

## 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  
at Mass General

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*Merit Cudkowicz*

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**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 **12/15/2022** (Version **5.0**) 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, single 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
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ATE	Active Treatment Extension
CC	Coordination Center
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DCC	Data Coordination Center
DSMB	Data and Safety Monitoring Board
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
FVC	Forced Vital Capacity
FDA	Food and Drug Administration
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 Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intent-to-Treat
LFTs	Liver Function Tests
LP	Lumbar Puncture
MGB	Mass General Brigham
MM	Medical 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
NfL	Neurofilament Light Chain
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PAV	Permanent Assisted Ventilation
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetic
RA	Reliance Agreement
RSA	Regimen-Specific Appendix
SAE	Serious Adverse Event
SDTs	Source Document Templates
SI	Site Investigator
sIRB	Single Institutional Review Board
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 randomly assigned with equal probability among 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 up to approximately 80 centers in the US.

### **Treatment Duration**

Treatment duration of the placebo-controlled period is a maximum of 24-weeks for each regimen. The duration of the Active Treatment Extension (ATE) period 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.

#### **Safety Objective:**

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

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

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

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

Change from baseline through week 24 in disease severity as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) total score and survival.

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

- Change from baseline through week 24 in respiratory function as assessed by slow vital capacity (SVC).
- Change from baseline through week 24 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 biofluid biomarkers.
- Changes in patient reported outcomes.

#### **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 occur every 4 weeks and will be clinic-, phone-, or telemedicine-based, as applicable. Additional assessments may be added and will be described in each RSA. The Master Protocol allows a 24-week duration of placebo-controlled treatment for an intervention and an additional Active Treatment Extension (ATE) period, as 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 -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
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	
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

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
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 <sup>11</sup>			X					X			
Assignment to a regimen	X										
Randomization within a regimen		X									
Administer/Dispense Study Drug			X <sup>8</sup>			X		X			
Study Drug Accountability/Compliance				X <sup>14</sup>	X	X	X <sup>14</sup>	X	X <sup>14</sup>	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. Coagulation panel will occur at the Master Protocol Screening and Week 16 Visits or as in the RSA. 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 Master Protocol 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 study drug 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 period 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 period 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.b](#)

<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> CSF collection may differ from the Schedule of Activities, and will be performed as described in each RSA.

<sup>12</sup> If required due to pandemic-related or other restrictions, Forced Vital Capacity (FVC) performed by a Pulmonary Function Laboratory evaluator 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 needed to protect the safety of the participant due to a pandemic, disability or other medical reason.

<sup>14</sup> Drug accountability will not be done at phone visits. A drug compliance check in will be conducted during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.



