


Sodium selenate as a disease-modifying treatment for mild–moderate Alzheimer’s disease: an open-label extension study

Lucy Vivash ^{1,2,3,4}, Charles B Malpas^{1,3,4,5}, Christopher M Hovens⁶, Amy Brodtmann^{3,7,8}, Steven Collins², Stephen Macfarlane⁹, Dennis Velakoulis^{10,11}, Terence J O’Brien^{1,2,3,4}

To cite: Vivash L, Malpas CB, Hovens CM, *et al*. Sodium selenate as a disease-modifying treatment for mild–moderate Alzheimer’s disease: an open-label extension study. *BMJ Neurology Open* 2021;**3**:e000223. doi:10.1136/bmjno-2021-000223

Received 20 September 2021
Accepted 22 November 2021

ABSTRACT

Introduction Sodium selenate is a potential disease-modifying treatment for Alzheimer’s disease (AD) which reduces hyperphosphorylated tau through activation of the protein phosphatase 2A enzyme. We have shown sodium selenate to be safe and well tolerated in a 24-week, phase 2a double-blind placebo-controlled randomised controlled trial (RCT), also reporting sodium selenate reduced neurodegeneration on diffusion-weighted MRI. This study assessed the safety and tolerability of chronic sodium selenate treatment (up to 23 months) in patients with AD who had been enrolled in the RCT. Cognitive measures served as secondary outcomes of potential disease-modification.

Methods An open-label extension study of sodium selenate (10 mg three times a day) in patients with AD who had completed the previous RCT. Twenty-eight patients were enrolled. Patients were regularly monitored for safety, adverse events (AEs) and protocol compliance. Cognitive tests were administered for measures of disease progression.

Results Sixteen patients were discontinued by the sponsor, and 12 discontinued for other reasons. Treatment duration ranged from 6 to 23 months. The majority of AEs were mild (83%), and 33% were treatment-related. Common treatment-related AEs were alopecia (21%) and nail disorder (32%), which both resolved either prior to or following cessation of treatment. Two serious AEs occurred, which were not treatment-related. Alzheimer’s Disease Assessment Scale—Cognitive Subscale 11 score increased 1.8 points over 12 months.

Discussion Chronic sodium selenate treatment is safe and well tolerated in patients with AD. Cognitive measures suggest a slowing of disease progression though this could not be confirmed as the study was not controlled. Further research into sodium selenate as a treatment for AD is warranted.

INTRODUCTION

Tauopathies collectively represent a constellation of over 20 clinicopathological neurodegenerative diseases of which Alzheimer’s disease (AD) is the most common.¹ Tauopathies are characterised by the presence

of aggregates of the tau protein in affected brain regions and the extent of these tau aggregates correlates with disease symptoms and predicts cognitive status.²

Tau aggregates are composed of hyperphosphorylated tau and as such represent a potential target for disease-modifying therapies.³ A reduction of hyperphosphorylated tau may be brought about by the upregulation of protein phosphatase 2A (PP2A), the major serine/threonine phosphatase in the human brain.^{4 5} Treatment with sodium selenate (VEL015) upregulates PP2A activity, and has been shown to reduce hyperphosphorylated tau levels in animal models of AD, epilepsy and traumatic brain injury.^{6–12} In transgenic AD models, treatment with sodium selenate has repeatedly demonstrated reversal of cognitive deficits alongside reductions in tau and markers of neuroinflammation.^{6 10–12} We have previously reported a phase 2a double-blind placebo-controlled randomised controlled trial (RCT) of sodium selenate (VEL015) in mild–moderate AD over 24 weeks.¹³ The study found that sodium selenate was safe and well tolerated in patients, but did not find any significant differences in cognitive measures between groups over the treatment period. Additional exploratory diffusion-weighted MRI endpoints found less degeneration in the white matter of patients treated with sodium selenate than placebo. Furthermore, a subsequent post hoc analysis found that patients who had higher selenium levels in their blood and cerebrospinal fluid (CSF) showed less cognitive decline than those with lower selenium levels.¹⁴

Here we report the open-label extension study of sodium selenate in patients with AD who completed the 24-week treatment period in the double-blind RCT of sodium selenate.



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Lucy Vivash;
lucy.vivash@monash.edu

The primary objective was to assess long-term (up to 23 months) safety and tolerability of sodium selenate in an AD population. Additional exploratory objectives investigated long-term cognitive measures to determine the effects of chronic sodium selenate treatment on disease progression.

METHODS

Participants

This was an open-label extension study (Velacor 002-E1) of patients with AD who completed the phase 2a randomised, double-blind placebo-controlled trial of VEL015 for the treatment of mild–moderate AD (see Malpas *et al*¹³ for details of the RCT). The study was conducted at three centres in Melbourne, Australia from October 2012 to November 2014.

