HEALEY ALS Platform Trial - Regimen B Verdiperstat

NCT04436510

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RGB REGIMEN-SPECIFIC STATISTICAL ANALYSIS PLAN (R-SAP)

Master Protocol	Platform Trial for the Treatment of Amyotrophic Lateral Sclerosis (ALS): A perpetual multi-center, multi-regimen, clinical trial evaluating the safety and efficacy of investigational products for the treatment of ALS
Regimen	RGB: Verdiperstat
Regimen Partner	Biohaven Pharmaceuticals, Inc
Regulatory Sponsor	Merit E. Cudkowicz, MD
Master Protocol Version	4.0, 31 Aug 2020
RSA Version	6.0, 02 Dec 2021
Master SAP Version	1.0, 24 Jun 2020
R-SAP Version	3.0, 22 Jul 2022

SAP APPROVAL SIGNATURES

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SAP REVISION HISTORY

Version	Date	Description of Changes
1.0	17 Mar 2022	Initial version
2.0	06 May 2022	Revision of Section 5.9 Survival to specify that both PAV-free survival and overall survival will be evaluated at both the Week 24 Visit time point and the last-participant-last-visit time point and to specify that PAV-free survival to the Week 24 Visit time point is the primary analysis of survival in this analysis plan. Revision of Section 6.5.5 CAFS to specify the following: 1. CAFS will be used as a supportive analysis for the secondary efficacy endpoints of HHD upper and lower extremity percentage and SVC, 2. Additional CAFS analyses will use multiple imputation to extend follow-up for participants who early terminate, withdraw consent, or are lost to follow-up, 3. Additional CAFS analyses will use time to death alone independent of any death equivalent, and 4. Primary inference from CAFS analyses will compare survival by time to death or death equivalent and will compare change in function to the last jointly observed time point.
3.0	22 Jul 2022	Revision of Section 4.2 Exploratory Endpoints to identify serum creatinine and serum and CSF neurofilament light chain (NfL) as exploratory biomarkers of neurodegeneration and neuromuscular degeneration and to include ALSAQ-40 domain scores and symptom index (SI) as exploratory endpoints. Revision of Section 5.1 ALSFRS-R to specify details of the calculation of pre-baseline slope. Revision of Section 5.5 Quantitative Voice Characteristics to include predicted vital capacity as an additional metric at the Baseline Visit. Revision of Section 5.6 Biofluid Biomarkers of Neurodegeneration to specify the assay techniques used to quantify serum creatinine and serum and CSF NfL and to specify that levels of serum and CSF NfL will be log-transformed in all analyses.

Version	Date	Description of Changes
3.0 (continued)	22 Jul 2022 (continued)	Revision of Section 5.7 ALSAQ-40 to specify calculation of domain scores and to revise calculation of overall ALSAQ-40 SI. Revision of Section 5.8 CNS-BFS to specify that the total score is referenced.Revision of Section 5.9 Survival to specify that time at risk begins at each participant's Baseline Visit and to specify that the date of PAV initiation, where applicable, will be imputed as the fifteenth day of a month if not specified more precisely. Revision of Section 6.1 Analysis Sets to add the Efficacy Common Mode of Administration (ECM) analysis set, to remove the restriction on protocol deviations that could be considered for exclusion from the Efficacy Per-protocol (EPP) analysis set must be classified as major protocol deviations, to specify the time point at which data is excluded from the EPP analysis set in the case of time-dependent exclusions, and to specify that data from placebo participants from other regimens would not be excluded from the EPP analysis set due to non-adherence to protocol-specified dosing. Revision of Section 6.2 Baseline Characterization to include ALSAQ-40 domain scores and SI. Revision of Section 6.5.2 Repeated-measures Model to add a fixed term for treatment group (removing the shared-baseline assumption at the recommendation of the FDA) and to specify a separate supportive analysis that includes fixed terms for centered baseline serum NfL level and centered baseline serum NfL level × visit interaction. Revision of Section 6.5.3 Random-slopes Model to add a fixed term for treatment group (removing the shared-baseline assumption) and to specify a separate supportive analysis that includes fixed terms for centered baseline serum NfL level and centered baseline serum NfL level × study month interaction. Revision of Section 6.5.4 Survival and Time to Clinical Events to clarify that survival analyses that include follow-up beyond the placebo-controlled period will be analyzed in the ERO analysis set, to include baseline age as an additional covariate in all adjusted models, and to specify an additional adjusted analysis that includes baseline serum NfL level as a covariate.

Version	Date	Description of Changes
3.0 (continued)	22 Jul 2022 (continued)	Revision of Section 6.5.5 CAFS to clarify that the primary CAFS analysis is specified in the ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report and to add two additional sets of CAFS analyses that adjust rank scores in linear models, one set that adjusts for time from ALS symptom onset, delta-FRS, baseline use of riluzole, and baseline use of edaravone, and one set that adjusts for the same set of covariates plus baseline serum NfL level. Revision of Section 6.5.6 HHD0 and $HHD0^2$ to remove reference to the shared-baseline assumption of the repeated-measures mixed model of Section 6.5.2 and to specify a separate analysis that adds baseline serum NfL level as an additional covariate. Revision of Section 6.5.7 Quantitative Voice Measures to remove reference to the shared-baseline assumption of the random-slopes mixed model of Section 6.5.3 and to add a fixed term for treatment group (removing the shared-baseline assumption) and to specify a separate analysis that includes fixed terms for centered baseline serum NfL level and centered baseline serum NfL level × B-spline interaction. Revision of Section 6.5.8 Placebo Multiple Imputation to specify regression over sequential visits by the fully conditional specification method, to remove reference to the shared-baseline assumption of the repeated-measures mixed model of Section 6.5.2, and to specify a separate analysis that adds baseline serum NfL level as an additional covariate. Revision of Section 6.5.11 Comparison of Controls across Regimens to specify separate analyses that add baseline serum NfL level as an additional covariate.

ABBREVIATIONS

ALP	Alkaline Phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire, 40-item version
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale, Revised
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	WHODrug Anatomical, Therapeutic, and Chemical class
ATS	American Thoracic Society
BLQ	Below the Limit of Quantitation
BMI	Body Mass Index
C-SSRS	Columbia Suicide Severity Rating Scale
CAFS	Combined Assessment of Function and Survival
CBC	Complete Blood Count
CKD	Chronic Kidney Disease
COVID-19	Coronavirus Disease 2019
CNS-BFS	Center for Neurologic Study Bulbar Function Scale
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
delta-FRS	Pre-baseline Slope in ALSFRS-R
DAP	Data Analysis Plan
DILI	Drug-induced Liver Injury
DNA	Deoxyribonucleic Acid
DRR	Disease Rate Ratio
ECC	Efficacy Concurrent Control
ECG	Electrocardiography or Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EPP	Efficacy Per-protocol
ERO	Efficacy Regimen-only
ELISA	Enzyme-linked Immunosorbent Assay
FAS	Full Analysis Set

ABBREVIATIONS (continued)

FVC	Forced Vital Capacity
GLI	Global Lung Initiative
hCG	Human Chorionic Gonadotropin
HHD	Hand-held Dynamometry
HLT	MedDRA High Level Term
ICF	Informed Consent Form
ITT	Intention-to-treat Principle
M-SAP	Master Statistical Analysis Plan
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MP	Master Protocol
MPRDR	ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report
NCI	National Cancer Institute
NEALS	Northeast ALS
NfL	Neurofilament Light Chain
NIV	Noninvasive Ventilation
OLE	Open-label Extension
PAV	Permanent Assisted Ventilation
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	MedDRA Preferred Term
RBC	Red Blood Cell
RDW	RBC Distribution Width
RGB	Regimen B (verdiperstat)
RSA	Regimen-specific Appendix
R-SAP	Regimen-specific Statistical Analysis Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

ABBREVIATIONS (continued)

SI	Symptom Index
SoA	Schedule of Activities
SOC	MedDRA System Organ Class
SRO	Safety Regimen-only
STF	Safety and Tolerability Full
STN	Safety and Tolerability Narrow
SVC	Slow Vital Capacity
TBL	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHODrug	World Health Organization Drug Dictionary Enhanced

Table of Contents

1. Governing Documents

This Regimen-specific Statistical Analysis Plan (R-SAP) for the verdiperstat regimen (RGB) specifies any modification from the default outcome measures, analysis samples, and planned analyses for the placebo-controlled period of the HEALEY ALS Platform Trial as specified in the Master SAP (M-SAP). The M-SAP and this R-SAP supplement the Master Protocol, the "ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report" (Appendix 1 to the Master Protocol), and the RGB Regimen-specific Appendix (RSA). Please refer to the Master Protocol and the RGB RSA for details on the rationale for the study design, eligibility criteria, conduct of the trial, clinical assessments and schedule of assessments, definitions and reporting of adverse events, data management conventions, and regulatory oversight and compliance procedures. The "ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report" (MPRDR) and any regimen-specific deviations described in the RGB RSA and this R-SAP are authoritative in defining the primary and interim analyses. In case of discrepancies between the RGB RSA and this R-SAP concerning use of shared placebos, this R-SAP is authoritative. In case of discrepancies between either SAP and the Master Protocol and the RGB RSA concerning matters of analysis other than the primary and interim analyses and use of shared placebos, the M-SAP and this R-SAP are authoritative. In case of discrepancies between the M-SAP and this R-SAP, this R-SAP is authoritative. On all matters not related to analysis, the Master Protocol and the RGB RSA are authoritative. The following table describes relationships among the relevant documents in adjudicating possible discrepancies with higher numbers indicating greater authority.

