Trial of Oxaloacetate in ALS (TOALS)

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Abstract

Background: Mitochondrial dysfunction is a critical therapeutic target in amyotrophic lateral sclerosis (ALS). Oxaloacetate (OAA) is a promising candidate therapy as it crosses the blood-brain barrier, reaches motor neurons, and enhances mitochondrial bioenergetics with positive preclinical data in ALS.

Methods: We conducted a prospective, phase 1B, dose escalation study using a standard 3+3 design to assess the safety profile and determine the maximum tolerated dose. Dose-limiting toxicity (DLT) was defined as any serious adverse event (SAE) requiring hospitalization or any adverse event (AE) attributed to OAA that required discontinuation of the medication. Dosages evaluated started at 1000 mg twice daily in Cohort 1 and, if tolerated, were escalated by 500 mg up to 2500 mg twice daily in the maximal dose Cohort 4. To determine target engagement, we evaluated a panel of mitochondrial biomarkers, platelet TDP-43 levels, and MR spectroscopy of brain glutathione from baseline and at the end of treatment.

Results: A total of 19 participants were screened, 18 enrolled, and one patient at the 2500 mg BID dose withdrew due to a DLT. OAA was overall well tolerated up to a dose of 2500 mg BID. Among the small sample of participants, no consistent signal of target engagement was observed, although in aggregate, post-exposure MRS determined that brain glutathione levels increased.

Conclusions: This study supports the safety and tolerability of OAA at doses up to 2500 mg BID in patients with ALS. A future trial would be warranted to confirm the maximum tolerated dose, to assess efficacy, and further explore target engagement.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of the upper and lower motor neurons with a multifactorial pathophysiology. The majority of patients with ALS are deceased within 3 to 5 years from symptom onset. The standard approach to multidisciplinary care has extended survival and includes 2 FDA-approved drugs, riluzole and edaravone, which together have a modest effect on survival and slowing of functional decline. There is an urgent need for better ALS therapies.[1,2]

While the exact underlying cause of this motor neuron degeneration remains uncertain, candidate mechanisms include glutamate excitotoxicity, free radical-mediated oxidative cytotoxicity, neuroinflammation, mitochondrial dysfunction, autoimmune processes, protein aggregation, and cytoskeletal abnormalities. Mitochondrial dysfunction may play a critical role in ALS neurodegeneration, an observation supported by human, animal model studies, and patient autopsies.[3-9]

Oxaloacetate (OAA), a small molecule that has a crucial role in cell metabolism, acts as a key intermediate in the Krebs cycle and is involved in gluconeogenesis. OAA may have neuroprotective effects by reducing glutamate levels and enhancing mitochondrial function. In pre-clinical studies, OAA reduces neuroinflammation, a known ALS pathological mechanism.[10] A phase 2 trial of OAA in Alzheimer's Disease (AD) was conducted at the University of Kansas Medical Center (KUMC, PI: R. Swerdlow), but at a lower dose than the current study.[11] We are interested in OAA as a potential therapeutic agent in ALS as it crosses the blood-brain barrier, accesses motor neurons, activates mitochondrial bioenergetics, and increases respiratory and glycolytic capacity. Furthermore, superoxide dismutase 1 (SOD1) G93A transgenic mice treated with OAA showed significantly delayed limb paralysis and demonstrated a trend of increased lifespan compared to untreated animals.[12] Here, we tested the safety, maximum tolerated dose, and biomarkers of target engagement of OAA in ALS.

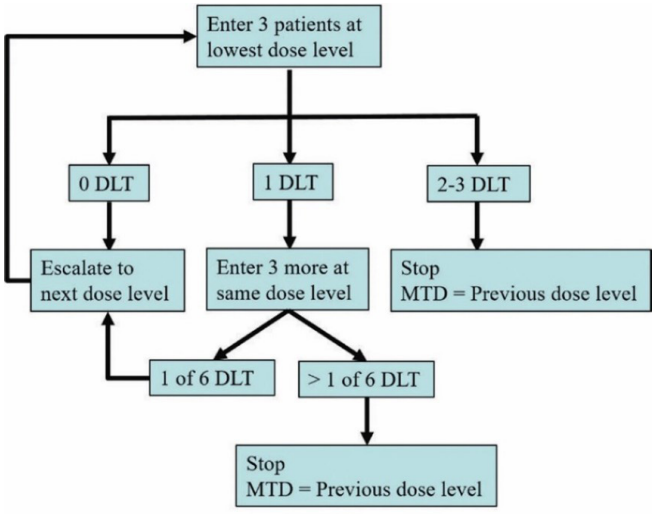
Methods

Trial Design:

We conducted a 28-day open-label, prospective 3+3 dose-ascending study of OAA in ALS to assess the safety profile and determine the maximum tolerated dose. The study was completed at KUMC from March 2020 to August 2023 (Figure 1). The trial was approved by the Institutional Review Board at the University of Kansas Medical Center. Written informed consent was obtained and documented from all participants in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The trial was registered on clinicaltrials.gov (NCT04204889).

The inclusion criteria included: a clinical diagnosis by a study investigator of laboratory-supported probable, probable, or definite ALS, according to the modified El Escorial criteria, 21 to 80 years of age, forced vital capacity (FVC) greater or equal to 50% of predicted, diagnosis of ALS within 3 years prior to enrollment, if patients took riluzole, edaravone, and/or sodium phenylbutyrate/taurursodiol for ALS, they were on a stable dose for at least thirty days prior to the baseline visit.[13] The exclusion criteria included: tracheotomy ventilation or non-invasive ventilation for > 23 hours per day, diagnosis of other neurodegenerative diseases (e.g., Parkinson disease, Alzheimer disease), clinically significant history of unstable medical illness (e.g., unstable angina, advanced cancer) 30 days prior to screening, current pregnancy or lactation, limited mental capacity such that the patient cannot provide written informed consent or comply with evaluation procedures, or receipt of any investigational drug within 30 days prior to enrollment. Study participants were recruited from the KUMC multidisciplinary ALS clinic. The oxaloacetate was provided by Terra Biological LLC as 500 mg capsules.

Figure 1. 3 + 3 research design



DLT = Dose Limiting Toxicity

MTD = Maximum Tolerable Dose

Outcomes and Measures:

Baseline characteristics included age, sex, and self-reported race and ethnicity. At the screening and baseline visits, we collected vitals, safety labs (complete blood count and comprehensive metabolic panel), concomitant medications, adverse events, physical exam, forced vital capacity, Magnetic Resonance Spectroscopy (MRS), and pharmacokinetic blood samples. At weeks 1, 2, and 3, participants were contacted by phone to capture adverse events and concomitant medication changes. On day 28 or the end of the study, we collected safety labs, medication use, adverse events, completed a physical exam, and MRS. Blood biomarkers were collected at baseline and day 28, or at the end of the study.

