

## **HEALEY ALS Platform Trial**

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PROTOCOL APPROVAL SIGNATURE PAGE

**HEALEY ALS Platform Trial**

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

**Merit Cudkowicz, MD, MSc**

Principal Investigator  
Director, Healey Center for ALS  
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\_\_\_\_\_  
**Signature**

\_\_\_\_\_  
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Healey Center for ALS at Mass  
General

\_\_\_\_\_  
**Signature**

\_\_\_\_\_  
**Date**

## STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements, including United States Code of Federal Regulations (CFR) Title 45 CFR Part 46 and Title 21 CFR Parts 50, 56, and 312.

SIGNATURE PAGE

I have read the attached ALS Platform Trial protocol entitled, “HEALEY ALS **Platform Trial**” dated **08/31/2020** (Version **4.0**) and agree to abide by all described protocol procedures. I agree to comply with the ICH Guideline on GCP, applicable FDA regulations and guidelines, including those identified in Title 21 CFR Parts 11, 50, 54, and 312, central Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

By signing the protocol, I agree to keep all information provided in strict confidence and to request the same from my staff. Study documents will be stored appropriately to ensure their confidentiality. I will not disclose such information to others without authorization, except to the extent necessary to conduct the study.

Site Name: \_\_\_\_\_

Site Investigator: \_\_\_\_\_

Signed: \_\_\_\_\_ Date: \_\_\_\_\_



## LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
BWH	Brigham and Women's Hospital
CC	Coordination Center
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
cIRB	Central Institutional Review Board
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DCC	Data Coordination Center
DSMB	Data and Safety Monitoring Board
DNA	Deoxyribonucleic Acid
DRR	Disease Rate Ratio
eCRF	Electronic Case Report Form
ECAS	Edinburgh Cognitive and Behavioral ALS Screen
ECG	Electrocardiogram
EDC	Electronic Data Capture
FVC	Forced Vital Capacity
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HHD	Hand Held Dynamometry
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISF	Investigator Site File
ISST	Interim-Specific Success Threshold
ITT	Intent-to-Treat
LFTs	Liver Function Tests
LP	Lumbar Puncture

MGH	Massachusetts General Hospital
MM	Medial Monitor
MoA	Mechanism of Action
MOP	Manual of Procedures
N	Number (typically refers to number of participants)
NCRI	Neurological Clinical Research Institute
NEALS	Northeast ALS Consortium
NeuroGUID	Neurological Global Unique Identifier
NDA	New Drug Application
NfL	Neurofilament Light Chain
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
p75 <sup>ECD</sup>	Neurotrophin Receptor p75 Extracellular domain
PHI	Protected Health Information
PHRC	Partners Human Research Committee
PI	Principal Investigator
PK	Pharmacokinetic
pNfH	Phosphorylated Neurofilament Heavy Chain
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials Database
QA	Quality Assurance
QC	Quality Control
RA	Reliance Agreement
RSA	Regimen-Specific Appendix
SAE	Serious Adverse Event
SDTs	Source Document Templates
SI	Site Investigator
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Serious, Unexpected, Suspected Adverse Drug Reaction
SVC	Slow Vital Capacity
TEC	Therapy Evaluation Committee
TMF	Trial Master File
US	United States
VC	Vital Capacity
WOCBP	Women of Childbearing Potential

## PROTOCOL SUMMARY

### **Study Title**

HEALEY ALS Platform Trial

### **Study Indication**

Amyotrophic Lateral Sclerosis (ALS)

### **Phase of Development**

Phase 2/3

### **Rationale and Study Design**

The HEALEY ALS Platform Trial is a perpetual multi-center, multi-regimen clinical trial evaluating the safety and efficacy of investigational products for the treatment of ALS.

The trial is designed as a perpetual platform trial. This means that there is a single Master Protocol dictating the conduct of the trial.

The Master Protocol describes the overall framework of the platform trial, including the target population, inclusion and exclusion criteria, regimen assignment and randomization schemes, study endpoints, schedule of assessments, trial design, the mechanism for adding and removing interventions, and the statistical methodology and recommended statistical methods for evaluating interventions.

Interventions (i.e., investigational products) are tested in trial regimens. Each trial regimen is described in its own Regimen-Specific Appendix (RSA) to the Master Protocol. The RSA will describe the nature of the intervention and its mechanism of action (MoA) including the mode and frequency of administration, dosage, the specific target population (to be selected within the pre-defined subsets of the Master Protocol), additional enrollment criteria (if any), sample size, and other specific intervention-related information and assessments (safety or other assessments that may be in addition to those outlined in the Master Protocol).

### **Allocation to Regimens**

Participants that provide consent to the Master Protocol will be screened for Master Protocol-level inclusion and exclusion criteria. Those determined eligible will be equally randomized across all active regimens. This perpetual platform trial will continue enrolling research participants if there are regimens that are enrolling. As soon as pre-defined criteria for futility or success (if applicable) are met, or the target number of randomized participants in a regimen has been reached, enrollment will stop in that regimen.

### **Number of Planned Participants and Treatment Arms**

The sample size enrolled in each regimen will be determined based on the specifics of the intervention, anticipated effect size, the expected variability in the enrolling population, and

number of treatment arms (e.g., dosage within a regimen, if applicable). Those participants that meet the Master Protocol inclusion and exclusion criteria will be randomly assigned to a regimen. Within each regimen, participants will then be randomized a second time in a 3:1 ratio to active treatment or matching placebo.

### **Planned Number of Sites**

Research participants will be enrolled from approximately 60 centers in the US.

### **Treatment Duration**

Treatment duration of placebo-controlled regimens is a maximum of 24-weeks for each regimen. An optional open label extension (OLE) may be offered and will be described in the respective RSAs.

### **Post-treatment Follow-up Duration**

Will be described in the RSAs.

### **Study Objectives and Endpoints**

#### **Default Primary Efficacy Objective:**

To evaluate the efficacy of multiple investigational products as compared to placebo on ALS disease progression.

#### **Secondary Efficacy Objective:**

- To evaluate the effect of multiple investigational products on selected secondary measures of disease progression, including survival.

#### **Safety Objective:**

- To evaluate the safety of multiple investigational products for ALS.

#### **Exploratory Efficacy Objective:**

- To evaluate the effect of multiple investigational products on selected biomarkers and endpoints.

#### **Default Primary Efficacy Endpoint:**

Change in disease severity as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) total score using a Bayesian repeated measures model that accounts for loss to follow-up due to mortality.

#### **Secondary Efficacy Endpoints:**

- Change in respiratory function as assessed by slow vital capacity (SVC).
- Change in muscle strength as measured isometrically using hand-held dynamometry (HHD) and grip strength.

- Survival.

**Safety Endpoints:**

- Treatment-emergent adverse and serious adverse events.
- Changes in laboratory values and treatment-emergent and clinically significant laboratory abnormalities.
- Changes in ECG parameters and treatment-emergent and clinically significant ECG abnormalities.
- Treatment-emergent suicidal ideation and suicidal behavior.

**Exploratory Efficacy Endpoints:**

- Changes in quantitative voice characteristics.
- Changes in biofluid biomarkers of neurodegeneration.
- Changes in patient reported outcomes.
- Change in respiratory function as assessed by home spirometry

**Investigational Products**

Investigational products will be tested at different times (in parallel and sequentially) as described in this Master Protocol. This Master Protocol describes the common framework of the study. Each investigational product will have its own RSA to the protocol.

## SCHEDULE OF ACTIVITIES

The Master Protocol sets out the minimum visit and assessment requirements that must be incorporated into each RSA. As per the Schedule of Activities (SOA) below, visits must occur every 4 weeks and will be clinic-, phone-, or telemedicine-based, as applicable. Additional assessments may be added by and must be described in each RSA. The Master Protocol allows a 24-week duration of placebo-controlled treatment for an intervention and additional activities and an optional OLE may be added per regimen and will be described in each RSA.

Activity	Master Protocol Screening <sup>1</sup>	Regimen Specific Screening <sup>1</sup>	Baseline	Week 2	Week 4 <sup>13</sup>	Week 8 <sup>13</sup>	Week 12	Week 16 <sup>13</sup>	Week 20	Week 24	Follow-Up Safety Call
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
	-42 to -1 Days	Refer to RSA	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	Refer to RSA
Written Informed Consent <sup>2</sup>	X	X									
Inclusion/Exclusion Review	X	X <sup>3</sup>									
Regimen Specific Screening procedure(s)		X									
ALS & Medical History	X										
Demographics	X										
Physical Examination	X										
Neurological Exam	X										
Vital Signs <sup>4</sup>	X		X		X	X		X		X	
Slow Vital Capacity	X <sup>12</sup>		X			X		X		X	
Muscle Strength Assessment			X			X		X		X	
ALSFRS-R	X		X		X	X	X	X	X	X	
Patient Reported Outcomes <sup>10</sup>			X			X		X		X	
12-Lead ECG	X									X	
Clinical Safety Labs <sup>5</sup>	X		X		X	X		X		X	

Activity	Master Protocol Screening <sup>1</sup>	Regimen Specific Screening <sup>1</sup>	Baseline	Week 2	Week 4 <sup>13</sup>	Week 8 <sup>13</sup>	Week 12	Week 16 <sup>13</sup>	Week 20	Week 24	Follow-Up Safety Call
	Clinic -42 to -1 Days	Clinic Refer to RSA	Clinic Day 0	Phone Day 14 ±3	Clinic Day 28 ±7	Clinic Day 56 ±7	Phone Day 84 ±3	Clinic Day 112 ±7	Phone Day 140 ±3	Clinic Day 168 ±7	Phone Refer to RSA
Concomitant Medication Review	X	X	X		X	X	X	X	X	X	X
Adverse Event Review <sup>6</sup>	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale			X		X	X		X		X	
Biomarker Blood Collection			X			X		X		X	
Biomarker Urine Collection			X			X		X		X	
DNA Collection <sup>7</sup> (optional)			X								
CSF Collection (optional)			X					X <sup>11</sup>			
Assignment to a regimen	X										
Randomization within a regimen		X									
Administer/Dispense Investigational product			X <sup>8</sup>			X		X			
Drug Accountability/Compliance				X	X	X	X	X	X	X	
Exit Questionnaire										X	
Vital Status Determination										X <sup>9</sup>	

<sup>1</sup> Master Protocol Screening procedures must be completed within 42 days to 1 day prior to the Baseline Visit. Refer to RSA for details about RSA Specific Screening procedures, if any, should be performed.

<sup>2</sup> During the Master Protocol Screening Visit, participants will be consented via the Master Protocol informed consent form (ICF). After a participant is assigned to a regimen, participants will be consented a second time via the regimen-specific ICF.

<sup>3</sup> At the Regimen Specific Screening Visit, participants will have regimen-specific inclusion and exclusion criteria assessed, if applicable.

<sup>4</sup> Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate and temperature. Height in cm measured at Master Protocol Screening Visit only.

<sup>5</sup> Clinical safety labs include hematology (CBC with differential), complete chemistry panel, liver function tests, thyroid function and urinalysis. Serum pregnancy testing will occur in women of child-bearing potential at the Master Protocol Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy.

<sup>6</sup> Adverse events that occur after signing consent form will be recorded.

<sup>7</sup> The DNA sample can be collected after the Baseline Visit if a baseline sample is not obtained or the sample is not usable.

<sup>8</sup> Administer first dose of investigational product only after Baseline Visit procedures are completed

<sup>9</sup> Vital status, defined as a determination of date of death or death equivalent or date last known alive, will be determined for each randomized participant at the end of the placebo-controlled portion of their follow-up (generally the Week 24 Visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant's last visit (LPLV) of the placebo-controlled portion of a given regimen. We may also ascertain vital status at later time points by using publicly available data sources as described in section 8.15.

<sup>10</sup> Each RSA will detail which PRO is collected at each Visit. Specific PRO collection may differ from this Schedule of Activities.

<sup>11</sup> If the CSF collection is unable to be performed for logistical reasons, such as scheduling, at the Week 16 Visit, it may be performed at the Week 24 Visit.

<sup>12</sup> If required due to pandemic-related restrictions, Forced Vital Capacity (FVC) performed by a Pulmonary Function Laboratory evaluator or with a study-approved home spirometer, or sustained phonation using a study approved method may be used for eligibility (Master Protocol Screening ONLY).

<sup>13</sup> Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic.



## STUDY WORKFLOW

Figure 1. Example Master Protocol Schema

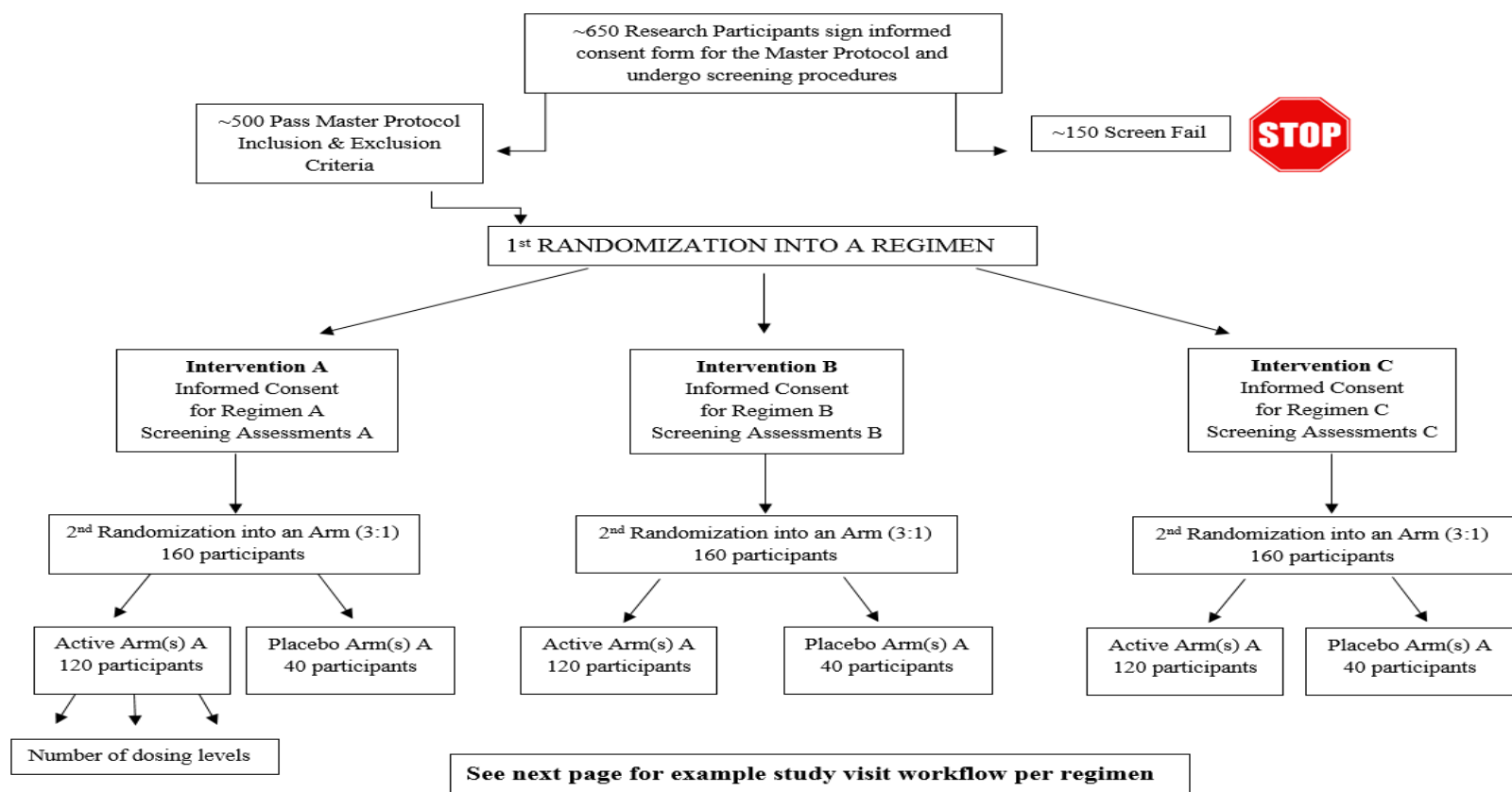


Figure 1 represents an example of the study schema assuming three concurrently enrolling regimens. The Master Protocol schema will change depending on the number of regimens that are enrolling at any given time. Intervention A investigates an active treatment with multiple dosing levels.

Figure 2. Example Study Visit Workflow per Regimen

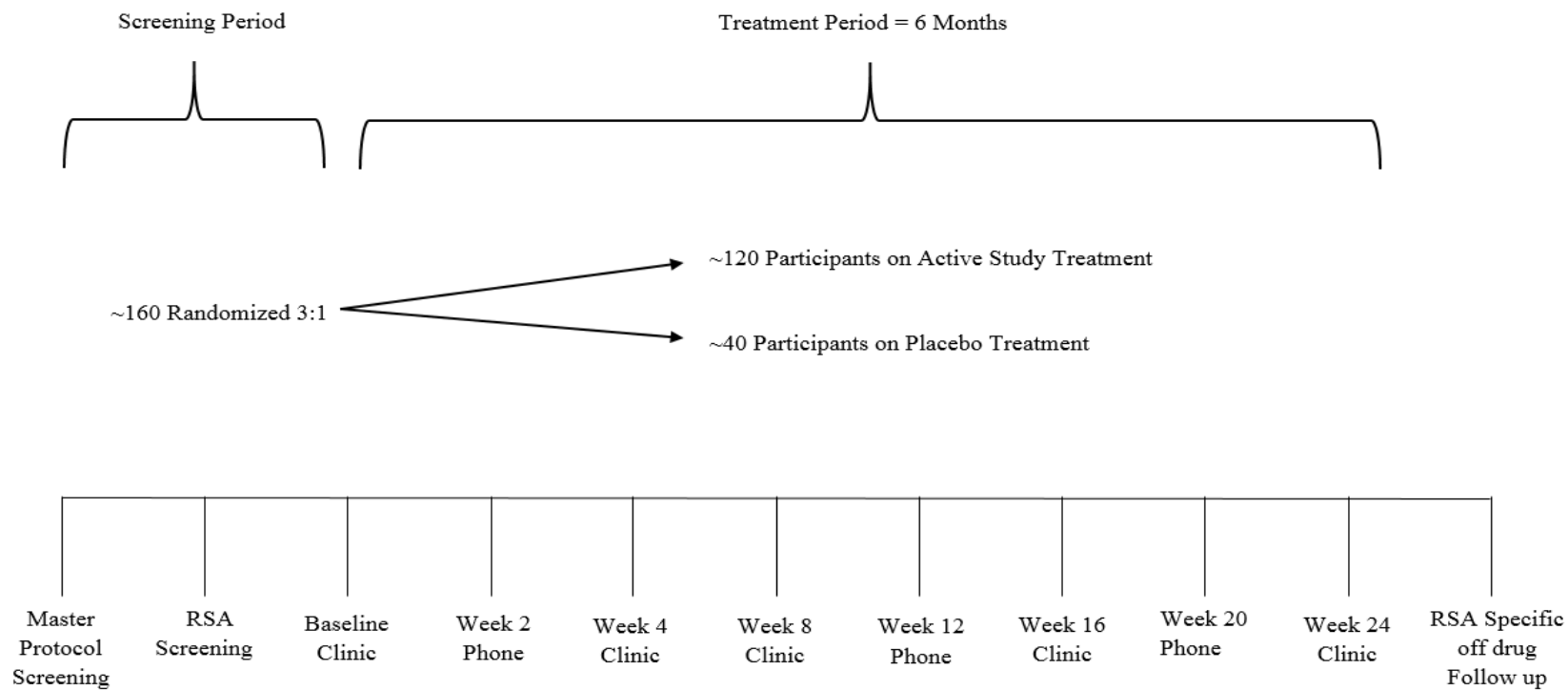


Figure 2 represents an example of the study visits that will occur over 24 weeks for all participants that are assigned to a regimen.

## **1 ETHICS/PROTECTION OF HUMAN PARTICIPANTS**

### ***1.1 Institutional Review Board***

This Master Protocol will be conducted in compliance with current GCP and Title 21 Part 56 of the United States of America CFR relating to IRBs. The IRBs of PHS, collectively known as the Partners Human Research Committee (PHRC), have been selected by the Northeast ALS Consortium (NEALS) to serve as the central IRB (cIRB) for the Master Protocol. PHRC is comprised of the IRBs of Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH) located in Boston, MA. NEALS is a non-profit group of researcher institutions, each of which is a NEALS Member, who collaboratively conduct clinical research in Amyotrophic Lateral Sclerosis and other motor neuron diseases. Sites participating in this Master Protocol must have an executed Central IRB Authorization Agreement (Reliance Agreement or RA) to rely on the PHRC to participate.

### ***1.2 Ethical Conduct of Study***

The study will be conducted in accordance with GCP defined by the ICH and the ethical principles of the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol and any amendments as well as the participant informed consent will receive central IRB approval prior to initiation of the study.

Study personnel involved in conducting this study will be qualified to perform their respective task(s) as confirmed by the site and collection of required documentation.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

### ***1.3 Participant Information and Consent***

This study will be conducted in compliance with Title 21 Part 50 of the United States of America CFR, Federal Regulations and ICH Guidance Documents pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, participants will be informed about the nature and purpose of the Master Protocol, participation/termination conditions, and risks and benefits. Participants will be given adequate time to ask questions and become familiar with the Master Protocol prior to providing consent to participate. Participants will give their documented

informed consent to participate in the Master Protocol and will be provided with a copy of the fully executed Master Protocol consent form for their records.

Participants meeting Master Protocol eligibility criteria will be randomly assigned to a regimen.

Participants will then be informed about the intervention specific to their assigned regimen and any participation/termination conditions or risks and benefits specific to that regimen.

Participants will give their written consent to participate in their assigned regimen and will be provided with a copy of the fully executed regimen-specific consent form for their records.

