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Journal

Muscle & Nerve, 71(1)

Authors

Bhai, Salman

Levine, Todd

Moore, Dan

et al.

Publication Date

2025

DOI

10.1002/mus.28287

Peer reviewed

Received: 28 November 2023 | Revised: 25 September 2024 | Accepted: 15 October 2024

DOI: 10.1002/mus.28287

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

A 40-week phase 2B randomized, multicenter, double-blind, placebo-controlled study evaluating the safety and efficacy of memantine in amyotrophic lateral sclerosis

Salman Bhai MD[1,2] | Todd Levine MD[3] | Dan Moore PhD[4] | Robert Bowser PhD[5] | Andrew J. Heim MS-CR[6] | Maureen Walsh BS[6] | Aziz Shibani MD[7] | Zachary Simmons MD[8] | James Grogan MD[8] | Namita A. Goyal MD[9] | Raghav Govindarajan MD[10] | Yessar Hussain MD[11,12] | Tania Papsdorf MD[13] | Tiffany Schwasinger-Schmidt MD, PhD[14] | Nick Olney MD[15] | Kim Goslin MD[15] | Michael Pulley MD, PhD[16] | Edward Kasarskis MD, PhD[17] | Michael Weiss MD[18] | Susan W. Katz PhD[19] | Suzan Moser MBA[10] | Duaa Jabari MD[20] | Omar Jawdat MD[6] | Jeffrey Statland MD[6] | Mazen M. Dimachkie MD[6] | Richard Barohn MD[10] | the Neuromuscular Study Group and Western ALS Consortium Memantine ALS Study Group

Correspondence
Salman Bhai, University of Texas Southwestern Medical Center, Dallas, Texas, USA.
Email: salman.bhai@utsouthwestern.edu

Funding information
U.S. Food and Drug Administration; FDA-OPD, Grant/Award Number: R01FD003937

Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease with no known cure, limited treatment options with minimal benefits, and significant unmet need for disease modifying therapies.

Aims: This study investigated memantine's impact on ALS progression, with an additional focus on the effects of memantine on cognitive and behavioral changes associated with the disease.

Methods: A randomized, double-blind, placebo-controlled clinical trial was conducted from December 2018 to September 2020. ALS patients were enrolled in-person and remotely across 13 sites in the United States. Participants were randomized to memantine (20 mg twice daily) or placebo in a 2:1 ratio and completed 36 weeks of treatment. The primary outcome of disease progression was assessed by the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), and blood was collected for biomarker analysis.

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-CBS, ALS Cognitive Behavioral Screen; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; CHIT-1, chitinase 1; CSF, cerebrospinal fluid; EAAT-2, excitatory amino acid transporter; FTD, frontotemporal dementia; FVC, forced vital capacity; NfL, neurofilament light chain; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NPI-Q, Neuropsychiatric Inventory Questionnaire; pNF-H, phosphorylated neurofilament heavy chain; ROS, reactive oxygen species; SOD1, superoxide dismutase-1; TNF-α, tumor necrosis factor-α.

All individuals of the Neuromuscular Study Group and Western ALS Consortium Memantine ALS Study Group listed in the Appendix Table A1 are authors in this study.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

For affiliations refer to page 70

Results: Of the 99 participants enrolled in the study, 89 were randomized to memantine or placebo (ages 24–83 years, male-to-female ratio ~3:2). Fifty-two participants completed the study treatment with no significant differences in disease progression, biomarker changes (including neurofilament light chain [NfL]), or neuropsychiatric testing noted between the groups. Initial NfL values correlated with the rate of ALSFRS-R decline.

Discussion: In this study, memantine did not impact ALS disease progression or neuropsychiatric symptoms. Trials with remote enrollment may help trial participation and success.

KEYWORDS
amyotrophic lateral sclerosis (ALS), biomarkers, memantine, motor neuron disease (MND), neurofilament

1 | INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disease without a known cure.[1] Despite multiple trials investigating therapies, success has been limited.[2] Riluzole, edaravone, and sodium phenylbutyrate–taurursodiol are the only three Food and Drug Administration approved medications for sporadic ALS.[3–8] Tofersen is approved for ALS associated with a superoxide dismutase-1 (SOD1) mutation.[9] The benefits of the drugs for sporadic ALS are marginal, and sodium phenylbutyrate–taurursodiol was recently withdrawn from the market due to lack of efficacy in a phase 3 clinical trial.[10] In this clinical trial, we tested the efficacy of memantine for ALS. This trial also measured the ALS Cognitive Behavioral Screen (ALS-CBS), a highly sensitive tool to detect frontal lobe related cognitive and behavioral changes.[11,12] In addition to testing the effectiveness of memantine, we also validated potential biomarkers to capture disease progression.

