HEALEY ALS Platform Trial - Regimen D Pridopidine

NCT04615923

Document Date: 15 Jul 2021

REGIMEN-SPECIFIC APPENDIX D

FOR PRIDOPIDINE

Regimen-Specific Appendix Date: 15 July 2021

Version Number: *2.0*

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SIGNATURE PAGE

I have read the attached Regimen-Specific Appendix (RSA) entitled, "Regimen D: Pridopidine", dated July 15, 2021 (Version 2.0) 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

AE	Adverse Event
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
BID	Twice Daily
Cmax	Maximum Concentration
CNS	Central Nervous System
CNS-BFS	Center for Neurologic Study Bulbar Function Scale
CNS-LS	Center for Neurologic Study Lability Scale
CYP	Cytochrome P450
dHMN	Distal Hereditary Motor Neuronopathies
DSMB	Data and Safety Monitoring Board
ECG	Electro Cardiogram
EM	Extensive Metabolizer
EoS	End of Study
ERK	Extracellular-signal-regulated kinase
FVC	Forced Vital Capacity
GFR	Glomerular Filtration Rate
HD	Huntington's Disease
HDPE	High-density polyethylene
HHD	Hand Held Dynamometry
IP	Investigational Product
iPSC	Induced pluripotent stem cells
ITT	Intent to Treat
MAM	Mitochondria-associated membrane
MATE1	Multi Drug and Toxin Extrusion Protein 1
MATE2-K	Multi Drug and Toxin Extrusion Protein 2-K
MN	Motor Neuron
MOP	Manual of Procedures
mHTT	Mutant Huntingtin
NMJ	Neuromuscular Junction
OLE	Open Label Extension
OCT1	Organic Cation Transporter 1
OCT2	Organic Cation Transporter 2
QD	Once Daily
PD-LID	Parkinson's Disease-Levodopa Induced Dyskinesias
PET	Positron emission tomography
PO	By Mouth
PPK	Population Pharmacokinetic Model
PM	Poor Metabolizer

PY	Participant-Years
QTcF	Fridericia-corrected QT
RSA	Regimen-Specific Appendix
S1R	Sigma-1 Receptor
SAE	Serious Adverse Event
SI	Site Investigator
SOA	Schedule of Activities
SVC	Slow Vital Capacity
TDD	Total Daily Dose

REGIMEN-SPECIFIC APPENDIX (RSA) SUMMARY

Regimen-Specific Appendix D
For pridopidine 45 mg oral capsule administered twice daily (BID) or its matching placebo.

Rationale and RSA Design
The proposed study is based on cumulative preclinical and clinical studies that demonstrate that pridopidine acts primarily as a Sigma-1 Receptor (S1R) agonist and demonstrates neuroprotective properties mediated by S1R. The purpose of this study is to evaluate the effect of pridopidine 45 mg BID on ALS functional decline, specifically bulbar, upper and lower limb, and respiratory function in participants with ALS.

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

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

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

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

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

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

Follow-up Duration
At the conclusion of the 24-week placebo-controlled treatment period of the study, all participants will either schedule a 28-day follow up phone call and end their participation in the regimen or have the option to receive pridopidine in the Open Label Extension (OLE) period of the study.

In the OLE, pridopidine will be provided by Prilenia Therapeutics, until the primary results of the 24 week double-blind portion of the study are available, or they terminate development of pridopidine for ALS.

Total Planned Trial Duration
For participants completing the placebo-controlled treatment period of the study, the planned amount of time for a participant in the trial is up to 34 weeks, or about 8 months. This duration assumes a 6-week screening window, a 24-week placebo-controlled treatment period, and a 4-

week safety follow-up period for those participants who do not enter the OLE period of the study. Participants will complete approximately 10 study visits during the placebo-controlled period of the study.

SCHEDULE OF ACTIVITIES – PLACEBO CONTROLLED PERIOD

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

Activity	Master Protocol or Regimen-Specific	Master Protocol Screening[1]	Regimen Specific Screening[1]	Base-line	Week 2	Week 4[14]	Week 8[19]	Week 12	Week 16[19]	Week 20	Week 24 or Early Term. Visit[14, 22]	Follow-Up Safety Call[11]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		-42 to -1 Days	-41 to 0 Day	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	28d ±3 days after last dose
Written Informed Consent[2]	**Master**	X	X									
Written Informed Consent - OLE	**Master**								X			
Inclusion/Exclusion Review	**Master**	X	X[3]									
ALS & Medical History	**Master**	X										
Demographics	**Master**	X										
Physical Examination	**Master**	X										
Neurological Exam	**Master**	X										
Vital Signs[4]	**Master**	X		X		X	X		X		X	
Slow Vital Capacity	**Master**	X[20]		X			X		X		X	
Home Spirometry	**Regimen**	X[20]		X			X		X		X	
Muscle Strength Assessment	**Master**			X			X		X		X	
ALSFRS-R	**Master**	X		X		X	X	X	X	X	X	
ALSAQ-40	**Regimen**			X							X	
CNS Bulbar Function Scale	**Regimen**			X			X		X		X	
CNS Lability Scale	**Regimen**			X			X		X		X	
12-Lead ECG	**Regimen**	X	X[15]	X[16]		X[16]					X[15, 16, 17]	
Clinical Safety Labs[5, 21]	**Master**	X		X		X	X		X		X	
Biomarker Blood Collection[21]	**Master**			X			X		X		X	

Activity	Master Protocol or Regimen-Specific	Master Protocol Screening[1]	Regimen Specific Screening[1]	Base-line	Week 2	Week 4[14]	Week 8[19]	Week 12	Week 16[19]	Week 20	Week 24 or Early Term. Visit[14, 22]	Follow-Up Safety Call[11]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		-42 to -1 Days	-41 to 0 Day	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	28d ±3 days after last dose
Plasma PK collection[21]	**Regimen**					X					X	
Biomarker Urine Collection	**Master**			X			X		X		X	
DNA Collection[7, 21] (optional)	**Master**			X								
CSF Collection (optional)	**Master**			X					X[13]			
Concomitant Medication Review	**Master**	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review[6]	**Master**	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	**Master**			X		X	X		X		X	
Install Smartphone App[23]	**Regimen**			X								
Voice Recording[9]	**Regimen**			X		X	X		X		X	
Uninstall Smartphone App	**Regimen**										X	
Randomization to Regimen	**Master**	X										
Randomization within Regimen	**Master**		X									
Administer/Dispense Investigational Product (IP)	**Master**			X[8]		X[18]	X		X		X[10,18]	
Drug Accountability/Compliance	**Master**				X[24]	X	X	X[24]	X	X[24]	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. The Regimen-Specific Screening Visit and Baseline Visit should be combined, if possible.
[2] During the Master Protocol Screening Visit, participants will be consented via the Platform Trial informed consent form (ICF). After a participant is randomized to a regimen, participants will be consented a second time via the regimen-specific ICF.
[3] At the Regimen Specific Screening Visit, participants will have regimen-specific eligibility criteria assessed.
[4] Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate and temperature. Height measured at Master Protocol Screening Visit only.
[5] Clinical safety labs include hematology (CBC with differential), complete chemistry panel, thyroid function and urinalysis. Serum pregnancy testing will occur in women of child-bearing potential at the Master Protocol Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy.

