

Protocol: ROAR-HMB

ROAR-HMB: A Widely Inclusive, Hybrid-Decentralized Pilot Trial Utilizing β -hydroxy- β -methylbutyrate to
lower IGFBP7 levels in People with ALS

IND Number: 182089

Duke IRB Protocol Number:

Temple IRB Protocol Number:

Everything ALS IRB Protocol Number:

Protocol Version Date: Version 9

August 31, 2026

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1 PURPOSE/HYPOTHESES

1.1 Primary Hypotheses

Primary hypotheses are as follows:

- a. β -hydroxy- β -methylbutyrate (HMB) administered for 9 months will decrease the rate of Revised ALS Functional Rating Scale (ALSFRS-R) progression by 50% relative to pre-treatment slope and to the slope in propensity matched controls

1.2 Secondary Hypotheses

Secondary Hypotheses are as follows:

- a. HMB treatment will be safe and tolerable over 9 months of treatment.
- b. HMB treatment will reduce serum and CSF neurofilament light chain measurements.
- c. HMB treatment will reduce serum and CSF IGBBP7 levels
- d. HMB treatment will increase the frequency of ALS reversals (defined by an improvement of 4 or more points in the ALSFRS-R over the course of 9 months) from less than 5% observed spontaneously to at least 10%.
- e. HMB will reduce the monthly rate of increase in Listener Effort Prediction Model (LEPM)-predicted Listener Effort (LE) compared to pre-treatment / baseline trajectory.
- f. HMB will improve the rate of decline in ROADS score relative to the slope of matched historical controls, indicating preservation of overall function.

2 BACKGROUND

2.1 Amyotrophic Lateral Sclerosis (ALS) and Its Treatment

ALS is a devastating motor neuron disease that causes rapidly progressive muscle weakness, disability, and premature death. In spite of a large number of attempted ALS trials, there are still no significant disease-modifying therapies for most patients with this condition (1).

2.2 Failure of Previous ALS Trials

There are several reasons that most previous ALS trials may have failed. First, the hypotheses could have been wrong. The hypotheses for many prior trials came from observations made in animal models of genetic ALS (1). How well the animal models predict human ALS, the vast majority of which is not genetic in origin, has been called into question (2). Second, the dosing in previous ALS trials may not have been adequate. Indeed, most ALS trials have not employed pharmacodynamic biomarkers to test their dosing regimen (3,4). Finally, ALS trials are often challenged by slow enrollment (5) and poor retention (6). Some of the enrollment and retention issues may have to do with misconceptions on the part of enrolling clinicians and potential participants (5), and some are due to increasingly narrow trial inclusion criteria, which seem to be necessary when looking for small degrees of ALSFRS-R slowing (7). Finally, people with ALS do become more disabled over time, and study burdens, including frequent trips to the study site, may eventually become impossible to bear (8).

2.3 Success of Previous Hybrid Virtual/Remote “ROAR” Trials

In order to address some of these issues, we created and have now conducted three “ROAR” (Replication of ALS Reversals) Trials (9-11). These tested over the counter supplements associated with dramatic motor improvements in people with ALS (“ALS Reversals”, 12), with the goal of replicating such large effects. Unusual design features included broad inclusion criteria, use of mostly virtual rather than in-person visits, use of pharmacodynamic biomarkers, and use of historical rather than placebo controls.

While these ROAR trials failed to show benefits from the products they tested, they enrolled more quickly, enrolled a more diverse (and generalizable) sample of patients, and retained patients at least as well as more typical ALS trials (9,10).

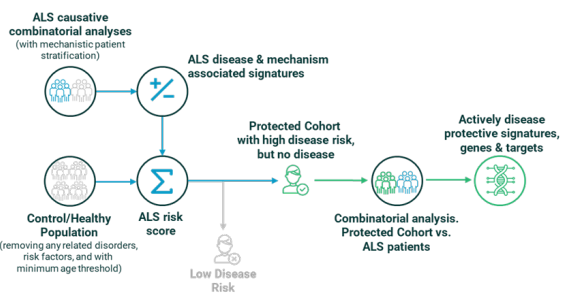
2.4 Targeting IGFBP7

Insulin-like growth-factor binding protein 7 (IGFBP7) is a non-competitive inhibitor of the IGF-1 receptor (13) which is now of interest in dementia and multiple sclerosis. IGFBP7 levels are significantly higher in the brains of patients with Alzheimer's dementia (14) and in the CSF of patients with multiple sclerosis (15) relative to healthy controls. In an Alzheimer's mouse model, injection of IGFBP7 into the hippocampus worsened performance on memory tasks, while injection of anti-IGFBP7 antibody improved them (14). These observations invite speculation that down regulation of IGFBP7 could be a therapeutic strategy in these diseases.

