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 Hovens 6, Amy Brodtmann 3,7,8, Steven Collins 2, Stephen Macfarlane 9, Dennis Velakoulis 10,11, Terence J O’Brien 1,2,3,4

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. Here we report the open-label extension study of sodium selenate in patients with AD who completed the previous RCT. Patients were enrolled, monitored for safety, adverse events and protocol compliance. Cognitive tests were administered for measures of disease progression.

Results Sixteen patients were enrolled. Patients were regularly monitored for safety, adverse events and protocol compliance. Cognitive tests were administered for measures of disease progression.

Discussion Chronic sodium selenate treatment is safe and well tolerated in patients with AD. Cognitive measures suggest a slowing of disease progression through this 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.

INTRODUCTION

Tauopathies collectively represent a constellation of 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.
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 al13 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 al13) 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 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 discoloration). 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 (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 2.71, 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
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=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=0.79, 95% CI 0.62 to 0.97, p=0.21) or ptau (b=0.12, 95% CI 0.23 to 0.35, p=0.08) were seen.

**DISCUSSION**

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

---

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

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

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, and the phase 1 open-label study in prostate cancer. Adverse events that occurred in fewer than two participants are not listed.

* Treatment period 24 weeks, n=20.
† 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. AE, adverse event; OLE, open-label extension; RCT, randomised controlled trial; TEAE, treatment emergent adverse event; UTI, urinary tract infection.
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

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline (n=28)</th>
<th>Week 6 (n=28)</th>
<th>Month 3 (n=27)</th>
<th>Month 6 (n=23)</th>
<th>Month 9 (n=18)</th>
<th>Month 12 (n=16)</th>
<th>Month 18 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog11</td>
<td>21.7 (8–42.7)*</td>
<td>ND</td>
<td>ND</td>
<td>21.7 (5.33–43)†</td>
<td>ND</td>
<td>23.5 (8–51.7)‡</td>
<td>26 (18.3–37.3)§</td>
</tr>
<tr>
<td>CFT</td>
<td>9 (1–24)¶</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>7 (0–20)</td>
<td>ND</td>
</tr>
<tr>
<td>COWAT</td>
<td>24 (2–57)**</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>22.3 (3–38)††</td>
<td>ND</td>
</tr>
<tr>
<td>DET</td>
<td>2.64 (2.36–3.09)</td>
<td>2.68 (2.38–3.17)</td>
<td>2.70 (2.40–3.04)</td>
<td>2.64 (2.39–2.98)</td>
<td>2.67 (2.39–2.95)</td>
<td>2.68 (2.39–2.99)</td>
<td>2.79 (2.40–2.95)</td>
</tr>
<tr>
<td>IDN</td>
<td>2.81 (2.53–3.13)</td>
<td>2.79 (2.69–3.08)*</td>
<td>2.80 (2.63–3.09)</td>
<td>2.81 (2.66–3.08)</td>
<td>2.82 (2.66–2.98)</td>
<td>2.85 (2.66–3.08)</td>
<td>2.84 (2.73–3.08)</td>
</tr>
<tr>
<td>OCL</td>
<td>0.766 (0.639–0.947)</td>
<td>0.785 (0.563–0.935)*</td>
<td>0.775 (0.358–0.924)</td>
<td>0.805 (0.552–0.924)</td>
<td>0.805 (0.515–0.947)</td>
<td>0.78 (0.487–0.947)‡</td>
<td>0.783 (0.717–0.9)</td>
</tr>
</tbody>
</table>

Data are presented as median (range).


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 or 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.
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.

**REFERENCES**


**Author affiliations**

1. Department of Neuroscience, Monash University, Melbourne, Victoria, Australia
2. Department of Medicine and Radiology, University of Melbourne, Melbourne, Victoria, Australia
3. Department of Neurology, Royal Melbourne Hospital, Parkville, Victoria, Australia
4. Department of Neurology, Alfred Hospital, Melbourne, Victoria, Australia
5. Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia
6. Department of Surgery, University of Melbourne, Melbourne, Victoria, Australia
7. Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia
8. The Dementia Centre, HammondCare, Melbourne, Victoria, Australia
9. The Neurology Unit, Royal Melbourne Hospital, Melbourne, Victoria, Australia
10. Melbourne Health Human Research Ethics Committee, Melbourne, Victoria, Australia

**Contributors**

L. Vivash 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, UCS, Anavax and Praxis. CM, BA, 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/.