[6] Adverse events that occur after signing the master protocol consent form will be recorded.
[7] The DNA sample can be collected after Baseline Visit if a baseline sample is not obtained or the sample is not usable.
[8] Administer first dose of IP only after Baseline Visit procedures are completed, except for the post-dose ECG.
[9] In addition to study visits outlined in the SOA, participants will be asked to complete twice weekly voice recordings at home.
[10] Drug will only be dispensed at this visit if the participant continues in the OLE.
[11] Participants will only have a Follow-Up Safety Call at this time if they *do not* continue on in the OLE. Participants who continue into OLE will have a Follow-Up Safety Call after their last dose of IP during the OLE period.
[12] Vital status, defined as a determination of date of death or death equivalent or date last known alive, will be determined for each randomized participant at the end of the placebo-controlled portion of their follow-up (generally the Week 24 Visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant's last visit (LPLV) of the placebo-controlled portion of a given regimen. We may also ascertain vital status at later time points by using publicly available data sources as described in section 8.15 of the Master Protocol.
[13] If the CSF collection is unable to be performed for logistical reasons, such as scheduling, at the Week 16 Visit, it may be performed at the Week 24 Visit.
[14] If a participant's visit occurs in the morning, the participant should be instructed that the morning dose of study medication should not be taken, and the morning dose should be administered in-clinic 1-2 hours prior to the **POST-DOSE** ECG. If a participant's visit occurs in the afternoon, the participant should be instructed to take the morning dose immediately upon waking in the morning, and the second dose should be administered in-clinic 1-2 hours prior to the **POST-DOSE** ECG.
[15] At the regimen-specific Screening visit (and Week 24 for participants enrolling in OLE) , QTcF will be determined by the mean of three, 10-second recordings of a 12-Lead ECG (performed at least 1 minute a part) **BEFORE** IP administration. For participants on Nuedexta, the Nuedexta dose should be taken within 6 hours **BEFORE** the ECG, refer to the MOP for additional guidelines.
[16] At Baseline and Week 4 (and Week 24 for participants enrolling in OLE) QTcF will be determined by a single 10-second 12-lead ECG, 1-2 hours **AFTER** IP administration. If stopping or monitoring rules are met, refer to Section 4.4. For participants on Nuedexta, the Nuedexta dose should be taken within 6 hours **BEFORE** the ECG, refer to the MOP for additional guidelines.
[17] For participants that will **NOT** be enrolling into the OLE, QTcF will be determined by a single 10-second 12 lead ECG **BEFORE** administration of the IP. If stopping or monitoring rules are met, refer to Section 4.4. For participants on Nuedexta, the Nuedexta dose should be taken within 6 hours **BEFORE** the ECG, refer to the MOP for additional guidelines.
[18] IP must be administered at Week 4 (and Week 24 for participants enrolling into the OLE) 1-2 hours prior to the **POST-DOSE** ECG.
[19] Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic, or other reasons.
[20] If required due to pandemic-related restrictions, Forced Vital Capacity (FVC) performed by a Pulmonary Function Laboratory evaluator or with a study-approved home spirometer, or sustained phonation using a study approved method may be used for eligibility (Master Protocol Screening ONLY).
[21] All blood draws should occur after the ECG is collected, or at least 1 hour prior to the ECG.
[22] If participant's visit occurs in the morning, the participant should be instructed not to take the morning dose at home but rather in-clinic after the **PRE-DOSE** ECG.
If visit occurs in the afternoon, morning dose should be taken immediately upon waking in the morning and the second dose after the **PRE-DOSE** ECG.
[23] Two smartphone apps should be installed on the participant's phone, once to collect the voice recordings and one to collect home spirometry.
[24] Drug accountability will not be done at phone visits. A drug compliance check in should be held during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.

SCHEDULE OF ACTIVITIES – OPEN LABEL EXTENSION (OPTIONAL)

Activity	Master Protocol or Regimen Specific	Open Label Extension (Optional)[5]							
		Week 2	**Week 4[7]**	**Week 8[11]**	**Week 12**	**Week 16[11]**	**Week 20**	**Week 24 and Q12 Wks [6, 13]**	**Follow-up Safety Call[4,6]**
		Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	112 ±7 days	140 ±3 days	196 ±14 days	28 ±3 days after last dose
Vital Signs[1]	**Master**		X	X		X		X	
Slow Vital Capacity	**Master**		X	X		X		X	
Home Spirometry	**Regimen**		X	X		X		X	
ALSFRS-R	**Master**		X	X	X	X	X	X	
ALSAQ-40	**Regimen**							X	
CNS Bulbar Function Scale	**Regimen**			X		X		X	
CNS Lability Scale	**Regimen**			X		X		X	
12-Lead ECG	**Regimen**		X[8]					X[9,15]	
Clinical Safety Labs[2,12]	**Master**		X	X		X		X	
Biomarker Blood Collection[12]	**Master**					X		X[9]	
Biomarker Urine Collection	**Master**					X		X[9]	
Concomitant Medication Review	**Master**	X	X	X	X	X	X	X	
Adverse Event Review[3]	**Master**	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	**Master**		X	X		X		X	
Administer/Dispense	**Master**		X[10]	X		X		X[14]	

Investigational Product (IP)									
Drug Accountability/ Compliance	**Master**	X[16]	X	X	X[16]	X	X[16]	X	

[1] Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate and temperature. Height in cm measured at Master Protocol Screening Visit only.
[2] Clinical safety labs include hematology (CBC with differential), complete chemistry panel, thyroid function and urinalysis. Serum pregnancy testing will occur in women of child-bearing potential at the Master Protocol Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy.
[3] Adverse events that occur after signing the master protocol consent form will be recorded.
[4] Participants who continue into the OLE will have a Follow-Up Safety Call (as described in the body of this RSA) after their last dose of IP during the OLE period.
[5] The duration of the OLE will be at least 24 weeks.
[6] Participants who continue into the OLE and early terminate will be asked to complete an Early Termination Visit and Follow-Up Safety Call as described in Section 6.1.10..
[7] If a participant's visit occurs in the morning, the participant should be instructed that the morning dose of study medication should not be taken, and the morning dose should be administered in-clinic 1-2 hours prior to the **POST-DOSE** ECG. If a participant's visit occurs in the afternoon, the participant should be instructed to take the morning dose immediately upon waking in the morning, and the second dose should be administered in-clinic 1-2 hours prior to the **POST-DOSE** ECG.
[8] QTcF will be determined by a single 10-second 12-lead ECG 1-2 hours **AFTER** IP administration. If stopping or monitoring rules are met refer to Section 4.4. For participants on Nuedexta, the Nuedexta dose should be taken within 6 hours **BEFORE** the ECG, refer to the MOP for additional guidelines.
[9] Biomarker Blood Collection, Biomaker Urine Collection and all regimen-specific samples will occur at OLE Weeks 24 and 52 only.
[10] IP must be administered at 1-2 hours prior to the **POST-DOSE** ECG.
[11] Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic, or other reason.
[12] All blood draws should occur after the ECG, or at least one hour prior to the ECG.
[13] At Week 24 and Final OLE visit, if participant's visit occurs in the morning, the participant should be instructed not to take the morning dose at home but rather in-clinic after the **PRE-DOSE** ECG. If visit occurs in the afternoon, morning dose should be taken immediately upon waking in the morning and the second dose after the PRE_DOSE ECG.
[14] IP will not be dispensed at the participant's final visit.
[15] At Week 24 and Final OLE visit,, QTcF will be determined by a single 10-second 12-lead ECG **BEFORE** IP administration. If stopping or monitoring rules are met refer to Section 4.4. For participants on Nuedexta, the Nuedexta dose should be taken within 6 hours before this ECG.
[16] Drug accountability will not be done at phone visits. A drug compliance check in should be held during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.

