orf72, chromosome 9 open reading frame 72.

Data are presented as median (range) for individual time points.

General linear mixed models were computed for each variable of interest, and output data presented as model estimate (*b*) and 95% confidence interval (CI). Baseline Test of Premorbid Function (TOPF) and Wechsler Abbreviated Scale of Intelligence version 2 (WASI-II) scores were included as covariates in the models investigating NUCOG, CVLT-II, and NIH toolbox measurements. Pearson's correlation was used to determine relationships between measures. Binomial logistic regression was performed to investigate the ability of baseline variables (CSF p-tau:t-tau, NFL, NUCOG, ZBI, and time from diagnosis) to differentiate "non-progressors" and "progressors."

Statistical analyses were performed using jamovi (v1.6.15).

### 3 | RESULTS

#### 3.1 | Participant demographics

Seventeen patients were screened and 12 were entered into the study (Figure 1). All participants completed the study. Participant demographics and baseline data are shown in Table 1. The study included four female and eight male participants with a median age of 61 years and median time since the bvFTD diagnosis of 14 months. Two partici-

**TABLE 2** Treatment-emergent adverse events that occurred in two or more participants

Adverse Events	Frequency
<b>Total TEAEs</b>	<b>12 (100%) 64</b>
<b>Solicited AEs</b>	<b>11 (92%) 32</b>
Nail changes	7 (58%) 7
Hair loss	5 (42%) 5
Muscle aches/cramps	3 (25%) 5
Headache	3 (25%) 3
Fatigue	3 (25%) 3
Diarrhea	2 (17%) 4
Lethargy	2 (17%) 3
<b>Unsolicited AEs</b>	<b>9 (75%) 32</b>
Fall	3 (25%) 3
Gout	2 (17%) 5
Faint (no LOC)	2 (17%) 2
Pruritis	2 (17%) 2

Data are presented as number of participants (percentage of total cohort) total number of events. Adverse events that occurred in fewer than two participants are not listed. TEAEs, Treatment Emergent Adverse Events; AEs, Adverse Events; LOC, loss of consciousness.

pants with no known family history of FTD had genetic testing undertaken during the study in the course of their clinical care. One was found to have a microtubule associated protein tau (MAPT) mutation and another was found to have the chromosome 9 open reading frame 72 (C9orf72) mutation, which was disclosed after their week 52 visit.

#### 3.2 | Safety and tolerability

Twelve patients (100%) experienced at least one treatment emergent AE (Table 2). Sixty-four AEs were reported over the study, 32 (50%) of which were determined to be possibly, probably, or definitely drug related. Most AEs were rated as mild (*n* = 44; 64.7%) and did not affect willingness to continue in the trial. The most common AEs were nail changes (*n* = 7; 58.3% of participants) and alopecia (*n* = 5; 41.7%). The single SAE, a herniated disc resulting in hospitalization, was not related to the treatment. Down-titration to 10 mg t.i.d. occurred in five participants due to AEs (*n* = 1 alopecia, *n* = 2 nail changes, *n* = 2 nail changes and alopecia). A second down-titration to 5 mg t.i.d. was enacted in one participant (due to nail changes and alopecia). Following this reduction the AEs resolved.

No clinically relevant findings in vital signs, electrocardiography (ECG), physical and neurological examinations, clinical laboratory results, or MRI safety assessments were observed.

#### 3.3 | Efficacy measures

Efficacy measures were available for 11 patients (one patient was unable to comply with any of the 12-month efficacy assessments).

**TABLE 3** Cognitive measures at baseline and week 52

	Baseline (n = 11)	Week 52 (n = 11)	Estimate	95% CI
NUCOG <sup>a</sup>	79.5 (47.5-93.0)	73.0 (19.0-97.0)	-0.172	(-0.290, -0.053)**
CBI	75 (32-106)	90 (32-125)	0.317	(0.178, 0.456)***
ZBI	28 (15-56)	36 (15-68)	0.1	(0.044, 0.166)**
RSMS	30 (15-50)	25 (0-47)	-0.165	(-0.230, -0.099)***
CVLT-II <sup>a</sup>	21 (13-32) <sup>b</sup>	25 (13-59) <sup>b</sup>	0.178	(0.035, 0.320)*
mini-SEA	24.0 (11.0-49.0) <sup>c</sup>	20 (7.0-24.0) <sup>c</sup>	-0.134	(-0.303, 0.036)

<sup>a</sup>NUCOG and CVLT-II scores corrected for baseline WASI and TOPF.

