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

NCT05740813

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REGIMEN-SPECIFIC APPENDIX F

FOR ABBV-CLS-7262

Regimen-Specific Appendix Date: July 23, 2024

Version Number: 3.0

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SIGNATURE PAGE

I have read the attached Regimen-Specific Appendix (RSA) entitled, "REGIMEN F: ABBV-CLS-7262" dated July 23, 2024 (Version 3.0) and agree to abide by all described RSA procedures. I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice, applicable FDA regulations and guidelines identified in 21 CFR Parts 11, 50, 54, and 312, central Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

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

Site Name: _____

Site Investigator: _____

Signed: _____ Date: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
ALSFRS-R	ALS Functional Rating Scale-Revised
ATE	Active Treatment Extension
CAFS	Combined Assessment of Function and Survival
CNS	Central nervous system
CNS-BFS	Center for Neurologic Study Bulbar Function Scale
CSF	Cerebrospinal fluid
ECG	Electrocardiogram
eIF2B	Eukaryotic translation initiation factor 2B
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
hERG	human ether-à-gogo-related gene
HHD	Hand-held dynamometry
IP	Investigational product
ISR	Integrated stress response
NfL	Neurofilament light chain
NHP	Non-human primate
NOAEL	No observed adverse effect level
PET	Positron emission tomography
PK	Pharmacokinetics
QD	Once daily
QTc	QT interval corrected
RSA	Regimen-Specific Appendix
SAE	Serious adverse event
SOA	Schedule of activities
SVC	Slow vital capacity
TESAE	Treatment-emergent serious adverse event

Abbreviation	Definition
US	United States

REGIMEN-SPECIFIC APPENDIX SUMMARY

Regimen-Specific Appendix F
For ABBV-CLS-7262

Rationale and RSA Design
ABBV-CLS-7262 is a prodrug that is converted *in vivo* to the pharmacologically active compound A-1684909. A-1684909 is a central nervous system (CNS)-penetrant, eukaryotic translation initiation factor 2B (eIF2B) activator that attenuates the integrated stress response (ISR), a highly conserved cellular mechanism hypothesized to be important in the pathophysiology of amyotrophic lateral sclerosis (ALS) and other neurodegenerative conditions when activated chronically (Costa-Mattioli et al. 2020).

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

When pre-defined criteria for futility for the regimen are met or the target number of randomized participants is reached, enrollment will be stopped, while allowing participants still in Regimen F screening to complete the process.

Number of Planned Participants and Treatment Groups
The number of planned participants for this regimen is approximately 300.

There are 3 treatment groups for this regimen: ABBV-CLS-7262 120 mg, ABBV-CLS-7262 240 mg, and placebo. 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.

Planned Number of Sites
Participants will be enrolled from up to approximately 80 centers in the US.

Treatment Duration
The maximum duration of the placebo-controlled treatment portion is 24 weeks. The duration of the Active Treatment Extension (ATE) period is planned for approximately 52 weeks from the first ATE visit of the final participant in Regimen F or until the primary results of the 24-week placebo-controlled period are available and a decision about further development has been made.

Follow-up Duration

At the conclusion of the 24-week placebo-controlled treatment period of the study, all participants will continue in the ATE period of the study. Any participant who stops study medication will have a 28-day follow up safety phone call and end their participation in the regimen. The duration of the ATE period is planned for approximately 52 weeks from the first ATE visit of the final participant in Regimen F.

Total Planned Trial Duration

Including the placebo-controlled treatment period and the integral ATE period, the total planned amount of time for a participant in the trial is a minimum of approximately 86 weeks. This duration assumes a 6-week screening window, 24-week placebo-controlled treatment period, a 52-week or longer ATE period, and a 4-week safety follow-up period.

SCHEDULE OF ACTIVITIES – PLACEBO CONTROLLED PERIOD

Activity (page 1 of 2)		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 or Early Term. Visit	Follow-Up Safety Call[11]
	Master Protocol or Regimen-Specific	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 after last dose +3 days
Written Informed Consent[2]	Master	X	X									
Inclusion/Exclusion Review	Master	X	X[3]									
ALS & Medical History	Master	X										
Demographics	Master	X										
Physical Examination	Master	X										
Neurological Exam	Master	X										
Vital Signs[4]	Master	X		X		X	X		X		X	
Slow Vital Capacity	Master	X[15]		X			X		X		X	
Muscle Strength Assessment	Master			X			X		X		X	
ALSFRS-R	Master	X		X		X	X	X	X	X	X	
ALSAQ-40	Regimen			X							X	
ROADS	Regimen			X			X		X		X	
CNS Bulbar Function Scale	Regimen			X			X		X		X	
12-Lead ECG	Regimen	X		X			X		X		X	
Clinical Safety Labs[5, 16]	Master	X		X		X	X		X		X	
Hormone Assessments[16,19]	Regimen		X			X			X		X	
Menstrual Cycle Questionnaire[18]	Regimen			X		X	X		X		X	
Coagulation Labs (PT, PTT, INR)	Regimen	X[21]							X			
Biomarker Blood Collection[16]	Master			X			X		X		X	
Plasma/Serum for Biomarkers [16]	Regimen			X			X		X		X	

Activity (page 2 of 2)		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 or Early Term. Visit	Follow-Up Safety Call[11]
	Master Protocol or Regimen-Specific	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 after last dose +3 days
Biomarker Urine Collection[17]	Master			X			X		X		X	
Biomarker Urine Collection[17]	Regimen			X			X		X		X	
Blood Sample for PK Analysis[16]	Regimen					X	X		X		X	
DNA Collection[7] (optional)	Master			X								
Blood RNA Collection[16]	Regimen			X			X				X	
CSF Collection[20]	Regimen			X							X	
Concomitant Medication Review	Master	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review[6]	Master	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	Master			X		X	X		X		X	
Install Smartphone App[14]	Regimen			X								
Voice Recording[9]	Regimen			X		X	X		X		X	
Uninstall Smartphone App	Regimen										X	
Assignment to the Regimen	Master	X										
Randomization within the Regimen	Master			X								
Administer/Dispense Investigational product	Master			X[8]		X	X		X		X[10]	
Drug Accountability/Compliance	Master				X	X	X	X	X	X	X	
Exit Questionnaire	Master										X	
Vital Status Determination[12]	Master										X	

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 randomized to a regimen, participants will be consented a second time via the regimen-specific ICF.

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

4 Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate, 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 childbearing 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 participant 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 2nd 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 IP, respectively.

21 If coagulation labs are not collected during the Master Protocol Screening visit they can be collected during the Regimen Specific Screening Visit.

SCHEDULE OF ACTIVITIES – ACTIVE TREATMENT EXTENSION PERIOD

Activity		Active Treatment Extension[5]												
		Baseline[14]	ATE Week 2	ATE Week 4[7]	ATE Week 8[7]	ATE Week 12	ATE Week 16[7]	ATE Week 20	ATE Week 24	ATE Week 28[7]	ATE Week 40[7]	ATE Week 52 or Early Term. Visit[6]	Ongoing ATE Visit	Follow-Up Safety Call[4, 6]
	Master Protocol or Regimen-Specific	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Phone	Clinic	Clinic	Clinic	Clinic	Phone
		Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day168 ±3	Day 196 ± 14	Day 280 ± 14	Day 364 ± 14	Q12 after week 52[13] ±7	28 days after last dose +3 days
Vital Signs[1]	Master			X	X		X			X	X	X	X	
Slow Vital Capacity	Master			X	X		X			X	X	X		
Muscle Strength Assessment	Master				X					X		X		
ALSFRS-R	Master			X	X	X	X	X	X	X	X	X	X	
ALSAQ-40	Regimen									X		X		
ROADS	Regimen									X		X		
CNS Bulbar Function Scale	Regimen				X		X			X	X	X		
Clinical Safety Labs[2]	Master			X	X		X			X	X	X	X	
Hormone Assessments	Regimen			X			X			X		X	X	
Menstrual Cycle Questionnaire[10]	Regimen			X	X		X			X	X	X	X	
Plasma/Serum for Biomarkers[9]	Regimen				X					X		X		
Biomarker Blood Collection[9]	Master						X			X		X		
Biomarker Urine Collection[8]	Master						X			X		X		
Biomarker Urine Collection[8]	Regimen				X					X		X		
Blood RNA Collection[9]	Regimen				X					X		X		

Coagulation Labs (PT, PTT, INR)[11]	Regimen						X				X			
CSF collection[15]	Regimen									X		X		
Concomitant Medication Review	Master		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review[3]	Master		X	X	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	Master			X	X		X			X	X	X	X	
Administer/Dispense Investigational Product	Master				X		X			X	X	X[14]	X[14]	
Drug Accountability/ Compliance	Master		X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	Regimen				X		X			X	X	X	X	
Vital Status Determination[12]	Regimen											X	X	

1 Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate, pulse oximetry, and temperature. Height in cm measured at Master Protocol Screening Visit only.

2 Clinical safety labs include hematology (CBC with differential), complete chemistry panel, thyroid function, and urinalysis. Serum pregnancy testing will occur in women of child-bearing potential. Two additional regimen-specific safety labs will be collected, amylase and lipase.

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

4 Participants who continue into ATE will have a Follow-Up Safety Call (as described in the body of this RSA) after their last dose of IP during the ATE period.

5 The duration of the ATE is approximately 52 weeks.

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

7 Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic, disability, or other medically necessary reason. If an in-clinic visit is conducted remotely for disability or a medically necessary reason, the next scheduled in-clinic visit must occur in-person unless otherwise approved by the Medical Monitor.

8 Urine biomarker sample should be collected pre-dose. Collection should preferably be of the 2nd morning urine, as a mid-stream collection.

9 Blood sample is drawn at pre-dose (within 2 hours prior to dosing in the clinic).

10 Menstrual Cycle Questionnaire to be collected in women of childbearing potential.

11 Required for participants who will be participating in the Optional CSF Collection (ATE Week 16 Coagulation Labs to be collected for the Week 28 Optional CSF Collection, Week 40 Coagulation Labs to be collected for the ATE Week 52 Optional CSF Collection).

12 Vital status, defined as a determination of date of death or PAV status or date last known alive, will be determined for each participant at the end of their follow-up (generally the Week 52 visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant 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 When a participant completes the ATE Week 52 assessments, if the results of the placebo-controlled period of the trial are not available and a decision about further development has not been made, the participant will continue treatment for additional periods of approximately 12 weeks. In such a case, an Ongoing Extension Visit should be completed in the clinic every 12

weeks (84 ± 7 days) until the results of the placebo-controlled period of the trial are available and a decision about further development has been made, or until discontinuation from the study.

14 Assessments collected during Week 24 visit in placebo-controlled phase are the same for the Baseline visit in the ATE phase

15 CSF collection is optional in the ATE. CSF may be collected up to one week prior to ATE Week 28 and ATE Week 52 Visits.

1. INTRODUCTION

Regimen F: ABBV-CLS-7262

1.1 ABBV-CLS-7262 Background Information

ABBV-CLS-7262 is a prodrug that is converted *in vivo* to the pharmacologically active compound A-1684909. A-1684909 is a CNS-penetrant, eIF2B activator that attenuates the ISR, a highly conserved cellular mechanism hypothesized to be important in the pathophysiology of ALS and other neurodegenerative conditions when activated chronically (Costa-Mattioli et al. 2020).