1 INTRODUCTION REGIMEN D: PRIDOPIDINE

Regimen D: Pridopidine

1.1 Pridopidine Background Information

Pridopidine is an investigational small molecule that acts primarily as a Sigma-1 Receptor (S1R) agonist (Johnston, et al. 2019; Sahlholm et al. 2013). The S1R is a highly conserved transmembrane protein located at the endoplasmic reticulum (ER) and specifically enriched in the sub-regions contacting mitochondria (Mitochondria Associated Membranes, MAM). It acts as a ligand-activated chaperone that modulates diverse cellular processes, including calcium signaling, ion channel signaling and the ER stress response (Hayashi and Su 2005; Su et al. 2010). Importantly, S1R activation exerts neuroprotective effects, acting to stimulate brain repair and plasticity, by modulating pathways common to many neurodegenerative diseases (Francardo et al. 2014; Hyrskyluoto et al. 2013; Luedtke et al. 2012; Vagnerova et al. 2006). Loss of the S1R exacerbates disease onset and progression in preclinical models of ALS (Mavlyutov et al, 2010; Watanabe et al, 2016). Importantly, mutations leading to complete loss-of-function (LOF) in the S1R gene are associated with juvenile onset of ALS. However, missense mutations that impair the S1R protein, but still retain some normal function, are associated with an adult form of ALS, showing a dose response between function of the S1R and age of onset of ALS. (Al-Saif, Al-Mohanna, and Bohlega 2011; Izumi et al. 2018; Watanabe et al. 2016).

Pridopidine demonstrates neuroprotective properties mediated by the S1R in several in vivo and in vitro models of neurodegeneration, including models of ALS. In ALS $SOD1^{G93A}$ motor neurons (MNs), pridopidine increases MN survival, improves axonal transport, and restores neuromuscular junction (NMJ) synaptic activity. These effects are exquisitely mediated by the S1R, as a genetic deletion of the S1R gene abolishes the protective effects of pridopidine. In-vivo, pridopidine treatment of $SOD1^{G93A}$ mice reduces toxic protein aggregates, enhances MN innervation, and ameliorates muscle fiber wasting (Ionescu et al. 2019).

In Huntington Disease (HD) models, pridopidine demonstrates a robust and dose-dependent neuroprotective effect against mutant huntingtin-(mHTT)-induced cell death in human HD induced pluripotent stem cells (iPSCs) and mouse HD cortical neurons (Eddings et al. 2019). Furthermore, pridopidine restores mitochondrial function, spine density, and aberrant calcium signalling (Ryskamp et al. 2017), all known features of neurodegenerative disorders.

1.1.1. Overview of the Nonclinical Development Program

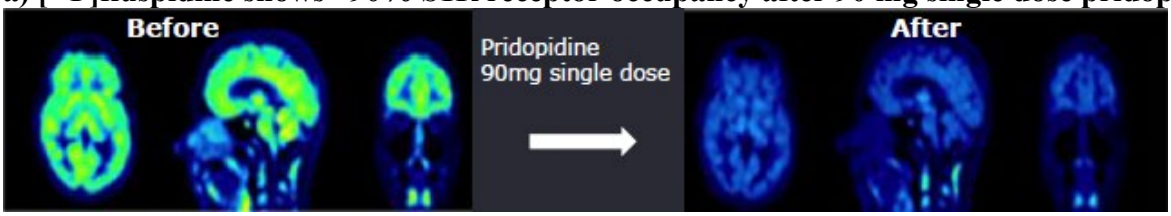
Pharmacology

The molecular target of pridopidine was assessed using *in-vitro* affinity binding assays to many central nervous system (CNS) receptor targets. These studies demonstrate that pridopidine has the highest affinity for the S1R, with low affinity for other receptors including the adrenergic α_{2C}, dopamine-D_3 and serotoninergic 5-HT_{1A} receptors (Johnston, et al. 2019; Sahlholm et al.

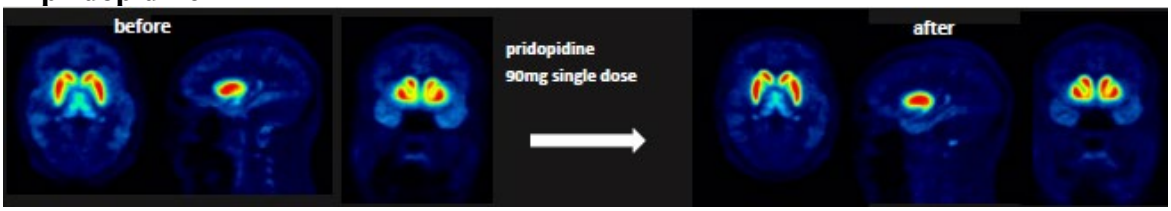
2013). Pridopidine has ~ 30-fold higher affinity towards the S1R vs D3Rs, and 100-500-fold higher affinity vs D2Rs. Selective binding of pridopidine to the S1R with no dopamine D2/D3R binding was confirmed using positron emission tomography (PET) imaging in rats (Sahlholm K, et al 2015), and in humans at 90 mg single dose (plasma exposure correlates to 45 mg BID at steady state) (Figure 1).

Figure 1: Pridopidine in vivo S1R Target Engagement in a PET Imaging Study in Humans

a) [^{18}F]fluspidine shows ~90% S1R receptor occupancy after 90 mg single dose pridopidine



b) [C^{11}]-fallypride shows ~3% D2R/D3R receptor occupancy after 90 mg single dose pridopidine



From: Grachev et al, EJNMMI, 2020

Representative PET images of a human brain showing complete 18F-Fluspidine (A) and [C^{11}]-fallypride (B) displacement after a single oral dose of 90 mg pridopidine (exposure correlates to 45 mg bid at steady state). **Before:** PET image 90 min after [^{18}F]-fluspidine or [C^{11}]- fallypride IV, without prior pridopidine administration (baseline). **After**: PET image 90 min after [^{18}F]-fluspidine or [C^{11}]-fallypride which was injected IV 2 hours post pridopidine oral administration. After 90 mg single-dose pridopidine, [^{18}F]-Fluspidine shows ~90% receptor occupancy and [C^{11}]-fallypride shows ~3% D2R/D3R occupancy.