Issues potentially requiring adjudication	Master Protocol	RGB RSA	MPRDR	M-SAP	RGB R-SAP
Use of shared placebos	1	4	2	3	5
Primary and interim analysis specifications not related to use of shared placebo	1	5	4	2	3
Statistical analysis specifications not related to use of shared placebo or primary and interim analyses	1	3	2	4	5
All matters not related to statistical analysis	4	5	1	2	3

2. Study Design

2.1 Overview

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. RGB evaluates the safety and efficacy of verdiperstat administered orally at a dosage of 600 mg BID vs. placebo. The RGB RSA describes the nature of the intervention and its mechanism of action, the mode and frequency of administration, additional eligibility criteria beyond those specified in the Master Protocol, additional enrollment procedures, and additions and modifications of safety and efficacy assessments relative to those outlined in the Master Protocol.

2.2 Study Objectives

Primary Efficacy Objective:

- To evaluate the efficacy of verdiperstat as compared to placebo on ALS disease progression.

Secondary Efficacy Objectives:

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

Safety Objectives:

- To evaluate the safety of verdiperstat for ALS patients.

Exploratory Efficacy Objectives:

- To evaluate the effect of verdiperstat on selected biomarkers and endpoints.
- To explore verdiperstat pharmacokinetics (PK) and pharmacodynamic (PD) effects.

2.3 Study Population

In addition to eligibility criteria specified in the Master Protocol, participants in RGB must not be taking strong inhibitors of CYP1A2 (i.e., ciprofloxacin, enoxacin, fluvoxamine, zafirlukast) or CYP3A4 (i.e., conivaptan, itraconazole, ketoconazole, posaconazole, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, and certain antiviral agents [cobicistat, danoprevir, ritonavir, elvitegravir, indinavir, lopinavir, paritaprevir, ombitasavir, dasabuvir, saquinavir, tipranavir, nelfinavir]) for chronic/long-term use, defined as more than two weeks.

Participants will be recruited from approximately 60 centers located throughout the US that are part of the Northeast ALS (NEALS) Consortium.

2.4 Participant Flow

Participants in RGB follow the consenting, Master screening, regimen assignment, regimen-specific screening, randomization to active or placebo treatment, and follow-up procedures and timing described in the M-SAP. Detailed descriptions of study procedures and timing are specified in the Master Protocol and the RGB RSA.

2.5 Regimen Allocation

Participants in RGB are those determined eligible for Master Protocol-level inclusion and exclusion criteria and randomly assigned to RGB, stratified by use of riluzole, edaravone, both, or neither at the time of screening for the Master Protocol. Details of regimen assignment are described in the Platform Trial Regimen Assignment Plan.

2.6 Treatment Allocation

Participants in RGB are randomly allocated in a 3:1 ratio to active or placebo treatment based on a pre-specified permuted-block randomization schedule, stratified by use of riluzole, edaravone, both, or neither at the time of screening for the Master Protocol.

2.7 Treatment Administration

Verdiperstat and placebo are supplied as matching reddish-beige, film coated, oval tablets. Each tablet of active study drug contains 300 mg of verdiperstat as the free base plus excipients generally recognized as safe for oral administration in an extended-release formulation.

The first dose of study drug should be administered while in the office/clinic on the day of the Baseline Visit after all visit assessments are complete. Participants should stay at the office/clinic for monitoring for approximately 30 minutes post-dose. From the Baseline Visit to the end of Week 1, participants should take one tablet of study drug per day. During Week 2, participants should take one tablet of study drug twice per day. Starting at the beginning of Week 3 and throughout the remainder of the study, participants should take two tablets of study drug twice per day. If tolerability issues are experienced, the titration schedule may be modified. If a participant is off study drug for more than 14 consecutive days, the participant should re-escalate using the titration paradigm described above.

Additional details of treatment administration are described in the RGB RSA.

2.8 Allocation Concealment

Allocation concealment is the same as described in the M-SAP.

2.9 RGB Schedule of Activities (SoA)

Activity	MP Scrn[1] Cln -42d to -1d	RGB Scrn[1] Cln -41d to 0d	Base-line Cln Day 0	Week 2[2] Phn Day 14±3	Week 4[18,19] Cln[5] Day 28±7	Week 8[18,19] Cln[5] Day 56±7	Week 12 Phn Day 84±3	Week 16[18,19] Cln[5] Day 112±7	Week 20 Phn Day 140±3	Week 24[3,18] Cln Day 168±7	Final Call[3,4] Phn 28d ±3 ALD
Written Informed Consent[5]	X	X									
Inclusion/Exclusion Review	X	X[6]									
ALS & Medical History	X										
Demographics	X										
Physical Examination	X										
Neurological Exam	X										
Vital Signs[7]	X		X		X	X		X		X	
Slow Vital Capacity	X[20]		X			C		C		X	
Home Spirometry	X[20]		X			X		X		X	
Muscle Strength Assessment			X			C		C		X	
ALSFRS-R	X		X		X	X	X	X	X	X	
ALSAQ-40			X							X	
CNS-BFS			X			X		X		X	
12-Lead ECG	X					C				X	
Clinical Safety Labs[8]	X		X		X	X		X		X	
Verdiperstat PK Samples[10]			X		C	C		C		X	
Verdiperstat PD Samples[10]			X		C	C		C		X	
Biomarker Blood Collection			X			C		C		X	
Biomarker Urine Collection			X			C		C		X	
DNA Collection[11] (optional)			X								
CSF Collection (optional)			X					C[17]			
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review[9]	X	X	X	X	X	X	X	X	X	X	X
Suicidality C-SSRS			X		X	X		X		X	
Install Smartphone Apps[21]			X								

Activity	MP Scrn[1] Cln -42d to -1d	RGB Scrn[1] Cln -41d to 0d	Base-line Cln Day 0	Week 2[2] Phn Day 14±3	Week 4[18,19] Cln[5] Day 28±7	Week 8[18,19] Cln[5] Day 56±7	Week 12 Phn Day 84±3	Week 16[18,19] Cln[5] Day 112±7	Week 20 Phn Day 140±3	Week 24[3,18] Cln Day 168±7	Final Call[3,4] Phn 28d ±3 ALD
Smartphone Voice Recording[12]			X		X	X		X		X	
Uninstall Smartphone App										X	
Regimen Assignment	X										
Randomization within RGB			X								
Administer/Dispense Study Drug			X[13]		X	X		X			
Drug Accountability/Compliance				X[2,22]	X	X	X[22]	X	X[22]	X	
Dose Escalation			X[15]	X[15]							
Exit Questionnaire										X	
Vital Status										X[16]	

Abbreviations: ALD = after last dose, ALS = amyotrophic lateral sclerosis, ALSAQ-40 = ALS Assessment Questionnaire, ALSFRS-R = ALS Functional Rating Scale Revised, BP = blood pressure, C = completed only if the visit is conducted in-clinic, CBC = complete blood count, Cln = Clinic visit, CNS-BFS = Center for Neurologic Study Bulbar Function Scale, CSF = cerebrospinal fluid, C-SSRS = Columbia-Suicide Severity Rating Scale, d = day, DNA = deoxyribonucleic acid, ECG = electrocardiogram, LFTs = liver function tests, MP = Master Protocol, PD = pharmacodynamic, Phn = Phone visit, RGB = the verdiperstat regimen, Scrn = Screening Visit.

[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] At the end of Week 2, an assessment of compliance and tolerance to this dose titration schedule will be conducted. The assessment will be conducted by phone. If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see RSA Section 5.3.2).

