REGIMEN-SPECIFIC APPENDIX [X]

FOR [Drug Name]

Regimen-Specific Appendix Date: MM/DD/YYYY

Version Number: X.X

TABLE OF CONTENTS

SIGNATURE PAGE

I have read the attached Regimen-Specific Appendix (RSA) entitled, "REGIMEN [X]: [Drug Name]" dated [Month DD, YYYY] (Version X.X) and agree to abide by all described RSA procedures. I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice, applicable FDA regulations and guidelines identified in 21 CFR Parts 11, 50, 54, and 312, central Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

By signing the RSA, 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

[Please update list as needed.]

Abbreviation	Definition
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
CNS-BFS	Center for Neurologic Study Bulbar Function Scale
OLE	Open Label Extension
RSA	Regimen-Specific Appendix
SAE	Serious adverse event

REGIMEN-SPECIFIC APPENDIX SUMMARY

Regimen-Specific Appendix [X]
For [INSERT NAME OF STUDY DRUG]

Rationale and RSA Design

[Insert brief description of drug, how it works, and the design for this RSA.]

Allocation to Treatment Regimens
Participants must first be screened under the Master Protocol and before they are randomized to a regimen.

As soon as pre-defined criteria for futility or success (if applicable) for the regimen are met, or the target number of randomized participants has been reached, enrollment will stop in the regimen.

Number of Planned Participants and Treatment Groups
The number of planned participants for this regimen is [160].

There are 2 treatment groups for this regimen, active and placebo. Participants will be randomized in a 3:1 ratio to active treatment or placebo (i.e., [120] active: [40] placebo).

Planned Number of Sites
Research participants will be enrolled from approximately 60 centers in the US.

Treatment Duration
The maximum duration of the placebo-controlled treatment portion is 24 weeks.

Follow-up Duration
At the conclusion of the 24-week placebo-controlled treatment period of the study, all participants will either schedule a [28]-day follow up phone call and end their participation in the regimen or have the option to receive [study drug name] in the Open Label Extension phase of the study. The duration of the Open Label Extension phase is planned for [52] weeks.

Total Planned Trial Duration
For participants completing the placebo-controlled treatment period of the study, the planned amount of time for a participant in the trial is up to [34] weeks, or about [8] months. This duration assumes a 6-week screening window, a 24-week placebo-controlled treatment period,

and a [4]-week safety follow-up period for those participants who do not enter the Open Label Extension. Participants will complete approximately 10 study visits during the placebo-controlled treatment period of the study.

If the participant opts into the subsequent Open Label Extension, the total planned amount of time for a participant in the trial is approximately [86] weeks. This duration assumes a 6-week screening window, 24-week placebo-controlled treatment period, a [52]-week Open Label Extension period, and a [4]-week safety follow-up period. Participants will complete 10 study visits across the planned [52]-week Open Label Extension phase of the study.

SCHEDULE OF ACTIVITIES – PLACEBO-CONTROLLED PERIOD

As per the Schedule of Activities (SOA) below, visits must occur every 4 weeks and will be clinic-, phone- or telemedicine based, as applicable. There is a maximum 24-week duration of placebo-controlled treatment for a Regimen.

[NOTE: THE MASTER PROTOCOL SETS OUT THE MINIMUM VISIT AND ASSESSMENT REQUIREMENTS THAT MUST BE INCORPORATED INTO EACH RSA. ADDITIONAL OPEN LABEL EXTENSION (OLE) AND OTHER FOLLOW-UP VISITS MAY BE ADDED.]

Activity (page 1 of 2)	Master Protocol or Regimen-Specific	Master Protocol Screening[1]	Regimen Specific Screening[1]	Baseline	Week 2	Week 4[14]	Week 8[14]	Week 12	Week 16[14]	Week 20	Week 24 or Early Term. Visit	Follow-Up Safety Call[11]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		-42 to -1 Days[17]	-41 to 0 Day[17]	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	[28] days after last dose ±[3] days
Written Informed Consent[2]	Master	X	X									
Written Informed Consent - OLE	Master								X			
Inclusion/Exclusion Review	Master	X	X[3]									
ALS & Medical History	Master	X										
Demographics	Master	X										
Physical Examination	Master	X										
Neurological Exam	Master	X										
Vital Signs[4]	Master	X		X		X	X		X		X	
Slow Vital Capacity	Master	X[15]		X			X		X		X	
Home Spirometry	Regimen	X[15]		X			X		X		X	
Muscle Strength Assessment	Master			X			X		X		X	
ALSFRS-R	Master	X		X		X	X	X	X	X	X	
ALSAQ-40	Regimen			X							X	
CNS Bulbar Function Scale	Regimen			X			X		X		X	
12-Lead ECG	Master	X									X	
Clinical Safety Labs[5]	Master	X		X		X	X		X		X	
Biomarker Blood Collection	Master			X			X		X		X	