Pharmacokinetics

The pharmacokinetic properties of pridopidine and its main non-active metabolite, TV-45065 [4-(3-(methylsulfonyl) phenyl) piperidine, previously named ACR30], have been investigated in several single- and repeat-dose studies in mice, rats, and dogs, as well as in single-dose studies in non-human primates. Studies using radiolabeled ^{14}C-pridopidine in both rats and dogs examined the absorption, distribution, and excretion of ^{14}C-pridopidine-related material, and investigated the metabolite profiles in whole blood, plasma and excreta. Plasma protein binding in-vitro was determined for pridopidine and its metabolite, TV-45065, as well as in-vitro and in-vivo binding of pridopidine to rodent brain tissue.

Pridopidine was shown to have high oral bioavailability in all species evaluated, with fast absorption. The pridopidine fraction that is bound to plasma proteins is relatively low in mouse, rat, rabbit, dog, monkey, and human, with 12% to 32% binding at 30 to 30000 ng/mL (human 26% to 32.2%). Pridopidine is primarily metabolized by cytochrome P450 (CYP 2D6) to one non-active metabolite, TV-45065, observed as the major metabolite in all species examined, validating the animal species used in the non-clinical studies conducted to characterize the safety

of pridopidine. At steady state, pridopidine is mainly excreted through the urine. In humans, the steady state plasma exposure of the metabolite is ~5% of the total drug exposure.

In-vitro, pridopidine shows no induction of CYP isoenzyme expression and does not cause inhibition of any tested CYP except for CYP2D6, in which metabolism-dependent inhibition was detected (auto-inhibition). Pridopidine is not actively transported by any of the tested transporters.

Similar to pridopidine, the metabolite TV-45065 was tested as an inhibitor or inducer of CYP, and only metabolism-dependent inhibition of CYP2D6 (at high concentrations) was observed.

Toxicology

The non-clinical safety profile of pridopidine has been evaluated in a battery of non-clinical studies, including safety pharmacology, genotoxicity, reproductive toxicity, and repeat-dose toxicity studies of up to 52 weeks. A battery of non-clinical abuse liability studies was also completed.

Pridopidine was not genotoxic in a standard battery of genotoxicity studies, including an in-vitro bacterial reverse mutation assay (Ames test), an in-vitro mouse lymphoma assay, and an in-vivo micronucleus assay in mice.

The principal adverse effects of pridopidine, observed at high doses in animals, were clinical signs of CNS toxicity including convulsions, tremors, recumbency, and hypo-activity.
In animal studies, there appears to be a relationship between exposure and convulsions. The maximum concentration in plasma (C_{max}) exposure causing convulsions started at about 6000 ng/mL in both rats and dogs, while no convulsions were observed at exposures below these levels in all studies. C_{max} exposure of 6000 ng/mL is ~9.7-fold higher than the anticipated mean peak plasma concentrations at 45 mg BID (618 ng/mL), the proposed dose for the ALS clinical trial.

In non-clinical abuse liability studies, including a physical dependence study in rats, drug discrimination studies in rats, and a self-administration study in non-human primates, pridopidine showed no propensity to produce physical dependence or gross behavioral changes, and was found to have a very low potential for abuse.

1.1.2. Overview of the Clinical Development Program

To date, 1,334 participants have received at least one dose of pridopidine across numerous clinical trials. Of these 1,334 participants, the large majority (74%, 987 participants) were exposed to a daily pridopidine dose of 45 mg BID, with the remaining participants exposed to a daily dose ranging between 10 mg to 112.5 mg BID. On a cumulative exposure level, approximately 1,300 participant-years of exposure to pridopidine have been accumulated.
The majority of participants exposed to pridopidine to date have been participants with HD.

To date, 13 studies have been conducted investigating the pharmacokinetics of pridopidine. Seven studies were used for the development of the population pharmacokinetic model (PPK), including phase 1 studies: ACR16C012, ACR16C013, ACR16C016, and ACR16C018; phase 2 studies: ACR16C009 (HART) and TV7820-CNS-20002 (PRIDE-HD); and a phase 3 study ACR16C008 (MermaiHD). Pridopidine steady-state pharmacokinetics are described by a 2-compartment linear model with first-order absorption. Of the covariates studied, only weight and participant CYP2D6 metabolizer status influenced apparent clearance.

Pridopidine has a relatively fast and almost complete absorption after oral administration, with individual Cmax occurring between 0.5 and 4 hours after dosing (the median time to maximum concentration in plasma [Tmax] is 1.25 to 2 hours). Food intake has no impact on the extent of absorption of pridopidine. After absorption, pridopidine is eliminated partly by urinary excretion and partly by hepatic metabolism (primarily via the CYP2D6 pathway), with a mean half-life (t½) of approximately 10 hours at steady-state. In extensive metabolizers (EMs), pridopidine is metabolized by CYP2D6 to 1 main metabolite (TV-45065). Conversely, poor metabolizers (PMs) depend on renal excretion as their main elimination pathway.

Prior to reaching steady-state pharmacokinetics, pridopidine is metabolized by CYP2D6 to one main inactive metabolite (TV-45065). However, since CYP2D6 undergoes auto-inhibition; the fraction of pridopidine that is metabolized by CYP2D6 decreases with multiple doses, renal elimination becomes a more important elimination pathway, and the fraction excreted unchanged increases. Steady state is reached after approximately 10 days.

Mild renal impairment (defined as glomerular filtration rate (GFR) of 60-89 mL/min/1.73 m^2) did not affect the steady-state pharmacokinetics of 45 mg of pridopidine once daily (QD). Participants with moderate renal impairment (defined as GFR of 30-59 mL/min/1.73 m^2) had 1.68-fold higher AUC and 1.26-fold higher Cmax values than matching healthy participants at steady state.

Studies in participants with hepatic impairment have not been performed, but PMs are expected to represent a worst-case scenario for hepatic impairment with minimal increase in pridopidine exposure (Cmax or AUC). In the PRIDE-HD study, no dose adjustment was implemented for PM participants, and this population was administered up to 112.5 mg BID with no difference in the safety profile. Therefore, no dose adjustments are proposed for participants with hepatic impairment.

The potential for drug-drug interactions with pridopidine is predicted to be very low, with the exception of co-administration of pridopidine with CYP2D6 substrates. Pridopidine is a CYP2D6 inhibitor, and increased exposures of co-administered CYP2D6 substrates are anticipated. Caution should be exercised with medications that are mainly eliminated via a CYP2D6-dependent pathway and have a narrow therapeutic index and/or have a concern related to QT prolongation.

Clinical Safety

All AEs across all clinical studies (22 studies) were combined into an integrated safety database. Since the majority of participants exposed to pridopidine to date have been on the 45 mg BID dosage regimen (74% of participants, 84% of the cumulative participant-years of exposure), AEs are presented for the following two groups:

(1) Pridopidine 45 mg BID - all participants who received pridopidine 45 mg BID at least one time but did not receive a dose higher than 45 mg BID
(2) Placebo - all participants in pridopidine clinical studies who did not receive a single dose of pridopidine

Due to the considerably different number of participant-years (PY) of exposure between the groups, an analysis of AE reporting rates corrected for participant-years of exposure was performed in addition to AE incidence.

