Radicava/Edaravone Findings in Biomarkers From Amyotrophic Lateral Sclerosis (REFINE-ALS)

Protocol and Study Design

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Abstract

Objectives
To identify putative biomarkers that may serve as quantifiable, biological, nonclinical measures of the pharmacodynamic effect of edaravone in amyotrophic lateral sclerosis (ALS) and to report real-world treatment outcomes.

Methods
This is a prospective, observational, longitudinal, multicenter (up to 40 sites) US study (Clinicaltrials.gov; NCT04259255) with at least 200 patients with ALS who will receive edaravone for 24 weeks (6 cycles; Food and Drug Administration–approved regimen). All participants must either be treatment naive for edaravone or be more than 1 month without receiving any edaravone dose before screening. Biomarker quantification and other assessments will be performed at baseline (before cycle 1) and during cycles 1, 3, and 6. Selected biomarkers of oxidative stress, inflammation, neuronal injury and death, and muscle injury, as well as biomarker discovery panels (EpiSwitch and SOMAscan), will be evaluated and, when feasible, compared with bio-banked samples. Clinical efficacy assessments will include the ALS Functional Rating Scale–Revised, King’s clinical staging, ALS Assessment Questionnaire-40, Appel ALS Score (Rating Scale), slow vital capacity, hand-held dynamometry and grip strength, and time to specified states of disease progression or death. DNA samples will also be collected for potential genomic evaluation. The predicted rates of progression and survival, and their potential correlations with biomarkers, will be evaluated. Adverse events related to the study will be reported.

Results
The study is estimated to be completed in 2022 with an interim analysis planned.

Conclusions
Findings may help to further the understanding of the pharmacodynamic effect of edaravone, including changes in biomarkers, in response to treatment.
Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease, characterized by the degeneration of nerve cells of the brain and spinal cord, predominantly upper and lower motor neurons. There is no cure for ALS. The current US Food and Drug Administration (FDA)-approved treatments for ALS are riluzole (Rilutek; Tigrutek) and edaravone (Radicava) (see FDA.gov). In a clinical trial, edaravone was shown to slow the decline in physical function in ALS.

Biomarkers in ALS are actively evaluated as important tools in designing and implementing clinical trials and monitoring treatment efficacy during trials. Numerous candidates of interest have been identified for various pathophysiologic aspects of ALS, including oxidative stress (e.g., 3-nitrotyrosine [3-NT]), 4-hydroxy-2,3-nonenal [4-HNE]), F2-isoprostanes, 8-hydroxydeoxyguanosine [8-OHdG], and uric acid, inflammation (e.g., matrix metalloproteinases [MMPs]), neuronal injury and death (e.g., neurofilaments [Nfs], urinary neurotrophin receptor p75 extracellular domain [p75NTRECD]), and muscle injury (e.g., creatinine). 3-NT, in particular, has been associated with response to edaravone, with changes observed as early as the first cycle and an almost undetectable level at 6 months, a reduction that correlated with improvements in ALS Functional Rating Scale–Revised (ALSFRS-R) scores. Nonetheless, many of these biomarkers still require more comprehensive validation.

Given the heightened interest in ALS biomarkers, we sought to study a wide spectrum of putative biomarkers in a broad population of patients with ALS undergoing treatment with edaravone to evaluate their potential use in understanding how the disease progresses and elucidating the mechanism of action and molecular pathways involved in the clinical response to edaravone.

Methods and Biomarker Descriptions

Study Objectives
The study aims to identify putative biomarkers that may serve as objective, quantifiable, biological measures of the pharmacodynamic effect of edaravone in ALS and to report clinical outcomes for edaravone in a real-world clinical setting.

Study Design
This is a prospective, observational, longitudinal study to be conducted at approximately 40 centers in the United States. The study is sponsored by Mitsubishi Tanabe Pharma America. The protocol design and selection of biomarkers and clinical assessments were guided by a steering committee consisting of practicing physicians with extensive background and experience in ALS. The study will be conducted in compliance with the institutional review board at all participating sites and the guidance and regulations from the US FDA, as well as in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices. Up to 300 adult patients with ALS will be enrolled to ensure that at least 200 patients will complete 6 cycles of treatment. A 4- to 12-week period is allocated for insurance approval (the patient is responsible for the commercial cost of edaravone) before the first treatment cycle. During this period, screening/baseline clinical and biomarker assessments will be performed. Participants will be followed from the enrollment date for up to 24 weeks after treatment initiation or until premature study discontinuation. The study design is shown in figure 1. The investigators and participants may discontinue treatment at any time and for any reason. Participants who discontinue edaravone will continue to be followed, and the investigators will continue to perform clinical and biomarker assessments up to the end of the study or until study discontinuation.