Activity (page 2 of 2)	Master Protocol or Regimen-Specific	Master Protocol Screening[1]	Regimen Specific Screening[1]	Baseline	Week 2	Week 4 [15]	Week 8[14, 15]	Week 12	Week 16[14, 15]	Week 20	Week 24 or Early Term. Visit[14]	Follow-Up Safety Call[11]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		-42 to -1 Days	-41 to 0 Day	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	[28] days after last dose ±[3] days
Biomarker Urine Collection	Master			X			X		X		X	
DNA Collection[7] (optional)	Master			X								
CSF Collection (optional)	Master			X					X[13]			
Concomitant Medication Review	Master	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review[6]	Master	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	Master			X		X	X		X		X	
Install Smartphone App[16]	Regimen			X								
Voice Recording[9]	Regimen			X		X	X		X		X	
Uninstall Smartphone App	Regimen										X	
Assignment to the Regimen	Master	X										
Randomization within the Regimen	Master		X									
Administer/Dispense Investigational product	Master			X[8]		X	X		X		X[10]	
Drug Accountability/Compliance	Master				X	X	X	X	X	X	X	
Exit Questionnaire	Master										X	
Vital Status Determination[12]	Master										X	
[Add regimen-specific activities]	Regimen											

1 Master Protocol Screening procedures must be completed within 42 days to 1 day prior to the Baseline Visit. [The Regimen-Specific Screening Visit and Baseline Visit should be combined, if possible.]

2 During the Master Protocol Screening Visit, participants will be consented via the Platform Trial informed consent form (ICF). After a participant is randomized to a regimen, participants will be consented a second time via the regimen-specific ICF.

3 At the Regimen Specific Screening Visit, participants will have regimen-specific eligibility criteria assessed.

4 Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate and temperature. Height measured at Master Protocol Screening Visit only.

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

6 Adverse events that occur after signing the consent form will be recorded.

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

8 Administer first dose of investigational product only after Baseline Visit procedures are completed.

9 In addition to study visits outlined in the SOA, participants will be asked to complete twice weekly voice recordings at home.

10 Drug will only be dispensed at this visit if the participant continues in the OLE.

11 Participants will only have a Follow-Up Safety Call at this time if they *do not* continue on in the OLE. Participants who continue into OLE will have a Follow-Up Safety Call after their last dose of investigational product during the OLE period.

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

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

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

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

16 Two smartphone apps should be installed on the participant's phone, once to collect the voice recordings and one to collect home spirometry.

17 Master Protocol Screening and Regimen Specific Screening visit window s are relative to Baseline (Day 0).

SCHEDULE OF ACTIVITIES – OPEN LABEL EXTENSION (OPTIONAL)

Activity (page 1 of 1)	Master Protocol or Regimen-Specific	Open Label Extension (Optional)[5]										
		Week 2	Week 4[8]	Week 8[8]	Week 12	Week 16[7]	Week 20	Week 24	Week 28[7]	Week 40[7]	Week 52 or Early Term. Visit[6, 7]	Follow-Up Safety Call[4, 6]
		Phone	Clinic	Clinic	Phone	Clinic	Phone	Phone	Clinic	Clinic	Clinic	Phone
		Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day168 ±3	Day 196 ± 14	Day 280 ± 14	Day 364 ± 14	[28] days after last dose ±[3] days
Vital Signs[1]	Master		X	X		X			X	X	X	
Slow Vital Capacity	Master		X	X		X			X	X	X	
Home Spirometry	Regimen		X	X		X			X	X	X	
ALSFRS-R	Master		X	X	X	X	X	X	X	X	X	
ALSAQ-40	Regimen								X		X	
CNS Bulbar Function Scale	Regimen			X		X			X	X	X	
Clinical Safety Labs[2]	Master		X	X		X			X	X	X	
Biomarker Blood Collection	Master					X			X		X	
Biomarker Urine Collection	Master					X			X		X	
Concomitant Medication Review	Master	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review[3]	Master	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	Master		X	X		X			X	X	X	
Administer/Dispense Investigational product	Master			X		X			X	X	X	
Drug Accountability/Compliance	Master	X	X	X	X	X	X	X	X	X	X	