Participants meeting additional eligibility criteria required by their assigned regimen, if any, will be randomized in a 3:1 ratio to receive either active treatment or matching placebo in that regimen.

In some situations, an individual may be re-assigned to multiple different regimens, if eligible. The procedures detailing the re-assignment process can be found in Section 8.1.2 Screen Failures and Re-Assignment.

## ***1.4 Changes in Conduct of the Study***

### *1.4.1 Protocol Amendments*

Any change to the Master Protocol will be documented in a protocol amendment, issued by the Sponsor. Master Protocol amendments will be submitted for approval to the central IRB prior to implementation. Written informed re-consent for continued participation in the study may be required by participants already enrolled in the Master Protocol.

As regimens are added to the Platform Trial, they will be submitted for approval to the central IRB prior to implementation. Each regimen will be added as an appendix to the Master Protocol prior to any participant being assigned to that regimen. Addition of regimens will not require re-consent. Regimens that are stopped for futility or ended early due to success (if applicable) will not result in an amendment to the Master Protocol.

### *1.4.2 Premature Termination of Study Sites*

The Sponsor reserves the right to terminate the participation of individual study sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter participants at an acceptable rate.

### ***1.5 Protocol Adherence***

Each Site Investigator (SI) must adhere to the Master Protocol detailed in this document and agree that any changes to the protocol must be approved by the Coordination Center (CC) cIRB. Each SI will be responsible for enrolling into the Master Protocol only those study participants who have met all Master Protocol eligibility criteria, and for enrolling into a Regimen only those study participants who have met the additional eligibility criteria (if any) of the corresponding RSA.

## 2 INTRODUCTION

### 2.1 *Background Information and Rationale*

ALS is a progressive, fatal neurodegenerative disease. ALS is characterized by motor neuron loss resulting in muscle weakness and atrophy, disability, and eventually death from failure of the ventilatory muscles<sup>1</sup>. The median age of onset is 55 years and average survival is 3-5 years after onset of first symptoms<sup>2</sup>. While the incidence of ALS is comparable to that of multiple sclerosis (approximately 2/100,000), its prevalence is much lower because of its rapid progression (about 5/100,000)<sup>3</sup>. The only FDA-approved disease modifying medications, riluzole and edaravone, confer only a modest survival benefit<sup>4</sup>.

While therapies for ALS remain limited, basic and translational ALS research has resulted in numerous influential discoveries in recent years, including breakthroughs in genetics and progress in our understanding of disease mechanisms, therapeutic targets, and biomarkers. These discoveries have led to a large pipeline of potential therapies that await testing in clinical trials, suggesting that we are at a time of great opportunity to translate advances in the understanding of ALS into meaningful treatments for people.

Given the poor prognosis and dearth of effective treatments, clinical trials are of primary importance for people with ALS, their families, their providers, and the entire ALS clinical and scientific community<sup>5</sup>. Clinical trials, however, can be complex, time-consuming, and expensive. Challenges to ALS clinical trials are both operational and scientific, and innovative clinical trials are needed to accelerate the path to effective treatments<sup>6-9</sup>.

Operational challenges include inefficiencies in institutional approvals and trial management that may lead to delays in study start-up, slow execution times, and sub-optimal recruitment and retention<sup>10</sup>. Barriers to trial access are so substantial that less than 10% of the ALS population is estimated to participate in clinical research<sup>11, 12</sup>. Fortunately, experience in selected disease-specific networks and federally-funded trial networks demonstrates that logistical trial challenges are surmountable with an infrastructure designed for efficiency and collaboration. In fact, clinical trial networks can be very productive if built with appropriate infrastructure, leadership, and cooperation. Several of these networks leverage efficient infrastructure models, such as the use of a single IRB, Master Clinical Trial Site Agreements, and centralized recruitment and retention strategies<sup>13</sup>.

Scientific challenges to ALS therapy development include disease rarity, patient heterogeneity, lack of validated surrogate endpoints, and a relatively rapid disease course. To overcome some of these barriers, the ALS trial community has stepped up biomarker discovery efforts and devoted substantial resources to the development of novel outcome measures for use in early phase clinical trials<sup>14, 15</sup>. Routine incorporation of these novel endpoints into clinical trials is a critical step forward and holds the promise to improve the chances of success of the drug development pipeline. Yet, progress is hindered by the lack of coordination among different biomarker discovery and outcome measure development efforts<sup>15</sup>. Several previous and current research projects target different patient populations and analyze novel biomarkers/outcome measures using different assays and procedures, and also include variable schedules of assessments. A

major, coordinated collaboration that includes academia, industry, and patient-advocacy organizations is needed to innovate the ALS clinical trial landscape<sup>6-9</sup>.

## ***2.2 Platform Trials: an efficient strategy to accelerate drug development and scientific discovery***

Traditionally, clinical trials are designed by a single sponsor to answer only one question: does a single investigational product work? These trials include a pre-specified number of treatment arms (generally limited to two or three arms) and have a finite duration based on the time required to answer the trial question. Moreover, each trial requires an expensive, ad hoc trial infrastructure that is dismantled at the end of the trial.

In contrast, platform trials are designed to investigate multiple investigational products in parallel and sequentially with the capability to adapt over time. Platform trials do not have a pre-specified end date: the platform remains open long-term and is available to evaluate new investigational products as they become available<sup>16</sup>. The trial infrastructure is built at the beginning and is shared across different treatments, leading to operational efficiencies. Investigational products are compared to a shared placebo group. Sharing of placebo participants is possible because all investigational products are evaluated using a common Master Protocol<sup>17</sup>. The Master Protocol describes the framework of the study, including the trial population, inclusion and exclusion criteria, regimen assignment and randomization schemes, a schedule of assessments, primary, secondary and exploratory outcomes, statistical methodology, and planned analyses that are common for all investigational products to be tested.

Platform trials are an ideal setting to advance the scientific understanding of the disease and novel endpoints with a coordinated strategy. Thanks to its coordinated structure and common data and sample acquisition processes, the platform trial can serve as a natural history registry and bio-repository from placebo participants<sup>17</sup>. With the testing of multiple investigational products using a common protocol and uniform data and sample acquisition processes, the platform is designed to answer multiple scientific questions and to serve as a source of data that can be used to enhance the design of other research projects. Further, accumulated learnings about endpoint behavior can be leveraged to adapt the Master Protocol so that future investigational products will be studied using more efficient biomarkers, outcome measures, and analyses<sup>17, 18</sup>.

## ***2.3 Investigational Product Profile***

In this trial, multiple investigational products for ALS will be tested simultaneously or sequentially. These investigational products will be provided by different partners, either pharmaceutical companies or academic groups.

This trial is designed as a perpetual platform trial. This means that there is a single Master Protocol dictating the conduct of the trial. The additional details that govern the testing of each investigational product will be summarized in separate RSAs.

During the trial, a regimen may be discontinued early due to futility or safety concerns. Additionally, a regimen may be added to the trial based on the ability of the trial to accommodate their incorporation.

Selection of interventions will be done by the Therapy Evaluation Committee (TEC) based on evidence supporting the intended mechanism of action, target engagement, previous pre-clinical data and Phase I or other clinical data (including safety data available for each compound), and compatibility with the Master Protocol.

Each RSA that is part of the Platform Trial for ALS will describe:

1. Specific additional inclusion or exclusion criteria for that investigational product. The RSA will include a summary of the product characteristics, including mechanism of action and pharmacology background, drug profile including a summary of available preclinical and clinical data including pharmacokinetic (PK)/pharmacodynamic, target of action, biomarker data, drug-drug interaction, safety data, and benefit-risk assessment. For a more detailed description of the investigational product profile, the RSA will refer to the current Investigator's Brochure.
2. Specific biomarker assessments not performed as part of the Master Protocol, if any, which are specific to the intervention and proposed mechanism of action.
3. Specific safety assessments not performed as part of the Master Protocol, if any, which are specific to known toxicology or potential safety concerns associated with the intervention.
4. Specific information on study methodology, such as the primary endpoint, maximum sample size, number of arms (e.g., to accommodate multiple dosages), and details for interim analyses for early futility and early success (if applicable).



### 3 Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
<b>Primary</b>		
To evaluate the efficacy of multiple investigational products on ALS disease progression.	Change in disease severity as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) total score using a Bayesian repeated measures model that accounts for loss to follow-up due to mortality	<i>The ALSFRS-R measures function in daily activities and is an established scale for monitoring disease progression in ALS.</i>
<b>Secondary</b>		
To test the effect of multiple investigational products on selected secondary measures of disease progression, including survival.	<ul style="list-style-type: none"> <li>• Change in respiratory function as assessed by slow vital capacity (SVC).</li> <li>• Change in muscle strength as measured isometrically using hand-held dynamometry (HHD) and grip strength.</li> <li>• Survival.</li> </ul>	<p><i>Decline in respiratory function is a direct result of the known pathophysiology of the ALS and demonstration of a treatment benefit on respiratory endpoints may also provide evidence of effectiveness.</i></p> <p><i>Loss of strength is a hallmark of disease progression in ALS and meaningful differences in muscle strength should be supportive of an effect on measures of function in activities of daily living.</i></p>
<b>Safety</b>		
	<ul style="list-style-type: none"> <li>• Treatment-emergent adverse and serious adverse events.</li> </ul>	<i>Toxicities associated with investigational products may</i>

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To evaluate the safety of multiple investigational products for ALS.	<ul style="list-style-type: none"> <li>• Changes in laboratory values and treatment-emergent and clinically significant laboratory abnormalities.</li> <li>• Changes in ECG parameters and treatment-emergent and clinically significant ECG abnormalities.</li> <li>• Treatment-emergent suicidal ideation and suicidal behavior.</li> </ul>	<i>manifest as clinical signs and symptoms, new diagnoses, laboratory or cardiac changes and abnormalities, or suicidality.</i>
Exploratory		
To test the effect of multiple investigational products on selected biomarkers and endpoints.	<ul style="list-style-type: none"> <li>• Changes in quantitative voice characteristics.</li> <li>• Changes in biofluid biomarkers of neurodegeneration.</li> <li>• Changes in patient reported outcomes.</li> <li>• Changes in respiratory function as assessed by home spirometry.</li> </ul>	<i>These endpoints have been chosen to provide greater understanding of ALS and may provide opportunities for identification of surrogate endpoints that are reasonably likely to predict clinical benefit and that might serve as a basis for accelerated approval in future trials.</i>

## 4 STUDY DESIGN

### 4.1 *Overall Study Design and Plan*

This is a perpetual, multicenter, multi-regimen, randomized, placebo-controlled, adaptive platform clinical trial evaluating the safety and efficacy of multiple investigational products simultaneously or sequentially in ALS.

There will be multiple interventional regimens, each consisting of the research participants receiving either the active investigational product or its matching placebo. Research participants, investigators and site staff will not be blinded to the regimen assignment, but they will be blinded to active product or matching placebo assignment. Regimens may start at different time points during the trial.

This Master Protocol describes the framework for the trial design population and the minimum inclusion and exclusion criteria for all regimens. Each RSA will contain intervention-specific information and will define any additional trial elements and regimen-specific eligibility criteria that may exist.

The number of research participants, the duration of treatment for each intervention, and the follow-up period will all be described in the RSA. The primary endpoint will be assessed for all interventions every 4 weeks, either on-site or via phone.

Interim analyses for regimens will begin when at least one regimen has 40 randomized participants within that regimen who have had the opportunity to complete at least 24 weeks of follow-up. Interim analyses will continue to occur simultaneously for all actively enrolling regimens every 3 months. A regimen is eligible to stop early for futility (all regimens) or for success (for applicable regimens only) at any interim analysis once there are 40 randomized participants within that regimen who have had the opportunity to complete at least 24 weeks of follow-up.

At each interim analysis, a set of possible changes or adaptations that an intervention is eligible for will be checked.

1. An intervention can be found to have failed to favorably modify the progression of disease and be deemed futile or unsafe. Upon meeting the criterion for futility, enrollment in that regimen would be discontinued and end of study procedures would be initiated. Research participants in that regimen may be re-screened for entry into the Master Protocol after the mandatory wash-out period, if eligible.

2. An intervention can be found to be successful at modifying the progression of disease (for RSAs that include early stopping rules for success). No further research participants will be assigned to that regimen, but participants already in that regimen may continue for the full, pre-specified duration of treatment, if the RSA dictates continuing exposure. The RSA may also specify that exposure is halted upon success. If exposure is halted, then research participants in that regimen may be re-screened for entry into the Master Protocol after the mandatory wash-out period, if eligible, or enter the OLE for that regimen, if one is offered.

Accrual and maximum exposure of enrolled participants may be reached for an intervention. In this case, this is the end of that regimen and all research participants in that regimen would have completed follow-up. Research participants may be re-screened for entry into the Master Protocol after the mandatory wash-out period, if eligible, or enter the OLE for that regimen, if one is offered.

If a regimen includes more than one active arm to allow for multiple dosing levels, then adaptive rules dictating the behavior of these arms can be included. This will be detailed in the RSA.

## 5 STUDY POPULATION

### 5.1 *Number of Research Participants*

Research participants that meet the Master Protocol inclusion and exclusion criteria listed below will be further screened and randomly assigned to a regimen.

The sample size enrolled in each regimen will be determined based on the specifics of the intervention, anticipated effect size, and number of treatment arms evaluated within that regimen.

### 5.2 *Master Protocol Inclusion and Exclusion Criteria*

#### 5.2.1 *Master Protocol Inclusion Criteria*

These are the inclusion criteria that research participants must meet to be eligible to enter the Master Protocol and are common for all regimens:

1. Sporadic or familial ALS diagnosed as clinically possible, probable, lab-supported probable, or definite ALS defined by revised El Escorial criteria (Appendix I).
2. Age 18 years or older.
3. Capable of providing informed consent and complying with study procedures, in the SI's opinion.
4. Time since onset of weakness due to ALS  $\leq$  36 months at the time of the Master Protocol Screening Visit.
5. Vital Capacity  $\geq$  50% of predicted capacity for age, height, and sex at the time of the Master Protocol Screening Visit measured by Slow Vital Capacity (SVC), or, if required due to pandemic-related restrictions, Forced Vital Capacity (FVC) measured in person or via telemedicine, or sustained phonation.
6. Participants must either not take riluzole or be on a stable dose of riluzole for  $\geq$  30 days prior to the Master Protocol Screening Visit. Riluzole-naïve participants are permitted in the study.
7. Participants must either not take edaravone or have completed at least one cycle of edaravone prior to the Master Protocol Screening Visit. Edaravone-naïve participants are permitted in the study.
8. Participants must have the ability to swallow pills and liquids at the time of the Master Protocol Screening Visit and, in the SI's opinion, have the ability to swallow for the duration of the study.
9. Geographically accessible to the site.

## 5.2.2 Master Protocol Exclusion Criteria

These following exclusion criteria are common for all regimens:

1. Clinically significant unstable medical condition (other than ALS) that would pose a risk to the participant, according to SI's judgment (e.g., cardiovascular instability, systemic infection, untreated thyroid dysfunction, or clinically significant laboratory abnormality or EKG changes).  
  
Lab abnormalities include, but are not limited to: Hemoglobin < 10 g/dL, White Blood Cells <  $3.0 \times 10^3/\text{mm}^3$ , Neutrophils, Absolute  $\leq 1000/\text{mm}^3$ , Eosinophils, Absolute  $\geq 500/\text{mm}^3$ , platelet count <  $150 \times 10^9/\text{L}$ , alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN), eGFR < 30 mL/min/1.73m<sup>2</sup>, thyroid-stimulating hormone (TSH) levels > 10 mIU/L or < 0.01 mIU/L.
2. Presence of unstable psychiatric disease, cognitive impairment, dementia or substance abuse that would impair ability of the participant to provide informed consent, in the SI's opinion.
3. Active cancer or history of cancer, except for the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin, cervical carcinoma in situ, prostatic carcinoma in situ, or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years.
4. Use of investigational treatments for ALS (off-label use or active participation in a clinical trial) within 5 half-lives (if known) or 30 days (whichever is longer) prior to the Master Protocol Screening Visit. (*Please refer to the Manual of Procedures (MOP) for current list of experimental therapies*)
5. Exposure at any time to any gene therapies under investigation for the treatment of ALS (off-label use or investigational).
6. If female, breastfeeding, known to be pregnant, planning to become pregnant during the study, or of child-bearing potential and unwilling to use effective contraception for the duration of the trial and for 3 months, or longer as specified in each RSA, after discontinuing study treatment.
7. If male of reproductive capacity, unwilling to use effective contraception for the duration of the trial and for 3 months, or longer as specified in each RSA, after discontinuing study treatment.
8. Anything that would place the participant at increased risk or preclude the participant's full compliance with or completion of the study, in the SI's opinion.
9. If a participant is being re-screened, the disqualifying condition has not been resolved, or the mandatory wash-out duration has not occurred.
10. For those participating in the optional CSF collection, contraindication to undergoing a lumbar puncture (LP) in the SI's opinion. Participants undergoing the LP must not be currently taking anticoagulation medications such as warfarin that would be a contraindication to LP; aspirin and non-steroidal anti-inflammatories are allowed.

If justified based on regimen's specific investigational product, additional inclusion or exclusion criteria (e.g., contraindications, laboratory parameters) will be listed in the RSA.

***Riluzole.*** Participants taking concomitant riluzole at study entry must be on a stable dose for 30 days prior to the Master Protocol Screening Visit and must intend to continue taking the same dosage throughout the study, unless the SI determines that riluzole should be discontinued or dose-adjusted for medical reasons.

***Edaravone.*** Participants taking concomitant edaravone at study entry must have completed at least one cycle of treatment prior to the Master Protocol Screening Visit and must intend to continue taking the same dosage throughout the study, unless the SI determines that edaravone should be discontinued or dose-adjusted for medical reasons.

***Date of ALS Symptom Onset.*** For the purposes of this study, the date of symptom onset will be defined as the date the participant first had symptoms of muscle weakness. To be eligible for this study, the date of symptom onset must be no greater than 36 months prior to the Master Protocol Screening Visit date.

## **6 PARTICIPANT SELECTION AND ENROLLMENT**

### ***6.1 Identifying Participants***

This study will be conducted at selected ALS centers in the US. Sites participating in this Master Protocol must be members of the Northeast ALS Consortium (NEALS). NEALS is a non-profit group of research institutions, each of which is a NEALS Member, who collaboratively conduct clinical research in ALS and other motor neuron diseases. Research participants will be recruited from these centers, after approval by the cIRB.

Information about all research participants enrolled into the trial will be recorded in the Electronic Data Capture (EDC) system. This information will include reasons for screening failure for participants not assigned to a regimen, as well as a log of all participants randomized within a regimen, irrespective of whether they have been treated with the intervention or not.

### ***6.2 Consenting Participants***

Written informed consent will be obtained from participants before any study procedures or assessments are done and after the study objectives and endpoints, methods, anticipated benefits, and potential hazards are explained. The willingness of the participant to participate in the study will be documented in writing on a consent form approved by the cIRB, which will be signed and dated by the participant. The SI will keep the original consent forms and a copy will be given to the participant. The participant will also be informed that they may refuse entry into the trial and are free to withdraw from the trial at any time without prejudice to future treatment.

Informed consent will be obtained by the site investigator or other licensed staff as outlined on the delegation of responsibility log who are trained on the study and listed on delegation logs as being authorized to obtain consent. The SI, or other licensed staff, will be involved in explaining the study and will play a role during the consent process, answering any questions in conjunction with the coordinator and ensuring that the process is carried out correctly. All participants will be offered the opportunity to discuss participation with a licensed physician Investigator and the participant's decision to accept or decline this opportunity will be documented in the research file. Site study staff performing consent must provide participants adequate information to allow for an informed decision about participation, facilitate the potential participant's understanding of the information, and provide ample time and opportunity to inquire about details of the trial. The SI, nor the site study staff, should coerce or unduly influence a potential participant to participate or to continue to participate in the study. Site study staff must continuously provide information as the clinical investigation progresses or as the participant or situation requires.



Informed consent will be conducted for the Master Protocol and subsequently for the applicable RSA to which that participant was assigned. Those participants who are not found eligible for the Master Protocol will not be consented for any RSA.

### **6.3 Ineligible Participants**

All sites will be required to collect demographic information including age, gender, race, and ethnicity, reasons for ineligibility for the Master Protocol for participants that have signed the Master Protocol consent form and are deemed ineligible for the Master Protocol.

Once assigned to a regimen, participant eligibility will be confirmed using regimen-specific inclusion and exclusion criteria, if any, during the Regimen-Specific Screening Visit. Reasons for ineligibility for the regimen must be documented.

### **6.4 Randomization**

#### *6.4.1 Randomization Procedures*

Randomization will be conducted using an interactive response technology (IRT) system. The randomization for the Master Protocol consists of a tiered randomization as described below and depicted in the Study Workflow.

1. Randomization equally to a regimen among all available regimens to which the participant has not previously been randomized.
2. Randomization to placebo or an active intervention in the assigned regimen, and randomization to the set of active sub-arms, if applicable.

In the first stage, after a participant is determined eligible according to the Master Protocol inclusion and exclusion criteria, a research participant will be randomized equally among all available regimens to which the participant has not previously been randomized. In the second stage, if a participant has been determined eligible for any inclusion and exclusion criteria specific to their assigned regimen, the research participant will be randomized 3:1 to the active intervention or the placebo for the regimen. If the regimen has multiple arms, a participant will also be randomized according to the allocation scheme for that regimen. The allocation scheme for regimens with multiple arms will be detailed in the respective RSA.

#### *6.4.2 Treatment Allocation*

Treatment group within a regimen will be assigned via the IRT system after a participant has been determined eligible for any inclusion and exclusion criteria specific to their assigned regimen.