The underlying pathophysiology of ALS is not fully understood; however, SOD1-related familial ALS implicates excess free radicals and excitotoxicity in the pathogenesis of ALS.[13,14] Additionally, recent evidence suggests that defective excitatory amino acid transporter (EAAT-2) in spinal cord glial cells impairs glial cell's ability to buffer glutamate at neuronal synapses.[15] A proposed mechanism linking overactivation of the *N*-methyl-D-aspartate (NMDA) receptor via glutamate is through the production of nitric oxide (NO), *S*-nitrosylation, and reactive oxygen species (ROS).[16] Together, they contribute to protein misfolding. The combination of glutamate-mediated excitotoxicity and free radical damage makes memantine a rationale therapeutic agent to trial in ALS. Memantine is a noncompetitive NMDA receptor antagonist, blocking the effects of glutamate, as well as ameliorating the excessive production of NO and the subsequent protein misfolding.[16–18] Additional data also suggests that memantine can downregulate systemic inflammatory pathways, such as by preventing microglial activation and reducing tumor necrosis factor-α (TNF-α) levels.[19] Memantine has been shown to prolong survival of mutant SOD1 transgenic mice, an animal model of ALS.[20]

An additional benefit of memantine is its impact on cognitive and behavioral symptoms, which has been shown in other neurodegenerative conditions including Alzheimer's and Parkinson's disease.[21,22] Nearly half of all ALS patients have signs of cognitive impairment and behavioral symptoms due to frontotemporal lobar degeneration.[23–25] On the severe end of the spectrum, frontotemporal dementia (FTD)–ALS highlights the concurrent neuropsychiatric comorbidity, though more subtle presentations occur within the spectrum between FTD and ALS.[23,24]

ALS clinical trials are limited due to the lack of validated biomarkers to track disease progression, stratify patients, and assess therapeutic impact. Several biomarkers for ALS progression have been proposed including phosphorylated neurofilament heavy chain (pNF-H) and neurofilament light chain (NfL). Elevated blood and cerebrospinal fluid (CSF) levels of pNF-H and NfL are observed in ALS patients compared to healthy controls and patients with neurologic diseases (not affecting the motor system).[26–31] Higher levels of pNF-H correlate with more rapid disease progression.[32,33] Additional biomarkers of interest include TNF-α and chitinase 1 (Chit-1), both of which have been shown to be elevated in the CSF and blood of ALS patients.[34,35] Given this data, we longitudinally measured for NfL, pNF-H, TNF-a, and Chit-1, along with the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) in this trial to validate these markers.

Small studies testing memantine in ALS have been conducted, resulting in conflicting results, thus providing the impetus for this study. An open label trial of 19 patients that were compared to historical controls found a 38% reduction in the rate of decline.[36] Additionally, 12 of the trial participants had clinical data prior to starting the trial, allowing for the comparison between pre-treatment and post-treatment rates of decline. Memantine treatment resulted in a reduction in the rate of disease progression in this small cohort. Another study evaluated the efficacy of memantine in 60 patients in a blinded placebo-controlled study and did not find any slowing of disease progression.[37] This larger trial serves to help clarify the impact of memantine on ALS progression.

2 | METHODS

2.1 | Trial design

This randomized, double-blind, placebo-controlled study took place from December 2018 to September 2020, enrolling 99 participants with 89 participants undergoing randomization to memantine versus placebo for 36 weeks. A total of 13 sites (The Western ALS Study Group, Table A1) across the United States enrolled participants for the study. Participants were required to be 18–85 years of age and have possible, laboratory-supported probable, probable, or definite ALS by El-Escorial criteria; a ALSFRS-R score >25; and had onset of symptoms within the 3 years prior to enrollment. The presence or absence of cognitive or behavioral issues did not impact enrollment selection. Riluzole and/or edaravone must have been on a stable dose for at least 30 days prior to the baseline visit. Potential participants were excluded if they had a history of liver disease, severe renal failure, a history of intolerance to memantine, concurrent or recent (within 30 days of study) investigational medications, or a co-morbid condition that would make trial completion unlikely. Additionally, females that were pregnant or breastfeeding and females of childbearing potential that were unwilling to use an effective means of birth control were excluded from the study. Initially, inclusion in the study required a functional vital capacity (FVC) >60% of the predicted value. Due to the COVID-19 pandemic and concerns about the risk of COVID-19 transmission via respiratory equipment, the FVC enrollment criterion was relaxed to allow patients to be enrolled if they had an FVC >60% within the 90 days prior to enrollment or the investigator did not believe the patient had significant shortness of breath or respiratory issues if an FVC within 90 days was not available. Remote enrollment and follow-up via phone or video conferencing were also instituted.

When enrolling participants remotely, all assessments were performed, except physical exams, FVC measurements, and biomarker/safety lab draws. The consent form was mailed to the potential subject's home or email address and reviewed by the potential subject with a study team member.