Activation of the ISR has been detected in ALS patient post-mortem spinal cord samples. ABBV-CLS-7262 is hypothesized to benefit patients with ALS by attenuation of a chronic ISR, restoration of protein synthesis, and dissolution of TDP-43-containing stress granules in nervous system tissue. In cells that were pretreated with arsenite, a strong ISR-inducing oxidative stressor, A-1684909 has been shown in a dose-response fashion to dissolve cytosolic G3BP1- (a canonical stress granule marker) and TDP-43 containing granules. In the absence of a known animal model of ALS that is dependent on activation of the ISR, the optic nerve crush model of ISR-dependent acute neuronal injury has been used to further demonstrate a neuroprotective role for ISR inhibition. In an experiment conducted in mice using the optic nerve crush model, treatment with ABBV-CLS-7262 resulted in significant neuroprotection of retinal ganglion cells delivered prior to or following (4 days after) the nerve crush injury.

ABBV-CLS-7262 was profiled in CNS, cardiovascular, and respiratory safety pharmacology studies. In the CNS and respiratory studies, ABBV-CLS-7262 produced no effects in rats through the highest dose of 300 mg/kg (maximum concentration [C_{max}] = 81.3 µg/mL A-1684909). A-1684909 produced inhibition of the human ether-à-gogo-related gene (hERG) tail current with an IC_{50} of 0.59 µg/mL in protein-free medium. However, in dogs ABBV-CLS-7262 did not cause changes in the QT interval corrected (QTc) at C_{max} of 51.5 µg/mL A-1684909. In addition, ABBV-CLS-7262 produced no changes to mean arterial pressure, heart rate, or other electrocardiogram (ECG) parameters through the highest dose of 300 mg/kg (C_{max} = 51.5 µg/mL A-1684909).

ABBV-CLS-7262 was profiled in a Good Laboratory Practice (GLP)–compliant toxicology package that includes completed 4-week, 13-week, 26-week (rat), and 39-week (dog) repeat oral dose studies in the rat and dog, as well as genetic toxicology studies. ABBV-CLS-7262 was not tolerated at 300 mg/kg/day in dogs and resulted in moribundity and early euthanasia after ≥9 days of dosing. In the rat and/or the dog, primary ABBV-CLS-7262-related findings included

effects in endocrine (pituitary, adrenal, and/or thyroid glands) and reproductive organs (testis, ovary, and/or prostate). At higher exposures, the effects in adrenal, prostate (dog) and ovary (rat) were considered adverse. The effects in the adrenal defined the lowest adverse effect level. The effects in these organs were consistent with inhibition of steroidogenesis in adrenal, testis, and ovary and secondary upstream or downstream effects. These endocrine modulatory effects and potential hormonal imbalances are generally monitorable in humans and are expected to be reversible. Additional adverse effects were seen in exocrine pancreas and kidney (rat) and non-adverse effects were also seen in kidney and liver, and on red cell mass and platelets. Findings were dose-responsive and generally monitorable and showed evidence of partial to complete reversibility. ABBV-CLS-7262 and A-1684909 did not demonstrate genotoxic activity *in vitro* or *in vivo*.

The safety, tolerability, and pharmacokinetics (PK) of ABBV-CLS-7262 were evaluated in humans in Study M20-015 (healthy subjects), Study M22-124 (healthy subjects), ongoing Study M24-192 (healthy subjects), ongoing study M23-471 (healthy subjects) and ongoing Study M20-405 (participants with ALS).

In completed Study M20-015 and Study M22-124, doses up to 600 mg (single dose) and 300 mg (QD for up to 14 consecutive days) were administered, with 135 healthy subjects having received ABBV-CLS-7262 and 33 healthy subjects having received placebo. There were no deaths, pregnancies, serious adverse events (SAEs) or discontinuations due to adverse events (AEs). All AEs were mild to moderate in severity. No dose-dependent pattern of AEs or laboratory abnormalities was identified, including hormonal laboratory measures, and generally no differences in AEs were seen between the placebo and ABBV-CLS-7262 treatment arms.

M24-192 is an ongoing study in 12 healthy subjects to evaluate perpetrator effects of ABBV-CLS-7262 on P-gp and BCRP transporters using digoxin and rosuvastatin as index substrates, respectively. ABBV-CLS-7262 300 mg was administered once daily for 8 days. All subjects have completed dosing. There were no deaths, pregnancies, SAEs, or discontinuations due to AEs. All AEs were mild to moderate in severity.

M23-471 is an ongoing positron emission tomography (PET) study in up to 15 healthy subjects to evaluate the relationship between A-1684909 plasma concentration and occupancy of eIF2B in the brain following a single dose of ABBV-CLS-7262. As of 01 August 2023, four subjects have received a single dose of ABBV-CLS-7262 up to 120 mg and completed imaging. There have been no deaths, pregnancies, SAEs, or discontinuations due to AEs. All AEs have been mild in severity.

Study M20-405 is an ongoing Phase 1b study to evaluate the safety, tolerability, PK, exploratory efficacy, and exploratory pharmacodynamics following administration of ABBV-CLS-7262 in participants with ALS. Upon enrollment, participants are randomized to one of three dosing cohorts (40 mg, 120 mg, or 280 mg once daily), and may receive ABBV-CLS-7262 or placebo (4:1 ratio) for 4 weeks before all participants transition to ABBV-CLS-7262 for the remainder of the study. As of 09 June 2023, enrollment was complete, and 31 participants had been randomized. Periodic reviews of the unblinded safety data by a study-specific Data Monitoring Committee have not resulted in modifications to the study protocol.

Pharmacokinetic data of ABBV-CLS-7262 and A-1684909 are available from Study M20-015 and Study M22-124. The exposures from these maximal single and multiple QD doses were below the 4-week and 13-week no-observed adverse effect level (NOAEL) exposures in dog, the most sensitive species. The human exposures in healthy adult subjects after multiple doses of 300 mg QD for 14 days exceeded the 39-week NOAEL in dog by 1.4-fold. The effect of a high fat meal was evaluated in Study M20-015 and results indicate there was no appreciable food effect on A-1684909 C_{max} or AUC, but food prolonged the median time to maximal A-1684909 plasma concentration (2.5 to 6 hours). In an investigation of the effects of a strong CYP3A4 inhibitor, A-1684909 C_{max} and AUC were increased by 2.3- and 8.5-fold, respectively. In an investigation of the perpetrator effects of ABBV-CLS-7262 on sensitive CYP2C9 and CYP2C19 substrates, ABBV-CLS-7262 did not increase the C_{max} or AUC of probe CYP2C9 and CYP2C19 sensitive substrates. Samples of cerebrospinal fluid (CSF) drawn at steady state in the multiple dose part of Study M20-015 showed dose-proportional mean (SD) concentrations of A-1684909 of 2.4 (0.47) ng/mL and 6.3 (3.0) ng/mL in the 150 mg and 300 mg dose cohorts, respectively. The mean dose-normalized concentration of A-1684909 in CSF across both dose cohorts was 0.019 ng/mL/mg ABBV-CLS-7262.

Preliminary PK data are available from Study M24-192. Following oral dosing of ABBV-CLS-7262 300 mg QD, the C_{max} and AUC_t of digoxin increased by 1.27- and 1.26-fold respectively, and the C_{max} and AUC_t of rosuvastatin increased by 2.25- and 1.85-fold, respectively. Therefore, BCRP is inhibited following administration of ABBV-CLS-7262, and P-gp is not significantly inhibited at doses up to 300 mg QD.

Positron emission tomography was used to investigate drug-target binding *in vivo* in cynomolgus macaque non-human primates (NHPs). Pre-dosing with differing amounts of A-1684909 allowed successful characterization of the relationship between A-1684909 plasma exposure and eIF2B occupancy in the brain. The plasma concentration of A-1684909 that was associated with 95% occupancy of eIF2B in the brain grey matter was 12.92 ng/mL in NHP; equivalent to 39.75 ng/mL in human after accounting for interspecies differences in plasma protein binding. Drug-

target binding in human is currently being investigated in ongoing study M23-471; human binding data are not yet available.

The totality of evidence from nonclinical toxicology and human studies to date suggests that ABBV-CLS-7262 is generally safe and well-tolerated. No efficacy studies in participants with ALS have been conducted to date using ABBV-CLS-7262.

Refer to the Investigator's Brochure for additional information on ABBV-CLS-7262.

1.2 ABBV-CLS-7262 Therapeutic Rationale

ABBV-CLS-7262 drug product consists of film-coated granules, to be administered orally on a QD schedule. The doses selected for this study are based on the totality of available evidence: *in vitro* TDP-43 stress granule dissolution data and an optic nerve crush mouse model of ISR-dependent acute neuronal injury to predict efficacious doses in patients with ALS, PK data from Study M20-015 (healthy subjects) to support adequate CSF exposure at the selected doses, and PET data in NHPs to support adequate (>95%) target occupancy at the selected doses. The planned doses of 120 mg and 240 mg are anticipated to be safe and well-tolerated based on the totality of safety data from human clinical studies in healthy subjects and participants with ALS to date.

The study population will include participants with both sporadic and familial forms of ALS.

ABBV-CLS-7262 is an investigational product (IP), which based on *in vitro* and *in vivo* evidence is hypothesized to benefit patients with ALS via attenuation of a chronic ISR, restoration of protein synthesis, and dissolution of TDP-43-containing stress granules in nervous system tissue. In addition to the proposed therapeutic rationale for the sporadic form of ALS, it is hypothesized that the mechanism of action of ABBV-CLS-7262 suppresses Repeat Associated Non-AUG (RAN) translation in C9orf72 mutation carriers and resultant production of dipeptide repeats (DPRs), potentially affording a unique benefit to this patient population. The encouraging nonclinical results, along with the favorable safety and tolerability profile in human studies to date, support testing the therapeutic hypothesis that ABBV-CLS-7262 may slow disease progression in people with ALS.

2. OBJECTIVES

2.1 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 dosing of ABBV-CLS-7262 QD.

Exploratory Objectives:

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

2.2 Study Endpoints

RCT Database Lock: Last Participant Completes Week 24

Primary Efficacy Endpoint:

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

Secondary Efficacy Endpoints:

- Change from baseline to Week 24 in function as assessed by 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 upper limb muscle strength as measured isometrically using hand-held dynamometry (HHD) and grip strength.
- Change from baseline to Week 24 in serum NfL.

- Change from baseline to Week 24 in activities of daily living (ADL) as assessed by the ALSAQ-40 ADL/independence domain score

Safety Endpoints:

- Treatment-emergent adverse and serious adverse events.
- Clinical laboratory tests, vital signs, and ECG parameters.
- Treatment-emergent suicidal ideation and suicidal behavior.