[3] Participants will only have a Follow-Up Safety Call at this time if they do not continue into the OLE or if they discontinue prior to Week 24. Participants who continue into OLE will have a Follow-Up Safety Call after their last dose of study drug during the OLE phase.

[4] Participants who continue into the OLE and then early terminate will be asked to complete an Early Termination Visit and Follow-Up Safety Call as described in the body of this RSA.

[5] During the Master Protocol Screening Visit, participants will be consented via the Master Protocol informed consent form (ICF). After a participant is randomized to a regimen, participants will be consented a second time via the RSA ICF.

[6] At the Regimen Specific Screening Visit, participants will have regimen-specific inclusion and exclusion criteria assessed, if applicable.

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

[8] Clinical safety labs include hematology (CBC with differential), complete chemistry panel, thyroid function (TSH) 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.

[9] Adverse events that occur after signing the master protocol consent form will be recorded.

[10] Myeloperoxidase protein and activity, and plasma concentrations of verdiperstat will be measured. For each sample, the time of the last verdiperstat or matching placebo dose prior to sample collection, time of the last meal prior to sampling and time of the PD/PK sample collection should be reported on the CRF.

[11] The DNA sample can be collected after baseline if a baseline sample is not obtained or the sample is not usable.

[12] In addition to study visits outlined in the SOA, participants may be asked to complete twice weekly voice recordings at home. During weeks when a participant is doing a voice recording in-clinic, he or she would only do one other voice recording at home that week.

[13] Administer first dose of investigational product (IP) only after Baseline Visit procedures are completed. Participants should take the first dose of IP while in the office/clinic on the day of the Baseline visit and stay at the clinic for approximately 30 minutes post-dose for observation.

[14] Investigational product will only be dispensed at this visit if the participant continues in the OLE.

[15] From start to end of Week 1, participants will ingest either 300 mg QD of verdiperstat or matching placebo QD. From start to end of Week 2, participants will ingest either 300 mg BID of verdiperstat or matching placebo BID. Starting with Week 3 and continuing to Week 24, participants will ingest either 600 mg BID of verdiperstat or matching placebo BID.

[16] Vital status, defined as a determination of date of death or death equivalent or date last known alive, will be determined for each randomized participant at the end of the placebo-controlled portion of their follow-up (generally the Week 24 Visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant's last visit 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.

[17] If the CSF collection cannot happen at the Week 16 Visit for logistical reasons such as scheduling, it can happen at the Week 24 Visit.

[18] Participants should be instructed to skip the morning dose of study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.

[19] 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 or other reason.

[20] 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).

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

[22] Drug accountability will not be done at phone visits. A drug compliance check in must be held during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.

3. General Considerations for Data Analysis

3.1 Statistical Software

Statistical software use for analyses is the same as described in the M-SAP.

3.2 Summary Statistics

Data summaries are the same as described in the M-SAP.

3.3 Precision

Precision of reported results is the same as described in the M-SAP.

3.4 Transformations

Data transformations are the same as described in the M-SAP.

3.5 Multiplicity Adjustments

Handling of multiplicity adjustments is the same as described in the M-SAP.

3.6 Missing Data

Handling of missing data is the same as described in the M-SAP. Clinic-based assessments that are missing due to COVID-19 restrictions or disruptions are considered missing at random.

4. Study Endpoints

4.1 Efficacy Endpoints

The primary and secondary efficacy endpoints are the same as described in the M-SAP. ALSFRS-R total score is considered the primary efficacy endpoint and hand-held dynamometry (HHD) upper and lower extremity percentages, slow vital capacity (SVC), and survival are considered key secondary efficacy endpoints in RGB.

4.2 Exploratory Endpoints

The following categories of exploratory endpoints will be evaluated:

- Change in ALSFRS-R domain scores
- Change in strength: HHD global percentage, HHD0, and $HHD0^2$,
- Change in quantitative voice characteristics as measured by Aural Analytics: maximum phonation time, pause rate, breathy vocal quality, pitch instability, regulation of voicing, articulatory precision, speaking rate, articulation rate, and monotonicity,
- Change in biofluid biomarkers of neurodegeneration and neuromuscular degeneration: serum creatinine and serum and cerebrospinal fluid (CSF) neurofilament light chain (NfL),
- Change in patient-reported outcomes: ALSAQ-40 physical mobility, independence in activities of daily living, eating and drinking, communications, and emotional reactions domain scores and ALSAQ-40 symptom index, CNS-BFS total score,
- Change in plasma concentrations of verdiperstat,
- Change in verdiperstat PD biomarkers: myeloperoxidase protein, total activity, and concentration-specific activity,
- Change in respiratory function as assessed by home spirometry, and
- Time to clinical events: first hospitalization due to a serious adverse event (SAE), first hospitalization due to an ALS-related SAE, first use of assisted ventilation, first placement of a feeding tube, first time reaching King's stage 4a or 4b, and first instance of any of the following events: hospitalization for an SAE, feeding tube placement, tracheostomy, initiation of permanent assisted ventilation (PAV), or death.

4.3 Safety Endpoints

In addition to the safety endpoints described in the M-SAP, the following RGB regimen-specific safety endpoint will be evaluated:

- Thyroid function: Proportion of participants with TSH ≥10 mIU/L, proportion of participants with signs or symptoms of hypothyroidism, and levels of free T3, free T4, and TSH.

5. Measurement Definitions

5.1 ALSFRS-R

The definitions of ALSFRS-R scores are the same as described in the M-SAP. Pre-baseline slope in ALSFRS-R (delta-FRS) is defined as 48 minus the baseline ALSFRS-R total score then divided by the number of months from onset of symptomatic weakness to the Baseline Visit. The number of months will be calculated as the difference in days from onset of symptomatic weakness to the Baseline Visit multiplied by 12 / 365.25. The date of onset of symptomatic weakness will be imputed as the fifteenth day of a month if not specified more precisely.

ALSFRS-R domain scores are exploratory measures of the primary efficacy endpoint ALSFRS-R total score.

5.2 SVC

The derivation of SVC percent-predicted of normal is the same as described in the M-SAP with age calculated as number of days from date of birth to the date of a given SVC assessment divided by 365.25 and with the following correspondence between self-identified race and race defined by Global Lung Initiative (GLI) classification:

Self-identified Race	GLI-defined Race
American Indian or Alaska Native	Mixed/Other
Asian	South East Asian
Black or African American	African American
Native Hawaiian or Other Pacific Islander	Mixed/Other
White	Caucasian
Unknown	Caucasian
Not reported	Caucasian
More than one race indicated	Mixed/Other

5.3 Home Spirometry

Home spirometry assesses FVC remotely using a smartphone app (ZEPHYRx, Albany, NY) and a handheld spirometer (Spirobank Smart, Medical International Research, Rome, Italy). Coordinators guide participants through 3 to 8 maneuvers with live-video coaching using the ZEPHYRx platform. Flow loops are classified for acceptability and repeatability using American Thoracic Society (ATS) criteria and are manually reviewed by the NEALS Outcomes Center (Barrow Neurological Institute, Phoenix, AZ). The maximum FVC accepted by the NEALS Outcomes Center is converted to percent of predicted normal using GLI norms based on sex, age at time of assessment, height at time of screening, and race. Age is calculated as number of days from date of birth to the date of a given home spirometry assessment divided by 365.25. Higher values indicate greater respiratory function.

5.4 HHD and Grip Strength

The derivation of HHD upper and lower extremity scores and HHD0 are the same as described in the M-SAP with the revision that HHD0 is a composite endpoint with death or death equivalent, whichever occurs first.

A second HHD time-to-event endpoint is defined as the time from the Baseline Visit to the second post-baseline occurrence of a muscle with a strength recording of 0 among those muscles that were non-zero at baseline or time to death or death equivalent, whichever occurs first ($HHD0^2$).

Time at risk for HHD0 and $HHD0^2$ will be censored at the last date at an HHD assessment was performed up to the end of the Week 24 Visit window.

HHD global average percentage, HHD0, and $HHD0^2$ are exploratory measures of the secondary endpoint HHD and grip strength.

5.5 Quantitative Voice Characteristics

Voice samples will be collected using the Aural Analytics app installed on either an Android or iOS-based smartphone. At each assessment, participants perform a set of speaking tasks: reading 5 prespecified sentences, reading 5 sentences chosen at random from a large sentence bank, repeating a consonant-vowel sequence, producing a sustained phonation, and counting on a single breath. Speech analysis will be performed by Aural Analytics to derive the following quantitative voice characteristics: maximum phonation time, pause rate, breathy vocal quality, pitch instability, regulation of voicing, articulatory precision, speaking rate, articulation rate, and monotonicity. Aural Analytics will use data on quantitative voice characteristics and participant age, sex, race, height, and weight to derive a prediction of vital capacity at the Baseline Visit.