### 6.4.3 *Blinding*

In this trial, investigational products may have a different mode (e.g., oral, subcutaneous) or frequency of administration and may be introduced at different time points. Each intervention arm will have its own concurrent, randomized placebo control arm.

Research participants, SIs, and everyone involved in the conduct of, final analysis of, or with any other interest in a given trial regimen will not be blinded to regimen assignments but will be blinded to the randomized treatment assignments within a regimen. The randomized treatment assigned for participants in that regimen will be kept secure and will only be accessed according to the Unblinded Personnel List and Procedures and the Emergency Unblinding Plan. In the event of a medical emergency that necessitates the unblinding of the Medical Monitor (MM) or an SI to safely provide care for a participant, emergency unblinding of that single participant may be undertaken as outlined below.

### 6.4.4 *Emergency Unblinding Plan*

Emergency unblinding for a research participant will only be undertaken when it is essential to treat the participant safely. It must only be used in an emergency when the identity of the treatment arm must be known to the SI to provide appropriate medical treatment or otherwise ensure the safety of research participants or others exposed to investigational products. In most cases, investigational product discontinuation and knowledge of the possible treatment assignments will be sufficient to treat a study participant who presents with an emergency condition. However, if unblinding is necessary, the blind may be broken only for that participant.

## 6.5 ***Discontinuation of Treatment and Terminations***

### 6.5.1 *Discontinuation of Investigational Product*

If the SI or designee is concerned about the use of a prohibited medication or other safety issues, then the investigational product may need to be discontinued.

If the investigational product for an RSA is administered orally, and a participant loses the ability to swallow the investigational product, the possibility of alternative modes of administration (e.g., via G-tube) will be detailed in the RSA.

A research participant may choose to discontinue the investigational product at any time for any reason. However, the SI or designee will encourage the research participant to follow the study protocol under the intent-to-treat principle (ITT). These research participants will be encouraged to follow the study visits, off treatment, up to the Week 24 visit, following the Schedule of Activities. At a minimum, collection of the ALSFRS-R, AEs, Concomitant Medications, CSSRS,

and other outcome measures should be encouraged. Loss to follow-up should be prevented whenever possible.

Upon discontinuation of investigational product, the research participant should return any unused product.

For all research participants, the reason for permanent discontinuation of investigational product must be recorded in the Case Report Form (CRF). These data will be included in the trial database and reported.

#### *6.5.2 Termination of Individual Research Participants*

An SI or designee may terminate a research participant if a medical condition or other situation occurs such that continued participation would not be in the best interest of the participant.

A research participant may withdraw consent for study participation. No justification is required for the decision.

Upon termination, the research participant should return any unused investigational product.

#### *6.5.3 Termination of the Master Protocol or a Regimen by the Investigational New Drug (IND) Holder/ Sponsor*

The IND-holder/Sponsor reserves the right to terminate the overall Master Protocol or any individual regimen at any time or during an interim analysis.

If there are regimen-specific criteria for terminating a regimen, they will be detailed in the RSA.

## 7 INVESTIGATIONAL PRODUCT AND PLACEBO

### 7.1 *Investigational Product*

Multiple investigational products (i.e., interventions, or active agents, from different regimen partners) will be tested in this Platform Trial.

Each investigational product will have an RSA in which the complete description of the tested product can be found. Each intervention may have multiple arms, such as different dosages or frequencies or routes of administration.

Each active agent will have a matching placebo. All regimens will be compliant with the Master Protocol, which outlines the majority of all clinical, biomarker, and safety assessments, making a shared placebo group both desirable and feasible.

#### 7.1.1 *Investigational Product Manufacturer*

Details identifying the investigational product manufacturer will be included in the corresponding RSA.

#### 7.1.2 *Labeling and Packaging*

Investigational product for each regimen will be provided by the regimen partner and will be described in the corresponding RSA. Packaging and labeling will follow Good Manufacturing Practices (GMP) regulations.

Samples of labels will be kept with the Trial Master Files (TMF).

The participants will be instructed to return all remaining investigational product including empty package material, if applicable, to the study site. Drug accountability will be performed as described in Section 7.2.

Details for packaging, labeling, and re-supply will be described in the corresponding RSA.

#### 7.1.3 *Acquisition and Storage*

Investigational product for all regimens will be received at the study site by designated study staff, handled and stored safely and properly at the site pharmacy or other designated location, and kept in a secure location to which only the trial pharmacist and designated pharmacy staff, SI, and clinical staff have access. Upon receipt, the investigational product will be stored according to the instructions specified on the labels. Storage conditions will be adequately

monitored and temperature in the area in which the investigational product is stored will be controlled, monitored and recorded, at a minimum daily.

In accordance with local regulatory requirements, the SI, designated site staff, or head of the medical institution (where applicable) at each site must document the amount of investigational product dispensed and/or administered to study participants, the amount received from the Central Pharmacy, and the amount destroyed upon completion of the study. An investigator is responsible for ensuring product accountability records are maintained throughout the course of the study. The research pharmacist or designated study staff will be responsible for maintaining an accurate record of the shipment and dispensing of investigational product in a drug accountability log.

Additional investigational product-specific details will be provided in the RSA.

#### *7.1.4 Destruction of Investigational Product*

Details on how the investigational product will be destroyed, who is responsible for the destruction, and how long documentation will be retained at sites, will be provided in the RSA.

#### *7.1.5 Investigator's Brochure*

An Investigator's Brochure will be provided for each regimen as a separate document to this protocol.

### **7.2 Dosage Changes**

Any changes in dosage, along with the circumstances surrounding those for such, will be described in the RSA.

### **7.3 Participant Compliance**

Compliance for each regimen will be defined in the RSA. In cases of non-compliance, the participant will be reminded of the importance of taking the investigational product per protocol.

### **7.4 Overdose**

Details on the actions to take in the event of an overdose will be included in the RSA.

### **7.5 Other Medications**

Throughout the study, participants may be prescribed concomitant medications deemed necessary to provide adequate care. Participants should not receive other investigational products during the study. This includes marketed agents at experimental dosages that are being tested for

the treatment of ALS. All concomitant medications and significant non-drug therapies, including supplements, received by a participant should be recorded on the appropriate source document and electronic Case Report Form (eCRF).

#### *7.5.1 Prohibited Medications*

Details on medications that may not be taken during the trial will be included in the RSA.

## 8 STUDY SCHEDULE

This section describes trial procedures that are common to all regimens tested in the ALS Platform Trial as detailed in the Master Protocol. Each regimen will follow these procedures and may add additional procedures as described in the corresponding RSA.

No study procedures should be performed prior to the signing of the Master Protocol ICF. All participants will sign the Master Protocol ICF prior to undergoing any study tests or procedures.

### Study Visit Recommendations:

1. Visit windows are consecutive calendar days and the target visit dates are calculated from the Baseline Visit – Day 0 (first day of investigational product administration).
2. Assessment of vital capacity should be performed at the start of a visit so as not to fatigue the participant with other testing.
3. The remaining clinical assessments should be administered in the same sequence as listed in the sections below and at approximately the same time of the day.
  - a. Any additional assessments that are included in an RSA for a given visit should be completed once the Master Protocol SOA for that visit is complete, unless otherwise specified in the RSA.
4. Outcomes for individual participants should be measured by the same evaluator throughout their participation in a regimen. Evaluators must be qualified, trained, and must fulfill certification criteria defined by the Sponsor. Training documentation must be filed in the Investigator Site File (ISF).
5. In-person visits may be conducted in-clinic, or by phone or telemedicine, or in-home.

If needed to protect the safety of the participant and study staff due to a pandemic, designated visits in the Schedule of Activities (i.e. Week 4, Week 8, and Week 16) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person. If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP. The following procedures should be completed in the suggested order and as per the Schedule of Activities: ALSFRS-R, home spirometry (Week 8 and 16 only), Voice Recording, AE Review, Columbia-Suicide Severity Scale, Concomitant Medications, CNS Bulbar Function Scale (Week 8 and 16 only), and IP Accountability/Compliance. Procedures for collecting IP Accountability/Compliance remotely are described in the MOPs. Additionally, selected vital signs and laboratory evaluations will be performed by a home health agency as described in the MOP. Vital signs include: systolic and diastolic pressure, respiratory rate, heart rate, and temperature. Laboratory evaluation includes hematology (CBC with differential), complete chemistry panel and thyroid function, and urinalysis. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy.

Vital Capacity: the default and preferred method for assessing Vital Capacity at Master Protocol Screening for eligibility is SVC performed by NEALS certified evaluators using a study-approved portable spirometer. If needed to protect the safety of the participants and/or site staff due to pandemic-related restrictions, vital capacity can be measured using one of the following methods to assess eligibility:

- SVC or FVC performed by Pulmonary Function Laboratory evaluator, or
- FVC measured with a study approved personal spirometer for home use, or
- Predicted Vital Capacity estimated by measuring sustained phonation, using a dedicated program for this purpose

When real time coaching is provided to participants, remote vital capacity closely matches values obtained in clinic with the test performed with a NEALS certified evaluator<sup>23</sup>.

At all subsequent visits to Master Protocol Screening, if SVC cannot be obtained due to pandemic-related risks, this outcome measure should be skipped and recorded as such in the applicable source documentation and EDC.

### ***8.1 Master Protocol Screening Visit***

The following procedures will be performed in-person to determine the participant's eligibility for the Master Protocol and are listed in order to be completed:

Obtain written Master Protocol informed consent from participant

Assess Master Protocol inclusion and exclusion criteria

Obtain ALS and medical history

Obtain demographics

Perform physical examination

Perform neurological examination

Measure vital signs including height and weight

Perform Vital Capacity\*

Administer ALSFRS-R questionnaire

Perform 12-lead electrocardiogram (ECG)

Collect blood samples for clinical screening assessments and, for women of child bearing potential (WOCBP), for pregnancy test

Collect urine sample for urinalysis

Review and document concomitant medications

Schedule the Regimen Specific Screening Visit if the participant passes screening for the Master Protocol

\* As noted above, vital capacity to assess eligibility can be performed by different methods. The default and preferred method is SVC performed by NEALS certified evaluators using a study-



approved portable spirometer. If due to pandemic-related restrictions the default method is not available, SVC or FVC can be performed by a Pulmonary Function Laboratory evaluator. If neither of these options are available, one of the following methods can be used to assess vital capacity during this visit:

- *Home Spirometry*

A home spirometer and instructions for use will be provided to the participant. The participant will perform the VC maneuver with realtime video coaching by the evaluator. Three to five VC maneuvers will be performed, consistent with the manner VC is obtained in clinic. The highest VC value will be used to assess eligibility.

- *Sustained Phonation*

Changes in quantitative voice characteristics will be measured utilizing Aural Analytics speech vitals application on a tablet provided to sites. The study coordinator will guide the participant through the speech task. The speech task includes the participant speaking and recording as prompted by the app: holding the “ah” sound for as long as possible. Sustained phonation was found to correlate with vital capacity in a study of 26 patients with ALS ( $r = 0.82$ ) (Shefner JM, Hahn S, Berisha V, Liss J, unpublished).

### *8.1.1 Regimen Assignment and Within-regimen Randomization*

If the participant meets all Master Protocol eligibility criteria, the participant will be randomly assigned to a regimen and will undergo informed consent for that regimen at their scheduled Regimen-Specific Screening Visit. The participant will then be randomized in a 3:1 ratio to active treatment or matching placebo for that regimen. If the intervention has multiple arms (for example, multiple dosages), a research participant will also be randomized according to the allocation scheme specific for that regimen.

### *8.1.2 Screen Failures and Re-Assignment*

Any participant who signs the Master Protocol consent form will be considered enrolled in the Platform Trial. If a participant fails the Master Protocol screening, *at a minimum* the following information should be captured and entered into the EDC system:

- Demographics (including any prior screening identifiers)
- Reason for screen failure
- Any eligibility criteria that were assessed prior to when the research participant failed to meet an inclusion criterion or met an exclusion criterion.

If a research participant fails to meet a Master Protocol eligibility criterion (e.g., duration of stable medication prior to enrollment, interval following last use of an investigational treatment, or other criteria as applicable), then that participant will be considered to have screen failed, and

may be re-screened for Master Protocol eligibility immediately after resolution of the disqualifying condition. If a participant is re-screened for Master Protocol eligibility, she or he must complete a full Master Protocol Screening Visit as outlined in section 8.1.

If a research participant meets Master Protocol eligibility, is assigned to a specific regimen, but does not meet additional regimen-specific inclusion and exclusion criteria for that regimen, then the research participant may be re-assigned immediately to a different regimen, provided that the participant meets additional regimen-specific inclusion and exclusion criteria, as applicable.

If a research participant meets Master Protocol eligibility, is assigned to a regimen, and is randomized within that regimen, but their participation in that regimen is discontinued, that participant may have the opportunity to be re-screened for the Master Protocol. The research participant must provide written informed re-consent to the Master Protocol and must still meet the Master Protocol inclusion and exclusion eligibility criteria in order to be re-assigned into a different regimen. Re-screening for the Master Protocol and potential re-assignment into a different regimen, if available, may occur due to the following situations:

- A regimen is stopped due to futility or success
  - The research participant may be re-screened after 30 days or 5 half-lives (if known), whichever is longer
- A research participant completes a regimen and declines participation in OLE, if available for that regimen
  - The research participant may be re-screened after 30 days or 5 half-lives (if known), whichever is longer
- A research participant discontinues participation in a regimen for personal reasons (e.g., inconvenience of the intervention, mode of administration, required assessments) or due to an adverse event, or is discontinued by the SI
  - The research participant may not be re-screened until after the date that their 24-Week Visit would have occurred, had they completed participation in that regimen.

## **8.2 Regimen Specific Screening Visit**

This visit will take place in-person after random assignment to a regimen. This visit may be combined with the Baseline Visit, please refer to the RSA for applicability. The following procedures will be performed and are listed in order to be completed:

Obtain written regimen-specific informed consent from participant  
Assess regimen-specific inclusion and exclusion criteria  
Concomitant medication review  
Assess and document AEs

### **8.3 Baseline Visit**

This visit will take place in-person after the regimen-specific Screening Visit. This visit may be combined with the Regimen Specific Screening Visit, please refer to the RSA for applicability. The following procedures will be performed and are listed in the order to be completed:

- Randomize within the regimen
- Collect vital signs
- Perform SVC
- Perform muscle strength testing
- Administer ALSFRS-R questionnaire
- Administer Patient Reported Outcomes Collect blood samples for Clinical Safety Labs, biomarkers, and optional DNA sequencing
- Collect urine sample for biomarkers
- Perform LP for CSF collection (optional)
- Review and document concomitant medications
- Assess and document AEs
- Administer the C-SSRS Baseline questionnaire
- Administer first dose of investigational product for the regimen, per the instructions in the RSA.
- Dispense investigational product to participant, per instructions in the RSA

### **8.4 Week 2 Telephone Visit**

This visit will take place  $14 \pm 3$  days after the Baseline Visit via telephone. The following procedures will be performed and documented and are listed in the order to be completed:

- Assess and document AEs
- Perform investigational product compliance
- Remind participant to bring in investigational product to the Week 4 Visit

### **8.5 Week 4 Visit**

This visit will take place in-person  $28 \pm 7$  days after the Baseline Visit. The following procedures will be performed and are listed in the order to be completed:

- Collect vital signs
- Administer ALSFRS-R questionnaire
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review and document concomitant medications
- Assess and document AEs
- Administer the C-SSRS Since Last Visit questionnaire
- Collect blood for optional DNA sequencing (if not done at Baseline)

Perform investigational product accountability and compliance  
Schedule next Study Visit  
Remind participant to bring in investigational product to the Week 8 Visit

### **8.6 Week 8 Visit**

This visit will take place in-person  $56 \pm 7$  days after the Baseline Visit. The following procedures will be performed and are listed in the order to be completed:

Collect vital signs including weight  
Perform SVC  
Perform muscle strength testing  
Administer ALSFRS-R questionnaire  
Ask participant to complete Patient Reported Outcomes  
Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable  
Collect urine sample biomarker analyses  
Collect blood sample for biomarker analyses  
Collect blood for optional DNA sequencing (if not done previously)  
Review and document concomitant medications  
Assess and document AEs  
Administer the C-SSRS Since Last Visit questionnaire  
Perform investigational product accountability and compliance

### **8.7 Week 12 Telephone Visit**

This visit will take place  $84 \pm 3$  days after the Baseline Visit via telephone. The following procedures will be performed and are listed in the order to be completed:

Administer ALSFRS-R questionnaire  
Review and document concomitant medications  
Assess and document AEs  
Perform investigational product compliance  
Schedule next Study Visit  
Remind participant to bring in investigational product to the Week 16 Visit

### **8.8 Week 16 Visit**

This visit will take place in-person  $112 \pm 7$  days after the Baseline Visit. The following procedures will be performed and are listed in the order to be completed:

Collect vital signs including weight

Perform SVC  
Perform muscle strength testing  
Administer ALSFRS-R questionnaire  
Ask participant to complete Patient Reported Outcomes  
Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable  
Collect urine sample biomarker analyses  
Collect blood sample for biomarker analyses  
Collect blood for optional DNA sequencing (if not done previously)  
Review and document concomitant medications  
Assess and document AEs  
Administer the C-SSRS Since Last Visit questionnaire  
Perform LP for CSF collection (optional)  
Perform investigational product accountability and compliance

### **8.9 Week 20 Telephone Visit**

This visit will take place  $140 \pm 3$  days after the Baseline Visit via telephone. The following procedures will be performed and are listed in order to be completed:

Administer ALSFRS-R questionnaire  
Review and document concomitant medications  
Assess and document AEs  
Perform investigational product compliance  
Schedule next Study Visit

### **8.10 Week 24 Visit**

This visit will take place in-person  $168 \pm 7$  days after the Baseline Visit. The following procedures will be performed and are listed in order to be completed:

Collect vital signs including weight  
Perform SVC  
Perform muscle strength testing  
Administer ALSFRS-R questionnaire  
Ask participant to complete Patient Reported Outcomes  
Perform 12-lead electrocardiogram (ECG)  
Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable  
Collect urine sample biomarker analyses  
Collect blood sample for biomarker analyses  
Collect blood for optional DNA sequencing (if not done previously)  
Review and document concomitant medications,

Assess and document AEs  
Administer the C-SSRS Since Last Visit questionnaire  
Perform investigational product accountability and compliance  
Ask participant to complete the Exit Questionnaire

### ***8.11 Follow-Up Safety Call***

Participants will have a Follow-Up Safety after their last dose of study drug. Additional details, including the timing of this call, can be found in the RSA. The following procedure will be performed at a minimum:

- Assess and document AEs
- Review and document concomitant medications

### ***8.12 Early Termination Visit & Follow-up Safety Call for Early Terminations***

Participants who withdraw consent or early terminate from the study will be asked to be seen for an in-person Early Termination Visit and complete a Follow-Up Safety Call.

The outcome measures that are required to be collected for each regimen, and the timing of and activities for the Early Termination Visit and Follow-Up Safety Call, will be detailed in the RSA.

### ***8.13 Protocol Deviations***

A protocol deviation is any noncompliance with the cIRB approved clinical trial protocol. The noncompliance may be either on the part of the participant, the SI, or the study site staff. Patient reported outcomes (e.g. ALSAQ-40 and CNS-BFS) not performed due a participant language barrier including procedures that were attempted but failed will not be reported as protocol deviations. A minor protocol deviation will be considered a departure from the protocol of relatively minor degree (such as study visit a day or two out of window due to participant being sick). A major deviation will be considered any significant deviation from the protocol that could affect significantly the conduct of the study, compromise efficacy assessments or create a safety risk for the participant. As a result of deviations, corrective actions are to be developed by the site with review by the CC and Study Monitors and implemented promptly.

All deviations from the protocol must be addressed in the participant's source documentation. Protocol deviations must be entered in the Protocol Deviations Log in the EDC system. All deviations will be reported to the cIRB per their guidelines.

### ***8.14 Missed Visits and Procedures***

Missed visits and any procedures not performed (not attempted) for reasons other than illness, injury or progressive disability (i.e., participant is physically unable to perform test) will be reported as protocol deviations.

Procedures or visits not performed due to illness, injury or disability, including procedures that were attempted but failed (e.g., blood samples unable to be drawn after multiple attempts, or weight unable to be obtained due to participant immobility) will not be reported as protocol deviations.

Investigational product compliance that is outside the limits set in the RSA will be reported as a protocol deviation (see RSA for further details).

Details and specific instructions regarding protocol deviations, including any exceptions to this standard procedure, are found in the study Manual of Procedures.

Missed assessments due to pandemic-related restrictions must be documented as such in the source documentation and in the EDC.

### ***8.15 Recording Deaths and Vital Status Determination***

Information on whether a participant has died may be obtained from the participant's family, from clinic notes, or from a publicly available data source like the Centers for Disease Control and Prevention (CDC) National Death Index or the Social Security Death Index. The vital status determination, defined as a determination of date of death or death equivalent or date last known alive, will be determined for each randomized participant at the end of the placebo-controlled portion of his or her follow-up (generally the Week 24 visit). If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant's last visit (LPLV) of the placebo-controlled portion of a given regimen. We may also ascertain vital status at later time points by using publicly available data sources.

## 9 CLINICAL ASSESSMENTS AND OUTCOME MEASURES

### 9.1 *Clinical Variables*

Assessments will be performed at designated time-points throughout the study for clinical evaluation. In addition to the assessments evaluated below, participants will provide information on their demographics, past medical history, including ALS, as well as concomitant medication usage.

Details of any additional specific clinical assessments required for a regimen will be reported in the corresponding RSA.

#### 9.1.1 *Vital Signs and Anthropometrics*

Vital signs include weight in kg or lbs, systolic and diastolic blood pressure in mmHg, pulse rate (radial artery)/minute, respiratory rate/minute, and temperature in °C or °F. **Height in cm or in will be measured and recorded at the Master Protocol Screening Visit (Visit 1) only.** This one-time height measurement must be used throughout the duration of the study.