Pharmacokinetics Endpoint:

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

Exploratory Endpoints:

- Change from baseline to Week 24 in ALSFRS-R domain scores.
- Change from baseline to Week 24 in lower limb and combined upper and lower limb muscle strength (HHD).
- Changes from baseline to Week 24 in biofluid biomarkers of neurodegeneration, ALS disease, and the ISR pathway.
- Changes from baseline to Week 24 in patient-reported outcomes including the ALSAQ-40 total score and domain scores (physical mobility, eating and drinking, communication, and emotional reactions) and CNS-BFS.
- Change from baseline to Week 24 in ALS disease severity based on King's Staging.
- Change from baseline to Week 24 in ROADS.
- Changes from baseline to Week 24 in quantitative voice characteristics.
- 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.

ATE Database Lock: Last Participant Completes ATE Week 52 or Discontinues from the Study

Efficacy Endpoints:

- Combined Assessment of Function and Survival (CAFS) from baseline to ATE Week 52.
- Change from baseline to ATE Week 52 in function as assessed by ALSFRS-R total score.
- Change from baseline to ATE Week 52 in respiratory function as assessed by slow vital capacity (SVC).
- Overall survival defined as death or death equivalent through to the end of the ATE period (per section 3.3).

- Changes from baseline to ATE Week 52 in activities of daily living (ADL) as assessed by the ALSAQ-40 ADL/independence domain score.

Safety Endpoints:

- Treatment-emergent adverse and serious adverse events.
- Clinical laboratory tests, vital signs, and ECG parameters.
- Treatment-emergent suicidal ideation and suicidal behavior.

Exploratory Endpoints:

- Change from baseline to ATE Week 52 in function assessed by ALSFRS-R domain scores
- Change from baseline through to the end of the ATE Period (per section 3.3) in function (ALSFRS-R total score and domain scores).
- Change from baseline to ATE Week 52 in upper limb, lower limb, and combined upper and lower limb muscle strength (HHD) and grip strength.
- Changes from baseline to ATE Week 52 in biofluid biomarkers of neurodegeneration, ALS disease, and the ISR pathway.
- Changes from baseline to ATE Week 52 in patient-reported outcomes including the ALSAQ-40 total score and domain scores (physical mobility, eating and drinking, communication, and emotional reactions) and CNS-BFS.
- Change from baseline to ATE Week 52 in ALS disease severity based on King's Staging.
- Change from baseline to ATE Week 52 in ROADS.
- Changes from baseline to ATE Week 52 in quantitative voice characteristics.

2.3 Study Comparisons

- The primary comparison of interest is between the ABBV-CLS-7262 120 mg dose group and the shared concurrent placebo group when evaluating primary and secondary endpoints in the RCT data set.
- The primary comparison of interest in ATE is between ABBV-CLS-7262 120 mg RCT/ ABBV-CLS-7262 120 mg ATE vs. placebo RCT/ ABBV-CLS-7262 120 mg ATE based on combined RCT and ATE data sets.
- Comparisons involving the ABBV-CLS-7262 240 mg dose group and comparisons other than the primary comparison of interest are exploratory for both RCT and ATE data sets.
- Dose-dependent contrasts are of primary interest for pharmacokinetic endpoints in RCT.

Detailed comparisons will be defined in the R-SAP.

3. RSA DESIGN

This study is a multi-center, randomized, placebo-controlled trial, testing active doses of ABBV-CLS-7262 (120 mg and 240 mg), given orally once daily versus placebo. A total of approximately 300 participants will be randomized. to ABBV-CLS-7262 120 mg, ABBV-CLS-7262 240 mg, or placebo.

3.1 Scientific Rationale for RSA Design

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

3.2 End of Participation Definition

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

If a participant initiates active treatment with IP in the ATE period, he or she is considered to have completed his or her participation in the ATE period of the Regimen if all planned ATE period visits, including the last visit or the last scheduled procedure shown in the SOA, have been completed. Participants may continue to receive investigational drug in the ATE beyond Week 52, until results from the placebo-controlled period of the study are available, as applicable.

3.3 End of Regimen Definition

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

The end of the ATE period in a Regimen occurs when all participants who have received active treatment with IP in the ATE period have completed their participation in the ATE period as defined in section 3.2.

4. RSA ENROLLMENT

4.1 Number of Study Participants

Approximately 300 participants will be randomized for this Regimen.

4.2 Inclusion and Exclusion Criteria

To be randomized to a Regimen, participants must meet the Master Protocol eligibility criteria. In addition, participants meeting all of the following inclusion and none of the exclusion criteria will be allowed to enroll in this Regimen:

4.2.1 RSA Inclusion Criteria

There are no additional RSA Inclusion Criteria from those described in the Master Protocol.

4.2.2 RSA Exclusion Criteria

1. Use of any moderate or strong CYP3A4 inhibitor or inducer within 10 days or 5 half-lives (whichever is longer) prior to Baseline (Table 1).
2. Use of any BCRP sensitive substrates with narrow therapeutic index as classified by the risk level "X" in the Lexicomp® drug interaction database (e.g., pazopanib, rimegepant, topotecan, and rosuvastatin ≥40 mg) within 10 days or 5 half-lives (whichever is longer) prior to Baseline (Table 2).
3. Any clinically significant ECG abnormalities, including QT interval corrected for heart rate using Fridericia's correction formula (QTcF) of > 450 msec for males or > 470 msec for females at Master Protocol Screening.
4. Abnormal adrenal function, defined as confirmed abnormal random cortisol (<5 µg/dL) or ACTH (>2x upper limit of normal) at Regimen Specific Screening.
    a. Participants may undergo repeat cortisol and ACTH testing once, in order to establish normal adrenal function. If repeat cortisol and ACTH testing is abnormal, at the Investigator's discretion, the participant may undergo cosyntropin stimulation testing to establish normal adrenal function to meet eligibility criteria.

4.3 Treatment Assignment Procedures

Each participant who meets all eligibility criteria for the Regimen will be randomized to receive ABBV-CLS-7262 120 mg, ABBV-CLS-7262 240 mg, or placebo QD for approximately 24 weeks of placebo-controlled treatment and will continue on to the ATE period for approximately

52 weeks with the possibility of extending participation until the results of the placebo-controlled portion of the trial are available and a decision has been made about future clinical development.

4.4 Active Treatment Extension Eligibility

Participants who complete the 24-week placebo-controlled period will participate in the ATE unless consent is withdrawn. Participants in the 120 mg and 240 mg active treatment groups will continue to receive the same assigned dose for the ATE period. Participants in the placebo group will be assigned to active treatment with 120 mg ABBV-CLS-7262 for the ATE period. The ATE will remain blinded to dose level and original placebo-controlled treatment assignment for sites, investigators, and participants.

5. INVESTIGATIONAL PRODUCT

5.1 Investigational Product Manufacturer

IP will be provided by Calico. ABBV-CLS-7262 granules and matching placebo granules are manufactured by AbbVie, Inc. under Good Manufacturing Practice (GMP).

5.2 Labeling, Packaging, and Resupply

ABBV-CLS-7262 granules and matching placebo granules are packaged in a foil-lined sachet. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will satisfy GMP Annex 13 requirements for labelling. All IP (i.e., sachet and kits) will be labelled with double-blind labels for the duration of the study. In the double-blind placebo-controlled period, the IP will be double-blinded to the sponsor, the regimen industry partner, sites, investigators, and participants. Unblinding for the sponsor and the regimen industry partner may occur after the database lock at the end of the double-blinded period. In the ATE period, IP will continue to be blinded to dose level and original placebo-controlled treatment assignment for sites, investigators, and participants, and each participant will be receiving active treatment with either 120 mg or 240 mg ABBV-CLS-7262.

Administration and supply of IP for each arm throughout the entire duration of the study (both the placebo-controlled period and the ATE period) will be as follows:

- ABBV-CLS-7262 120 mg: One sachet of 120 mg ABBV-CLS-7262 and one matching placebo sachet QD
- ABBV-CLS-7262 240 mg: Two sachets of 120 mg ABBV-CLS-7262 QD
- Placebo: Two placebo sachets QD

IP will be supplied by the Regimen industry partner or designated representative. No IP will be shipped to a site until a site is activated to begin enrolling participants in this Regimen.

5.3 Acquisition, Storage, and Preparation

ABBV-CLS-7262 is a small molecule prodrug that is converted *in vivo* to the pharmacologically active compound A-1684909. Matching placebo is identical to ABBV-CLS-7262 but contains no active ingredient. ABBV-CLS-7262 and matching placebo granules are packaged in foil-lined sachets. Two sachet types will be utilized in this study, active (containing 120 mg ABBV-CLS-7262) and matching placebo. Sachets will be blinded to both dose level and treatment randomization.

	Investigational Product Active	Investigational Product Placebo
Investigational Product Name	ABBV-CLS-7262	Placebo
Active Ingredient	ABBV-CLS-7262 (oral prodrug of A-1684909)	Not applicable
Mode or Route of Administration	Oral	Oral
Dosage Form	Film-coated granules	Film-coated granules
Sachet Dosage Strength	120 mg	Not applicable
Dose Level	120 mg = 1 sachet (plus 1 placebo sachet) and 240 mg = 2 sachets	Not applicable
Frequency of Administration	Once daily	Once daily
Storage Conditions	Store between 2° and 25°C (36° and 77°F). Protect from moisture and freezing.	Store between 2° and 25°C (36° and 77°F). Protect from moisture and freezing.

IP is to be stored between 2°C and 25°C (36°F and 77°F). The participant will be advised to keep all IP in a cool, dry place that is away from moisture and out of direct sunlight. Verbal and written instructions for proper storage, handling, and administration of the IP will be given to the participant and will include instructions to contact the study site immediately if they experience problems with the IP and/or administration. Site storage conditions should be monitored by the site personnel and reviewed by the study monitor during site visits.

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

IP will be administered in the clinic on all in-clinic visit days. Therefore, participants must not take their dose of IP until they arrive in the clinic. All other doses of IP will be administered by the participant/caregiver at home. All doses are to be administered once daily; additional details are provided in the regimen-specific Manual of Procedures. The IP may be administered with or without food, and may be mixed with apple sauce or yogurt. If the participant's disease progresses such that they cannot swallow the IP dose, administration of the IP through alternative methods should be discussed with the Medical Monitor (e.g., for consultation on

administration through an appropriate gastrostomy tube [G-tube], if necessary). Duration of treatment will be 24 weeks in the placebo-controlled period and approximately 52 weeks in the ATE period.

5.5 Justification for Dosage

The primary dose selected for this study (120 mg) is based on the totality of available evidence: *in vitro* TDP-43 stress granule dissolution data and an optic nerve crush mouse model of ISR-dependent acute neuronal injury to predict an efficacious exposure in patients with ALS, PK data from Study M20-015 (healthy subjects) to support adequate CSF exposure at the selected dose, and PET data in NHPs to support adequate (>95%) target occupancy in the brain at the selected dose. PK modeling and simulation project that a dosage regimen of ABBV-CLS-7262 120 mg QD will provide sustained plasma trough concentrations greater than 40 ng/mL (the efficacious exposure threshold predicted by *in vitro* and *in vivo* data) in more than 95% of participants with ALS. Please see Section 1.1 for additional details.