<sup>b</sup>CVLT-II baseline (n = 9), week 52 (n = 7).

<sup>c</sup>mini-SEA (n = 7) baseline and week 52.

Data are presented as median (range). NUCOG, neuropsychiatry unit cognitive screening tool; CBI, Cambridge behavioral Inventory; ZBI, Zarit burden index; RSMS, revised self monitoring scale; CVLT-II, California verbal learning test version 2; mini-SEA, mini-social and emotional assessment, 95% CI, 95% confidence interval

**TABLE 4** CSF and serum proteins levels at baseline and week 52

Analyte	Baseline (n = 11)	Week 52 (n = 10)	Estimate	95% CI
CSF t-tau	152 (86.3-321)	147 (75.4-217) <sup>a</sup>	-0.238	-0.768, 0.292
CSF p-tau	31.1 (14.4-67.3)	25.5 (13.7-48.3) <sup>a</sup>	-0.0341	-0.103, 0.035
Serum t-tau	0.608 (0.022-1.87)	0.852 (0.068-2.95)	0.0051	-0.001, 0.012
Serum p-tau	1.30 (0.512-2.82)	1.12 (0.728-1.86)	-0.0035	-0.008, 0.002
CSF NfL	2413 (683-4416)	1908 (666-5031) <sup>a</sup>	-3.70	(-11.0, 3.61)

<sup>a</sup>(n = 9).

Data are presented as median (range). CSF, cerebrospinal fluid; t-tau, total tau, p-tau phosphorylated tau; NfL, neurofilament light chain; 95% CI, 95% confidence interval

PBVC from baseline to week 52 ranged from -6.51% to -0.26% (median -1.59%). Two distinct groups were identified, one showing relatively little brain atrophy (n = 7, PBVC less than -1.77%, median -1.23%) and the second group showing considerable atrophy (n = 4, PBVC -6.51% to -2.44%, median -5.96%).

NUCOG total score showed a small but statistically detectable decrease from baseline to week 52 over the whole study population ( $b = -0.172$ ; 95% CI -0.29, -0.053; Table 3). Similar declines in function and behavior were observed on the CBI ( $b = 0.317$ ; 95% CI 0.178, 0.456), ZBI ( $b = 0.1$ ; 95% CI 0.025, 0.166), and RSMS ( $b = -0.165$ ; 95% CI -0.23, -0.099). No change was observed on the mini-SEA ( $b = -0.134$ ; 95% CI -0.303, 0.036) and a small improvement was observed on the CVLT-II ( $b = 0.178$ ; 95% CI 0.035, 0.32). Within the NIH toolbox, a small decline was measured on the picture vocabulary ( $b = -0.249$ ; 95% CI -0.42, -0.078) and the processing speed subtests ( $b = -0.32$ ; 95% CI -0.58, -0.06) but no other measures (Supplement 2, Table 1).

No evidence for change was observed in CSF t-tau ( $b = 0.468$ ; 95% CI -1.16, 2.10; Table 4), p-tau ( $b = -0.022$ ; 95% CI -0.094, 0.05), or NfL ( $b = -3.70$ ; 95% CI -11.0, 3.61). Serum t-tau ( $b = 0.005$ ; 95% CI -0.001, 0.012) and p-tau levels ( $b = -0.004$ ; 95% CI -0.008, 0.002) were also unchanged.