Patients will be prescribed edaravone in accordance with the US prescribing information of the product. The decision to prescribe edaravone to the participants will be made independently of the decision to enroll them in the study. The recommended dose of edaravone is an IV infusion of 60 mg administered over a 60-minute period. For the first treatment cycle, patients will receive edaravone daily for 14 days, followed by a 14-day drug-free period. In subsequent treatment cycles (cycles 2–6, for a total of 24 weeks), participants will receive daily edaravone for 10 days out of 14 days; each treatment cycle will be followed by a 14-day drug-free period. Edaravone can be administered at the study site, at an infusion center, or at the participant’s home. Blood and urine samples will be collected and processed at the clinical study sites.

Participants
Eligible participants will be male or female patients, aged 18 years or older at enrollment, with a diagnosis of ALS. All participants must either be naive to edaravone or be more than 1 month without receiving any edaravone dose before screening. All enrolled patients must have been prescribed edaravone by the treating physician in accordance with good clinical judgment and within the approved indication before study enrollment. These patients must be able to obtain commercial edaravone and be likely to complete 6 cycles of treatment per investigator estimation. Taking current edaravone patients off of their active treatment or delaying the start of treatment so they can become eligible for the study is highly discouraged. Participants will be excluded from the study if they have any contraindication to edaravone or are participating in another interventional clinical trial.

Standard Protocol Approvals, Registrations, and Patient Consents
The study is registered with Clinicaltrials.gov (identification number: NCT04259255). The study will be conducted in compliance with current Good Clinical Practice defined by the International Conference on Harmonisation and the ethical principles of the Declaration of Helsinki. The study protocol was approved by all relevant institutional review boards. All participants must provide written informed consent before any study-related activities are performed.
Assessments

An assessment schedule is shown in figure 1. At 0–2 days before starting edaravone treatment, assessments for biomarkers, clinical outcomes, and safety events will be conducted. Assessments of biomarkers, ALSFRS-R, and vital capacity will be conducted at all visits during both on- and off-treatment periods, whereas all other clinical outcomes and safety assessments will be conducted during the off-treatment period on visits 2 and 4 of cycle 1, visit 6 of cycle 3, and visit 8 of cycle 6.

Biomarker Assessments

Biomarker quantification will be performed at baseline and during cycles 1, 3, and 6. Assessments during on and off periods in the drug cycle will be used for peak/trough analyses. Urine and blood (for plasma and serum) samples will be collected at prespecified time points throughout the study (figure 1). Selected biomarkers of oxidative stress, inflammation, and neuronal injury and death, as well as biomarker discovery panels (e.g., EpiSwitch and SOMAscan), will be evaluated (table 1; also see next section). As an option, blood samples may be collected at the screening/baseline (before administration of treatment) or any subsequent study visit and stored for genome sequencing and other research purposes.

Clinical Assessments

Clinical outcome assessments will be performed at baseline and at prespecified time points throughout the study; they include ALSFRS-R, King’s clinical staging, ALS Assessment Questionnaire-40, Appel ALS Score (selected sites), measurement of slow vital capacity, hand-held dynamometry (selected sites), and bilateral grip strength (selected sites) (table 2). Additional assessments of disease progression will include the time to milestones of disease progression, including wheelchair use, speech loss, initiation of noninvasive ventilation, tube feeding, and death. Most outcome assessments are evaluated at off-drug visits. ALSFRS-R score and slow vital capacity will be evaluated more frequently, at both on-drug and off-drug visits, for a more comprehensive assessment of correlation with biomarkers during the entire treatment period. In parallel, via Origent modeling, clinical data collected in the study will be used to (1) predict real-world treatment outcomes for up to 36 weeks, (2) predict patients’ rates of progression and survival (using the Pooled Resource Open-Access ALS Clinical Trials database), and (3) correlate changes in biomarkers with predicted rates of disease progression.

