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RESEARCH ARTICLE

Pilot trial of inosine to elevate urate levels in amyotrophic lateral sclerosis

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Abstract

Objective: To test the safety, tolerability, and urate-elevating capability of the urate precursor inosine taken orally or by feeding tube in people with amyotrophic lateral sclerosis (ALS). **Methods**: This was a pilot, open-label trial in 25 participants with ALS. Treatment duration was 12 weeks. The dose of inosine was titrated at pre-specified time points to elevate serum urate levels to 7–8 mg/dL. Primary outcomes were safety (as assessed by the occurrence of adverse events [AEs]) and tolerability (defined as the ability to complete the 12-week study on study drug). Secondary outcomes included biomarkers of oxidative stress and damage. As an exploratory analysis, observed outcomes were compared with a virtual control arm built using prediction algorithms to estimate ALSFRS-R scores. **Results**: Twenty-four out of 25 participants (96%) completed 12 weeks of study drug treatment. One participant was unable to comply with study visits and was lost to follow-up. Serum urate rose to target levels in 6 weeks. No serious AEs attributed to study drug and no AEs of special concern, such as urolithiasis and gout, occurred. Selected biomarkers of oxidative stress and damage had significant changes during the study period. Observed changes in ALSFRS-R did not differ from baseline predictions. **Interpretation**: Inosine appeared safe, well tolerated, and effective in raising serum urate levels in people with ALS. These findings, together with epidemiological observations and preclinical data supporting a neuroprotective role of urate in ALS models, provide the rationale for larger clinical trials testing inosine as a potential disease-modifying therapy for ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease primarily affecting motor neurons resulting in progressive atrophy and paralysis of voluntary muscles.[1] Median survival is 3 years after the onset of symptoms and 90% of patients die within 5 years.[2] Riluzole and edaravone, the only FDA-approved disease-modifying agents to treat ALS, confer modest clinical benefit.[3,4] There is an urgent need to develop novel treatments for ALS.

Oxidative stress has been implicated in ALS pathogenesis based on both autopsy and laboratory studies,[5] a role that has been strengthened by the recent finding that intravenously administered edaravone, a putative antioxidant,[6–9] slows down ALS disease progression. Urate, the end-product of human purine metabolism, is an endogenous antioxidant[10,11] and proposed neuroprotectant[12–15] and its levels may be increased by edaravone treatment.[6,16] High urate levels correlate with improved survival in ALS epidemiologic studies[17–23] and with favorable

outcomes in other neurodegenerative diseases, most notably Parkinson's disease (PD).[24–26] Further, urate is neuroprotective in several models of neurodegeneration.[12,27–32]

This growing body of evidence provides the rationale for human trials of urate elevation, which can be accomplished via administration of its precursor inosine. Indeed, urate elevation is rapidly advancing from the bench to the bedside in PD where a phase 2 clinical trial demonstrated safety and tolerability of inosine to increase serum and cerebrospinal fluid urate[33,34] and a phase 3 trial is ongoing to test the clinical efficacy of this approach (NCT02642393).

Here we report the safety, tolerability, and urate-elevating capability of the urate precursor inosine in people with ALS as the first clinical trial to test the urate elevation in ALS. We also tested the effect of inosine administration on putative biomarkers of oxidative stress and damage as possible measures of target engagement. Specifically, we tested the impact of inosine on plasma levels of 3-nitrotyrosine, a marker of tyrosine nitration mediated by reactive nitrogen species, whose levels were previously found to be elevated in SOD1 transgenic mice and people with ALS.[35,36] We also measured the levels of glutathione, a free radical scavenger, and the ferric-reducing antioxidant power (FRAP), a measure of total plasma antioxidant capacity, as these measures were previously found to be altered in ALS[37,38] and modulated by urate either *in vitro* or in other patient populations.[27,34] Finally, we used a novel algorithm to predict clinical progression (ALSFRS-R total score) and compared predictions to observed values in this open-label, pilot trial as a test of efficacy or, conversely, futility of this intervention.

Methods

This study is an investigator-initiated, open-label, pilot clinical trial that enrolled participants at Massachusetts General Hospital (MGH) between March 2015 and March 2016. The Partners Human Research Committee approved this study. The trial is registered on clinicaltrials.gov (NCT02288091).

Participant selection criteria

At screening, eligible participants had a diagnosis of possible, probable laboratory-supported, probable, or definite ALS by El Escorial criteria.[39] Screening serum urate levels had to be <5.5 mg/dL for inclusion in the study. The 5.5 mg/dL eligibility threshold was selected as the approximate population median and to allow for a meaningful increase in serum urate without pushing levels dangerously high. Urine pH had to be ≥5.5 at screening to exclude participants with acidic urine, a major determinant of uric acid urolithiasis.[40] There were no restrictions in vital capacity, disease duration, or riluzole use. Presence of a feeding tube was not exclusionary as study drug could be administered orally or via feeding tube. Participants had to be willing and able to participate in brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) studies. Exclusion criteria included a history of gout, urolithiasis, stroke, myocardial infarction, symptomatic coronary artery disease, peripheral arterial disease, congestive heart failure, uncontrolled hypertension, unstable psychiatric disease, cognitive impairment, or dementia, and pregnancy. Allopurinol and probenecid (which are commonly used to treat gout) were exclusionary. Participants were allowed to take a standard multivitamin daily, but were not allowed to take more than 300 mg of vitamin C daily in addition to a standard multivitamin as high doses of vitamin C may reduce urinary pH. Use of thiazides was permitted as long as the participant was on a stable dose from at least 1 week prior to screening as thiazides are known to increase urate levels.