The exploratory dose selected for this study (240 mg) intends to provide (1) supportive safety data and (2) exploratory dose- and exposure-response data. Non-clinical toxicology studies support dosing at 120 mg and 240 mg QD (refer to ABBV-CLS-7262 IB for details). Doses up to 300 mg QD have been well-tolerated in healthy subjects for up to 14 consecutive days, and doses up to 280 mg QD have been well-tolerated in participants with ALS in the ongoing Phase 1b Study M20-405.

5.6 Dosage Changes

There is not an option for dose reduction for this Regimen because of the drug packaging and supply. If a participant experiences a serious treatment-emergent AE that is deemed by the investigator as having a reasonable possibility of being related to IP and leads to suspension of IP, the Investigator may elect to rechallenge with IP in consultation with the Medical Monitor. Additional attempts for rechallenge beyond the first attempt should also be discussed with the Medical Monitor.

5.7 Participant Compliance

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

Participants should be reminded of the proper administration, storage, and handling of IP at each clinic visit to maintain optimal compliance with the treatment. For ongoing assessment of

compliance, participants should bring all unused sachets to each clinic visit. Inventory of all unused sachets that the participant has not taken will be recorded on the Drug Accountability Log by the responsible study personnel. Reported compliance outside of 80 – 120% should be discussed with the Medical Monitor. Discontinuation of IP treatment for significant noncompliance is at the SI's discretion. This decision, if made, should be noted in the Study Treatment Exposure Log.

5.8 Overdose

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

- Overdose of the investigational product, where 'overdose' is defined as consuming more than three times the assigned dose amount within a 24-hour period or consuming the investigational product with a strong CYP3A4 inhibitor.
- Suspected abuse/misuse of the investigational product.
- Inadvertent or accidental exposure to the investigational product.
- Medication error involving IP (with or without participant exposure to the investigational product, e.g., name confusion).

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

5.9 Prohibited Medications

After enrollment, medication to treat treatment emergent illness(es) is generally permitted; however, the following therapies are expressly prohibited as described below:

- Use of any moderate or strong CYP3A4 inhibitor or inducer within 10 days or 5 half-lives (whichever is longer) prior to Baseline and throughout the study (including, but not limited to, medications listed in Table 1).
- Use of any BCRP sensitive substrates with narrow therapeutic index as classified by the Risk level 'X' in the Lexi-Comp® Drug interaction database within 10 days or 5 half-lives (whichever is longer) prior to Baseline and throughout the study (limited to medications listed in Table 2).

Moderate or strong CYP3A4 inhibitors or inducers are excluded on the basis that CYP3A4 is the major metabolizing enzyme of the pharmacologically active form of ABBV-CLS-7262 (A-1684909). In healthy adult subjects (Study M20-015), when ABBV-CLS-7262 was administered with multiple doses of itraconazole, a strong CYP3A4 inhibitor, the geometric mean C_{max} and AUC_{inf} of A-1684909 were increased by 2.3- and 8.5-fold, respectively.

Sensitive substrates of BCRP with narrow therapeutic index are excluded on the basis that BCRP is inhibited following multiple doses of ABBV-CLS-7262 300 mg QD (Study M24-192). Absorption of sensitive substrates of BCRP may be increased up to approximately 2-fold when taken concomitantly. While sensitive substrates of BCRP with narrow therapeutic index are prohibited (Table 2), other sensitive substrates of BCRP that do not possess a narrow therapeutic index should be used with caution (Table 3).

If a prohibited concomitant medication is required (e.g., in medically urgent situations), an appropriate wash-out period for ABBV-CLS-7262 should be discussed on a case-by-case basis with the Medical Monitor.

If moderate or strong CYP3A4 **inducer** (Table 1) administration is required, no specific washout of ABBV-CLS-7262 is required before the first dose of the required concomitant medication, but ABBV-CLS-7262 administration should be suspended.

If moderate or strong CYP3A4 **inhibitors** (Table 2), or BRCP sensitive substrates with a narrow therapeutic index (Table 3) need to be administered and no contact with the Medical Monitor can be established, the recommended time between the last dose of ABBV-CLS-7262 and the first dose of the required concomitant medication administration is 16 hours.

If a prohibited concomitant medication is administered and IP is suspended, approval from the Medical Monitor is required prior to IP being restarted. Administration of any prohibited medications during the study period should be recorded as a minor protocol deviation.

Table 1 Moderate and Strong CYP3A4 Inducers

Moderate CYP3A4 Inducers	Strong CYP3A4 Inducers
Bosentan Efavirenz Etravirine Lurasidone Modafinil Nafcillin	Avasimibe Carbamazepine Phenytoin Rifampin St. John's Wort

NOTE: This is not a comprehensive list. Concomitant use of Relyvrio™ (sodium phenylbutyrate plus tauroursodeoxycholic acid [TUDCA]) is not exclusionary (see Master Protocol for guidelines on the use of Relyvrio™ during the trial).
Source: Sychev DA, Ashraf GM, Svistunov AA, et al. The cytochrome P450 isoenzyme and some new opportunities for the prediction of negative drug interaction in vivo. *Drug Des Devel Ther*. 2018;12:1147-56.

Table 2 Moderate and Strong CYP3A4 Inhibitors

Moderate CYP3A4 Inhibitors	Strong CYP3A4 Inhibitors
Aprepitant Ciprofloxacin Darunavir Diltiazem Erythromycin Fluconazole Fosamprenavir Grapefruit juice (normal concentration) Imatinib Verapamil	Clarithromycin Conivaptan Grapefruit juice (high concentration) Itraconazole Ketoconazole Lopinavir Nefazodone Posaconazole Ritonavir (taken alone or in combination, e.g., PAXLOVID™) Saquinavir Telaprevir Telithromycin Voriconazole

NOTE: This is not a comprehensive list.
Source: Sychev DA, Ashraf GM, Svistunov AA, et al. The cytochrome P450 isoenzyme and some new opportunities for the prediction of negative drug interaction in vivo. *Drug Des Devel Ther*. 2018;12:1147-56.

Table 3 BCRP Sensitive Substrates with Narrow Therapeutic Index

BCRP Sensitive Substrates with Narrow Therapeutic Index
Pazopanib Rimegepant Topotecan Rosuvastatin ≥40 mg

Source: Lexicomp® drug interaction database

While not excluded, some medications should be used with caution while a participant is in the study. When taken together with ABBV-CLS-7262, the prescriber should monitor for increased effect or toxicity to BCRP sensitive substrates with risk level 'C' or 'D' in the Lexicomp® drug interaction database including those medications listed in Table 4:

Table 4 BCRP Sensitive Substrates Subject to Clinical Monitoring

BCRP Sensitive Substrates	
D: Consider therapy modification	C: Monitor therapy
Alpelisib Berotralstat Cladribine Mitoxantrone Ubrogepant Rosuvastatin >5 mg and < 40 mg	Glecaprevir and Pibrentasvir Rosuvastatin ≤5 mg Sulfasalazine Talazoparib

Any medication (prescription, non-prescription), vaccine, or therapy that is taken by or administered to the participant during the course of the study must be recorded in the eCRF.

5.10 ABBV-CLS-7262 Regimen-Specific Clinical Safety and Laboratory Tests

For details on preclinical safety, toxicology, clinical safety and PK (effects in humans) for ABBV-CLS-7262 please refer to the ABBV-CLS-7262 Investigator's Brochure.

Hormone Assessments

Based on findings in animals, the study will include specific hormonal assessments (see below) as part of the laboratory panel.

These will include:

- Adrenocorticotrophic hormone (ACTH)
- Cortisol
- Testosterone (total) *(males only)*
- Luteinizing hormone (LH) *(males only)*
- Thyroid panel (TSH, free T4, T3)

Management of Abnormal Cortisol and ACTH

A cosyntropin stimulation test may be performed in the event a participant experiences a Screening, Baseline, or post-Baseline value of:

- Confirmed (by repeat testing, as applicable) basal cortisol <5 µg/dL or
- Confirmed (by repeat testing, as applicable) ACTH >2 × upper limit of normal

If a participant has a normal response to cosyntropin stimulation test, the participant should continue in the study per protocol; otherwise, the participant should discontinue IP. Normal response to cosyntropin stimulation test is a minimum cortisol concentration of 18 µg/dL after intravenous (IV) cosyntropin injection.

If a participant has an abnormal response to cosyntropin stimulation test, the following recommendations below should be followed:
• If during Regimen Specific Screening, subject will be considered a screen failure
• If post-Baseline, suspend the IP
• Refer to an endocrinologist for evaluation and follow up.

Digestive Enzyme Assessments

Based on findings in animals, the study will include specific laboratory chemistry assessments including serum lipase and amylase for all participants.

Management of Abnormal Lipase

If a participant experiences a Screening, Baseline, or post-Baseline value of lipase > 3 x upper limit of normal with or without signs and symptoms, please contact the Medical Monitoring team for instructions on next steps.

Additional Laboratory Tests
Coagulation parameters (Prothrombin time, International normalized ratio, Activated partial thromboplastin time) will be collected for all participants in consideration of the lumbar puncture procedure.

Clinically significant laboratory abnormalities are those that are identified as such by the Investigator. The following factors may contribute to clinical significance if the observed laboratory abnormality:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of IP
- Has accompanying or inducing symptoms or signs
- Is otherwise judged by the Investigator as clinically significant

Menstrual Cycle Questionnaire

A menstrual cycle questionnaire will be collected for women of childbearing potential during each visit. This menstrual cycle questionnaire will capture the days of menstruation, along with information about the quality of menstrual flow. The menstrual cycle questionnaire will be completed throughout the entirety of the study and assessed by a qualified healthcare provider. Changes from baseline that are clinically significant or abnormal per Investigators judgement should be recorded as adverse events. Additional information about assessment of the menstrual cycle questionnaire is detailed in the regimen-specific MOP.

6. REGIMEN SCHEDULE

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

- ALSAQ-40
- CNS Bulbar Function Scale
- ROADS
- Additional clinical safety laboratory assessments (i.e., amylase, lipase)
- Additional vital sign assessments (i.e., pulse oximetry)
- Hormone safety laboratory assessments
- Blood samples for PK analysis
- Coagulation laboratory assessments in advance of lumbar puncture
- Menstrual cycle questionnaire for women of childbearing potential
- Blood RNA collection
- Voice recording
- Smartphone application installation and removal

Cardiac monitoring will be more frequent in the Regimen than specified in the Master protocol.

The Regimen will expand the analyses of biomarkers from collections of plasma/serum and urine from those that are pre-specified in the Master protocol.

The Regimen will have scheduled CSF sampling by lumbar puncture at baseline and Week 24, and optional CSF sampling at ATE Week 28 and ATE Week 52. If CSF is not attempted at baseline or Week 24 visits (refer to sections 6.1 and 6.7), a minor protocol deviation will be recorded. If Baseline CSF collection is attempted but unsuccessful, the Week 24 CSF collection should still be attempted.

Modifications to Regimen Schedule

Designated visits in the SOA (i.e., Week 4, Week 8, and Week 16) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic, disability, or other medically necessary reason. If an in-clinic visit is conducted remotely for disability or a medically necessary reason, the next scheduled in-clinic visit must occur in-person unless otherwise approved by the Medical Monitor.