Correlation analyses showed strong relationships between efficacy variables. Change in NUCOG correlated with PBVC ( $r = 0.81$ ; 95% CI 0.41, 0.95; Figure 2A) and change in serum t-tau ( $r = 0.73$ ; 95% CI 0.19, 0.93; Figure 2B). PBVC correlated with change in serum t-tau ( $r = 0.65$ ;

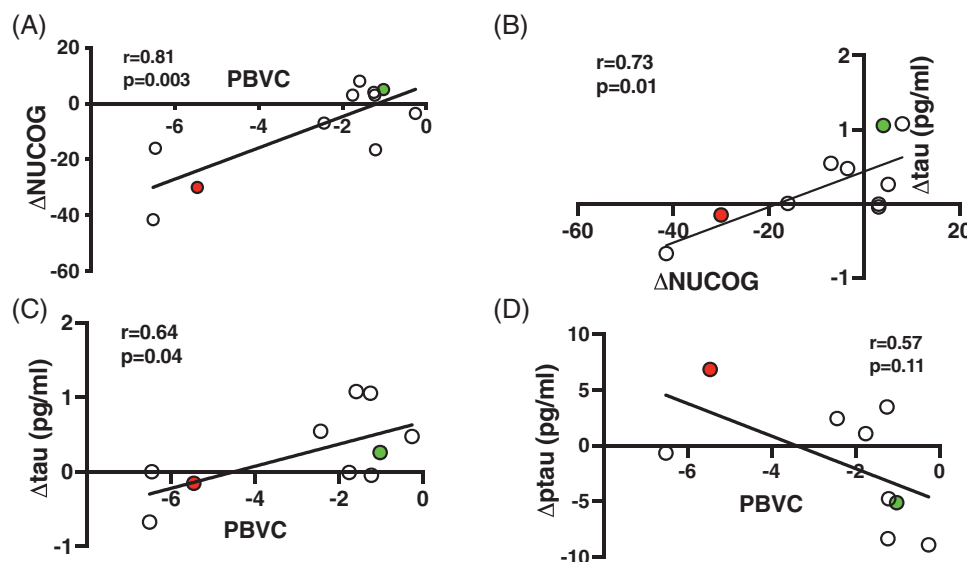
95% CI 0.03, 0.91; Figure 2C) and trended toward significance with CSF p-tau ( $r = -0.57$ ; 95% CI -0.9, 0.15; Figure 2D).

### 3.4 | Sub-analysis of “non-progressors”

Exploratory analysis of the “non-progressor” group (n = 7, PBVC less than 1.77) showed no decline on the NUCOG ( $b = -0.03$ ; 95% CI -0.14, 0.07) and ZBI ( $b = 0.05$ ; 95% CI -0.04, 0.13), and the improvement on the CVLT-II remained ( $b = 0.24$ ; 95% CI 0.087, 0.395). The declines on the CBI ( $b = 0.22$ ; 95% CI 0.05, 0.40) and RSMS ( $b = -0.18$ ; 95% CI -0.265, -0.102) remained, and a worsening was also observed on the mini-SEA ( $b = -0.229$ ; 95% CI -0.421, -0.036). Serum t-tau levels increased, but this was not significant ( $b = 0.009$ ; 95% CI 0.002, 0.02). No other changes in protein biomarkers were observed (data not shown). Down-titration occurred in two of seven “non-progressors” compared to three of four “progressors” (Fisher’s exact test,  $P = .24$ ). Of interest, the participant with the MAPT mutation was a “non-progressor” and the C9orf72 expansion was a “progressor”.

### 3.5 | Baseline characteristics of “non-progressors”

Baseline NfL levels correctly classified the majority of participants as “non-progressors” or “progressors” (Figure 3A-B; cutoff 3588 pg/mL,