Inclusion criteria for Velacor 002 -E1 were: completion of visit 6 (end of treatment) of the Velacor 002 RCT; baseline of Velacor 002-E1 study to be completed no more than 2 months after the last scheduled visit of the Velacor 002 study; female participants had to be of non-child bearing potential, and male participants had to agree to use appropriate contraception for the duration of the study; it was required that the participants live in the community and have at least 5 hours contact per week with their study partner; written informed consent had to be obtained from the participant or their legally authorised representative and their study partner.

Exclusion criteria were as for the Velacor 002 study (see Malpas *et al*¹³) with the following addition: participants who had experienced persistent or unresolved adverse events (AEs) thought to be related to the study drug in the Velacor 002 study and where the event was classified as \geq grade 3 severity, or where the event required permanent cessation of the study drug. None of these additional exclusion criteria applied to any potential participants in this study.

Of the 36 patients who completed the original trial, 28 agreed to participate in the open-label extension study.

Procedures and treatment

The study was retrospectively registered on the Australian New Zealand Clinical Trials Registry in February 2013 (ACTRN12613000170729) due to an oversight by the study sponsor. Recruitment was ongoing and no participant had withdrawn or completed the study at the time of registration. Written informed consent was obtained from the participant or their legally authorised representative and the participant's study partner. The duration of the study was intended to be 25 months (24 months of treatment and 1 month of follow-up), however, for financial reasons the study was discontinued by the sponsor prior to completion (treatment discontinued on October 2014, last follow-up visit November 2014). Participants received a supranutritional dose (10 mg three times a day, oral) of VEL015 for the duration of the trial.

The schedule of clinical visits was as follows: baseline, 6 weeks, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months (end of treatment) and 25 months (post-treatment follow-up). Due to early closure of the study, no participants completed the 24-month treatment period (treatment period 6–23 months). A lumbar puncture was performed after at least 10 months of treatment with sodium selenate (n=7, range 10–22 months) for measurement of protein biomarkers.

The following protocol deviations/missing data were noted during the study: baseline Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) not performed for n=5 patients; controlled oral word association test (COWAT) not performed for n=1 patient; category fluency test (CFT) not performed for n=2; Month 6 ADAS-Cog not performed for n=2; Month 12 ADAS-Cog not performed for n=2; COWAT and one card learning memory task (OCL) not performed for n=1; Month 18 ADAS-Cog not performed for n=6. Computer error caused the missing data for the OCL, participant refusal or administrative error was the reason for missing ADAS-Cog, COWAT and CFT data.

The primary objective was to assess the safety and tolerability of treatment with sodium selenate over 24 months. The secondary objective was to assess the effect of sodium selenate on cognition, measured by the ADAS-Cog11, Cogstate Brief Battery, COWAT and CFT over 24 months.

Primary outcomes

Safety measures included AEs (unsolicited and solicited via diary cards), vital signs, physical and neurological examinations, laboratory evaluations (haematology, biochemistry and urinalysis) and ECG. AEs were defined as an untoward medical event that occurred while on the study, irrespective of whether it was related to treatment. Serious AEs (SAEs) were those that resulted in death, were life threatening, required or prolonged hospitalisation or resulted in significant or persistent disability.

Secondary outcomes

Cognitive measures were repeated throughout the treatment period. A computerised battery (Cogstate Brief Battery) consisting of the OCL, identification reaction time task (IDN) and detection reaction time task (DET) were administered at each visit (CogState). The ADAS-Cog11 was measured at baseline, 6 months, 12 months and 18 months and early discontinuation visits. The COWAT and CFT were measured at baseline, 12 months and early discontinuation. The Mini-Mental Status Exam (MMSE) was measured at baseline and only repeated at early discontinuation visits.

CSF levels of beta-amyloid 42, total tau and phospho-tau were measured at National Dementia Diagnostics Laboratory (Parkville, Melbourne Australia) as previously described.¹³

Statistical analyses

Statistical analyses were primarily conducted on the intention to treat (ITT) population. Data were included for all participants who had complete data for the relevant analysis. A modified per protocol (mPP) consisted of participants who were still on treatment when the study was closed ($n=16$). General linear mixed models (GLMMs) were used to analyse primary outcome data. For all outcome variables, a random intercept was specific for each participant, as well as a random slope for time. Parameters were estimated using restricted maximum likelihood. Baseline MMSE was included as covariate in all models. Additional analyses including treatment allocation in the RCT as an additional covariate. Sensitivity analyses based on MMSE score (≤ 20 and >20) and analysis of the mPP populations were also performed. Post hoc analyses with baseline hippocampal volume, amyloid- β and total-tau CSF levels, and serum and CSF selenium levels as additional covariates were also computed for the cognitive measures. Baseline characteristics are presented as median (range) or frequency (%), AEs as number of patients affected (number of events). Model parameters are reported as unstandardised coefficients with 95% CIs. Marginal (conditional) effects were computed and plotted to understand individual and group trajectories.