## STUDY WORKFLOW

Figure 1. Example Master Protocol Schema

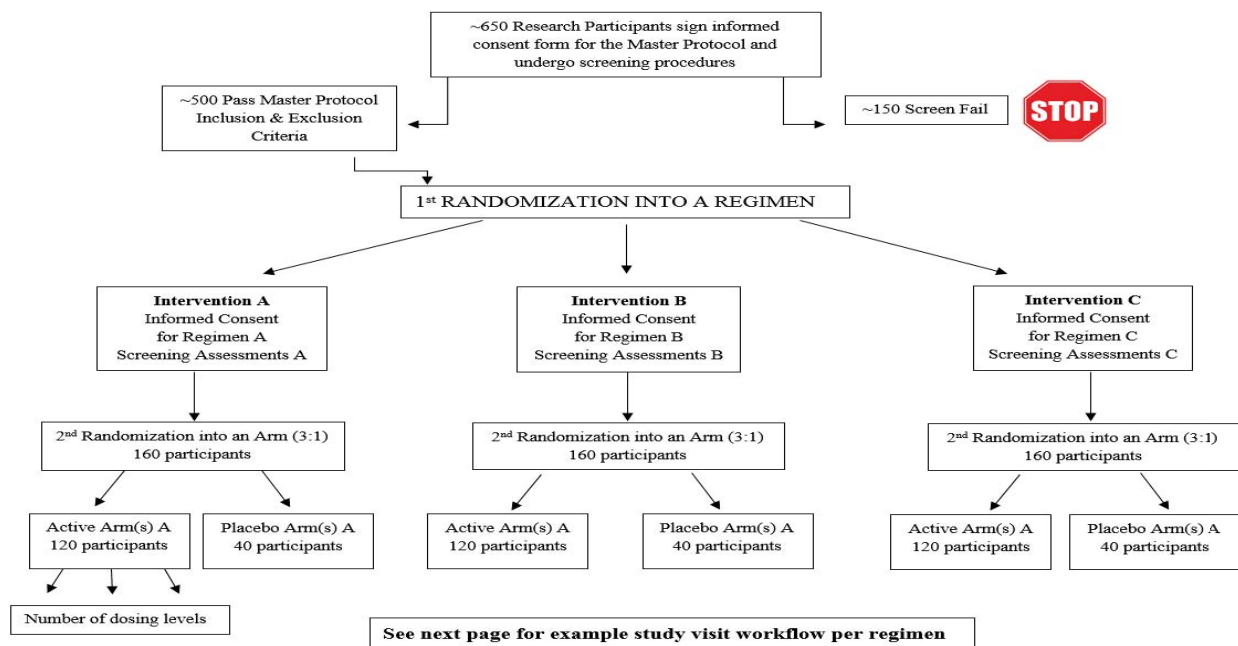


Figure 1 represents an example of the study schema assuming three concurrently enrolling regimens. The Master Protocol schema will change depending on the number of regimens that are enrolling at any given time. Intervention A investigates an active treatment with multiple dosing levels. In this example, regimen sample size is 160 participants, actual regimen sample size will be specified in each RSA.

Figure 2. Example Study Visit Workflow per Regimen

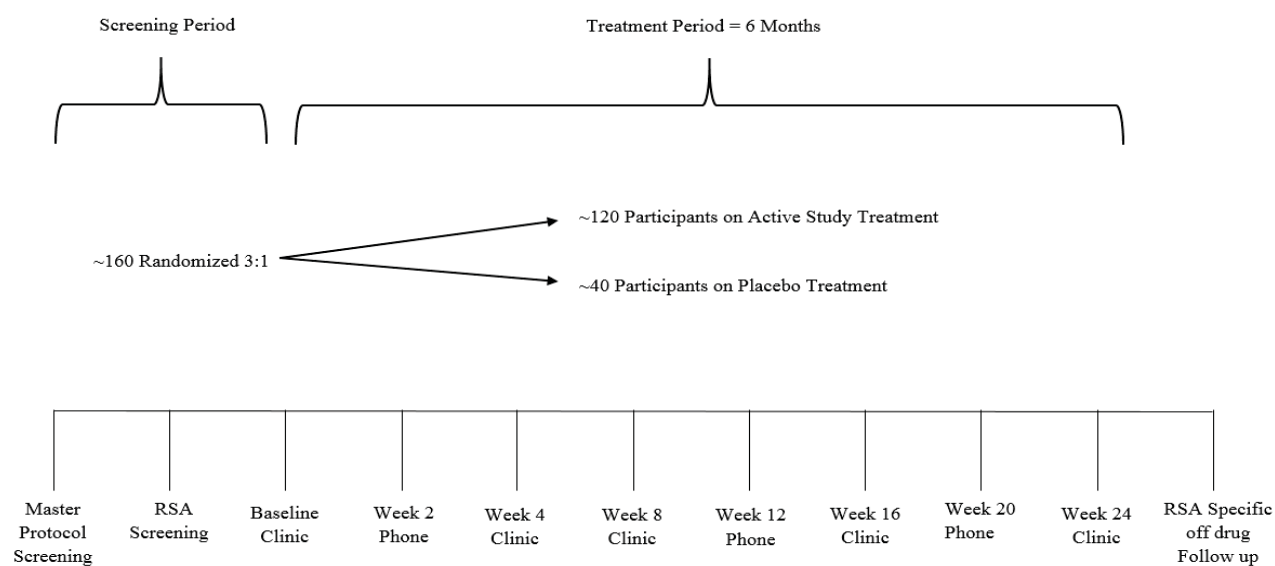


Figure 2 represents an example of the study visits that will occur over 24 weeks for all participants that are assigned to a regimen. In this example, regimen sample size is 160 participants, actual regimen sample size will be specified in each RSA.