**FIGURE 2** Correlation analyses between efficacy variables. (A) Change in neuropsychiatry unit cognitive screening tool (NUCOG) score plotted against percentage brain volume change (PBVC,  $n = 11$ ). (B) Change in NUCOG plotted against change in serum total-tau (t-tau,  $n = 10$ ). (C) Change in PBVC plotted against change in serum t-tau ( $n = 10$ ). (D) PBVC plotted against change in CSF phosphorylated-tau (p-tau,  $n = 9$ ). The green circle highlights the participant with the microtubule associated protein tau (MAPT) mutation, and the red circle the participant with the chromosome 9 open reading frame 72 (C9orf72) expansion. ΔNUCOG, change in neuropsychiatry unit cognitive screening tool; PBVC, percentage brain volume change; Δtau, change in tau; Δptau, change in phosphorylated tau

sensitivity 85.7%, specificity 100%, odds ratio [OR] 0.996, 95% CI 0.99, 1.0), with lower NFL levels predicting “non-progressors.” Baseline p-tau:t-tau ratio also predicted progressor status (Figure 3C–D; cutoff 0.26, sensitivity 71.4%, specificity 75%, OR  $2.52 \times 10^7$ , 95% CI  $4.41 \times 10^{-5}$ ,  $1.44 \times 10^{19}$ ), with higher ratios predicting “non-progressors.” Time from diagnosis, baseline NUCOG, and ZBI did not differentiate progressor status (data not shown).

## 4 | DISCUSSION

This study reports a Phase 1b trial of sodium selenate as a treatment for bvFTD. The main study findings are (1) sodium selenate is safe and well-tolerated in patients with bvFTD; (2) a small decline in cognition and behavior was observed in the participants over the course of treatment; (3) no overall change in t-tau or p-tau levels was observed following treatment; (4) a small number of participants showed substantial brain volume loss, whereas the majority showed a relatively slow brain atrophy rate; (5) reanalysis of efficacy measures in “non-progressors” found no evidence for change in cognitive or behavioral measures in these participants; and (6) baseline p-tau:t-tau ratio and NFL concentration were predictive of progressor status.

This study extends our previous work investigating sodium selenate in patients with Alzheimer’s disease (AD).<sup>6,7</sup> The increased dose and treatment period was associated with an increased frequency but not an increased severity of AEs compared to our previous AD trial. In agreement with our previous work, alopecia and nail disorders were the most common AEs, occurring in 58% and 42% of participants,

respectively. Most importantly, all participants completed the study. Five participants required a down-titration of dose because of AEs, a greater proportion of which were “progressors”, but this did not reach statistical significance.