RESULTS

Cohort

Twenty-eight patients were enrolled in this study. Age at baseline was 69.5 years (57–83 years), 17 (61%) participants were men and 19 (68%) had the APOE4 allele. Median MMSE score was 19 (5–28). Twelve participants (42%) discontinued from the trial prior to the study stopping, two participants (7%) withdrew due to AEs, two (7%) withdrew consent, one (4%) withdrew due to disease progression, one (4%) was discontinued due to initiating a prohibited medication and six (21%) were lost to follow-up. Study participation for the remaining 16 patients was terminated by the sponsor at the time it was decided to terminate the trial. Treatment duration for these participants ranged from 6 to 23 months (median=16.8 months). The CONSORT-style participant flow chart is shown in figure 1.

Safety and tolerability

Twenty-four patients (86%) experienced at least one treatment emergent AE (TEAE, table 1). A total of 87 events were experienced over the course of the study, 29 (33%) of which were determined to be drug-related. Most AEs were rated as mild (83%) and did not affect the participant's willingness to continue in the trial. Two participants (7%) discontinued study treatment due to alopecia (mild–moderate hair thinning) and nail changes (increased brittleness and discolouration). Two SAEs occurred, one participant had an episode of psychosis (resulting in the participant's discontinuation from the

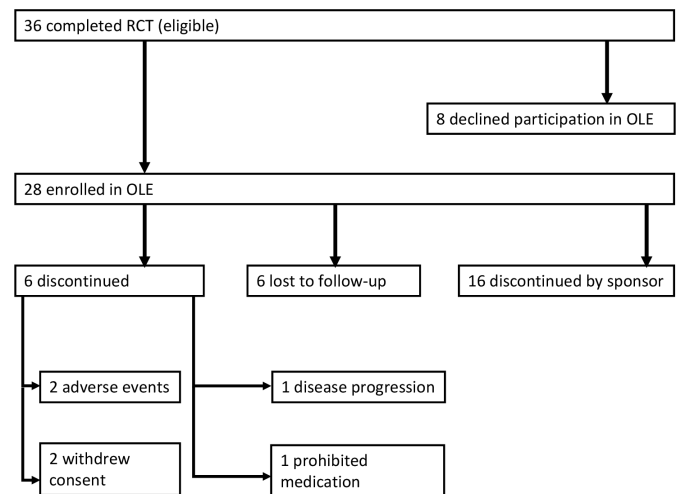


Figure 1 Participant flow diagram showing initial recruitment numbers and those included in the intention to treat and modified per protocol populations. OLE, open-label extension; RCT, randomised controlled trial.

study) and another suffered a broken patella, neither of these were deemed to be treatment-related.

With the exception of nail changes and alopecia, AEs resolved without interruption or stopping of study medication. Alopecia ($n=6$) was reported 4 weeks after commencement of the open-label study (range 1–24 weeks), adjusting for previous treatment with sodium selenate (10 mg) in the double-blind phase, alopecia was reported after 10 weeks of treatment (range 1–26 weeks). Alopecia resolved without intervention in two participants, and resolved following cessation of therapy in the other four participants.

Similarly, nail changes ($n=9$) occurred 16 weeks following the commencement of the open-label study (range 8–88 weeks; correcting for prior exposure, median 20 weeks, range 8–112 weeks). This resolved without intervention in three patients, and following the end of treatment in the remaining six patients.

Table 1 shows all AEs that occurred more than once in this cohort, as compared with the rate of AEs in previous clinical trials of sodium selenate. Despite a longer treatment period, overall, the frequency of AEs was similar or lower than the previously reported studies.^{13 15}

Cognitive measures

Table 2 and figures 2 and 3 show the cognitive measures throughout the treatment period. There was no evidence for change in the DET ($b=2.66$, 95% CI 2.61 to 2.717, $p=0.08$, figure 2A) or OCL ($b=0.773$, 95% CI 0.745 to 0.802, $p=0.99$, figure 2B), with evidence for an increase over time in the IDN ($b=2.84$, 95% CI 2.81 to 2.883, $p<0.001$, figure 2C). Covarying for baseline MMSE did not alter the results, with evidence for an increase over time in the IDN ($b=2.84$, 95% CI 2.805 to 2.876, $p=0.012$) but not the other tasks. Subanalyses based on MMSE score produced a similar pattern of results, with no evidence for effects of time in participants with an MMSE >20