Intervention

Participants were treated with inosine for 12 weeks (open-label). Inosine was administered as 500 mg capsules that could be taken orally or via feeding tube after mixing the capsule content with water or food, which has been found to have minimal or no effect on the ability of oral inosine to raise serum urate levels (https://clinicaltrials.gov/show/NCT02614469). Treatment was initiated gradually with one capsule taken twice a day for the first 2 weeks of the study. The inosine dose was then titrated at weeks 2, 4, 6, and 9 following a pre-specified titration algorithm[33] to achieve urate levels in the target range of 7–8 mg/dL. Inosine dosing was terminated after 12 weeks. Permitted dosages ranged from one capsule daily (each morning) up to two capsules 3 times daily for a maximum intake of 3 g of inosine per day.

Study overview

Participants signed an informed consent form at screening. Medical history, detailed ALS history, physical and neurological examinations, medication review, vital signs, and laboratory tests were performed to determine eligibility. For eligible participants, the baseline visit (Day 0), when study drug was initiated, occurred within 21 days of screening. Follow-up visits consisted of phone calls that occurred 2, 4, 6, and 9 weeks after baseline as well as an in-person visit at week 12. Inosine dose titration occurred at each phone call visit based on the urate levels measured from blood drawn prior to the visit at local Quest

Diagnostics patient care centers and measured at a central Quest Diagnostic Laboratory. A final phone call occurred at week 16, 4 weeks after participants stopped study drug (Figure 1).

Study procedures

Clinical measurements included safety labs, slow vital capacity (SVC), and the ALS Functional Rating Scale-Revised (ALSFRS-R) questionnaire. SVC and safety labs were performed at the Baseline and Week 12 visits. The ALSFRS-R was administered in-person at the Baseline and at Week 12 visits and by phone at the Week 4 and Week 9 phone calls. Biomarkers of oxidative stress and damage were measured at the Baseline and Week 12 visits by plasma sample assays and MRSI (described below) (Figure 1).

Biofluid biomarker assays

FRAP assay

Ferric-reducing antioxidant power (FRAP), a measure of total plasma antioxidant capacity, was determined as previously described.[41] In this colorimetric assay, a blue color develops when ferric tripyridyltriazine (Fe(III)-TPTZ) complex is reduced to the ferrous form by the added plasma sample. By using an excess of Fe(III)-TPTZ, absorption at 560 nm is proportional to the antioxidant capacity in the plasma. Antioxidant capacity is expressed as equivalent concentrations of the standard ferrous (II) chloride (ranging from 0.03 to 1.0 mmol/L). Plasma samples were diluted 1:2 in the assay buffer and analyzed in triplicate in three 96-well assay plates with inter-assay coefficient of variation (CV) <10%.

Total glutathione (GSH) content

Samples of whole blood collected in EDTA tubes were diluted 1:4 in ice-cold 5% metaphosphoric acid. After quick mixing, precipitated proteins were removed by low-speed centrifugation and the supernatant was stored at −70°C until assay. Total GSH content was measured by enzyme colorimetry using an HT Glutathione Assay Kit (Trevigen, Inc.) as per the manufacturer's protocol.

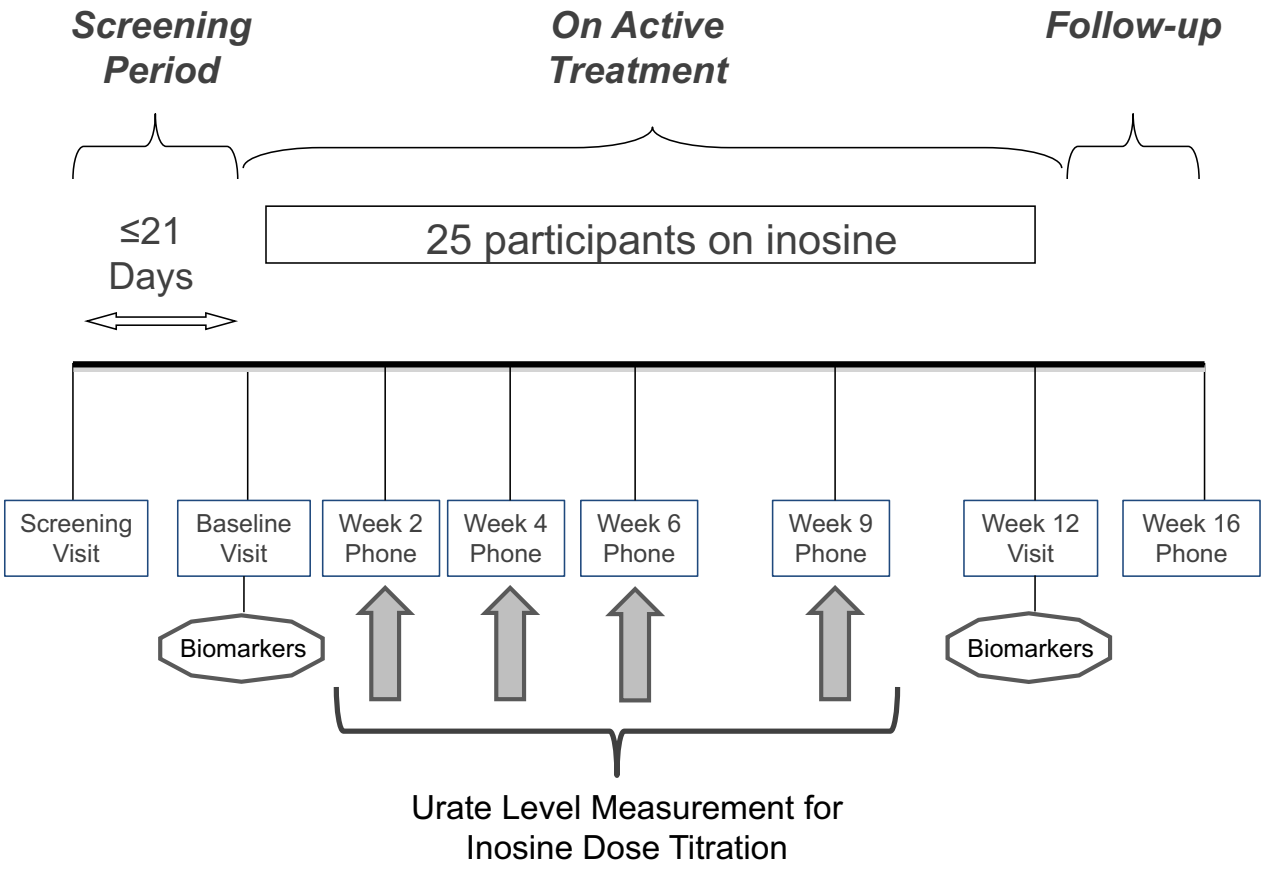

Figure 1. Study schema.