## **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 Mass General Brigham (MGB) IRBs located in Boston, MA, collectively known as the MGB Human Research System (MGB HRS), have been selected by the Northeast ALS Consortium (NEALS) to serve as the single IRB (sIRB) for the Master Protocol. 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 sIRB Authorization Agreement (Reliance Agreement or RA) to rely on the MGB HRS 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 sIRB 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 not performed as clinic visit standard of care (e.g., vital signs, weight), 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 sIRB 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 sIRB 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 sIRB. 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, edaravone, and Relyvrio 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 HEALEY ALS Platform Trial will describe:

1. Specific additional inclusion or exclusion criteria for that investigational product, if any. 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, prohibited medications (as applicable) 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
Primary		
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 and survival	<i>The ALSFRS-R measures function in daily activities and is an established scale for monitoring disease progression in ALS.</i>
Secondary		
To test the effect of multiple investigational products on selected secondary measures of disease progression.	<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>
Safety		
	<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 people with 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 biofluid biomarkers.</li> <li>• Changes in patient reported outcomes.</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 treatment 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 and this blind will be maintained throughout the ATE period of the study. 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 12 weeks. 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. The default design for a regimen will include stopping early only for futility.

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

- 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.

- 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 through week 24 of the placebo-controlled period. Research participants will continue in the ATE period or may be re-screened for entry into the Master Protocol after the mandatory wash-out period, if eligible.
- If a regimen includes more than one active arm to allow for multiple dosing levels or other variations in treatment, then rules specifying the allocation to 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 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.
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.
7. Participants must either not take edaravone or have completed at least one cycle (typically 14 days) of edaravone prior to the Master Protocol Screening Visit.
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.
10. Participants must either not take Relyvrio/ Albrioza or have started Relyvrio/ Albrioza  $\geq$  30 days prior to the Master Protocol Screening Visit.

### 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.

Clinically significant abnormal liver or kidney function is exclusionary. The following values [alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN) or estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73m<sup>2</sup>] are exclusionary regardless of clinical symptoms.

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 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 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.

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 stable dosage throughout the study.

***Edaravone.*** Participants taking concomitant edaravone at study entry must have completed at least one cycle of treatment (typically 14 days) prior to the Master Protocol Screening Visit and must intend to continue taking the same stable dosage throughout the study.

***Relyvrio/ Albrioza.*** Participants taking concomitant Relyvrio/ Albrioza at study entry must have started  $\geq 30$  days prior to the Master Protocol Screening Visit

If the SI determines that riluzole, edaravone or Relyvrio/ Albrioza should be discontinued or dose-adjusted for medical reasons, this will not be considered a protocol deviation. If extenuating circumstances cause doses to be missed for reasons not intended or medically indicated (scheduling, drug availability, etc.), this will not be considered a protocol deviation. If riluzole, edaravone or Relyvrio/ Albrioza is stopped for any non-medical reason (participant preference), this will be recorded as a minor protocol deviation. If initiation of riluzole, edaravone or Relyvrio/ Albrioza therapy begins at any point during participation, this will be recorded as a minor protocol deviation

***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 sIRB.

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 screen 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, not performed as clinic visit standard of care (e.g., vital signs, weight), 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 sIRB, 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 who are trained on the study and 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.

Participants may be required to re consent to the Master Protocol if new procedures or information is added in the future. Should a participant need to re consent, this should occur during the participant's next in-person visit. If the participant's next in-person visit is conducted remotely, re consent may also be completed remotely using the following procedures:

1. The site staff provides a copy of the informed consent form to the participant.
2. The participant reads through the consent form but does not sign.
3. The Site Investigator, or other study staff member approved and delegated to obtain informed consent, contacts the participant and reviews the informed consent form with the participant over the phone or via telemedicine.
4. The participant signs the informed consent form and provides the original signed consent form back to the site.