[Add regimen-specific activities]	Regimen											

1 Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate and temperature. Height in cm measured at Master Protocol Screening Visit only.
2 Clinical safety labs include hematology (CBC with differential), complete chemistry panel, thyroid function and urinalysis. Serum pregnancy testing will occur in women of child-bearing potential at the Master Protocol Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy.
3 Adverse events that occur after signing the consent form will be recorded.
4 Participants who continue into OLE will have a Follow-Up Safety Call (as described in the body of this RSA) after their last dose of study drug during the OLE period.
5 The duration of the OLE is [52] weeks.
6 Participants who continue into the OLE and then withdraw consent or early terminate will be asked to complete an Early Termination Visit and Follow-Up Safety Call as described in the body of this RSA.
7 Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic.

1. INTRODUCTION

Regimen [X]: [Name of Study Drug]

1.1 [Name of Study Drug] Background Information

[Include:

- The name and description of the study intervention/investigational products(s)
- A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance
- A summary from relevant clinical trials
- Discussion of important literature and data that are relevant to the trial and that provide background for the trial
- Applicable clinical, epidemiological, or public health background or context of the study
- Importance of the study and any relevant treatment issues or controversies]

1.2 [Name of Study Drug] Therapeutic Rationale

[Include a description of, and justification for, the route of administration, dosage, dosing regimen, intervention periods, or behavioral intervention methods and selection of study population. Include a statement of the hypothesis.]

2. OBJECTIVES

2.1 Study Objectives and Endpoints

[Note: Objectives and endpoints are intended to match the Master Protocol, and they are also intended to be uniform across regimens. If a regimen makes changes to secondary or exploratory endpoints or objectives, please add them below.]

Primary Efficacy Objective:
To evaluate the efficacy of [insert drug name] as compared to placebo on ALS disease progression.

Secondary Efficacy Objective:

- To evaluate the effect of [insert drug name] on selected secondary measures of disease progression, including survival.

Safety Objective:

- To evaluate the safety of [insert drug name] for ALS.

Exploratory Efficacy Objective:

- To evaluate the effect of [insert drug name] on selected biomarkers and endpoints.

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

Secondary Efficacy Endpoints:

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

Safety Endpoints:

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

Exploratory Efficacy Endpoints:

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

3. RSA DESIGN

This study is a multi-center, randomized, placebo-controlled trial, testing active dose of [study drug name] ([dosage amount]), given [orally, subcutaneously, etc.] daily versus placebo. Participants will be randomized 3:1 active: placebo.

3.1 Scientific Rationale for RSA Design

- This RSA is designed to correspond with the design of the Master Protocol and the goals of the Platform Trial.

[Note: The text above is the default text for this section. If a regimen needs to alter this text, please be sure that the new text covers the bullet points below.

- [Describe the rationale for the type and selection of control and design.
- Describe known or potential problems associated with the control group chosen in light of the specific disease (ALS) and intervention being studied.]

3.2 End of Participation Definition

A participant is considered to have completed his or her participation in the placebo-controlled period of the Regimen if all planned placebo-controlled period visits, including the last visit or the last scheduled procedure shown in the Schedule of Activities (SOA), have been completed.

If a participant initiates open-label investigational product in the OLE period, he or she is considered to have completed his or her participation in the OLE period of the Regimen if all planned OLE period visits, including the last visit or the last scheduled procedure shown in the SOA, have been completed.

3.3 End of Regimen Definition

The end of the placebo-controlled period in a Regimen occurs when all randomized participants have completed their participation in the placebo-controlled period as defined in section 3.2.

The end of the OLE period in a Regimen occurs when all participants who initiated open-label investigational product in the OLE period have completed their participation in the OLE period as defined in section 3.2.

3.4 Regimen Termination

[If an industry partner has additional requested reasons for termination, they should be outlined here. Otherwise, the Regimen will follow the Master Protocol's section on regimen termination, and the section of this RSA on Regimen Termination can be omitted.]

4. RSA ENROLLMENT

4.1 Number of Study Participants

Approximately one hundred-sixty [160] participants will be randomized for this Regimen.

4.2 Inclusion and Exclusion Criteria

In order to be randomized to a Regimen, participants must meet the Master Protocol eligibility criteria. In addition, participants meeting all of the following inclusion and exclusion criteria will be allowed to enroll in this Regimen:

4.2.1 RSA Inclusion Criteria

1.
2.

4.2.2 RSA Exclusion Criteria

1.
2.

4.3 Treatment Assignment Procedures

Each participant who meets all eligibility criteria for the Regimen will be randomized to receive either [insert active treatment units per day] or placebo for approximately [24 weeks] of placebo-controlled treatment.