3-nitrotyrosine (3-NT) assay

Plasma levels of 3-NT were quantified using a competitive ELISA kit according to the manufacturer's instructions (Biovision Inc). Plasma samples were assayed in triplicate with inter-assay CV <10%.

Neuroimaging

Magnetic resonance spectroscopic imaging

All MRI and MRSI measurements were performed using a clinical 3T MR scanner (Tim Trio, Siemens, Erlangen) equipped with a 32-channel phased receive array head coil and a gradient system capable of 40 mT/m maximum amplitude and 200 T/m/s maximum slew rate. Patients had two MRSI scans, one scan immediately before the treatment start (Baseline) followed by a second scan at the end of the treatment (Week 12). Glutathione (GSH) levels were imaged with a J-difference spectral editing 3D MRSI sequence[42] which included LASER excitation, MEGA editing, spiral spectro-spatial encoding, real-time navigation for motion, and shimming with acquisition parameters: TR/TE = 1600/68 ms, FOV = 200 × 200 × 172, matrix 14 × 14 × 12, NA = 10, TA = 12:05 min. MEGA editing was obtained with Gaussian pulses of 60 Hz bandwidth applied in an interleaved fashion at 4.57 ppm (ON) and at −10 ppm (OFF) to edit the GSH signal at 2.95 ppm in the difference (ON-OFF) spectrum. GSH was quantified from the difference spectra while levels of N-acetylaspartate (NAA), creatine, choline, glutamine and glutamate were quantified from the OFF spectra. 3D MRSI data were fitted with LCModel[43] software using difference and OFF basis sets to quantify metabolite levels. The threshold for acceptable goodness of fit was set to 25% Cramer-Rao lower bound (CRLB) for GSH in the difference spectrum and 20% CRLB for NAA in the OFF spectrum. 3D metabolic maps were reconstructed from the LCModel fits using a combination of different neuroimaging software such as MINC (Montreal Neurological Institute), FSL (FMRIB Software Library, Oxford, UK) and MATLAB (Mathworks, Natick, MA) imaging tools, as detailed in Andronesi et al.[42] The GSH and NAA signals were normalized relative to the level of total creatine (tCr), assuming an average creatine concentration of 8 mmol/L. Metabolic maps (GSH/tCr and NAA/tCr) were further coregistered to the anatomical brain image (T1-weighted, MEMPRAGE) using robust register tools[44] of Freesurfer software. Brain segmentation obtained from Freesurfer was used to calculate mean values of GSH/tCr and NAA/tCr in the anatomical regions of interests (motor cortex and underlying white matter).

Statistical analysis

The primary outcome of safety was assessed by the occurrence of adverse events (AEs). The primary outcome of tolerability was defined as the ability to complete the 12-week study on study drug. AEs were coded to preferred terms from the MedDRA library (version 16.1). All analyses were carried out using R (R version 3.3.2).

Feasibility was assessed with respect to the accuracy of serum urate titration. This was assessed both with respect to individual sampling times and participant averages after reaching full titration. Secondary outcomes assessing target engagement included antioxidant capacity (FRAP), GSH, and 3-NT levels in plasma and GSH and NAA levels as measured in the precentral motor cortex by MRSI, normalized to total creatine (tCr). Mean visit-specific serum urate levels and 12-week change in plasma and MRSI biomarker levels were estimated from repeated-measures mixed models with a fixed effect of visit and unstructured within-person covariance. Pearson correlations were calculated to compare 12-week changes in plasma and MRSI biomarker measures to 12-week change in serum urate.

As an exploratory analysis, a virtual control arm was built using prediction algorithms to estimate ALSFRS-R total scores throughout the 16-week post-treatment follow-up period. The prediction algorithm was an advanced machine learning predictive modeling tool for longitudinal prediction of ALSFRS-R that was developed using the PRO-ACT database and the Gradient Boosting Machine (GBM) (v.2.1.3, Ridgeway, 2017) R package. The predictive core of the regression model was a GBM internally validated through a 10-fold cross-validation procedure on the PRO-ACT database using 40 common baseline variables available in the PRO-ACT dataset and baseline visit for the 25 participants in this study. During model training, the distribution, number of trees, interaction depth, minimum number of observations per node, shrinkage, and bagging fraction were set to Gaussian, 500, 7, 10, 0.01, and 0.5, respectively. Default values were used for the other parameters of the GBM algorithm, as provided by the GBM R package Version 2.1.3 (available at: https://cran.r-project.org/web/packages/gbm/gbm.pdf).

The effect of inosine treatment was estimated as the difference between the observed ALSFRS-R total scores and the visit-specific virtual control arm predictions. A linear mixed model with no intercept term, the observed minus predicted difference as the outcome, a fixed effect for continuous time, and a random slope for each subject was used to estimate treatment effect. Futility of serum urate elevation was pre-specified as an upper 95% confidence bound on the estimated difference in rate of change

in ALSFRS-R total score below a minimum clinically important difference of 0.1 units per month.