#### 9.1.2 *Clinical Safety Laboratory Tests*

The following laboratory tests will be performed for safety at the Master Protocol Screening to determine eligibility and at the following visits: Screening, Week 4, Week 8, Week 16, and Week 24/ET

- Hematology with differential panel: complete blood count with differential (hematocrit, hemoglobin, platelet count, RBC indices, Total RBC, Total WBC, and WBC & differential)
- Blood chemistry panel/Liver function tests (LFTs): alanine aminotransferase (ALT (SGPT)), aspartate aminotransferase (AST (SGOT)), albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine (estimated Glomerular Filtration Rate [eGFR] will be calculated using the MDRD equation and creatinine clearance will be calculated using the Cockcroft-Gault equation), glucose, magnesium, phosphate, potassium, sodium, thyroid-stimulating hormone (TSH), total bilirubin and total protein
- Urinalysis: albumin, bilirubin, blood, clarity, color, glucose, ketones, nitrate, pH, protein, specific gravity, urobilinogen and WBC screen
- Serum human chorionic gonadotrophin (hCG) for WOCBP (collected only at Master Protocol Screening Visit, and as necessary throughout course of study)



All participants will have clinical safety laboratory tests at the designated visits outlined in the schedule of activities. All laboratory samples will be analyzed at a central laboratory. The SI may order additional local testing, if needed, to further assess an AE, or if there is any suspicion that a participant may be pregnant, throughout the course of the study.

### *9.1.3 12-Lead ECG*

A standard 12-lead ECG will be performed for safety at the screening visit to determine eligibility and for safety as outlined in the schedule of activities. Tracings will be reviewed by a central ECG reader and a copy of the tracings will be kept on site as part of the source documents.

### *9.1.4 Physical Examination*

A physical examination will be performed and recorded. The following systems will be examined: head/neck, eyes, ears, nose and throat, cardiovascular, lungs, abdomen, musculoskeletal, central nervous system, extremities, and skin.

### *9.1.5 Neurological Examination*

A neurological examination will be performed and recorded. Examination will include assessment of mental status, motor and sensory function, reflexes, and coordination/cerebellar function.

### *9.1.6 Columbia-Suicide Severity Rating Scale*

The US FDA recommends the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The C-CASA was developed to assist the FDA in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. One such assessment instrument is the C-SSRS. The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior.

At the Baseline Visit, the C-SSRS Baseline version will be administered. This version is used to assess suicidality over the participant's lifetime.

At all other visits, the Since Last Visit version of the C-SSRS will be administered. This version of the scale assesses suicidality since the participant's last visit.

If there is a positive response to question 4 or 5 on the severity of ideation subscale or any positive response on the suicidal behavior subscale of suicide attempt or suicidal ideation by the participant during the administration of the C-SSRS during the treatment period, the appropriately qualified clinician will be notified during the study visit to determine the appropriate actions required to ensure the participant's safety. The site must ensure that the

participant is seen by a licensed physician (or other qualified individual as required by local institutional policy) before leaving the study site. The SI will determine whether the participant should remain on study drug. Reference to the Clinical Triage Guidelines Using the C-SSRS can be found here [https://cssrs.columbia.edu/wp-content/uploads/C-SSRS\\_Triage\\_example\\_guidelines.pdf](https://cssrs.columbia.edu/wp-content/uploads/C-SSRS_Triage_example_guidelines.pdf).

It is recommended that a medically licensed physician, nurse, nurse practitioner, or physician assistant to assess the C-SSRS. All evaluators must be certified to perform the C-SSRS; specific certification requirements are outlined in the study operations manual. Certification is required prior to performing the C-SSRS.

## **9.2 Endpoints**

Details of any additional specific endpoints required for a regimen will be described in the corresponding RSA.

### *9.2.1 ALS Functional Rating Scale - Revised*

The ALSFRS-R is a quickly administered (5 minutes) ordinal rating scale used to determine participants' assessment of their capability and independence in 12 functional activities. Each functional activity is rated 0-4 for a total score that ranges from 0 to 48. Higher scores indicate better function. Initial validity in ALS patients was established by documenting that, change in ALSFRS-R scores correlated with change in strength over time, was closely associated with quality of life measures, and predicted survival. The test-retest reliability is greater than 0.88 for all test items. The advantages of the ALSFRS-R are that all 12 functional activities are relevant to ALS, it is a sensitive and reliable tool for assessing activities of daily living function in those with ALS, and it is quickly administered. With appropriate training the ALSFRS-R can be administered with high inter-rater reliability and test-retest reliability. The ALSFRS-R can be administered by phone with good inter-rater and test-retest reliability. The equivalency of phone versus in-person testing, and the equivalency of study participant versus caregiver responses have also been established. Additionally, the ALSFRS-R can also be obtained using a web-based interface with good concordance with in-person assessment. All ALSFRS-R evaluators must be NEALS certified.

### *9.2.2 Slow Vital Capacity*

The vital capacity (VC) will be determined using the upright slow VC (SVC) method. All evaluators performing SVC, must be NEALS certified. The SVC will be measured using the study-approved portable spirometer, and assessments will be performed using a face mask. A

printout from the spirometer of all VC trials will be retained. Three VC trials are required for each testing session, however up to 5 trials may be performed if the variability between the highest and second highest VC is 10% or greater for the first 3 trials. Only the 3 best trials are recorded on the CRF. The highest VC recorded is utilized for eligibility. At least 3 measurable VC trials must be completed to score VC for all visits after screening. Predicted VC values and percent-predicted VC values will be calculated using the Quanjer Global Lung Initiative equations.

### ***9.2.3 Measures of Muscle Strength***

Hand Held Dynamometry: HHD will be used as a quantitative measure of muscle strength for this study. Six proximal muscle groups will be examined bilaterally in both upper and lower extremities (shoulder flexion, elbow flexion, elbow extension, hip flexion, knee flexion, and knee extension), all of which have been validated against maximum voluntary isometric contraction (MVIC) testing<sup>19</sup>. In addition, wrist extension, abductor pollicis brevis, abductor digiti minimi, first dorsal interosseous contraction and ankle dorsiflexion will be measured bilaterally; these muscles are often affected in ALS.

Bilateral Hand Grip: Bilateral hand grip will be measured using a Jamar hand dynamometer to test the maximum isometric strength of the hand and forearm muscles, measured in pounds.

### ***9.2.4 Training and Validation***

All evaluators must be NEALS trained and certified to perform the ALSFRS-R, SVC, and HHD assessments; specific certification requirements are outlined in the MOP. Certification and training will be provided by the Barrow Outcome Center. Certification occurs via a formal evaluation of reliability and accuracy of performance of these measures. Repeat certification will be required on an annual basis for all outcome measures. It is strongly preferred that a single evaluator performs all measures throughout the study, as much as possible.

### ***9.2.5 Patient Reported Outcomes***

Patient reported outcomes will be assessed in this trial and will be defined in the RSA.

## ***9.3 Biofluid Collection***

All samples will be labeled with a code. The code will not include any identifiable information but will be linked to a specific participant, visit, and sample by data entry of the code into the EDC. There is no scheduled date on which the samples will be destroyed. Samples may be stored for research until they are used, damaged, decayed or otherwise unfit for analysis. Participants have the option of declining participation in this portion of the study at any time by withdrawing their consent to have their sample used. However, it will not be possible to destroy samples that may have already been used.

Specific instructions regarding the collection, processing, storage, and shipment of these samples will be provided in the Study MOP.

Details of any additional specific biofluid samples required for a regimen will be described in the corresponding RSA.

### *9.3.1 DNA Collection*

All participants will provide a blood sample for deoxyribonucleic acid (DNA) extraction for genome sequencing during one of the five in-person study visits, preferably at the Baseline Visit. The DNA sample can be collected after the Baseline Visit if a baseline sample is not obtained for any reason or the sample is not usable.

### *9.3.2 Blood Biomarker Sample Collection*

All participants will provide blood samples for biomarker assessments.

### *9.3.3 Urine Collection*

Urine samples will be collected at Baseline, Week 8, Week 16 and Week 24 study visits. Up to 10mL of urine may be collected.

### *9.3.4 Lumbar Puncture*

The lumbar puncture is optional.

For subjects consenting to a LP, it will be performed to collect CSF at the Baseline and Week 16 Visits. If the CSF collection cannot happen at the Week 16 Visit for logistical reasons such as scheduling, it can happen at the Week 24 Visit. Study staff should document the time of study drug dose administered. The SI will discuss all potential LP risks to the subjects including:

- Local pain at injection site
- Reaction to anesthetic agents
- Bleeding at needle entrance site
- Infection at needle entrance site
- Post-LP low-pressure headache

Extensive experience with research LP in Alzheimer's disease reveals a very low incidence of complication, including the incidence of post-LP headache (Zetterberg et al., 2010). Fewer than 2.6% of patients in a memory disorder clinic developed post-LP headache, and only a single patient in a cohort of over 1,000 had a headache lasting more than 5 days (Zetterberg et al., 2010). No other local or generalized complications occurred.

The procedure must be performed by the SI or another licensed practitioner with experience and training in performing LPs, and must be listed on the site delegation log. When possible, LPs should be performed with an atraumatic Sprotte needle to reduce the risk of post-LP headache.

## 10 SAFETY AND ADVERSE EVENTS

The AE definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and ICH guidelines. The SI will carefully monitor each participant throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is also important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

### ***10.1 Definitions of AEs, Suspected Adverse Drug Reactions & SAEs***

#### *10.1.1 Adverse Event and Suspected Adverse Drug Reactions*

An AE is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (e.g., skin rash, peripheral edema, etc.), or clinically significant abnormal test results (e.g., lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (e.g., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

1. Clinical: symptoms reported by the participant or signs detected on examination.
2. Ancillary Tests: abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures, the results of which are not being captured as AEs).

For the purposes of this study, symptoms of progression/worsening of ALS, including ‘normal’ progression, will be recorded as adverse events.

The following measures of disease progression will not be recorded as adverse events even if they worsen (they are being recorded and analyzed separately): SVC results, ALSFRS-R results, and muscle strength results.

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the SI and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the SI to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the SI.

Participants will be monitored for adverse events from the time they sign consent for the Master Protocol until completion of their participation as defined in the RSA.

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current regimen applicable Investigator’s Brochure. An unexpected, suspected adverse drug reaction is any unexpected adverse event that for which, in the opinion of the SI or Sponsor, there is a reasonable possibility that the investigational product caused the event.

#### *10.1.2 Serious Adverse Events*

A SAE is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
  - a. This serious criterion applies if the study participant, in the view of the SI or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE that might hypothetically have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
  - a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled “procedure” or a “treatment” is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
  - a. This criterion applies if the “disability” caused by the reported AE results in a substantial disruption of the participant’s ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the participant (whether the participant is male or female).

6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience, and will therefore, not be considered an SAE. An example of this would include a social admission (participant admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the SI or Sponsor, there is a reasonable possibility that the investigational product caused the event.

The SI is responsible for classifying adverse events as serious or non-serious.

## ***10.2 Assessment and Recording of Adverse Events***

The SI will carefully monitor each participant throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. All AEs will be collected and reported in the EDC system and compiled into reports for monthly reviewing by the MM for the Master Protocol. The Master Protocol MM shall promptly review all information relevant to the safety of the investigational product, including all SAEs. Special attention will be paid to those that result in permanent discontinuation of the investigational product(s) being studied, whether serious or non-serious.

### *10.2.1 Assessment of Adverse Events*

At each visit (including telephone interviews), the participant will be asked if they have had any problems or symptoms since their last visit in order to determine the occurrence of adverse events. If the participant reports an adverse event, site staff will probe further to determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease



6. Action taken regarding investigational product
7. Outcome

### *Severity of Event*

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

### *10.2.2 Relatedness of Adverse Event to Investigational Product*

The relationship of the AE to the investigational product should be specified by the SI based on temporal relationship and his/her clinical judgment, using the following definitions:

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

### *10.2.3 Recording of Adverse Events*

All clinical Adverse Events and Key Study Events (e.g., Mortality, Pregnancy, PAV, and Tracheostomy) are recorded in the participant’s study binder. The site should enter the AE and Key Study Event information into the EDC system as soon as possible after learning of the event or receiving an update on an existing event.

Entries on the AE Log (and into the EDC system) will include the following: description of the event, severity, seriousness, date of onset, date of resolution, relationship to investigational product, action taken, and primary outcome of event.

### ***10.3 Adverse Events and Serious Adverse Events - Reportable Events***

The following are considered reportable events and must be reported to the CC within 24 hours of the site being notified of the event: all events that meet the above criteria for SAEs.

The timelines for reporting dosage changes are described in each RSA as applicable.

The MM also reviews AE reports, compiled by Data Management, as described in the safety monitoring plan. The MM will review blinded study data on enrollment, abnormal laboratory results and protocol deviations. These reports will collectively be known as the Medical Monitor Report.

The MM communicates with the IND Holder / Sponsor, the DSMB, and the CC as needed for reporting of SAEs to the FDA within the required timeframe per FDA investigational new drug application (IND) regulations.

All AEs that meet the criteria for a serious, unexpected, suspected adverse drug reaction (SUSAR), for which there is a reasonable possibility that the investigational product caused the event, in the opinion of the IND Holder / Sponsor, will be submitted to FDA in an expedited fashion.

Death, respiratory failure and hospitalization for routine procedures (i.e., g-tube placement) will not be reported individually in an expedited manner because they are anticipated to occur in the study population at some frequency independent of drug exposure. The DSMB will review aggregate analysis of these events and the sponsor will submit an IND safety report if the aggregate analysis indicates these events occur more frequently in any of the active drug treatment groups, as compared to the concurrent placebo group.

## 11 STATISTICAL CONSIDERATIONS

The statistical considerations specified here describe the overall structure and statistical design of the platform trial and propose recommended statistical details for evaluating individual regimens. Additional details regarding the master protocol recommended design are specified in Appendix I. Regimen-specific deviations from the Master Protocol recommended design are allowed and full statistical details are provided in separate RSAs specific to each regimen. In the case of any deviation between this protocol, Appendix I or the RSAs on matters related to analysis, the order of reference will be first the RSAs, followed by Appendix I, and lastly this protocol.

Interim analyses will be performed by a distinct team of unblinded statisticians. All other analyses will be performed either on blinded data or after database lock for a given regimen.

### *11.1 Statistical Design Overview*

The primary aim of the trial is to compare the effectiveness of novel/emerging therapies to placebo for participants with ALS. The master protocol will include multiple regimens where a regimen is defined as both an active treatment and the corresponding randomized placebo.

The recommended primary efficacy endpoint is the change in the ALSFRS-R assessment, as measured from baseline through 24 weeks, every 4 weeks. The primary analysis is a Bayesian repeated measures model that compares each regimen-specific active treatment to a shared placebo group that is common across all regimens, as specified in Section 2.2 of Appendix I (ALS Master Protocol Recommended Design and Simulation Report Index)

Participants in the master protocol will be randomized in two stages; first to one of the actively enrolling regimens for which the participant meets the RSA requirements; and then 3:1 to active treatment or placebo within the regimen. The master protocol recommended design enrolls a maximum of 160 participants in each regimen.

New regimens are launched and added in parallel to existing regimens already being investigated in the platform. Regimens exit the platform either after completing all planned accrual and follow-up or by meeting criteria for success (if applicable) or futility at pre-defined interim analyses. The criteria are defined in Appendix I.

Interim analyses will be conducted on active regimens that have sufficient data, defined as having at least 40 randomized participants within that regimen who have had the opportunity to complete at least 24 weeks of follow-up. Interim analyses will occur globally across the platform every three months. If a regimen is not stopped early, then the regimen-specific final

analysis will take place when all its randomized participants have had the opportunity to complete follow-up.

## ***11.2 Analysis Plan***

### *11.2.1 Primary Analysis Population and Shared Control*

The primary analysis dataset uses all available longitudinal data (ALSFERS-R total score assessments at 0, 4, 8, 12, 16, 20 and 24 weeks) as well as mortality within 24 weeks on participants within the primary analysis population.

The primary analysis population for each analysis regimen is based on the intent to treat (ITT) principle and includes all participants randomized to the active treatment arm within the analysis regimen, and all participants in a shared control group. The shared control group includes all participants concurrently randomized to the control arm within the analysis regimen, participants randomized to the control arm across other actively enrolling regimens (concurrent shared controls) and previously completed regimens (non-concurrent shared controls) within the master protocol. Concurrent shared controls are defined as participants randomized to placebo control who were randomized within a 6-month window of the start and stop of randomization of the analysis regimen.

The master protocol allows for additional and more restrictive inclusion/exclusion criteria within a regimen specific appendix (RSA). However, these additional inclusion/exclusion criteria will be limited and will be allowed only for safety or mechanism of action. Major additional RSA inclusion/exclusion criteria that can be assessed for all participants entering the platform will be used to subset the shared control to include only shared control participants that meet these additional assessed RSA inclusion/exclusion criteria. Major additional RSA inclusion/exclusion criteria that will be used to subset the shared control will be limited to those criteria that have the potential to lead to significant differences in the patient population in terms of the rate of disease progression within the primary analysis population and will be pre-specified within each RSA.

### *11.2.2 Primary Efficacy Analysis*

Unless otherwise specified in the RSA, the primary analysis for each analysis regimen is a Bayesian repeated measures model of ALSFRS-R total score that accounts for loss of follow-up due to mortality. The repeated measures ALSFRS-R model measures the slowing in the rate of progression for ALSFRS-R in treated participants relative to control and uses all available longitudinal data for all participants within the primary analysis population. To account for loss of follow-up due to mortality, an exponential proportional hazards mortality component is included within the primary analysis model with a shared treatment effect parameter that is

common to the treatment effect within the repeated measures model of ALSFRS-R. The shared treatment effect between the ALSFRS-R and mortality components allows the participants who were loss to follow-up due to mortality to inform treatment effect estimates beyond their censored ALSFRS-R longitudinal data. The degree to which treatment effects on mortality inform the shared treatment effect parameter depends on the mortality rate within the study.

The ALSFRS-R repeated measures model is based on a linear rate of progression in ALSFRS-R for placebo participants and a proportional slowing in the rate of progression for treated participants at each time point. The treatment effect is quantified by the disease rate ratio (DDR), which represents the relative change to the rate of decline of ALSFRS-R of treated participant relative to a placebo participant (i.e. a proportional slowing). The model incorporates participant-level random effects in the baseline value of the ALSFRS-R (intercept) and in the rate of progression (slope); covariate effects to account for covariate-explainable differences in rates of progression based on participant-specific baseline covariates; and regimen-specific random effects in the rate of progression (slope). Regimen-specific random effects are used to account for potential differences in the shared control group not explained by the included covariates. Full specification of the primary efficacy analysis is described in Appendix I.

### *11.2.3 Handling of Missing Data*

The Bayesian repeated measures model of ALSFRS-R naturally accommodates differential length of follow-up and utilizes all available longitudinal data for each participant. The model also accommodates missing data due to death (via included mortality component), as well as missing data at random (i.e. due to reasons unrelated to disease progression). No imputation is planned for the primary efficacy analysis. However, planned sensitivity analyses will investigate the impact of missing data on the primary analysis results.

### *11.2.4 Handling of Re-Screened and Repeat Participants*

Upon completion of a regimen, a research participant may be re-screened into the master protocol and assigned to another regimen after 30 days or 5 half-lives (if known), whichever is longer. Those participants who have been re-screened and meeting inclusion/exclusion criteria at each subsequent randomization will be denoted as repeat participants with a new baseline visit and set of observations for each regimen to which they were assigned. The baseline visit for each regimen is defined as the visit after assigned to that regimen. Within the primary analysis, sets of observations from a repeat participant across multiple regimens will be treated as independent conditional on baseline covariates within each regimen. After the required washout period and adjusting for progression during previous regimens in the primary analysis (pre-baseline ALSFRS-R slope), it is not expected that future ALSFRS-R progression will be associated with prior treatment or placebo received in the previous regimen.

### *11.2.5 Inclusion of Multiple Doses*

If an RSA includes multiple doses under investigation, the primary analysis will be a pooled analysis of all active doses compared to the shared control. Additionally, secondary analyses will be specified within the RSA to investigate each active dose separately.

## ***11.3 Interim Analyses and Trial Adaptations***

Multiple interim analyses will allow each regimen to stop randomization early for success (if applicable) or futility, with interims occurring simultaneously for all actively enrolling regimens with sufficient data. Interims will begin when at least one regimen within the master protocol has 40 randomized participants (30 active and 10 control) with the opportunity to complete at least 24 weeks of follow-up. Subsequent interims will occur every 3 months. If a regimen has not stopped early for success or futility at an interim analysis, the regimen-specific final analysis will take place when all participants randomized to that regimen (120 active and 40 control) have had the opportunity to complete follow-up.

### *11.3.1 Regimen Success*

Success may be declared for a regimen at an interim analysis (if applicable) or at the final analysis if the posterior probability that the treatment is superior to placebo group is greater than an interim-specific success threshold (ISST). Interim-specific success thresholds for the posterior probabilities of superiority will be based on an Haybittle-Peto boundary with an overall one-sided Type I error of 2.5% per regimen.

### *11.3.2 Regimen Futility*

Futility will be declared for a regimen at an interim analysis if the posterior probability that the treatment slows disease progression by at least 10% is less than 5%.

## ***11.4 Secondary, Exploratory, and Sensitivity Analyses***

### *11.4.1 Secondary Efficacy Analyses*

As a secondary analysis, a joint rank test of mortality and ALSFRS-R will be performed. The analysis will rank all participants based first on survival time within 24 weeks and second, if they survived, on the change in ALSFRS-R total score from 0 to 24-weeks<sup>20-22</sup>. An ANCOVA will be performed on the ranks to adjust for important covariates.

