HEALEY ALS Platform Trial – Regimen F ABBV-CLS-7262

NCT05740813

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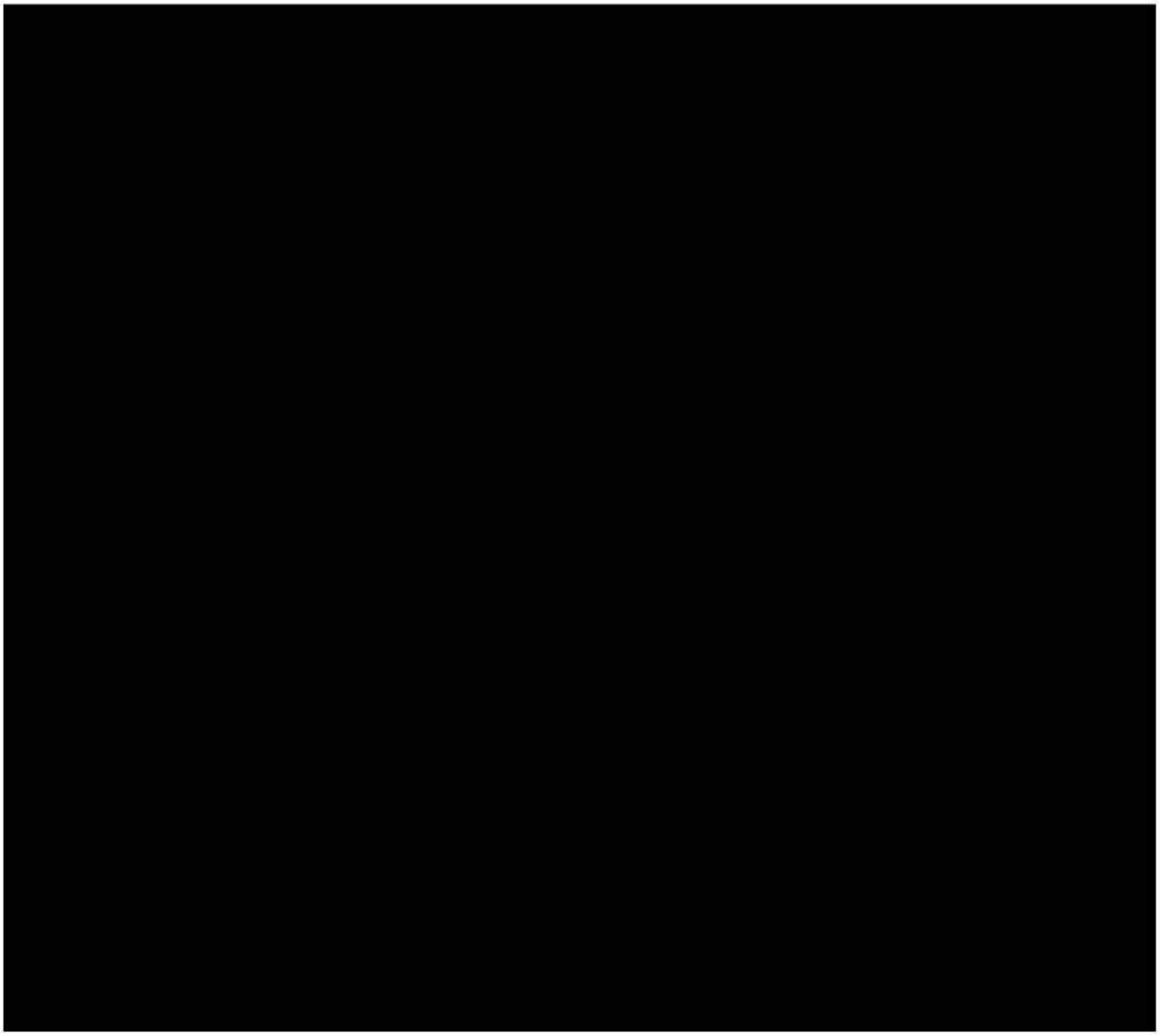
RGF REGIMEN-SPECIFIC STATISTICAL ANALYSIS PLAN (R-SAP)

Title	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	RGF: ABBV-CLS-7262
Regimen Partner	Calico Life Sciences, LLC
Regulatory Sponsor	Merit E. Cudkowicz, MD
Master Protocol Version	5.0, 15 Dec 2022
RSA Version	3.0, 23 Jul 2024
Master SAP Version	3.0, 06 Feb 2023
R-SAP Version	3.0, 13 Aug 2024

SAP APPROVAL SIGNATURES



SAP REVISION HISTORY

Version	Date	Description of Changes
1.0	17 Aug 2023	Initial version
2.0	15 Nov 2023	Revision of Section 5.4 Biofluid Biomarkers to describe two sets of analyses of baseline serum samples for quantitation of NfL concentrations (one set for use as a baseline covariate and one set run on a single plate and for use estimating longitudinal changes in NfL concentration) and to remove description of proteomic, metabolomic, and transcriptomic analyses. Revision of Appendix 2 to attach the Monitoring Abuse Potential of ABBV-CLS-7262 in Clinical Trials, Ad-Hoc Statistical Reporting Plan, Version 1.0 – June 28, 2023.
3.0	13 Aug 2024	Revision of Section 2.2 Study Objectives to add serum NfL concentration as a secondary efficacy objective. Revision of Section 3.2 Summary Statistics to add empirical cumulative distribution functions for continuous secondary endpoints. Revision of Section 3.3 Precision to modify the threshold p-value to report as <0.001. Revision of Section 4.1 Efficacy Endpoints to add ALSFRS-R total score and ALSAQ-40 ADL domain score as secondary efficacy endpoints and to re-order the list of secondary efficacy endpoints to match the order specified in Section 6.5.1 Hierarchical Testing. Revision of Section 4.3 Exploratory Endpoints to add urinary $p75^{ECD}$ and ALSAQ-40 total score and remove ALSAQ-40 ADL symptom index and domain score as exploratory endpoints. Revision of Section 4.4 Safety Endpoints to define 30 days after the last dose of study drug in the RCT as the cut-off for defining safety events as treatment emergent and to add changes in vital signs as safety endpoints. Revision of Section 5.4 Biofluid Biomarkers to specify methods of analysis of plasma NfL, CSF NfL, CSF GDF-15, CSF FGF21, and urinary $p75^{ECD}$. Revision of Section 5.10 TRICALS Risk Profile to correct the equation specifying the risk score. Revision of Section 6.1 Analysis Sets to specify that only participants randomized to placebo within RGG at or prior to the date when the last RGF participant was randomized are included in the ECC and SCC analysis sets.

Version	Date	Description of Changes
3.0 (continued)	13 Aug 2024	Revision of Section 6.3 Primary Efficacy Analysis and Supportive Analyses to specify that the population about which inference will be drawn is all patients with ALS and to specify that analyses described in Sections 6.5.2 through 6.5.5 are supportive of the primary analysis. Revision of Section 6.5.1 Hierarchical Testing to add ALSFRS-R total score and ALSAQ-40 ADL domain score as secondary efficacy endpoints and to re-order the list of secondary efficacy endpoints. Revision of Section 6.5.2 Repeated-measures Model to itemize the endpoints that will be analyzed by this model. Revision of Section 6.5.4 Time-to-event Endpoints to specify that time-to-event endpoints for clinical events will be analyzed in the FAS, ECC, and ERO analysis sets. Revision of Section 6.5.7 Subgroup Analyses to remove plasma NfL and add serum NfL by median split as subgroups. Revision of Section 8. References to add Shepheard et al. 2022. Revision of Appendix 1, Section 3.1 Simulation Scenarios to clarify assumptions related to the effects of standard of care medications.

ABBREVIATIONS

ACTH	Adrenocorticotrophic Hormone
ADL	Activities of Daily Living
ALD	After Last Dose
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 Aminotransferase
AST	Aspartate Aminotransferase
ATC	WHODrug Anatomical, Therapeutic, and Chemical Class
ATE	Active Treatment Extension
BCRP	Breast Cancer Resistance Protein
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
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
delta-FRS	Pre-baseline Slope in ALSFRS-R
DNA	Deoxyribonucleic Acid
DRR	Disease Rate Ratio
ECC	Efficacy Concurrent Control
ECM	Efficacy Common Mode of Administration
ECG	Electrocardiography or Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ENCALS	European Network for the Cure of ALS

ABBREVIATIONS (continued)

EPP	Efficacy Per-protocol
ERO	Efficacy Regimen-only
ET	Early Termination
FAS	Full Analysis Set
FGF21	Fibroblast Growth Factor 21
FVC	Forced Vital Capacity
GDF-15	Growth Differentiation Factor 15
GLI	Global Lung Initiative
hCG	Human Chorionic Gonadotropin
HHD	Hand-held Dynamometry
ICF	Informed Consent Form
INR	International Normalized Ratio
ITT	Intention-to-treat Principle
IV	Intravenous
LH	Luteinizing Hormone
LPLV	Last Participant Last Visit
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 Protein
P-gp	P-glycoprotein
PAV	Permanent Assisted Ventilation
PK	Pharmacokinetics
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials
PT	Prothrombin Time
PTT	Activated Partial Thromboplastin Time

ABBREVIATIONS (continued)

QD	Qua Dia (Once Daily)
QT	ECG Interval between the Q and T Peaks
RBC	Red Blood Cell
RDW	RBC Distribution Width
RGF	Regimen F (ABBV-CLS-7262)
RNA	Ribonucleic Acid
ROADS	Rasch-built Overall ALS Disability Scale
RSA	Regimen-specific Appendix
R-SAP	Regimen-specific Statistical Analysis Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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
T3	Triiodothyronine
T4	Thyroxine
TBL	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
TRICALS	Treatment Research Initiative to Cure ALS
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHODrug	World Health Organization Drug Dictionary Enhanced

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1. Governing Documents

This Regimen-specific Statistical Analysis Plan (R-SAP) for the Calico ABBV-CLS-7262 regimen (RGF), including the "ALS Master Protocol Regimen F (ABBV-CLS-7262) Primary Analysis, Design & Simulation Report" (RGF PADSR) as Appendix 1, 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" (MPRDR, Appendix 1 of the M-SAP), and the RGF Regimen-specific Appendix (RSA). Please refer to the Master Protocol and the RGF 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 MPRDR, any regimen-specific deviations described in the RGF RSA, and this R-SAP, including Appendix 1, are authoritative in defining the primary and interim analyses. In case of discrepancies between the RGF 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 RGF 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. In case of discrepancies between the MPRDR and RGF PADSR (Appendix 1 of this R-SAP) concerning the primary and interim analyses, the RGF PADSR is authoritative. On all matters not related to analysis, the Master Protocol and the RGF 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	RGF RSA	MPRDR	M-SAP	RGF R-SAP
Use of shared placebos	1	4	2	3	5
Primary and interim analysis specifications not related to use of shared placebo	1	4	3	2	5
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. RGF evaluates the safety and efficacy of ABBV-CLS-7262 administered orally, once daily (QD) at dosages of 120 mg and 240 mg vs. placebo. The RGF 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 ABBV-CLS-7262 on ALS disease progression.