5.6 Biofluid Biomarkers of Neurodegeneration

Blood biomarkers of neurodegeneration, including biomarkers of neuromuscular dysfunction, will be assayed. These will include serum creatinine and serum and CSF neurofilament light chain (NfL). Serum creatinine will be assayed by the kinetic Jaffe method (test 001370, Labcorp, Burlington, NC). NfL will be assayed by single-molecule array (Simoa; Quanterix, Billerica, MA). Levels of serum and CSF NfL that are reported to be below the limit of quantitation will be imputed at the limit of quantitation. Levels of serum and CSF NfL will be log-transformed in all analyses.

5.7 ALSAQ-40

The description of the ALSAQ-40 instrument and item-level scores are the same as described in the M-SAP. Each of the five domains will be scored as the mean of all domain-specific items multiplied by 25 (range 0 to 100). An overall symptom index (SI) will be scored as the mean of the five domain scores. A domain score will be missing if more than 20% of the items are missing; otherwise, item non-response will be mean-imputed from other completed items from the same assessment. The ALSAQ-40 SI will be missing if any domain scores are missing. Higher scores indicate worse quality of life.

5.8 CNS-BFS

The definition of CNS-BFS total score is the same as described in the M-SAP.

5.9 Survival

The primary definition of survival time is the same as described in the M-SAP with the clarification that PAV is defined as more than 22 hours per day of noninvasive or invasive

mechanical ventilation for more than seven consecutive days. The date of PAV initiation, where applicable, will be imputed as the fifteenth day of a month if not specified more precisely. A secondary survival endpoint of death alone, independent of any death equivalent, is also defined.

Time at risk for the composite endpoint of death or death equivalent and time at risk for the endpoint of death alone will be measured from each participant's Baseline Visit. Time at risk will be censored at two time points: (1) at the Week 24 Visit as defined in the M-SAP, and (2) at a subsequent assessment of death or death equivalent scheduled approximately at the end of placebo-controlled follow-up of the last RGB participant. The primary analysis of survival will evaluate PAV-free survival to the Week 24 Visit time point.

5.10 King's ALS Clinical Staging System

The King's ALS Clinical Staging System (Roche et al. 2012) is a 4-level ordinal scale with the first three levels indicating the number (1, 2, or 3) of distinct central nervous system regions (bulbar, upper limb, and lower limb) with neuromuscular dysfunction and levels 4a and 4b indicating nutritional or respiratory failure secondary to ALS, respectively.

Participants will be classified to King's stage 1, 2, 3, 4a, or 4b based on scores from ALSFRS-R assessments according to a published derivation (Balendra et al. 2014). Bulbar involvement is defined as a score less than 4 on any of the ALSFRS-R questions in the bulbar domain (questions 1, 2, and 3). Upper limb involvement is defined as a score less than 4 on either of the ALSFRS-R questions related to hand function (questions 4 and 5A). Lower limb involvement is defined as a score less than 4 on the ALSFRS-R question about walking (question 8). Nutritional failure is defined as responding that the participant uses gastrostomy for greater than 50% of their nutrition. Respiratory failure is defined as a score of 0 on the ALSFRS-R question addressing dyspnea (question 10 or R-1) or a score less than 4 on the ALSFRS-R question about use of mechanical ventilation (question 12 or R-3). Participants without evidence by ALSFRS-R scores of involvement of any of the three central nervous system regions will be scored as King's stage 1 due to their confirmed diagnosis with ALS. Participant may meet criteria for both King's stage 4a and 4b.

5.11 Hospitalization and Other Clinical Events

Times to the following clinically relevant events are defined:

- Time to first hospitalization due to a serious adverse event (SAE),
- Time to first hospitalization due to an ALS-related SAE,
- Time to first use of assisted ventilation,
- Time to first placement of a feeding tube,
- Time to King's stage 4a or 4b, and
- Time to first instance of hospitalization for an SAE, feeding tube placement, tracheostomy, initiation of PAV, or death.

Time at risk for each event will be measured from each participant's Baseline Visit. Time to first hospitalization excludes hospitalizations for elective procedures. ALS-related SAEs are those indicated as related to ALS disease progression by the site investigator. Participants who are already using assisted ventilation or have a feeding tube at the time of the Baseline Visit will be

excluded from analysis of those endpoints. Death or death equivalent will be considered an outcome for each of the events listed, forming a composite endpoint.

Time at risk for these events will be censored at the Week 24 Visit, if completed, the date of consent withdrawal, if withdrawn, or the last date at which the status of each endpoint is known prior to the end of the Week 24 Visit window for participants lost to follow-up. Time to King's stage 4a or 4b is interval censored between ALSFRS-R assessments.

5.12 Pharmacodynamic Biomarkers

Myeloperoxidase protein and activity levels in plasma samples collected at Baseline and Weeks 4, 8, 16, and 24 will be assayed among participants randomized to active treatment. Details of the assay techniques will be specified when known.

5.13 Clinical Safety Laboratory Tests

Clinical safety labs include hematology, blood chemistry panel, liver function tests, thyroid function, urinalysis, and pregnancy testing in women of childbearing potential as specified in Section 9.1.2 Clinical Safety Laboratory Tests of the Master Protocol:

- Hematology: hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC distribution width (RDW), RBC morphology, white blood cell (WBC) count, and counts and percentages of basophils, eosinophils, lymphocytes, monocytes, and neutrophils;
- Blood chemistry panel: bicarbonate, chloride, potassium, sodium, calcium, magnesium, phosphate, blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) four-variable equation, creatinine clearance calculated using the Cockcroft-Gault equation, and glucose;
- Liver function tests: alanine aminotransferase (ALT [SGPT]), aspartate aminotransferase (AST [SGOT]), alkaline phosphatase (ALP), albumin, total protein, total bilirubin (TBL);
- Thyroid function tests: thyroid-stimulating hormone (TSH), reflex T3 and T4 when TSH levels are abnormal;
- Urinalysis: clarity, color, specific gravity, pH, microalbumin, protein, glucose, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and blood; and
- Pregnancy: qualitative and quantitative serum human chorionic gonadotropin (hCG).

Clinical safety labs will also include derived measures of potential drug-induced liver injury (DILI), including those that potentially meet the Hy's law criteria, as distinct safety lab outcomes.

Three potential DILI criteria will be defined:

- ALT or AST >3x ULN with TBL >1.5x ULN
- AST or ALT >3x ULN with TBL >2x ULN
- AST or ALT >3x ULN with TBL >2x ULN and ALP <2x ULN (potential Hy's Law cases)

where ULN is upper level of normal and all levels are measured on the same day.

6. Statistical Methodology

6.1 Analysis Sets

The ITT analysis set is henceforth referred to as the Full Analysis Set (FAS) and defined as follows:

- Full Analysis Set (FAS): Participants who were randomized within RGB plus placebo participants from specified regimens, classified according to their randomized treatment assignment. Observations made after premature permanent discontinuation of study drug are included in this sample, should such participants remain on study. Observations completed after regimen data lock are excluded. Participants determined to not meet ALS diagnostic criteria are excluded.

The definition of the STF analysis set is revised as follows:

- Safety Full (STF) Set: Participants who initiated treatment within RGB plus placebo participants from specified regimens who are not known to be ineligible for RGB and who initiated treatment in their respective regimen, classified according to the treatment they actually received. Observations made after premature permanent discontinuation of study drug are included in this sample, should such participants remain on study. Observations completed after regimen data lock are excluded.

An analysis set restricting shared placebo participants to those regimens in which study drug is administered by the same route as RGB is defined as follows:

- Efficacy Common Mode of Administration (ECM) Set: The subset of participants in the FAS analysis set who are in regimens in which study drug is administered by the same route as RGB.

The definitions of the ECC, ERO, STN, and SRO analysis sets are the same as described in the M-SAP with reference to the ITT analysis set now referencing the FAS analysis set. The following analysis set is specific to RGB:

Efficacy Per-protocol (EPP) Set: The subset of participants in the FAS analysis set who initiated study treatment and who were not involved in protocol deviations that affected the scientific integrity of the trial as documented prior to data lock, classified according to the treatment they actually received. Inclusion or exclusion from the EPP analysis set of any participant for whom treatment assignment was unblinded prior to data lock will be governed by the prespecified criteria above. If a participant's data is truncated for inclusion in the EPP analysis set due to non-adherence to protocol-specified dosing, clinical events observed up to 28 days after the censoring event will be included in the EPP analysis set. For all other events leading to truncation of a participant's data, no events beyond that date will be included. Data from placebo participants shared from other regimens will not be truncated due to non-adherence to protocol-specified dosing.