The incidence and rate (events/participant years) of AEs in the pridopidine 45 mg BID group (n=981, participant years= 1091) and placebo group (n=338, participant years=148.8) was evaluated across the integrated safety analysis of the 22 trials.

The integrated analysis of safety data from the 22 pridopidine clinical studies, primarily conducted in Huntington Disease (HD) participants, indicated that the adverse events (AE) profile of the 45 mg BID dose is generally comparable with that of placebo. Pooled analysis suggests no increased risk of cardiac toxicity, exacerbation of psychiatric complications, or suicidality attributed to the 45 mg BID dose.

Over all in the integrated dataset, the rate of participants reporting at least 1 AE was similar between the placebo group (rate=2.35 events/participant year) and the pridopidine 45 mg BID group (rate =1.81 events/participant year). Most AEs for participants in both the placebo and pridopidine 45 mg BID groups were reported as mild or moderate in severity. Severe AEs occurred with a similar frequency across treatment groups.

Serious adverse events (SAEs) were observed across both active and placebo groups. There was a slight increase in the number of participants with SAEs in the active groups compared with the placebo group, but no dose-dependence was observed (detailed in the IB safety section).

AEs indicating Proarrhythmic Potential

Across the integrated safety database (22 trials), the rate (events/participant year) of AEs of QT prolongation was higher in the placebo group (rate=0.013 events/participant year) compared to the pridopidine 45 mg BID group (rate=0.005 events/participant year) (Table 1).

The 52-week placebo-controlled PRIDE-HD study included 5 treatment arms: placebo, pridopidine 45 mg BID, pridopidine 67.5 mg BID, pridopidine 90 mg BID, and pridopidine 112.5 mg BID. The AE data from this trial provides a more sensitive analysis of dose-dependency and is thus analyzed separately. The number of participant-years of exposure was similar in each of the treatment groups in this study; therefore, only tables of AE incidence were generated.

In the PRIDE-HD trial, there was a higher overall incidence of AE-reports of QT prolongation (unrelated to any other proarrhythmic event) in pridopidine-treated participants compared to placebo-treated participants:1.5% in pridopidine-treated participants vs 0% in placebo-treated participants. However, there was no evidence of dose-response (Table 2).

In accordance with the ICH E14 Guideline, Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, the safety database was analyzed for rates of clinical events indicating a proarrhythmic potential, and the rates observed in treated and control participants were compared. An analysis of the full safety database that includes all participants treated with at least one dose of pridopidine found no events of torsade de pointes following treatment with pridopidine at doses of up to 112.5 mg BID. One case of mild ventricular arrhythmia was reported.

Exposure-response analysis of QT Prolongation

The PRIDE-HD trial incorporated extensive electrocardiogram (ECG) monitoring and a pharmacokinetic (PK) sampling schedule that captured peak plasma concentrations over 52 weeks.

ECGs and PK data from the PRIDE-HD study resulted in a comprehensive exposure-response analysis, including data from >400 HD participants, treated with 5 doses of pridopidine (including placebo), for up to 1 year.

A concentration-dependent effect of pridopidine on the QTcF interval was observed with a slope of 0.012 ms per ng/mL (90% CI: 0.0109 to 0.0127 ms per ng/mL).
At the proposed dose of 45 mg BID, the predicted QT effect (ΔΔQTcF) in participants with HD was 6.6 ms (with an upper bound of the 90% confidence interval of 8 ms), which is not clinically meaningful.

In summary, in the PRIDE-HD study, QT prolongation was found to be an adverse drug reaction associated with the use of pridopidine. At 45 mg BID, the dose to be tested in the ALS trial, there is no clinical significance of QT prolongation.

Table 1 Clinical Events indicating Proarrhythmic Potential across Entire Safety Database

	Placebo		**Pridopidine 45 mg BID**	
	Incidence N=338	Rate PY = 148.8	Incidence N=981	Rate PY = 1091
QT Prolongation	2 (0.6%)	Rate = 0.013	5 (0.5%)	Rate = 0.005
Torsade de pointes	0	0	0	0
Sudden death	0	0	0	0
Ventricular arrhythmias	0	0	1 (0.1%)	Rate=0.0009
Ventricular tachycardia	0	0	0	0
Ventricular fibrillation	0	0	0	0
Ventricular flutter	0	0	0	0
Syncope	1 (0.3%)	Rate =0.007	16 (1.6%)	Rate =0.016

PY= participant year; rate is events/participant year

Table 2 Clinical Events indicating Proarrhythmic Potential in Placebo-Controlled Period of the PRIDE-HD Study

	PRIDE-HD					
	Placebo N=82	**45 mg BID N=81**	**67.5 mg BID N=82**	**90 mg BID N=81**	**112.5 mg BID N=82**	**All Pridopidine N=327**
QT Prolongation	0	2 (2.5%)	0	1 (1.2%)	2 (2.5%)	5 (1.5%)
Torsade de pointes	0	0	0	0	0	0
Sudden death	0	0	0	0	0	0
Ventricular arrhythmias	0	0	0	0	0	0
Ventricular tachycardia	0	0	0	0	0	0
Ventricular fibrillation	0	0	0	0	0	0
Ventricular flutter	0	0	0	0	0	0
Syncope	0	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	4 (1.2%)

In the PRIDE-HD study, there were no participants exhibiting QTcF>500 ms. Seven participants exhibited QTcF >480 ms (3 subjects in each of the 45 mg BID and 112.5 mg BID groups and one subject in the 90 mg BID group) and 4 participants exhibited change-from-baseline QTcF (ΔQTcF) >60 ms (1 subject each in the pridopidine 45 mg and pridopidine 90 mg BID groups and 2 subjects in the pridopidine 112.5 mg BID group) at any time point during the study.

1.2. Pridopidine Therapeutic Rationale

Target engagement in humans and prior evidence of clinical efficacy

The proposed dose for the HEALEY ALS Platform Trial Regimen D is 45 mg BID. At this dose, pridopidine shows near to complete occupancy of the S1R in human brains (>90% S1R occupancy) with negligible (~3%) binding to the D2/D3Rs, suggesting its dominant pharmacological effect at this dosage is mediated via the S1R.

The S1R regulates cellular signaling pathways that are commonly impaired in various neurodegenerative disorders, such as calcium signaling, mitochondrial function, and spine loss. Loss of function (LOF) mutations in S1Rs are associated with juvenile ALS and missense mutations with adult-onset ALS. LOF mutations are also associated with distal hereditary motor neuronopathies (dHMN). Pridopidine, via activation of the S1R, exerts neuroprotective properties in numerous preclinical models including ALS, HD, PD and AD and may, therefore, have therapeutic effects in ALS.