Safety Assessments

Safety parameters, including adverse events (AEs), will be assessed prospectively throughout the study. Serious and nonserious AEs that are considered related to study procedures, including treatment with edaravone, by the site investigator will be reported. Safety assessments will be conducted at baseline/screening and during off-drug visits.

Data Management and Statistical Methods

All data analysis will be conducted at the Massachusetts General Hospital Biostatistics Center. Data and biomarker workflow is shown in figure 2.
Sample size is calculated to achieve enough statistical power as pertains to the selected assessments. A single treatment group of 225 participants will provide 80% power for a statistically significant difference of at least 0.21 in ALSFRS-R scores between baseline and post-24-week treatment, assuming a common SD of 0.70, a correlation between pairs of 0.25, 2-sided testing, and an alpha level of 0.05. In comparison, 0.21 is greater than 10 times less than that observed in the original phase 2 and 3 studies that showed that edaravone is beneficial in delaying the ALS progression.\(^1^7\) In addition, a sample size of 225 participants with the same correlation assumption has 80% power in a 2-sided test at the 0.05 level to detect a mean paired difference in 8-OHdG biomarker (ng/mL) of 0.15, assuming a pooled SD of 0.5.\(^1^8\)

The analysis set will include all enrolled patients who received at least 1 dose of edaravone. Postbaseline values and absolute change from baseline in the continuous outcome variables will be summarized with descriptive statistics and tested vs 0 using a paired t test. Longitudinal changes during the 24-week study will be estimated by a linear mixed-effects model adjusting for within-participant variability and residual variation. Time to specified King’s clinical stages (all except stage 5), permanent assisted ventilation, and tracheostomy-free survival, as well as overall survival, will be assessed with Kaplan-Meier analyses. A Cox regression model will be used to analyze the relationship between independent variables at baseline and time to event. Oregent modeling (e.g., regression) will be applied to both clinical and biomarker data to evaluate longer-term treatment outcomes and determine rates of disease progression and survival and any correlation with biomarkers. An interim analysis has been planned to gauge the feasibility of the study and the quality of the data.

**Data Availability**

Data are available on request to Mitsubishi Tanabe Pharma America, Inc, from researchers at academic institutions.

**Discussion**

REFINE-ALS is a prospective, observational, longitudinal clinical study conducted in a broad, real-world population of patients with ALS treated with edaravone and is aimed at improving our understanding and application of biomarkers as they pertain to the use of edaravone in ALS. The potential use of biomarkers in patient care and in research and clinical trials are the applications of interest. This is an important and growing area of research as biomarkers are increasingly recognized and being actively evaluated as potential assessment and evaluation tools in clinical studies not only in ALS but also in a variety of other diseases. In the latter, some biomarkers have already been qualified to be used in clinical practice and drug development by the US FDA (see FDA.gov). The results of this study aim to address this unmet need with more practical data on a broad range of biomarkers from edaravone-treated patients in a real-world setting. An interim analysis has been planned to ascertain the feasibility of the study, including providing insights into whether meaningful data can be generated early during the course of the study, whether the study design was sound and the sample size was appropriate, and whether biomarkers change from baseline with edaravone treatment.

There are several strengths to the study. First, a broad range of biomarkers was chosen to ensure a more complete understanding of their roles in patients undergoing treatment with edaravone. They were grouped based on their reported involvements in oxidative stress, inflammation, neuronal injury and death, and muscle injury. In addition, exploratory biomarker panels based on epigenetic and proteomic technologies were included.