Recent studies suggest that this could also be true in ALS. Increased IGFBP7 mRNA expression occurs in multiple mouse models of SOD1 ALS (16). A single nucleotide variant in an IGFBP7 promotor, which appears to reduce IGFBP7 levels in the brain, is associated with an ALS "reversal" phenotype (17). IGFBP7 protein levels were also recently shown to be significantly elevated in the blood of patients with ALS relative to healthy controls (18); while this small study failed to find an association between IGFBP7 blood levels and either progression rate or ALS reversal, it was likely underpowered, and it focused on IGFBP7 blood levels which may not reflect CSF or brain levels (19).

Our group has just conducted and published on 3 additional studies which add even more support for IGFBP7 as an ALS target (20). The first was an "Actively Protective Combinatorial Analysis (21)."

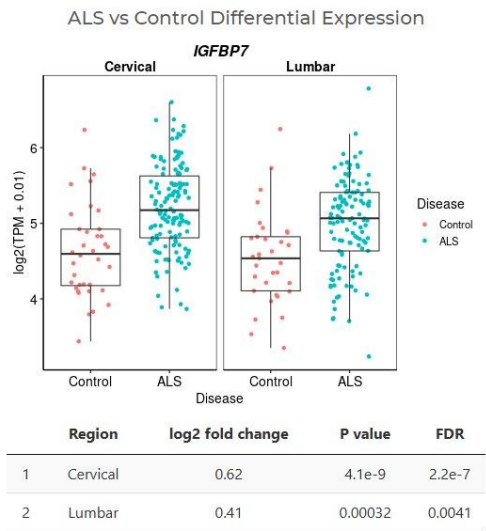
Figure 1. Actively Protective Combinatorial Analysis



Here, whole genome sequence datasets from Project MinE and Answer ALS were analyzed in the PrecisionLife combinatorial analytics platform (21) to identify combinations of SNP genotypes that, when observed together in patients, are strongly associated with the risk of developing ALS (referred to as ‘causative’ analyses). An “actively protective” analysis was then run, to identify SNP combinations that distinguished the healthy “high risk” participants from those with disease (21). We identified an IGFBP7 antisense (IGFBP7-AS1) in the ALS-resistant participants.

We next analyzed publicly available data from the New York Genome Center ALS Consortium (22). This included post-mortem mRNA sequencing from the cervical, thoracic and lumbar spine from 154 people with ALS compared to 49 non-neurological controls (22,23). Here we found significantly elevated IGFBP7 mRNA expression in the cervical and lumbar spinal cord relative to healthy controls (Figure 2).

Figure 2. IGFBP7 Expression in the Spinal Cord



No differences were seen in other IGF binding proteins nor IGF-1 itself (data not shown).

Finally, we interrogated the publicly available Answer ALS database of mRNA expression in induced pluripotent stem cell-derived motor neurons from ALS patients (24). IGFBP7 mRNA was 152.6% higher in induced pluripotential stem cell-derived motor neuron cells from patients with ALS versus those from healthy controls.

Taken together, all these different studies suggest that lowering IGFBP7 could be a reasonable strategy for attempting to prevent or slow ALS progression.

2.5 HMB

β -hydroxy- β -methylbutyrate (HMB) is a metabolite of leucine which has been extensively tested in human trials as a method for improving muscle bulk and motor performance (reviewed in 25,26). It is available without a prescription as a nutritional supplement (ex. 27). In one small placebo-controlled trial, HMB treatment reduced serum IGFBP7 levels (28). While this is the primary reason for using HMB in this trial, it can cause other changes that might be relevant to people living with ALS including increasing muscle bulk and strength (25-30).

3 DESIGN & PROCEDURES

3.1 Design Overview

This will be a widely inclusive, three-center, open-label pilot trial enrolling 100 people living with ALS. Duke (25 participants) and Temple (25 participants) will be traditional sites that consent, screen and follow participants in person. Everything ALS (50 participants) will be a decentralized site providing virtual consenting, screening and follow up. This decentralized site will empower patients to participate even if they live far from Duke or Temple and cannot travel.

Following informed consent, each site's coordinator will perform screening. As part of screening, all participants will be required to have a serum calcium and serum vitamin D, and pre-menopausal females will be required to have a urine pregnancy test. At Duke and Temple these tests will be performed on site. At Everything ALS, patients will be required to get it done via their primary care doctor and submit it to the Everything ALS coordinator.

All participants who pass screening will provide demographics, disease characteristics, co-morbidities, and concomitant medications. They will have a baseline ALSFRS-R score obtained and a baseline slope

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of Listener Effort Prediction Model (LEPM)-predicted Listener Effort (LE) progression (<2 min each, enrollment to month 3 will be used to determine baseline slope, references 32-34) using the EverythingALS HIPAA-compliant mobile app on their own phones/tablets prior to HMB treatment initiation. Each LEPM-LE speech session flows as follows: the app first prompts participants to perform a 5-second background environment noise-check, proceeding only if sufficiently quiet, then guides participants through 3 randomly selected, phonetically balanced Harvard Sentences to read aloud at normal speaking rate and loudness, followed by a picture description task (≤ 1 minute), and concludes with ALSFRS-R and ROADS self-entry. Participants will additionally be offered a web-based AI-assisted ALSFRS-R (ALSFRS-AI) module (35), which delivers the same items through a standardized conversational interface with embedded explanations and clarifying prompts to reduce inter-rater and site-to-site variability while preserving patient-friendly, flexible dialogue. Additionally, Motor Movement Exam (MME) score, a novel self-administered app-based assessment of 46 motor tasks across bulbar, upper/lower extremity, and trunk regions (36) based on ALS Motor Observational Telemedicine Objective Rasch-built assessment (36,37), will be obtained remotely via EverythingALS app to track strength preservation and detect subtle motor decline over time.