4.4 Open Label Extension Eligibility

Participants who complete the 24-week placebo-controlled period on study drug will be eligible to participate in the OLE. [Insert any additional OLE eligibility criteria as applicable.]

5. INVESTIGATIONAL PRODUCT

5.1 Investigational Product Manufacturer

[Provide details regarding the investigational product manufacturer.]

5.2 Labeling, Packaging, and Resupply

[Provide details regarding packaging, labeling, and resupply.]

5.3 Acquisition, Storage, and Preparation

[Provide investigational product-specific details.]

5.4 Study Medication/Intervention, Administration, Escalation, and Duration

[Describe the Regimen intervention/medication.]

5.5 Justification for Dosage

[Provide a justification for the route of administration, planned maximum dosage, and dosing regimen, including starting dose, of the study intervention(s).]

5.6 Dosage Changes

- [If applicable, the conditions under which a dose change will be made, particularly regarding failure to respond or to toxic or untoward changes in stipulated indicators (e.g., white blood cell count in cancer chemotherapy).
- Address dose modifications for specific abnormal laboratory values of concern or other adverse events that are known to be associated with the planned Regimen intervention.]

5.7 Participant Compliance

- [Indicate whether compliance of participants with the Regimen intervention is to be assessed
- Provide details as to how compliance will be assessed (e.g., pill counts, electronic monitoring devices, adherence questionnaires)]

5.8 Overdose

Certain safety events that occur in association with investigational product may require reporting. These safety events include, but are not limited to, the following:

- Overdose of the investigational product, where ‘overdose’ is defined as [insert definition]

- Suspected abuse/misuse of the investigational product
- Inadvertent or accidental exposure to the investigational product
- Medication error involving study drug (with or without participant exposure to the investigational product, e.g., name confusion)

These safety events should be reported to the Coordination Center whether they result in an AE/SAE or not. Safety events associated with an AE/SAE should also be reported in the EDC. In the event of overdose, study staff should monitor the participant and provide supportive care as needed. The SI should also contact the Medical Monitor within 24 hours of the SI's awareness.

5.9 Prohibited Medications

- [List all concomitant intervention(s) that are prohibited during Regimen participation
- Describe procedure for handling situation(s) when participant uses prohibited intervention during Regimen participation.]

5.10 [Name of Drug] Known Potential Risks and Benefits

5.10.1 Known Potential Risks

[Include a review of relevant literature, which should be referenced. Add relevant websites, etc., from which the information could be drawn.

Describe in detail any physical, psychological, social, legal, economic, or any other risks to participants that the Principal Investigator (PI) foresees, addressing each of the following:

- Immediate risks
- Long-range risks
- Rationale for the necessity of such risks
- Alternative data gathering procedures that have been considered or will be considered
- Why alternative procedures may not be feasible
- Why the value of the information to be gained outweighs the risks involved.]

5.10.2 Known Potential Benefits

[If the research is potentially beneficial, describe in detail any physical, psychological, social, legal, economic, or any other benefits to participants that are foreseen.

Note: Payment to participants, whether as an inducement to participate or as compensation for pain and inconvenience, is not considered a "benefit."]

6. REGIMEN SCHEDULE

In addition to procedures in the Master Protocol, the following regimen-specific procedures will be conducted during the study:

- Home Spirometry
- ALSAQ-40
- CNS Bulbar Function Scale
- Voice recording
- Smartphone installation and removal
- [Insert any additional regimen-specific procedures, if applicable. List should match order of activities in SOA.]

Modifications to Regimen Schedule Due to a Pandemic

Designated visits in the Schedule of Activities (i.e., Week 4, Week 8, and Week 16) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic. If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP.

In addition to the procedures in the Master Protocol that should be conducted during the phone or telemedicine and remote visits, the following regimen-specific procedures should be completed:

- Home Spirometry (Week 8 and 16 only)
- Voice Recording
- CNS Bulbar Function Scale (Week 8 and 16 only)

Details on collection of the CNS Bulbar Function Scale, dispensing IP during remote visits, and documenting participants' willingness to participate in OLE are described in the MOP.