**Oxidative Stress**

An increase in oxidative stress has been proposed to play a role in ALS. The oxidative stress biomarkers to be analyzed in the study include 4-HNE, F2-isoprostanes, 8-OHdG (also known as 8-Oxo-7,8-dihydro-2′-deoxyguanosine or 8-Oxo-dG), and 3-NT.\(^5\)\(^,^1^9\) 4-HNE is one of the main, and most toxic, peroxidation products of omega-6 fatty acid lipids.\(^5\) Significantly elevated levels of 4-HNE, measured by high-performance liquid chromatography, have been found in the serum and CSF of patients.
with sporadic ALS compared with healthy individuals and those with other neurologic diseases, and the levels may also correlate with the severity of disease.\textsuperscript{5} Increased 4-HNE has been associated with aberrant modification of proteins, some of which include the membrane transport systems that protect neurons from excitotoxic and metabolic injury that can culminate in motor neuron degeneration.\textsuperscript{20} F2-isoprostanes, prostaglandin-like compounds formed in vivo primarily by free radical–catalyzed peroxidation of arachidonic acid, have been found to be elevated in the urine of patients with ALS.\textsuperscript{7,19} 8-OHdG is an oxidized nucleoside of DNA and may be a marker of generalized oxidative stress and an indicator for DNA damage and repair.\textsuperscript{21} Patients with sporadic ALS have been found to have significantly higher levels of 8-OHdG than healthy individuals.\textsuperscript{5} Serum urate, in contrast, may have a protective influence on neuronal cell death because of its antioxidant properties.\textsuperscript{9} In patients with ALS, serum urate levels are reduced compared with those in healthy individuals, and lower urate levels may be associated with greater rates of decline in ALSFRS-R and forced vital capacity.\textsuperscript{15} Furthermore, higher baseline uric acid levels correlate with a lower risk of mortality; specifically, up to a 39\% reduction in risk of death was found in men with ALS for every 1 mg/dL increase in uric acid levels.\textsuperscript{8,9} 3-NT, a marker of oxidative damage, is mediated by peroxynitrite.\textsuperscript{6} The 3-NT levels have been found to be elevated in the motor neurons of the spinal cord and the CSF of some patients with ALS\textsuperscript{5,22} whereas in others, no differences were observed.\textsuperscript{23,24} Notably, the amount of 3-NT in the CSF decreased to almost undetectable levels after 6 months of treatment with edaravone.\textsuperscript{16}

### Inflammation

MMPs form a protein family of zinc-containing endopeptidases that play a role in neuroinflammation and may be involved in neurodegeneration. The MMP-9 subtype is expressed in motor neurons in the spinal cord. In patients with ALS, the expression of MMP-9 has been shown to be elevated in the serum and CSF, and in a prospective study, its increased level in the CSF has been associated with rapidly progressing ALS (evaluated by monthly changes on the Medical Research Council sum score).\textsuperscript{10,25} Of interest, in a SOD1 mouse model of ALS, inhibition of MMP-9 appeared to reduce the degeneration of motor neurons and delay muscle denervation, as well as prolong survival.\textsuperscript{26}

### Neuronal Injury and Death

Nfs and p75NTRECD\textsubscript{SCD} are 2 potential biomarkers for neuronal injury and death. Nfs are neuronal intermediate filament proteins that are composed of light, medium, and heavy chain subunits, and mutations in the heavy chain gene have been associated with increased susceptibility to ALS.\textsuperscript{11,12} Patients with ALS have higher levels of both heavy and light Nf chain proteins in the blood and CSF than healthy people, which may be associated with more rapid disease progression and reduced survival.\textsuperscript{12,27} The light Nf chain and the phosphorylated form of Nf heavy chain were found to be elevated in presymptomatic individuals at genetic risk for ALS\textsuperscript{28} and potentially in those

### Table 2 Clinical Assessments

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Measures</th>
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<tbody>
<tr>
<td>ALSFRS-R</td>
<td>Assessment of patient's capability and independence in 12 functional activities (i.e., speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency)</td>
</tr>
<tr>
<td>ALSAQ-40</td>
<td>A patient-reported outcome assessment for physical mobility, activities of daily living and independence, eating and drinking, communication, and emotional reactions</td>
</tr>
<tr>
<td>Appel ALS Score</td>
<td>Measure of dysfunction for bulbar, respiratory, muscle strength, and lower and upper extremity function</td>
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<tr>
<td>Slow vital capacity</td>
<td>Measure of respiratory muscle strength</td>
</tr>
<tr>
<td>Hand-held dynamometry</td>
<td>Quantitative measure of muscle strength in 6 muscle groups (i.e., shoulder flexion, elbow flexion, elbow extension, hip flexion, knee flexion, and knee extension) and for wrist extension, first dorsal interosseous contraction, and ankle dorsiflexion</td>
</tr>
<tr>
<td>Bilateral grip strength</td>
<td>Quantitative measure of isometric strength of the hand and forearm muscles</td>
</tr>
<tr>
<td>Milestones of disease progression</td>
<td>Record date of onset for wheelchair use, speech loss, initiation of noninvasive ventilation, and tube feeding</td>
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Abbreviations: ALS = amyotrophic lateral sclerosis; ALSAQ-40 = ALS Assessment Questionnaire-40; ALSFRS-R = ALS Functional Rating Scale–Revised.