-

Applicable analysis sets (FAS, ECM, EPP, STF, and STN) will include shared placebo participants from regimens A and C only. Data from shared placebo participants will include visits and events that occurred on or before the date of the final placebo-controlled period follow-up of a regimen A, B, or C participant. As only concurrently enrolling regimens are

contributing to efficacy analyses, the FAS and ECC analysis sets are synonymous and only the FAS analysis set will be referenced. As regimen A is administered by subcutaneous injection and regimen C is administered orally, only regimen C will contribute shared placebo participants for the ECM and STN analysis sets.

6.2 Baseline Characterization

The baseline characteristics summarized for participants randomized within RGB are the same as specified in the M-SAP with the addition of ALSAQ-40 domain scores and SI, CNS-BFS total score, King's stage, weight, body mass index (BMI), serum urate concentration, serum creatinine concentration, and serum NfL concentration.

6.3 Primary Efficacy Analysis and Supportive Analyses

The primary analysis for RGB is a Bayesian shared-parameter, repeated-measures model of ALSFRS-R that accounts for loss of follow-up due to mortality. Details of the model, including documentation of operating characteristics under a range of scenarios, are provided in the "ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report" (Appendix 1 to the Master Protocol). The Bayesian shared-parameter, repeated-measures model will be applied to the FAS analysis set as the primary analysis, to the ECM and ERO analysis sets as sensitivity analyses, and to the EPP analysis sets as a supportive analysis.

The estimand of the primary analysis is the relative rate of disease progression (the "disease rate ratio" or DRR) of active treatment relative to placebo in the FAS population under an assumption that active treatment slows mean time to death or death equivalent by the same proportion as treatment slows the mean rate of functional progression as measured by change in ALSFRS-R total score over time. The estimand is defined by the following attributes:

- Treatment: verdiperstat administered orally at a dosage of 600 mg BID vs. placebo.
- Population: FAS population as defined in Section 6.1.
- Variables: time to death or death equivalent and rate of change in ALSFRS-R total score from baseline to the Week 24 Visit.
- Intercurrent event 1: treatment discontinuation due to death: no ALSFRS-R data from participants who reach the death or death equivalent endpoint are included in the analysis, handled via mortality component in model, composite variable strategy approach.
- Intercurrent event 2: treatment discontinuation not due to death: handled via treatment policy approach, all data will be used including data collected during the placebo-controlled period after treatment discontinuation regardless of concomitant medication, for those participants who have not been censored due to mortality. Missing data post-treatment will not be imputed, handled via missing at random assumption.
- Population-level summary: mean ratio of hazard or progression rate of active treatment relative to placebo.

6.4 Interim Analysis

RGB will be considered for early stopping for futility according to the interim analysis schedule and definition specified in the "ALS Master Protocol Recommended Statistical Analysis, Design

and Simulation Report" (Appendix 1 to the Master Protocol). RGB will not be stopped early for success.

6.5 Secondary Efficacy Analyses

6.5.1 Hierarchical Testing

Primary inference for secondary efficacy endpoints will be based on analysis of the FAS analysis set using a repeated-measures linear mixed model for functional endpoints (see Section 6.5.2 below) and by Kaplan-Meier product-limit estimates and log-rank test for the primary survival endpoint (see Section 6.5.4 below). The sequence for testing secondary efficacy endpoints is the following:

1. HHD upper extremity percentage,
2. SVC,
3. HHD lower extremity percentage, and
4. Survival.

If the primary analysis indicates a significant slowing in disease progression from the Bayesian shared-parameter, repeated-measures model of ALSFRS-R and mortality, then each secondary efficacy endpoint in succession would be declared significant in the specified sequence using a comparison-wise criterion of two-tailed $p < 0.05$. After the first failure to declare significance, no endpoints lower in the hierarchy can be significant. This sequential closed-testing procedure controls the overall type 1 error rate at 5%. Nominal comparison-wise p-values for secondary efficacy endpoints will also be reported.

6.5.2 Repeated-measures Model

The specification of the repeated-measures linear mixed model and the primary linear contrast for estimating differences in 24-week change from baseline in a given continuous efficacy endpoint (ALSFRS-R total and domain scores, HHD upper extremity, lower extremity, and global average percentages, SVC, FVC by home spirometry, serum creatinine, serum NfL, ALSAQ-40 domain scores and SI, and CNS-BFS total score) are revised from those specified in the M-SAP to include a main effect of treatment.

The model will include fixed terms for discrete visit, treatment group, treatment group × visit interaction, centered time since symptom onset and centered time since symptom onset × visit interaction, centered delta-FRS and centered delta-FRS × visit interaction, centered baseline riluzole use and centered baseline riluzole × visit interaction, and centered baseline edaravone use and centered baseline edaravone × visit interaction. The following equations describe the model with regimen random effects:

$$Y_{ij} = a_{k(i)} + \gamma_1 t_i + \gamma_{2,j} v_j + \boldsymbol{\gamma_3'} \boldsymbol{z_i} + \gamma_{4,j}\, t_i v_j + \boldsymbol{\gamma_{5,j}'} \boldsymbol{z}_i\, v_j + \epsilon_{ij}$$
$$a_k \sim N(0, \sigma_r^2),\ \boldsymbol{\epsilon_{i\cdot}} \sim N(\mathbf{0}, \boldsymbol{R}),\ \mathrm{Cov}\left(b_{k(i)}, \epsilon_{ij}\right) = 0 \qquad \text{(eqn. 1)}$$

where Y_{ij} is a given efficacy endpoint measured in participant i at visit j, $a_{k(i)}$ is a random intercept for regimen k to which participant i was assigned, v_j is an indicator variable for visit j, $\boldsymbol{z}_i$ is the vector of covariates (centered time since onset, centered delta-FRS, centered baseline riluzole use, and centered baseline edaravone use) for participant i, t_i is an indicator variable for treatment t to which participant i was assigned, γ_1, $\gamma_{2,j}$, $\boldsymbol{\gamma_3}$, $\gamma_{4,j}$, and $\boldsymbol{\gamma_{5,j}}$ are estimated parameters

and vectors of parameters for the fixed effects, and ϵ_{ij} is the residual for participant i at visit j. The regimen-specific random effects are normally distributed with mean 0 and variance $\sigma^2_{r.}$ The vector of residuals for a given participant are normally distributed with mean **0** and an unstructured covariance matrix **R**. The regimen-specific random effect for a given participant and residuals for that participant are uncorrelated.

The following SAS code specifies the model:

```
proc mixed data=xxx method=reml;
  class regimen id trtrnd visit;
  model Value = trtrnd|visit
                sx2bl|visit dFRS|visit rlz|visit edv|visit / solution cl;
  random intercept / subject=regimen type=vc;
  repeated visit / subject=id type=un;
```

where `id` is a participant study identifier, `trtrnd` is the randomly assigned treatment group, `visit` is the visit identifier, `Value` is value of the efficacy endpoint being tested for a given participant at a given visit, `sx2bl` is years since ALS symptom onset centered at the sample median, `dFRS` is pre-baseline slope centered at the sample median, `rlz` is an indicator of riluzole use at baseline, and `edv` is an indicator of edaravone use at baseline. The primary estimate will be the treatment-dependent difference in change from baseline to the Week 24 Visit. The estimate and its 95% Wald confidence bounds will be obtained by a linear contrast of adjusted means. The following SAS code specifies the linear contrast for a regimen with one active treatment assuming an endpoint measured every 8 weeks and that the sort order for treatment group has the active group last and visits are sorted chronologically:

```
  estimate "3|Act vs Plb|dWk 24" trtrnd*visit 1 0 0 -1  -1 0 0 1 / cl;
```

A significant difference in 24-week change from baseline in the direction of greater improvement or less worsening among participants randomized to active treatment would support inference of benefit from active treatment for the efficacy endpoint being tested.

The estimand estimated by the primary linear contrast of the repeated-measures linear mixed model is the mean difference in 24-week change from baseline of a given continuous efficacy endpoint in the active treatment group relative to the placebo group in the FAS population. The estimand is defined by the following attributes:

- Treatment: verdiperstat administered orally at a dosage of 600 mg BID vs. placebo.
- Population: FAS population as defined in Section 6.1.
- Variables: absolute change in endpoint from baseline to the Week 24 Visit.
- Intercurrent event: treatment discontinuation: handled via treatment policy approach, all data will be used including data collected during the placebo-controlled period after treatment discontinuation. Missing data post-treatment, including data missing due to death, will not be imputed, handled via missing at random assumption.
- Population-level summary: difference in conditional means of active treatment relative to placebo.