6.1 Baseline Visit

This visit will take place on Day 0. The following procedures will be performed for the regimen schedule:

- Home Spirometry
- ALSAQ-40

- CNS Bulbar Function Scale
- Install smartphone app
- Voice recording
- [Insert regimen-specific procedures]
- Dispense IP
- Administer first dose of IP in clinic *after* all Baseline procedures have been completed
- Remind participant to bring in investigational product to the next visit

6.2 Week 2 Telephone Visit

This visit will take place 14 ± 3 days after the Baseline Visit via telephone. The following procedures will be performed for the regimen schedule:

- [Insert regimen-specific procedures]

6.3 Week 4 and 8 Visits

Participants should be instructed to hold investigational product on the day of the study visit. Investigational product should not be taken until after study visit procedures are complete.

These visits will take place on Days 28 ± 7 and 56 ± 7 days, respectively. The following procedures will be performed for the regimen schedule:

- Home Spirometry [Week 8 Only]
- CNS Bulbar Function Scale [Week 8 only]
- Voice recording
- [Insert regimen-specific procedures]
- Dispense IP
- Remind participant to bring in investigational product to the next visit

6.4 Week 12 Telephone Visit

This visit will take place 84 ± 3 days after the Baseline Visit via telephone. The following procedures will be performed for the regimen schedule:

- [Insert regimen-specific procedures]

6.5 Week 16 Visit

Participants should be instructed to hold investigational product on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.

This visit will take place on Day 112 ± 7 days. The following procedures will be performed for the regimen schedule:

- Document participant's willingness to participate in the OLE
- Home Spirometry
- CNS Bulbar Function Scale
- Voice Recording
- [Insert regimen-specific procedures]
- Dispense IP
- Remind participant to bring in investigational product to the next visit

6.6 Week 20 Telephone Visit

This visit will take place 140 ± 3 days after the Baseline Visit via telephone. The following procedures will be performed for the regimen schedule:

- [Insert regimen-specific procedures]

6.7 Week 24 Visit or Early Termination Visit

Participants should be instructed to hold investigational product on the day of the study visit. Investigational product should not be taken until after study visit procedures are complete.

This visit will take place on Day 168 ± 7 days. The following procedures will be performed for the regimen schedule:

- Home Spirometry
- ALSAQ-40
- CNS Bulbar Function Scale
- Voice recording
- Uninstall smartphone app
- [Insert regimen-specific procedures]
- Dispense IP (**Drug is only dispensed at this visit if the participant is continuing in the Open Label Extension.**)

- Remind participant to bring investigational product to the next visit (only if continuing in OLE)

6.8 Follow-Up Safety Call

Participants will have a Follow-Up Safety Call [28±3] days after their last dose of investigational product. Participants will complete this visit who

1. Have their last dose of investigational product prior to completing the placebo-controlled period (both those who continue following ITT or discontinue early);
2. Complete the placebo-controlled period but who do NOT continue on into the Open Label Extension.

Participants who continue into Open Label Extension are exempt from the requirement of this visit.

The following procedures will be performed:

- Assess and document AEs

6.9 Process for Early Terminations

Participants who withdraw consent or early terminate from the study and do not complete the protocol will be asked to be seen for an in-person Early Termination Visit and complete a Follow-Up Safety Call.

The in-person Early Termination Visit should be scheduled as soon as possible after a participant early terminates. If the participant early terminates or withdraws consent during the placebo-controlled portion of the Regimen, all assessments that are collected at the Week 24 in-clinic visit should be conducted. The Follow-Up Safety Call should be completed approximately [28] days after the last dose of investigational product.

If the Early Termination Visit occurs approximately [28±3] days after the last dose of investigational product, the information for the Follow-Up Safety Call can be collected during the Early Termination Visit, and a separate Follow-Up Safety Call does not need to be completed. If the in-person Early Termination Visit does not occur within [28±3] days of the last dose of investigational product, the Follow-Up Safety Call should occur approximately [28] days after the last dose of investigational product and the Early Termination Visit will be completed after the Follow-Up Safety Call.

If a participant decides to discontinue investigational product, but will complete the protocol, an in-person Early Termination Visit and Follow-Up Safety Call is not necessary.

6.10 Open Label Extension

Participants who have completed the placebo-controlled portion of the trial on study drug will be eligible to continue in the Open Label Extension (OLE) as outlined in the SOA. Participants will first be asked about their desire to continue in the OLE at the Regimen-Specific Screening Visit. They will also be asked to *re-confirm* whether they want to continue in the OLE at the Week 16 Visit of the placebo-controlled period.

Modifications to Regimen Schedule Due to a Pandemic

Designated visits in the Schedule of Activities (i.e., Week 4, Week 8, Week 16, Week 28, Week 40) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic. If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP.