Results

Study population and urate elevation

Thirty-two volunteers were screened for this trial and 25 eligible individuals initiated treatment. Baseline characteristics of study participants are summarized in Table 1. Participant enrollment and follow-up for the trial are shown in Figure 2. Urate levels were effectively raised from a mean of 4.1 ± 1.0 mg/dL at Screening to pre-specified target levels of 7–8 mg/dL by Week 6 (Figure 3). The accuracy of serum urate titration is presented in Figure S1.

Safety and tolerability

The trial met its primary endpoints for safety and tolerability. Ninety-six percent (24/25) of the participants completed the study on study drug. No dose reduction was performed in any of the participants due to AEs or other reasons. The participant who did not complete the study did not comply with blood draws to monitor urate levels and was lost to follow-up. There were no serious adverse events (SAEs) related to study drug. No AEs of special concern, such as urolithiasis and gout, occurred. AEs occurring in at least 5% of participants are summarized in Table 2 by MedDRA preferred term.

Table 1. Baseline characteristics of study participants.

N	25
Male gender	28%
White race	92%
Age (years)	61.2 ± 8.4
Bulbar onset	36%
Riluzole use	72%
SVC (percent predicted)	86.4 ± 30.5
ALSFRS-R	35.6 ± 5.3
Months since symptom onset	27.2 ± 17.0
Months since diagnosis	15.1 ± 15.0
Diagnostic delay (months)	12.1 ± 6.4
EEC definite	28%
EEC probable	24%
EEC probable lab-supported	28%
EEC possible	20%
Urate at screening (mg/dL)	4.1 ± 1.0
BMI (kg/m^2)	26.2 ± 5.7

Data are presented as either percentages or means (±SD). SVC is presented as percent of predicted values. Diagnostic delay represents the time from symptom onset to diagnosis.: ALSFRS-R, ALS functional rating scale revised; BMI, body mass index; EEC, El Escorial Criteria; *N*, number of subjects; SD, standard deviation; SVC, slow vital capacity.

Biomarkers

Plasma FRAP increased significantly (12-week change = 422 μmol/L, standard error (SE) = 69.6 μmol/L, $P < 0.001$) and 3-NT decreased significantly (12-week change = −4.5 ng/mL, SE = 1.8 ng/mL, $P = 0.02$) (Figure 4). Twelve-week change in plasma FRAP was positively correlated with change in serum urate ($r = 0.74$, $P < 0.001$), while 12-week change in 3-NT was not ($r = 0.37$, $P = 0.10$).

GSH levels measured in plasma and GSH/tCr and NAA/tCr levels in the motor cortex did not change significantly over the study period (plasma GSH = −9.8, SE = 10.8, $P = 0.38$; GSH/tCr = −0.004, SE = 0.0024, $P = 0.09$; NAA/tCr = −0.029, SE = 0.0252, $P = 0.3$). Twelve-week changes in these biomarkers were not correlated with change in serum urate ($r < 0.21$, $P > 0.38$).

Disease progression and prediction models

ALSFRS-R total scores declined throughout the 12-week study period from 35.6 ± 5.3 at baseline to 33 ± 7.3 at Week 12. Observed ALSFRS-R total scores deviated little from those predicted from baseline characteristics assuming no treatment (Figure 5). The estimated difference in rate of progression was a slowing by 0.01 points per month (SE = 0.21, 95% CI −0.43 to 0.42, $P = 0.98$). The upper 95% confidence bound exceeded a slowing by 0.1 points per month, the minimum clinically important difference, indicating that serum urate elevation is not futile based on these data.

Discussion

The trial met its primary endpoints, demonstrating the feasibility, safety, and tolerability of using inosine to elevate urate levels in people with ALS. Participants were ALS patients at greater risk of clinical progression based on having serum urate levels below the population median of 5.5 mg/dL.[17–22] In this population, treatment with inosine was safe and well tolerated at doses that elevated serum urate concentrations from a mean of 4.1 mg/dL to target levels of 7 to 8 mg/dL.

In ALS observational studies, high urate levels are predictive of improved survival.[17–23] Whether these associations reflect a causal protective role of urate is unknown though growing evidence supports urate as a neuroprotectant in several models of neurodegeneration, including a cellular model of ALS.[12,27–32,45] In this pilot trial, the addition of biomarkers to track oxidative (and closely related nitrosative)[13,46] stress and damage supported the