### Figure 2 Data and Biomarker Workflow

![Data and Biomarker Workflow](image-url)
with upper motor neuron-dominant disease as opposed to those with typical ALS.\textsuperscript{12,28,29} Notably, both Nf heavy and light chains have shown high sensitivity and specificity in classifying ALS vs various control groups.\textsuperscript{30,31}

p75NTR expression is increased in motor neurons upon cellular injury, and this increase has been shown to lead to neuronal injury and death. Mice that lacked the receptors had significantly more surviving motor neurons following axotomy than did those whose receptors were intact.\textsuperscript{13} In patients with ALS, urinary p75NTR\textsuperscript{ECD} level is significantly higher than in people without the disease.\textsuperscript{14} Moreover, higher p75NTR levels were associated with more rapidly progressive disease, based on prospective clinical follow-up.\textsuperscript{14} In addition, urinary p75NTR\textsuperscript{ECD} level increases over time as the disease worsens, supporting its role as a candidate biomarker of disease progression.\textsuperscript{14}

**Muscle Injury**

Creatinine has historically been postulated as a biomarker for muscle mass, given that people with higher muscle mass have higher levels of creatinine.\textsuperscript{32} Patients with ALS, compared with healthy controls, have lower levels of creatinine.\textsuperscript{15} Lower creatinine levels in patients with ALS may also correlate with worsening of the disease, as assessed by the ALSFRS-R score and forced vital capacity.\textsuperscript{15}

**Biomarker Discovery Panels**

EpiSwitch and SOMAscan are 2 high-throughput platforms designed to identify and evaluate epigenetic and proteomic biomarkers, respectively. EpiSwitch is a technology platform for identifying epigenetic biomarkers by analyzing changes in genomic architecture. It has been used as a biomarker modality in a range of diseases and, in ALS, has been reported to show potential utility as a diagnostic aid and a prognostic tool to assess disease progression rates after a diagnosis is made.\textsuperscript{33–39} SOMAscan is an aptamer-based proteomics assay for protein biomarkers that is capable of high-throughput measurement of human protein analytes in serum, plasma, and other biologic matrices with high sensitivity and specificity.\textsuperscript{40} SOMAscan has been reported to show potential utility in diagnosing, assessing risks, predicting and assessing therapeutic response, and providing mechanistic insights into disease pathophysiology in various diseases, including Duchenne muscular dystrophy,\textsuperscript{41} Alzheimer disease,\textsuperscript{42} and inflammatory bowel disease.\textsuperscript{43}

Another strength of the study is the inclusion of a fuller spectrum of the disease via broad inclusion criteria and a real-world patient population. Accordingly, more robust and clinically relevant insights and results are envisioned for both the evaluations of biomarkers and the reporting of real-world treatment outcomes for edaravone. Biomarkers were selected to represent several biological components in ALS and mechanism(s) of action of edaravone. In addition, high-throughput platforms for discovery and testing of novel biomarkers that span both the genomic and proteomic landscape may extend the capacity of the study to better identify and evaluate putative candidates. The selected biomarkers in the study have been chosen based on their association with the disease, including potential correlation with treatment outcomes, as demonstrated in previous studies.

Limitations of the study included the absence of a parallel control group that may allow for a comparison of clinical responses with the treated group and the lack of pretreatment longitudinal biomarker data that may provide a more comprehensive understanding of the longitudinal changes in the selected biomarkers.