In addition to the procedures in the Master Protocol that should be conducted during the phone or telemedicine and remote visits, the following regimen-specific procedures should be completed:

- Home Spirometry
- CNS Bulbar Function Scale (Week 8, 16, 28, 40, 52 only)

6.10.1 Week 2 OLE Telephone Visit

This visit will take place via telephone 14 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Perform investigational product compliance
- [Insert regimen-specific procedures]
- Remind participant to bring investigational product to the next visit

6.10.2 Week 4 OLE Visit

This visit will take place in-person 28 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Home Spirometry
- Administer ALSFRS-R questionnaire
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Dispense investigational product to participant
- [Insert regimen-specific procedures]
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

6.10.3 Week 8 OLE Visit

This visit will take place in-person at 56 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Home Spirometry
- Administer ALSFRS-R questionnaire
- CNS Bulbar Function Scale
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- [Insert regimen-specific procedures]
- Dispense investigational product to participant
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

6.10.4 Week 12 OLE Telephone Visit

This visit will take place via telephone at 84 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Perform investigational product compliance
- [Insert regimen-specific procedures]
- Remind participant to bring investigational product to the next visit

6.10.5 Week 16 OLE Visit

Participants should be instructed to hold investigational product on the day of the study visit. Investigational product should not be taken until after study visit procedures are complete.

This visit will take place in-person at 112 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Home Spirometry
- Administer ALSFRS-R questionnaire
- CNS Bulbar Function Scale
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collect urine sample for biomarker analyses
- Collect blood sample for biomarker analyses
- [Insert regimen-specific procedures]
- Dispense investigational product to participant
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

6.10.6 Week 20 OLE Telephone Visit

This visit will take place via telephone at 140 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire
- Review concomitant medications

- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- [Insert regimen-specific procedures]
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

6.10.7 Week 24 OLE Telephone Visit

This visit will take place via telephone at 168 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- [Insert regimen-specific procedures]
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

6.10.8 Week 28 OLE Visit

Participants should be instructed to hold investigational product on the day of the study visit. investigational product should not be taken until after study visit procedures are complete.

The Week 28 OLE Visit will take place in-person 196 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Home Spirometry
- Administer ALSFRS-R questionnaire
- ALSAQ-40
- CNS Bulbar Function Scale
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collect urine sample biomarker analyses
- Collect blood sample for biomarker analyses
- [Insert regimen-specific procedures]

- Dispense investigational product to participant
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

6.10.9 Week 40 OLE Visit

The Week 40 OLE Visit will take place in-person 280 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Home Spirometry
- Administer ALSFRS-R questionnaire
- CNS Bulbar Function Scale
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Dispense investigational product to participant
- [Insert regimen-specific procedures]
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

6.10.10 Week 52 OLE Visit

Participants should be instructed to hold investigational product on the day of the study visit. Investigational product should not be taken until after study visit procedures are complete.

The Week 52 OLE Visit will take place in-person 364 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Home Spirometry
- Administer ALSFRS-R questionnaire
- ALSAQ-40
- CNS Bulbar Function Scale

- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collect urine sample biomarker analyses
- Collect blood sample for biomarker analyses
- [Insert regimen-specific procedures]
- Perform investigational product compliance

6.10.11 Follow-Up Safety Call

Participants will have a Follow-Up Safety Call [28±3] days after their last dose of investigational product. Participants will complete this visit who

3. Have their last dose of investigational product prior to completing the Open Label Extension (those who discontinue early);
4. Complete the Open Label Extension

The following procedures will be performed:

- Assess and document AEs

6.10.12 Process for Early Terminations

Participants who withdraw consent or early terminate from the study and do not complete the protocol will be asked to be seen for an in-person Early Termination Visit and complete a Follow-Up Safety Call.

The in-person Early Termination Visit should be scheduled as soon as possible after a participant early terminates. If the participant early terminates or withdraws consent during the OLE period, all assessments that are collected at the OLE Week [52] in-clinic visit should be conducted. The Follow-Up Safety Call should be completed approximately [28] days after the last dose of investigational product.

If the Early Termination Visit occurs approximately [28±3] days after the last dose of investigational product, the information for the Follow-Up Safety Call can be collected during the Early Termination Visit, and a separate Follow-Up Safety Call does not need to be completed. If the in-person Early Termination Visit does not occur within [28±3] days of the last dose of investigational product, the Follow-Up Safety Call should occur approximately [28] days

after the last dose of investigational product and the Early Termination Visit will be completed after the Follow-Up Safety Call.