***Once received at the site, the individual who consented the participant via phone or telemedicine signs the informed consent form.***

### ***6.3 Ineligible Participants***

All sites will be required to collect demographic information including age, gender, race, and ethnicity, and 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 by meeting all inclusion and no 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 a given trial regimen will not be blinded to regimen assignments but will be blinded to the randomized treatment assignments within a regimen, and this blind will be maintained through the ATE period of the study, as outlined in the HEALEY ALS Platform Trial Blinding and Unblinding Plan. In the event of a medical emergency that necessitates the unblinding of the Medical Monitor (MM) or a 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 (including lack of safety data collected), 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 and through the ATE period of the study, 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. For participants followed under the ITT principle, an in-person Early Termination Visit will be completed after they discontinue follow up under the ITT principle. A Follow-Up Safety Call at the time study drug is discontinued may not be required, as long as the participant is followed under the ITT principle for a minimum of 28 days.

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

A 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 File (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 each RSA.

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 or defer to site specific policies.

#### ***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 HEALEY 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 due to a pandemic, disability or other medical reason, 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 study Manual of Procedures (MOP). The following procedures should be completed in the suggested order and as per the Schedule of Activities: ALSFRS-R, AE Review, Columbia-Suicide Severity Rating Scale, Concomitant Medications, and IP Accountability/Compliance; each RSA may describe additional activities. Procedures for collecting IP Accountability/Compliance remotely are described in the study MOPs. Additionally, selected vital signs and laboratory evaluations may be performed by a home health agency as described in the study MOP. Vital signs include: systolic and diastolic pressure, respiratory rate, heart rate, and temperature. Laboratory evaluation includes hematology (CBC with differential), coagulation parameters, 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 within the Master Protocol Screening period 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 by a Pulmonary Function Laboratory evaluator to assess eligibility. At all subsequent visits to Master Protocol Screening, if SVC cannot be obtained due to a pandemic, disability or other medical reason, this outcome measure should be skipped, recorded as such in the applicable source documentation, and a protocol deviation reported.

Clinical Safety Labs: the default and preferred method for collecting clinical safety labs is by using the study specific central laboratory as described in the study MOP. If needed to protect the safety of the participant due to a pandemic, disability or other medical reason, clinical safety labs can be collected using one of the following methods:

- Home health agency as described in the study MOP, or
- Local site laboratory resources, or
- Independent labs offering such services as described in this protocol and/or local to the participant (e.g. primary care physician)

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

The following procedures will be performed in-person, after Master Protocol informed consent is obtained, to determine the participant's eligibility for the Master Protocol and are listed in preferred order to be completed:

Assess Master Protocol inclusion and exclusion criteria

Obtain ALS and medical history

Obtain demographics

Perform Vital Capacity

Perform physical examination

Perform neurological examination

Measure vital signs including height and weight

Administer ALSFRS-R questionnaire

Perform 12-lead electrocardiogram (ECG)

Collect blood samples for clinical screening assessments (including coagulation parameters) 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

### *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. If eligible, 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 the participant's NeuroSTAMP)
- 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 time-dependent 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. Safety labs required for the site investigator to determine eligibility, can be repeated during the Master Protocol screening period, if necessary. If a participant is re-screened for Master Protocol eligibility, they 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.

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 their Week 24 Visit in the placebo-controlled period and terminates their participation in the study
  - 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 preferred 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 preferred 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 (as described in the RSA)

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 preferred order to be completed:

Assess and document AEs

Drug Compliance Check-In

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 preferred 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 preferred 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 preferred order to be completed:

Administer ALSFRS-R questionnaire  
Review and document concomitant medications  
Assess and document AEs  
Drug Compliance Check-In  
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 preferred 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 (including coagulation parameters) 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 (as described in the RSA)  
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 preferred order to be completed:

Administer ALSFRS-R questionnaire  
Review and document concomitant medications  
Assess and document AEs  
Drug Compliance Check-In  
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 preferred 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 terminate their participation in the study early 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 sIRB 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, and 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 the Sponsor determines negatively affect: (1) the rights or welfare of the participant; (2), risk benefit assessment; or (3) the integrity of the data (ability to draw valid conclusions from the study data). As a result of deviations, corrective and preventative actions are to be developed by the site with review by the CC and Study Monitors and implemented promptly.

All deviations from the protocol will be recorded in the participant's source documentation. Protocol deviations must be entered in the Protocol Deviations Log in the EDC system. Deviations will be reported to the sIRB 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.