Secondary Efficacy Objective:

- To evaluate the effects of ABBV-CLS-7262 on selected secondary measures of ALS disease progression, including survival.
- To evaluate the effects of ABBV-CLS-7262 on serum neurofilament light chain (NfL) as a biomarker of ALS disease progression.

Safety Objectives:

- To evaluate the safety of ABBV-CLS-7262 in patients with ALS.

Pharmacokinetics Objective:

- To quantify the steady state concentrations of A-1684909 and/or any active or inactive metabolites in plasma after long-term oral QD dosing of ABBV-CLS-7262.

Exploratory Objectives:

- To evaluate the effects of ABBV-CLS-7262 on selected biomarkers and exploratory endpoints.

2.3 Study Population

In addition to eligibility criteria specified in the Master Protocol, participants in RGF must not have used any moderate or strong CYP3A4 inhibitor or inducer or any P-gp or BCRP sensitive substrates with narrow therapeutic index within 10 days or 5 half-lives (whichever is longer) prior to the Baseline Visit, any clinically significant ECG abnormalities, including a prolonged QT interval corrected for heart rate, or abnormal adrenal function, defined as confirmed abnormal random cortisol or ACTH levels. Detailed eligibility criteria are specified in the Master Protocol and the RGF RSA.

Participants will be recruited from approximately 80 centers located throughout the US that are part of the Northeast ALS (NEALS) Consortium.

2.4 Participant Flow

Participants in RGF follow the consenting, Master screening, regimen assignment, regimen-specific screening, randomization to one of two active dosages or placebo treatment, and follow-up procedures and timing described in the M-SAP, including follow-up during both the placebo-controlled period (RCT) and the active treatment extension (ATE). Detailed descriptions of study procedures and timing are specified in the Master Protocol and the RGF RSA.

2.5 Regimen Allocation

Assignment of participants to RGF is the same as described in the M-SAP.

2.6 Treatment Allocation

Approximately 300 participants assigned to RGF who are determined eligible will be randomly allocated to one of two ABBV-CLS-7262 dosages or placebo. Approximately 165 will be randomized to ABBV-CLS-7262 administered QD at a dosage of 120 mg, approximately 60 participants will be randomized to ABBV-CLS-7262 administered QD at a dosage of 240 mg, and approximately 75 participants will be randomized to placebo. Treatment assignments are based on a pre-specified permuted-block randomization schedule stratified for all combinations of use vs. non-use of riluzole, edaravone, and sodium phenylbutyrate/taurursodiol (Relyvrio® or Albrioza®) at the time of screening for the Master Protocol. The first 240 participants will be assigned in a 2:1:1 allocation ratio to 120 mg ABBV-CLS-7262, 240 mg ABBV-CLS-7262, or placebo. The final approximately 60 participants will be assigned in a 3:1 allocation ratio to 120 mg ABBV-CLS-7262 or placebo by interpreting any assignments to 240 mg ABBV-CLS-7262 as an assignment to 120 mg ABBV-CLS-7262.

2.7 Treatment Administration

Details of treatment administration are described in the applicable RSA.

2.8 Allocation Concealment

Allocation concealment is the same as described in the M-SAP with the following modification for RGF. Study drug is dispensed in kits containing two types of packets of granules, type A and type B. Kits for participants randomized to the 240 mg dosage contain 120 mg of ABBV-CLS-7262 in both type A and type B packets. Kits for participants randomized to the 120 mg dosage contain 120 mg of ABBV-CLS-7262 in type A/B packets and placebo granules in type B/A packets (contents of type A vs. type B packets in the 120 mg kits is blinded here to maintain full concealment). Kits for participants randomized to placebo contain placebo granules in both type A and type B packets. Except for the designation of packets as type A vs. type B, both active and placebo packets and granules are identical in appearance.

2.9 RGF Schedule of Activities (SoA) – Placebo Controlled Period

Activity	Master Protocol Screening[1]	Regimen Specific Screening[1]	Baseline	Week 2	Week 4[13]	Week 8[13]	Week 12	Week 16[13]	Week 20	Week 24/ET	Follow-Up Safety Call[11]
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
	-42 to -1 Days[15]	-41 to 0 Days[15]	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 ALD +3
Written Informed Consent[2]	X	X									
Inclusion/Exclusion Review	X	X[3]									
ALS & Medical History	X										
Demographics	X										
Physical Examination	X										
Neurological Exam	X										
Vital Signs[4]	X		X		X	X		X		X	
Slow Vital Capacity	X		X			X		X		X	
Muscle Strength Assessment			X			X		X		X	
ALSFRS-R	X		X		X	X	X	X	X	X	
ALSAQ-40			X							X	
ROADS			X			X		X		X	

Activity	Master Protocol Screening[1]	Regimen Specific Screening[1]	Baseline	Week 2	Week 4[13]	Week 8[13]	Week 12	Week 16[13]	Week 20	Week 24/ET	Follow-Up Safety Call[11]
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
	-42 to -1 Days[15]	-41 to 0 Days[15]	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 ALD +3
CNS Bulbar Function Scale			X			X		X		X	
12-Lead ECG	X		X			X		X		X	
Clinical Safety Labs[5,10]	X		X		X	X		X		X	
Hormone Assessments[16,19]		X			X			X		X	
Menstrual Cycle Questionnaire[18]			X		X	X		X		X	
Coagulation Labs (PT, PTT, INR)	X[21]							X			
Biomarker Blood Collection[16]			X			X		X		X	
Plasma/Serum for Biomarkers[16]			X			X		X		X	
Biomarker Urine Collection (Master)[17]			X			X		X		X	
Biomarker Urine Collection (RGF)[17]			X			X		X		X	
Blood Sample for PK Analysis[16]					X	X		X		X	
DNA Collection[7] (optional)			X								
Blood RNA Collection[16]			X			X				X	
CSF Collection[20]			X							X	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review[6]	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale			X		X	X		X		X	
Install Smartphone App[14]			X								
Voice Recording[9]			X		X	X		X		X	
Uninstall Smartphone App										X	
Assignment to the Regimen	X										
Randomization within the Regimen			X								
Administer/Dispense Study Drug			X[8]		X	X		X		X[10]	
Drug Accountability/Compliance				X	X	X	X	X	X	X	
Exit Questionnaire										X	
Vital Status Determination[12]										X	

1 Master Protocol Screening procedures must be completed within 42 days to 1 day prior to the Baseline Visit. Baseline Visit cannot occur until after all Regimen-Specific eligibility criteria have been assessed and confirmed, including return of hormone assessment lab results.

2 During the Master Protocol Screening Visit, participants will be consented via the Platform Trial informed consent form (ICF). After a participant is assigned 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, pulse oximetry, 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. Two additional regimen-specific safety labs will be collected, amylase and lipase.

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 once weekly voice recordings at home.

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

11 Participants will only have a Follow-Up Safety Call at this time if they *do not* continue on in the ATE. Participants who continue into ATE will have a Follow-Up Safety Call 28 + 3 days after their last dose of investigational product during the ATE period.

12 Vital status, defined as a determination of date of death or PAV status 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 Regimen. We may also ascertain vital status (death or date last known alive only) at later time points by using publicly available data sources as described in section 8.15 of the Master Protocol.

13 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, disability, or a medically necessary reason. If an in-clinic visit is conducted remotely for disability or medically necessary reason, the next scheduled in-clinic visit must occur in-person unless otherwise approved by the Medical Monitor.
14 One smartphone app should be installed on the participant's phone to collect the voice recordings.
15 Master Protocol Screening and Regimen-Specific Screening visit windows are relative to Baseline (Day 0).
16 Blood sample is drawn at pre-dose (within 2 hours prior to dosing in the clinic and preferably within 15 minutes prior to dosing in the clinic).
17 Urine biomarker sample is collected pre-dose (within 2 hours prior to dosing in the clinic and preferably within 15 minutes prior to dosing in the clinic). Collection should preferably be of the second morning urine, as a mid-stream collection if possible.
18 Menstrual Cycle Questionnaire to be collected only in women of childbearing potential.
19 Hormone Assessments include ACTH, Cortisol, Testosterone (males only), LH (males only), and Thyroid panel (TSH, free T4, T3).
20 CSF collection is scheduled for this Regimen during the placebo-controlled period. CSF may be collected up to one week prior to Baseline and Week 24 Visits and must be collected prior to receiving RCT or ATE study drug, respectively.
21 If coagulation labs are not collected during the Master Protocol Screening Visit, they can be collected during the Regimen-Specific Screening Visit.

3. General Considerations for Data Analysis

3.1 Statistical Software

Statistical analyses will be performed using SAS (SAS Institute, NC, USA), R (R Foundation for Statistical Computing, Vienna, Austria), or JAGS (Plummer, SourceForge).

3.2 Summary Statistics

Data will be summarized with respect to disposition, demographics, pre-treatment characteristics, efficacy endpoints, safety endpoints, and tolerability. Summary statistics for continuous variables will include the number of observations, the mean, median, standard deviation, inter-quartile range, and range. Summaries of continuous secondary endpoints will include empirical cumulative distribution functions (eCDF). Summaries of categorical data will include counts, denominators, and percentages.