All participants were given a schedule to increase dosage: one tablet (10 mg memantine or placebo) daily for 2 weeks, then one tablet twice daily for 2 weeks, then one tablet in the morning and two tablets in the evening for 2 weeks, and lastly, two tablets twice daily to reach the goal dose of memantine 20 mg (or placebo two tablets) twice daily. Participants continued memantine 20 mg (or placebo two tablets) twice daily for the remainder of the 36 weeks of memantine (or placebo), unless they could not tolerate the dose. If a dose escalation was not tolerated, participants reverted to the previously tolerated dose for 1 week and then the dose escalation was repeated. During the study, if a dose was not tolerated, participants could remain in study at the current dose, reduce the daily dose by 10 mg (or one tablet), or withdraw from the study. Participants had two opportunities to reduce the dose by 10 mg (or one tablet) daily, and if the dose was still not tolerated, the subject was withdrawn from the study. The minimum required dose to remain in the study was 10 mg (or one tablet) daily. Because past studies tested 10 mg BID and had conflicting results, we hypothesized that a higher dose would assist in answering whether memantine has an impact or not. Additionally, a higher dose (40–60 mg/day) was used for complex regional pain syndrome and was tolerated.[38] Therefore, we decided to use a higher dose than what is used routinely in dementia. The FDA regulatory branch and the FDA Orphan Products Development funding branch both agreed with this approach.

2.2 | Sample size, randomization, and blinding

A total of 89 participants were randomly assigned memantine or placebo in a 2:1 ratio using a predetermined randomization formula. The active and placebo medications were identically encapsulated by the research pharmacy at the University of Iowa.

The study was designed to have 80% power to detect a 40% reduction in slope. This was based on a Phase I study by Todd Levine et al. that found ~27% reduction in ALSFRS-R slope.[36]

2.3 | Outcomes and measures

The primary outcome measure was disease progression as measured by the ALSFRS-R during the study. The ALSFRS-R is a 12-question rating scale used to determine each subject's capability for and independence in daily activities that strongly correlates with survival. This is a commonly used scale in ALS clinical trials and has high inter-rater reliability and test–retest reliability in person and through virtual assessment.[39,40] For this study, ALSFRS-R was measured at screening and at 4-week intervals through 36 weeks.

2.4 | Secondary outcomes

Blood samples for biomarker analysis were collected at screening and weeks 4, 12, 24, and 36. Samples were collected at a similar time of the day for all participants to account for daily variability and to standardize the time from the last dose of memantine. Standard operating procedures were used for blood collection, processing plasma, and storage at −80°C. All biomarker analyses were performed at the Barrow Neurological Institute. The concentration of pNF-H concentration in blood is determined using a human pNF-H ELISA Kit (Iron Horse Diagnostics, Inc., Phoenix, AZ). All samples were analyzed in triplicate within each experiment, and all experiments were performed at least twice. NfL levels were measured using the Simoa NfL assay (Quanterix). Chit-1 levels in blood were determined using a commercially available ELISA kit (LifeSpan BioSciences, Inc., Seattle, WA). TNF-α levels in plasma were measured using a commercial ELISA kit (R&D Systems, Inc.). All assays were performed following manufacturers' instructions.

2.5 | Exploratory outcomes

In addition to the ALS-CBS, the Neuropsychiatric Inventory Questionnaire (NPI-Q), a validated practical measure to assess for behavioral change, was used to measure neuropsychiatric changes.[41] Since memantine has been shown to slow the progression of behavioral and cognitive decline in other neurodegenerative diseases, there may be potential for a positive impact in ALS patients. The ALS-CBS and NPI-Q assessments were administered by certified evaluators at screening and weeks 4, 12, 24, and 36.

2.6 | Statistical analysis

The primary comparison for efficacy was based on a linear mixed effects model fit to the ALSFRS-R data for the 89 participants followed over 36 weeks. The model calculated fixed effects for intercept, placebo slope (rate of decline of ALSFRS-R), and change in slope for those treated with memantine. Random effects included are for individual subject variation in intercept, slope, and random error at each time point. The test for treatment effect was based on the change in slope due to treatment, as estimated by the model. Testing for significance was two-sided at a 10% level of significance. Analysis was limited to participants who received at least one treatment dose and had at least two measurements (one at baseline and one after treatment). Biomarker and exploratory endpoints were analyzed using a linear mixed effects model fit to the data. All analyses were prespecified, non-hierarchical. There was no adjustment for multiple analyses. Deaths were treated as equivalent to drop-outs. This model weighed each subject inversely by his or her estimated variance so that participants with missing values received less weight than those with complete data. All statistical testing was two-sided, and $p < .05$ was considered significant. Statistical analysis was performed using Stata (version 12, College Station, TX).

3 | RESULTS

We enrolled 99 participants with 10 screen failures resulting in 89 randomized participants (Figure 1) between the ages of 24 and 83 years. Enrolled participants included a male-to-female ratio of approximately 3:2 (men $n = 60$), and the majority were Caucasian ($n = 90$, 91%).