Vital status, defined as a determination of date of death or PAV status or date last known alive and date last known to be PAV-free, will be determined by site study staff for each randomized participant throughout the placebo-controlled portion of their follow-up (generally the Week 24 visit, as indicated in the SOA). At approximately the time of the last patient last visit (LPLV) of the placebo-controlled period of a given regimen, a second vital status check will be completed by site study staff for each randomized participant. When prompted by the Coordination Center, sites will contact all randomized participants to assess vital status.

We may also ascertain vital status at later time points. An outside vendor will be used to ascertain death or date of last known alive for all randomized participants by using publicly available data sources. When prompted by the Coordination Center, sites will provide demographic information (e.g. participant name, date of birth, last known address) to the vendor using a secure method.



## 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/Baseline as described in the RSA, 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)

Additionally, coagulation parameters (Prothrombin time, International normalized ratio, Activated partial thromboplastin time) will be collected for all participants at the Master Protocol Screening and Week 16 Visits.

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, unless needed to protect the safety of the participant due to a pandemic, disability or other medical reason, they are collected by a home health agency, local site laboratory or independent laboratory. The SI may order additional local testing or a retest at the central laboratory, if needed, to further assess an AE, or if there is any suspicion that a participant may be pregnant, or if a result could not be obtained throughout the course of the study. If additional testing is required to obtain results, the participant may be asked to return to repeat blood collection for such missing results.

#### *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>.

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 study 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 ALSFRS-R and every two years for SVC and HHD 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 Laboratory Manual.

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 consenting to DNA collection will provide a blood sample for deoxyribonucleic acid (DNA) extraction for genome sequencing during 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 (LP) procedure will be performed to collect CSF, as described in each RSA.

Study staff should document the time of study drug dose administered.

Coagulation parameters (Prothrombin time, International normalized ratio, Activated partial thromboplastin time) will be collected for all participants at the Master Protocol Screening and Week 16 Visits.

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,. 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 source and 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 records. 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, or any

unexpected AE that is deemed related to the study drug, which would have implications for the conduct of the study (e.g., requiring a significant and usually safety-related change to the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent or investigator's brochure)

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](#) (ALS Master Protocol Recommended Design and Simulation Report) to the Master Protocol Statistical Analysis Plan (M-SAP). Regimen-specific deviations from the Master Protocol recommended statistical design are allowed and full statistical details are provided in separate regimen specific statistical analysis plans (R-SAPs) for each regimen. In the case of any deviation between this protocol and [Appendix I](#) of the M-SAP, [Appendix I](#) of the M-SAP takes precedence. In case of any deviation with an R-SAP, the order of precedence is specified in the R-SAP.

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 from baseline through week 24 in disease severity as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) total score and survival. The primary analysis is a Bayesian shared parameter analysis of ALSFRS-R and survival that compares each regimen-specific active treatment to a shared placebo group that is common across all regimens, as specified in [Appendix I](#) of the M-SAP, [Section 2.2](#) (ALS Master Protocol Recommended Design and Simulation Report Index). The primary survival endpoint is the composite event of death or a death equivalent of progression to PAV. PAV is defined as use of noninvasive or invasive mechanical ventilation for more than 22 hours per day for more than seven consecutive days. The date of PAV initiation is the first day of the consecutive days.

Participants in the master protocol will be randomized in two stages; first to one of the actively enrolling regimens after the participant is determined eligible based on Master Protocol criteria; and then 3:1 to active treatment or placebo within the regimen after the participant is determined eligible based on any regimen-specific eligibility criteria. The master protocol recommended design is 160 participants randomized within 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 recommended early stopping criteria for success (if applicable) and futility are defined in [Appendix I](#) of the M-SAP. Early stopping criteria are non-binding.

Early stopping criteria will be evaluated for 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 12 weeks. 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 24-week-placebo-controlled follow-up.

## ***11.2 Analysis Plan***

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

The primary analysis dataset uses all available longitudinal data (ALSFRS-R total score assessments at 0, 4, 8, 12, 16, 20 and 24 weeks, and assessments during the placebo-controlled follow up period that substitute for missed scheduled visits, including early termination visits) as well as survival within 24 weeks for 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, all participants concurrently randomized to the control arm within the analysis regimen, and control participants from all contributing regimens. 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 participants randomized to the control arm in previously completed regimens (non-concurrent shared controls). Concurrent shared controls are defined as participants randomized to placebo control who were randomized within a 6-month (defined as 180 days) window of the first and last randomization within the analysis regimen.