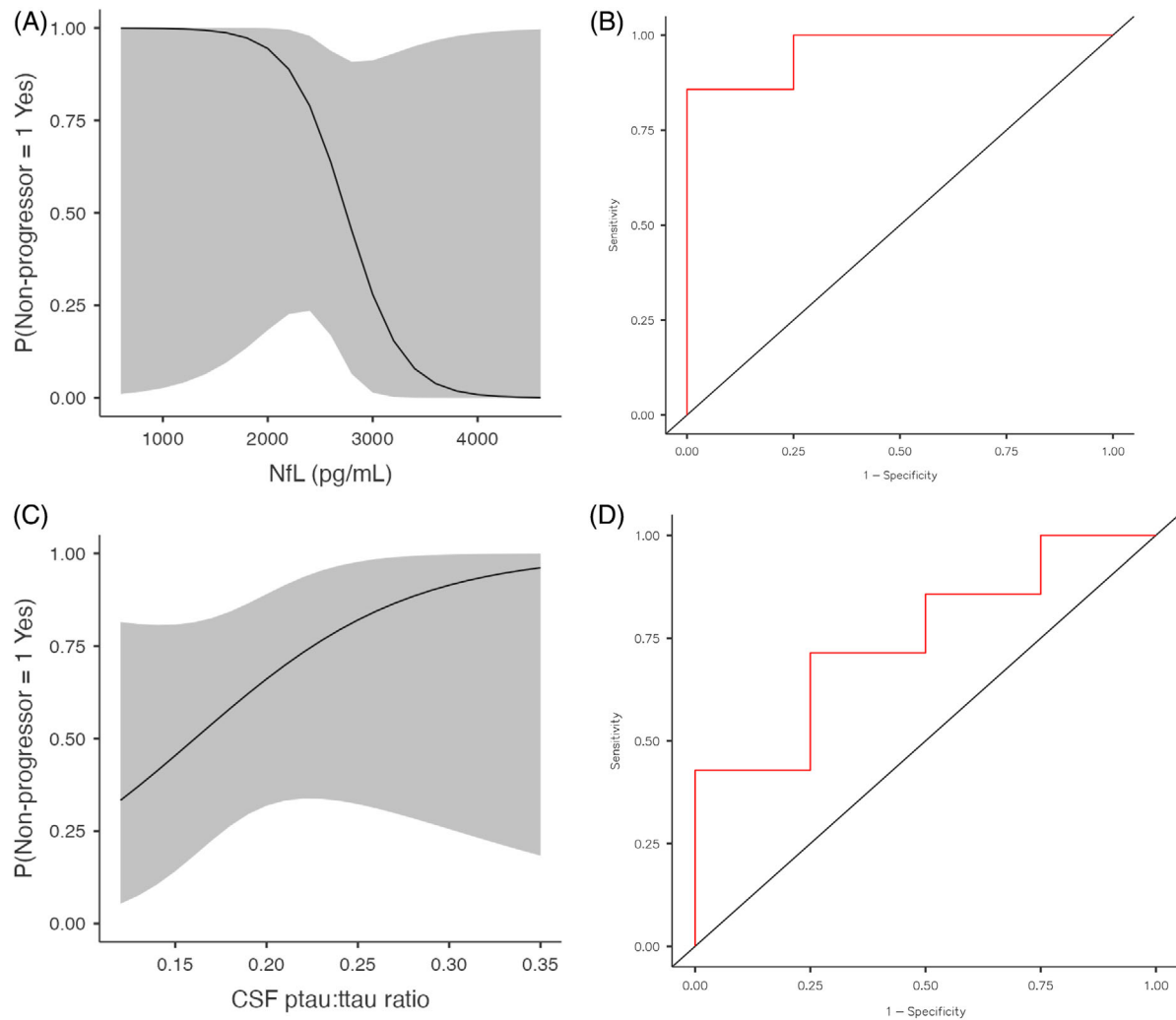
The efficacy measures showed a small decline in cognition, behavior, and carer burden over the 52 weeks of treatment. To our knowledge, no studies have reported non-interventional longitudinal data on NUCOG or ZBI (full version) in bvFTD patients. In an RCT of memantine, Vercelletto et al.<sup>20</sup> reported median changes on ZBI of  $-6.5$  and  $-14$  points in memantine and placebo-treated groups, respectively, in line with the 8-point change observed in our study.

A 5-point/year decline in RSMS total score, as observed in our study, is in keeping with the natural history of bvFTD, suggesting that treatment with sodium selenate did not affect the disordered behavior seen in bvFTD.<sup>21</sup>

Using the Addenbrooke’s Cognitive Examination, annualized change was reported to be  $\approx 10$  points/year, indicating substantial cognitive decline in patients with bvFTD.<sup>22</sup> Although not directly comparable, the change in NUCOG scores observed in this study could indicate a slowing of cognitive decline. The finding of improved CVLT-II score is surprising, as rapid decline in memory impairment has been reported previously.<sup>23</sup>

Protein biomarker levels were unchanged over the course of the study. Whether these measures change in the natural progression of bvFTD is unknown, and therefore it is not possible to interpret the significance of the lack of change in these measures following treatment with sodium selenate. To our knowledge there are no reports of longitudinal studies of CSF t-tau or p-tau levels in patients with bvFTD.





**FIGURE 3** Binomial logistic regression of baseline predictors of treatment response. (A) CSF NfL cutoff for treatment response. (B) CSF NfL receiver-operating characteristic curve. (C) CSF p-tau:t-tau cutoff for treatment response. (D) CSF p-tau:t-tau receiver-operating characteristic curve

Longitudinal CSF NfL levels in a single case of genetic FTD, showing no change over time.<sup>24</sup> In a recent longitudinal study in patients with FTLT, there was no change in t-tau levels, but a significant increase in NfL levels over time ( $\approx 1$  year apart).<sup>25</sup> More longitudinal studies are warranted to evaluate these biomarkers as end points for future clinical trials.