For the 89 randomized participants, baseline characteristics did not significantly differ between the treatment and placebo groups (Table 1). A total of 36 (40%) participants dropped out of the study due to adverse experience ($n = 19$, 21%), death ($n = 6$), patient request ($n = 6$), and lost to follow-up ($n = 5$). An additional subject ($n = 1$) discontinued the study treatment and continued follow-up through 40 weeks. Three deaths were the result of ALS progression and complications: one from pneumonia, one from cardiac arrest, and one from respiratory failure. In the memantine group, the most common adverse event that led to discontinuation was dizziness ($n = 4$). Primary endpoint analysis was performed on participants who had more than one ALSFRS-R performed.

3.1 | Outcomes

3.1.1 | Disease progression

Patients treated with memantine did not show a significant difference compared to placebo in the rate of ALSFRS-R decline for each subject,

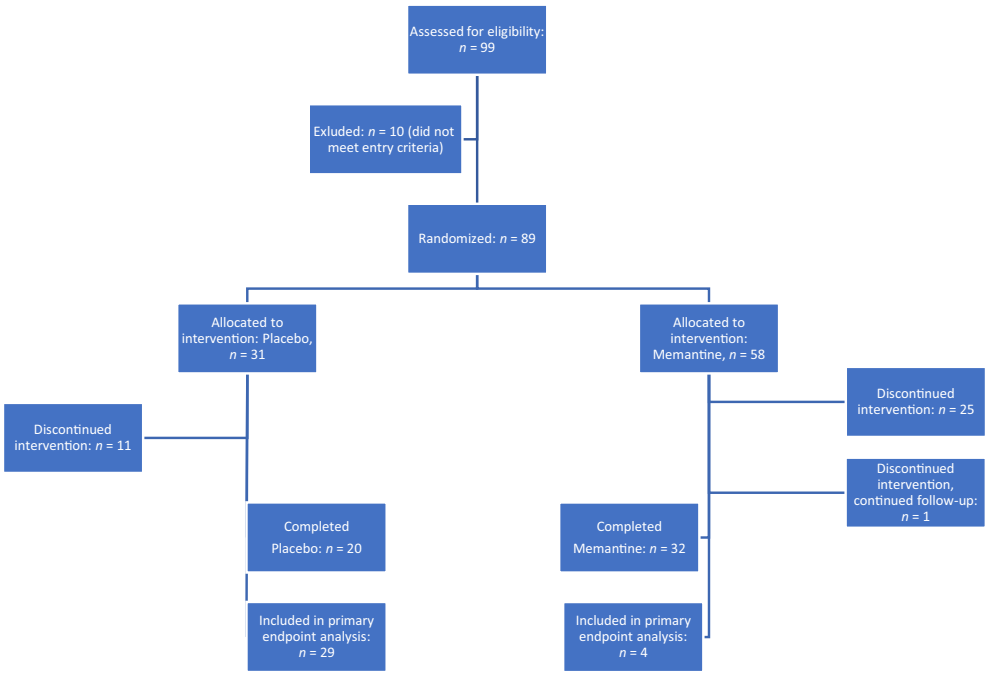

FIGURE 1 Study flow diagram. Ninety-nine subjects were enrolled, and 89 subjects were randomized to memantine versus placebo in a 2:1 ratio. Primary endpoint analysis was performed on subjects that had greater than one Revised Amyotrophic Lateral Sclerosis Functional Rating Scale score.

TABLE 1 Baseline characteristics.

	Memantine	Placebo	*p*-value
Number of participants	58	31	N/A
Number of females (%)	27 (47%)	10 (32%)	.19
Number of bulbar onset (%)	18 (31%)	4 (13%)	.048
Number taking riluzole (%)	38 (66%)	20 (65%)	.92
Number taking edaravone (%)	2 (3%)	3 (10%)	.23
Mean age in years (SD/range)	62.3 (11/24–83)	63.2 (12.1/ 38–81)	.71
Mean duration of symptoms in months (SD/range)	11.31 (5.44/1–25)	11.61 (6.44/1–27)	.82
Mean baseline % predicted vital capacity (SD/range)	85.3 (16.6/43–119)	82.02 (15.2/38–104)	.41
Mean baseline ALSFRS-R (SD/range)	36.3 (5.5/25–45)	38.1 (5.37/26–47)	.15
Mean baseline TNF-α (SD/range)	1.11 (0.27/0.68–1.85)	1.17 (0.49/0.71–3.22)	.64
Baseline NfL (SD/range)	232.7 (180/13.9–936.3)	175.5 (153/24.6–670.1)	.10
Baseline Chit-1 (SD/range)	40.0 (31.4/0–187)	44.4 (34.7/11–175)	.57
Baseline pNFH (SD/range)	199 (283/1–1701)	133 (191/0–990)	.21
Baseline CBS-Cog (SD/range)	15.9 (2.8/7–20)	16.5 (2.7/8–20)	.32
Baseline CBS-Behavioral (SD/range)	37.4 (8.2/12–45)	40.9 (6.8/17–45)	.05
Baseline NPI-Q total (SD/range)	3.75 (4.2/0–19)	2.39 (3.8/0–16)	.15
Baseline NPI-Q distress (SD/range)	4.2 (5.5/0–27)	2.6 (4.8/0–20)	.20

Abbreviations: ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; CBS, Cognitive Behavioral Screen; CHIT-1, chitinase 1; NfL, neurofilament light chain; NPI-Q, Neuropsychiatric Inventory Questionnaire; pNF-H, phosphorylated neurofilament heavy chain; TNF-α, tumor necrosis factor-α.