Our source of HMB will be Life Extension's "Wellness Code® Muscle Strength & Restore Formula". This product is supplied as a powder, which is ideal for people living with ALS who might develop dysphagia, as it can be dissolved in shakes or smoothies or tube feeds. The dose will be 3g daily (1 scoop) for 9 months. Each can of this product contains 30 servings so participants will receive 3 cans at months 0 (after confirming that they pass all inclusion and exclusion criteria), 3 cans at month 3 and 3 cans at month 6. The product can be mixed into any liquid and taken orally or by feeding tube. The product should be stored in a cool dry place, away from moisture.

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For those who enroll at Duke or Temple, blood will be drawn at screening, month 3, month 6, and month 9 for neurofilament light chain (NfL) and IGFBP7 levels. For patients at Duke or Temple who consent to lumbar puncture, CSF will be drawn at screening and month 3 for NfL and IGFBP7 levels as well. No blood or CSF is being obtained from the Everything ALS participants).

Each month after baseline, participants will be contacted by phone by each site's study coordinator to review adverse events, new co-morbidities, and concomitant medications, and to generate a new clinician-administered ALSFRS-R score. In addition to these scheduled monthly assessments, ALSFRS-R will be collected more frequently (bi-weekly) through ALSFRS-R self-entry and/or AI-assisted ALSFRS-R (ALSFRS-AI) conducted via the EverythingALS app / web depending on participant preference platform supplementing the staff-administered ALSFRS-R obtained by telehealth or in-clinic. Speech measures will continue to be collected bi-weekly remotely via the EverythingALS app, as described above. MME will be collected monthly via the same App.

For Duke and Temple participants, at screening, month 3, month 6 and month 9 they will be asked to return for in person blood draws for NfL and IGFBP7 levels. Those who sign the additional consent for lumbar punctures will have CSF drawn at screening and month 3 and this will be checked for NfL and IGFBP7 levels. ALSFRS-R is routinely measured as part of clinical care. All of the described blood tests and investigational treatments are being performed exclusively for research purposes. No blood or CSF is being obtained from the Everything ALS participants).

Participants will also be asked to return in person for the last visit (month 9) to review adverse events, new co-morbidities, and concomitant medications, and to generate a new clinician-administered ALSFRS-R score.

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The total time commitment for each of the 100 planned participants is 9 months. Schedules of events for the traditional sites (Duke/Temple) and the decentralized site (Everything ALS) are shown below. At the end of each person's participation, any leftover study drug will be collected by the participant's enrolling site and destroyed according to each site's drug destruction protocol.

Table 1: Duke/Temple Schedule of Events by Month (note that all visits have a window of +/- 3 days)

Event	0M In Person	1M Virtual	2M Virtual	3M In Person	4M Virtual	5M Virtual	6M In Person	7M Virtual	8M Virtual	9M In Person
Enrollment										
Consent and Screening	X									
Demographics and Disease Characteristics	X									
Screening Labs (Calcium, Vitamin D, Urine Pregnancy Test ¹)	X									
Clinical Assessments										
ALSFRS-R Score ⁵	X	X	X	X	X	X	X	X	X	X
Co-morbidities	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Study Status (on study, completed, lost to follow up, or died)	X	x	x	x	x	x	x	x	x	x
Study Intervention										
Study Drug (HMB)	Dispense 3 cans			Dispense 3 cans			Dispense 3 cans			
Biomarkers										
NfL and IGFBP7 Blood Draw ²	X			X			X			X
NfL and IGFBP7 Lumbar Puncture (for consenting patients) ³	X			X						
Remote Monitoring										
EverythingALS App — Speech, ROADS & MME ⁴	X	X	X	X	X	X	X	X	X	X

¹Urine pregnancy test will be obtained for pre-menopausal females who have not had one by their own doctor in the past 7 days

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²NfL and IGFBP7 blood draws will be for research purposes only

³NfL and IGFBP7 lumbar punctures will be for research purposes only

⁴LEPM-LE Speech collected remotely via EverythingALS app bi-weekly throughout study. MME and ROADS will be collected remotely via EverythingALS app monthly. Monthly visits may include review of remote speech data compliance and quality.