Table 1 Treatment emergent adverse events that occurred in two or more participants

	Sodium selenate OLE	Sodium selenate RCT* (treatment arm)	Sodium selenate phase 1 open label†
Total TEAEs	24 (86%) 87	19 (95%)	Not reported
Solicited AEs	19 (68%) 29	14 (70%) 53	
Nail changes	9 (32%) 10	2 (10%) 3	5 (26%)
Hair loss	6 (21%) 6	Nil	8 (42%)
Fatigue	4 (14%) 4	7 (35%) 7	9 (47%)
Lethargy	3 (11%) 3	6 (30%) 6	5 (26%)
Vomiting	2 (7%) 2	Nil	4 (21%)
Headache	2 (7%) 2	7 (35%) 7	3 (16%)
Dizziness	2 (7%) 2	4 (20%) 4	4 (21%)
Unsolicited AEs	24 (86%) 58	7 (35%) 12	
Arthralgia	4 (14%) 4	2 (10%) 2	2 (10%)
Cold	4 (14%) 4	Nil	Not reported
Fall	2 (7%) 4	Nil	Not reported
UTI	2 (7%) 3	Nil	Not reported
Hypertension	2 (7%) 2	Nil	Not reported
Back pain	2 (7%) 2	Nil	Not reported
Influenza	2 (7%) 2	Nil	Not reported
Constipation	2 (7%) 2	Nil	4 (21%)

Data are presented as number of participants (percentage of total cohort) total number of events. For comparison, the frequency of adverse events in the treatment group in the randomised controlled trial is also reported,¹³ and the phase 1 open-label study in prostate cancer.¹⁵ Adverse events that occurred in fewer than two participants are not listed.

*Treatment period 24 weeks, n=20.¹³

†Treatment period 12 weeks, n=19, doses ranged from 5 mg daily to 30 mg three times a day, n=12 on a treatment dose >30 mg/day. Only adverse events at least possibly related to treatment reported.¹⁵

AE, adverse event; OLE, open-label extension; RCT, randomised controlled trial; TEAE, treatment emergent adverse event; UTI, urinary tract infection.

(n=10) and in patients with an MMSE ≤ 20 (n=18) on the DET and OCL. In the IDN, the effect of time remained for both MMSE >20 (b=2.797, 95% CI 2.732 to 2.862, p=0.043) and in patients with an MMSE ≤ 20 (b=2.866, 95% CI 2.822 to 2.91, p=0.001).

There was evidence for an increase in ADAS-Cog11 score overtime (b=24.81, 95% CI 20.53 to 29.08, p=0.002, figure 3A), and decreases on the CFT (b=8.56, 95% CI 6.82 to 10.31, p=0.019, figure 3B) and COWAT (b=24.53, 95% CI 19.75 to 29.31, p=0.035, figure 3C). Covarying for baseline MMSE did not alter the results, with the effects of time remaining for all three tests (ADAS-Cog b=24.53, 95% CI 20.95 to 28.11, p<0.001, CFT b=9.09, 95% CI 7.63 to 10.55, p<0.001, COWAT b=25.56, 95% CI 21.45 to 29.66, p=0.004). When analysed based on MMSE cut-offs, the effect of time on the ADAS-Cog was lost (MMSE >20, b=18.55, 95% CI 13.18 to 23.92, p=0.16, MMSE ≤ 20 , b=28.04, 95% CI 23.06 to 33.02, p=0.13), but remained for the COWAT and CFT.

Follow-up analyses showed adding RCT treatment group, baseline hippocampal volume, baseline total tau and baseline CSF and serum selenium levels as additional covariates did not alter the results for any of the cognitive measures. There was evidence for baseline amyloid- β levels affecting the IDN (b=2.85, 95% CI 2.81 to 2.882,

p=0.022) and OCL (b=0.775, 95% CI 0.747 to 0.803, p=0.036) but no other measures.

Despite worsening over time on some measures, the rate of decline is very slow. The median absolute change on the ADAS-Cog11 from baseline to month 6 was 0 points, from month 6 to 12 was 1.8 points, and from month 12 to 18 was 2.5 points.

Analysis of cognitive measures was also performed on the mPP population (n=16). As with the ITT analysis, there was no evidence for an effect of time on the DET or OCL, but the IDN was affected by time (b=2.83, 95% CI 2.78 to 2.88, p<0.001). Similar evidence for the effects of time was seen on the ADAS-Cog11 (b=23.42, 95% CI 19.01 to 27.84, p=0.003) and CFT (b=8.31, 95% CI 6.29 to 10.33, p=0.02), but not for the COWAT (b=24.06, 95% CI 18.48 to 29.7, p=0.07).