Assessments of treatment outcomes, including ALSFRS-R and King’s clinical staging, will be reported. Robust, real-world data on the clinical outcomes of edaravone may improve the evidence-based management of patients with ALS by filling the gap between the evidence generated by randomized clinical trials and their effect in the real world, particularly for a heterogeneous disease such as ALS. Clinical data collected at baseline and treatment response at both on- and off-drug periods will allow for detailed pharmacodynamic evaluation of edaravone in a real-world setting. Potential correlation between changes in biomarkers and treatment outcomes may help guide their use in clinical practice and research. In particular, identifying a biomarker that can predict change in patients’ clinical status (e.g., ALSFRS-R) or the anatomic spread of ALS based on the number of affected regions (e.g., King’s ALS clinical staging) may be useful in clinical practice and drug development.

The findings of this study may help to further the understanding of the pharmacodynamic effect of edaravone during the treatment period, which involves 2 weeks on drug and 2 weeks off drug. Biomarkers that may show a strong correlation with disease progression and treatment outcomes may form a panel of biomarkers to be potentially added to a patient registry study, where they will be analyzed for their feasibility and validity to become incorporated into the clinical treatment plan for edaravone. These biomarkers will comprise an important assessment tool not only for patients’ daily treatment regimens but also for future clinical programs. Additional insights may be gained into the mechanisms of action of treatments such as edaravone by differentiating the treatment effect across different pathophysiologic axes. Finally, the findings of this study will provide additional real-world experience with edaravone as it relates to both safety and clinical outcomes.

**Acknowledgment**

The authors thank Dr. Rakesh Patel, University of Alabama, Birmingham, for providing invaluable comments and suggestions throughout the study planning phase, particularly pertaining to the use of oxidative stress biomarkers in ALS. They also thank p-value communications for providing support for technical writing, editing, and publication assistance.
**TAKE-HOME POINTS**

- REFINE-ALS is a prospective, observational, longitudinal clinical study conducted in a broad population of patients with ALS treated with edaravone in a real-world setting.
- The study aims to improve our understanding and application of biomarkers as they pertain to the use of edaravone in ALS, particularly their potential use in patient care and in research and clinical trials.
- The study will also evaluate both safety and clinical outcomes of edaravone in a real-world setting.

**Study Funding**

The study was funded by Mitsubishi Tanabe Pharma America, Inc. (MTPA).

**Disclosure**

J. Berry and B. Brooks are consultants for MTPA. A. Genge is on the advisory board for Alexion, AL-S Pharma, AveXis, Biogen, Brainstorm, Clene Nanomedicine, MTPA, Novartis, Roche, and Sanofi. T. Heiman-Patterson reports personal fees from MTPA and Cytokinetics as a consultant on the publications committee; she is a consultant for ITF Pharma; she also reports funding for clinical trials from Amylyx, Cytokinetics, MTPA, Orion, and UCB. S. Appel reports no disclosures. M. Benatar reports grants from the NIH, the ALS Association, the Muscular Dystrophy Association, the Centers for Disease Control and Prevention, the Department of Defense, and Target ALS during the conduct of the study and personal fees from Mitsubishi Tanabe Pharma, AveXis, and Genentech, outside of the submitted work; in addition, he has a provisional patent entitled “Determining Onset of Amyotrophic Lateral Sclerosis”; he also serves as a site investigator on clinical trials funded by Biogen and Orphazyme. R. Bowser is founder and president of Iron Horse Diagnostics, a company focused on commercialization of diagnostic and prognostic indicators of neurologic diseases; he also reports grants from the NIH, the ALS Association, the Muscular Dystrophy Association, and Target ALS during the conduct of this study; he received personal fees from Mitsubishi Tanabe Pharma as a consultant and is on the scientific advisory board of Aural Analytics. M. Cudkowicz reports no disclosures. C. Gooch is a consultant in ALS therapeutics and research for MTPA, a member of the Board of Trustees for the ALS Association, and a member of the editorial board for the *Journal of Neurology*. J. Shefner reports funding from the NIH, the ALS Association, the ALS Finding a Cure Foundation, Amylyx, Apic Bioscience, Cytokinetics, and Mitsubishi Pharma America and reports personal fees from Cytokinetics, MTPA, Neurosense, and Orphazyme. J. Westra is an employee of Oxford BioDynamics, Inc. W. Agnese and C. Merrill are former employees of MTPA. S. Nelson and S. Apple are employees of MTPA. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

**Publication History**


**Appendix Authors**

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