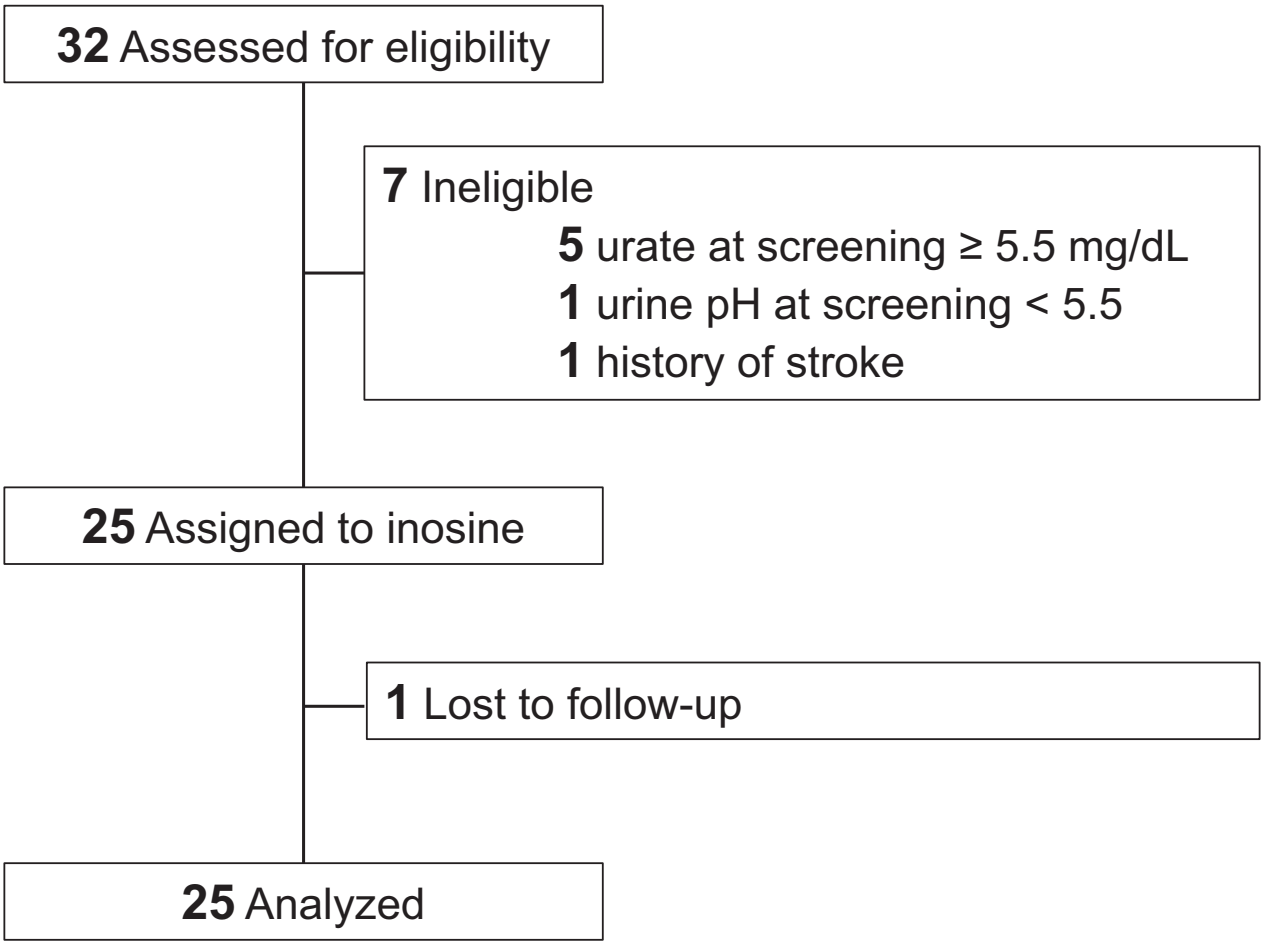

Figure 2. CONSORT diagram: participant enrollment and follow-up for the trial.

biologically relevant effects of inosine. Inosine treatment resulted in increased antioxidant capacity and reduced 3-NT measured in plasma. The increase in plasma antioxidant capacity correlated with serum urate level changes, consistent with PD studies[34] and with the observation that urate is a major contributor to FRAP.[41] This finding also suggests that homeostatic mechanisms do not attenuate the increase in plasma antioxidant capacity attributable to urate elevation. The reduction in tyrosine nitration (as measured by plasma 3-NT levels) is intriguing in light of evidence suggesting that tyrosine nitration is implicated in ALS pathogenesis[35,47–49] and may be one of the targets of edaravone, which may also raise serum urate levels.[6,16] These findings support the need to further investigate urate-mediated pathways to identify potential therapeutic targets that may affect oxidative stress and damage and, in turn, ALS disease progression.

Our study was limited by design (small sample size, open-label treatment, short duration of follow-up). As urate elevation has known safety risks and as inosine is available as an over-the-counter supplement and patients may decide to self-administer, we felt that it was important to examine the safety profile of urate elevation in a clinical trial. Chronic elevation of urate is associated with an increased risk of developing gout and urolithiasis. In fact, symptomatic urolithiasis developed in 3 out of 50 (6%) participants receiving inosine for up to 24 months in a PD trial.[33] In this small, short-term trial, we did not observe any cases of urolithiasis. Of note, we excluded patients at greatest risk of known side effects of increased urate (e.g., individuals with a history of kidney stones or with acidic urine), and we closely monitored urate levels by performing frequent blood draws and applying a pre-specified algorithm to maintain urate levels within target values. It is reasonable to assume that with longer exposures, AEs of special concern (i.e., urolithiasis and gout) may occur, especially if inosine administration is not carefully monitored. For this reason, we believe patients with ALS should not take inosine until its