CSF protein levels were only available for seven participants. No change in amyloid- β (b=0.07, 95% CI -0.69 to 0.83, p=0.86), tau (b=-0.62, 95% CI -1.49 to 0.25, p=0.21) or ptau (b=-0.12, 95% CI -0.23 to -0.01, p=0.08) were seen.

DISCUSSION

This open-label extension study investigated long-term treatment with sodium selenate in patients with AD. The

Table 2 Cognitive measures at each visit

	Baseline (n=28)	Week 6 (n=28)	Month 3 (n=27)	Month 6 (n=23)	Month 9 (n=18)	Month 12 (n=16)	Month 18 (n=10)
ADAS-Cog11	21.7 (8–42.7)*	ND	ND	21.7 (5.33–43)†	ND	23.5 (8–51.7)‡	26 (18.3–37.3)§
CFT	9 (1–24)¶	ND	ND	ND	ND	7 (0–20)	ND
COWAT	24 (2–57)**	ND	ND	ND	ND	22 (3–38)††	ND
DET	2.64 (2.36–3.09)	2.68 (2.38–3.17)	2.70 (2.40–3.04)	2.64 (2.39–2.98)	2.67 (2.39–2.95)	2.68 (2.39–2.99)	2.79 (2.40–2.95)
IDN	2.81 (2.53–3.13)	2.79 (2.69–3.08)*	2.80 (2.63–3.09)	2.81 (2.66–3.08)	2.82 (2.66–2.98)	2.85 (2.66–3.08)	2.84 (2.73–3.08)
OCL	0.766 (0.639–0.947)	0.785 (0.563–0.935)*	0.775 (0.358–0.924)	0.805 (0.552–0.924)	0.805 (0.515–0.947)	0.78 (0.487–0.947)‡	0.783 (0.717–0.9)

Data are presented as median (range).

*n=23.

†n=21.

‡n=14.

§n=4.

¶n=26.

**n=27.

††n=15.

n=9.

ADAS-Cog11, Alzheimer's Disease Assessment Scale—Cognitive Subscale; CFT, category fluency test; COWAT, controlled oral word association test; DET, detection reaction time task; IDN, identification reaction time task; OCL, one card learning memory task.