### *11.4.2 Secondary Endpoints*

Secondary endpoints and analyses will be detailed within each RSA.

### *11.4.3 Exploratory Analyses*

Exploratory endpoints and the corresponding analyses are described in an Endpoint Evaluation Appendix. Such analyses will evaluate alternative functional endpoints and biofluid biomarkers for monitoring disease progression and as potential surrogates for long-term survival (assessed at the conclusion of each regimen).

### *11.4.4 Sensitivity Analyses*

Additional sensitivity analyses of the primary efficacy analysis will be conducted for various definitions of the analysis population (e.g. depending on definition of shared controls), and to evaluate the impact of modeling assumptions and missing data. Further details are provided in Appendix I.

## ***11.5 Safety Analyses***

Safety data, including any deaths, treatment-emergent adverse events (TEAE), vital signs, ECGs, and clinical laboratory test results, will be summarized descriptively for each treatment group using the ST sample. The frequency and type of any observed suicidal ideation or suicidal behavior will be described. Descriptive statistics of continuous measures will be provided for the observed data and for the change from baseline at each measured time point. Time-to-death or death equivalent will be estimated by Kaplan-Meier product-limit estimates. Adverse events will be summarized by treatment group as counts of events and as the proportion of participants experiencing any given type of TEAE as classified by MedDRA system organ class, high level term, and preferred term and classified according to severity, relatedness, and outcome. Laboratory test results will be classified as below the lower limit of normal, within normal limits and above the upper limit of normal. Shift tables will be used to summarize changes from baseline to each visit by treatment group. Clinically significant out-of-range laboratory tests are recorded as adverse events and will be documented in the TEAE summaries. Additional safety assessments may be specified in the RSA.

## ***11.6 Sample Size Justification***

Clinical trial simulation is used to quantify operating characteristics for each regimen. In particular, virtual participant outcomes are created under different assumptions for key design parameters including placebo rates of progression for ALSFRS-R, measurement error for ALSFRS-R, mortality rates, treatment effects on ALSFRS-R, treatment effects on mortality, dropout rates and accrual rates. For each set of simulation assumptions (i.e. a scenario), many trials are simulated and virtually executed, including all interim analyses for early success and early futility. Trial operating characteristics are summarized across all simulated trials for each scenario. Complete details and results are provided in Appendix I.

Based on the simulations outlined in Appendix I, under the null scenario there is an overall one-sided Type I error rate of 2.1% per regimen; with a 0.3% probability the regimen achieves early success. The average duration of the regimen is 14 months enrolling an average of 155 participants. There is a 29.0% chance that the regimen will be stopped early for futility.

The master protocol recommended design has 62%, 78%, and 89% power to detect a slowing in the rate of ALSFRS-R progression of 25%, 30% and 35% respectively when the mortality HR is the same as the disease ratio for ALSFRS-R progression. When there is no benefit in mortality and a 30% slowing in ALSFRS-R progression the power drops to 73%. When there is a negative effect on mortality and a 30% slowing in ALSFRS-R progression, the power drops further to 69%. The probability that the regimen will stop early for success in these scenarios is between 21% and 53% with average regimen durations ranging from 13-14 months. Finally, there is less than 1% chance in these scenarios that the regimen will be stopped early for futility.



## **12 DATA COLLECTION, MANAGEMENT, MONITORING, AND REPORTING**

The EDC system will be developed to facilitate the collection, management, monitoring, and reporting of study data for the Master Protocol.

### ***12.1 Quality Assurance***

Protocol procedures are reviewed with the SI and associated personnel prior to the study to ensure the accuracy and reliability of data. Each SI must adhere to the protocol detailed in this document and agree that any changes to the protocol must be approved by the CC prior to implementing the change unless it is to address immediate participant safety.

### ***12.2 Role of Data Management***

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets. The Neurological Clinical Research Institute (NCRI) will serve as the Data Coordination Center (DCC) for the Master Protocol and is responsible for developing, testing, and managing the clinical data systems and management activities. All data will be managed in compliance with NCRI policies and applicable regulatory requirements.

#### ***12.2.1 Data Collection***

Site personnel will collect data onto paper source documents as appropriate and into electronic source documents (e.g., voice sample data). Values from paper source documents will be transcribed into the corresponding eCRFs in the EDC system by site personnel; electronically captured data will be transmitted to their respective vendors for consolidation and reconciliation with the study EDC system. Clinical sites will be monitored to ensure compliance with the study protocol, data management requirements, and GCP.

#### ***12.2.2 Data Entry and Edit Checks***

Site personnel are instructed to enter collected data into the EDC system shortly after of a visit. Please note: SAEs must be entered into the EDC system and reported to the CC within 24 hours of site awareness of the SAE. Data collection is the responsibility of the staff at the site under the supervision of the SI as specified in the delegation log for that site. During the study, the SI must maintain complete and accurate documentation for the study.

To ensure accuracy and completeness of the data set, logic and range checks as well as in-form rules will be built into the EDC system, and electronic queries will be created to track potential data issues. The sites will only have access to the queries concerning their own participants.

### ***12.2.3 Data Lock Process***

The EDC system will have the ability to lock each trial regimen independently to prevent any modification of data once a trial regimen is closed. Once this option is activated, every user will have read-only access to the data until all access is revoked following NCRI DM procedures. The specific database lock procedures are detailed in the DM Standard Operating Procedures (SOP).

### ***12.3 Role of Study Monitors***

All aspects of the trial, including the individual regimens, will be monitored by qualified individuals designated by the Sponsor. Monitoring will be conducted according to GCP and applicable government regulations. The SIs will agree to allow monitors access to the clinical supplies, dispensing and storage areas, and to the clinical files of the study participants, and, if requested, agree to assist the monitors. Monitoring visits will be conducted according to a pre-defined Monitoring Plan.

#### ***12.3.1 Clinical Monitoring***

Study Monitors will visit each study site during the course of the study to review source documentation, ICF, and the clinical facilities to ensure the study is conducted in accordance with the study protocol and compliance with ICH/GCP and regulatory guidelines. Investigators are responsible for allowing access to all source documents and medical records related to the subject's participation in the study. Monitoring visits will occur at defined intervals per the Study Monitoring Plan. Study monitor(s) will identify study non-compliance and if appropriate, the study monitor(s) will assist the site with developing a corrective and preventative action plan. All significant noncompliance will be communicated to the Sponsor. Regimen specific monitoring activities will be specified in the appendices of the Master monitoring plan.

#### ***12.3.2 Monitoring Report***

The Study Monitors will provide monitoring reports to the Study Team and, if requested, will provide reports of protocol compliance to the Study Sponsor and other applicable parties as detailed in the Study Monitoring Plan.

### ***12.4 Data and Safety Monitoring Board***

An independent DSMB will be assembled for the trial. A DSMB Charter will detail the processes of this group. The DSMB will receive blinded and unblinded summary reports of the frequency of all clinical adverse events and safety laboratory tests for each trial regimens at planned

periodic meetings throughout the study as specified in the DSMB Charter. The DSMB will receive separate reports per trial regimen to review independently. Placebo data from all trial regimens will be compiled into a single report for review. Meetings will be held in-person or via teleconference.

Summaries of serious adverse events and enrollment per trial regimen will be provided to the DSMB by the Study Biostatisticians as specified in the DSMB Charter. AE(s) of Special Interest events occurring within 24 hours of dosing for any given treatment arm, and any severe unexpected serious adverse events for a treatment arm are considered events of interest and will be reported in real-time (within 1 business day of CC awareness) to the DSMB. The DSMB can ask to receive the SAE reports more frequently. As necessary, the DSMB can review the frequencies of clinical and laboratory abnormalities. Recommendations for modification or termination of the trial based on safety data will be made by the DSMB to the Sponsor. The DSMB will review safety data throughout the trial and may stop enrollment into a treatment arm for safety if they determine that there is a significant difference in the rate of a particular adverse event that would indicate a risk that is greater than the possible benefit of the investigational product. A notable increase in the frequency of any adverse event should be examined by the DSMB although it may not lead to a recommendation by the DSMB.

Prior to each DSMB meeting, the CC will provide an update to the DSMB on enrollment, data quality (missing data), and protocol adherence for each treatment arm. The CC will be responsible for communication with the DSMB.

Complete information can be found in the DSMB Charter.

### ***12.5 Neurological Global Unique Identifier***

A participant Neurological Global Unique Identifier (NeuroGUID), or its derivatives, will be used as the identifier for participant's samples participating in this study. The NeuroGUID is an 11-character string that is generated using encryption technology and algorithms licensed by the NCRI from the NIH in 2013.

The NeuroGUID is generated on a secure website that utilizes 128-bit Secure Socket Layer by using an irreversible encryption algorithm that accepts ten identifying data elements, (e.g., last name at birth, first name at birth, sex at birth, day, month and year of birth, city and country of birth, etc.), and creates a series of coded strings ("hashes") that are encrypted and sent to a secure server. The server produces a unique randomly generated alphanumeric string or NeuroGUID. No identifying information is stored in the system; it is simply used to guarantee the uniqueness of a NeuroGUID. If the same information is entered again, the same NeuroGUID will be returned.

## ***12.6 Data Handling and Record Keeping***

The SI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Source document templates (SDTs) will be provided for use and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents and discrepancies should be explained.

### ***12.6.1 Confidentiality***

Study participant medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the participant's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. All local and federal guidelines and regulations regarding maintaining study participant confidentiality of data will be adhered to.

Data generated by this study must be available for inspection by representatives of the US FDA, the Office for Human Research Protections (OHRP), the sponsor, all pertinent national and local health and regulatory authorities, the CC or their representative, Study Monitoring personnel, and the central IRB.

### ***12.6.2 Retention of Records***

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drugs, including CRFs (if applicable), consent forms, laboratory test results, and medical inventory records, must be retained by the SI for two years after marketing application approval. If no application is filed, these records must be kept for two years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The CC or their representative will notify the SIs of these events. The SIs should retain all study documents and records until they are notified in writing by the Sponsor or their representative.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

## ***12.7 Reporting, Publications, and Notification of Results***

### *12.7.1 Publication Policy*

The HEALEY ALS Platform Trial Executive Committee will set the policy for publication of results from the HEALEY ALS Platform Trial and all RSAs. No data or results generated from the HEALEY ALS Platform Trial or its RSAs may be published without written agreement from the HEALEY ALS Platform Trial Executive Committee.

The responsibilities of the HEALEY ALS Platform Trial Executive Committee are outlined in the HEALEY ALS Platform Trial Governance Plan.

### *12.7.2 Data and Sample Sharing*

Data and sample sharing policies will be specified in the legal agreements governing the trial.

### *12.7.3 Trial Registration*

The Master Protocol and each RSA will be registered on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). Results will be posted to [ClinicalTrials.gov](http://ClinicalTrials.gov) according to applicable regulations.

## 13 APPENDICES

### *Appendix I: ALS Master Protocol Recommended Design and Simulation Report Index*

#### **1.0 Introduction**

The ALS Master Protocol is a multicenter, randomized, placebo-controlled, adaptive, perpetual platform trial. The primary aim of the trial is to compare the effectiveness of novel/emerging therapies to placebo for participants with ALS. The master protocol will include multiple regimens where a regimen is defined as both an active treatment and the corresponding randomized placebo. Participants in the master protocol will be randomized in two stages; first to one of the actively enrolling regimens; and then 3:1 to active treatment or placebo within the regimen.

This document describes the master protocol recommended primary endpoint, primary analysis, and interim analyses. This will be the default statistical design and primary analysis for all regimens investigated in this master protocol. The recommended design is intended to provide confirmatory evidence of efficacy.

Each regimen will have a regimen-specific appendix (RSA). Deviations from the master protocol recommended statistical design are permitted. The exact statistical design along with complete operating characteristics for each regimen will be specified in the RSA.

The master protocol recommended primary efficacy endpoint is disease progression as measured by ALSFRS-R assessment at baseline through 24 weeks. The primary analysis is a Bayesian shared parameter analysis of ALSFRS-R and mortality. The primary analysis compares each regimen-specific active treatment to a shared control group.

The master protocol recommended design enrolls a maximum of 160 participants in each regimen, with 120 participants randomized to active treatment and 40 randomized to placebo control. There are frequent interim analyses in order to potentially stop a regimen early for success or for futility. Interim analyses will be conducted at the same time for all regimens within the master protocol, every three months of trial time. A regimen is eligible for these interim analyses once a minimum specified amount of data has been observed for that regimen.

#### **2.0 Primary Efficacy Analysis**

The following describes the Bayesian shared parameter primary analysis method of function and mortality for each regimen, the primary analysis population, prior distributions for all model parameters, and specific posterior summaries of interest that will be used in the design. We denote the regimen being analyzed as the “analysis regimen” throughout.

## 2.1 Primary Analysis Population and Shared Control

The primary analysis population for each analysis regimen is based on the intent to treat (ITT) principle and includes all participants randomized to the active treatment arm within the analysis regimen, all participants concurrently randomized to the control arm within the analysis regimen, and control participants from other regimens from a shared control.

The primary analysis dataset uses all available longitudinal data (ALSFRS-R measurements at 0, 4, 8, 12, 16, 20 and 24 weeks) for those who have not been censored due to mortality as well as mortality within 24 weeks on participants within the primary analysis population.

The shared control group will include participants randomized to the control arm across other actively enrolling regimens (concurrent shared controls) and previously completed regimens (non-concurrent shared controls) within the master protocol. Concurrent shared controls are defined as participants on a control arm who were randomized within a 6-month window of the start and stop of randomization of the analysis regimen. For example, if the analysis regimen enrolls from Month 12 – Month 24 in the platform, the concurrent shared controls will include all available data from all participants randomized between Month 6 and Month 30 within the platform across all regimens. Sections 2.0-6.0 describe the proposed primary efficacy analysis, simulations and operating characteristics for the first three regimens enrolling within the platform.

Finally, the master protocol allows for additional and more restrictive inclusion/exclusion criteria within a regimen specific appendix (RSA). However, these additional inclusion/exclusion criteria will be limited and will be allowed based only on restrictions due to safety or mechanism of action. Major additional RSA inclusion/exclusion criteria that can be assessed for all participants entering the platform will be used to subset the shared control to include only shared control participants that meet these additional assessed RSA inclusion/exclusion criteria. Major additional RSA inclusion/exclusion criteria that will be used to subset the shared control will be limited to those criteria that have the potential to lead to significant differences in the patient population in terms of the rate of disease progression within the primary analysis population and will be pre-specified within each RSA. The first three regimens enrolling within the platform will not include any major additional inclusion/exclusion criteria.

## 2.2 Bayesian Shared Parameter Model of Function and Mortality

The primary analysis for each analysis regimen is a Bayesian repeated measures model of ALSFRS-R that accounts for loss of follow-up due to mortality. The repeated measures The primary analysis for each analysis regimen is a Bayesian shared parameter model of function and mortality with the following components:

- **Function:** Bayesian repeated measures model of ALSFRS-R at baseline through 24 weeks for all participants who have not experienced mortality. Participants

who have experienced mortality will not contribute to the functional component of the analysis. The Bayesian repeated measures model of ALSFRS-R measures the slowing in the rate of progression for ALSFRS-R in treated participants relative to control for survivors.

- **Mortality:** Exponential proportional hazards model of mortality through 24 weeks that measures the mortality hazard ratio in treated participants relative to control.
- **Shared Treatment Effect:** A shared treatment effect parameter (slowing in time of the progression of the disease) is common between the function and mortality components and provides an overall all estimate of the treatment effect that is averaged across the two endpoints. This shared parameter corresponds to a slowing in the rate of ALSFRS-R progression as well as a slowing in the time to mortality.

The ALSFRS-R repeated measures component of survivors is based on a linear rate of progression in ALSFRS-R for placebo participants and a proportional slowing in the rate of progression for treated participants at each time point. The model incorporates participant-level random effects in the baseline value of the ALSFRS-R (intercept) and in the rate of progression (slope); covariate effects to account for covariate-explainable differences in rates of progression based on participant-specific baseline covariates; regimen-specific differences in baseline values, rates of progression and measurement error, and a time-trend effect to accommodate non-concurrently randomized controls. Assuming there are  $N_{func}$  total participants who have survived, let the ALSFRS-R at timepoint  $j$  for participant  $i$  be labelled  $Y_{ij}$ , for  $j = 0, 4, 8, 12, 16, 20$ , and 24 weeks and  $i = 1, \dots, N_{func}$ . The Bayesian repeated measures model for ALSFRS-R is

$$Y_{ij} = \gamma_i - \beta_i * \exp(\theta_{t(i)} + \delta X_i + \alpha_{d(i)} + \eta_{r(i)}) * \left(\frac{j * 12}{52}\right) + \epsilon_{ij};$$

$$\epsilon_{ij} \sim N(0, \sigma_{r(i),t(i)}^2).$$

The mortality component is an exponential proportional hazards model that assumes a constant baseline hazard rate for all control participants. Given the low expected rate of mortality within this study (5%) and to avoid over-parameterization, we do not include covariate, regimen-specific, or time-trend effects in the mortality component. Assuming there are  $N_{mort}$  total participants, the hazard rate of mortality per month for participants  $i = 1, \dots, N_{mort}$  is denoted  $\lambda_i$  and is

$$\lambda_i = \lambda_0 \exp(\theta_{t(i)}); i = 1, \dots, N_{mort}.$$

The shared parameter model makes use of the following additional notation:

- Treatment arm:  $t(i)$  denotes the treatment arm,  $T$ , to which participant  $i$  is randomized where  $T = 0,1$  corresponds to placebo and active arm, respectively.



- Regimen:  $r(i)$  denotes the regimen,  $R$ , to which participant  $i$  is randomized where  $R = 1, \dots, N_r$  corresponds to the analysis regimen ( $R=1$ ) and all other  $N_r$ , enrolling regimens respectively.
- Time of Randomization:  $d(i)$  denotes the time of randomization,  $d$ , for participant  $i$ . The time of randomization is expressed as an ordinal discrete outcome that where  $d = 0$  is the current time period for concurrent controls (defined as in Section 2.1 with those participants randomized within 6 months from the start or finish of randomization within the analysis regimen) and  $d = 1, \dots, D$  are the number of additional 6-month intervals preceding the start of the current time period.
- Baseline Covariates:  $X_i$  is a vector of dimension  $C$  of baseline covariates for participant  $i$  that have been standardized.

Each parameter in the above model and the prior distribution assumed for each parameter is described below in Sections 2.2.1 – 2.2.7. The majority of the prior distributions are chosen to be non-informative (large amount of variability and uncertainty) to allow the posterior distributions to reflect what is observed in the data.

### 2.2.1 Treatment Effect ALSFRS-R and Mortality

The disease rate ratio (DRR) under treatment  $T$  is the parameter  $\exp(\theta_T)$ . For a placebo participant, the DRR is set equal to 1 ( $\theta_0 = 0$ ). Thus, the DRR parameter for active treatment represents the relative change to the rate of decline of ALSFRS-R and the rate of mortality of treated participant relative to a placebo participant. The estimated DRR can also be interpreted as the average rate of decline in function and mortality, with the weights across function and mortality depending on the proportion of participants with observed mortality. Appropriately, more weight is given to mortality relative to function as the proportion of observed mortality increases. If the DRR is less than 1 then the rate of disease progression on function and mortality for actively treated participants is slower than that for placebo. The DRR value represents the proportional slowing in time (or increase) of the disease. A DRR = 0.75 corresponds to a 25% slowing in the rate of functional progression and time to mortality and a value of 0.25 represents a 75% slowing in the rate of functional progression and time to mortality.

The prior distribution for the DRR for the regimen-specific active treatment,  $T=1$ , is uniform between 0 and 2; placing equal weight on a DRR<1 and DRR>1:

$$\exp(\theta_1) \sim Unif(0,2).$$

### 2.2.2 Random Intercept and Slope Effects for ALSFRS-R

Participant-specific random intercept effects,  $\gamma_i, i = 1, \dots, N$ , represent the participant-specific expected ALSFRS-R at the time of randomization. Participant-specific random slope effects,  $\beta_i, i = 1, \dots, N$ , represent the participant-specific rate of decline per month in ALSFRS-R expected under placebo.

Participant-level random intercept effects are modelled using a hierarchical normal distribution with overall treatment arm and regimen-specific population mean,  $\mu_{\gamma,R,T}; T = 0,1$ , and  $R = 1, \dots, N_r$  with a normal hyper-prior, and an overall population standard deviation,  $\sigma_{\gamma}$ , with a uniform hyper-prior:

$$\begin{aligned}\gamma_i &\sim N(\mu_{\gamma,r(i),t(i)}, \sigma_{\gamma}^2); i = 1, \dots, N; \\ \mu_{\gamma,R,T} &\sim N(38, 10^2); T = 0,1; R = 1, \dots, N_R \\ \sigma_{\gamma} &\sim Unif(0,10).\end{aligned}$$

The normal hyper-prior on the mean of the participant-level random intercept effects is non-informative with a mean of 38 (mean value observed in historical trials within the PRO-ACT database) with a standard deviation of 10. The uniform hyper-prior on the standard deviation is non-informative with a range from 0 to 10 (twice observed SD of the participant-level intercepts in historical trials within the PRO-ACT database).

Participant-level random slope effects are modelled using a hierarchical normal distribution with overall population mean,  $\mu_{\beta}$ , with a normal hyper-prior; and an arm-specific population standard deviation,  $\sigma_{\beta,T}; T = 0,1$ , with a uniform hyper-prior:

$$\begin{aligned}\beta_i &\sim N(\mu_{\beta}, \sigma_{\beta,t(i)}^2); i = 1, \dots, N; \\ \mu_{\beta} &\sim N(1, 1^2); \\ \sigma_{\beta,T} &\sim Unif(0,2); T = 0,1.\end{aligned}$$

The mean and variance of the participant-level random effects are estimated from the data. This is done by placing hyperprior distributions on the relevant parameters in the random effects distribution and using the observed data to estimate the hyper-parameters. Non-informative distributions are used for these hyper-priors to ensure that the data determine the corresponding hyper-prior estimates and the estimated random effect distributions. In particular, the normal hyper-prior on the mean of the participant-level random slope effects is non-informative with a mean of 1 (mean value observed in historical trials within the PRO-ACT database) with a standard deviation of 1. The uniform hyper-prior on the standard deviation is non-informative with a range from 0 to 2 (over twice observed SD of the participant-level intercepts in historical trials within the PRO-ACT database).