Brain atrophy over the 12-month treatment period varied considerably across the group, from  $-0.26\%$  to  $-6.46\%$ , which may indicate that, for some participants, sodium selenate treatment impacted the neurodegenerative process. However, we acknowledge that no definitive conclusions about a treatment effect can be made in the absence of a control group. Correlation analyses also showed a differentiation of groups on various efficacy measures—with those with reduced brain atrophy showing little or no change on NUCOG, increases in serum t-tau, and decreases in CSF p-tau, whereas those with the greater brain atrophy showed clear and substantial disease progression on NUCOG and the opposite effect on serum and CSF proteins. These results support the hypothesis that the treatment is having an effect in a sub-

group of participants, and the mechanism of action of sodium selenate, with decreases in CSF p-tau levels and increases in serum t-tau levels demonstrating tau clearance from the central nervous system into the periphery.

A previous study reported annual atrophy rates of  $3.18\%$  in FTD (compared to  $0.47\%$  in healthy aging).<sup>19</sup> Using a  $50\%$  reduction in brain atrophy ( $1.81\%$ ) as a cut-off for “non-progressors,” we further investigated the efficacy measures in this group. Sub-analysis of “non-progressors” eradicated the decline in some but not all of the cognitive and behavioral tests. The participant with the *MAPT* mutation was a “non-progressor” and the participant with the *C9orf72* expansion was a “progressor,” which also supports the hypothesized mechanism of action of sodium selenate for reducing tau burden in bvFTD cases associated with tau pathology.

One of the potentially most important findings was the prediction of “non-progressors” from baseline CSF measures. The baseline NfL concentration had  $92.9\%$  accuracy for determining progressor status in this cohort at a cutoff of  $3588$  pg/mL, similar to that previously

reported for differentiating pathologically confirmed FTLD-tau from FTLD-TDP43 across the FTLD spectrum.<sup>24,26</sup> Similarly, baseline p-tau:t-tau ratio predicted progressor status, with a cutoff of 0.26. Previously, a p-tau:t-tau ratio of 0.121 was reported for differentiating FTLD-tau and FTLD-TDP43 across the FTLD spectrum.<sup>26</sup> However, differences in the analysis methods (ELISA vs Simoa) and the combination of FTLD syndromes investigated in previous studies mean the results are not directly comparable. Further work on a larger sample is needed to determine whether these measures are markers of underlying pathology and progressor status in patients with bvFTD, and whether this can be influenced by sodium selenate treatment.

This study has several limitations. First, the sample size limits the confidence in the conclusions that can be drawn; however, the treatment period was long, and the safety and tolerability profile is similar to that which we have observed previously in trials of sodium selenate treatment. Second, the study was neither blinded nor controlled, which may have affected the cognitive and behavioral measures. To combat this, imaging and biospecimen biomarkers were included, as these are unaffected by bias and were analyzed blinded. Nonetheless without a comparator group it is not possible to draw conclusions on the efficacy measures, and thus a randomized trial has recently commenced.<sup>27</sup> Third, the study was limited by the lack of specific biomarkers for tracking bvFTD—there is no consensus on whether p-tau and t-tau levels change with the natural history of bvFTD; the global MRI measure used here, although sensitive, is not specific to bvFTD. A greater understanding of bvFTD natural history is needed to determine which measures are most appropriate for measuring treatment effect in future clinical trials. Finally, except for the two participants with known genetic mutations, underlying pathology was unknown in the study participants—our hypothesis, supported by the baseline CSF measures, is that “non-progressors” had a tau-based pathology, and “progressors” a non-tau-based pathology. The development of new diagnostic tests such as tau-PET will increase the possibilities for clinical trials that specifically target the underlying pathology in bvFTD.

## 5 | CONCLUSION

This Phase 1b open-label trial demonstrated that 12 months of treatment with sodium selenate is safe and well tolerated in patients with bvFTD. A double-blind, placebo-controlled study is warranted to evaluate potential efficacy in slowing or stopping disease progression in patients with bvFTD.

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## SUPPORTING INFORMATION

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