6 OUTCOME MEASURES AND ASSESSMENTS

7.1 Voice Analysis

In addition to the scheduled in clinic voice recordings, voice samples will be collected twice per week, using an app installed on either an android or iOS based smartphone. The app characterizes ambient noise, then asks patients to perform a set of speaking tasks: reading sentences -- 5 fixed and 5 chosen at random from a large sentence bank-- repeating a consonant-vowel sequence, producing a sustained phonation, and counting on a single breath. Voice signals are uploaded to a HIPAA-compliant web server, where an AI-based analysis identifies relevant vocal attributes. Quality control (QC) of individual samples will occur by evaluation of voice records by trained personnel.

7.2 ALSAQ-40

The Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ-40) is a patient self-report health status patient-reported outcome. The ALSAQ-40 consists of forty questions that are specifically used to measure the subjective well-being of patients with ALS and motor neuron disease.

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers can also help, if needed.

7.3 Center for Neurologic Study Bulbar Function Scale

The Center for Neurologic Study Bulbar Function Scale (CNS-BFS) is a patient self-report scale that has been developed for use as an endpoint in clinical trials and as a clinical measure for evaluating and following ALS patients. The CNS-BFS consists of three domains (swallowing, speech, and salivation), which are assessed with a 21-question, self-report questionnaire.

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers can also help, if needed.

7.4 Home Spirometry

Remote/home-based forced vital capacity will be measured with the MIR Spirobank Smart spirometer. Instructions for use will be provided to the participant. The participant will perform the vital capacity maneuver with real time video coaching (or phone coaching, if video is not

available) by the evaluator. Three to five vital capacity maneuvers will be performed, consistent with the manner vital capacity is obtained in clinic.

7 BIOFLUID COLLECTION

[Include details of any biofluid samples required for the Regimen that are not already included in the Master Protocol using the format below.]

8.1 [Insert sample type]

[Insert description of sample and purpose of sample collection/how it will be used.]

9 REGIMEN-SPECIFIC STATISTICAL CONSIDERATIONS

[The sections below contain template language that may be modified for specific regimens, if needed. The HEALEY team will work with partner companies to draft this text.]

9.1 Deviations from the Default Master Protocol Trial Design

[The statistical design for this regimen will be in accordance with the default statistical design described in Appendix I of the Master Protocol.]

9.2 Regimen Specific Operating Characteristics

[Clinical trial simulation is used to quantify operating characteristics for this regimen (refer to the regimen SAP for further details).]

9.3 Sharing of Controls from other Regimens

[The primary analysis of this regimen will include sharing of all controls from the other regimens. This is justified by the minor differences in inclusion/exclusion criteria of the RSA, such that there are no expected systematic differences in the primary endpoint between the controls across regimens.]

APPENDIX I: THE ALSAQ-40

ALSAQ-40

Please complete this questionnaire as soon as possible. If you have any difficulties filling in this questionnaire by yourself, please have someone help you. However it is **your** responses that we are interested in.

The questionnaire consists of a number of statements about difficulties that you may have experienced **during the last 2 weeks.** There are no right or wrong answers: your first response is likely to be the most accurate for you. **Please check the box that best describes your own experiences or feelings.**

Please answer every question even though some may seem very similar to others, or may not seem relevant to you.

All the information you provide is **confidential.**

The following statements all refer to difficulties that you may have had **during the last 2 weeks**.
Please indicate, by checking the appropriate box, how often the following statements have been true for you.

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot walk at all
please check **Always/cannot walk at all.**

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question.*

	Never	Rarely	Some-times	Often	Always or cannot walk at all
1. I have found it difficult to walk short distances, e.g. around the house.	☐	☐	☐	☐	☐
2. I have fallen over while walking.	☐	☐	☐	☐	☐
3. I have stumbled or tripped while walking.	☐	☐	☐	☐	☐
4. I have lost my balance while walking.	☐	☐	☐	☐	☐
5. I have had to concentrate while walking.	☐	☐	☐	☐	☐