### 2.2.3 Regimen-Specific Random Effects ALSFRS-R

The increase or decrease in the rate of progression for placebo participants for all regimens compared to that of the analysis regimen is the parameter  $\exp(\eta_r)$ . For the analysis regimen ( $r=1$ ), the effect is assumed to be 1 ( $\eta_1 = 0$ ).

The log of the regimen-specific random effects,  $\eta_r$ , will be modelled using a hierarchical model to allow for dynamic borrowing within the shared control across different regimens:

$$\begin{aligned}\eta_r &\sim N(0, \sigma_\eta^2); r = 2, \dots, N_r; \\ 1/\sigma_\eta^2 &\sim \text{Gamma}(1, .05^2).\end{aligned}$$

The gamma (shape and rate parameterization) hyper-prior assumes a mean on the variance of  $.05^2$  and a standard deviation that is equal to the mean. These parameters are informed based on estimated between-trial variability in rates of progression for ALSFRS-R from historical trials with a weight of evidence of 2 data points.

### 2.2.4 Time-Trend Effects ALSFRS-R

The log of the time-trend effects will be modelled using a simple normal dynamic linear model where the distribution of each time-trend effect is normal with a mean equal to the effect at the previous time period and a standard deviation that has a uniform hyper-prior:

$$\begin{aligned}\alpha_0 &= 0; \\ \alpha_d &\sim N(\alpha_{d-1}, \sigma_\alpha^2); d = 1, \dots, D; \\ \sigma_\alpha &\sim \text{Unif}(0,2).\end{aligned}$$

### 2.2.5 Baseline Covariate Effects ALSFRS-R

Covariates included in the primary efficacy analysis are: time since onset, pre-baseline slope of ALSFRS-R, riluzole and edaravone use. Continuous covariates will be standardized. Missing covariates for a participant will be imputed using the median value for that covariate. Covariate effects are modelled as  $\exp(\delta_c)$ ,  $c = 1, \dots, C$ , accounting for covariate-explainable variability in the rate of ALSFRS-R progression due to participant-specific baseline covariates.

Prior distributions for the log of the covariate effects are independent and identically distributed as:

$$\delta_c \sim N(0, 1^2); c = 1, \dots, C.$$

### 2.2.6 Residual Errors ALSFRS-R

The residual errors for the individual observations,  $\epsilon_{ij}, i = 1, \dots, N$  and  $j = 0, \dots, 24$  are modelled as independent normal distributions with a mean of 0 and with an treatment arm and regimen-specific standard deviation of  $\sigma_{R,T}; T = 0,1; R = 1, \dots, N_R$ .

The prior distribution for the standard deviation of the residual error term in each arm are independent and identically distributed as:

$$\sigma_{R,T} \sim \text{Unif}(0,4); T = 0,1; R = 1, \dots, N_r.$$

The uniform prior distribution is non-informative, ranging from 0 to 4 (over twice that observed in historical trials within the PRO-ACT database).

### 2.2.7 Baseline Mortality Hazard Rate

The baseline mortality hazard rate per month common across all placebo participants is  $\lambda_0$ . The prior distribution for the placebo mortality hazard rate is distributed as Gamma (shape and rate parametrization):

$$\lambda_0 \sim \text{Gamma}(.01,1);$$

with a mean of 0.01 and a standard deviation of 1. This prior distribution is centered on the value observed within the PRO-ACT database and is non-informative with a weight of evidence of 1 month of exposure.

## 2.3 Posterior Summaries

The Bayesian posterior distribution of all model parameters is calculated using Markov chain Monte Carlo (MCMC). The algorithm allows the generation of at least  $M = 100,000$  draws from the joint posterior distribution for all model parameters. In particular, summaries of the Bayesian posterior distribution for the DRR under the regimen-specific active treatment,  $\exp(\theta_1)$ , will be provided including the mean and 95% credible intervals; the probability that the treatment is superior to placebo,  $Pr(\exp(\theta_1) < 1)$ ; and the probability the treatment slows the rate of progression by at least 10%,  $Pr(\exp(\theta_1) < .9)$ .

## 3.0 Success Thresholds, Interim Analyses and Trial Adaptations

Interim analyses will occur simultaneously for all actively enrolling regimens. Interims will begin when at least one regimen within the master protocol has 40 randomized participants (30 active and 10 control) with the opportunity to complete at least 24 weeks of follow-up.

Subsequent interims will occur every 3 months. At an interim analysis, a regimen can either stop early for success or for futility. A regimen is eligible to stop early for success or for futility once there are 40 randomized participants within that regimen with the opportunity to complete at least 24 weeks of follow-up. If a regimen has not stopped early for success or futility at an interim analysis, the regimen-specific final analysis will take place when all participants randomized to that regimen (120 active and 40 control) have had the opportunity to complete 24 weeks of follow-up.

### **3.1 Regimen Success**

Early success stopping at interim analyses for the first three regimens will not be conducted. Success will be declared for a regimen at the final analysis if the posterior probability that the treatment,  $T=I$ , is superior to placebo group is greater than .98:

$$Pr(\exp(\theta_1) < 1) > .979.$$

The threshold for the final analysis of .979 was chosen to control type I error at 2.5% across all Null simulation scenarios (except for when the analysis regimen has a slower rate of progression on ALSFRS-R compared to all other regimens) without futility stopping.

### **3.2 Regimen Futility**

Futility will be declared for a regimen at an interim analysis if the posterior probability that the treatment,  $T=I$ , slows disease progression by at least 10% is less than 5%:

$$Pr(\exp(\theta_1) < .9) < .05.$$

## **4.0 Sensitivity Analyses of Primary Efficacy Analysis**

The following secondary and sensitivity analyses will be performed for the primary efficacy analysis and will be conducted on the primary analysis population unless otherwise specified.

### **4.1 Key Secondary Joint Rank Analysis of ALSFRS-R and Mortality**

As a key supportive analysis, a joint rank test of survival and function will be performed. The analysis will rank all participants based first on survival time and second, if they survived, the change in ALSFRS-R from 0 to 24-weeks as described in Berry et al. 2013 (Berry, 2013). An ANCOVA will be performed on the ranks to adjust for important covariates described in Section 2.2.5. This secondary analysis will be performed on the primary analysis population as well as the sensitivity analysis populations described in Section 4.2.

## 4.2 Sensitivity of Analysis Population

As sensitivity analyses, the Bayesian primary analysis model will be applied to the following analysis populations:

- **Concurrent Shared Control Population:** All participants randomized to the active treatment arm or placebo arm within the analysis regimen and all participants randomized to the placebo arm across other regimens within the master protocol who have been randomized within a 6-month window of when the analysis regimen has been enrolling.
- **Common Mode of Administration Population:** All participants randomized to the active treatment arm or placebo arm within the analysis regimen and all participants randomized to the placebo arm across other regimens within the master protocol that have the same mode of administration.
- **Regimen Only Population:** All participants randomized to the active treatment arm or placebo arm within the analysis regimen only. Because the population only involves one regimen, certain aspects of the analysis model will require modification (e.g. no regimen-specific effects).

## 4.3 Sensitivity Analysis for Handling Missing Data

The Bayesian repeated measures component of ALSFRS-R naturally accommodates differential length of follow-up and utilizes all available longitudinal data for each participant who has not been censored due to mortality. Additionally, we provide the following sensitivity analyses to missing (not due to mortality) ALSFRS-R data within the Bayesian repeated measures component of ALSFRS-R.

- Impute all missing ALSFRS-R based on last observation carried forward.
- Impute all missing ALSFRS-R as 0 for both treatment and control arms.
- Impute all missing ALSFRS-R as the worst value observed within the combined treatment and control arms for both treatment and control arms.
- Impute all missing ALSFRS-R as the worst value observed within the respective treatment/control arms.

## 4.4 Shared Parameter Model Sensitivity Analyses

The following analyses will be conducted to test the sensitivity of the results to the primary efficacy model assumptions.

- The functional component of the primary analysis model, the Bayesian repeated measures model of ALSFRS-R, will be updated to allow for different rates of progression within

each 4-week interval to assess the sensitivity of the results to the linearity assumption in the primary efficacy analysis.

- The shared parameter primary analysis model will be updated to allow for different treatment effects across time (4-week intervals) for the functional component and a different treatment effect between function and mortality.
- The shared parameter primary analysis model will be updated to allow for different treatment effects between function and mortality.
- The shared parameter primary analysis model will be updated to explore a range of degrees of fixed borrowing of controls across regimens. In particular, the variance of the regimen-specific random slope effects (Section 2.2.3) will be fixed across a set of values ranging from  $0.001^2$  (full borrowing) to 10 (no borrowing):

$$\eta_r \sim N(0, \sigma_\eta^2); r = 2, \dots, N_r;$$
$$\sigma_\eta^2 = .001^2, .01^2, .05^2, .1^2, .5^2, 1^2, 5^2, 10^2.$$

Summaries of the estimated treatment effect and estimated differences across regimens within each sensitivity analysis will be provided to assess the robustness of the primary analysis results to the degree of borrowing within the shared control.

## 5.0 Clinical Trial Simulations

Clinical trial simulation is used to provide simulated example trials and to quantify operating characteristics for each regimen. In particular, virtual participant outcomes are created under different assumptions for key design parameters including placebo rates of progression for ALSFRS-R, measurement error for ALSFRS-R, mortality rates, treatment effects on ALSFRS-R, treatment effects on mortality, dropout rates and accrual rates. For each set of simulation assumptions (i.e. a scenario), many trials are simulated and virtually executed, including all interim analyses for early success and early futility. Trial operating characteristics are summarized across all simulated trials for each scenario.

### 5.1 Virtual Participant ALSFRS-R Simulation

Participant-level ALSFRS-R data at each timepoint is simulated using placebo data from the Pooled Resource Open-Access ALS Clinical Trials Database (PRO-ACT) with a bootstrap approach. In particular, a simulation database is created from the PRO-ACT database using each placebo participant with at least 3 ALSFRS-R measurements over the course of at least 24 weeks. For each of these participants, an intercept, slope and residual standard-error is calculated from a participant-specific linear regression of the measured ALSFRS-R within the PRO-ACT database as a function of the month of each measured visit. These linear regression values as well as baseline covariates are recorded for each participant within the simulation database.

Within the current simulations, a subset of the PRO-ACT simulation database is sampled based on those participants that have a time since onset less than 3 years and have a slow vital capacity or forced vital capacity (SVC / FVC) greater than 50% (N=2636). Within this subset, the average subject-specific slope (ALSFRS-R decline per month) is -1.05 with a SD of 0.79. The average residual standard error is 1.77.

To create a dataset of participant-level ALSFRS-R scores at each 4-week visit for each simulated clinical trial from the PRO-ACT simulation database, the following steps are taken:

- Choose a participant,  $i$ , from the PRO-ACT simulation database and record values of the participant-specific intercept ( $\gamma_i$ ), slope ( $\beta_i$ ), residual standard error ( $\sigma_i^2$ ), and baseline covariates.
- Simulate participant-specific ALSFRS-R at 0, 4, 8, 12, 16, 20 and 24 weeks ( $j$ ) from:

$$Y_{i,j} \sim N(\gamma_i + (\beta_i + \theta_{t(i)}) * \frac{j*12}{52}, \sigma_i^2);$$

assuming  $\theta_0 = 0$  for placebo and  $\theta_1$  is found such that  $(\hat{\beta} + \theta_1)/\hat{\beta} = 1 - \text{assumed \% slowing of treatment}$ ; where  $\hat{\beta}$  is the average slope across all subjects.

The treatment effect within the simulations is introduced as an additive effect to avoid introducing differences in the variance of the participant-specific rates of progression between the treatment and control arms. This is to provide a conservative estimate of power as the multiplicative effect of treatment on the rate of progression decreases the variance of participant-level slopes in the treatment arm as the treatment becomes more effective.

## 5.2 Base Simulation Scenarios and Sensitivity Scenarios

All trial simulations assume there are 3 regimens within the platform; all are enrolling within the same population and randomizing concurrently (as defined in Section 2.1). Treatment effect assumptions will vary across the first regimen and operating characteristics will be reported for this regimen. The other two regimens will be assumed to be Null (no benefit on ALSFRS-R or mortality).

The trial simulations are performed under a base scenario (set of simulation assumptions) as well as numerous sensitivity scenarios. In particular, a simulation scenario is defined by 6 different parameters (Table 5.2.1). This set of 6 parameters characterizes various nuisance parameters, but also key assumptions on the endpoints such as their variability and the behavior of the control arm and treatment effect. We define a “base case” set of values for these 6 parameters as well as two sensitivity analysis values. The table below lists each of these 6 parameters along with the base case value and the two sensitivity analysis values.

Table 5.2.2 describes treatment effect assumptions. We simulate the base case of parameter values from Table 5.2.1 under all treatment effect scenarios in Table 5.2.2 and consider this as the primary set of operating characteristics for this trial (6 scenarios). Then, for each of 6 parameters that define a scenario, we vary one sensitivity analysis value at a time from the base case assumptions. For the first 5 parameter values we simulate under the null treatment effect and the common treatment effect with 30% slowing and a HR of .7 (10 sensitivity analyses



across 2 treatment effect assumptions). For parameter 6 (mortality rate) we simulate under 4 treatment effect scenarios (Null, Common Effect with HR=.7 and Slowing=30%, No Mortality Benefit, and Worse Mortality). All sensitivity scenarios will be simulated with and without futility stopping.

Parameter	Base Case	Sensitivity Analysis Values	
		a	b
1. Accrual rate (pts/mo)	40	20	60
2. Non-mortality dropout rate per month	2%	4%	6%
3. Timing of Start of Enrollment of Other Regimens	1 Month apart	3 Months apart	6 Months apart
4. ALSFRS-R Slope Distribution	Same as PRO-ACT	10% Slower Progression and less variable	10% Faster Progression and more variable
5. ALSFRS-R Measurement Error	Same as PRO-ACT	10% less	10% more
6. 24-Week Mortality Rate	5%	10%	20%

Scenario	ALSFRS-R Slowing (1-DRR)	Mortality HR
<b>Null</b>	0%	1.0
<b>Common Mortality and Function Benefit</b>	25%	.75
	30%	.70
	35%	.65
<b>No Mortality Benefit</b>	30%	1.0
<b>Worse Mortality</b>	30%	1.3

## 6.0 Example Trials and Operating Characteristics

For each scenario and treatment effect we simulate 10000 clinical trials. We present example simulated trials as well as overall average operating characteristics across all simulated trials. In particular, for each simulation scenario and treatment effect, we report the following regimen-specific operating characteristics for the first regimen:

- Mean duration (months)

- Mean sample size randomized to the regimen
- Probability of early success, total probability of success, and cumulative probability of stopping for success as a function of trial duration.
- Probability of early futility and cumulative probability of stopping for futility as a function of trial duration.
- Average estimate of the treatment effect and estimate of the treatment effect as a function of total trial duration.

## 6.1 Example Trials

Figures 6.1.1 – 6.1.6 show simulated example trials. The example trials have been provided to demonstrate how the results from the shared parameter analysis incorporates both mortality and function, how the results change as more participants experience mortality, and how results from the shared parameter analysis compare to that of a joint rank analysis. Each simulated trial shows results from: 1) the primary shared-parameter analysis, 2) the key support sensitivity joint rank analysis, and 3) independent analyses of mortality and function.

The first 3 simulated example trials and the last 3 example trials assume differences across mortality, but the same underlying ALSFRS-R functional data. This results in different observed functional data for the survivors as well as different observed mortality data for each example trial. Within each set of example trials (1-3 and 4-6), we show results for 6-month mortality rate of 5, 20 and 40% on the control arm. Under the first 3 simulated example trials (Figures 6.1.1-6.1.3) the true DRR of function is 0.70 (30% slowing in rate of progression on function) and the true DRR of mortality is 1.0 (HR of 1.0). Under the next 3 simulated trials (Figures 6.1.4-6.1.6) the true DRR for function is 1.0 and the true DRR for mortality is 1.3. Additionally, within example trials 4-6, we assume participant-level correlation between mortality and function on the treatment arm. In particular, on the treatment arm, the participants with the worst decline on function are the ones who are more likely to experience mortality. On the control arm there is no correlation between mortality and function. This is a pathological example that results in less severe participants contributing to the functional component within the treatment arm and an apparent slight positive benefit in function of treatment survivors compared to control. The slight positive benefit in function is combined with a slight negative effect on mortality that results in an overall combined null effect within the shared parameter analysis as well as the joint rank analysis.

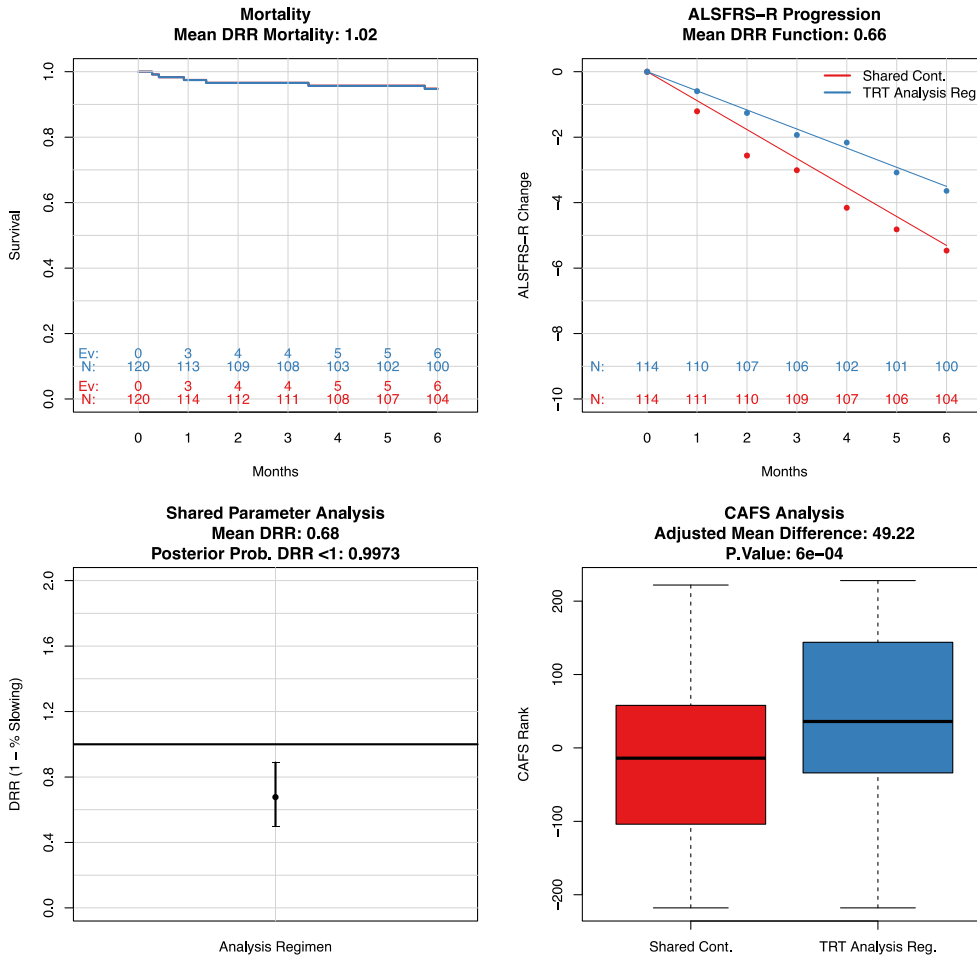
All example trial figures show the following:

- Top left plot: Mortality data and results from a mortality only analysis. Kaplan-Meier curve with blue = treated and red = shared control. Number of events (EV) and number of participants at risk (N) are shown at the bottom of the plot for each arm and within each month window. Plot title shows posterior mean estimate of the mortality DRR (or HR) for the mortality only component analysis (exponential proportional hazards analysis).

- Top right plot: ALSFRS-R data and results from a function only analysis. ALSFRS-R change from baseline from baseline through 6 months with blue = treated and red = shared control. Circles are raw mean estimates for the change from baseline at each month per arm. Lines represent the fitted means from a Bayesian repeated-measures analysis on ALSFRS-R (independent of mortality). Number of participants (N) are shown at the bottom of the plot for each arm and within each month window. Participants who have experienced mortality are not included in the functional analysis. Plot title shows posterior mean estimate of the functional DRR (or 1-% slowing in progression) for the ALSFRS-R only component analysis.
- Bottom left plot: Results from the primary Bayesian shared parameter analysis (Section 2.2). Mean and 95% CI for the overall treatment effect (DRR or 1-% slowing in time of progression) that is common across mortality and function. Plot title shows posterior mean estimate of the overall DRR (or 1-% slowing in time of progression) as well as the posterior probability that the treatment slows disease progression.
- Bottom right plot: Results from the joint rank CAFS analysis (Section 4.1). Boxplots of the ranks under the treated group (blue) and shared control (red). Plot title gives the mean estimated differences in ranks (adjusted for covariates) as well as the one-sided p-value for the joint rank analysis.