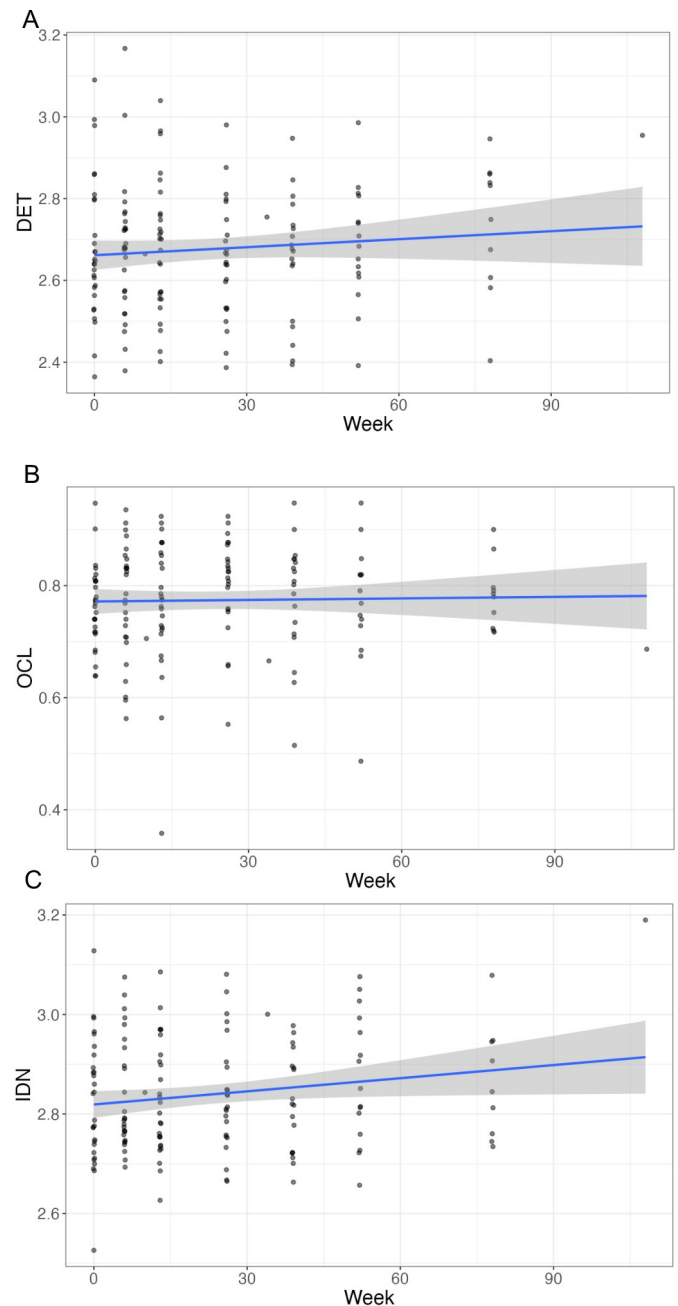


Figure 2 The computerised cognitive battery scores over the course of the study. (A) Detection (DET) score, (B) one card learning (OCL) score, (C) identification (IDN) score. No evidence for change was seen in the detection of one card learning tests, with the identification test showing a significant worsening over the course of the study ($p < 0.001$). Individual patient scores are displayed as data points. The thick blue line and grey shaded area represent the mean score and 95% CI.

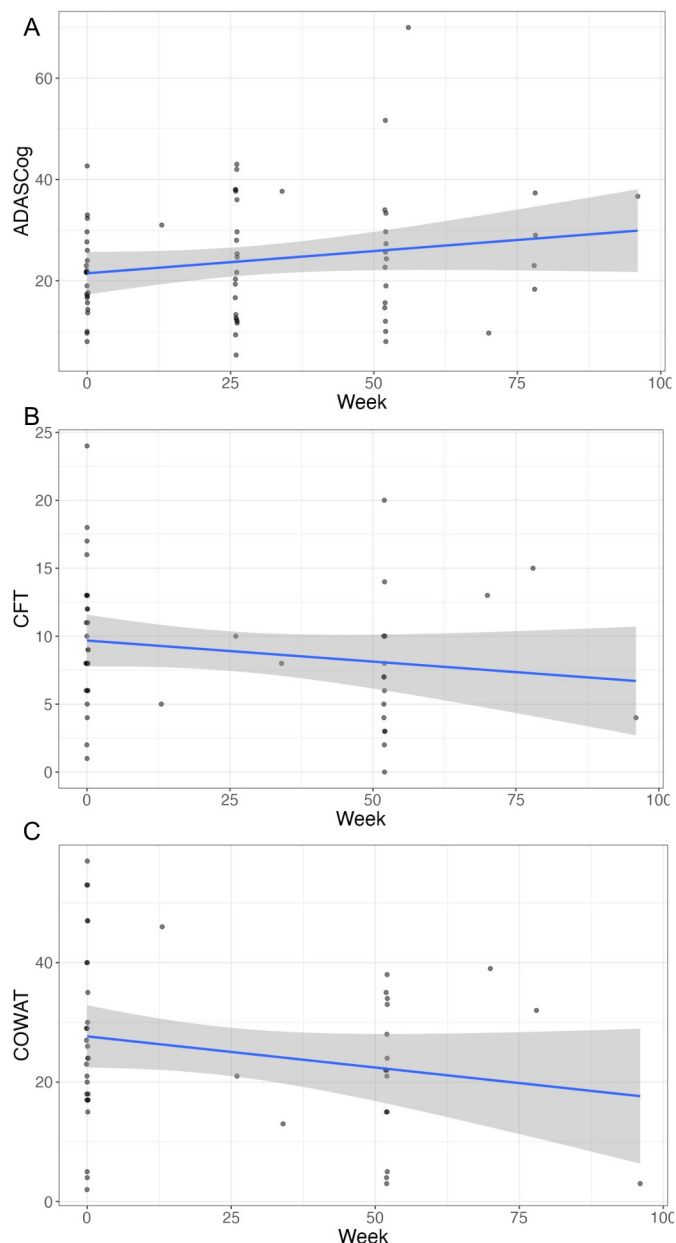


Figure 3 Pen and paper cognitive test scores over the course of the study. (A) ADAS-Cog11 score, (B) CFT score, (C) COWAT score. Worsening performance over time was seen for all tests, demonstrated by a significant increase in the ADAS-Cog score ($p=0.002$) and significant decrease in the CFT ($p=0.019$) and COWAT ($p=0.035$). Individual patient scores are displayed as data points. The thick blue line and grey shaded area represent the mean score and 95% CI. ADAS-Cog11, Alzheimer's Disease Assessment Scale—Cognitive Subscale; CFT, category fluency test; COWAT, controlled oral word association test.