The PRIDE-HD study was a 52-week, double-blind, phase 2 trial to evaluate the efficacy and safety of pridopidine in participants with HD. Post-hoc analysis of data from PRIDE-HD demonstrated pridopidine 45 mg BID significantly maintained total functional capacity (TFC) in early HD participants at 52 weeks. (Reilmann, Olanow, et al. 2019)

TFC is the most widely accepted and validated tool for assessing disease stage and correlates with advancing pathology and disease progression (Shoulson and Fahn 1979; Marder et al. 2000). Decline in TFC parallels the decline in other measures, including motor, cognitive, neuropsychiatric, and functional assessments (Tabrizi et al. 2013; 2012; Dorsey et al. 2013). It has been used as an endpoint in more than ten other clinical trials of drugs seeking to demonstrate impact on HD progression, none of which were positive.

Pridopidine 45 mg BID also demonstrates a good safety profile. An integrated analysis of adverse events (AEs) was performed using a large safety database (over 1,300 participants) generated from 22 clinical studies with pridopidine. This analysis shows that the AE profile of pridopidine 45 mg BID is comparable to placebo. These results further suggest that there is no increased risk of psychiatric symptoms or cardiac toxicity with pridopidine 45 mg BID.
Taken together, compelling preclinical data and clinical data demonstrate that pridopidine 45 mg BID has:

(1) Robust and selective human in-vivo S1R target engagement (PET imaging)
(2) Neuroprotective effects in numerous preclinical models of neurodegeneration, including ALS, HD, PD and AD
(3) Significant effect on maintaining total functional capacity at 52 weeks in early HD participants in comparison to placebo in a double-blind study, and
(4) A favorable safety and tolerability profile

These, and the genetic link between the S1R and ALS, justify a study to test the clinical benefits of pridopidine in ALS.

Dosing Regimen

The proposed dose to be tested in the planned study is 45 mg twice daily (BID), taken in the morning and in the early afternoon (approximately 7 to 10 hours after the morning dose).

There will be a titration period leading up to the proposed dose whereby participants will initiate pridopidine at 45mg once daily (QD) and then increase to 45mg BID after 2 weeks.

2 STUDY OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective:

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

Secondary Efficacy Objective:

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

Safety Objective:

- To evaluate the safety of pridopidine in ALS patients.

Exploratory Efficacy Objective:

- To evaluate the effect of pridopidine on selected biomarkers and endpoints.

Primary Efficacy Endpoint:

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

Secondary Efficacy Endpoints:

- Change in bulbar function as measured by the ALSFRS-R bulbar subdomain (Q1-Q3) score among participants with bulbar dysfunction at baseline.
- Change in bulbar function as measured by the ALSFRS-R bulbar subdomain (Q1-Q3) score among all randomized participants.
- Change in speech as measured by the ALSFRS-R speech domain score (Q1) among all randomized participants.
- Change in respiratory function as measured by slow vital capacity (SVC).
- Change in bulbar function as measured by the ALSFRS-R bulbar subdomain (Q1-Q3) score among participants with rapid pre-baseline progression.
- Time to first evidence of bulbar dysfunction.
- Change in muscle strength as measured isometrically using hand-held dynamometry (HHD) and grip strength.
- Survival.

Safety Endpoints:

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

Exploratory Efficacy Endpoints:

- Changes in quantitative voice characteristics.
- Changes in biofluid biomarkers of neurodegeneration.
- Changes in patient reported outcomes (e.g. CNS-BFS, CNS-LS).
- Change in respiratory function as assessed by home spirometry.

3 RSA DESIGN

This study is a multi-center, randomized, placebo-controlled trial, testing active dose of pridopidine (45mg BID), given orally daily versus placebo. Participants will be randomized 3:1 active: placebo.

The study will consist of a screening/baseline visit, a 2-week double-blind, placebo-controlled up-titration period, a 22-week double-blind, full-dose, placebo-controlled treatment period, and a 28-day safety follow-up period (after the last dose of IP) for those participants who do not enter the Open Label Extension (OLE) period of the study.

After signing informed consent, participants will undergo screening assessments to determine eligibility and eligible participants will be randomly assigned in a 3:1 ratio to 1 of 2 study intervention groups:

- Treatment Arm 1 (active): pridopidine 45 mg orally (PO), BID (total daily dose of 90 mg after two week up-titration period at 45mg PO, QD)
- Treatment Arm 2 (control): matching placebo, PO BID

During the 2 week up-titration period (starting on Day 1), all participants will self-administer 1 capsule of study intervention PO once daily (QD) in the morning. In the full-dose treatment period (starting on Day 14) study intervention will be taken BID, in the morning and in the afternoon (approximately 7-10 hours apart). Participants who complete all scheduled visits will have the option of participating in the OLE period of the study.

Throughout the study, participants will be assessed through on-site clinic visits and telephone calls, as specified in the Schedule of Activities (SoA) table.

For participants who complete all scheduled visits, their final visit will be the Follow-Up Safety Call (28 days after the Week 24 clinic visit), unless participants continue on in the OLE. Participants who discontinue study intervention early will be encouraged to complete all other visits as scheduled for the full course of the study per ITT. For participants who withdraw early from the placebo-controlled period, an in-person Early Termination Visit and a Follow-up Safety Call should be conducted. At the Early Termination Visit the same procedures as described for the Week 24 visit should be conducted. At the Follow-up Safety Call, information on clinical status should be collected.

Participants who complete the full study regimen (24 weeks) will have the option to enroll into the OLE period of the study and receive pridopidine 45 mg orally BID (total daily dose of 90 mg), following a 2 week up-titration period at QD.

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 ended his or her participation in the placebo-controlled period of the Regimen if they:

- Complete planned placebo-controlled period visits, as described in the SOA, including participants on or off study drug
- Early terminate from the study and complete the Early Termination Visit and Follow-Up Phone call as described in Section 6.1.11
- Withdraw consent to continue participation in the study or are lost to follow-up

3.3 End of Regimen Definition

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

4 RSA ENROLLMENT

4.1 Number of Study Participants

Approximately one hundred-sixty 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 exclusion criteria at the Regimen Screening Visit 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. Participants with a confirmed prolonged Fridericia-corrected QT (QTcF) interval (defined as a QTcF interval of >450 ms for men and >470 ms for women).

2. Participants with clinically significant heart disease, clinically significant history of arrhythmia, symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia, or presence of left bundle branch block.

3. Participants with known history of long QT syndrome or a first degree relative with this condition.

4. Participants using prohibited medications within the 4 weeks prior to the Regimen Specific Screening Visit, as detailed in section 5.9.

5. Participants using the following medications at the time of the Regimen Specific Screening Visit:
    a. Nuedexta – at a dosage higher than 20 mg dextromethorphan + 10 mg quinidine BID
    b. Citalopram – at a dosage higher than 20 mg/day
    c. Escitalopram – at a dosage higher than 10 mg/day
6. Participants with a known allergy to any ingredient of the study intervention (pridopidine, silicified microcrystalline cellulose, and magnesium stearate).

4.3 Treatment Assignment Procedures

Each participant who meets all eligibility criteria for the Regimen will be randomized to receive either pridopidine 45 mg BID or placebo for approximately 24 weeks of placebo-controlled treatment.