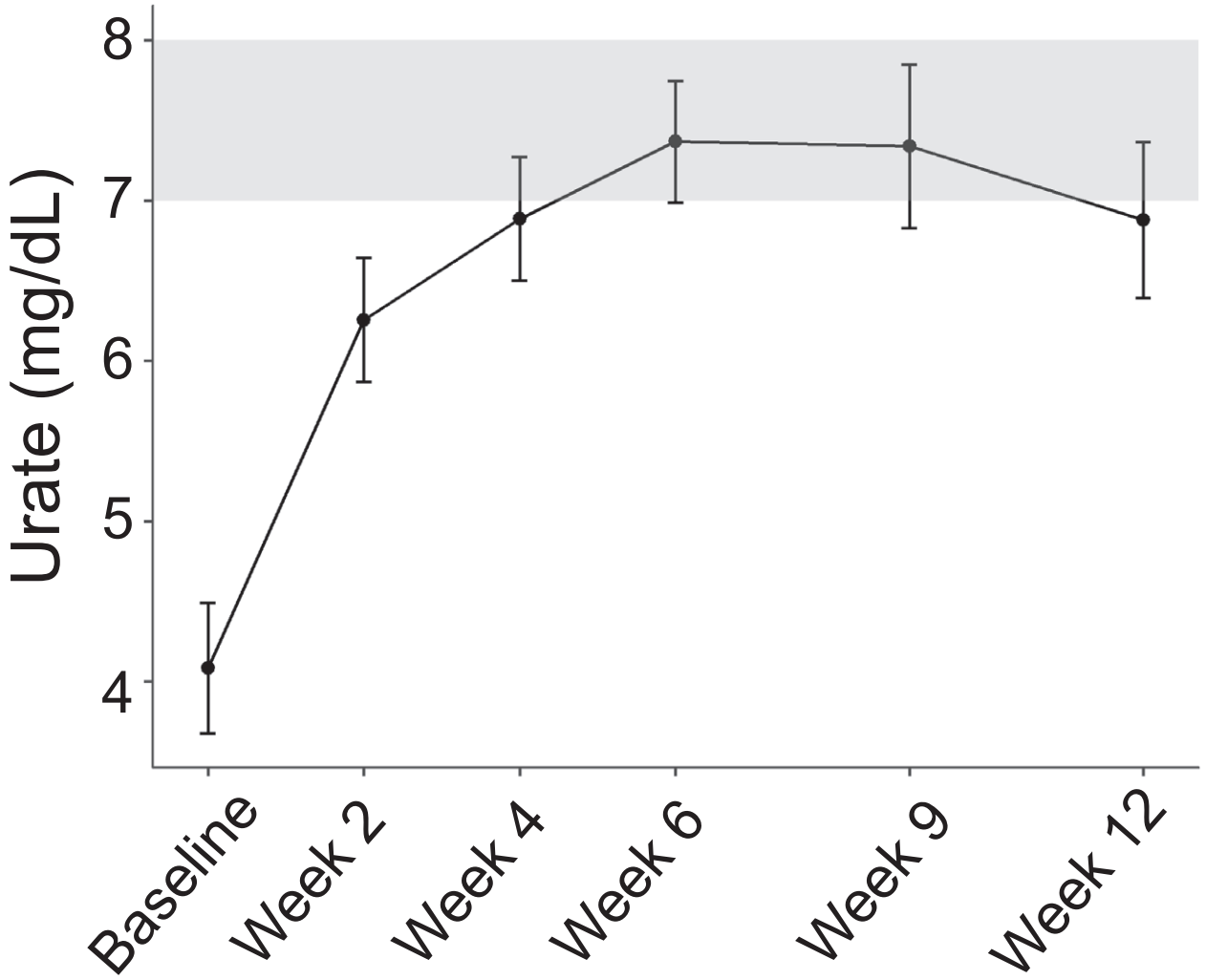

Figure 3. Mean serum urate levels in study participants during treatment (with 95% confidence bounds). Target urate levels were 7 to 8 mg/dL (shaded area).

benefit-to-risk ratio is more fully evaluated in the context of larger clinical trials. Future trials are needed to test whether urate levels can be safely raised long-term and whether treatment with inosine has an impact on survival and disease progression in ALS. We have recently launched a placebo-controlled phase II trial of inosine in ALS (NCT03168711) whose goals are to test longer exposures to inosine (20 weeks) in a multi-center setting with central monitoring of urate levels and titration of inosine dose. This trial will serve as a helpful stepping stone in preparation for a future multicenter pivotal trial testing the effects of inosine on clinical outcomes. Another limitation of our findings is that we did not observe a correlation between urate levels and GSH levels measured either in plasma or in

Table 2. Adverse events.

Adverse Event	Inosine (N = 25)
Fall	32%
Weight loss	16%
Worsened weakness	12%
Worsened dysphagia	8%
Ankle sprain	8%
Weakness of arms	8%
Constipation	8%
Decreased appetite	8%
Fatigue	8%

Adverse events occurring in at least 5% of participants are shown. Events related to expected ALS disease progression were captured as Adverse Events.