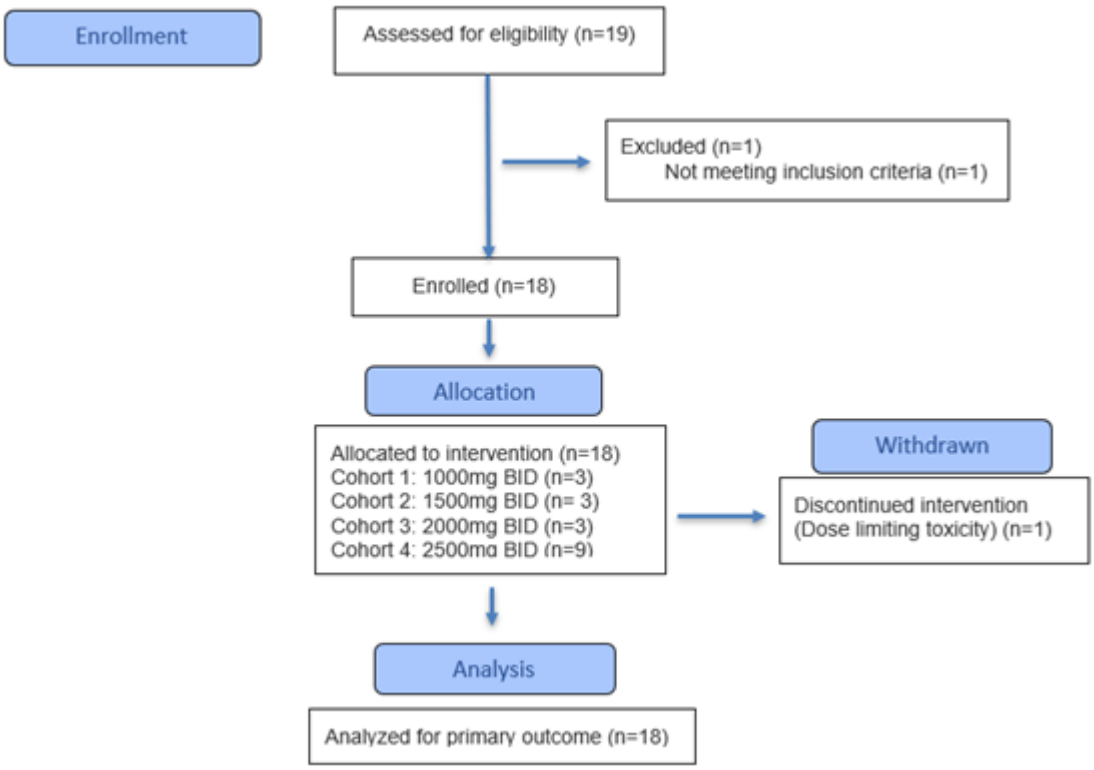
The primary outcome for the study was dose-limiting toxicities (DLT). We defined DLT as any serious adverse event related to OAA requiring hospitalization, or any AE related to OAA requiring stopping the medication, including a twofold increase in AST and/or ALT, and/or a 1.5 times increase in creatinine level. The maximum tolerated dose was defined as the maximal dose at which there were ≤ 30% DLTs.

To evaluate secondary target engagement, we included the following secondary outcomes: MRS, blood pharmacokinetics (PKs), blood mitochondrial biomarkers, and platelet TDP43. PK was measured pre-dose, 1 hour post dose, and 4 hours post dose at the baseline visit.

A panel of blood mitochondrial biomarkers was examined in peripheral blood mononuclear cells (PBMCs), and the mitochondrial functional index (MFI) was calculated. Blood was collected in ACD tubes and processed within 30 hours of blood draw. PBMCs were isolated using Accuspin tubes, histopaque 1077, and differential centrifugation. Approximately 2 million PBMCs were stained with Annexin V+MitoTracker, MitoSox+ Hoechst, and TMRE+ Hoechst as previously described.[14] Briefly, cells were incubated with 40 nM MitoTracker, 5 μM MitoSox/10 ng Hoechst, and 200 nM TMRE/10 ng Hoechst (in separate tubes) for 30 minutes at 37°C/5% CO2 in Hanks Balanced Salt Solution (HBSS with Ca2+/Mg2+). MitoTracker cells are washed and then stained with Annexin V in binding buffer, then diluted for flow cytometry analysis. MitoSox and TMRE stained cells are washed with HBSS and diluted for flow cytometry analysis, where 10,000 cells per tube were analyzed. All values were normalized to Hoechst signal. Fluorescent measures were completed within 30 hours of blood draw. The MFI algorithm; MFI = log [MitoTracker x TMRE)/ (MitoSox x Annexin V)] provides an overall picture of mitochondrial health and function. The MFI biomarker is listed in the utility patent no. 63/824,391 (Mitochondrial Functional Index) as of June 16, 2025.[14,15]

Platelet TDP-43 was assessed using capillary electrophoretic immunoassay (CEI).[16,17] Briefly, protein concentrations were determined using a BCA assay, and equal protein concentrations were used for CEI as previously described to measure total TDP43 (Proteintech Cat# 10782-2-AP) and p S409/410/12 TDP-43 (Proteintech Cat# 80007-1-RR).

Figure 2. CONSORT flow diagram



CEI data were used to calculate the Predicted Phosphorylation Value (PPV), defined as the ratio of pTDP-43 to total TDP-43 (PPV = pTDP-43 / total TDP-43). This algorithmic approach provides a practical and internally normalized surrogate measure of the relative extent of TDP-43 phosphorylation. The PPV thus serves as a useful metric for assessing TDP-43 post-translational modification in platelets and may offer insight into its relevance to platelet biology and neurodegenerative disorders such as ALS.