3.3 Precision

Results will generally be reported to 3 significant figures. Percentages will generally be reported to 0.1 percentage points. P-values will generally be reported to two digits when greater than or equal to 0.095, to three digits when greater than or equal to 0.001 and less than 0.095, and as <0.001 for all smaller values.

3.4 Transformations

Data that are strictly positive, continuous, and strongly right skewed will typically be log-transformed prior to any inferential testing. Skewness greater than 3 will be used as a guide in determining which variables to transform. This R-SAP will be updated as needed prior to regimen data lock to indicate which variables warrant transformation and how they will be transformed. Original, untransformed values will be used for all summaries. Any data transformations used in the primary and interim analyses are described in the MPRDR (Appendix 1 of the M-SAP).

3.5 Multiplicity Adjustments

A single primary analysis is planned. The default criterion for significance at the final analysis is adjusted to ensure an overall one-sided type 1 error rate less than 0.025 in the absence of early stopping for futility. If the primary efficacy endpoint meets the success criteria, secondary efficacy endpoints will be tested comparing the ABBV-CLS-7262 120 mg dose versus placebo in a pre-specified order using a fixed sequence procedure with a two-sided alpha level of 0.05 for each endpoint. After the first failure to declare significance, no endpoints lower in the sequence can be significant. Nominal comparison-wise p-values will also be reported for all analyses unless otherwise specified.

3.6 Missing Data

If baseline values of a given measure are missing, the last observed pre-treatment value will be used. Missing baseline covariates will be imputed using the mean of the respective covariate. For any baseline covariate that is transformed for analysis, means will be imputed after transformation. Instances of missing baseline covariates are assumed to be rare. This R-SAP will be updated as needed prior to regimen data lock if the prevalence of missing baseline covariates warrants more careful handling.

For analyses that depend on visit-specific data, off-schedule post-baseline observations, e.g., those collected as part of an Early Termination Visit or an unscheduled visit, will be used in place of the closest missing scheduled visit that preserves the true visit sequence if the observation time is as close or closer to the missing scheduled visit than to any other post-baseline scheduled visit. Other observations will not be carried forward. For analyses that do not depend on visit-specific data, observations will be analyzed according to the actual time observed.

The planned mixed model analyses, where applied, yield estimates that are unbiased conditional on the observed values under a missing at random assumption. Secondary analyses of efficacy endpoints that accommodate missing values are described below (see Sections 6.5.5 and 6.5.6).

4. Study Endpoints and Comparisons

4.1 Efficacy Endpoints

The primary efficacy endpoint is change from baseline through Week 24 in disease severity as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) total score and survival.

Secondary efficacy endpoints include change from baseline to Week 24 in ALSFRS-R total score, change from baseline to Week 24 in respiratory function as assessed by slow vital capacity (SVC), change from baseline to Week 24 in muscle strength of upper extremities as measured isometrically using hand-held dynamometry (HHD) and grip strength, , change from baseline to Week 24 in serum neurofilament light chain protein (NfL) concentration, and change from baseline to Week 24 in activities of daily living (ADL) as assessed by the ALS Assessment Questionnaire, 40-item version (ALSAQ-40) independence in activities of daily living (ADL) domain score.

4.2 Pharmacokinetic Endpoint

The following pharmacokinetic (PK) endpoints will be evaluated:

- Steady state concentrations of A-1684909 and any active or inactive metabolites of interest in plasma.

4.3 Exploratory Endpoints

Change from baseline to Week 24 of following exploratory endpoints will be evaluated:

- Muscle strength: HHD lower extremity percentage, HHD global percentage,
- Biofluid biomarkers of neurodegeneration, ALS disease, and the ISR pathway, including: plasma and cerebrospinal fluid (CSF) NfL, serum creatinine, urinary $p75^{ECD}$ (normalized to urinary creatinine), CSF GDF-15, CSF FGF21
- Patient-reported outcomes: ALSAQ-40 physical mobility, eating and drinking, communications, and emotional reactions domain scores and total score, CNS-BFS total score, ROADS total score,
- ALSFRS-R: bulbar, fine motor, gross motor, fine and gross motor combined, and respiratory domain scores,
- King's ALS Clinical Staging System stage and,
- Quantitative voice characteristics: maximum phonation time, pause rate, breathy vocal quality, pitch instability, regulation of voicing, articulatory precision, speaking rate, articulation rate, and monotonicity.

Change of secondary and exploratory endpoints from baseline to other time points and average rates of change from baseline to Week 24 will also be estimated in the ECC and ERO analysis sets (see Section 6.1 Analysis sets below for definitions).

The following exploratory time-to-event endpoints will be evaluated:

- 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, death or death equivalent, death alone.

4.4 Safety Endpoints

The safety endpoints collected up to 30 days after the last dose of study drug in the RCT will be included in the safety analysis. For participants who enroll in the ATE, only safety endpoints before ATE baseline will be included. The following safety endpoints will be evaluated:

- 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 , and

- Changes in vital signs and treatment-emergent and clinically significant vital sign abnormalities, and
- Treatment-emergent suicidal ideation and suicidal behavior .

Reported proportions will use as their denominator all participants in the applicable Safety sample (see Section 6.1 below). Clinically significant laboratory, ECG, and vital sign abnormalities will be reported as adverse events.

4.5 Study Comparisons

The primary comparison of interest is between the ABBV-CLS-7262 120 mg dosage group and the shared concurrent placebo group when evaluating primary, secondary, and exploratory endpoints. Comparisons involving the ABBV-CLS-7262 240 mg dosage group and comparisons other than the primary comparison of interest are exploratory. Dose-dependent contrasts are of primary interest for pharmacokinetic endpoints.

5. Measurement Definitions

5.1 ALSFRS-R

The definition and scoring of the ALSFRS-R are the same as described in the M-SAP.

5.2 SVC

The definition and quantitation of SVC are the same as described in the M-SAP.

5.3 HHD and Grip Strength

The definition and quantitation of HHD and grip strength are the same as described in the M-SAP.

5.4 Biofluid Biomarkers

The definition and quantitation of serum NfL and serum creatinine are the same as described in the M-SAP with the following modifications. Serum NfL concentrations will be estimated from baseline serum samples twice. The first analysis of baseline serum samples for quantitation of serum NfL will be completed late enough to include baseline serum samples from all participants who will be included in the primary efficacy analysis for RGF and early enough that results from that analysis will be available at the time of database lock for clinical data from the 24-week placebo-controlled period. Serum NfL concentrations estimated from this first analysis will only be used as a covariate in analyses that include baseline serum NfL as a covariate. The second analysis of baseline serum samples for quantitation of serum NfL will be completed in combination with all other available serum samples collected during the 24-week placebo-controlled follow-up of participants who will be included in the primary efficacy analysis for RGF. All samples from a given participant in this second analysis will be analyzed on a single plate to minimize potential batch effect and serum NfL concentrations estimated from this second analysis will be used to estimate longitudinal changes in serum NfL as an efficacy endpoint. If baseline serum NfL concentrations for a given sample are not the same between the two analyses, they will be handled separately based on the above descriptions.

The following regimen-specific biomarkers will be assayed: plasma NfL, CSF NfL, CSF GDF-15, CSF FGF21, and urinary $p75^{ECD}$. Plasma NfL, CSF NfL, CSF GDF-15, and CSF FGF21 will be quantified by automated chemiluminescent enzyme immunoassay (LUMIPULSE G System, Fujirebio, Malvern, PA). Urinary $p75^{ECD}$ will be assayed following Shepheard et al. (2022). Concentrations will be normalized to urinary creatinine concentration measured in the same sample and expressed as ng $p75^{ECD}$ per mg creatinine. Following Shepheard et al. (2022), urinary $p75^{ECD}$ from samples with urinary creatinine less than 0.3 ng/mL or greater than 3.0 ng/mL will be excluded from analysis.

5.5 Patient-reported Outcomes

5.5.1 ALSAQ-40

The Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40, Jenkinson et al. 1999; Jenkinson et al. 2003) is a 40-item ALS-specific health-related quality-of-life instrument completed by participants for assessing quality of life in five domains: physical mobility (10 items), independence in activities of daily living (10 items), eating and drinking (3 items), communication (7 items), and emotional reactions (10 items). For each item, participants are asked to rate the degree to which a specific statement describing difficulties of living with ALS applies to the participant's personal experience over the past two weeks on a 5-point scale from 0 ("Never") to 4 ("Always").

The total score will be calculated as the mean of all 40 items multiplied by 25 (range 0 to 100). Each of the five domains will be scored as the mean of all domain-specific items multiplied by 25 (range 0 to 100). The total score and each domain score will be missing if more than 20% of the applicable items are missing; otherwise, item non-response will be mean-imputed from other completed items from the same assessment. Higher scores indicate worse quality of life.

5.5.2 CNS-BFS

The Center for Neurologic Study Bulbar Function Scale (CNS-BFS, Smith et al. 2018) is a 21-item instrument completed by participants for assessing bulbar function in three domains: speech, swallowing, and sialorrhea. For each domain, participants are asked to rate the degree to which each of seven statements describing an aspect of bulbar dysfunction apply to the participant's personal experience over the past week on a scale from 1 ("Does not apply") to 5 ("Applies most of the time"). Subjects unable to speak are assigned a value of 6 for each item comprising the speech domain. The total score is the sum of all items (range 21 to 112). Higher scores indicate worse bulbar dysfunction.

5.5.3 ROADS

The Rasch-built Overall ALS Disability Scale (ROADS, Fournier et al. 2020) is a 28-item instrument completed by participants for assessing overall functional disability associated with ALS. Each item assesses the participant’s ability to perform a stated task on a scale from 0 ("unable to perform") to 2 ("normal"). Participants are instructed to rate their ability based on how a given task is usually performed; items should be scored as 2 (normal) if the task is performed as quickly and easily as it was before experiencing symptoms of ALS; items should be scored as 1 (abnormal) if it is harder to perform the task, the task takes more time or effort, or the task is performed with the assistance of a device or another person. The sum of the item scores is normed to a linearly-weighted total score (range 0 to 146). Higher scores indicate better function.

5.6 Survival

The definition of the survival endpoints of death or death-equivalent and death-only for the placebo-controlled period are the same as described in the M-SAP.