4.4 ECG Monitoring

In addition to the ECG performed at the Master Protocol Screening visit, additional ECG monitoring with stopping and monitoring rules will be completed as described below:

QT Stopping Rules:

- QTcF > 500 ms or
- QTcF > 480 ms AND ΔQTcF > 60 ms from regimen baseline value (pre-dose)
    - The regimen baseline QTcF value is the average of triplicate ECGs collected **pre-dose** during the regimen Screening Visit.
    - For all subsequent visits the ΔQTcF is calculated using the regimen baseline QTcF value (pre-dose), as described above (average triplicate screening QTcF).
        - For Baseline post dose visit only, ΔQTcF is calculated from the initial printout, as the ERT Overread will not be available at the time of the Baseline Visit.
        - For all other ECGs (i.e.Week 4 and Week 24), ΔQTcF should be calculated using the baseline QTcF pre-dose (average triplicate screening QTcF) **from the ERT Overread.**
    - For participants who transition into the OLE, the new baseline QTcF is the average triplicate QTcF collected **pre-dose** during the Week 24 visit.
- If a participant meets either of the above stopping rules, IP must be held and the participant will be asked to return to the clinic after 3-14 days for a follow up ECG.
- If the local ECG reading results at the site match either of the above stopping rules, the IP will be held until the ERT overread report is received. If the ERT overread does not confirm a participant meets the stopping rule above, then the participant can restart the study drug.
- If a participant meets either of the above stopping rules, confirmed by the ERT overread, IP must be discontinued and the participant will be asked to return to the clinic after 3-14 days for a follow up ECG.

QT Monitoring Rule:

- QTcF > 480 ms OR ΔQTcF > 60 ms from regimen baseline value (pre-dose)
    - The regimen baseline QTcF value is the average of triplicate ECGs collected **pre-dose** during the regimen Screening Visit.
    - For all subsequent visits the ΔQTcF is calculated using the regimen baseline QTcF value (pre-dose), as described above (average triplicate screening QTcF).
        - For Baseline post dose visit only, ΔQTcF is calculated from the initial printout, as the ERT Overread will not be available at the time of the Baseline Visit.

        - For all other ECGs (i.e.Week 4 and Week 24), ΔQTcF should be calculated using the baseline QTcF pre-dose (average triplicate screening QTcF) **from the ERT Overread.**
    - For participants who transition into the OLE, the new baseline QTcF is the average triplicate QTcF collected **pre-dose** during the Week 24 visit.

- The first time a participant meets the Monitoring Rule they will be asked to return to the clinic after 3-14 days and repeat a post-dose ECG (1-2 hours AFTER administration of IP).
    - If the local ECG reading results at the site meet the Monitoring Rule, the participant can continue the IP per protocol until the ERT central ECG report is received. If the central read confirms meeting Monitoring Rule, the participant will stay on IP (per protocol) and will be asked to return for a follow-up ECG after 3-14 days.

- The second time a participant meets the Monitoring Rule, the participant should decrease IP to QD dosing.
    - A follow-up post-dose ECG (1-2 hours AFTER administration of IP) should occur 3-14 days after decreasing to QD dosing.
    - If the participant meets the monitoring rule again during this follow-up ECG, the participant must discontinue IP.

Figure 2: ECG Monitoring Flow for Regimen Specific Screening Visit to Assess for Regimen D Eligiblility* (before IP administration):

Initial ECG assessment will be done to assess eligibility (Figure 2):

- QTcF will be measured by a mean of 3 (triplicate) 12-lead ECG assessments
  - Three 10-second ECG recordings should be performed, with at least one minute between each recording. QTcF will be automatically calculated by the ECG machine, and will be copied onto source documents. Mean QTcF from the three ECG recordings will be calculated manually. The SI should review and confirm the mean QTcF value.
- If the mean QTcF is >450 ms for men and >470 ms for women, then participant will screen fail and will not be randomized within the regimen.
- For participants on Nuedexta, the Nuedexta dose should be taken within 6 hours before triplicate ECG.

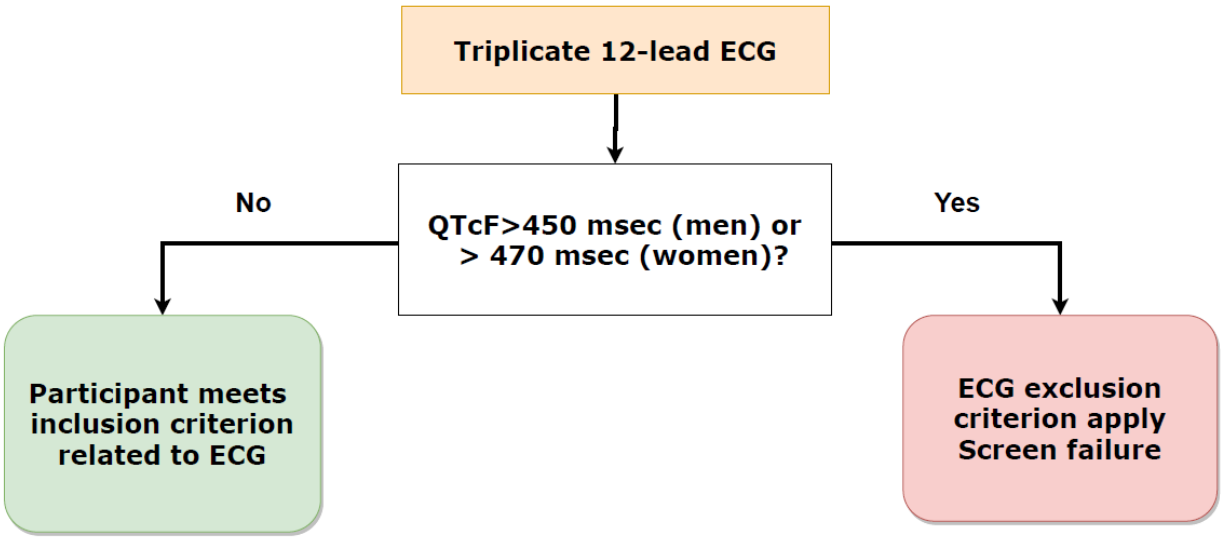
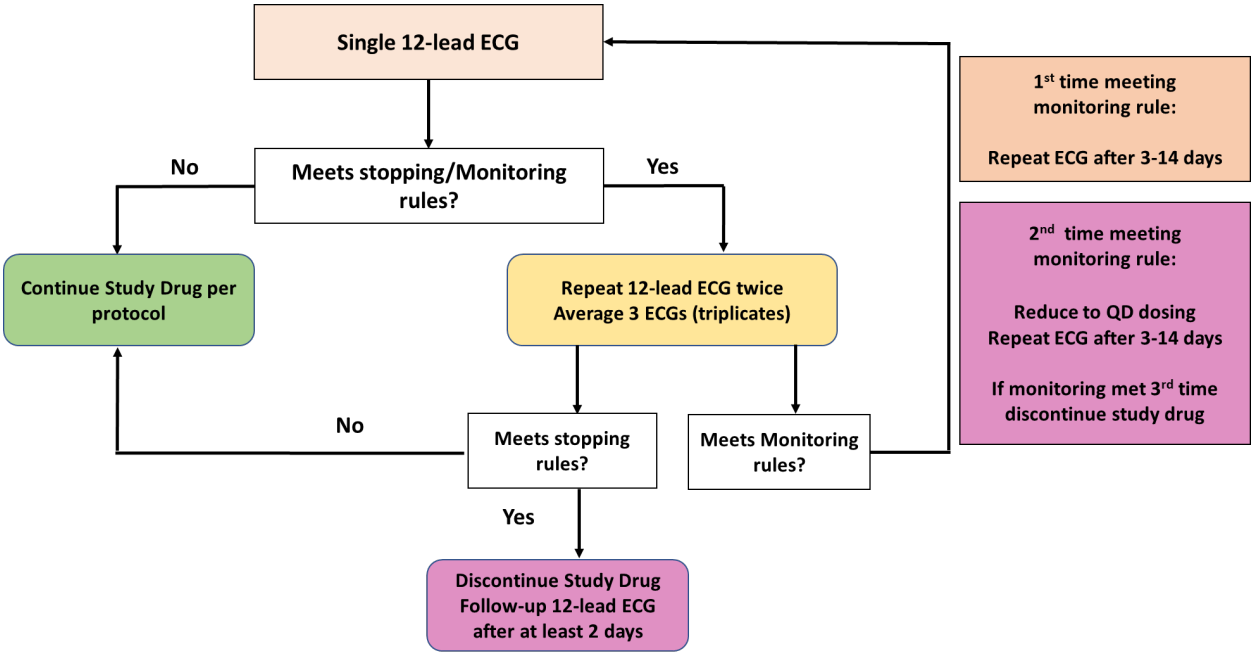