The most common AEs were nail disorders and alopecia, occurring in ~30% and ~20% of participants, respectively. There was significant variability in the time course of the development of these AEs, with some participants reporting alopecia within a week of commencing sodium selenate treatment, and others after 6 months of treatment. Similarly, nail changes were reported within 8

weeks of starting treatment, or after 2 years of treatment. This suggests that there is considerable variability in participants' sensitivity to sodium selenate and the development of these specific AEs that warrants further investigation and understanding.

The frequency of other TEAEs was low, and for the majority of AEs, the frequency was lower than seen in the RCT,¹³ which was of much shorter duration.

The unsolicited AEs were mild, of low frequency, and similar to those observed in other studies in this population. Only two SAEs were reported, neither of which was judged to be related to the study treatment.

The secondary outcomes of this trial were to study the long-term effects of sodium selenate treatment on measures of cognition and cognitive decline in patients with AD. Cognitive decline was observed on the majority of cognitive instruments, however, the rate of decline was slowed compared with the previous RCT and that expected for the natural history of the disease.¹⁶

Schrag *et al*¹⁶ reported that a change of 3 points on the ADAS-Cog11 over 6 months was the minimal clinically relevant change for trials, with a change of 2 points observed in patients with no clinically meaningful change. The 4.3 point increase in the ADAS-Cog11 score over 18 months (and only 1.8 points over 12 months) represents a potentially clinically meaningful slowing of disease progression. Similarly, the IDN showed only a very small increase in response time over the course of the study, potentially indicating a slowing of disease progression. This effect of time was lost on the majority of cognitive measures when analysing the subset of participants with an MMSE >20, suggesting a slowing or halting of disease progression in patients with milder disease at the commencement of the study.

Limitations

Due to financial considerations, the study was prematurely terminated limiting the conclusions that can be drawn from this study. The longer-term results are impacted by considerably fewer patients reaching the 12-month and 18-month timepoints than the 6-month timepoint. This is reflected in the vastly larger CIs seen at these later timepoints.

The ADAS-Cog has been the ubiquitous clinical endpoint for AD trials for over 30 years. Given the lack of successful trials of new therapies, the validity and usefulness of the ADAS-Cog as an endpoint has been questioned. The ADAS-Cog has excessive variance due to both patient heterogeneity and measurement error.¹⁷ More sensitive measures of cognitive change, such as markers of arbitrary associative learning should be considered as tools for screening potential participants, as well as potential outcome measures.^{18 19} The Food and Drug Administration has advised it will now consider functional outcomes as trial endpoints.¹⁷ Functional outcomes, such as improvements or maintenance in activities of daily living, present the potential for meaningful endpoints for patients and their families.

In conclusion, this open-label long-term extension study has shown that treatment with sodium selenate is safe and well-tolerated drug in patients with AD at a dose of 30 mg per day for up to 23 months. Due to incomplete data, cognitive measures were unable to definitively provide evidence to support or refute that sodium selenate can slow cognitive decline in patients with AD. The results suggest sodium selenate warrants further investigation as a potential disease-modifying treatment for AD and other neurodegenerative diseases with a tau-based pathogenesis.

Author affiliations

- ¹Department of Neuroscience, Monash University, Melbourne, Victoria, Australia
²Department of Medicine and Radiology, University of Melbourne, Melbourne, Victoria, Australia
³Department of Neurology, Royal Melbourne Hospital, Parkville, Victoria, Australia
⁴Department of Neurology, Alfred Hospital, Melbourne, Victoria, Australia
⁵Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia
⁶Department of Surgery, University of Melbourne, Melbourne, Victoria, Australia
⁷Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia
⁸Eastern Cognitive Disorders Clinic, Monash University, Melbourne, Victoria, Australia
⁹The Dementia Centre, HammondCare, Melbourne, Victoria, Australia
¹⁰Neuropsychiatry Unit, Royal Melbourne Hospital, Melbourne, Victoria, Australia
¹¹Melbourne Neuropsychiatry Centre, University of Melbourne, Melbourne, Victoria, Australia

Contributors LV drafted the manuscript and as guarantor takes full responsibility for the content of the manuscript. All authors contributed to study design in conjunction with Velacor Therapeutics. All authors contributed to data analysis and interpretation. All authors edited the manuscript and approved the final version independent of Velacor Therapeutics.

Funding This work was funded by Velacor Therapeutics.

Disclaimer The funder had a role in the study design but did not have any role in the data analysis or interpretation, nor had any role in the preparation of or decision to publish this manuscript.