5.7 King's ALS Clinical Staging System

The definition and scoring of the King's ALS Clinical Staging System are the same as described in the M-SAP with the addition of a fifth stage indicating death. Participants who die or reach a death equivalent will be assigned to stage 5.

5.8 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.

5.9 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, and
- Time to King's stage 4a or 4b.

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.

5.10 TRICALS Risk Profile

The Treatment Research Initiative to Cure ALS (TRICALS) Risk Profile is based on the the European Network for the Cure of ALS (ENCALS) survival prediction model (Westeneng et al. 2018). The TRICALS score will be calculated at baseline as follows:

$$\begin{aligned}\text{Profile} = {} & 0.474\left[(VC/100)^{-1} + (VC/100)^{-1/2}\right] - 2.376\left[(DD/10)^{-1/2} + ln(DD/10)\right] \\ & - 1.839(dFRS + 0.1)^{-1/2} - 0.264(AAO/100)^{-2} + 0.271\ \text{Bulbar} \\ & + 0.238\ \text{Definite} + 0.415\ \text{FTD}\end{aligned}$$

where *VC* is vital capacity in units of percent-predicted using GLI norms as defined in Section 5.2, *DD* is diagnostic delay calculated as (date of diagnosis – date of symptom onset) / 365.25 x 12, *dFRS* is pre-baseline slope of ALSFRS-R total score as defined in Section 5.1, *AAO* is age at symptom onset calculated as (date of symptom onset – date of birth) / 365.25, Bulbar is an indicator of initial site of onset in the bulbar region, Definite is an indicator for classification as definite ALS by revised El Escorial criteria, and FTD is an indicator for frontotemporal dementia. While participants are not evaluated for frontotemporal dementia at baseline, given that presence of dementia defined broadly is an exclusion criterion at screening, TRICALS scores will be calculated assuming that participants do not have frontotemporal dementia.

5.11 Pharmacokinetic Concentrations

Steady state concentrations of A-1684909 in plasma will be assayed using validated liquid chromatography-tandem mass spectrometry methods by AbbVie. Additional active or inactive metabolites of interest in plasma may also be assayed using validated or non-validated methods. For summaries, A-1684909 and metabolite levels that are below the limit of quantitation will be reported as zero. For analyses, A-1684909 and metabolite levels will be log-transformed and levels that are below the limit of quantitation will be imputed at the limit of quantitation divided by two.

Repeated measures analysis (linear mixed effects) of the log-transformed dose-normalized A-1684909 plasma trough concentrations will be performed to evaluate dose proportionality. Dose, visit (Week 4, Week 8, Week 16, and Week 24), and their interaction will be fixed effects. The effect of dose will be estimated from a one degree of freedom contrast between the ABBV-CLS-7262 120 mg and 240 mg dose groups averaged over the four visits. The hypothesis will be that there is no significant effect of dose on the dose-normalized concentrations across all visits.

5.12 Participant Compliance

For objective analysis, participants who are non-compliant with study drug administration will be identified by plasma concentrations of A-1684909 that are less than 10 ng/mL at any visit during the placebo-controlled period of the study.

5.13 Clinical Safety Laboratory Tests

The list of clinical safety labs and the definitions of measures of potential drug-induced liver injury (DILI) are the same as described in the M-SAP with the following additional analyses:

- Digestive enzymes: amylase, lipase
- Hormones: ACTH, cortisol, total testosterone (males only), luteinizing hormone (males only)
- Thyroid function: free T4, T3
- Cosyntropin stimulation testing: abnormal response is defined as a maximum cortisol concentration less than 18 µg/dL after intravenous (IV) cosyntropin injection.

5.14 Menstrual Cycle Questionnaire

A menstrual cycle questionnaire will be completed by women of childbearing potential during each clinic visit. The menstrual cycle questionnaire will capture the days of menstruation and information about the quality of menstrual flow and will be assessed by a qualified healthcare provider. Additional information about assessment of the menstrual cycle questionnaire is detailed in the RGF Manual of Procedures.

6. Statistical Methodology

6.1 Analysis Sets

The following analysis sets will be used for testing efficacy, pharmacokinetics, and safety endpoints:

- Efficacy Full Analysis Set (FAS): Participants who were randomized within RGF plus placebo participants from Regimens A, B, C, D, E, G, 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 will be excluded. Participants determined to not meet ALS diagnostic criteria are excluded.
- Efficacy Concurrent-controls (ECC) Set: The subset of participants in the FAS analysis set who were randomized within RGF or randomized to placebo within RGG at or prior to the date when the last RGF participant was randomized, exclusive of RGG participants who were also randomized within RGF. This is the primary analysis set for primary and secondary analyses.
- Efficacy Regimen-only (ERO) Set: The subset of participants in the FAS analysis set who were randomized within RGF.
- Efficacy Common Mode of Administration (ECM) Set: The subset of participants in the FAS analysis set from Regimens B, C, D, F, G, and any other regimens in which study drug is administered orally.
- Efficacy Per-protocol (EPP) Set: The subset of participants in the ECC analysis set who initiated study treatment and who meet other requirements for protocol compliance as specified in the R-SAP, including compliance taking study drug (defined in Section 5.12), classified according to the treatment they actually received. If a participant's data are truncated for inclusion in the EPP analysis set due to a time-dependent event (e.g., non-adherence to protocol-specified dosing, initiation of a prohibited medication, initiation of a medication approved for treatment of ALS), clinical events observed after the censoring event will be excluded from the EPP analysis set. Data from placebo participants shared from other regimens will not be truncated due to non-adherence to protocol-specified dosing. Final specification of participants included vs. excluded from the EPP analysis set will be defined prior to data lock.
- Pharmacokinetic Analysis (PKA) Set: Participants who received at least one dose of active ABBV-CLS-7262 within RGF and from whom at least one PK sample was collected.

- Safety Full (STF) Set: Participants who received at least one dose of study drug within RGF plus placebo participants from Regimens A, B, C, D, E, G who had an opportunity to complete placebo-controlled follow-up, who are not known to be ineligible for RGF, and who received at least one dose of study drug 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.
- Safety Concurrent Control set (SCC): The subset of participants in the STF analysis set who were randomized within RGF or randomized to placebo within RGG at or prior to the date when the last RGF participant was randomized, exclusive of RGG participants who were also randomized within RGF.
- Safety Narrow (STN) Set: The subset of participants in the STF analysis set who were exposed to interventions administered orally.
- Safety Regimen-only (SRO) Set: The subset of participants in the STF analysis set who were randomized within RGF.

The meaning of regimen data lock and the criteria for inclusion of data for placebo participants assigned to other regimens at the time of regimen data lock will be defined in the HEALEY ALS Platform Trial Data Management Plan and the HEALEY ALS Platform Trial Data Sharing Plan. Specifically, concurrent placebo participants from RGG randomized at or prior to the date when the last RGF participant was randomized will be included for RGF analysis.

6.2 Baseline Characterization

The specification of baseline characteristics is the same as described in the M-SAP with the addition of ALSFRS-R domain scores, ALSAQ-40 domain scores and symptom index, CNS-BFS total score, ROADS total score, quantitative voice characteristics, TRICALS score, and CSF NfL concentration.

6.3 Primary Efficacy Analysis and Supportive Analyses

The primary analysis for RGF is a Bayesian shared-parameter model of function and survival. The model will include both ABBV-CLS-7262 treatment groups and the placebo group with primary inference based on comparison of the 120 mg dosage vs. placebo in the ECC analysis set. Details of the model, including documentation of operating characteristics under a range of scenarios, are provided in the MPRDR (Appendix 1 of the M-SAP). Additional details of operating characteristics specific to RGF are provided in Appendix 1 of this R-SAP.

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 ECC 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: ABBV-CLS-7262 120 mg treatment vs. placebo.
- Population: patients diagnosed with ALS.

- 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 or death equivalent: 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 or death equivalent: 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 and will be handled via missing at random assumption.
- Population-level summary: mean ratio of hazard or progression rate of active treatment relative to placebo estimated by DRR.

Supportive analyses are described in Sections 6.5.2 through 6.5.5.

6.4 Interim Analysis

RGF will be considered for early stopping for futility at 12-week intervals. RGF will not be considered for early stopping for success. Details of the interim analysis schedule, the futility stopping rule, and documentation of operating characteristics under a range of scenarios, are provided in the MPRDR (Appendix 1 of the M-SAP).

6.5 Secondary Efficacy Analyses

6.5.1 Hierarchical Testing

Principal inference for secondary efficacy endpoints will be based on comparison of the ABBV-CLS-7262 120 mg dosage vs. placebo in the ECC analysis set using a repeated-measures linear mixed model for the following endpoints (see Section 6.5.2 below). The default sequence for testing is the following:

1. Change from baseline to Week 24 in ALSFRS-R total score in the ECC analysis set,
2. Change from baseline to Week 24 in respiratory function as assessed by slow vital capacity (SVC) and measured as percent predicted using GLI normal values in the ECC analysis set.
3. Change from baseline to Week 24 in upper limb muscle strength as assessed isometrically using HHD and grip strength and measured as average percent change from baseline among maneuvers with non-zero strength at baseline in the ECC analysis set,
4. Change from baseline to Week 24 in log-transformed serum NfL in the ECC analysis set, and
5. Change from baseline to Week 24 in ALSAQ-40 ADL domain score in the ECC analysis set.

If the primary analysis indicates a significant slowing in disease progression from the Bayesian shared-parameter model of function and survival, then each secondary efficacy endpoint would be declared significant in the specified sequence using a criterion of two-sided alpha of 0.05. After the first failure to declare significance, no endpoints lower in the hierarchy can be

significant. 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 model is modified from that described in the M-SAP by changing the response measure to be a calculated change from baseline, removing baseline observations from the response, and adding the baseline observation and its interaction with visit as additional covariates. The following endpoints will be analyzed: ALSFRS-R total and domain scores, SVC, HHD upper, lower, and global percentages, log-transformed serum, plasma, and CSF NfL, CSF GDF-15, CSF FGF21, urinary $p75^{ECD}$, ALSAQ-40 total and domain scores, CNS-BFS total score, and ROADS total score.