The Master Protocol allows for additional and more restrictive eligibility criteria specified in a regimen specific appendix (RSA). These additional eligibility criteria will be limited and will be allowed only to ensure participant safety or based on mechanism of action. Major additional regimen-specific eligibility criteria are those that have the potential to lead to significant differences in the patient population with respect to the rate of disease progression. If these criteria can be assessed for all participants entering the platform, then they may be used to subset the shared control to include only those participants that meet these additional regimen-specific

eligibility criteria in the primary analysis. If a subset of the shared control will be used in the primary analysis due to major additional regimen-specific eligibility criteria, this will be pre-specified within each RSA.

### *11.2.2 Primary Efficacy Analysis*

Unless otherwise specified in the RSA or R-SAP, the primary analysis for each analysis regimen is a Bayesian shared parameter model of function and survival. The functional component is a repeated measures ALSFRS-R model that measures the slowing in the mean rate of progression for ALSFRS-R in active treatment participants relative to control participants and uses all available longitudinal data for all participants within the primary analysis population. The survival component is an exponential proportional hazards model. The functional and survival components are connected through a shared common treatment effect (slowing in rate of progression of the disease). The shared treatment effect between the functional and survival 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 active treatment participants at each time point. The treatment effect is quantified by the disease rate ratio (DRR), which represents the ration of the rate of decline of disease progression (rate of ALSFRS-R and mortality rate) of active treatment participant relative to placebo participants (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](#) of the M-SAP.

### *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 data missing 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 potential effect of missing data on inference and estimates from the primary analysis.

#### *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 meet eligibility criteria for a subsequent randomization will be analyzed as new participants with new baseline visits and sets of observations for each regimen to which they were assigned. The baseline visit for each regimen is defined as the visit after assignment to and randomization within 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 active treatment or placebo received in the previous regimen.

#### *11.2.5 Inclusion of Multiple Doses*

If an RSA includes multiple doses under investigation, the recommended primary analysis will be a pooled analysis of all active doses compared to the shared control. Additionally, secondary analyses will be specified within the R-SAP 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 12 weeks. If a regimen is not stopped early for success (if applicable) or futility at an interim analysis, the regimen-specific final analysis of the placebo-controlled period will take place after all participants randomized to that regimen have had the opportunity to complete 24-weeks of follow-up. The default design for a regimen will include stopping early only for futility.

#### *11.3.1 Regimen Success*

The default design for a regimen will not include early stopping for success. If early stopping for success is included in a regimen, success will be declared based on the posterior probability that the active treatment is superior to the placebo group. The posterior probability for declaring success is specified in [Appendix I](#) of the M-SAP and determined based on clinical trial simulations to achieve an overall one-sided Type I error of 2.5%.



### *11.3.2 Regimen Futility*

Futility will be declared for a regimen at an interim analysis if the posterior probability that active treatment slows disease progression relative to placebo by at least 10% is less than 5%. Early stopping for futility in non-binding.

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

### *11.4.1 Secondary Efficacy Analyses*

As a secondary analysis, a joint-rank test of function and survival will be performed. The analysis will rank each pair of participants based first on survival time during the 24-week placebo-controlled period and second, if they both survived or one was censored prior to the observed survival endpoint of the other, on the change in ALSFRS-R total score from baseline to the last jointly observed visit up to 24-weeks<sup>20-22</sup>. The summed ranks will be analyzed by linear regression to adjust for important covariates.

### *11.4.2 Secondary Endpoints*

Secondary endpoints and analyses will be detailed within each RSA and R-SAP.

### *11.4.3 Exploratory Analyses*

Exploratory endpoints and their corresponding analyses will be detailed within each RSA and R-SAP. Such analyses may evaluate alternative functional endpoints and biofluid biomarkers for monitoring disease progression.

### *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 potential effect of modeling assumptions and missing data. Further details are provided in [Appendix I](#) of the M-SAP.

## ***11.5 Safety Analyses***

Safety data, including deaths and death-equivalents, treatment-emergent adverse events (TEAE), and changes in vital signs, ECGs, and clinical laboratory test results, will be summarized for each treatment group among all participants who initiate treatment. 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 by Common Terminology Criteria for Adverse Events (CTCAE) grade and 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 R-SAP.