⁵ALSFRS-R will be collected via multiple modalities: ALSFRS-R self-entry and AI-assisted ALSFRS-R (ALSFRS-AI) through the EverythingALS App / platform (bi-weekly frequency), plus clinician-administered ALSFRS-R via telehealth or in-clinic visits (monthly) to maximize assessment frequency while minimizing participant burden.

Table 2: Everything ALS Schedule of Events by Month (note that all visits have a window of +/- 3 days)

Event	0M Virtual	1M Virtual	2M Virtual	3M Virtual	4M Virtual	5M Virtual	6M Virtual	7M Virtual	8M Virtual	9M Virtual
Enrollment										
Consent and Screening	X									
Demographics and Disease Characteristics	X									
Coordinator Review of PCP's Calcium, Vitamin D and Urine Pregnancy Tests ¹	X									
Clinical Assessments										
ALSFRS-R Score ⁵	X	X	X	X	X	X	X	X	X	X
Co-morbidities	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Study Status (on study, completed, lost to follow up, or died)	X	x	x	x	x	x	x	x	x	x
Study Intervention										
Study Drug (HMB)	Dispense 3 cans			Dispense 3 cans			Dispense 3 cans			
Remote Monitoring										
EverythingALS App — ALSFRS-R, Speech, ROADS & MME ⁴	X	X	X	X	X	X	X	X	X	X

¹Urine pregnancy test will be obtained via each participant's primary care doctor for pre-menopausal females

²ALSFRS-R will be collected via multiple modalities: ALSFRS-R self-entry and AI-assisted ALSFRS-R (ALSFRS-AI) through the EverythingALS App / platform (bi-weekly frequency), and ALSFRS-R via telehealth to maximize assessment frequency while minimizing participant burden.

³LEPM-LE Speech collected remotely via EverythingALS app bi-weekly throughout study. Monthly virtual visits may include review of remote speech data compliance and quality. MME and ROADS will be collected remotely via EverythingALS app monthly.

3.2 Participants

Participants will be people with ALS who are cared for by Dr. Bedlack's team at Duke or Dr. Heiman-Patterson's team at Temple, or who contact our sites inquiring about this study. Everything ALS will be a decentralized site that will empower patients to participate even if they live far from Duke or Temple and cannot travel (a primary investigator will be identified before this site is opened). 100 total participants will be enrolled (25 at Duke, 25 at Temple, 50 at Everything ALS).

3.2.1 Inclusion Criteria

Each participant must meet all of the following criteria at screening and baseline (unless otherwise specified) to participate in the study:

1. Male or female aged at least 18 years.
2. Sporadic or familial ALS diagnosed as per Gold Coast Criteria (38).
3. Patient is able to understand and express informed consent (in the opinion of the site investigator).
4. Patient is able to read and write English.
5. Patient is expected to survive for the duration of the trial.

6. Women must not be pregnant (will have evidence of a negative pregnancy test obtained by study team at baseline, or by local physician within past 7 days or be post-menopausal)
7. Women must not be able to become pregnant (e.g., post-menopausal, surgically sterile, or using adequate birth control methods) for the duration of the study and three months after study completion. Adequate contraception includes abstinence, hormonal contraception (oral contraception, implanted contraception, injected contraception, or other hormonal contraception, for example patch or contraceptive ring), intrauterine device (IUD) in place for ≥ 3 months, barrier method in conjunction with spermicide, or another adequate method.

3.2.2 Exclusion Criteria

Participants will be excluded for any of the following:

1. Actively or recently (within past 30 days) participating in another intervention trial.
2. Currently or recently (within 30 days) taking HMB
3. Prior side effects from HMB deemed to be significant by the investigator
4. Patient has a medical or psychiatric illness that could in the investigator's opinion interfere with the patient's ability to participate in this study.
5. Pregnant women or women currently breastfeeding.
6. Elevated serum calcium or vitamin D levels.
7. Life expectancy shorter than the duration of the trial.

3.3 Recruitment & Compensation

This study will be conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations (CFR), Federal Regulations, and ICH Guidance Documents pertaining to informed consent, and all local regulatory requirements and laws.

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Participants will be recruited from Dr. Bedlack's Duke ALS Clinic or Dr. Heiman-Patterson's Temple ALS Clinic or via the Everything ALS website or will have called our centers to inquire about the study. Since our clinics and our phone lines are open to all relevant demographic groups, all groups will have access to this study. In addition, we will post the following on the Duke ALS Clinic, Temple ALS clinic, and EverythingALS websites: "ROAR-HMB Study is now open. Call "coordinator name" at telephone (#) for details." No compensation will be provided.

3.4 Consent Process

Consent will be obtained by Dr. Bedlack or Dr. Heiman-Patterson or the Everything ALS Primary Investigator, or by the coordinators at Duke, Temple or Everything ALS. Potential participants will be given all the time they need to review the written consent and ask questions about it. No study procedures will occur prior to the consent form being signed.