### 6.1.1 Example Trial 1

Figure 6.1.1 shows an example trial where there is 5% 6-month mortality, a DRR of 1.0 on mortality and 0.70 of on function. There are 6 total participants who experience mortality on both the treated and control arms. The posterior mean mortality DRR (HR) estimate for an independent exponential proportional hazards analysis of mortality is 1.02. Of the survivors, the overall rate mean change from baseline at 6 months is -3.7 and -5.5 for treated and shared control respectively. The posterior mean ALSFRS-R DRR (1- % slowing in functional progression) estimate for an independent repeated measures analysis of function for the survivors is 0.66. The shared parameter analysis provides an overall posterior mean estimate of the DRR across mortality and function of 0.68 (weighted more heavily towards the functional estimate given that 95% of the participants contribute to this component). The posterior probability that treatment slows progression is 99.73%. The joint rank CAFS analysis results are comparable to the shared parameter analysis (one-sided p-value of 0.0006).



**Figure 6.1.1:** Example Trial 1. 5% 6-Month Mortality Rate. DRR of 1.0 on Mortality. DRR of 0.70 on Function.

### 6.1.2 Example Trial 2

Figure 6.1.2 shows the same underlying functional data as Example Trial 1, but with increased mortality rate (20% 6-month mortality) and a DRR of 1.0 on mortality. The total number of participants who experience mortality are 22 and 23 on the treated and control arms respectively. The posterior mean mortality DRR (HR) estimate for an independent exponential proportional hazards analysis of mortality is 0.98. Of the survivors, the overall rate mean change from baseline at 6 months is -4 and -5.5 for treated and shared control respectively. The posterior mean ALSFRS-R DRR (1- % slowing in functional progression) estimate for an independent repeated measures analysis of function is 0.70. The shared parameter analysis provides an overall posterior mean estimate of the DRR across mortality and function of 0.75 (posterior probability DRR <1 is 98%). This overall estimate of the DRR is weighted more heavily towards the mortality effect than what was observed in example trial 1 (Figure 6.1.1 overall effect of 0.68). This demonstrates that as we observe more mortality data, the overall treatment

effect is influenced more by the effect of mortality. The joint rank CAFS analysis results are comparable to the shared parameter analysis (one-sided p-value of 0.0232).

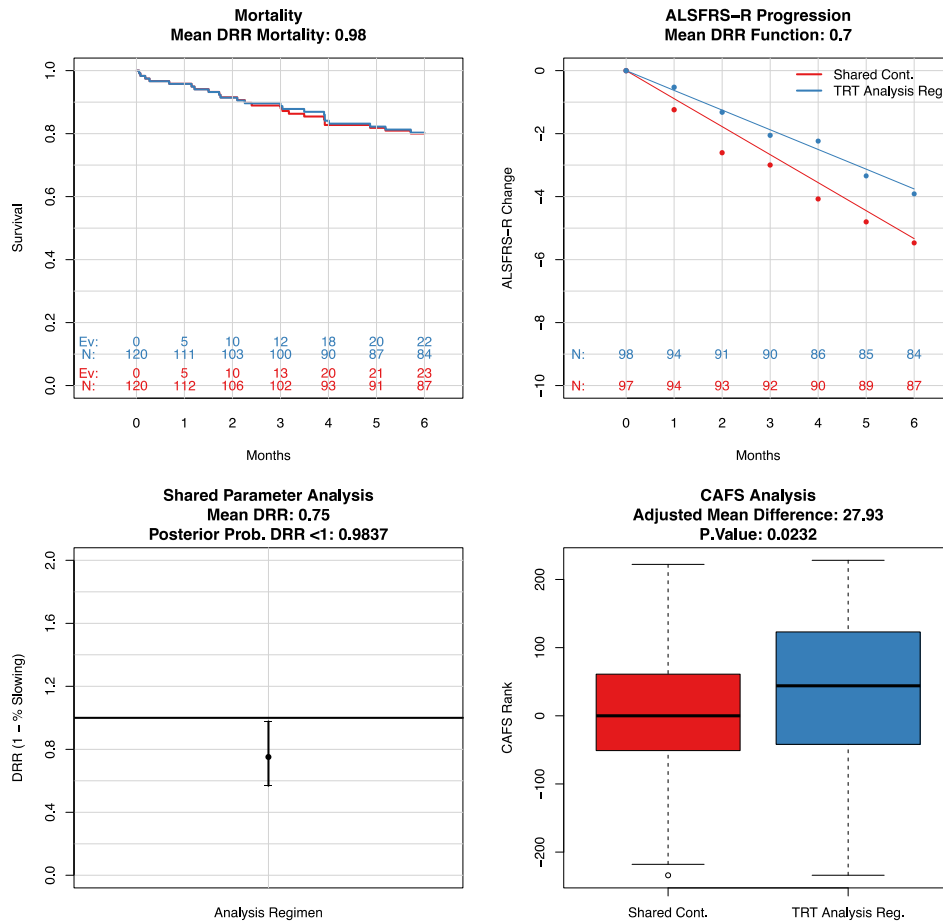


Figure 6.1.2: Example Trial 2. 20% 6-Month Mortality Rate. DRR of 1.0 on Mortality. DRR of 0.70 on Function.

### 6.1.3 Example Trial 3

Figure 6.1.3 shows the same underlying functional data as Example Trial 1 and 2, with increased mortality of 40% 6-month mortality and a DRR of 1.0 on mortality. The total number of participants who experience mortality are 42 and 44 on the treated and control arms respectively. The posterior mean mortality DRR (HR) estimate for an independent exponential proportional hazards analysis of mortality is 0.98. Of the survivors, the overall rate mean change from baseline at 6 months is -4.1 and -6.0 for treated and shared control respectively. The posterior mean ALSFRS-R DRR (1- % slowing in functional progression) estimate for an independent repeated measures analysis of function is 0.68. The shared parameter analysis provides an overall posterior mean estimate of the DRR across mortality and function of 0.78 (posterior probability DRR <1 is 97%). This overall estimate of the DRR is weighted more heavily towards the mortality effect than what was observed in example trials 1 and 2. This demonstrates that as we observe more mortality data, the overall treatment effect is influenced

more by the effect of mortality. The joint rank CAFS analysis results are comparable to the shared parameter analysis (one-sided p-value of 0.0132).

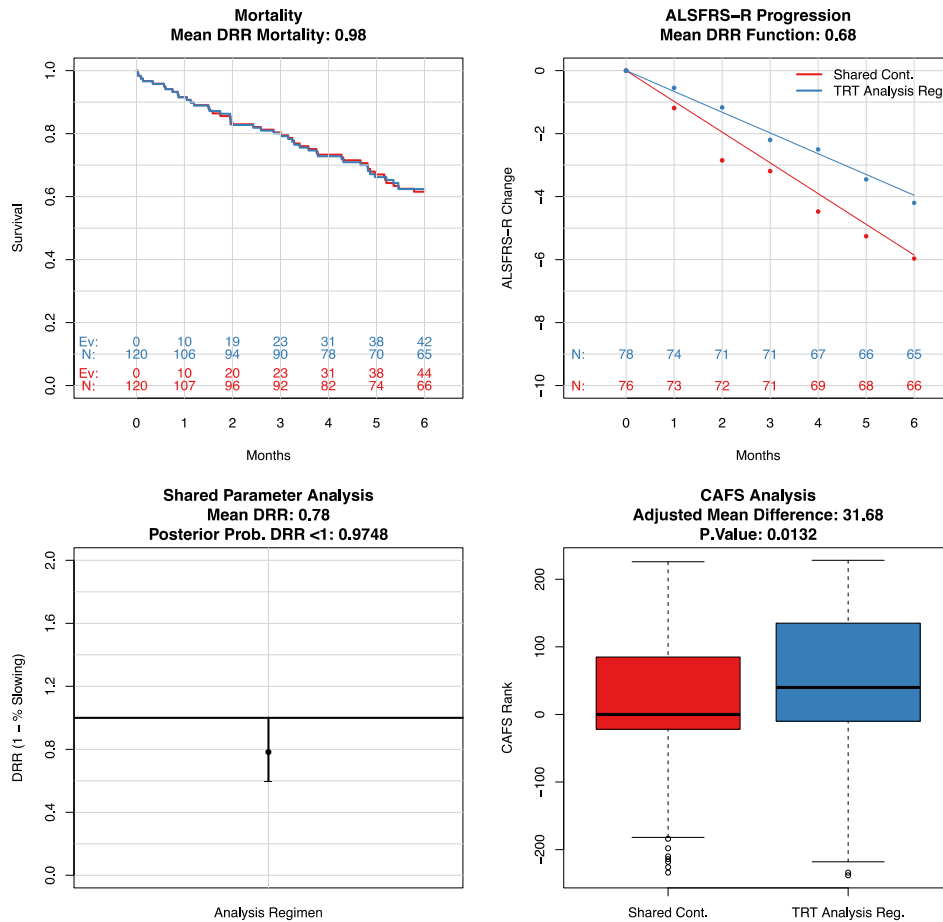
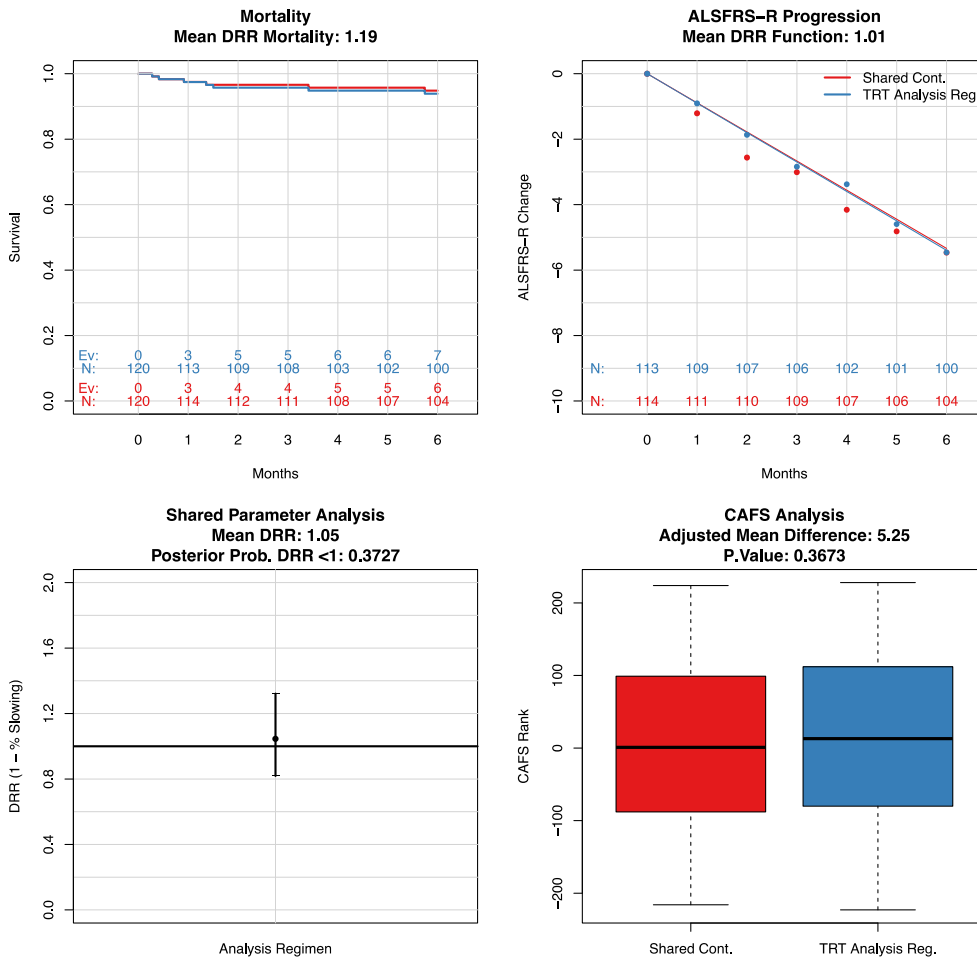


Figure 6.1.3: Example Trial 3. 40% 6-Month Mortality Rate. DRR of 1.0 on Mortality. DRR of 0.70 on Function.

### 6.1.4 Example Trial 4

Figure 6.1.4 shows an example trial where there is 5% 6-month mortality on the control arm, a DRR of 1.0 on function and 1.3 on mortality. Those who experience mortality on the treated arm are more likely to also have a worse functional decline. There are 7 and 6 total participants who experience mortality on the treated and control arms respectively. The posterior mean mortality DRR (HR) estimate for an independent exponential proportional hazards analysis of mortality is 1.19. Of the survivors, the overall rate mean change from baseline at 6 months is -5.5 for both treated and shared control arms. The posterior mean ALSFRS-R DRR estimate for an independent repeated measures analysis of function for the survivors is 1.01. Given the low mortality rate, we do not see a bias in the functional component analysis of the survivors. The shared parameter analysis provides an overall posterior mean estimate of the DRR across mortality and function of 1.05 (posterior probability DRR <1 is 37%). The joint rank CAFS analysis results are comparable to the shared parameter analysis (one-sided p-value of 0.3673).

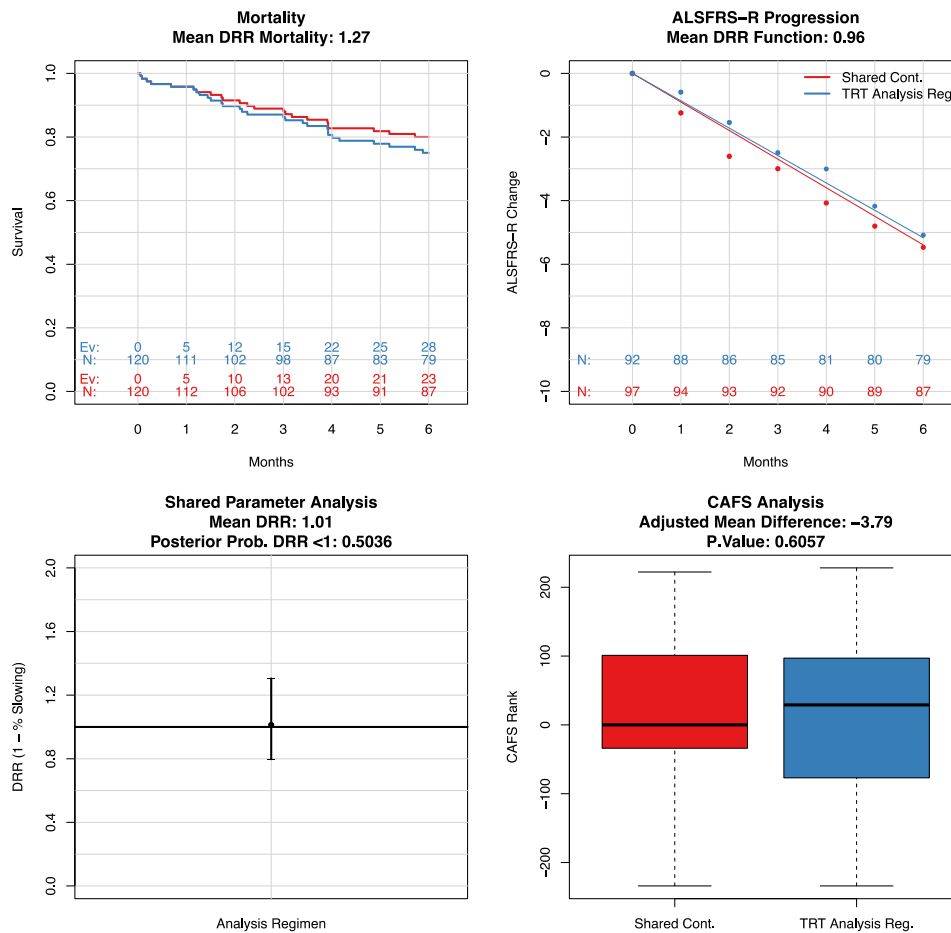


**Figure 6.1.4:** Example Trial 4. 5% 6-Month Mortality Rate. DRR of 1.3 on Mortality. DRR of 1.0 on Function.

### 6.1.5 Example Trial 5

Figure 6.1.5 shows the same underlying functional data as example trial 4, with an increase in mortality rate of 20% 6-month mortality on the control arm, a DRR of 1.0 on function and 1.3 on mortality. Those who experience mortality on the treated arm are more likely to also have a worse functional decline. There are 28 and 23 total participants who experience mortality on the treated and control arms respectively. The posterior mean mortality DRR (HR) estimate for an independent exponential proportional hazards analysis of mortality is 1.27 (slight negative effect of treatment on mortality). Of the survivors, the overall rate mean change from baseline at 6 months is -5.0 and -5.5 for treated and shared control arms respectively. The posterior mean ALSFRS-R DRR estimate for an independent repeated measures analysis of function for the survivors is 0.96 (slight positive benefit of treatment on function). The shared parameter analysis provides an overall posterior mean estimate of the DRR across mortality and function of 1.01

(posterior probability DRR <1 is 50%). The joint rank CAFS analysis results are comparable to the shared parameter analysis (one-sided p-value of 0.6057).



**Figure 6.1.5:** Example Trial 5. 20% 6-Month Mortality Rate. DRR of 1.3 on Mortality. DRR of 1.0 on Function.

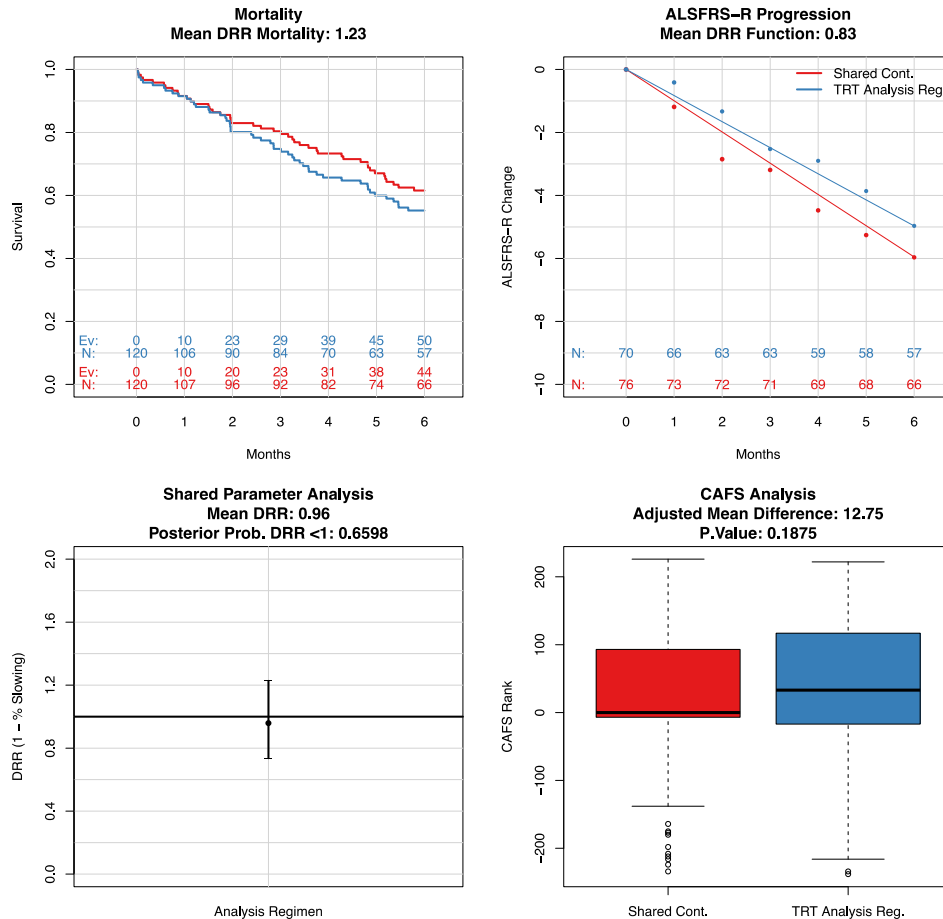
### 6.1.6 Example Trial 6

Figure 6.1.6 shows the same underlying functional data as example trials 4 and 5, with an increase in mortality rate of 40% 6-month mortality on the control arm, a DRR of 1.0 on function and 1.3 on mortality. Those who experience mortality on the treated arm are more likely to also have a worse functional decline. There are 50 and 44 total participants who experience mortality on the treated and control arms respectively. The posterior mean mortality DRR (HR) estimate for an independent exponential proportional hazards analysis of mortality is 1.23 (slight negative effect of treatment on mortality). Of the survivors, the overall rate mean change from baseline at 6 months is -5.0 and -6.0 for treated and shared control arms respectively. The posterior mean ALSFRS-R DRR estimate for an independent repeated measures analysis of function for the survivors is 0.83 (slight positive benefit of treatment on function). The shared parameter analysis



provides an overall posterior mean estimate of the DRR across mortality and function of 0.96 (posterior probability DRR <1 is 66%). The joint rank CAFS analysis results are comparable to the shared parameter analysis (one-sided p-value of 0.1875).

**Figure 6.1.6:** Example Trial 6. 40% 6-Month Mortality Rate. DRR of 1.3 on Mortality. DRR of 1.0 on Function.



**Figure 6.1.6:** Example Trial 6. 40% 6-Month Mortality Rate. DRR of 1.3 on Mortality. DRR of 1.0 on Function.

## 6.2 Operating Characteristics Base Scenarios

Table 6.2.1 shows the overall operating characteristics for a single regimen under the master protocol recommended design for the Base simulation scenarios with futility stopping. Additionally, Table 6.2.2 summarizes the observed treatment effect estimates in each simulated trial as a function of the trial duration and outcome.

Under the null scenario there is an overall one-sided Type I error rate of 2.4% for the regimen. The average duration of the regimen is 14 months. There is a 28.0% chance that the regimen will be stopped early for futility.

The master protocol recommended design has 61%, 77%, and 88% power to detect a slowing in the rate of disease progression of 25%, 30% and 35% respectively when mortality and function have a common treatment effect. When there is no benefit in mortality and a 30% slowing in ALSFRS-R progression the power drops from 77% to 72%. When there is a negative effect on mortality and a 30% slowing in ALSFRS-R progression, the power drops further to 68%. Finally, there is less than 1% chance in these scenarios that the regimen will be stopped early for futility.