TABLE 2 Linear mixed effects model fit to ALSFRS-R data.

Memantine versus placebo tests	Change in slope (ALSFRS-R)	*p*-value
Unadjusted (SD)	−0.005 (0.067)	.94
Adjusted for Symptom Duration (SD)	−0.007 (0.067)	.92
Adjusted for initial FVC and Symptom Duration (SD)	−0.021 (0.074)	.77

Note: Test for treatment effect from LME model.
Abbreviations: ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC, forced vital capacity; SD, standard deviation

TABLE 3 Rate of change for potential biomarkers for ALS in the Memantine and Placebo groups.

Outcome	Memantine ($n = 58$)	Placebo ($n = 31$)	*p*-value
NfL	1.40 (0.66)	0.84 (0.42)	.28
pNFH	−0.26 (0.68)	−0.26 (0.42)	.99
TNF-α	0.0006 (0.0028)	−0.0021 (0.0017)	.22
Chit-1	0.025 (0.18)	−0.002 (0.07)	.79

Note: LME model fit to biomarker data. Data reported is average slope change per week with the standard error.
Abbreviations: ALS, amyotrophic lateral sclerosis; CHIT-1, chitinase 1; NfL, neurofilament light chain; pNF-H, phosphorylated neurofilament heavy chain; TNF-α, tumor necrosis factor-α.

regardless of the number of visits (Table 2). The rate of decline in ALSFRS-R, when converted to a monthly rate, was −1.26 in the memantine group and −1.23 in the placebo group. Individual subject ALSFRS-R data is available in Supplementary Figures 1 and 2. A total of six participants, two in the placebo arm and four in the memantine arm, had only one visit; thus, there is no slope for these participants and is not included in the primary outcome analysis.

We fit a series of linear mixed effects models to the data, accounting for the number of study visits per subject. We also added two covariates, symptom duration and initial FVC, as those two covariates have influenced ALSFRS-R rates of decline. No factors were statistically significant, including treatment (Table 2). Initial body mass index did not impact disease progression (data not shown). Due to the COVID-19 pandemic, initial FVC values were limited to 71 participants; FVC values are not available for four placebo participants and 14 memantine participants.

3.1.2 | Biomarkers

No biomarker, including NfL, p-NF-H, TNF-α, and Chit-1, showed significant treatment effect (Table 3). There was no difference in the plasma Nfl levels between the treatment (232.7 pg/mL) and control (175.5 pg/mL) groups (Table 1). Similarly, there were no differences in plasma TNF-α, pNF-H, and Chit-1 levels between the two groups (Table 1). For NfL, the rate of increase is directly related to the starting value: The highest initial values had the greatest increase over time.