Competing interests The authors report the following disclosures outside of this study: LV reports personal fees from Biogen Australia and research funding from Biogen, LMI and Eisai. CMH reports issued patents US 9,415,063 and US 8,920,951. TJOB reports research funding from Biogen, Eisai, UCB, Anavex and Praxis. CM, AB, SC, SM and DV have nothing to disclose.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Melbourne Health Human Research Ethics Committee, Melbourne, Victoria, Australia, reference 2012.191 Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified study data will be available subject to request to and approval by Melbourne Health Human Research Ethics Committee (research@mh.org.au; study reference 2012.191).

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Lucy Vivash <http://orcid.org/0000-0002-1182-0907>

REFERENCES

- Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. *Annu Rev Neurosci* 2001;24:1121–59.
- Giannakopoulos P, Herrmann FR, Bussière T, *et al*. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. *Neurology* 2003;60:1495–500.
- Gong C-X, Iqbal K. Hyperphosphorylation of microtubule-associated protein tau: a promising therapeutic target for Alzheimer disease. *Curr Med Chem* 2008;15:2321–8.
- Gong CX, Lidsky T, Wegiel J, *et al*. Phosphorylation of microtubule-associated protein tau is regulated by protein phosphatase 2A in mammalian brain. Implications for neurofibrillary degeneration in Alzheimer's disease. *J Biol Chem* 2000;275:5535–44.
- Goedert M, Jakes R, Qi Z, *et al*. Protein phosphatase 2A is the major enzyme in brain that dephosphorylates tau protein phosphorylated by proline-directed protein kinases or cyclic AMP-dependent protein kinase. *J Neurochem* 1995;65:2804–7.
- van Eersel J, Ke YD, Liu X, *et al*. Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. *Proc Natl Acad Sci U S A* 2010;107:13888–93.
- Liu S-J, Zheng P, Wright DK, *et al*. Sodium selenate retards epileptogenesis in acquired epilepsy models reversing changes in protein phosphatase 2A and hyperphosphorylated tau. *Brain* 2016;139:1919–38.
- Tan XL, Wright DK, Liu S, *et al*. Sodium selenate, a protein phosphatase 2A activator, mitigates hyperphosphorylated tau and improves repeated mild traumatic brain injury outcomes. *Neuropharmacology* 2016;108:382–93.
- Smith SM, Zhang Y, Jenkinson M, *et al*. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 2002;17:479–89.
- Ahmed T, Van der Jeugd A, Caillierez R, *et al*. Chronic sodium selenate treatment restores deficits in cognition and synaptic plasticity in a murine model of tauopathy. *Front Mol Neurosci* 2020;13:570223.
- Van der Jeugd A, Parra-Damas A, Baeta-Corral R, *et al*. Reversal of memory and neuropsychiatric symptoms and reduced tau pathology by selenium in 3xTg-AD mice. *Sci Rep* 2018;8:6431.
- Zhang Z-H, Wen L, Wu Q-Y, *et al*. Long-Term dietary supplementation with selenium-enriched yeast improves cognitive impairment, reverses synaptic deficits, and mitigates tau pathology in a triple transgenic mouse model of Alzheimer's disease. *J Agric Food Chem* 2017;65:4970–9.
- Malpas CB, Vivash L, Genc S, *et al*. A Phase IIa Randomized Control Trial of VEL015 (Sodium Selenate) in Mild-Moderate Alzheimer's Disease. *Journal of Alzheimer's Disease* 2016;54:223–32.
- Cardoso BR, Roberts BR, Malpas CB, *et al*. Supranutritional sodium selenate supplementation delivers selenium to the central nervous system: results from a randomized controlled pilot trial in Alzheimer's disease. *Neurotherapeutics* 2019;16:192–202.
- Corcoran NM, Hovens CM, Michael M, *et al*. Open-label, phase I dose-escalation study of sodium selenate, a novel activator of PP2A, in patients with castration-resistant prostate cancer. *Br J Cancer* 2010;103:462–8.
- Schrag A, Schott JM, Alzheimer's Disease Neuroimaging Initiative. What is the clinically relevant change on the ADAS-Cog? *J Neurol Neurosurg Psychiatry* 2012;83:171–3.
- Sabbagh MN, Hendrix S, Harrison JE. FDA position statement "Early Alzheimer's disease: Developing drugs for treatment, Guidance for Industry". *Alzheimers Dement* 2019;5:13–19.
- Fowler KS, Saling MM, Conway EL, *et al*. Paired associate performance in the early detection of DAT. *J Int Neuropsychol Soc* 2002;8:58–71.
- Barnett JH, Blackwell AD, Sahakian BJ, *et al*. The Paired Associates Learning (PAL) Test: 30 Years of CANTAB Translational Neuroscience from Laboratory to Bedside in Dementia Research. *Curr Top Behav Neurosci* 2016;28:449–74.