Inference from this analysis is supportive of inference from the Bayesian shared-parameter, repeated-measures model for the primary endpoint and is the primary analysis for secondary

endpoints. A separate supportive analysis will include centered baseline serum NfL level and the interaction of centered baseline serum NfL level and visit as additional covariates.

6.5.3 Random-slopes Model

The specification of the random-slopes linear mixed model and the primary linear contrast for estimating differences in mean rate of progression in a given continuous efficacy endpoint (ALSFRS-R total and domain scores, HHD upper extremity, lower extremity, and global average percentages, SVC, FVC by home spirometry, quantitative voice characteristics, serum creatinine, serum NfL, ALSAQ-40 domain scores and SI, and CNS-BFS total score) are revised from those specified in the M-SAP to include a main effect of treatment and to specify that study months are calculated as the difference in days from the Baseline Visit to the date of assessment of a given endpoint multiplied by 12 / 365.25.

The model will include fixed terms for month since the Baseline Visit, treatment group, treatment group × month interaction, centered years since ALS symptom onset and centered years since ALS symptom onset × month interaction, centered delta-FRS and centered delta-FRS × month interaction, centered baseline riluzole use and centered baseline riluzole use × month interaction, and centered baseline edaravone use and centered baseline edaravone use × month interaction. The following equations describe the model with regimen random effects:

$$\begin{gathered} Y_{ij} = \gamma_1 + a^0_{k(i)} + b^0_i + \gamma_2 t_i + \boldsymbol{\gamma_3'} \boldsymbol{z_i} \\ + \left(\gamma_4 + a^1_{k(i)} + b^1_i + \gamma_5 t_i + \boldsymbol{\gamma_6'} \boldsymbol{z_i}\right) m_{ij} + \epsilon_{ij} \\ \{a^0_k, a^1_k\} \sim N(\mathbf{0}, \boldsymbol{\Sigma_r}), \{b^0_k, b^1_k\} \sim N\left(\mathbf{0}, \boldsymbol{\Sigma_p}\right), \epsilon_{ij} \sim N(0, \sigma^2_\epsilon) \\ \mathrm{Cov}(\boldsymbol{a_k}, \boldsymbol{b_k}) = \mathbf{0}, \mathrm{Cov}(\boldsymbol{a_k}, \boldsymbol{\epsilon_{i\cdot}}) = \mathbf{0}, \text{ and } \mathrm{Cov}(\boldsymbol{b_k}, \boldsymbol{\epsilon_{i\cdot}}) = \mathbf{0} \end{gathered} \quad \text{(eqn. 2)}$$

where Y_{ij} is a given efficacy endpoint measured in participant i at visit j, $a^0_{k(i)}$ and $a^1_{k(i)}$ are random intercept and slope for regimen k to which participant i was assigned, b^0_i and b^1_i are random intercept and slope for participant i, $\boldsymbol{z_i}$ is the vector of covariates (centered time since onset, centered delta-FRS, centered baseline riluzole use, and centered baseline edaravone use) for participant i, m_{ij} is the time from baseline to observation j for participant i in months calculated as days x 12 / 365.25, t_i is an indicator variable for treatment t to which participant i was assigned, γ_1, γ_2, $\boldsymbol{\gamma_3}$, γ_4, γ_5, and $\boldsymbol{\gamma_6}$ are estimated parameters and vectors of parameters for the fixed effects, and ϵ_{ij} is the residual for observation j for participant i. The regimen-specific random effects are normally distributed with mean $\mathbf{0}$ and unstructured covariance matrix $\boldsymbol{\Sigma_r}$. The participant-specific random effects are normally distributed with mean $\mathbf{0}$ and unstructured covariance matrix $\boldsymbol{\Sigma_p}$. The residuals for a given participant are normally distributed with mean 0 and variance σ^2_ϵ. The regimen-specific random effects, participant-specific random effects, and residuals are uncorrelated.

The following SAS code specifies the model:

```
proc mixed data=xxx method=reml;
  class regimen id trtrnd;
  model Value = trtrnd|month
                sx2bl|month dFRS|month rlz|month edv|month / solution cl;
  random intercept month / subject=regimen type=un;
  random intercept month / subject=id type=un;
```

where `month` is time in months from the Baseline Visit (assuming 12 months in an average of 365.25 days per year) and other fields are the same as identified above in Section 6.5.2. The primary estimand will be the treatment-dependent difference in slopes. The estimate and its 95% Wald confidence bounds will be obtained by a linear contrast of adjusted means. The following SAS code specifies the linear contrast for a regimen with one active treatment assuming that the sort order for treatment group has the active group last:

```
estimate "3|Act vs Plb|Slope (/mn)" month 0 trtrnd*month -1 1 / cl;
```

A significant difference in slopes in the direction of greater improvement or less worsening among participants randomized to active treatment would support inference of benefit from active treatment for the efficacy endpoint being tested.

The estimand estimated by the primary linear contrast of the random-slopes linear mixed model is the difference in mean rate of progression of a given continuous efficacy endpoint in the active treatment group relative to the placebo group in the FAS population. The estimand is defined by the following attributes:

Treatment: verdiperstat administered orally at a dosage of 600 mg BID vs. placebo.

Population: FAS population as defined in Section 6.1.

Variables: mean rate of change in endpoint from baseline to the Week 24 Visit.

Intercurrent event: treatment discontinuation: handled via treatment policy approach, all data will be used including data collected during the placebo-controlled period after treatment discontinuation. Missing data post-treatment will not be imputed, handled via missing at random assumption.

Population-level summary: difference in conditional mean slopes of active treatment relative to placebo.

Inference from these analyses is supportive of inference from the Bayesian shared-parameter, repeated-measures model for the primary endpoint and inference from the repeated-measures linear mixed model for secondary endpoints. A separate supportive analysis will include centered baseline serum NfL level and the interaction of centered baseline serum NfL level and study month as additional covariates.

6.5.4 Survival and Time to Clinical Events

Survival and time to hospitalizations and clinical events will be analyzed in the FAS, ECM, ERO, EPP, STF, SFN, and SRO analysis sets. Survival analyses that include follow-up beyond the placebo-controlled period will be analyzed in the ERO analysis set. The summaries and analyses of time to death or death equivalent are the same as specified in the M-SAP with the revision to include baseline age as an additional covariate in adjusted models, with the addition that the endpoints of time to death independent of occurrence of death equivalents and time to each of the hospitalization and clinical events will be separately analyzed using the same models, and with an additional adjusted analysis that includes baseline serum NfL level as a covariate. Analysis of time to King's stage 4a or 4b will accommodate interval censoring between ALSFRS-R assessments and will be stratified by baseline King's stage.

6.5.5 CAFS

The primary CAFS analysis is as specified in the MPRDR. Additional, unadjusted CAFS analyses are the same as specified in the M-SAP, including specification that pair-wise comparison of change in ALSFRS-R total score for participants who cannot be ranked by time to death or death equivalent is to the maximum follow-up time at which both participants have an observation, and with the following additions:

1. HHD upper and lower extremity percentage and SVC will be analyzed by CAFS by substituting change from baseline for those secondary efficacy endpoints in place of ALSFRS-R total score,
2. An additional set of CAFS analyses will use multiple imputation to extend follow-up of ALSFRS-R total score, HHD upper and lower extremity percentage and SVC for participants who early terminate, withdraw consent, or are lost to follow-up,
3. An additional set of CAFS analyses for ALSFRS-R total score, HHD upper and lower extremity percentage and SVC will use time to death alone independent of any death equivalent,
4. An additional set of CAFS analyses for ALSFRS-R total score, HHD upper and lower extremity percentage, and SVC will adjust rank scores in a linear model with the following covariates: time from ALS symptom onset, delta-FRS, baseline use of riluzole, and baseline use of edaravone, and
5. An additional set of CAFS analyses for ALSFRS-R total score, HHD upper and lower extremity percentage, and SVC will adjust rank scores in a linear model with the following covariates: time from ALS symptom onset, delta-FRS, baseline use of riluzole, baseline use of edaravone, and baseline serum NfL level.