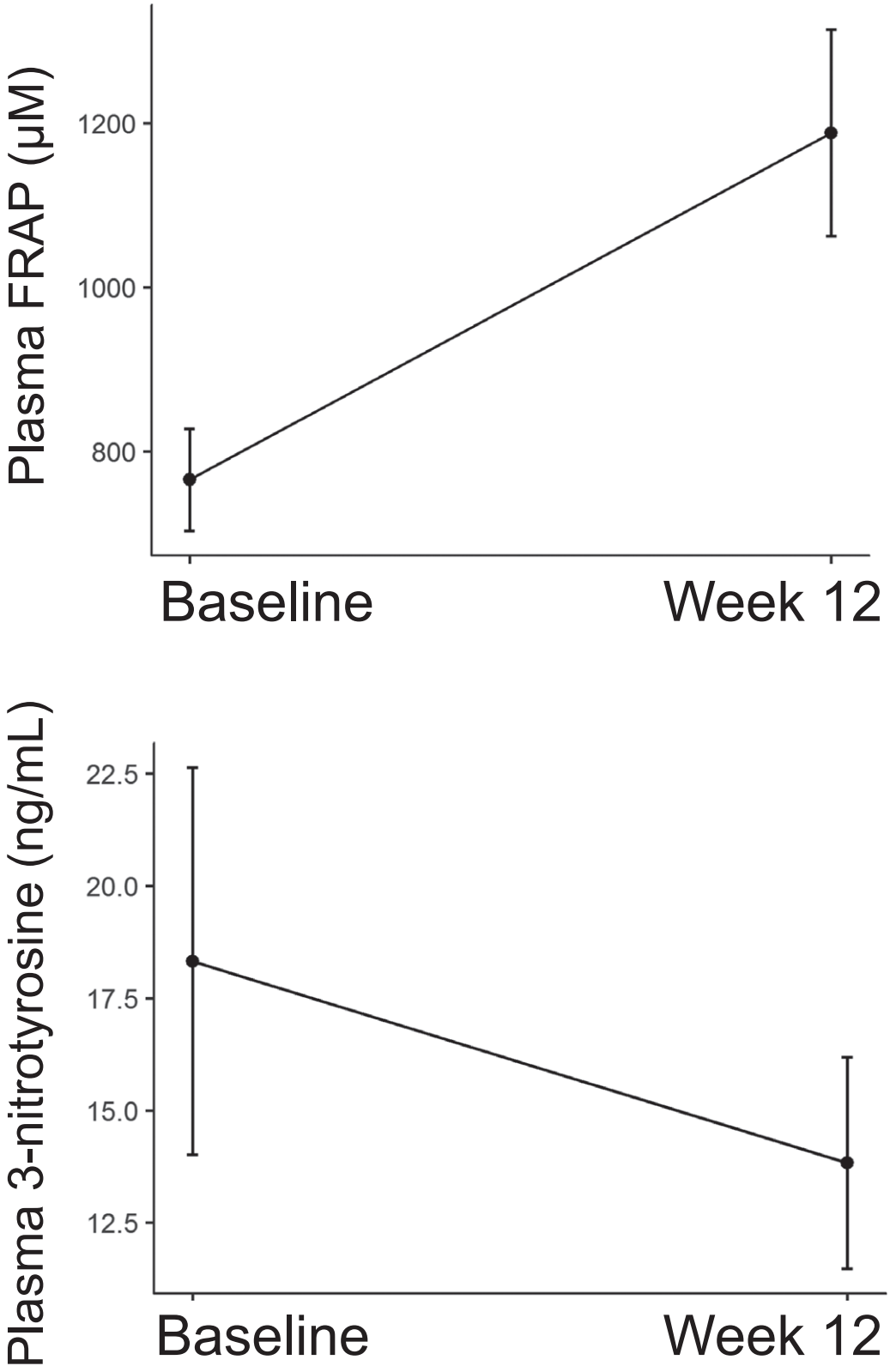

Figure 4. Mean FRAP (A) and 3-NT (B) levels measured in plasma at baseline and after 12 weeks of inosine treatment (with 95% confidence bounds).

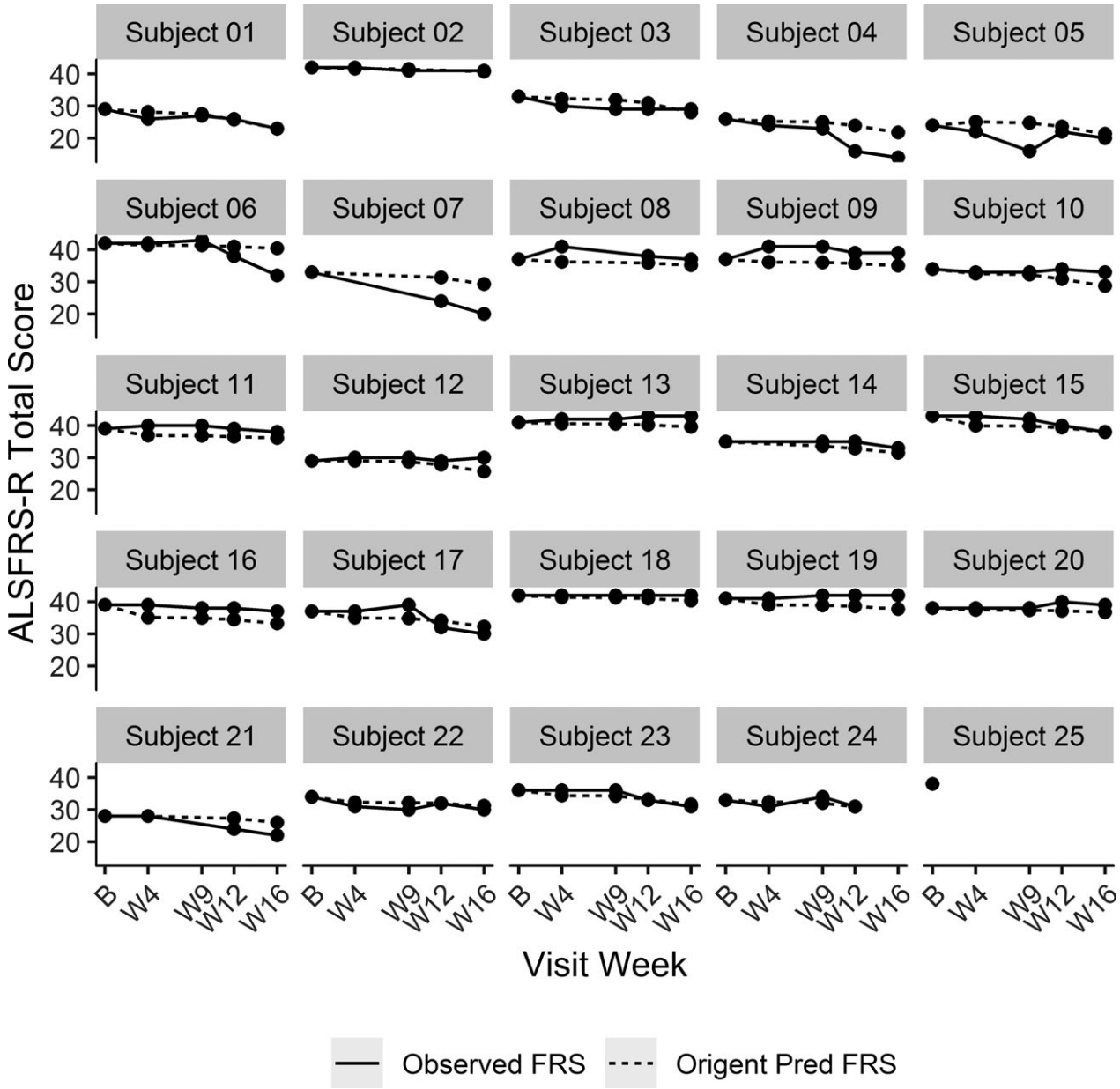

Figure 5. Participant-specific ALSFRS-R total score trajectories throughout the study period. ALSFRS-R was measured for each participant at B (Baseline), W4 (Week 4), W9 (Week 9), W12 (Week 12), and W16 (Week 16). B and W12 were in-person visits; W4, W9, and W16 were phone calls. The W16 phone call occurred 4 weeks after discontinuation of study drug per protocol. Prediction algorithms were used to estimate ALSFRS-R total scores in individual study participants based on their baseline characteristics. Solid lines: observed ALSFRS-R total scores. Dotted lines, predicted ALSFRS-R total scores.