*Please make sure that you have checked **one box for each question** before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you are not able to perform the activity at all please check **Always/cannot at all**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
6. Walking had worn me out.	☐	☐	☐	☐	☐
7. I have had pains in my legs while walking.	☐	☐	☐	☐	☐
8. I have found it difficult to go up and down the stairs.	☐	☐	☐	☐	☐
9. I have found it difficult to stand up.	☐	☐	☐	☐	☐
10. I have found it difficult to move from sitting in a chair to standing upright.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
11. I have had difficulty using my arms and hands.	☐	☐	☐	☐	☐
12. I have found turning and moving in bed difficult.	☐	☐	☐	☐	☐
13. I have had difficulty picking things up.	☐	☐	☐	☐	☐
14. I have had difficulty holding books or newspapers, or turning pages.	☐	☐	☐	☐	☐
15. I have had difficulty writing clearly.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
16. I have found it difficult to do jobs around the house.	☐	☐	☐	☐	☐
17. I have found it difficult to feed myself.	☐	☐	☐	☐	☐
18. I have had difficulty combing my hair or brushing and/or flossing my teeth.	☐	☐	☐	☐	☐
19. I have had difficulty getting dressed.	☐	☐	☐	☐	☐
20. I have had difficulty washing at the bathroom sink.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
21. I have had difficulty swallowing.	☐	☐	☐	☐	☐
22. I have had difficulty eating solid food.	☐	☐	☐	☐	☐
23. I have had difficulty drinking liquids.	☐	☐	☐	☐	☐
24. I have had difficulty participating in conversations.	☐	☐	☐	☐	☐
25. I have felt that my speech has not been easy to understand.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
26. I have stuttered or slurred my speech.	☐	☐	☐	☐	☐
27. I have had to talk very slowly.	☐	☐	☐	☐	☐
28. I have talked less than I used to do.	☐	☐	☐	☐	☐
29. I have been frustrated with my speech.	☐	☐	☐	☐	☐
30. I have felt self-conscious about my speech.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question*

	Never	Rarely	Some-times	Often	Always
31. I have felt lonely.	☐	☐	☐	☐	☐
32. I have been bored.	☐	☐	☐	☐	☐
33. I have felt embarrassed in social situations.	☐	☐	☐	☐	☐
34. I have felt hopeless about the future.	☐	☐	☐	☐	☐
35. I have worried that I am a burden to other people.	☐	☐	☐	☐	☐

*Please make sure that you have checked **one box for each question** before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question*

	Never	Rarely	Some-times	Often	Always
36. I have wondered why I keep going.	☐	☐	☐	☐	☐
37. I have felt angry because of the disease.	☐	☐	☐	☐	☐
38. I have felt depressed.	☐	☐	☐	☐	☐
39. I have worried about how the disease will affect me in the future.	☐	☐	☐	☐	☐
40. I have felt as if I have lost my independence	☐	☐	☐	☐	☐

*Please make sure that you have checked one **box for each question.***

Thank you for completing this questionnaire.

APPENDIX II: THE BULBAR FUNCTION SCALE (CNS-BFS)

BULBAR FUNCTION SCALE (CNS-BFS)						
SIALORRHEA	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	
1. Excessive saliva is a concern to me.	❍	❍	❍	❍	❍	
2. I take medication to control drooling.	❍	❍	❍	❍	❍	
3. Saliva causes me to gag or choke.	❍	❍	❍	❍	❍	
4. Drooling causes me to be frustrated or embarrassed.	❍	❍	❍	❍	❍	
5. In the morning I notice saliva on my pillow.	❍	❍	❍	❍	❍	
6. My mouth needs to be dabbed to prevent drooling.	❍	❍	❍	❍	❍	
7. My secretions are not manageable.	❍	❍	❍	❍	❍	
				TOTAL Sialorrhea Score: _____		
SPEECH	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	**Unable to Communicate by Speaking (6)**
1. My speech is difficult to understand.	❍	❍	❍	❍	❍	❍
2. To be understood I repeat myself.	❍	❍	❍	❍	❍	❍
3. People who understand me tell other people what I said.	❍	❍	❍	❍	❍	❍
4. To communicate I write things down or use devices such as a computer.	❍	❍	❍	❍	❍	❍
5. I am talking less because it takes so much effort to speak.	❍	❍	❍	❍	❍	❍

6. My speech is slower than usual.	❍	❍	❍	❍	❍	❍
7. It is hard for people to hear me.	❍	❍	❍	❍	❍	❍
				TOTAL Speech Score: _____		
SWALLOWING	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	
☐ Feeding tube is in place						
1. Swallowing is a problem.	❍	❍	❍	❍	❍	
2. Cutting my food makes it easier to chew and swallow.	❍	❍	❍	❍	❍	
3. To get food down I have switched to a soft diet.	❍	❍	❍	❍	❍	
4. After swallowing I gag or choke.	❍	❍	❍	❍	❍	
5. It takes longer to eat.	❍	❍	❍	❍	❍	
6. My weight is dropping because I can't eat normally.	❍	❍	❍	❍	❍	
7. Food gets stuck in my throat.	❍	❍	❍	❍	❍	
				TOTAL Swallowing Score: _____		
				OVERALL SCORE: _____		

REFERENCES

[Please insert list of references used for this RSA.]