MRS: Brain glutathione (GSH) levels were measured via an advanced MR spectroscopy method, the multiple quantum chemical shift imaging (CSI) technique that is specially designed for GSH at 3T (Skyra, Siemens, Erlangen, Germany).[18-20] GSH is a vital antioxidant in the cerebral antioxidant defense system and is known to be a sensitive, quantitative indicator of oxidative stress, which is a major contributing factor in ALS.[21] We have demonstrated lower brain GSH in patients with progressive multiple sclerosis (MS) and patients with Alzheimer's disease (AD) compared with their age- and sex-matched controls.[18,22,23] In our previous study, we observed significant increases in brain GSH concentrations following one month of OAA treatment in patients with AD, particularly in the frontal and frontoparietal regions.[24] Accordingly, in the present study, we chose to measure brain GSH from a slab encompassing the frontal and parietal regions, consistent with our previous studies. GSH CSI acquisition parameters were TR/ TE = 1500/115 ms, FOV = 200 x 200 mm2, matrix size = 10 x 10, slice thickness = 2.5 cm, number of averages = 8. GSH signals were quantified using simultaneously measured creatine signals as internal concentration references.[20]

MRI: T1-weighted MRI (MPRAGE sequence, TR/TE/TI = 2000/3.98/830 ms, matrix = 176 × 256 × 256, FOV = 176 × 256 × 256 mm3, GRAPPA acceleration factor = 2) was also acquired for GSH quantification as well as regional brain volumes and cortical thickness using FreeSurfer software.[25]

Statistical Analysis:

The primary and secondary outcome measures were assessed with each dosing cohort in the 3+3 study design. For each dose, three subjects were enrolled and assessed for a dose-limiting toxicity (DLT). If none of the three subjects had a DLT, then three new subjects were enrolled at the next (higher) dose level. However, if one of the three had a DLT, then three additional patients were enrolled at the current dose. If none of the next three patients (i.e., so only 1/6 in total) experienced a DLT, then we continued to enroll three new subjects at the next (higher) dose. If any of the three additional subjects, or two or more of the original three subjects, at a given dose experience a DLT, dosing would be stopped. The next lower dose was then defined as the maximum tolerated dose. The sample size for this study was determined based on our 3+3 dose escalation design.

Additional analyses for this study included assessments of pre- versus post-treatment changes in biomarker measures as a function of dose. Pharmacokinetic samples were collected at baseline visit, pre-dose, 1 hour, and 4 hours post-dose. We treated dose as a continuous measure, so there were three

to six replicates at each dose for analysis. We used ordinary least square regression for analysis and conducted residual analysis to assess model assumptions. We planned to create spaghetti plots of individual subject trajectories and generate descriptive statistics as a case study approach to initially assess PK.

Results

Between March 2020 and August 2023, we screened 19 subjects, and 18 received OAA (Figure 2). One participant's screen failed due to low (less than 50%) forced vital capacity. One subject discontinued treatment on day 10/11 due to adverse events of nausea, vomiting, and diarrhea. These gastrointestinal events were considered DLT (Table 1). There were no deaths during the study. Data was analyzed for 18 subjects.

Participants were mostly middle-aged Caucasian white males with limb-onset ALS. The average time from symptom onset at the time of screening was 1.9 years.

Outcomes and measures:

Across the four cohorts, 34 adverse events were reported (Table 2). The highest incidence of adverse events was gastrointestinal and occurred in cohort 4 with a dose of 2500mg BID.