The multiple imputation model used to extend follow-up of functional scores for participants who early terminate, withdraw consent, or are lost to follow-up will use linear regression with covariates of time since symptom onset, delta-FRS, baseline riluzole use, baseline edaravone use, and each observed functional score prior to a missing assessment.

Inference from CAFS analyses is supportive of inference from the Bayesian shared-parameter, repeated-measures model for the primary outcome and supportive of inference from the repeated-measures model for the secondary outcomes of HHD upper extremity score, SVC, and HHD lower extremity score. Primary inference from CAFS analyses will compare survival by time to death or death equivalent, will compare change in function to the last jointly observed time point, and will adjust for the specified covariates.

6.5.6 HHD0 and HHD0^2

Analyses of HHD0 are the same as specified in the M-SAP with the addition of parallel analyses of HHD0^2, with a separate analysis that includes baseline serum NfL level as an additional covariate, and with the clarification that time to zero strength for both analyses is interval censored between HHD assessments.

Inference from these analyses is supportive of inference from the repeated-measures linear mixed model for HHD upper and lower extremity scores.

6.5.7 Quantitative Voice Measures

Given the high frequency of voice recordings, a repeated-measures analysis with unstructured covariance is overly flexible but the assumption of linear change required by the random-slopes

model may be overly rigid. To complement estimates from the random-slopes linear mixed model, quantitative voice characteristics will be analyzed in a linear mixed model in which the temporal profile for both fixed and random terms is modeled using cubic B-splines with knots at 8 and 16 weeks. The model will include fixed terms for B-splines (4 terms), treatment group (2 levels), treatment group × B-spline interaction, centered time since symptom onset and centered time since symptom onset × B-spline interaction, centered delta-FRS and centered delta-FRS × B-spline interaction, centered baseline riluzole use and centered baseline riluzole × B-spline interaction, and centered baseline edaravone use and centered baseline edaravone × B-spline interaction The model will include random regimen-specific intercepts and slopes with unstructured covariance, random participant-specific B-splines (5 terms) with unstructured covariance, and a first-order autoregressive structure for residuals. A simplified covariance structure assuming no regimen-level covariance, heterogeneous compound symmetric covariance among the random B-splines, conditional independence of residuals, or a combination of the three simplifying assumptions will be used if the full model fails to converge. The primary estimand will be the treatment-dependent difference in 24-week change from baseline. The estimate and its 95% Wald confidence bounds will be obtained by a linear contrast of adjusted means. A separate analysis will include centered baseline serum NfL level and the interaction of centered baseline serum NfL level and B-splines as additional covariates.

6.5.8 Placebo Multiple Imputation

Placebo multiple imputation analyses are the same as specified in the M-SAP and will be applied to ALSFRS-R total score, HHD upper and lower extremity percentages, and SVC.

The following SAS code specifies the imputation for an endpoint measured every 8 weeks:

```
proc mi data=work.outcomes seed=xxx nimpute=50 out=work.out_mi01
        minimum=. . . . . x x x x maximum=. . . . . y y y y minmaxiter=1000;
  class rlz edv trtrnd;
  fcs reg(Wk08 = sx2bl dFRS rlz edv Wk00);
  fcs reg(Wk16 = sx2bl dFRS rlz edv Wk00 Wk08);
  fcs reg(Wk24 = sx2bl dFRS rlz edv Wk00 Wk08 Wk16);
  mnar model( Wk08 Wk16 Wk24 / modelobs=(trtrnd="0"));
  var sx2bl dFRS rlz edv Wk00 Wk08 Wk16 Wk24;
run;
```

where `Wk00`, `Wk08`, `Wk16`, and `Wk24` are the values of a given efficacy endpoint at the Baseline, Week 8, Week 16, and Week 24 Visits, respectively, `trtrnd` has a value of zero (0) for participants randomized to placebo, and `x` and `y` take appropriate values to specify the range of a given outcome measure (i.e., 0 and 48 for ALSFRS-R total score; 0 and . for HHD upper and lower extremity percentages and SVC).

Inference from these analyses is supportive of inference from the Bayesian shared-parameter, repeated-measures model for the primary endpoint and assess sensitivity to the missing data assumption of the repeated-measures linear mixed model for secondary endpoints in the FAS analysis set. A separate analysis will include centered baseline serum NfL level as an additional covariate in both imputation stages.

6.5.9 Additional Sensitivity Analyses of Primary and Key Secondary Outcomes

Sensitivity analyses of primary and key secondary efficacy outcomes are the same as specified in the M-SAP.

6.5.10 Subgroup Analyses

In addition to the subgroups specified in the M-SAP, the following additional subgroups will be analyzed in the random-slope model (see Section 6.5.3) for primary and secondary efficacy endpoints in the FAS analysis set:

- Baseline use of riluzole and edaravone (neither, riluzole only, edaravone only, both),
- Age (less than 65 years vs. 65 years or older),
- Sex (female vs. male),
- Race (white vs. any minority race with greater than 5% prevalence in the sample),
- Ethnicity (Hispanic or Latino vs. non-Hispanic or Latino),
- Weight (less than 70 kg, 70 to less than 85 kg, 85 kg or more),
- BMI (less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 kg/m^2 or more),
- Chronic kidney disease (CKD) stage (stage 1 or better [eGFR 90 mL/min/1.73m^2 or more], stage 2 [eGFR 60 to 89 mL/min/1.73m^2], stage 3 or worse [eGFR less than 60 mL/min/1.73m^2]),
- Time since onset of weakness (less than 18 months vs. 18 months or longer),
- Baseline serum NfL concentration (by median split), and
- Site (individual sites with at least 5 participants per treatment group and all participants from sites with fewer than 5 participants per treatment group pooled).

For each classification, unknown, not reported, and missing will be considered one group. All individuals not included in a specified subgroup will be combined into a mixed, "other" group. The "other" group will be included in analyses if its prevalence is greater than 5%; otherwise, the "other" group will be excluded.

In cases where a model for a given subgroup and endpoint fails to converge, the covariance terms for the regimen-specific random effects will be simplified from unstructured covariance of intercepts and slopes to separate, uncorrelated variance components for intercepts and slopes. If convergence still fails, regimen-specific intercepts and slopes will be modeled as fixed effects. If convergence still fails, the participant-specific random effects will be simplified from unstructured covariance of intercepts and slopes to separate, uncorrelated variance components for intercepts and slopes.

6.5.11 Comparison of Controls across Regimens

Comparisons of placebo participants across regimens are the same as specified in the M-SAP with separate analyses that include baseline serum NfL level as an additional covariate in adjusted analyses plus applicable interaction terms as relevant to a given model.

6.5.12 Pharmacokinetic Analyses

Pre-dose concentrations of verdiperstat in plasma will be summarized by treatment group and visit in the ERO sample. Concentrations below the limit of quantitation (BLQ) will be replaced with one half of the lower limit of quantitation. Summaries will include number of observations, number and percentage with concentrations BLQ, arithmetic mean, median, standard deviation, minimum, maximum, geometric mean, geometric coefficient of variation (calculated as sqrt(exp(variance of log-transformed concentrations) – 1)), and 95% confidence bounds for the geometric mean assuming log-normally distributed data.

Plasma concentration data of verdiperstat may be subjected to population pharmacokinetic analysis to derive population estimates of pharmacokinetic parameters and test the effect of various covariates such as age, weight, and sex. Details of the analysis will be described in a separate data analysis plan (DAP). This analysis may be performed by combining data from the current study with data from other studies of verdiperstat, if deemed appropriate. The population pharmacokinetic analysis will be performed by Biohaven and reported in a separate modelling report.

6.5.13 Pharmacodynamic Biomarker Analyses

Change in myeloperoxidase protein and activity levels in plasma will be summarized by treatment group and visit in the ERO sample. Summary statistics will be provided for the values, change from baseline, and percent change from baseline at each scheduled assessment time point. Myeloperoxidase protein and activity levels in plasma will be analyzed in a repeated-measures linear mixed model that includes fixed terms for visit, time from last dose of verdiperstat, and time from last meal.

6.6 Safety Analyses

6.6.1 Treatment-emergent Adverse Events

Summaries and analyses of treatment-emergent adverse events (TEAE) are the same as specified in the M-SAP with the following revisions.

TEAEs are defined as those adverse events with onset dates in the interval from double-blind treatment initiation to the earliest of the Final Safety Visit, the date the participant dies, early terminates, or is lost to follow-up, 28 days after last dose of study drug, or the date of first dose of study drug during participation in the OLE, if so exposed. Adverse events with onset on the day of double-blind treatment initiation and adverse events with incompletely specified onset date where the ambiguous date spans the day of double-blind treatment initiation or the earliest of the events above that define the end of the treatment-emergence interval will be assumed to be treatment emergent except for those known to precede first exposure to study drug.