At the first visit, prior to initiation of any study-related procedures, subjects will be informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits, and will sign an informed consent document that has been agreed to and approved by each site's IRB. If a subject is unable to provide written informed consent due to a physical inability to hold and pen and write, written informed consent may be obtained from the subject's legal representative. The original signed copy will be kept in the subject's research record, and a copy will be provided to the subject.

3.5 Capacity to Give Consent

Only potential participants with appropriate capacity to provide informed consent will be offered a consent form.

3.6 Costs to Subjects

There is no cost for participating in this study.

3.7 Withdrawal of Subjects

If subjects wish at any time to withdraw from the research, they will be able to do so by contacting the study coordinator or principal investigator who will document the subject's decision to withdraw. In the case of longitudinal studies, subjects will be allowed the option to decline to give a follow-up sample at any time while still remaining an active participant in the study. The subject can either decline on a one-time basis or decline permanently to give follow-up samples, either of which would be documented by the study coordinator without the need to withdraw the subject from the study.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

3.8 Risk Assessment

The investigational HMB-containing product being used in this trial (27) has received "GRAS" classification from the FDA and is available without a prescription. HMB has been used at the same dose we are using in many animal and human trials, with excellent safety and tolerability reported (reviewed in 26, 30). Google AI search suggests that some people on the Internet have reported experiencing mild stomach pain, bloating, constipation, muscle cramps, itching, rash and increased urination. Participants will be provided with contact numbers for the research staff. All sites will have an appropriate staff member available 24 hours a day, 7 days a week in the event of an emergency. Participation in this research study is purely for research purposes and is not intended to provide any direct benefit to the volunteers other than altruism (knowledge that they are helping investigators develop better treatments and potentially helping other patients down the road). No at risk populations such as minors, prisoners, pregnant women, or cognitively impaired adults will be included in this study. Participating, or choosing not to participate in the study, will not impact standard of care options for their ALS including participation in Dr. Bedlack's or Dr. Heiman-Patterson's multi-disciplinary ALS clinic and access to FDA-approved medications for treating ALS.

3.8.1 Blood draw

Blood will be drawn by a certified phlebotomist, nurse, or physician according to standard hospital techniques. There may be slight pain and bruising or bleeding at the site. There is a rare risk for infection.

3.8.2 Lumbar Puncture

For participants who consent to it, spinal fluid will be obtained by qualified personnel at Duke and Temple. This is generally considered a safe procedure, with the most common adverse events being pain, soreness, bleeding or bruising at the insertion site and post-procedure headache. Very rare side effects include skin or spinal infection, leg pain or numbness, and nerve damage.

3.9 Outcome Measures

3.9.1 ALS Functional Rating Scale, Revised (ALSFRS-R) and Rasch-Built Overall ALS Disability Scale (ROADS)

ALSFRS-R is a quickly administered (five minute) ordinal rating scale (ratings 0-4) used to determine patients' assessments of their capability and independence in 12 functional activities. All 12 activities are relevant to people living with ALS. Initial validity was established by correlating change in ALSFRS-R scores with change in strength over time, and it was closely associated with quality of life measures and predicted survival (39). The test-retest reliability is greater than 0.88 for all items. The ALSFRS-R declines fairly linearly during the course of ALS and it has been validated for telephone use (40) and self-administration across digital remote formats, with self-reported versions demonstrating excellent reliability (ICC=0.93), equivalent sensitivity to change, and high agreement with clinician-administered scores (41,42). The clinician-administered ALSFRS-R is our primary efficacy measure, and it will be determined 8 times for each participant (at baseline and at each of the subsequent telephone or in

person visits). Additionally, we will collect self-entry and AI-assisted ALSFRS at higher flexible frequency (bi-weekly).

ROADS (Rasch-Built Overall ALS Disability Scale) is a 28-question, self-reported disability scale developed using Rasch methodology, with each item scored 0, 1, or 2. It was developed and validated in a cohort of 243 patients with ALS (47). Unlike the ALSFRS-R, ROADS is linearly weighted, meaning a 1-point change represents a consistent, measurable unit of disability across the entire scale, and it demonstrated improved item targeting and excellent test-retest reliability (ICC=0.97) compared with the ALSFRS-R. ROADS will be collected monthly via self-entry in the EverythingALS App.

3.9.2 *Speech (Listener Effort)*

Listener effort (LE) is a perceptual rating of the amount of work necessary for a listener to understand speech, rated by an expert speech-language pathologist on a visual analog scale from 0 (easily understood) – 100 (unintelligible even with full effort) and it has proven to be one of the most robust overall measures of dysarthria (32-34). It is a clinically meaningful measure that correlates strongly with the ALSFRS-R speech subscore but offers finer granularity and greater sensitivity to early changes in bulbar function. Unlike traditional clinical scales, LE can detect subtle changes in speech that may not yet affect intelligibility, making it particularly useful for early monitoring of ALS progression.