Given the expected accrual rate, interim analyses will begin approximately 7 months into the trial. Therefore, the final analysis for a regimen is expected to occur around 16 months after that regimen is initiated. Table 6.2.2 summarizes the observed treatment effect estimates that would lead to early stopping for futility or final success. If a regimen stops at the first interim analysis for futility, the average treatment effect estimate (DRR) is 1.35. The smallest observed DRR stopping for futility at this look across all simulated trials was 1.13, corresponding to a 13-35% increase in the rate of disease progression for treatment relative to placebo. At later analyses, 10-13 months from the start of the regimen, the average treatment effect estimate (DRR) observed among regimens that stopped for futility was 1.16-1.21 and the smallest observed DRR across all simulated trials observed to stop for futility at these looks was 1.05-1.08, corresponding to a 5-8% increase in the rate of disease progression for treatment relative to placebo. Regimens never stopped early for futility if observed treatment effect was less than 1 (signaling a slowing in the rate of progression) and only stopped for futility if there was at least a 5% estimated increase in the rate of progression under treatment.

Scenario (% Slowing ALSFRS-R)	HR Mort.	Mean Duration (Months)	Prob. Success	Prob. Early Futility	Mean Estimated DRR
0%	1	14	0.024	0.28	1.05
25%	.75	15	0.61	0.01	0.75
30%	.7	15	0.77	0.00	0.69
35%	.65	15	0.88	0.00	0.64
30%	1	15	0.72	0.00	0.71
30%	1.3	15	0.68	0.01	0.72

?

Interim /Final	Approx. Trial Duration (Months)	Early Futility		Success	
		Mean	Min	Mean	Max

<b>1</b>	<b>7</b>	1.35	1.13	-	-
<b>2</b>	<b>10</b>	1.21	1.08	-	-
<b>3</b>	<b>13</b>	1.16	1.05	-	-
<b>Final</b>	<b>16</b>	-	-	0.65	0.82

### 6.3 Operating Characteristics Integration of Mortality and Function

This section provides sensitivity of the overall operating characteristics to the assumptions of an overall 5% 6-month mortality rate as well as the assumption that mortality and function have a common treatment effect. All operating characteristics in this section assume no futility stopping.

Table 6.3 provides Type I error, power and DRR estimates for the base scenario (5% 6-month mortality) as well as scenarios when the mortality rate is increased (10-20% 6-month mortality). Power and average DRR estimates are provided for treatment effect scenarios where the true DRR for mortality and function is the same and equal to .70 and when the true DRR for mortality and function is different (null or negative effect on mortality).

Under the null scenario when the true DRR equals 1.0 for function and true HR=1.0 for mortality, the type I error and the estimated DRR are not sensitive to the assumption of the percentage of 6-month mortality.

Under scenarios when the treatment effect for mortality is null or worse (true HR=1.0 or HR=1.3) and there is a 30% slowing in ALSFRS-R (true DRR=0.70), the power and estimated DRR decrease as the rate of mortality increases. This is due to the overall treatment effect being more heavily weighted by the mortality effect. The average estimated DRR equals 0.69 when the true DRR and HR parameters equal 0.70. Under a 20% 6-month mortality rate and a true DRR equal to 0.70, the average estimated DRR equals 0.75 and 0.81 when the true mortality HR equals 1.0 and 1.3, respectively, thereby decreasing the estimated functional treatment effect by 6-12% (absolute) compared to the scenario with both true DRR and true HR equal 0.70.

**Table 6.3: Base and Sensitivity Scenarios on Combining Mortality and Function; No Early Futility Stopping**

Scenario	DRR ALSFRS-R= 1.0		DRR ALSFRS-R = .70					
	DRR Mort. = 1.0		DRR Mort. = .70		DRR Mort. = 1.0		DRR Mort. = 1.3	
	Type I Error	Mean Est. DRR	Power	Mean Est. DRR	Power	Mean Est. DRR	Power	Mean Est. DRR
Base (5% Mort. Rate)	0.024	1.01	0.77	0.69	0.72	0.71	0.68	0.72
10% Mort. Rate	0.023	1.01	0.77	0.69	0.67	0.72	0.57	0.75
20% Mort. Rate	0.024	1.01	0.77	0.69	0.56	0.75	0.35	0.81

### 6.4 Operating Characteristics Differences Across Regimens

This section provides sensitivity of the overall operating characteristics to the assumption that regimens within the shared control have the same ALSFRS-R distributions. In particular, we look at the sensitivity of operating characteristics to differences across the regimens in the rate of progression of ALSFRS-R as well as differences in the residual error of ALSFRS-R. All operating characteristics in this section assume no futility stopping.

Table 6.4 provides Type I error, power and DRR estimates for the base scenario (all regimens have the same ALSFRS-R progression rate and residual error) as well as scenarios when the analysis regimen differs from all other regimens in terms of the ALSFRS-R progression rate and ALSFRS-R residual error. Power and DRR estimates are provided for treatment effect scenarios where the DRR for mortality and function is the same and equal to .70 and when the DRR for mortality and function is different (null or negative effect on mortality).

Under the extreme assumption that participants in the analysis regimen progress at a 10% slower rate of progression on ALSFRS-R than those in all other regimens, there is an increased Type I error of 6% and a small positive bias in the treatment effect estimate of .96 (4% slowing in progression). Under the assumption that participants in the analysis regimen progress at a 10% faster rate of progression on ALSFRS-R than those in all other regimens, the Type I error decreases to 1% with a small negative bias in the treatment effect estimate equal to 1.05 (5% increase in progression). The sensitivity of these results is due to the borrowing across regimens for the shared control.

In addition to the primary analysis, sensitivity analyses will be provided with regards to the shared control (Section 4.2) to assess differences in rates of progression across regimens and how treatment effect estimates differ under the analysis regimen when the treated group is compared to only the regimen-specific controls and compared to only the controls with the same mode of administration.

Operating characteristics are not sensitive to differences in the ALSFRS-R residual error for the analysis regimen compared to other regimens other than having an increase or decrease in power when ALSFRS-R under the analysis regimen has more or less residual error.

<b>Table 6.4: Base and Sensitivity Scenarios on Differences Across Regimens; No Early Futility Stopping; Common Mortality and Function Effect</b>				
<b>Scenario</b>	<b>Null DRR 1.0</b>		<b>Alternative DRR 0.70</b>	
	<b>Type I Error</b>	<b>Mean Est. DRR</b>	<b>Power</b>	<b>Mean Est. DRR</b>
Base	0.024	1.01	0.77	0.69
ALSFRS-R Slower Progress Analysis Reg.	0.060	0.96	0.85	0.66
ALSFRS-R Faster Progress Analysis Reg.	0.010	1.05	0.67	0.72
ALSFRS-R Lower Resid. Error Analysis Reg.	0.024	1.01	0.79	0.69
ALSFRS-R Higher Resid. Error Analysis Reg.	0.023	1.01	0.75	0.69

## 6.5 Operating Characteristics Additional Sensitivity Scenarios

This section provides additional sensitivity results of the overall operating characteristics to the assumptions of accrual rates, dropout rates, timing of enrolling additional regimens, and distributional assumptions of ALSFRS-R common to all regimens. All operating characteristics in this section assume no futility stopping.

Table 6.5 shows the overall power (under a DRR of .70 for Mortality and Function) and Type I error for the base scenarios as well as all additional sensitivity scenarios described in Section 5.2 without futility stopping.

Under all Null scenarios, Type I error is controlled at 2.5% or less without futility stopping. Type I error decreases as there is less shared controls in the final analysis (faster accrual and regimens enrolling further apart).

Under all scenarios where the treatment effect is common between ALSFRS-R slowing and mortality (DRR is 0.70) the power of the trial ranges between 56-79%. Power is the lowest when the regimens start six months apart since the first regimen will have less shared control. Mean DRR estimates range from 0.69 – 0.71 (29-31% slowing).

<b>Table 6.5: Base and Sensitivity Scenarios with No Early Futility Stopping; Common Mortality and Function Effect</b>				
<b>Scenario</b>	<b>Null DRR 1.0</b>		<b>Alternative DRR 0.70</b>	
	<b>Type I Error</b>	<b>Mean Est. DRR</b>	<b>Power</b>	<b>Mean Est. DRR</b>
Base	0.024	1.01	0.77	0.69
Slower Accrual	0.025	1.01	0.77	0.69
Faster Accrual	0.020	1.01	0.76	0.69
4% Dropout	0.024	1.01	0.74	0.69
6% Dropout	0.024	1.01	0.71	0.69
Reg. Start 3 Months Apart	0.023	1.02	0.67	0.70
Reg. Start 6 Months Apart	0.021	1.03	0.56	0.71
ALSFRS-R Slower Progress All Reg.	0.023	1.01	0.75	0.69
ALSFRS-R Faster Progress All Reg.	0.023	1.01	0.78	0.69
ALSFRS-R Lower Resid. Error All Reg.	0.023	1.01	0.79	0.69
ALSFRS-R Higher Resid. Error All Reg.	0.023	1.01	0.75	0.69

## 7.0 References

Berry, J. D. e. a., 2013. The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials.. *Amyotrophic lateral sclerosis and frontotemporal degeneration*, Volume 14.3, pp. 162-168.

## ***Appendix II: El Escorial World Federation of Neurology Criteria for the Diagnosis of ALS***

Information obtained from the web site: [www.wfnals.org](http://www.wfnals.org).

The diagnosis of Amyotrophic Lateral Sclerosis [ALS] requires:

A - The presence of:

(A:1) evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination,

(A:2) evidence of upper motor neuron (UMN) degeneration by clinical examination, and

(A:3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination, together with

B - The absence of:

(B:1) electrophysiological and pathological evidence of other disease processes that might

explain the signs of LMN and/or UMN degeneration, and

(B:2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

### **CLINICAL STUDIES IN THE DIAGNOSIS OF ALS**

A careful history, physical and neurological examination must search for clinical evidence of UMN and LMN signs in four regions [brainstem, cervical, thoracic, or lumbosacral spinal cord] (see Table 1) of the central nervous system [CNS]. Ancillary tests should be reasonably applied, as clinically indicated, to exclude other disease processes. These should include electrodiagnostic, neurophysiological, neuroimaging and clinical laboratory studies. Clinical evidence of LMN and UMN degeneration is required for the diagnosis of ALS. The clinical diagnosis of ALS, without pathological confirmation, may be categorized into various levels of certainty by clinical assessment alone depending on the presence of UMN and LMN signs together in the same topographical anatomic region in either the brainstem [bulbar cranial motor neurons], cervical, thoracic, or lumbosacral spinal cord [anterior horn motor neurons]. The terms Clinical Definite ALS and Clinically Probable ALS are used to describe these categories of clinical diagnostic certainty on clinical criteria alone:

A. Clinically Definite ALS is defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in three regions.

B. Clinically Probable ALS is defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

C. Clinically Probable ALS - Laboratory-supported is defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region,

and LMN signs defined by EMG criteria are present in at least two limbs, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

D. Clinically Possible ALS is defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable - Laboratory-supported ALS cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

**Table 1**

	Brainstem	Cervical	Thoracic	Lumbosacral
Lower motor neuron signs weakness, atrophy, fasciculations	jaw, face, palate, tongue, larynx	neck, arm, hand, diaphragm	back, abdomen	back, abdomen, leg, foot
Upper motor neuron signs pathologic spread of reflexes, clonus, etc.	clonic jaw gag reflex exaggerated snout reflex pseudobulbar features forced yawning pathologic DTRs spastic tone	clonic DTRs Hoffman reflex pathologic DTRs spastic tone  preserved reflex in weak wasted limb	loss of superficial abdominal reflexes pathologic DTRs spastic tone	clonic DTRs - extensor plantar response pathologic DTRs spastic tone  preserved reflex in weak wasted limb



**Appendix III: ALS Functional Rating Scale – Revised (ALSFRS-R)**

**ALSFRS-R**

**QUESTIONS:**

**SCORE:**

1. Speech   
4 = Normal speech processes  
3 = Detectable speech disturbances  
2 = Intelligible with repeating  
1 = Speech combined with nonvocal communication  
0 = Loss of useful speech
2. Salivation   
4 = Normal  
3 = Slight but definite excess of saliva in mouth; may have nighttime drooling  
2 = Moderately excessive saliva; may have minimal drooling  
1 = Marked excess of saliva with some drooling  
0 = Marked drooling; requires constant tissue or handkerchief
3. Swallowing   
4 = Normal eating habits  
3 = Early eating problems – occasional choking  
2 = Dietary consistency changes  
1 = Needs supplemental tube feeding  
0 = NPO (exclusively parenteral or enteral feeding)
4. Handwriting   
4 = Normal  
3 = Slow or sloppy; all words are legible  
2 = Not all words are legible  
1 = No words are legible but can still grip a pen  
0 = Unable to grip pen
- 5a. Cutting Food and Handling Utensils (patients without gastrostomy)   
4 = Normal  
3 = Somewhat slow and clumsy, but no help needed

- 2 = Can cut most foods, although clumsy and slow; some help needed
- 1 = Food must be cut by someone, but can still feed slowly
- 0 = Needs to be fed

5b. Cutting Food and Handling Utensils (alternate scale for patients with gastrostomy)

- 4 = Normal
- 3 = Clumsy, but able to perform all manipulations independently
- 2 = Some help needed with closures and fasteners
- 1 = Provides minimal assistance to caregivers
- 0 = Unable to perform any aspect of task

6. Dressing and Hygiene

- 4 = Normal function
- 3 = Independent, can complete self-care with effort or decreased efficiency
- 2 = Intermittent assistance or substitute methods
- 1 = Needs attendant for self-care
- 0 = Total dependence

7. Turning in Bed and Adjusting Bed Clothes

- 4 = Normal function
- 3 = Somewhat slow and clumsy, but no help needed
- 2 = Can turn alone, or adjust sheets, but with great difficulty
- 1 = Can initiate, but not turn or adjust sheets alone
- 0 = Helpless

8. Walking

- 4 = Normal
- 3 = Early ambulation difficulties
- 2 = Walks with assistance
- 1 = Nonambulatory functional movement only
- 0 = No purposeful leg movement

9. Climbing Stairs

- 4 = Normal
- 3 = Slow
- 2 = Mild unsteadiness or fatigue
- 1 = Needs assistance

0 = Cannot do

R-1. Dyspnea

4 = None

3 = Occurs when walking

2 = Occurs with one or more of the following: eating, bathing, dressing

1 = Occurs at rest, difficulty breathing when either sitting or lying

0 = Significant difficulty, considering using mechanical respiratory support

R-2 Orthopnea

4 = None

3 = Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows

2 = Needs extra pillow in order to sleep (more than two)

1 = Can only sleep sitting up

0 = Unable to sleep without mechanical assistance

R-3 Respiratory Insufficiency

4 = None

3 = Intermittent use of BiPAP

2 = Continuous use of BiPAP during the night

1 = Continuous use of BiPAP during the night and day

0 = Invasive mechanical ventilation by intubation or tracheostomy

Evaluator's Initials: \_\_\_\_\_

**Appendix IV: Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline Version**

Information obtained from: <http://www.cssrs.columbia.edu/>

<b>SUICIDAL IDEATION</b>	
<i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i>	Lifetime: Time He/She Felt Most Suicidal
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <b>Have you wished you were dead or wished you could go to sleep and not wake up?</b> If yes, describe:	<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>
<b>2. Non-Specific Active Suicidal Thoughts</b> General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan. <b>Have you actually had any thoughts of killing yourself?</b> If yes, describe:	<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <b>Have you been thinking about how you might do this?</b> If yes, describe:	<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <b>Have you had these thoughts and had some intention of acting on them?</b> If yes, describe:	<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <b>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</b> If yes, describe:	<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>
<b>INTENSITY OF IDEATION</b>	
<i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i>  _____	Most Severe
<b>Most Severe Ideation:</b> <b>Type # (1-5) Description of Ideation</b>	
<b>Frequency</b> <b>How many times have you had these thoughts?</b> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____
<b>Duration</b> <b>When you have the thoughts, how long do they last?</b> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	_____

<p><b>Controllability</b>  <b>Could/can you stop thinking about killing yourself or wanting to die if you want to?</b>  (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty  (2) Can control thoughts with little difficulty (5) Unable to control thoughts  (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts</p>	<p>_____</p>
<p><b>Deterrents</b>  <b>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</b>  (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you  (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you  (3) Uncertain that deterrents stopped you (0) Does not apply</p>	<p>_____</p>
<p><b>Reasons for Ideation</b>  <b>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</b>  (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on  (2) Mostly to get attention, revenge or a reaction from others living with the pain or how you were feeling)  (3) Equally to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on  and to end/stop the pain. living with the pain or how you were feeling)  (0) Does not apply</p>	<p>_____</p>

<p><b>SUICIDAL BEHAVIOR</b>  <i>(Check all that apply, so long as these are separate events; must ask about all types)</i></p>	<p><b>Lifetime</b></p>
<p><b>Actual Attempt:</b>  A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <b>any</b> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b>, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.  Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.  <b>Have you made a suicide attempt?</b>  <b>Have you done anything to harm yourself?</b>  <b>Have you done anything dangerous where you could have died?</b>  <b>What did you do?</b>  <b>Did you _____ as a way to end your life?</b>  <b>Did you want to die (even a little) when you _____?</b>  <b>Were you trying to end your life when you _____?</b>  <b>Or did you think it was possible you could have died from _____?</b>  <b>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</b> (Self-Injurious Behavior without suicidal intent)  If yes, describe:  <b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p>	<p><b>Yes No</b>  <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts  _____  <b>Yes No</b>  <input type="checkbox"/> <input type="checkbox"/></p>

<p><b>Interrupted Attempt:</b>  When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>).  Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.  <b>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</b>  If yes, describe:</p>			<p>Yes No  <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted  _____</p>	
<p><b>Aborted Attempt:</b>  When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.  <b>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</b>  If yes, describe:</p>			<p>Yes No  <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted  _____</p>	
<p><b>Preparatory Acts or Behavior:</b>  Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).  <b>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</b>  If yes, describe:</p>			<p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p>	
<p><b>Suicidal Behavior:</b>  Suicidal behavior was present during the assessment period?</p>			<p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p>	
<p><b>Answer for Actual Attempts Only</b></p>		<p>Most Recent Attempt Date:</p>	<p>Most Lethal Attempt Date:</p>	<p>Initial/First Attempt Date:</p>
<p><b>Actual Lethality/Medical Damage:</b>  0. No physical damage or very minor physical damage (e.g., surface scratches).  1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).  2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).  3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).  4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).  5. Death</p>		<p>Enter Code  _____</p>	<p>Enter Code  _____</p>	<p>Enter Code  _____</p>
<p><b>Potential Lethality: Only Answer if Actual Lethality=0</b>  Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).  0 = Behavior not likely to result in injury  1 = Behavior likely to result in injury but not likely to cause death  2 = Behavior likely to result in death despite available medical care</p>		<p>Enter Code  _____</p>	<p>Enter Code  _____</p>	<p>Enter Code  _____</p>

**Appendix V: Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version**

Information obtained from: <http://www.cssrs.columbia.edu/>

<b>SUICIDAL IDEATION</b>	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>2. Non-Specific Active Suicidal Thoughts</b> General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>INTENSITY OF IDEATION</b>	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). <b>Most Severe Ideation:</b> _____ <b>Type # (1-5) Description of Ideation</b>	Most Severe
<b>Frequency</b> <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____
<b>Duration</b> <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	_____
<b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts	_____

<p><b>Deterrents</b>  <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i></p> <p>(1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you  (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you  (3) Uncertain that deterrents stopped you (0) Does not apply</p>	<p>_____</p>
<p><b>Reasons for Ideation</b>  <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i></p> <p>(1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on  (2) Mostly to get attention, revenge or a reaction from others living with the pain or how you were feeling)  (3) Equally to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on and to end/stop the pain living with the pain or how you were feeling)  (0) Does not apply</p>	<p>_____</p>

<p><b>SUICIDAL BEHAVIOR</b>  <i>(Check all that apply, so long as these are separate events; must ask about all types)</i></p>	<p>Since Last Visit</p>
<p><b>Actual Attempt:</b>  A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <b>any</b> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b><i>There does not have to be any injury or harm</i></b>, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.</p> <p><b><i>Have you made a suicide attempt?</i></b>  <b><i>Have you done anything to harm yourself?</i></b>  <b><i>Have you done anything dangerous where you could have died?</i></b>  <b><i>What did you do?</i></b>  <b><i>Did you _____ as a way to end your life?</i></b>  <b><i>Did you want to die (even a little) when you _____?</i></b>  <b><i>Were you trying to end your life when you _____?</i></b>  <b><i>Or did you think it was possible you could have died from _____?</i></b>  <b><i>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</i></b> (Self-Injurious Behavior without suicidal intent)  If yes, describe:</p> <p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p>	<p><b>Yes No</b>  <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts  _____</p> <p><b>Yes No</b>  <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Interrupted Attempt:</b>  When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>).</p> <p>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.</p> <p><b><i>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</i></b>  If yes, describe:</p>	<p><b>Yes No</b>  <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted  _____</p>



<p><b>Aborted Attempt:</b> When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.</p> <p><b><i>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</i></b></p> <p>If yes, describe:</p>	<p><b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted _____</p>
<p><b>Preparatory Acts or Behavior:</b> Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).</p> <p><b><i>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</i></b></p> <p>If yes, describe:</p>	<p><b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?</p>	<p><b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicide:</b></p>	<p><b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/></p>
<p><b><i>Answer for Actual Attempts Only</i></b></p>	<p>Most Lethal Attempt Date:</p>
<p><b>Actual Lethality/Medical Damage:</b></p> <p>0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death</p>	<p><i>Enter Code</i> _____</p>
<p><b>Potential Lethality: Only Answer if Actual Lethality=0</b></p> <p>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care</p>	<p><i>Enter Code</i> _____</p>

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