In addition to summaries specified in the M-SAP, the following categories of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term: (a) all adverse events, including those not classified as TEAEs, (b) fatal TEAEs, and (c) TEAEs that occurred during a participant's COVID-19 infection (defined as 5 days prior to symptom onset to end of COVID-19 symptoms or end of double-blind follow-up, if ongoing).

TEAEs indicating COVID-19 infection are the following: Asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, COVID-19 treatment, Post-acute COVID-19 syndrome, SARS-CoV-

2 antibody test positive, SARS-CoV-2 RNA increased, SARS-CoV-2 sepsis, SARS-CoV-2 test false negative, SARS-CoV-2 test positive, SARS-CoV-2 viraemia, Suspected COVID-19.

Treatment-dependent differences in the proportion of participants experiencing a given type of TEAE will not be tested. Treatment-dependent differences in TEAE incidence rates in units of number per 100 participant years will be estimated as differences rather than ratios, will include comparison-wise 95% confidence intervals with variance estimates obtained by the delta method, and will be provided for overall classes of TEAEs not further classified by MedDRA term (all TEAEs, serious TEAEs, severe TEAEs, TEAEs leading to discontinuation of study drug, TEAEs resulting in death, and TEAEs of special interest) and TEAEs with at least 5% prevalence in the active arm.

Listings will document all adverse events (including those not classified as treatment emergent), TEAEs, serious TEAEs, severe TEAEs, related TEAEs, TEAEs leading to discontinuation of study drug, TEAEs resulting in death, and TEAEs of special interest.

6.6.2 Safety Labs

Summaries and analyses of clinical safety labs are the same as specified in the M-SAP with the revision that lab results collected more than 28 days after last dose of study drug will not be tabulated, that abnormal levels will be classified to a toxicity grade based on quantitative grading using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and with the addition that maximum toxicity over all post-baseline visits that occur within 28 days or fewer after last dose of study drug will be included in shift tables along with visit-specific shifts.

The proportion of participants with TSH ≥10 mIU/L and the proportion with signs or symptoms of hypothyroidism will be presented as shift tables vs. the status of each participant at baseline for each visit and over all post-baseline visits that occur within 28 days or fewer after last dose of study drug by treatment group in all safety samples. The absolute level and the absolute change from baseline for free T3, free T4, and TSH will be summarized as means, standard deviations, medians, and ranges at each visit by treatment group in all safety samples.

6.6.3 ECG Results

Summaries of ECG parameters and findings are the same as specified in the M-SAP with the revision that ECG parameters and findings collected more than 28 days after last dose of study drug will not be tabulated.

6.6.4 Vital Signs and Weight

Summaries and analyses of vital signs and weight are the same as specified in the M-SAP with the revision that vital signs and weight collected more than 28 days after last dose of study drug will not be tabulated.

6.6.5 Suicidality

Summaries of suicidality are the same as specified in the M-SAP with the revision that suicidality noted more than 28 days after last dose of study drug will not be tabulated.

6.7 Other Analyses

6.7.1 Participant Disposition

All participants consented to the Master Protocol between the time of the first and last consent of a participant assigned to a regimen included in the FAS analysis set will be summarized as a single set for the following events: consented to the Master Protocol, failed screening for the Master Protocol, other reasons not assigned to a regimen (including timing out of the screening window, death, withdrawal of consent, early termination, and administrative termination), and assigned to a regimen. Reasons for Master Protocol screen failure will be summarized.

All participants in the above sample assigned to a regimen will be summarized as two sets (final screening for RGB vs. final screening for a non-RGB regimen) for the following events: consented to a regimen, failed screening for a regimen, other reasons not randomized within a regimen (including timing out of the screening window, death, withdrawal of consent, early termination, and administrative termination), and randomized within a regimen. If a given individual is screened multiple times prior to randomization within a regimen, then the final screening experience of that individual will be summarized. Reasons for RGB screen failure will be summarized separately for all participants screened for RGB whether that was their final screening experience or not.

All participants in the FAS analysis set will be summarized as two sets (randomization to active study drug vs. randomization to placebo) for the following events: initiated regimen-specific study drug, prematurely terminated study participation due to death, withdrawal of consent, early termination, loss to follow-up, or administrative termination, completed 24-week follow up, and completed a safety follow-up visit vs. continued into the OLE. Reasons for withdrawal of consent or early termination after randomization will be summarized.

Any randomized participants excluded from the FAS and EPP analysis sets or included in the FAS analysis set but not contributing to the primary analysis will be identified in a listing together with the reason for their exclusion.

6.7.2 Study Drug Compliance and Tolerance

Summaries of study drug compliance and tolerance are the same as specified in the M-SAP with the clarification that summaries will be reported for the ERO and SRO analysis sets and that date of permanent discontinuation of study drug is the date of last use of double-blind study drug among all participants in a given analysis set.

The number of days of exposure to study drug will be calculated in three ways:

- as the number of days from dose initiation to the final safety assessment during the placebo-controlled period, inclusive,
- as the number of days from dose initiation to drug withdrawal, inclusive, less any interval during which use of study drug was interrupted (individual missed doses will not be subtracted unless noted in the dosage management log), and
- as the number of days from dose initiation to the earlier of final contact during the placebo-controlled period or 28 days after last dose of study drug, inclusive.

The proportion of participants who interrupted study drug or reduced study drug dosage and the time to first study drug interruption or dosage reduction will be summarized. The number of days of exposure to a reduced dosage of study drug will be summarized.

6.7.3 Concomitant Medication Use

Summaries of concomitant medication use are the same as specified in the M-SAP with the clarification that medications taken at baseline and those initiated after first dose of study drug will be separately summarized and will be classified by ATC Therapeutic class and WHODrug Preferred base name.

6.7.4 Medical History

Medical histories will be summarized by MedDRA system organ class, high level term, and preferred term in the STF and SRO analysis sets.

6.7.5 Blindedness

The proportions of participants and site investigators who report on the Exit Questionnaire a guess of active vs. placebo treatment assignment, each level of surety of that guess, and each of five pre-specified reasons for making a treatment assignment will be summarized by treatment group in the FAS and ERO analysis sets. Treatment-dependent differences in the proportion guessing active treatment assignment will be tested among all respondents and among those stating they are at least somewhat sure of their guess by Fisher's exact test and the difference in proportion guessing active treatment assignment will be estimated with confidence bounds.

6.7.6 Protocol Deviations

The number of major and minor protocol deviations will be summarized by type of deviation and treatment group in all analysis sets. Listings of all protocol deviations will be produced.

6.7.7 Impact of COVID-19 Pandemic

The proportions of planned assessments missed due to COVID-19 restrictions or disruptions will be summarized by treatment group, visit, and type of assessment in the FAS and ERO analysis sets. Protocol deviations that resulted from COVID-19 restrictions or disruptions will be summarized by treatment group and type of deviation in the FAS and ERO analysis sets.

A listing will document participants with assessments missed due to COVID-19 restrictions or disruptions and those experiencing protocol deviations that resulted from COVID-19 restrictions or disruptions and will describe the manner affected by COVID-19.

7. Validation

7.1 Primary Efficacy Analysis

Validation of the primary efficacy analysis is the same as specified in the M-SAP.

7.2 Secondary, Exploratory, and Safety Analyses

Validation of secondary, exploratory, and safety analyses are the same as specified in the M-SAP.

8. References

The following references are cited in addition to those specified in the M-SAP:

Balendra R, Jones A, Jivraj N, Knights C, Ellis CM, Burman R, Turner MR, Leigh PN, Shaw CE, Al-Chalabi A. Estimating clinical stage of amyotrophic lateral sclerosis from the ALS Functional Rating Scale. Amyotroph Lateral Scler Frontotemporal Degener. 2014 Jun;15(3-4):279-84.

Roche JC, Rojas-Garcia R, Scott KM, Scotton W, Ellis CE, Burman R, Wijesekera L, Turner MR, Leigh PN, Shaw CE, Al-Chalabi A. A proposed staging system for amyotrophic lateral sclerosis. Brain. 2012 Mar;135(Pt 3):847-52.

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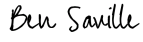
Ben Saville ben@berryconsultants.net Ben Saville Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 50221BD2-F3C9-432B-9863-2C6FEC7283AD Using IP Address: 72.182.14.11 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 7/22/2022 5:56:02 PM Viewed: 7/22/2022 6:27:23 PM Signed: 7/22/2022 6:28:00 PM
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