The following equations describe the model with regimen random effects:

$$\begin{gathered}\left(Y_{ij} - Y_{i0}\right) = a_{k(i)} + \gamma_1 t_i + \gamma_{2,j} v_j + \boldsymbol{\gamma_3' z_i} + \gamma_{4,j}\, t_i v_j + \boldsymbol{\gamma_{5,j}' z_i}\, v_j + \epsilon_{ij} \\ a_k \sim N(0, \sigma_r^2),\ \boldsymbol{\epsilon_{i\cdot}} \sim N(\mathbf{0}, \boldsymbol{R}),\ \mathrm{Cov}\left(b_{k(i)}, \epsilon_{ij}\right) = 0\end{gathered} \qquad \text{(eqn. 1)}$$

where Y_{ij} is a given efficacy endpoint measured for participant i at visit j, Y_{i0} is a given efficacy endpoint measured for participant i at baseline, $a_{k(i)}$ 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 baseline value of the given efficacy endpoint, centered time since onset, centered delta-FRS, centered baseline log-transformed serum NfL level, centered baseline riluzole use, centered baseline edaravone use, and centered baseline sodium phenylbutyrate/taurursodiol 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 σ^2_r. The vector of residuals for a given participant are normally distributed with mean $\mathbf{0}$ and an unstructured covariance matrix $\mathbf{R}$. The regimen-specific random effect for a given participant and residuals for that participant are uncorrelated. Satterthwaite's approximation will be used to estimate denominator degrees of freedom.

The following SAS code specifies the model:

```
proc mixed data=xxx method=reml;
  class regimen id trtrnd visit;
  model Delta = trtrnd|visit
                baseval|visit sx2bl|visit dFRS|visit nfl|visit
                rlz|visit edv|visit amx|visit / solution cl ddfm=sat;
  random intercept / subject=regimen type=vc;
  repeated visit / subject=id(regimen) type=un;
```

where `id` is a participant study identifier, `trtrnd` is the randomly assigned treatment group, `visit` is the visit identifier, `Delta` is change from baseline of the efficacy endpoint being tested for a given participant at a given visit, `baseval` is the baseline value of the efficacy endpoint, `sx2bl` is months since ALS symptom onset, `dFRS` is pre-baseline slope, `nfl` is baseline log-transformed serum NfL level, `rlz` is an indicator of riluzole use at baseline, `edv` is an indicator of edaravone use at baseline, and `amx` is an indicator of sodium phenylbutyrate/taurursodiol use at baseline.

Primary inference will be based on analysis of the ECC analysis set. Results from the FAS, ERO, ECM, and EPP analysis sets will be interpreted as sensitivity analyses. The following endpoints are added for analysis by this model in the ECC, FAS, and ERO analysis sets: ALSAQ-40 domain scores and overall symptom index, CNS-BFS total score, ROADS total score, and CSF NfL concentration. Only ALSFRS-R total score, HHD upper extremity percentage, and SVC will be analyzed in the ECM and EPP analysis sets. The model terms are expanded to include two active treatment groups, ABBV-CLS-7262 120 mg and 240 mg, and their interactions with visit. Primary inference will be based on comparison of the ABBV-CLS-7262 120 mg dosage vs. placebo.

The following SAS code specifies the primary linear contrast for an endpoint measured every 8 weeks assuming that the sort order for treatment group is placebo, ABBV-CLS-7262 120 mg, and ABBV-CLS-7262 240 mg and that visits are sorted chronologically:

```
estimate "3|120 vs PBO|dWk 24" trtrnd*visit 0 0 -1  0 0 1  0 0 0 / cl;
```

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 ABBV-CLS-7262 120 mg treatment group relative to the placebo group in the ECC population. The estimand is defined by the following attributes:

- Treatment: ABBV-CLS-7262 120 mg treatment vs. placebo.
- Population: ECC set 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 and will be handled via missing at random assumption implemented through MMRM framework.
- Population-level summary: difference in conditional means of active treatment relative to placebo.

A nominally significant difference in 24-week change from baseline in the direction of greater improvement or less worsening among participants randomized to ABBV-CLS-7262 120 mg treatment would support inference of benefit from ABBV-CLS-7262 for the efficacy endpoint being tested. Inference from this analysis is supportive of inference from the Bayesian shared-parameter, repeated-measures model for the primary endpoint.

6.5.3 Random-slopes Model

The specification of the random-slopes model is the same as described in the M-SAP with the following modifications. The following endpoints are added for analysis by this model in the ECC, FAS, and ERO analysis sets: ALSAQ-40 domain scores and overall symptom index, CNS-BFS total score, ROADS total score, quantitative voice characteristics, and log-transformed CSF NfL concentration. Only ALSFRS-R total score, HHD upper extremity percentage, and SVC will be analyzed in the ECM and EPP analysis sets. The model terms are expanded to include the baseline value of a given efficacy endpoint and its interaction with month since baseline is added as an additional covariate and to include two active treatment groups, ABBV-CLS-7262 120 mg

and 240 mg, and their interactions with month. Principal inference will be based on comparison of the ABBV-CLS-7262 120 mg dosage vs. placebo. Satterthwaite's approximation will be used to estimate denominator degrees of freedom.

The following SAS code specifies the model:

```
proc mixed data=xxx method=reml;
  class regimen id trtrnd;
  model Value = trtrnd|month
                baseval|month dFRS|month nfl|month
                rlz|month edv|month amx|month / solution cl ddfm=sat;
  random intercept month / subject=regimen type=un;
  random intercept month / subject=id(regimen) 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 following SAS code specifies the primary linear contrast assuming that the sort order for treatment group is placebo, ABBV-CLS-7262 120 mg, and ABBV-CLS-7262 240 mg:

```
  estimate "3|120 vs PBO|Slope (/mn)" month 0 trtrnd*month -1 1 0 / cl;
```

The estimand estimated by the primary linear contrast of the random-slopes model is the difference in mean rate of change from baseline to the Week 24 visit of a given continuous efficacy endpoint in the ABBV-CLS-7262 120 mg treatment group relative to the placebo group in the ECC population. The estimand is defined by the following attributes:

- Treatment: ABBV-CLS-7262 120 mg treatment vs. placebo.
- Population: ECC population as defined in Section 6.1.
- Variables: 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, including data missing due to death, will not be imputed and will be handled via missing at random assumption implemented through the random-slopes model.
- Population-level summary: difference in rate of change of active treatment relative to placebo.

A nominally significant difference in slopes in the direction of greater improvement or less worsening among participants randomized to ABBV-CLS-7262 120 mg treatment would support inference of benefit from ABBV-CLS-7262 for the efficacy endpoint being tested. Inference from this analysis is supportive of inference from the Bayesian shared-parameter, repeated-measures model for the primary endpoint.

6.5.4 Time-to-event Endpoints

The specification of survival analyses is the same as described in the M-SAP with the following modifications. Principal inference will be based on analysis of the ECC analysis set. Inference from analysis of time to the composite survival endpoint of death or death equivalent to the Week 24 time point is supportive of inference from the Bayesian shared-parameter, repeated-

measures model for the primary endpoint. Results from analysis of time to death or death equivalent in the FAS, ERO, ECM, and EPP analysis sets will be interpreted as sensitivity analyses. Only death/death-equivalent and death-alone will be analyzed in the ECM and EPP analysis sets. The time-to-event endpoints for clinical events will be analyzed in the FAS, ECC, and ERO analysis sets. Right-censored clinical events will be summarized by the same methods and analyzed by the same set of models as are specified for survival endpoints. Interval-censored clinical events will be analyzed using interval-censored methods. The model terms are expanded to include two active treatment groups, ABBV-CLS-7262 120 mg and 240 mg. Principal inference will be based on comparison of the ABBV-CLS-7262 120 mg dosage vs. placebo. For right-censored endpoints, summaries will include treatment-specific counts of the cumulative number of participants with events and the number of participants at risk for a first event at baseline, 8, 16, and 24 weeks after baseline, and inclusive of all RCT follow-up. For interval censored endpoints, summaries will include the number of participants at risk at baseline and the number of participants left censored, interval censored, and right censored at the end of RCT follow-up. Summaries will include treatment-specific times to 10%, 25%, and 50% percentiles of the estimated survival curves.

6.5.5 CAFS

The specification of CAFS analyses is the same as described in the M-SAP with the following modification. Ranking by ALSFRS-R total score and death/death-equivalent is added for analysis by this model in the ECC, FAS, and ERO analysis sets at the RCT Week 24 time point. Functional endpoints for analysis at the RCT Week 24 time point will include ALSFRS-R total score, HHD upper extremity percentage, and SVC. Only ALSFRS-R total score with death/death-equivalent will be analyzed in the ECM and EPP analysis sets. The CAFS analysis of ALSFRS-R total score and death/death-equivalent at the RCT Week 24 time point in the ECC analysis set with adjustment for time from symptom onset, delta-FRS, baseline use of edaravone, baseline use of riluzole, baseline use of sodium phenylbutyrate/taurursodiol, and baseline log-transformed serum NfL is a key sensitivity analysis of the primary Bayesian shared-parameter model.

6.5.6 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 partial linear B-splines with knots at 4, 8, and 16 weeks. The model will include fixed terms for B-splines, treatment group, treatment group × B-spline interaction and time since symptom onset, delta-FRS, baseline use of edaravone, baseline use of riluzole, baseline use of sodium phenylbutyrate/taurursodiol, and baseline log-transformed serum NfL and their interactions with the B-splines. In analyses of phonation time, age and height will be added as covariates. Covariates will be centered at their means. Articulatory precision will be cube-root transformed (transformed value = sign(original value) * abs(original value)^(1/3)) prior to analysis, and estimates and their 95% confidence bounds will be back-transformed (transformed estimate = (original estimate)^3).

The model will include random regimen-specific intercepts and slopes with unstructured covariance, random participant-specific B-splines 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 principal estimate will be the difference between ABBV-CLS-7262 120 mg vs. placebo in 24-week change from baseline. The estimate and its 95% Wald confidence bounds will be obtained by a linear contrast of adjusted means.

6.5.7 Subgroup Analyses

The specification of subgroup analyses is the same as described in the M-SAP with the following modifications. Analyses will use the ECC analysis set focusing on comparisons between ABBV-CLS-7262 120 mg vs. placebo at 24-week change from baseline. Early disease state is defined as all ALSFRS-R questions scored 2 or greater, SVC 80%-predicted or greater, time since symptom onset less than 24 months, and El Escorial definite or probable. Baseline CSF GDF-15 concentration (median split), baseline CSF FGF21 concentration (median split), and baseline serum NfL concentration (median split) are added as additional subgroup analyses to explore treatment efficacy of ABBV-CLS-7262 in different subgroup populations. Body mass index (BMI), baseline symptom severity defined by ALSFRS-R questions scored 2 or greater, baseline plasma NfL, and site are removed as subgroups.

6.5.8 Comparison of Controls across Regimens

The specification of comparisons of controls across regimens is the same as described in the M-SAP with the addition that comparisons will be made across regimens in both the FAS and ECC analysis sets.

6.5.9 Pharmacodynamic Biomarker Analyses

Change in pharmacodynamic biomarkers will be summarized by treatment group and visit in the ERO analysis set. Summary statistics 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. Summaries will include observed values, absolute change from baseline, and percent change from baseline at each scheduled assessment time point.

The effect of treatment on pharmacodynamic biomarker response will be estimated in the repeated-measure model (see Section 6.5.2). Pearson and Spearman correlations between change in levels of pharmacodynamic biomarkers and concurrent change in ALSFRS-R total scores and SVC percent-predicted will be estimated at each visit among participants with complete data.

6.6 Safety Analyses

6.6.1 Treatment-emergent Adverse Events

Summaries of treatment-emergent adverse events (TEAEs) are the same as described in the M-SAP with the addition of the SCC analysis set and the addition of summaries of abuse-related TEAEs (see Appendix 2 Monitoring Abuse Potential of ABBV-CLS-7262 in Clinical Trials, Ad-Hoc Statistical Reporting Plan, Version 1.0 – June 28, 2023).

6.6.2 Safety Labs

Summaries of safety labs are the same as described in the M-SAP with the addition of the SCC analysis set and the addition of summaries for assays specific to RGF: amylase, lipase, ACTH, cortisol, total testosterone (males only), luteinizing hormone (males only), TSH, free T4, T3, and abnormal cosyntropin stimulation response.

6.6.3 ECG Results

Summaries of ECG results are the same as described in the M-SAP with the addition of the SCC analysis set and shift tables for abnormal findings.

6.6.4 Vital Signs and Weight

Summaries of vital signs are the same as described in the M-SAP with the addition of the SCC analysis set. Weight will be analyzed in the FAS, ECC, and ERO analysis sets in the repeated-measures and random-slope mixed models.

6.6.5 Suicidality

Summaries of suicidality are the same as described in the M-SAP with the addition of the SCC analysis set.

6.7 Other Analyses

6.7.1 Participant Disposition

Summaries of participant disposition are the same as described in the M-SAP.

6.7.2 Study Drug Compliance and Tolerance

Summaries of study drug exposure and tolerance are the same as described in the M-SAP. The proportion of participants who are compliant with study drug as defined in Section 5.12 will be summarized for participants in the ABBV-CLS-7262 120 mg and 240 mg treatment groups. Drug accountability discrepancies will be listed according to Appendix 2.

6.7.3 Concomitant Medication Use

Summaries of concomitant medication use are the same as described in the M-SAP with the clarification that use at baseline refers to use of a concomitant medication at the time of first dose of study drug, and that initiation after first dose of study drug is defined as first use of a concomitant medication after first dose of study drug that was not being taken at the time of first dose of study drug.

6.7.4 Medical History

Summaries of medical histories are the same as described in the M-SAP with the addition of a summary for the SCC analysis set.

6.7.5 Blindedness

Summaries of blindedness are the same as described in the M-SAP with the addition of a summary for the ECC analysis set.

6.7.6 Protocol Deviations

Summaries of protocol deviations are the same as described in the M-SAP.

7. Validation

7.1 Primary Efficacy Analysis

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

7.2 Secondary, Exploratory, and Safety Analyses

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

8. References

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

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Shepheard SR, Karnaros V, Benyamin B, Schultz DW, Dubowsky M, Wuu J, Chataway T, Malaspina A, Benatar M, Rogers ML. Urinary neopterin: A novel biomarker of disease progression in amyotrophic lateral sclerosis. Eur J Neurol. 2022 Apr;29(4):990-9.

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Westeneng HJ, Debray TPA, Visser AE, van Eijk RPA, Rooney JPK, Calvo A, Martin S, McDermott CJ, Thompson AG, Pinto S, Kobeleva X, Rosenbohm A, Stubendorff B, Sommer H, Middelkoop BM, Dekker AM, van Vugt JJFA, van Rheenen W, Vajda A, Heverin M, Kazoka M, Hollinger H, Gromicho M, Körner S, Ringer TM, Rödiger A, Gunkel A, Shaw CE, Bredenoord AL, van Es MA, Corcia P, Couratier P, Weber M, Grosskreutz J, Ludolph AC, Petri S, de Carvalho M, Van Damme P, Talbot K, Turner MR, Shaw PJ, Al-Chalabi A, Chiò A, Hardiman O, Moons KGM, Veldink JH, van den Berg LH. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. Lancet Neurol. 2018 May;17(5):423-433.

Appendix 1.

ALS Master Protocol Regimen F (ABBV-CLS-7262)

Primary Analysis, Design & Simulation Report

July 31st, 2023

Table of Contents

1.0 Introduction

This document describes the primary endpoint, primary analysis, and interim analyses for Regimen F (ABBV-CLS-7262).

Regimen F follows the recommended design, primary endpoint and primary analysis from the ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report Dated February 6, 2023 (Appendix I of the HEALEY ALS Platform Trial Master Statistical Analysis Plan v3.0) with 2 minor differences:

1) Inclusion of two doses (120 and 240 mg QD) with primary inference being focused on the 120 mg QD dose, referred to as the anchor dose. Interims for futility will require both doses to meet the requirement for futility (Section 2.1 and 2.3).