Table 1. Baseline demographics

Variable	Summary
Enrolled, (N) %	18
Sex, (N) %	
Female	3 (17%)
Male	15 (83%)
Age (years), median (IQR)	61 (54, 66)
Non-Hispanic/Non-Latino N (%)	18 (100%)
Caucasian, N (%)	18 (100%)
Participant Status, N (%)	
Completed Study	17 (94%)
Discontinue/DLT	1 (6%)
Mean symptom duration years (SD/range)	1.93 (1.13/ 0.59-4.74)
Vital status deceased as of 2026	12 (67%)
Taking riluzole	17 (94%)
Taking edaravone	13 (72%)
Taking sodium phenylbutyrate/ taurursodiol	3 (17%)

Table 2. Adverse events

System Organ Class Verbatim Term	Cohort 1 Dose 1000 mg BID (N=3)	Cohort 2 Dose 1500 mg BID (N=3)	Cohort 3 Dose 2000 mg BID (N=3)	Cohort 4 Dose 2500 mg BID (N=9)	All Subjects (N=18)
Subjects with ≥1 AE (%)	***3 (100%)***	***2 (66.7%)***	***3 (100%)***	***7 (77.8%)***	***15 (83.3%)***
Gastrointestinal	***3 (100%)***	***1 (33.3%)***	***3 (100%)***	***5 (55.6%)***	***12 (66.6%)***
Nausea	1 (33.3%)	0	0	3 (33.3%)	4 (22.2%)
Heartburn	1 (33.3%)	1 (33.3%)	0	2 (22.2%)	4 (22.2%)
Upset Stomach	0	0	2 (66.7%)	1 (11.1%)	3 (16.7%)
Diarrhea	0	0	0	1 (11.1%)	1 (5.6%)
Episodes of Sporadic Diarrhea	0	0	0	1 (11.1%)	1 (5.6%)
Intermittent Heartburn	1 (33.3%)	0	0	0	1 (5.6%)
Intermittent Indigestion	0	0	1 (33.3%)	0	1 (5.6%)
Stomach Pain	1 (33.3%)	0	0	0	1 (5.6%)
Vomiting	0	0	0	1 (11.1%)	1 (5.6%)
General Disorders	***0***	***0***	***1 (33.3%)***	***1 (11.1%)***	***2 (11.1%)***
Chills	0	0	0	1 (11.1%)	1 (5.6%)
Fatigue	0	0	1 (33.3%)	0	1 (5.6%)
Fever	0	0	0	1 (11.1%)	1 (5.6%)
Influenza-A	0	0	0	1 (11.1%)	1 (5.6%)
Musculoskeletal	***0***	***1 (33.3%)***	***0***	***1 (11.1%)***	***2 (11.1%)***
Increased Muscle Cramping	0	0	0	1 (11.1%)	1 (5.6%)
Increased Muscle Fasciculations	0	1 (33.3%)	0	0	1 (5.6%)
Shoulder Aches	0	0	0	1 (11.1%)	1 (5.6%)
Respiratory	***0***	***0***	***0***	***2 (22.2%)***	***2 (11.1%)***
Cough	0	0	0	2 (22.2%)	2 (11.1%)
Shortness of Breath	0	0	0	1 (11.1%)	1 (5.6%)
Cardiac Disorder	***0***	***0***	***1 (33.3%)***	***0***	***1 (5.6%)***
Tachycardia	0	0	1 (33.3%)	0	1 (5.6%)
Nervous System	***0***	***0***	***1 (33.3%)***	***0***	***1 (5.6%)***
Headache	0	0	1 (33.3%)	0	1 (5.6%)
Psychiatric Disorder	***0***	***0***	***0***	***1 (11.1%)***	***1 (5.6%)***
Insomnia	0	0	0	1 (11.1%)	1 (5.6%)
Skin and Subcutaneous Tissue Disorders	***0***	***0***	***1 (33.3%)***	***0***	***1 (5.6%)***
Hyperhidrosis	0	0	1 (33.3%)	0	1 (5.6%)
Vascular	***0***	***0***	***0***	***1 (11.1%)***	***1 (5.6%)***
Thrombus	0	0	0	1 (11.1%)	1 (5.6%)

N= # of subjects
N= # of events

The mitochondrial function index (previously MHI) was analyzed for 17 participants at screening and day 28.

Figure 3: MFI by cohort pre-dose and post-dose.