If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP.

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

- Voice Recording
- ROADS
- Menstrual cycle questionnaire for women of child-bearing potential

Details on performing assessments and dispensing IP during remote visits are described in the MOP.

6.1 Regimen Screening Visit

This visit will take place up to 41 Days prior to Baseline (Day 0). The following procedures will be performed for the regimen schedule:

- Hormone Assessments
    - Hormone Assessments include ACTH, Cortisol, Testosterone (males only), LH (males only), and Thyroid panel (TSH, free T4, T3)
    - NOTE: Central laboratory turnaround time for hormone assessment results may take several days. The Baseline Visit should not be scheduled until after the results are received.

6.2 Baseline Visit

This visit will take place on Day 0. All baseline assessments are to be collected prior to administration of the first dose of IP. The following procedures will be performed for the regimen schedule:

- ALSAQ-40
- ROADS
- CNS Bulbar Function Scale
- 12-lead ECG
- Menstrual cycle questionnaire (for women of childbearing potential)
- Collection of blood and urine samples [pre-dose]
    - Plasma/serum for biomarker analyses
    - Collect urine for biomarker analyses

    - Collect blood RNA
- Lumbar puncture for CSF collection
    - Lumbar puncture may occur up to one week prior to Baseline Visit.
- Install smartphone app
- Voice recording
- Dispense investigational product (IP)
- Administer first dose of IP in clinic *after* all Baseline procedures have been completed
- Review instructions for proper dosing and IP administration
- Remind participant to bring any unused IP to the next visit

6.3 Week 2 Telephone Visit

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

- Perform IP compliance (remind of the importance of compliance)
- Remind participant to bring any unused IP to the next visit
- Review of Concomitant Medications and Adverse Events

6.4 Week 4 and 8 Visits

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

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

- CNS Bulbar Function Scale [Week 8 only]
- ROADS [Week 8 only]
- 12-Lead ECG [Week 8 only]
- Menstrual cycle questionnaire (for women of childbearing potential)
- Collection of blood and urine samples [pre-dose]
    - Hormone safety laboratory tests [Week 4 only]
    - Collect plasma/serum for biomarker analyses [Week 8 only]
    - Collect urine for biomarker analyses [Week 8 only]
    - Collect blood RNA [Week 8 only]
    - Blood sample for PK analysis
- Voice recording
- Dispense IP

- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)
- Remind participant to bring any unused IP to the next visit

6.5 Week 12 Telephone Visit

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

- Perform IP compliance (remind of the importance of compliance)
- Remind participant to bring any unused IP to the next visit
- Review of Concomitant Medications and Adverse Events

6.6 Week 16 Visit

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

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

- ROADS
- CNS Bulbar Function Scale
- 12-Lead ECG
- Menstrual cycle questionnaire (for women of childbearing potential)
- Collection of blood and urine samples [pre-dose]
  - Hormone safety laboratory tests
  - Coagulation laboratory tests
  - Collect plasma/serum for biomarker analyses
  - Collect urine for biomarker analyses
  - Blood sample for PK analysis
- Voice Recording
- Dispense IP
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)
- Remind participant to bring any unused IP to the next visit

6.7 Week 20 Telephone Visit

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

- Perform IP compliance (remind of the importance of compliance)
- Remind participant to bring any unused IP to the next visit
- Review of Concomitant Medications and Adverse Events

6.8 Week 24 Visit or Early Termination Visit

Participants should be instructed to hold IP on the day of the study visit. Investigational product should not be taken until after study visit procedures are complete. Participants not continuing into ATE should not take IP at this visit.

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

- ALSAQ-40
- ROADS
- CNS Bulbar Function Scale
- 12-Lead ECG
- Menstrual cycle questionnaire (for women of childbearing potential)
- Collection of blood and urine samples [pre-dose]
    - Hormone safety laboratory tests
    - Collect plasma/serum for biomarker analyses
    - Collect urine for biomarker analyses
    - Collect blood RNA
    - Blood sample for PK analysis
- Lumbar puncture for CSF collection
    - Lumbar puncture may occur up to one week prior to the Week 24 visit, and should be completed prior to dispensing or administration of any ATE IP.
- Voice recording
- Uninstall smartphone app
- Dispense IP (**Drug is only dispensed at this visit if the participant is continuing in the ATE**)
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)
- Remind participant to bring any unused IP to the next visit (only if continuing in ATE)

6.9 Follow-Up Safety Call

Participants will have a Follow-Up Safety Call 28 + 3 days after their last dose of IP. Participants who continue into ATE will not complete the follow up safety call during placebo-controlled phase.

The following procedures will be performed:

- Review of Concomitant Medications and Adverse Events

6.10 Process for Early Terminations

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

The in-person Early Termination Visit should be scheduled as soon as possible after a participant decides to early terminate. If the participant early terminates during the placebo-controlled portion of the Regimen, all assessments that are collected at the Week 24 in-clinic visit should be conducted. The Follow-Up Safety Call should be completed approximately 28 days after the last dose of IP. If a participant is unable to be seen in-person, safety assessments and others that can be done remotely should be performed.

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

If a participant decides to discontinue IP, but will be followed under the Intent To Treat (ITT) principle, an in-person Early Termination Visit and Follow-Up Safety Call are not necessary. Participants who are followed under ITT are eligible to continue into the ATE portion of the study, but are not eligible to re-initiate IP.

6.11 Active Treatment Extension

Participants who have completed the placebo-controlled portion of the trial will be eligible to continue in the ATE as outlined in the SOA.

Modifications to ATE Regimen Schedule

Designated visits in the SOA (i.e., ATE Week 4, ATE Week 8, ATE Week 16, ATE Week 28, ATE Week 40) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic, disability, or other medically necessary reason. If an in-clinic visit is conducted remotely for disability or a medically necessary reason, the next scheduled in-clinic visit must occur in-person unless otherwise approved by the Medical Monitor.

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

- ALSAQ-40 (as scheduled at ATE Week 28)
- ROADS (as scheduled at ATE Week 28)
- Menstrual cycle questionnaire for women of child-bearing potential

Details on performing assessments and dispensing IP during remote visits are described in the MOP.

6.11.1 ATE Week 2 Telephone Visit

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

- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Perform IP compliance (remind of the importance of compliance)
- Remind participant to bring any unused IP to the next visit

6.11.2 ATE Week 4 Visit

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

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

- Collect vital signs including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- Review concomitant medications

- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collection of blood samples [pre-dose]
    - Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
    - Hormone safety laboratory tests
- Menstrual cycle questionnaire (for women of child-bearing potential)
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)
- Remind participant to bring any unused IP to the next visit

6.11.3 ATE Week 8 Visit

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

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

- Collect vital signs including weight
- Perform SVC
- Muscle strength assessment
- Administer ALSFRS-R questionnaire
- CNS Bulbar Function Scale
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collection of blood and urine samples [pre-dose]
    - Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
    - Plasma/serum for biomarker analyses
    - Collect urine for biomarker analyses
    - Collect blood RNA
- Menstrual cycle questionnaire (for women of child-bearing potential)
- 12-Lead ECG
- Dispense IP to participant
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)
- Remind participant to bring any unused IP to the next visit

6.11.4 ATE Week 12 Telephone Visit

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

- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Perform IP compliance (remind of the importance of compliance)
- Remind participant to bring any unused IP to the next visit

6.11.5 ATE Week 16 Visit

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

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

- Collect vital signs including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- CNS Bulbar Function Scale
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collection of blood and urine samples [pre-dose]
    - Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
    - Hormone safety laboratory tests
    - Coagulation laboratory tests (if proceeding with optional CSF sampling at Week 24)
    - Collect blood and urine for biomarker analyses
- Menstrual cycle questionnaire (for women of child-bearing potential)
- 12-Lead ECG
- Dispense IP to participant
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous in-clinic visit)
- Remind participant to bring any unused IP to the next visit

6.11.6 ATE Week 20 Telephone Visit

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

- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Perform IP compliance (remind of the importance of compliance)
- Remind participant to bring any unused IP to the next visit

6.11.7 ATE Week 24 Telephone Visit

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

- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Perform IP compliance (remind of the importance of compliance)
- Remind participant to bring any unused IP to the next visit

6.11.8 ATE Week 28 Visit

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

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

- Collect vital signs including weight
- Perform SVC
- Muscle strength assessment
- Administer ALSFRS-R questionnaire
- ALSAQ-40
- CNS Bulbar Function Scale
- ROADS
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collection of blood and urine samples [pre-dose]

    - Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
    - Hormone safety laboratory tests
    - Plasma/serum for biomarker analyses
    - Collect blood and urine for biomarker analyses
    - Collect blood RNA
- Menstrual cycle questionnaire (for women of childbearing potential)
- 12-Lead ECG
- Lumbar puncture for CSF collection (optional)
    - Lumbar puncture may occur up to one week prior to the ATE Week 28 Visit.
- Dispense IP to participant
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)
- Remind participant to bring any unused IP to the next visit

6.11.9 ATE Week 40 Visit

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

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

- Collect vital signs including weight
- Perform SVC
- Administer ALSFRS-R questionnaire
- CNS Bulbar Function Scale
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collection of blood and urine samples [pre-dose]
    - Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
    - Coagulation laboratory tests
- Menstrual cycle questionnaire (for women of childbearing potential)
- 12-Lead ECG
- Dispense IP to participant
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)

- Remind participant to bring any unused IP to the next visit

6.11.10 ATE Week 52 Visit

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

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

- Collect vital signs including weight
- Perform SVC
- Muscle strength assessment
- Administer ALSFRS-R questionnaire
- ALSAQ-40
- CNS Bulbar Function Scale
- ROADS
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collection of blood and urine samples [pre-dose]
    - Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
    - Hormone safety laboratory tests
    - Plasma/serum for biomarker analyses
    - Collect blood and urine for biomarker analyses
    - Collect blood RNA
- Menstrual cycle questionnaire (for women of childbearing potential)
- 12-Lead ECG
- Lumbar puncture for CSF collection (optional)
    - Lumbar puncture may occur up to one week prior to the ATE Week 52 Visit.
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)
- Vital status determination

If the results of the placebo-controlled period are not available and a decision about future development has not been made:

- Dispense IP to participant; inform of next visit to occur in 12 weeks

6.11.11 Ongoing Extension Visit

For applicable participants who consent to continue in the ATE period after completing the assessments at ATE Week 52, the Ongoing Extension Visit will take place in-person approximately every 12 weeks (84 ±7 days) thereafter, until the results of the placebo-controlled period of the study are available and a decision has been made about future development. At each of these visits, the following procedures will be performed:

- Collect vital signs including weight
- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collection of blood and urine samples [pre-dose]
    - Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
    - Hormone safety laboratory tests
- Menstrual cycle questionnaire (for women of childbearing potential)
- 12-Lead ECG
- Perform IP compliance (remind of the importance of compliance, count number of unused sachets remaining in participant's supply from the previous clinic visit)

If the results of the placebo-controlled period are not available and a decision about future development has not been made:

- Dispense IP to participant; inform of next visit to occur in 12 weeks

6.11.12 Follow-Up Safety Call in ATE

Participants will have a Follow-Up Safety Call 28 + 3 days after their last dose of IP.