2) The primary analysis population includes all participants in the Full Analysis Set who were randomized within Regimen F or randomized to placebo within Regimen G, exclusive of Regimen G participants who previously randomized within Regimen F (Section 2.1).

The design for Regimen F enrolls approximately 300 participants. Approximately 165 participants will be randomized to ABBV-CLS-7262 120 mg, approximately 60 participants will be randomized to ABBV-CLS-7262 240 mg, and approximately 75 participants will be randomized to placebo.

This document serves to provide:

- Modifications to the primary analysis model to include a treatment effect for both doses of ABBV-CLS-7262, details of primary success criteria for the anchor dose, and details of futility criteria including both doses.
- A list of sensitivity analyses that will be performed.
- Simulations custom to Regimen F that include 300 participants enrolled to both doses within Regimen F and concurrent shared controls from Regime G.

2.0 Overview of Primary Analysis and Design

2.1 Primary Analysis

The primary analysis population includes the subset of participants in the Full Analysis Set who were randomized within Regimen F or randomized to placebo within Regimen G, exclusive of Regimen G participants who previously randomized within Regimen F (Efficacy Concurrent Controls analysis set).

The primary analysis is a Bayesian shared parameter analysis of mortality and function (ALSFRS-R) and is described in the ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report Section 2.0 Dated February 6, 2023 (Appendix I of the HEALEY ALS Platform Trial Master Statistical Analysis Plan v3.0). For Regimen F, the model will be modified to include independent treatment effects for each dosage of ABBV-CLS-7262.

The treatment effect for *T=0,1,2* (control, anchor, and high dose respectively) is parameterized as the disease rate ratio (DRR): $\exp(\theta_T)$. For a placebo patient, the DRR is set equal to 1 ($\theta_0 = 0$). The prior distribution for the DRR for the anchor dose and high dose in Regimen ABBV-CLS-7262, *T=1,2,* is uniform between 0 and 2, placing equal weight on a DRR<1 and DRR>1:

$$\exp(\theta_T) \sim Unif(0,2), T = 1,2.$$

The primary analysis will compare the anchor dose to control. The comparison of the high dose to control will be a secondary analysis.

2.2 Regimen Success

The primary analysis in Regimen F will test the anchor dose, T=1, compared to placebo. Success will be declared for the anchor dose at the final analysis if the posterior probability that the dose is superior to placebo group is greater than .975:

$$Pr\,(\exp(\theta_1) < 1) > .975.; for\ anchor\ dose$$

The threshold for the final analysis of .975 was chosen to control type I error at 2.5% in the null scenario without futility stopping.

2.3 Interim Analyses and Regimen Futility

Interim analyses occur simultaneously for all regimens within the platform that have participants active in their placebo-controlled period. Interim analyses occur

approximately every 12 weeks. The first interim analysis for Regimen F will be performed after there are 60 randomized participants within Regimen F who have had the opportunity to complete at least 24 weeks of follow-up. At an interim analysis, Regimen F can stop early only for futility. If Regimen F is not stopped early for futility at an interim analysis, then the Regimen F final analysis will take place after all participants randomized within Regimen F have had the opportunity to complete 24 weeks of follow-up and final data for the Regimen F placebo-controlled period have been locked.

The primary analysis population for early interims on futility will include the subset of participants in the Full Analysis Set who were randomized within Regimen F or randomized to placebo within Regimen G, exclusive of Regimen G participants who previously randomized within Regimen F.

For interim analyses, due to constraints on when serum NfL data is received, the covariate of baseline log-transformed serum NfL level will not be included in the primary analysis model.

Futility will be declared for Regimen F at an interim analysis if the posterior probabilities that the anchor dose, T=1, and the high dose, T=2, slow disease progression by at least 10% are both less than 5%:

$$Pr\,(exp(\theta_1) < .9) < .05 \;\; and \;\; Pr\,(exp(\theta_2) < .9) < .05$$

2.4 Goodness of Fit Diagnostics and Sensitivity Analyses of Primary Efficacy Analysis

The goodness-of-fit diagnostics, supportive analyses, and sensitivity analyses will be performed for the primary efficacy analysis and will be conducted on the primary analysis population unless otherwise specified. Analyses will follow those specified in Section 4.0 of the ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report Dated February 6, 2023 (Appendix I of the HEALEY ALS Platform Trial Master Statistical Analysis Plan v3.0) with the following modifications:

- Concurrent shared control population will serve as the primary analysis population and a sensitivity analysis with all shared controls from Regimens A-G will be conducted.

3.0 Clinical Trial Simulations

Clinical trial simulation is used to provided simulated example trials and to quantify operating characteristics for each regimen. Virtual patient outcomes are created under different assumptions for key design parameters (see ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report Section 5.1 Dated February 6, 2023 [Appendix I of the HEALEY ALS Platform Trial Master Statistical Analysis Plan v3.0] for description of simulation method). For each set of simulation assumptions (i.e., a scenario), many trials are simulated and virtually executed, including all interim analyses for early futility. Trial operating characteristics are summarized across all simulated trials for each scenario.

3.1 Simulation Scenarios

Trial simulations for Regimen F assume that Regimen F is the 6th regimen with a 7th regimen (Regimen G) also enrolling concurrently with a total of N=240 and 60 controls in Regimen G. Under the primary concurrent only shared control analysis there is expected to be a total of N=165 treated on the anchor 120mg dose in Regimen F and N=135 shared controls. Treatment effect assumptions will vary across the anchor dose for Regimen F and operating characteristics will be reported for this regimen/dose. The other 6 regimens will be assumed to be Null (no benefit on ALSFRS-R or mortality).

Additional simulation assumptions are:

- Accrual of 40 participants per month
- Non-mortality dropout rate of 2% per month
- Mortality rate of 5% over 24 weeks.
- ALSFRS-R slope distribution and measurement error for Regimen F is the same as PRO-ACT
- Rates of usage and effects of Standard of care (SOC). Effects of SOC will be multiplicative effects to the individual rates of progression applied first before any treatment effect (see below).
    - Edaravone usage at baseline is 25% with an assumed 30% slowing over natural progression for those participants who are on edaravone
    - Relyvrio usage at baseline is 60% with an assumed 25% slowing over natural progression for those participants who are on Relyvrio
    - The treatment effect for those participants on both edaravone and Relyvrio is capped at 30% slowing.

Treatment effects for Regimen F will be simulated under the Null with 0% slowing in disease progression and under an alternative with 30% slowing in disease progression. The 30% slowing due to treatment in Regimen F is assumed to be an additional, additive effect on top of any effect of the standard of care (see SOC effect above). This additive effect on the slope will be specific to each SOC group (those not on edaravone or Relyvrio, those only on edaravone, those only on Relyvrio, and those on both) based on the expected control rate of progression within that subgroup to achieve a 30% slowing.

Simulations are performed without futility stopping.

3.2 Operating Characteristics Primary Analysis

For each scenario and treatment effect, we simulate 10000 clinical trials. We present overall average operating characteristics across all simulated trials. All simulations do not include early futility stopping. For each simulation scenario and treatment effect, we report the following regimen-specific operating characteristics for the first regimen:

- Probability of regimen success
- Average estimate of the treatment effect.

Table 3.2.1 shows the overall operating characteristics for Regimen F under the proposed design for the base simulation scenarios with and without futility stopping. The regimen has greater than 80% power to detect a 30% slowing of mortality and function in the

anchor dose. Under the null there is no bias and an estimated 2.5% type I error and a 11% probability of stopping early for futility.

Table 3.2.1: Operating Characteristics Primary Analysis Anchor Dose				
Scenario	**Power / Type I Error No Futility**	**Effect Estimate No Futility**	**Prob. Stop Early Futility**	**Power / Type I Error w/ Futility**
Null (0% Slowing)	0.025	1.00	0.10	0.025
30% slowing of Function and Mortality	0.843	0.70	<0.001	0.843
30% slowing of Function only, 0% slowing of Mortality	0.801	0.71	<0.001	0.801

Appendix 2.

Please see the attached Monitoring Abuse Potential of ABBV-CLS-7262 in Clinical Trials, Ad-Hoc Statistical Reporting Plan, Version 1.0 – June 28, 2023.

Monitoring Abuse Potential of ABBV-CLS-7262 in Clinical Trials

Ad-Hoc Statistical Reporting Plan

Version 1.0 – June 28, 2023

Introduction

New drugs that are known to affect the central nervous system (CNS) or are chemically or pharmacologically similar to other drugs with known abuse potential, or that produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) are required to be evaluated for their abuse potential per U.S. Food and Drug Administration (FDA) [21 CFR 314.50(d)(5)(vii)]. Data from all clinical trials during development are required to support the New Drug Application submission. Refer to the *FDA Guidance for Industry: Assessment of Abuse Potential of Drugs*, dated January 2017.

Purpose:

As part of this evaluation, this statistical reporting plan outlines how abuse-related adverse events and drug accountability discrepancies will be summarized and reported in the clinical study report (CSR) for each clinical trial of ABBV-CLS-7262.

For the purposes of this monitoring and statistical reporting plan, the term "abuse-related" refers to adverse events or other clinical information that are related to the assessment of abuse potential of a new drug, which are presented in Appendix B.

For a list of the applicable clinical trial protocol numbers, refer to Appendix A.

For shells of the planned tables and listings, refer to Appendix C.

Definitions and Conventions

Software

All tables and listings will be generated using SAS version 9.4 or higher.

Analysis Set

The Abuse Potential Analysis Set (APAS) will include all enrolled subjects who receive at least 1 dose of study drug (ABBV-CLS-7262 or placebo).

Treatment Groups

Adverse event (AE) data will be summarized by study, part, treatment, and/or period (as applicable) as outlined in the statistical analysis plan (SAP) for each clinical trial (e.g., ABBV-CLS-7262 or placebo, or ABBV-CLS-7262 dose level).

Summary of Abuse-Related Adverse Events

In accordance with the SAP for the clinical trial, AEs will be coded using preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher. Treatment-emergent adverse events (TEAEs) will be defined as any event that begins or worsens in severity after the first dose of study drug and for up to 30 days after the last dose of study drug. Abuse-related AEs will be defined as any TEAEs with preferred terms corresponding to the list in Appendix B.