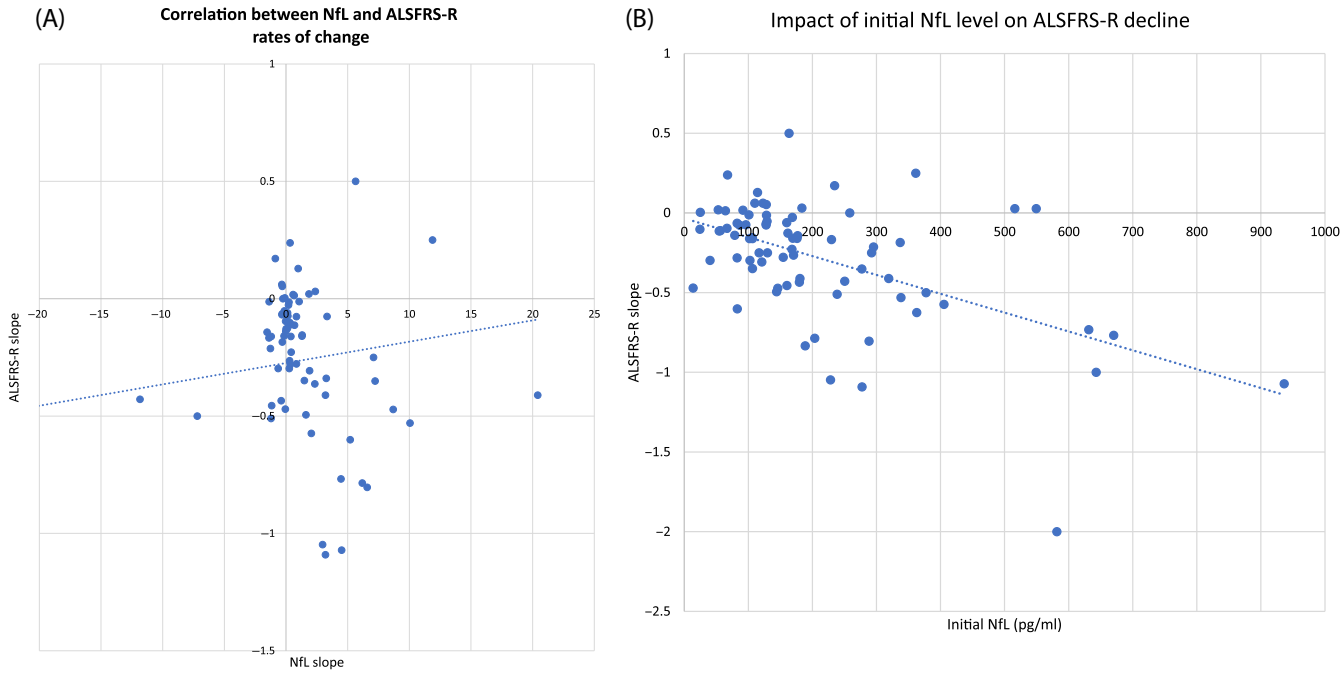

FIGURE 2 (A) Correlation between NfL and ALSFRS-R rates of change. Change in NfL values throughout the study showed a weak correlation ($r = 0.28$, $p = .02$) to ALSFRS-R decline. (B) Impact of Initial NfL Level on ALSFRS-R decline. Initial baseline NfL values showed a strong correlation ($r = -0.53$, $p < .001$) to ALSFRS-R decline.

TABLE 4 Rate of change of ALS-CBS and NPI-Q in the memantine and placebo groups.

Outcome	Memantine	Placebo	*p*-value
ALS-CBS cognitive	0.007 (0.011)	−0.016 (0.013)	.19
ALS-CBS behavioral	0.008 (0.025)	−0.069 (0.032)	.06
NPI-Q total	0.014 (0.015)	0.012 (0.021)	.96
NPI-Q distress	0.033 (0.022)	0.005 (0.031)	.48

Note: LME model fit to neurocognitive data. Data reported is average slope change per week with the standard error.
Abbreviations: ALS, amyotrophic lateral sclerosis; CBS, Cognitive Behavioral Screen; NPI-Q, Neuropsychiatric Inventory Questionnaire.

Individual subject biomarker data is available in Supplementary Figures 3 and 4. As disease progressed in participants, NfL had a weak correlation with ALSFRS-R (Figure 2). Elevated baseline levels of NfL correlated strongly with faster disease progression (Figure 2B). There was no correlation between any study biomarker and disease progression, as measured by ALSFRS-R, when combining the treatment and placebo groups (data not shown).

3.1.3 | Behavioral measures

From the ALS-CBS tool, the cognitive and behavioral subscales were analyzed separately. The baseline scores did not differ between the groups (Table 1). There was no difference between the treatment and control groups. While memantine reduced the decline in the ALS-CBS cognitive and behavioral subscales, the results were not statistically significant (Table 4). The NPI total and distress scores did not differ between the treatment and control groups (Table 4).

3.1.4 | Adverse events

A total of 299 adverse events were reported in 77 participants throughout the duration of the study. There were eight (14%) participants in the memantine group and three (10%) participants in the placebo group with serious adverse events. During the study, there were three (5%) deaths in the memantine group and three (10%) in the placebo group. There were 50 participants (56%) in the memantine group and 23 (74%) participants in the placebo group who experienced adverse events that were not classified as serious adverse events. In the memantine group, fall (26%), dizziness (26%), confusion (17%), and constipation (14%) were the most frequently reported adverse events. In the placebo group, fall (16%), constipation (16%), rash (13%), and headache (10%) were the most frequently reported adverse events. The most common reason for drug discontinuation was dizziness, a known complication of the drug.

4 | DISCUSSION

Memantine up to 40 mg daily did not slow the progression of ALS. This study adds to the literature showing that memantine is not a disease-modifying therapy for ALS. Trials repurposing drugs are

commonly conducted to rapidly identify effective treatment for ALS. Several therapeutic candidates are being trialed, some with promising ex vivo screening on reprogrammed cells from ALS patients.[2,42] Current treatments focus on symptomatic improvement in patients. Though memantine can improve neurocognitive symptoms, our study showed that memantine did not influence CBS and NPI scores compared to placebo. This may be potentially due to patient-to-patient variability leading to a poor fit to the linear model. Additionally, this trial was designed to detect a larger effect based on previous data from a trial with memantine, but unfortunately, this effect was not seen in this trial. Despite the scientific rationale for the use of memantine in the treatment of ALS, our study was unable to detect any benefit of memantine in participants with ALS. This highlights our incomplete understanding of the pathophysiology of ALS and the need for better pre-clinical models.