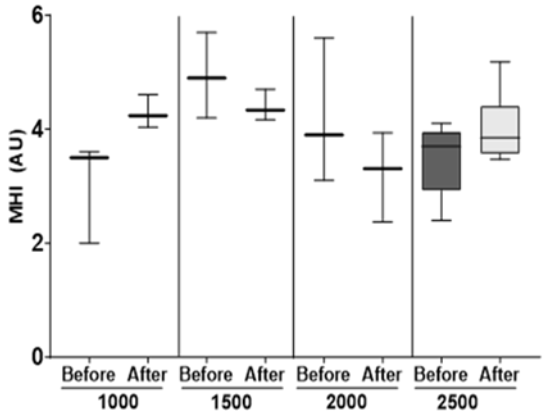
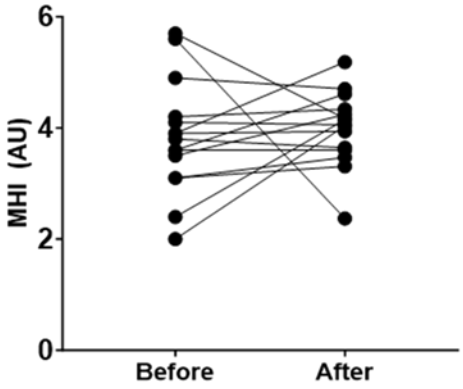


Figure 4: MFI collective pre-dose and post-dose.



Analysis of Predictive Phosphorylation Value (P-TDP-43 / Total TDP-43), PPV

Figure 5: PPV by cohort pre-dose and post-dose.

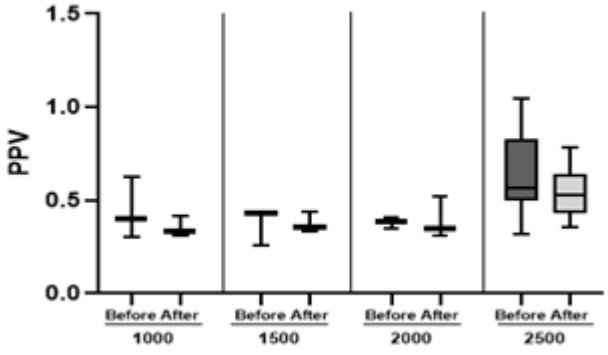
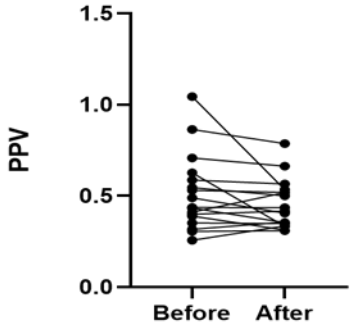


Figure 6: PPV collective pre-dose and post-dose.



MRS: Among 18 subjects, 12 of them successfully completed the MR scanning procedures. We observed consistent GSH spectral patterns across the frontal and parietal regions and across time, as shown in Figure 7. When all dose groups were combined, brain GSH levels increased significantly following OAA treatment ($p = 0.036$, $n = 12$, two-tailed, paired t-test).

Discussion

In the study, OAA was overall safe and well-tolerated in ALS patients up to 2500 mg twice daily. Across the four dosing cohorts, a total of 34 adverse events were reported. Of these, 12 of the 18 patients enrolled (66.7%) reported an adverse event that was determined to be related to OAA and classified as mild in severity. There was one serious adverse event, Influenza-A, which was assessed as not related to OAA. The highest incidence of adverse events was seen in cohort 4 with a dose of 2500 mg BID. Of the adverse events in cohort 4, 55.6% were gastrointestinal. Specifically, the adverse events included nausea, heartburn, upset stomach, diarrhea, stomach pain, and vomiting.

Due to one patient experiencing a DLT at the 2500mg BID dose, an additional 3 subjects were enrolled with no further DLTs. Gastrointestinal adverse events were reported in dosing cohorts 1, 3, and 4, with the highest prevalence in the 2500mg BID cohort. The higher frequency of adverse events in the 2500mg BID dosing cohort may influence the choice of OAA dosage in future ALS trials.