The following procedures will be performed:

- Assess and document AEs

6.11.13 Process for Early Terminations in ATE

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

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

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

7. OUTCOME MEASURES AND ASSESSMENTS

7.1 Voice Analysis

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

7.2 ALSAQ-40

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

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers or study staff can also help, if needed but should only assist in transferring the participant's responses to the form, and should not provide any assistance with determining answers.

7.3 Center for Neurologic Study Bulbar Function Scale

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

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers or study staff can also help, if needed, but should only assist in transferring the participant's responses to the form, and should not provide any assistance with determining answers.

7.4 King's Clinical Staging System

The King's ALS Clinical Staging System measures the clinical progression of ALS. The King's Clinical Staging will be derived from the ALSFRS-R items (Balendra et al 2014). It is

hierarchical and is not therefore a functional scale. There is a correlation between the natural course of the disease and that of the King's ALS Clinical Staging System since the majority of ALS patients progress from one stage to the next during the course of their disease. The King's ALS Clinical Staging System consists of 5 disease stages. The 3 first stages are based upon the number of El Escorial central nervous system regions involved in the disease (bulbar, cervical, thoracic, lumbar), measured by weakness, wasting, spasticity, dysphagia, or dysarthria. Grading an ALS patient Stage 1 means that there is 1 territory with functional signs, Stage 2 corresponds to the involvement of a second region and Stage 3 means three anatomical regions are functionally affected by the motor neuron degenerative process. Stage 4 implies the presence of prognostic criteria referring to the presence of nutritional failure (Stage 4A) or respiratory failure (Stage 4B). Nutritional failure is defined by the requirement for gastrostomy and respiratory failure is defined by the requirement for noninvasive ventilation based upon the National Institute for Clinical Excellence Motor Neuron Disease Guidelines (Roche et al 2012). The last stage, Stage 5, corresponds to death (Roche et al 2012).

7.5 ROADS

The Rasch-Built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS) is a patient reported outcome of function (Fournier et al 2020). It is a 28-question validated, linear, self-report questionnaire created with Rasch modeling. Rasch modeling uses statistical principles to enhance scale validity (Vanhoutte et al 2015). Prior to analysis, ROADS raw scores are converted to normed whole numbers. The scale and conversion table are publicly available (https://med.emory.edu/departments/neurology/programs_centers/emory_als_center/_documents/roads.pdf).

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers or study staff can also help, if needed but should only assist in transferring the participant's responses to the form, and should not provide any assistance with determining answers.

7.6 Vital Status Determination

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

We may also ascertain vital status at later time points as described in section 8.15 of the Master Protocol. An outside vendor will be used to ascertain death or date of last known alive for all randomized participants by using publicly available data sources. When prompted by the Coordination Center, sites will provide demographic information (e.g. participant name, date of birth, last known address) to the vendor using a secure, encrypted portal.

8. BIOFLUID COLLECTION

8.1 Blood Samples for Pharmacokinetic Analysis

One blood sample for PK analysis will be drawn at each clinic visit during the placebo-controlled period of the study. Samples must be drawn within 2 hours prior to the dosing time in the clinic (pre-dose), but preferably within 15 minutes prior to dosing. The actual date and time (24-hour clock time) of each sample must be recorded. Sampling outside of this guideline, or sampling after IP administration will be recorded as a minor protocol deviation.

Instructions for the collection, handling, and disposal of biological samples are provided in the laboratory manual.

Concentrations of A-1684909 in plasma will be determined using validated liquid chromatography-tandem mass spectrometry methods by AbbVie.

Concentrations of A-1684909 in plasma will be tabulated and summarized by visit and dose level.

Concentrations of possible metabolite(s) of A-1684909 in plasma or serum may be assayed using validated or non-validated method(s), and measured, tabulated, and summarized in the same way.

Additional analysis may be performed if useful in the interpretation of the data.

8.2 Blood Biomarker Sample Collection

Blood samples will be collected for exploratory biomarker analyses, which may include (but are not limited to) quantification of secreted factors related to drug mechanism of action or ALS disease progression (e.g., NfL), as well as proteomic and metabolomic analyses.

Samples must be drawn within 2 hours prior to the dosing time in the clinic (pre-dose). The actual date and time (24-hour clock time) of each sample must be recorded. Sampling outside of this guideline, or sampling after IP administration will be recorded as a protocol deviation.

8.3 RNA Sample Collection

Blood samples for ribonucleic acid (RNA) extraction will be collected to evaluate gene expression related to the ISR and ALS as well as for transcriptomic analyses.

Samples must be drawn within 2 hours prior to the dosing time in the clinic (pre-dose). The actual date and time (24-hour clock time) of each sample must be recorded. Sampling outside of this guideline, or sampling after IP administration will be recorded as a minor protocol deviation.

8.4 Urine Biomarker Sample Collection

Urine samples will be collected for quantifying biomarkers related to the ISR and to ALS disease progression.

Samples must be collected within 2 hours prior to the dosing time in the clinic (pre-dose). The actual date and time (24-hour clock time) of each sample must be recorded. Sampling outside of this guideline, or sampling after IP administration will be recorded as a protocol deviation.

8.5 Lumbar Puncture and CSF Biomarker Sample Collection

Lumbar puncture in this RSA is scheduled for all participants who the Investigator has determined are medically appropriate candidates for the procedure. The Investigator should review the participant's medical history, anatomy, and laboratory values (PT, PTT, INR, platelets), to make this determination.

Lumbar puncture must be performed by the Investigator or another licensed practitioner with experience and training in performing LPs. If the Investigator determines fluoroscopy-guided or ultrasound-guided lumbar puncture is preferred it may be used at the discretion of the local clinical site staff if it is standard of care for the institution.

CSF samples will be collected at Baseline and Week 24. Optional lumbar puncture for CSF collection can be performed during the ATE period at Week 28, Week 52 and in the case of early termination. CSF samples will be collected for analysis of biomarkers indicative of the ISR status in the CNS as well as of biomarker related to ALS disease progression. CSF samples may also be used for genetic biomarker research.

9. REGIMEN-SPECIFIC STATISTICAL CONSIDERATIONS

Two ABBV-CLS-7262 doses (120 mg and 240 mg) are included for this regimen. The analysis specified in the M-SAP will be applied to each ABBV-CLS-7262 dose group against placebo and the analysis of 120 mg dose group against placebo is the primary contrast. A detailed analysis plan specific to ABBV-CLS-7262 is defined in the regimen-specific statistical analysis plan (R-SAP).

9.1 Deviations from the Default Master Protocol Trial Design

Regimen F (ABBV-CLS-7262) follows the recommended design, primary endpoint, and primary analysis described in the ALS Master Protocol Recommended Statistical Analysis, Design and Simulation Report (MPRDR, Appendix I of the Master Statistical Analysis Plan [SAP] v3.0, dated Feb 06, 2023) with two minor differences specified in the Regimen F Statistical Analysis, Design and Simulation Report (Appendix I to the RGF R-SAP): 1) two active arms are included at ABBV-CLS-7262 dosages of 120 and 240 mg QD with the primary analysis being performed on the 120 mg QD dose, referred to as the anchor dose, and 2) the Efficacy Concurrent Controls analysis set that includes only concurrent controls is used for primary analysis.

Specifics regarding the design, primary endpoint, primary analysis, and interim analyses for Regimen F (ABBV-CLS-7262) are provided in Appendix I to the RGF R-SAP where there are differences from the MPRDR.

The design for Regimen F (ABBV-CLS-7262) 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. A total of approximately 225 participants will be randomized to active treatment and approximately 75 participants will be randomized to placebo, providing an overall ratio of active:placebo of 3:1. The primary analysis population includes all participants randomized to Regimen F (ABBV-CLS-7262), and will additionally include concurrent shared controls as defined in RGF R-SAP Appendix I.

No interim analysis is planned to stop the regimen early for efficacy. Interim analysis for futility is planned with minor differences from what is presented in the MPRDR to accommodate multiple doses and are specified in Appendix I to the RGF R-SAP.

Key secondary and other efficacy endpoints for the ABBV-CLS-7262 Regimen following RCT and ATE database locks are presented in Section 2.2. More detailed information and the control of Type 1 error rate can be found in the R-SAP.

9.2 Sharing of Controls from other Regimens

Concurrent shared controls for the primary analysis in Regimen F (ABBV-CLS-7262) are defined in the R-SAP.

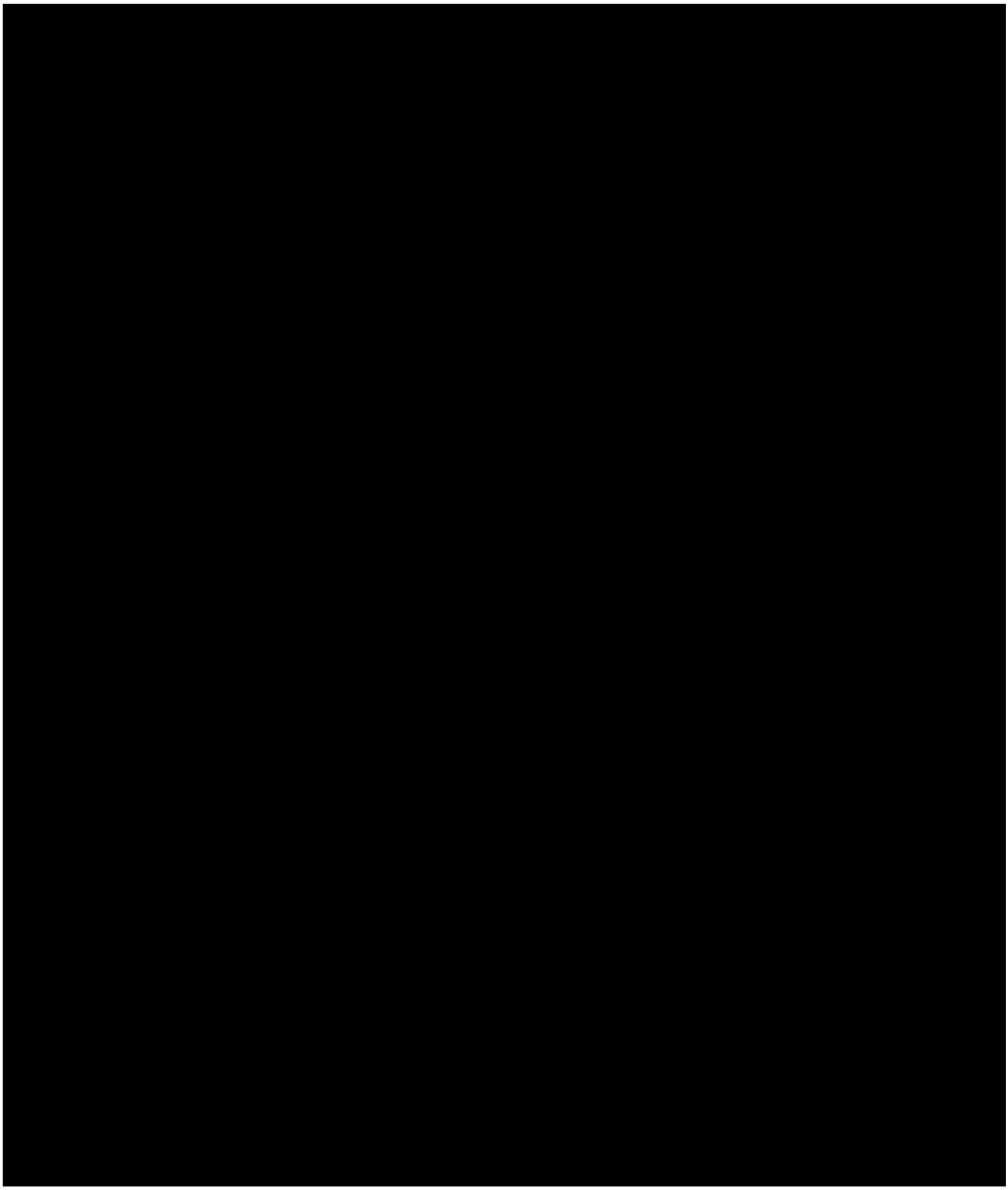
Additional supportive/sensitivity analyses with other shared control populations (both concurrent and non-concurrent controls from other past or actively enrolling regimens in the Platform) may be performed. Definitions of these analysis populations with additional details are provided in Appendix I to the RGF R-SAP.