This trial did not employ advanced trial design, such as Bayesian adaptive designs, or patient stratification, both of which may help improve efficiency and ability to detect therapeutic efficacy. These strategies have shortcomings given the heterogeneity in ALS. To support future patient stratification, we measured several biomarkers, including NfL, TNF-α, pNF-H, and Chit-1, as biomarkers throughout the study, though none differed between the treatment and control groups. We showed that the initial NfL value correlated with the rate of decline in ALSFRS-R and could potentially be used to predict patients with faster rates of progression. Our study did not show a correlation between changes in NfL and the rate of decline in ALSFRS-R. Data is limited for the use of NfL as a surrogate biomarker for treatment response in ALS. In the phase 3 study of Tofersen, an antisense oligonucleotide targeting SOD1 messenger RNA, NfL levels were reduced, leading to FDA approval for treatment of familial SOD1 ALS; however, ALSFRS-R was similar between the treatment placebo groups.[9] Like previous studies, we showed that baseline NfL levels have a prognostic value in ALS: higher baseline levels of NfL correlate with faster decline.[29–32]

Due to the COVID-19 pandemic, remote assessments for clinical trials became a necessity and were rapidly implemented.[43,44] Typically, trials are limited to subjects living near the study site or to participants with the socioeconomic means to travel. These factors limit diversity, enrollment goals, and feasibility in rare diseases. Large, multi-site trials can mitigate some challenges, yet the cost and administrative needs can then become a barrier. By quickly training our clinical staff and coordinators across our study sites, we were able to reach our prespecified enrollment goals. Remote assessments have been shown to improve diverse representation, expand access, and potentially reduce costs.[45–47] However, remote evaluations present new challenges such as technological barriers related to study infracture and requirements for patients as well as burden on the patient to input data.[44,46] The technological requirements for participants to engage in the study may also perpetuate inequities. Future ALS trials can aim to reduce burden on patients and their caregivers by remotely consenting patients and evaluating certain outcome measures remotely.

Limitations to our study include the sample size, which may have been too small to identify a small benefit of memantine. Additionally, there was incomplete data on a few participants due to limited visits, partially due to the COVID-19 pandemic. Data was partially limited due to the COVID-19 pandemic. FVC was not conducted in all participants, affecting more participants randomized to memantine. Additionally, six participants had only one ALSFRS-R evaluation. We do not expect these factors to significantly affect the analyses. Importantly, this study demonstrated the feasibility of an almost entirely remote clinical trial. After the COVID-19 pandemic impacted the US population's ability to travel, this study was a success story in that enrollment improved post-pandemic. For ALS patients, travel to sites can be laborious and may limit patient selection and generalizability. This study highlights a potential barrier for future ALS studies that can be addressed by relying on remote monitoring.

5 | CONCLUSION

In this phase II randomized, double-blind, placebo-controlled study of memantine for the treatment of ALS, we found that memantine did not slow the progression of ALS. Additionally, memantine did not alter NfL or other measured biomarkers. Memantine did not have any impact on the neuropsychiatric measures (ALS-CBS or NPI-Q). Despite the challenges of the COVID-19 pandemic, we demonstrated the feasibility of remote enrollment and monitoring of participants. Hybrid in-person and remote ALS clinical trials may improve enrollment numbers and diversity of participants.

AUTHOR CONTRIBUTIONS

Salman Bhai: Writing – original draft; writing – review and editing; data curation. **Todd Levine:** Conceptualization; investigation; funding acquisition; writing – original draft; writing – review and editing; visualization; validation; methodology; project administration; supervision; resources. **Dan Moore:** Software; formal analysis; project administration; data curation; supervision; resources; methodology; visualization; validation; conceptualization; writing – original draft; writing – review and editing. **Robert Bowser:** Methodology; formal analysis; software; project administration; resources; investigation; validation; visualization; conceptualization; writing – original draft; writing – review and editing; data curation; supervision. **Andrew J. Heim:** Writing – original draft; writing – review and editing; project administration; investigation; methodology; visualization; validation; conceptualization. **Maureen Walsh:** Investigation; methodology; project administration; visualization; validation; conceptualization. **Aziz Shibani:** Investigation; resources. **Zachary Simmons:** Investigation; resources. **James Grogan:** Investigation; resources. **Namita A. Goyal:** Investigation; resources. **Raghav Govindarajan:** Investigation; resources. **Yessar Hussain:** Investigation; resources. **Tania Papsdorf:** Investigation; resources. **Tiffany Schwasinger-Schmidt:** Investigation; resources. **Nick Olney:** Investigation; resources. **Kim Goslin:** Investigation; resources. **Michael Pulley:** Investigation; resources. **Edward Kasarskis:** Investigation; resources. **Michael Weiss:** Investigation; resources. **Susan W. Katz:** Formal

analysis; data curation; software. **Suzan Moser:** Writing – original draft; writing – review and editing; investigation; project administration. **Duaa Jabari:** Investigation; resources. **Omar Jawdat:** Investigation; resources. **Jeffrey Statland:** Investigation; resources. **Mazen M. Dimachkie:** Investigation; resources. **Richard Barohn:** Conceptualization; investigation; funding acquisition; writing – original draft; writing – review and editing; visualization; methodology; project administration; supervision; resources; validation.