In a prospective study of 292 individuals with ALS, LE demonstrated excellent intra- and inter-rater reliability, with intraclass correlation coefficients between 0.94 and 0.95, and tracked disease progression with an average rate of change of 0.77 points per month. LE showed greater sensitivity to change than the ALSFRS-R (34). LE outperformed other speech and clinical features with the highest sensitivity (effect size 0.88 SD/month vs 1.07 for ALSFRS-R total score, 0.69 for ALSFRS-R bulbar subscore), while articulatory precision (0.79) and pause rate (0.63) showed strong precision but lacked comparable clinical meaningfulness (Dr. Eric Macklin, personal correspondence). LE emerged as a

reliable, remotely collectible, and clinically meaningful speech outcome measure for ALS trials (submitted to the FDA as a Clinical Outcome Assessment under Drug Development Tool (DDT)# 000200).

A machine learning Listener Effort Prediction Model (LEPM, U.S. Patent Pending) automatically estimates LE directly from speech recordings, eliminating the need for a professional rating for every sample. This model, trained on acoustically annotated data, achieved an R^2 of 0.83 ± 0.07 against expert SLP ratings on a held-out test set, indicating that predicted LE closely matches clinician-assessed LE and remains stable across repeated measures (34). Pre- and post-treatment LEPM-predicted LE slopes will be calculated offline from pre-/post-treatment sessions to assess treatment effects on speech progression.

3.9.3 Motor Movement Exam

Motor Movement Exam (MME) score, a novel self-administered app-based assessment of 46 motor tasks across bulbar, upper/lower extremity, and trunk regions (36) based on ALS Motor Observational Telemedicine Objective Rasch-built assessment (36,37), will be obtained remotely via EverythingALS app to track strength preservation and detect subtle motor decline over time. MME will be included in this study as an exploratory measure, with the goal of characterizing its longitudinal behavior and its correlation with the ALSFRS-R and ROADS. MME will be collected monthly via the EverythingALS App.

3.9.4 Neurofilament Light Chain

Neurofilaments are neuron-specific components of the cytoskeleton (reviewed in 43). They exist in heavy, medium, and light chain forms. Neurofilament light chain levels are elevated in the spinal fluid and the blood of patients with ALS and other neurodegenerative diseases, and higher levels predict more severe disease progression (43). These levels rise dramatically when asymptomatic carriers of ALS-causing genetic mutations begin to convert to an ALS phenotype (43). In a trial of an antisense oligonucleotide called Tofersen, a significant reduction in neurofilament light chain levels predicted a

much later improvement in ALSFRS-R progression and survival (44,45). As a secondary efficacy screen, we will measure blood neurofilament light chain levels at baseline, month 3, month 6 and month 9, and CSF levels at baseline and month 3.

3.9.5 IGFBP7

As described above, insulin-like growth-factor binding protein 7 (IGFBP7) is a non-competitive inhibitor of the IGF-1 receptor (13) which is now of interest in dementia and multiple sclerosis (14, 15). We have made multiple recent observations suggesting that it is a plausible target for an ALS therapeutic as well (16-20). As a secondary efficacy screen, we will measure serum IGFBP7 levels at baseline, month 3, month 6, and month 9, and CSF levels at baseline and month 3.

3.10 Treatment

Our source of HMB will be Life Extension's "Wellness Code Muscle Strength & Restore Formula (27). Like other products from this company, this has undergone independent third party testing to ensure purity (45), is certified via Good Manufacturing Practices (46) is registered with NSF (46) and has a certificate of analyses (COA) available. This product is supplied as a powder, which is ideal for people living with ALS who might develop dysphagia, as it can be dissolved in shakes or smoothies or tube feeds. The dose will be 3g daily for 9 months, which has previously been shown to be safe and well-tolerated, and to reduce IGFBP7 blood levels in humans (29). The company has confirmed that this is stable at room temperature and can be shipped to participants (if necessary) at ambient temperature. Participants will receive printed instructions for how to take the product.

4 DATA ANALYSES AND STATISTICAL CONSIDERATIONS

4.1 ALSFRS-R and ROADS Efficacy Analyses

Within each treatment arm, we will compare on-treatment ALSFRS-R slope (month 0 to month 9) to the measured pre-treatment slope (assuming ALSFRS-R was 48 at ALS onset), and also to the slope of matched historical controls from a natural history database. We will compare on-treatment ROADS slope (month 0 to month 9) to the slope of matched historical controls, drawn from the published ROADS dataset (47), de-identified ROADS data obtained from Dr. Christina Fournier (Emory University) under a data transfer agreement, and the EverythingALS Austen Speech Cohort natural history dataset.

4.2 Speech (Listener Effort) Efficacy Analyses

Within each treatment arm, we will compare on-treatment LEPM-predicted LE slope (month 0 to month 9) to the measured pre-treatment slope (assuming LE was 0 at ALS onset), and also to the slope of matched historical controls from a natural history databases (e.g., EverythingALS Radcliff Study, Target ALS).