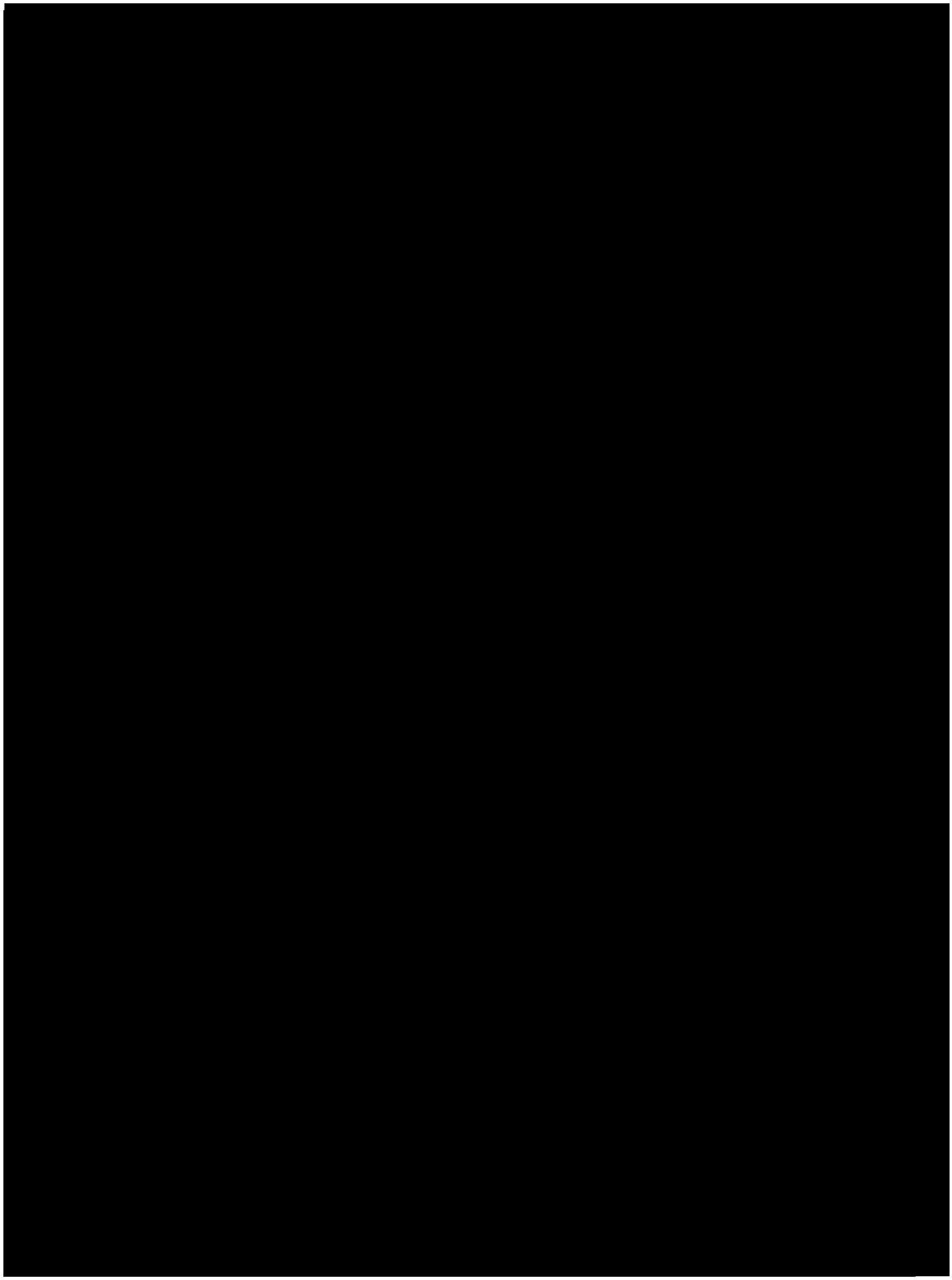
9.3 Regimen Specific Operating Characteristics

Clinical trial simulations customized for Regimen F (ABBV-CLS-7262) are provided in Appendix I to the R-SAP. The primary comparison of the anchor dose (120 mg) to placebo control is powered at approximately 80% to detect a 30% slowing in disease progression (common to mortality and function decline). The type I error of the regimen is 2.5% assuming no systematic differences in rates of progression across regimens contributing to the concurrent controls. More details are provided in Appendix I to the R-SAP.

Given the sample size of 165 participants on 120 mg (RCT treatment)/120 mg (ATE treatment) and 75 participants on placebo (RCT treatment)/120 mg (ATE treatment), the study will also have approximately 85% power on the CAFS at ATE Week 52, and approximately 80% power for survival through to the end of the ATE period. Such calculations were performed with assumptions for an 18-month survival rate of 70% for placebo RCT/120 mg ATE group and an 86% survival rate for 120 mg RCT /120 mg ATE group at ATE Week 52, with a 12-month accrual period (totaling a maximum study duration of 30 months) and 13% drop-out rate due to non-mortality reasons. The treatment difference for change from baseline in ALSFRS-R total score was assumed 20% slowing of disease progression rate versus delayed initiation of ABBV-CLS-7262 with a standard deviation of 9.0 at ATE Week 52 (accounting for a partial cross-over effect). An exponential distribution was assumed for power assessment of CAFS and survival endpoints. These tests for power analysis were done with a two-sided significance level of 0.05.

APPENDIX I: THE ALSAQ-40





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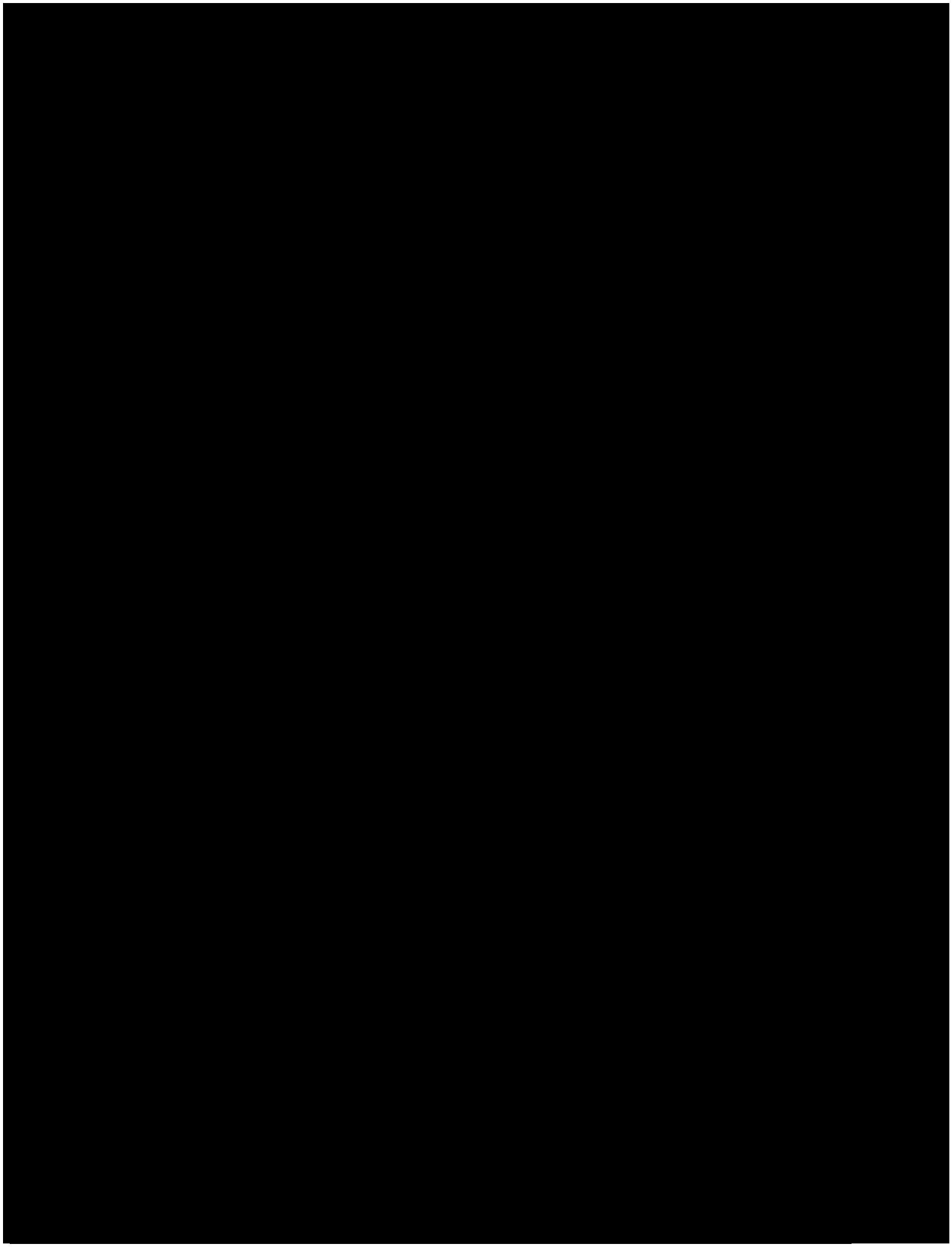