AFFILIATIONS

[1]University of Texas Southwestern Medical Center, Dallas, Texas, USA
[2]Neuromuscular Center, Institute for Exercise and Environmental Medicine, Texas Health Dallas, Dallas, Texas, USA
[3]Honor Health, Scottsdale, Arizona, USA
[4]Calico Consulting, Livermore, California, USA
[5]Barrow Neurological Institute, Phoenix, Arizona, USA
[6]University of Kansas Medical Center, Kansas City, Kansas, USA
[7]Nerve and Muscle Center of Texas, Houston, Texas, USA
[8]Penn State Hershey Medical Center, Hershey, Pennsylvania, USA
[9]University of California, Irvine, California, USA
[10]University of Missouri, Columbia, Missouri, USA
[11]Austin Neuromuscular Center, Austin, Texas, USA
[12]University of Texas Dell Medical School, Austin, Texas, USA
[13]Access TeleCare, Dallas, Texas, USA
[14]University of Kansas School of Medicine-Wichita, Wichita, Kansas, USA
[15]Providence Brain and Spine Institute, Portland, Oregon, USA
[16]University of Florida College of Medicine Jacksonville, Jacksonville, Florida, USA
[17]University of Kentucky, Lexington, Kentucky, USA
[18]University of Washington, Seattle, Washington, USA
[19]Syneos Health, Morrisville, North Carolina, USA
[20]Cedars-Sinai Medical Center, Los Angeles, California, USA

FUNDING INFORMATION

This work was funded by FDA-OPD Grant no. R01FD003937.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in ClinicalTrials.gov at https://clinicaltrials.gov/, reference number NCT02118727.

ETHICS STATEMENT

This Investigational New Drug study was approved by the US Food and Drug Administration and Institutional Review Board for each site. Participants gave informed written consent prior to enrolling in the study, in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study was registered at clinicaltrials.gov (NCT02118727). A Data Safety Monitoring Board followed the study progress to review adverse events.

ORCID

Salman Bhai https://orcid.org/0000-0003-4702-9380
Andrew J. Heim https://orcid.org/0009-0003-0845-6635
Zachary Simmons https://orcid.org/0000-0001-8574-5332
Tiffany Schwasinger-Schmidt https://orcid.org/0000-0002-6084-7866
Michael Weiss https://orcid.org/0000-0003-4064-1032
Jeffrey Statland https://orcid.org/0000-0003-0790-5315

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SUPPORTING INFORMATION

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

How to cite this article: Bhai S, Levine T, Moore D, et al. A 40-week phase 2B randomized, multicenter, double-blind, placebo-controlled study evaluating the safety and efficacy of memantine in amyotrophic lateral sclerosis. *Muscle & Nerve*. 2025;71(1):63-72. doi:10.1002/mus.28287

APPENDIX A: NEUROMUSCULAR STUDY GROUP AND WESTERN ALS CONSORTIUM MEMANTINE ALS STUDY GROUP

TABLE A1 Study sites.

Site	Investigator(s)	Study nurses/ coordinators
Nerve and Muscle Center of Texas	Aziz Shaibani, MD	Chantae Oates, BS
Penn State Hershey Medical Center	Zachary Simmons, MD, James Grogan, MD	Dodi Schaak, BS, Heidi Runk, BS
University of Kansas Medical Center	Mazen Dimachkie, MD, Jeffrey Statland, MD, Omar Jawdat, MD, Duaa Jabari, MD	Katie Lillig, BS, Collin Gerringer
University of California, Irvine	Namita A. Goyal, MD	Marie Wencel, BS
University of Missouri	Richard Barohn, MD, Raghav Govindarajan, MD	Natalie Taylor, BSN
Austin Neuromuscular Center	Yessar Hussain, MD	Casey Kafena, AGACNP-BC
Cox Medical Center	Tania Papsdorf, MD	Jessica Ratcliff, MS
University of Kansas, Wichita	Tiffany Schwasinger-Schmidt, MD, PhD	Trisha Steele, BS
Providence Health Sciences	Nick Olney, MD, Kim Goslin, MD	Ashley Adamo, BS
HonorHealth Neurology	Todd Levine, MD	Camille Fajardo, BS
University of Florida Jacksonville	Michael Pulley, MD, PhD	Alyssa Ruckel, MPH, Yasmeen Shabbir, MBBS
University of Kentucky	Ed Kasarskis, MD, PhD	Meghann Bruno, BSN
University of Washington	Michael Weiss, MD	Laura Sissons-Ross, BS

Note: Biostatistics: Dan Moore. Data management: Sravani Chandaka and Mary Penne Mays. DSMB: Special thanks to the DSMB members: Nicholas Silvestri (chair), Jonathan Katz, Andrea Swenson, Jose Americo Fernandes, and Alex Karanevich.