4.3 Motor Movement Exam

MME will be analyzed as an exploratory endpoint. We will characterize the rate of change in MME score over the 9-month treatment period and assess its correlation with concurrently collected ALSFRS-R and ROADS scores. Additionally, EverythingALS is expanding longitudinal MME collection under the Path to Trials observational study (IRB approved), which may yield an independent MME natural history cohort by the time the ROAR HMB data are analyzed.

Commented [RBMP1]: EverythingALS: we need a description of how it will be analyzed

4.4 ALS Reversals

To look for an increase in the frequency of ALS reversals, we will count the number of participants who have an ALSFRS-R score that improves by 4 points or more over 9 months of treatment. The observed

frequency of spontaneous ALS reversals defined in this way is less than 5% (30). We will look for an increase in this frequency to at least 10% (1 in 10).

4.5 Biomarker Analyses

As described above, we also plan to examine blood and CSF biomarkers. Serum samples will be obtained from all individuals in the study at baseline, month 3 (3 months into treatment), month 6 (6 months into treatment) and month 9 (9 months into treatment). For those who agree to it, CSF samples will be collected at Baseline and month 3.

4.5.1 Neurodegeneration Biomarker: Neurofilament Light Chain

Serum Neurofilament light chain will be measured utilizing available ELISA kits along with standard concentration curves. All spectrophotometric assays will be performed with a Molecular Devices (Sunnyvale, CA) Spectramax 190 spectrophotometer. All assays will be performed in duplicate according to the manufacturers' instructions. Serum neurofilament light chain (NfL) concentrations will be measured in serum using an automated ELISA instrument (ELLA; Biotechne) with a premade cartridge (Cat. No. SPKCE-CS-011450). The lower limit of quantification (LLOQ) was reported as 2.70 pg/mL by the manufacturer. Samples are allowed to clot for 30 minutes at room temperature before centrifugation for 15 minutes at 1000 x g. Samples will be assayed immediately or aliquoted and stored at $\leq -20^{\circ}\text{C}$. For assay performance, samples will undergo a 2-fold dilution with Sample Diluent.

CSF neurofilament light chain (NfL) concentrations will be measured in 25 μL cerebrospinal fluid, diluted 1:1 with sample diluent SD13. This assay will be run in triplicate using an automated ELISA instrument (ELLA; Bio-Techne) with a premade cartridge (Cat. No. SPCKB-PS-002448). The lower limit of quantification (LLOQ) is reported as 2.70 pg/mL by the manufacturer. This assay will be carried out in

accordance with suggested manufacturer protocol and mean concentrations will be used as processable output instead of raw results.

4.5.2 IGFBP7

IGFBP7 will be measured using an automated ELISA instrument (ELLA; Biotechne) with a premade cartridge (Cat. # SPCKB-PS-003329). The limit of detection (LOD) of human IGFBP-2 is 14.6 pg/mL and the range in controls 56,869 – 232,314 pg/ml. Samples are allowed to clot for 30 minutes at room temperature before centrifugation for 15 minutes at 1000 x g. Samples will be assayed immediately or aliquoted and stored at ≤ -20 °C. For assay performance, samples will undergo a 10-fold dilution with Sample Diluent.

4.6 Statistical Analyses

The statistical analyses will be performed at Temple. This study is designed to evaluate the ALSFRS-R data in two different ways. The first evaluates each subject at different time points (before, during and after treatment). This design (differences on the same subject at various time points) reduces variability and allows for greater statistical power. The second compares ALSFRS-R progression during treatment in each arm to a propensity matched group of controls derived from the Natural History database. For parametric variables (NfL, IGFBP7) statistical significance will be determined by repeated measures ANOVA. For non-parametric variables (ALS FRS score), we will use the Friedman test. ROADS will be analyzed the same way, compared to matched historical controls, using the Friedman test. For parametric variables, statistical differences between groups will be determined by analysis of variance (ANOVA) and the Kruskal–Wallis test will be used for non-parametric variables. Determinations will be considered significant if $p < 0.05$. Statistical calculations will be accomplished with the aid of data analysis software, Systat 13.1 (Systat Software, Chicago, IL).

For LEPM-predicted slope analysis, we will use a random-slopes linear mixed model. The primary linear contrast estimates differences in mean rate of progression for continuous efficacy endpoints such as LEPM, including main effects of treatment and centered site of symptom onset (bulbar vs. non-bulbar), plus their interactions with visit (time) as covariates. Study months are calculated as the difference in days from the Baseline Visit to the assessment date multiplied by 12/365.25. This directly compares pre-treatment (0-3 months) and on-treatment (3-9 months) progression slopes while accounting for irregular visit timing and participant variability through random slopes. MME will be analyzed using a random-slopes linear mixed model and correlated with ALSFRS-R and ROADS slopes; if a Path to Trials MME comparator natural history cohort becomes available by analysis time, on-treatment slope will also be compared to it.