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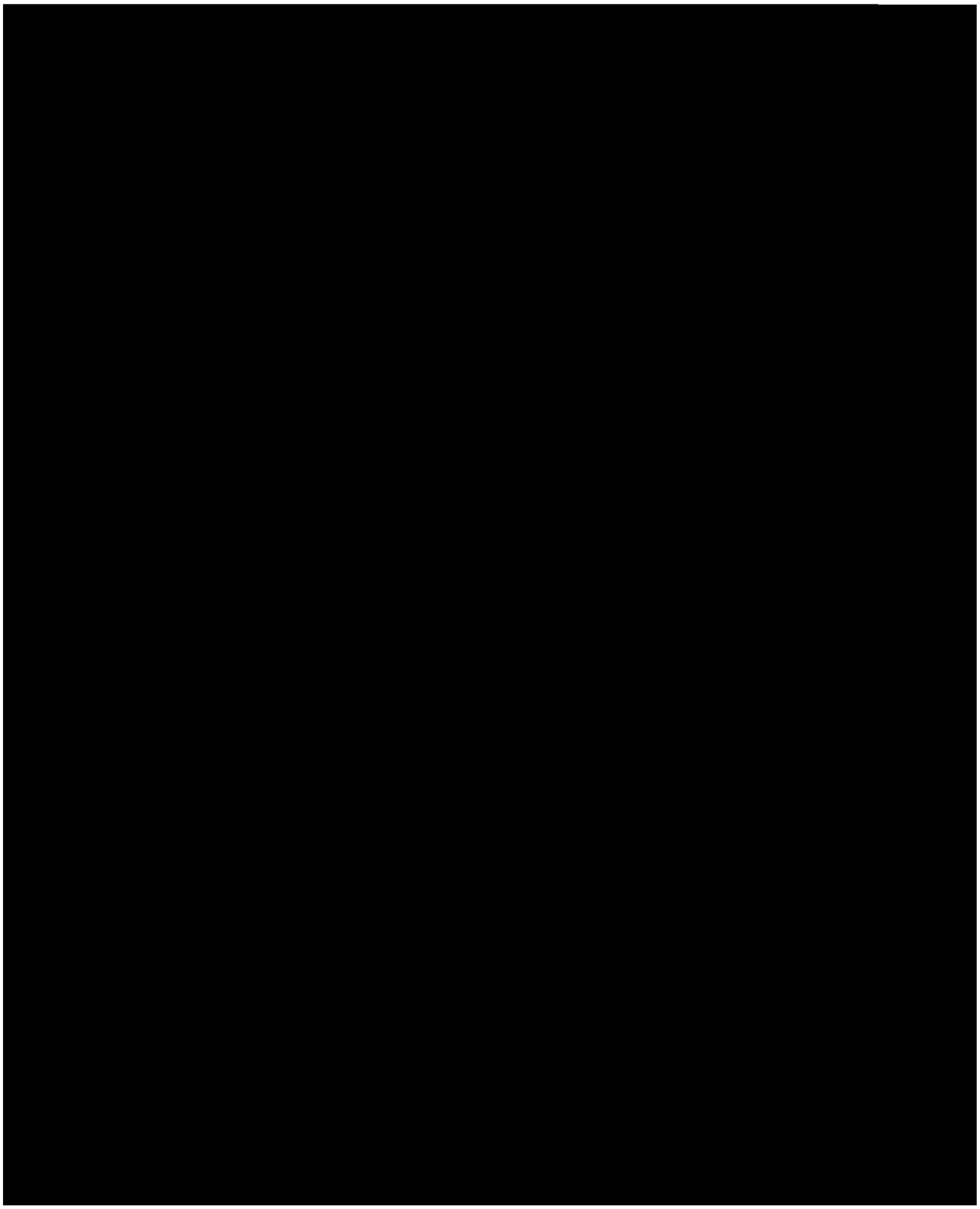

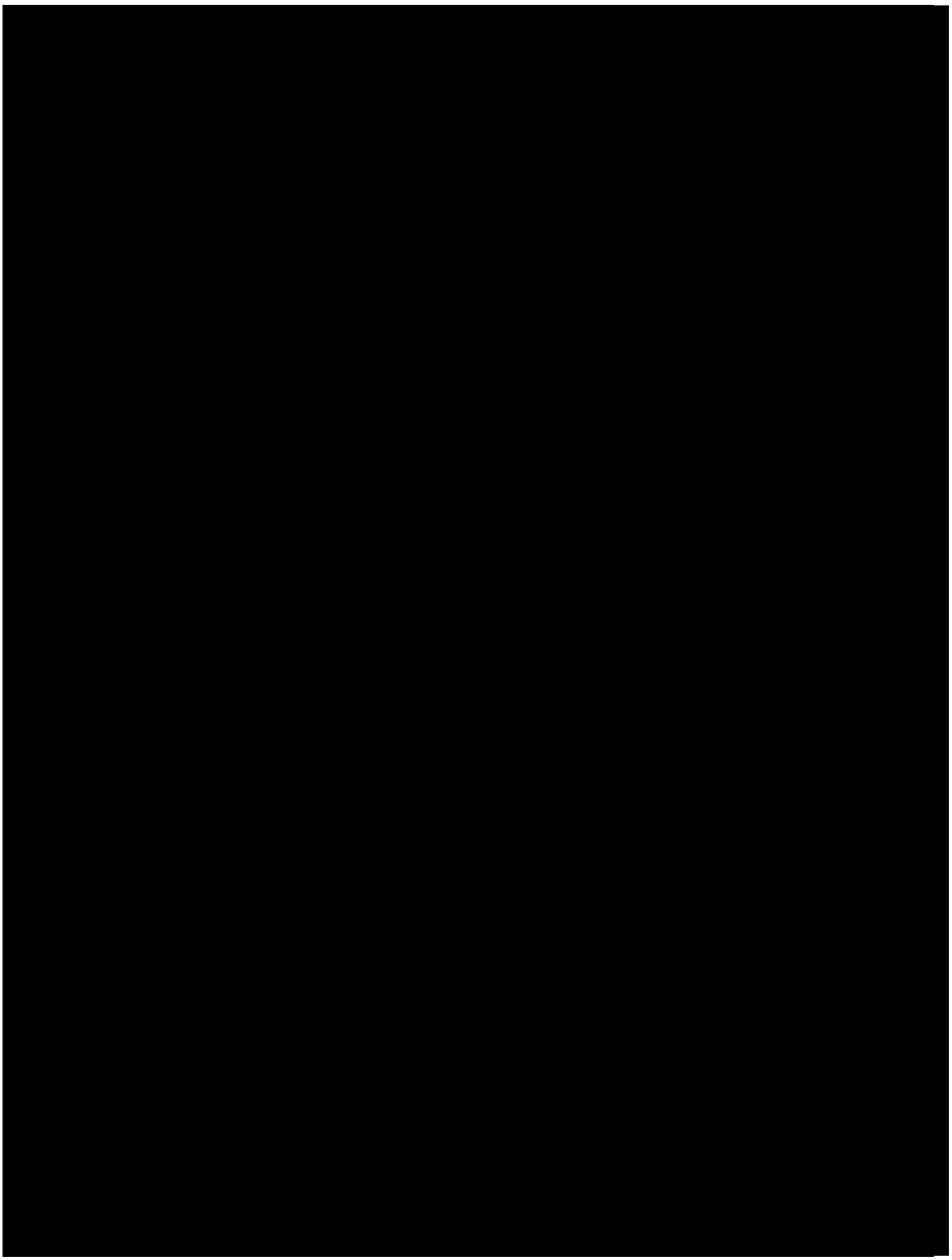

APPENDIX II: THE BULBAR FUNCTION SCALE (CNS-BFS)

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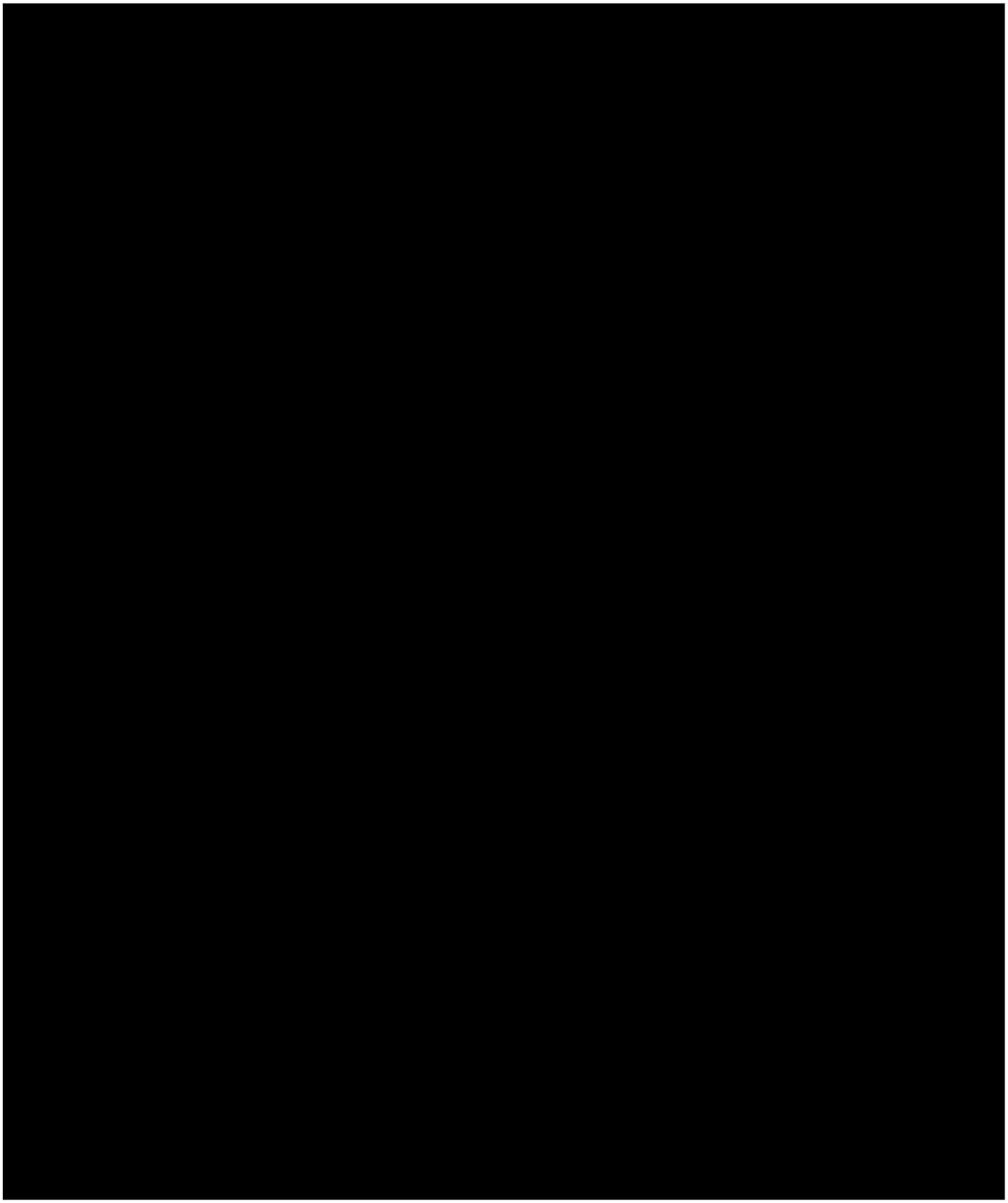
APPENDIX III: RASCH OVERALL ALS DISABILITY SCALE (ROADS)



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