the brain (by MRSI), despite a reduction in 3-NT in plasma. Urate cellular targets are not completely known but may include induction of Nrf2-mediated antioxidant response pathways that ultimately lead to release of GSH by astrocytes.[27,28] These negative GSH findings may be due to lack of sensitivity of the assays, the lack of a biological effect of inosine on these pathways in humans, or the short duration of exposure to inosine. Future studies are needed to clarify whether raising urate levels has antioxidant effects and, if so, how to best measure urate's impact on antioxidant pathways in people with ALS.

A recent trend in the field of ALS is to explore the utility of prediction algorithms as an adjunct to clinical

care and/or clinical trials.[21,50–52] We evaluated the apparent efficacy of serum urate elevation using a virtual control arm derived using a novel prediction algorithm. Observed ALSFRS-R total scores were remarkably close to those predicted for untreated patients based on the baseline characteristics of participants, suggesting no dramatic benefit from serum urate elevation; however, lack of an observable treatment effect of inosine on ALSFRS-R should not be over-interpreted because this trial lacked power to detect all but a very large effect over a short period of observation. We rejected a conclusion of futility. A larger study is needed to evaluate the clinical efficacy of inosine for the treatment of people with ALS.

In conclusion, we demonstrated the safety, tolerability, and urate-elevating capability of the urate precursor inosine in people with ALS. Taken together with convergent epidemiological, biological, and clinical data pointing to urate as a potential neuroprotectant, this study supports the growing clinical trial pipeline aimed at testing the ability of inosine to slow clinical progression in PD (NCT02642393) and ALS (NCT03168711).

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Author Contribution

Eric Macklin, PhD and James Chan, MA conducted all statistical analyses (MGH Biostatistics Center). Drs. Paganoni and Macklin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Sabrina Paganoni: study concept/design; data acquisition; analysis/interpretation of data; drafting/revising the manuscript. Katharine Nicholson, Eva Ratai: data acquisition; analysis/interpretation of data; drafting/revising the manuscript. James Chan: analysis/interpretation of data; drafting/revising the manuscript. Eric Macklin, Michael A. Schwarzschild, and Merit Cudkowicz: study concept/design; analysis/interpretation of data; drafting/revising the manuscript. Mark Levine-Weinberg and Christopher Breen: data acquisition; drafting/revising the manuscript.. Rachit Bakshi: data acquisition; analysis/interpretation of data; drafting/revising the manuscript. Daniela Grasso Anne-Marie Wills, Samad Jahandideh, Albert A. Taylor, Danielle Beaulieu, and David L. Ennist: analysis/interpretation of data; drafting/revising the manuscript.. Ovidiu Andronesi: data acquisition; analysis/interpretation of data; drafting/revising the manuscript.

Conflict of Interest

Katharine Nicholson has received research funding from ALS Finding a Cure. James Chan reports no disclosures. Eric Macklin has served on Data and Safety Monitoring Boards for Acorda Therapeutics and Shire Human Genetic Therapies and has received research funding from the Adolph Coors Foundation, the ALS Association, ALS Therapy Alliance, ALS Therapy Development Institute, Autism Speaks, Biotie Therapies, the California Institute of Regenerative Medicine, the Michael J. Fox Foundation, the Muscular Dystrophy Association, FDA, HRSA, PCORI, and NIH. Mark Levine-Weinberg reports no disclosures. Christopher Breen reports no disclosures. Rachit Bakshi reports no disclosures. Daniela Grasso reports no disclosures. Anne-Marie Wills has received research funding from the ALS Association, National Parkinson's Foundation, and participated in clinical trials funded by Acorda, Sanofi/Genzyme, Bristol-Myers Squibb, Biogen and Pfizer. She is a consultant for Accordant/CVS Caremark. Samad Jahandideh is an employee of Origent Data Sciences. Albert A. Taylor is an employee of Origent Data Sciences. Danielle Beaulieu is an employee of Origent Data Sciences. David L. Ennist is an employee of Origent Data Sciences. Ovidiu Andronesi reports no disclosures. Eva-Maria Ratai is a member on the Advisory Board for BrainSpec, Inc. Michael A. Schwarzschild has served on advisory boards for the Cure Parkinson's Trust, CBD Solutions, and the Michael J. Fox Foundation (MJFF). He has served on steering committees of trials funded by MJFF, Biotie Therapies/Acorda Therapeutics and NIH. He receives research grant support from the NIH, DoD, MJFF, Parkinson's Foundation and Target ALS Foundation. Merit Cudkowicz has provided consulting for Cytokinetics, Astra Zeneca, Lilly, Genentech, Biogen-IDEC, Voyager, and Biohaven. Sabrina Paganoni has received research funding from the NIH (Career Development Award 2K12HD001097-16), Target ALS, the Salah Foundation, the Spastic Paraplegia Foundation, the ALS Association, ALS Finding a Cure, the American Academy of Neurology and Amylyx.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Accuracy of serum urate titration. The figure represents the percentage of participants whose urate levels were on target (7–8 mg/dL) versus below target or above target at different time points (participants had serum urate levels measured at time Baseline and at weeks 2, 4, 6, 9, and 12). An average of 41% of samples collected at weeks 6, 9, and 12 were within the target range (40% less than 7.0 mg/dL and 19% above 8 mg/dL). An average of 48% of participants had a mean serum urate level from weeks 6, 9, and 12 that were within the target range.