The number and percentage of subjects having abuse-related AEs will be tabulated by primary System Organ Class (SOC) and MedDRA preferred term with further breakdowns by severity rating and relationship to study drug (as evaluated by the Investigator). Severity rating will be assigned according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher, or as otherwise defined in the SAP for the clinical trial. Subjects reporting more than one abuse-related AE for a given MedDRA preferred term will be counted only once for that term using the most severe incident and the incident with the maximum relationship to study drug. Subjects reporting more than one type of abuse-related AE within a SOC will be counted only once for that SOC.

Listing of Drug Accountability Discrepancies

Drug accountability discrepancies may identify participants who are overusing or abusing study drug.

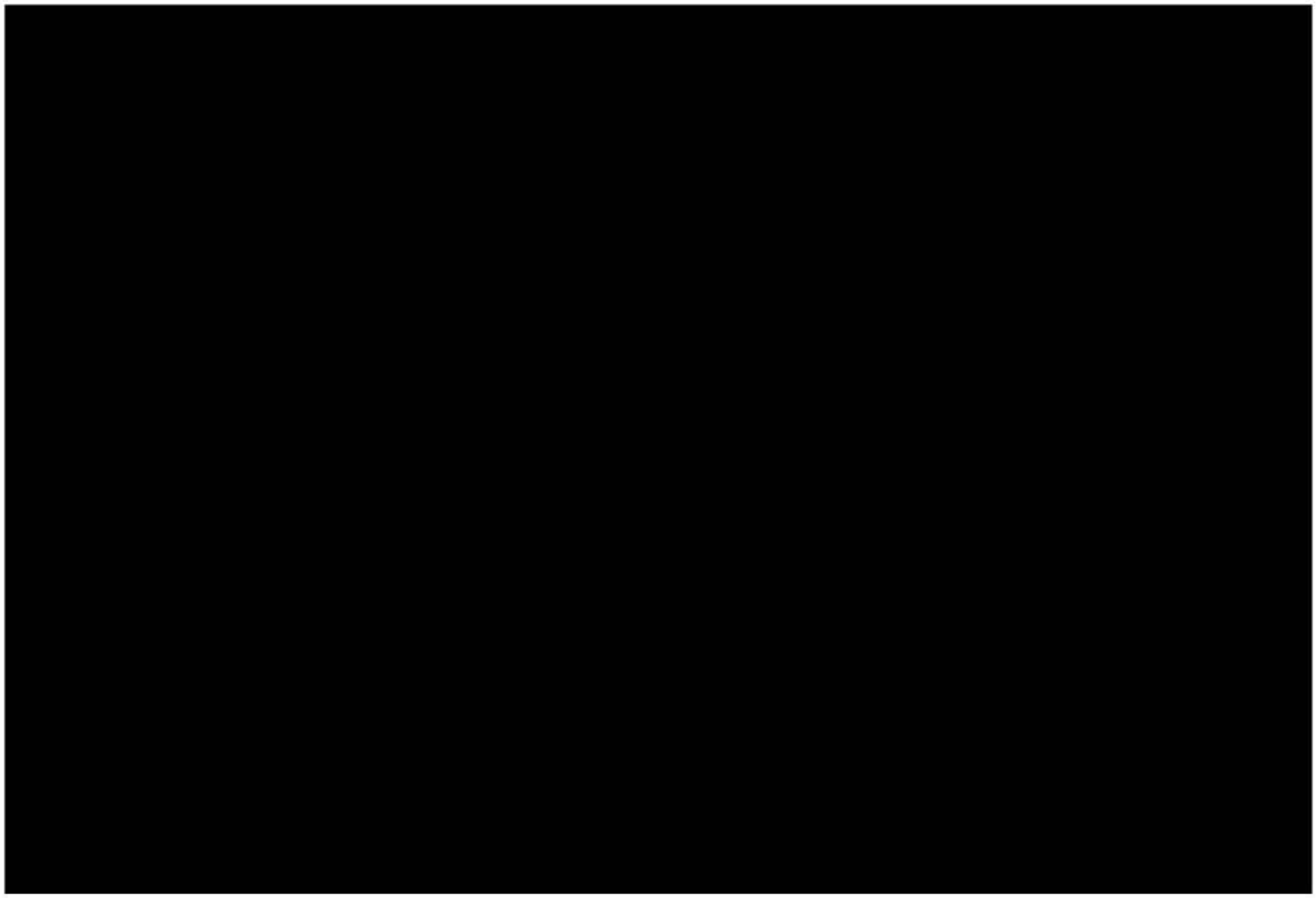
Drug accountability discrepancies (i.e., instances of participants failing to return unused study drug sachets) are identified in outpatient studies through an eCRF.

The expected return amount of the unused drug is calculated for each participant by:

$$Expected\ Return\ Amount = Dispensed\ Amount\ (\#sachets) - Dose\left(\frac{\#sachets}{day}\right) \times Days\ Supply\ (\#days)$$

For outpatient studies only (see Appendix C), a listing will be generated for drug accountability discrepancies where the number of unused sachets that are returned is less than the expected return amount.

Signatures



Appendix A – Protocol Numbers

Study Name	Protocol Number	Inpatient/Outpatient
A Phase 1 First-in-Human Study of ABBV-CLS-7262 in Healthy Subjects to Evaluate Safety, Tolerability, Pharmacokinetics, Food Effect, and Drug-Drug Interaction	M20-015	Inpatient
Assessment of the Relative Bioavailability of ABBV-CLS-7262 Formulations in Healthy Adult Volunteers	M22-124	Inpatient
A Randomized, Double-Blind, Placebo-Controlled Study to Assess Safety, Tolerability, and Pharmacokinetics Following Multiple Doses of ABBV-CLS-7262 in Subjects with Amyotrophic Lateral Sclerosis Followed by an Active Treatment Extension	M20-405	Outpatient
A Phase 1b Open-label Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Exploratory Efficacy Following ABBV-CLS-7262 Administration in Adult and Pediatric Subjects with Vanishing White Matter Disease	M23-523	Outpatient
A Phase 1 Study to Evaluate the Drug-Drug Interaction Between ABBV-CLS-7262, Rosuvastatin, and Digoxin Following Multiple Doses of ABBV-CLS-7262	M24-192	Inpatient
An Open-Label, Positron Emission Tomography, Phase 1 Study with [^{18}F]A-1684909 to Determine Occupancy of eIF2B in the Brain Following Oral Dosing with ABBV-CLS-7262	M23-471	Inpatient

HEALEY ALS Platform Trial – Regimen F ABBV-CLS-7262	M20-473	

Appendix B – Abuse-Related Adverse Event Terms

A list of Preferred Terms for AEs which are related to the assessment of abuse potential (based on the *FDA Guidance for Industry – Assessment of Abuse Potential of Drugs*, dated January 2017) was compiled as recommended and approved by the Agency.

List of Preferred Terms for Monitoring of Abuse Potential of ABBV-CLS-7262

MedDRA Code	Preferred Term
10000381	Accidental overdose
10001022	Acute psychosis
10001488	Aggression
10001497	Agitation
10010305	Confusional state
10011953	Decreased activity
10012239	Delusion
10012335	Dependence
10076227	Disorganised speech
10013395	Disorientation
10013457	Dissociation
10013462	Dissociative disorder
10013496	Disturbance in attention
10061108	Disturbance in social behaviour
10013573	Dizziness
10013654	Drug abuse
10061111	Drug abuser
10013663	Drug dependence
10052237	Drug detoxification
10066053	Drug diversion
10061132	Drug level above therapeutic
10013722	Drug level increased
10064773	Drug rehabilitation
10050837	Drug screen
10049177	Drug screen positive
10052804	Drug tolerance
10052805	Drug tolerance decreased
10052806	Drug tolerance increased
10079381	Drug use disorder
10013752	Drug withdrawal convulsions
10013753	Drug withdrawal headache
10013754	Drug withdrawal syndrome
10014551	Emotional disorder
10015535	Euphoric mood

MedDRA Code	Preferred Term
10016322	Feeling abnormal
10016330	Feeling drunk
10016352	Feeling of relaxation
10016754	Flashback
10019063	Hallucination
10019070	Hallucination, auditory
10019071	Hallucination, gustatory
10019072	Hallucination, olfactory
10062824	Hallucination, synaesthetic
10019074	Hallucination, tactile
10019075	Hallucination, visual
10019079	Hallucinations, mixed
10021403	Illusion
10061215	Impulse-control disorder
10021567	Impulsive behaviour
10021588	Inappropriate affect
10022523	Intentional overdose
10074903	Intentional product misuse
10076308	Intentional product use issue
10024796	Logorrhoea
10027374	Mental impairment
10027940	Mood altered
10033295	Overdose
10037211	Psychomotor hyperactivity
10037213	Psychomotor retardation
10061920	Psychotic disorder
10079254	Psychotic symptom
10038001	Rebound effect
10038743	Restlessness
10039897	Sedation
10039906	Seizure
10041349	Somnolence
10042008	Stereotypy
10066169	Substance abuse
10067688	Substance abuser
10076595	Substance dependence
10070964	Substance use
10079384	Substance use disorder
10072387	Substance-induced mood disorder
10072388	Substance-induced psychotic disorder
10043431	Thinking abnormal

MedDRA Code	Preferred Term
10081010	Withdrawal catatonia
10048010	Withdrawal syndrome

Appendix C – Shells for Tables and Listings

Table Number	Table Name
Table X_1	Abuse-Related Adverse Events by System Organ Class and Preferred Term
Table X_2	Abuse-Related Adverse Events by System Organ Class, Preferred Term, and Maximum Relationship to Study Drug
Table X_3	Abuse-Related Adverse Events by System Organ Class, Preferred Term, and Maximum Severity Grade

Listing Number	Listing Name
Listing X_1	Participant-Level Drug Accountability Discrepancies

Table X_1
Abuse-Related Adverse Events by System Organ Class and Preferred Term
Abuse Potential Analysis Set

System Organ Class Preferred Term (MedDRA Version XX.X)	Treatment 1 (N=XXX) n (%)	Treatment 2 (N=XXX) n (%)	Overall (Active) (N=XXX) n (%)	Placebo (N=XXX) n (%)
Any Abuse-Related Adverse Event	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Nervous System Disorders	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Dizziness	X (X.X)	X (X.X)	X (X.X)	X (X.X)

In this table, the term "abuse-related" refers to the adverse events and other clinical information that is related to the assessment of abuse potential of a new drug

Table X_2
Abuse-Related Adverse Events by System Organ Class, Preferred Term, and Maximum Relationship to Study Drug
Abuse Potential Analysis Set

System Organ Class Preferred Term (MedDRA Version XX.X) Relationship[#]	Treatment 1 (N=XXX) n (%)	Treatment 2 (N=XXX) n (%)	Overall (Active) (N=XXX) n (%)	Placebo (N=XXX) n (%)
Any Abuse-Related Adverse Event	X (X.X)	X (X.X)	X (X.X)	X (X.X)
No reasonable possibility	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Reasonable possibility	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Nervous System Disorders	X (X.X)	X (X.X)	X (X.X)	X (X.X)
No reasonable possibility	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Reasonable possibility	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Dizziness	X (X.X)	X (X.X)	X (X.X)	X (X.X)
No reasonable possibility	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Reasonable possibility	X (X.X)	X (X.X)	X (X.X)	X (X.X)

A subject reporting more than one abuse-related adverse event for a given preferred term will only be counted once using the incident with a possible relationship to ABBV-CLS-7262 (i.e., a reasonable possibility of being related to ABBV-CLS-7262)

[#]Relationship to study drug as assessed by the Investigator

In this table, the term "abuse-related" refers to the adverse events and other clinical information that is related to the assessment of abuse potential of a new drug

Table X_3
Abuse-Related Adverse Events by System Organ Class, Preferred Term, and Maximum Severity Grade
Abuse Potential Analysis Set

System Organ Class Preferred Term (MedDRA Version XX.X) Severity[#]	Treatment 1 (N=XXX) n (%)	Treatment 2 (N=XXX) n (%)	Overall (Active) (N=XXX) n (%)	Placebo (N=XXX) n (%)
Any Abuse-Related Adverse Event	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Mild	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Moderate	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Severe	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Nervous System Disorders	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Mild	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Moderate	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Severe	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Dizziness	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Mild	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Moderate	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Severe	X (X.X)	X (X.X)	X (X.X)	X (X.X)

A subject reporting more than one abuse-related adverse event for a given preferred term will only be counted once using the incident with a possible relationship to ABBV-CLS-7262 (i.e., a reasonable possibility of being related to ABBV-CLS-7262)

[#]Severity as assessed by the Common Terminology Criteria for Adverse Events (CTCAE)

In this table, the term "abuse-related" refers to the adverse events and other clinical information that is related to the assessment of abuse potential of a new drug

Listing X_1
Participant-Level Drug Accountability Discrepancies
Abuse Potential Analysis Set

Subject Id	Kit Id	Dispensed Sachet Amount	Expected Return Amount	Unused Sachets NOT Returned	Any Abuse-Related Adverse Event Preferred Term(s)
XXX-XXX	XXX-XXX	X	X	X	Dizziness
	XXX-XXX	X	X	X	
XXX-XXX	XXX-XXX	X	X	X	Drug abuse

AEs and kit on the same line are not necessarily temporally connected.

In this table, the term "abuse-related" refers to the adverse events and other clinical information that is related to the assessment of abuse potential of a new drug

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Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Payment Events	**Status**	**Timestamps**
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To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at ben@calicolabs.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

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Status: Completed
Subject: Complete with Docusign: HEALEY ALS Platform RGF R-SAP v3.0 20240813.pdf
Source Envelope:
Document Pages: 58
Signatures: 8
Envelope Originator:
Certificate Pages: 7
Initials: 0
Brittney Harkey
AutoNav: Enabled
BHARKEY@MGH.HARVARD.EDU
EnvelopeId Stamping: Disabled
IP Address: 35.22.60.192
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

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Status: Original
8/13/2024 9:24:42 AM
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Signer Events	Signature	Timestamp
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Editor Delivery Events	Status	Timestamp
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Intermediary Delivery Events	Status	Timestamp
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Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	8/13/2024 9:43:36 AM
Certified Delivered	Security Checked	8/15/2024 12:36:49 AM
Signing Complete	Security Checked	8/15/2024 12:37:22 AM
Completed	Security Checked	8/15/2024 12:37:22 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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To advise Insight OBO The Massachusetts General Hospital of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at jhenrique@mgh.harvard.edu and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

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