## ***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](#) of the M-SAP.

Simulations outlined in [Appendix I](#) of the M-SAP, provide example operating characteristics of the recommended design for the first 3 regimens enrolling in the platform across a range of simulation assumptions. Under the null scenario there was an overall one-sided Type I error rate of 2.4% per regimen. The average duration of the regimen was 14 months and there was a 28% chance that the regimen would meet the criterion for early stopping for futility.

The Master Protocol recommended design has 61%, 77%, and 88% power to detect a slowing in the rate of ALSFRS-R progression of 25%, 30% and 35% respectively when function and survival have a common treatment effect. When there is no benefit for survival and a 30% slowing in ALSFRS-R progression the power drops to 72%. When there is a negative effect on survival and a 30% slowing in ALSFRS-R progression, the power drops further to 68%. There is less than a 1% chance in these scenarios that the regimen would meet the criterion for early stopping 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, EMR data, etc). 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 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 Study Monitoring Plan.

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

The Study Monitors will provide monitoring reports to the Sponsor and, if requested, and when required, will provide reports of protocol compliance to the 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 sIRB.

### ***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: 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 II: 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 III: Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline 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.	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. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i> 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. <i>Have you actually had any thoughts of killing yourself?</i> 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.” <i>Have you been thinking about how you might do this?</i> 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.” <i>Have you had these thoughts and had some intention of acting on them?</i> 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. <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:	<b>Yes No</b> <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). Ask about time he/she was feeling the most suicidal.  <hr/> <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	_____
<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> (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	_____
<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> (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	_____

<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>	<b>Lifetime</b>
<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>	<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____  <b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>

<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><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:			<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____	
<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><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> If yes, describe:			<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____	
<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><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> If yes, describe:			<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>	
<b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?			<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>	
<b><i>Answer for Actual Attempts Only</i></b>		Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
<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		Enter Code _____	Enter Code _____	Enter Code _____
<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		Enter Code _____	Enter Code _____	Enter Code _____

## Appendix IV: 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:	<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 during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i> 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.” <i>Have you been thinking about how you might do this?</i> 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 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:	<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. <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:	<b>Yes No</b> <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	_____

<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> (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	_____
<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> (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	_____

<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>	Since Last Visit
<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. <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: <b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b>	<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____ <b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>
<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><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:	<b>Yes No</b> <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____



<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></p> <p><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></p> <p><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></p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicide:</b></p>	<p><b>Yes No</b></p> <p><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).</p> <p>1. Minor physical damage (e.g., lacerations; first-degree burns; mild bleeding; sprains).</p> <p>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).</p> <p>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).</p> <p>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).</p> <p>5. Death</p>	<p><i>Enter Code</i></p> <p>_____</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).</p> <p>0 = Behavior not likely to result in injury</p> <p>1 = Behavior likely to result in injury but not likely to cause death</p> <p>2 = Behavior likely to result in death despite available medical care</p>	<p><i>Enter Code</i></p> <p>_____</p>

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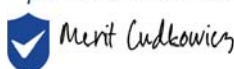
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Sabrina Paganoni Spaganoni@mgh.harvard.edu MD PhD MGH Security Level: Email, Account Authentication (Required)	  Signature Adoption: Pre-selected Style Signature ID: 58705BF6-1CB8-42A8-8752-1BEB826294FA Using IP Address: 132.183.13.11  With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/2/2023 3:48:20 PM Viewed: 2/2/2023 3:55:29 PM Signed: 2/2/2023 3:55:42 PM
Electronic Record and Signature Disclosure: Accepted: 2/2/2023 3:55:29 PM ID: 809c890f-6afc-47e8-be0b-ad071e6730bb		
In Person Signer Events	Signature	Timestamp
Editor Delivery Events	Status	Timestamp
Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp
Witness Events	Signature	Timestamp
Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	2/2/2023 3:48:20 PM
Certified Delivered	Security Checked	2/2/2023 3:55:29 PM
Signing Complete	Security Checked	2/2/2023 3:55:42 PM
Completed	Security Checked	2/2/2023 3:55:42 PM
Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

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