**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. 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.

Tau aggregates are composed of hyperphosphorylated tau and as such represent a potential target for disease-modifying therapies. 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. 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. In transgenic AD models, treatment with sodium selenate has repeatedly demonstrated reversal of cognitive deficits alongside reductions in tau and markers of neuroinflammation. 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. 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.

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.
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.\(^{15}\) 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 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.\(^{15}\)) 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 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 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 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 (10mg) 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.

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 2.71, 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
(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 cutoffs, 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 2.18 to 2.89, p=0.001). Similar evidence for the effects of time was seen on the ADAS-Cog11 (b=23.42, 95% CI 20.32 to 26.52, 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
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The primary outcome was to assess the longer-term safety and tolerability of sodium selenate treatment. The results show that chronic (up to 23 months) treatment with sodium selenate was safe and well tolerated with relatively low levels of treatment-related AEs reported over the course of the study.

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            | ND             | ND             |
| COWAT            | 24 (2–57)**    | ND            | ND            | ND            | ND            | ND             | 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=9.
¶ n=26.
** n=27.
†† n=15.
* n=14.

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).

The computerised cognitive battery scores over the course of the study. (A) Detection (DET) score. (B) Identification (IDN) score. (C) One card learning (OCL) score. The thick blue line and grey shaded area represent the mean score and 95% CI.
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, 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. Schrag et al 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. 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. The Food and Drug Administration has advised it will now consider functional outcomes as trial endpoints. 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.

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REFERENCES
1 Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annu Rev Neurosci 2001;24:1121–59.
2 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.
3 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.
4 Gong CX, Lidesky T, Wiegel J, et al. Phosphorylation of microtubule-associated protein tau is regulated by protein phosphatase 2A in mammalian brain. Implications for neurofilibrillary degeneration in Alzheimer’s disease. J Biol Chem 2000;275:5353–44.
5 Goedert M, Jaques R, Qi Z, et al. Protein phosphatase 2A is the major endogenous inhibitor of tau protein phosphorylated by proline-directed protein kinases or cyclic AMP-dependent protein kinase. J Neurochem 1995;65:2804–7.
6 van Ensels 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.
7 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.
8 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. Neuropycharmacology 2016;108:382–93.
9 Smith SM, Zhang Y, Jenkins M, et al. accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17:479–89.
10 Ahmed T, Van der Jeugd A, Cailliere 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.
11 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 SStg-AD mice. Sci Rep 2018;8:6431.
12 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;65:4970–6.
13 Malpas CB, Vivash L, Genc S, et al. A Phase Ill Randomized Control Trial of VEL015 (Sodium Selenate) in Mild-Moderate Alzheimer’s Disease. Journal of Alzheimer’s Disease 2016;54:223–32.
14 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.
15 Corcoran NM, Havens 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.
16 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.
17 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.
18 Fowler KS, Saling MM, Conway EL, et al. Paired associate performance in the early detection of DAT. J Int Neuropsychol Soc 2002;8:68–71.
19 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.