5 SAFETY AND ADVERSE EVENTS

5.1 Adverse Events Monitoring

All adverse events (AEs), whether observed by the Investigator, elicited from the participant, or volunteered by the participant, and whether ascribed to the study or its treatments or not, will be recorded. This will include the following: a brief description of the event, the date of onset, the date of resolution, the duration and type of the event, the severity, contributing factors and any action taken with respect to the study drug. This recording will commence with the institution of protocol-specific procedures (including any pretreatment procedures) and continue at each study visit or telephone contact until 4 weeks following the last study related visit.

For each adverse event, the relationship to the study drug will be recorded as one of the choices on the following scale:

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DEFINITE Causal relationship is certain (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge procedure if necessary).

PROBABLE High degree of certainty for causal relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge [re-challenge is not required] and other causes have been eliminated or are unlikely).

POSSIBLE Causal relationship is uncertain (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, de-challenge/re-challenge information is either unknown or equivocal and while other potential causes may or may not exist, a causal relationship to the study drug does not appear probable).

UNLIKELY Not reasonably related, although a causal relationship cannot be ruled out (i.e., while the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug).

NOT RELATED No possible relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible).

The severity of each adverse event must be recorded as one of the choices on the following scale:

MILD No limitation of usual activities

MODERATE Some limitation of usual activities

SEVERE Inability to carry out usual activities

The expectedness of an AE must be indicated when reporting adverse events. An unexpected adverse event is any adverse experience for which the specificity or severity of the event is not consistent with the known side effects of one of the study treatments, as described in section 3.8 above.

5.2 Reporting of Serious Adverse Events

A serious adverse drug event (SAE) is defined as any adverse event that occurs during the study that results in any of the following outcomes: death, a life-threatening adverse event (i.e., the participant was at immediate risk of death from the event as it occurred; does not include an event, that had it occurred in a more severe form, might have caused death), inpatient hospitalization or prolongation of existing hospitalization (hospitalizations scheduled before enrollment for an elective procedure or treatment of a pre-existing condition which has not worsened during participation in the study will not be considered a serious adverse event), a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions), a congenital anomaly/birth defect, a medically important event or required medical intervention to avoid one of the above outcomes. In addition to the above procedures for AEs, all SAEs will be reported to the IRB within 24 hours of recording. All serious adverse event information will be followed until resolution, or an appropriate end point is reached. This may involve contacting other clinicians responsible for the participant's care to obtain information on diagnoses, investigations performed, and treatment given.

Fatal or life-threatening, unexpected adverse events deemed related to the study drug will be reported to the FDA by telephone, facsimile, or in writing as soon as possible, but no later than 7 calendar days after first knowledge by the Sponsor. Serious, unexpected adverse events deemed related to the study drug that are not fatal or life-threatening, will be reported to the FDA by telephone, facsimile, or in writing as soon as possible, but no later than 15 calendar days after first knowledge by the sponsor-investigator.

5.3 Data & Safety monitoring

Adverse events will be tracked throughout the study as described above and below. There is no formal safety monitoring plan or DSMB, nor are there any formal stopping rules. PI will review and sign off on all adverse events and promptly report these to the IRB.

6 DATA HANDLING AND RECORD KEEPING

The Site Investigator (SI) is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the eCRF derived from source documents should be consistent with the source documents and discrepancies should be explained. Bio-samples will be kept in a locked, access-controlled laboratory. If samples are sent for analysis elsewhere, no identifiable information will be included.

Each site will maintain its own electronic database.

7 GLOBAL UNIQUE IDENTIFIER (GUID)

A patient Global Unique Identifier (GUID) will be used as an identifier. The GUID is an 11-character string that is generated using encryption technology and algorithms licensed by the NCRI from the National Institutes of Health (NIH). The GUID is generated on a secure website that utilizes 128-bit Secure Socket Layer (SSL). The GUID is generated using an irreversible encryption algorithm – it accepts twelve identifying data elements, (e.g., last name at birth, first name at birth, gender at birth, day, month and year of birth, city, and country of birth, etc.), and produces a unique random-generated character string, or GUID. No identifying information is stored in the system; it is simply used to generate the GUID. If the same information is entered again, the same GUID will be returned. Participants will be given the option to opt out of sharing their de-identified information across studies.

8 SECURITY INFORMATION

Paper electronic case report forms as well as the computers containing study Redcap databases will be stored in locked offices at Duke and Temple University. These paper forms and all Redcap data and data from the EverythingALS App will be de-identified with the exception of birth dates of birth and acquisition dates for study data (it is necessary for sites to share these at the end of the study in order to combine datasets, calculate outcome measure slopes and run statistics)

9 GOOD CLINICAL PRACTICES AND HUMAN SUBJECTS PROTECTION TRAINING

The investigators and coordinators involved with the conduct of this study will be certified in Good Clinical Practices (GCP) and Human Subjects Protection training. Human Subjects Protection training certification will be obtained by completing approved training, such as the online computer based training offered by the NIH Office of Human Subjects Research (<http://ohsr.od.nih.gov>).

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