The mitochondrial biomarker, MFI indicated that lower and higher doses may better target mitochondrial function. However, n=3 in most cohorts limits a definite conclusion. Future studies should examine target engagement of mitochondrial function, as preclinical and in vitro studies show that OAA modulates mitochondrial function.[10,26]

Figure 7: Brain GSH maps before and after OAA treatment in a patient with ALS. (SEE FIGURE LEGEND BELOW)

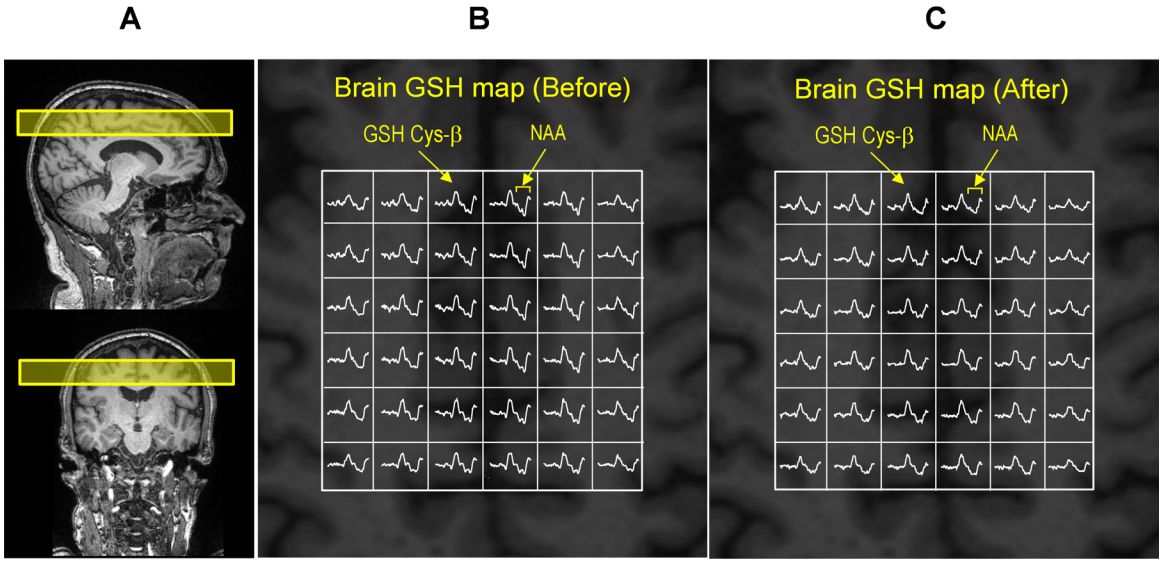


Figure 7. Representative brain GSH maps from longitudinal measurements before and after OAA treatment in a patient with ALS.

(A) T1-weighted MR images in two orientations (top: sagittal, bottom: coronal) with brain GSH chemical shift imaging (CSI) slab (2.5 cm thickness) indicated in yellow rectangles. (B) Partial views of brain GSH CSI demonstrate consistent detection of GSH signals in the brain of a patient with ALS before (left) and after (right) OAA treatment at 3 T. Brain GSH CSI spectra from the same participant are overlaid on anatomical MR images. The spectral range shown for GSH is 3.5-2.5 ppm.
PK: OAA was not detected in the PK samples. We cannot determine the exact reason for this observation.

The observed increase in brain GSH levels following OAA treatment is consistent with previously reported brain GSH increases in patients with AD, suggesting potential target engagement of the treatment.[24] In contrast, regional brain volume and cortical thickness measures in the precentral, thalamus, and brainstem regions did not show significant changes.

PPV - Predicted Phosphorylation Value (PPV), defined as the ratio of pTDP-43 to total TDP-43, showed no statistically significant difference before and after OAA intake. This potential biomarker may require further validation in ALS.

Study limitations include a small study sample, short duration of drug exposure, and inability to measure OAA levels. The COVID-19 pandemic caused trial recruitment to be slow, limited the number of subjects with MRS data collection, and the number of participants willing to stay onsite for the 4-hour post dose PK sample collection.

In this study, OAA was safe and well-tolerated in ALS patients at 2500 mg twice daily. Despite a small sample size, we observed positive target engagement based on MRS data, and TDP-43 PPV remained overall stable. We could not measure a reliable OAA plasma signal. This may be due to assay limitation or rapid metabolism of OAA, though we cannot exclude limited oral bioavailability of OAA. A reasonable next step would be to explore OAA in a larger trial powered to further evaluate efficacy and target engagement

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