Figure 3: ECG Monitoring Flow for Regimen Specific Baseline post-dose and Week 4 post-dose Visits*



*For participants on Nuedexta, the Nuedexta dose should be taken within 6 hours before the ECG

QTcF value will be automatically calculated by the ECG machine, and will be copied into source documents (Figure 3):

- QTcF will be measured by a single 12-lead ECG, 1-2 hours post-dose administration.
- If QTcF meets Stopping/Monitoring Rules, then ECG will be repeated twice[1] and the QTcF will be determined by the average of the 3 ECGs.
- If the average QTcF meets Stopping Rules, IP will be held, and a follow-up ECG will be performed as soon as practicable (but at least 2 days after stopping IP) to ensure recovery from QT-prolongation.
- If the average QTcF meets Monitoring Rule for the 1st time, participant will be instructed to continue on IP per-protocol and have a follow up, post-dose ECG after 3 -14 days
- If a participant meets the Monitoring Rule for the second time, the participant will be instructed to decrease IP to QD dosing for the remainder of the study.
    - A follow-up ECG should occur 3-14 days after decreasing to QD dosing. If the participant meets the monitoring rule for the 3rd time, the participant must discontinue IP immediately.

[1] Standard ECG procedure for abnormal QTcF readings will be for the ECG to be repeated twice (at least 5 minutes after the 1st ECG, and with an interval of at least 1 minute between each of the 2 additional 10-second recordings), and the mean of the 3 measurements will be used to determine final QTcF.

ECG Monitoring Flow at Week 24 for Participants <u>not</u> Enrolling into the OLE

QTcF will be automatically calculated by the ECG machine, and will be copied into source documents:

- QTcF will be measured by **<u>a single</u>** 12-lead **pre-dose** ECG.
    - For participants taking Nuedexta, the Nuedexta dose should be taken within 6 hours before the ECG
- If QTcF meets Stopping/Monitoring Rules, then ECG will be repeated twice[2] and the QTcF will be determined by the average of the 3 ECGs.
- If the average QTcF meets Stopping Rules, IP will be <u>stopped</u>, and a follow-up ECG will be performed as soon as practicable (but at least 2 days after stopping IP) to ensure recovery from QT-prolongation.

ECG Monitoring Flow at Week 24 for Participants <u>who choose to</u> Enroll into the OLE

- Baseline QTcF for the purpose of OLE will be measured by **<u>a mean of 3 (triplicate)</u>** 12-lead **pre-dose** ECG assessments
    - Three 10-second ECG recordings should be performed, with at least one minute in between each ECG recording. QTcF will be automatically calculated by the ECG machine, and will be copied onto source documents. Mean QTcF from the three ECG recordings will be calculated manually and used as Baseline pre-dose QTcF for the OLE. The SI should review and confirm the mean QTcF.
- For participants taking Nuedexta, the Nuedexta dose should be taken within 6 hours before the ECG.
- If the mean QTcF is >450 ms for men and >470 ms for women at the Week 24 Visit, then participant will not be eligible to continue into the OLE.
- The OLE IP should then be administered to the participant, and **a single** 10-second ECG should be collected 1-2 hours after administration of the OLE IP.
- If QTcF meets Stopping/Monitoring Rules <u>then</u> ECG will be repeated twice[2] and the QTcF will be determined by the average of the 3 ECGs.
- If the mean QTcF meets Stopping Rules, IP will be held , and a follow-up ECG will be performed as soon as practicable (but at least 2 days after stopping IP) to ensure recovery from QT-prolongation.
- If the mean QTcF meets Monitoring Rule, participant may continue on IP per-protocol and have another ECG after 3 -14 days.
- If a participant meets the Monitoring Rule for the second time, the participant may decrease to QD dosing for the remainder of the study.
- A follow-up ECG should occur 3-14 days after decreasing to QD dosing. If the participant meets the monitoring rule during this follow-up ECG, the participant must discontinue IP immediately.

[2] Standard ECG procedure for abnormal QTcF readings will be for the ECG to be repeated twice (at least 5 minutes after the 1st ECG, and with an interval of at least 1 minute between each of the 2 additional 10-second recordings), and the mean of the 3 measurements will be used to determine final QTcF.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Manufacturer

Pridopidine active drug product and matching placebo are manufactured by Teva Pharmaceutical Industries, Ltd or by Apotek Production & Laboratories AB (APL) and will be provided centrally by the Sponsor or subsidiary, or designee.

The investigational product will be oral capsules containing 45 mg of pridopidine and matching placebo capsules (as the control treatment product) identical in appearance.
Pridopidine capsules contain the active ingredient pridopidine and inactive excipients. The excipients are silicified micro crystalline cellulose and magnesium stearate.

The investigational product will be produced and packed in 60 count bottles provided by Apotek Produktion & Laboratorier AB, Sweden.

5.2 Labeling, Packaging, and Resupply

IP will be provided in high-density polyethylene (HDPE) bottles labeled with child resistant caps. All packaging and labeling operations for IP will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements. Participants will be provided with sufficient IP supplies to cover the period until their next study visit when IP will be dispensed. Each bottle will be labelled with the protocol number, storage information, warning language (i.e., as required by local legislation for investigational drug products), dosing and storage instructions.

5.3 Acquisition, Storage, and Preparation

At each investigational site, the IP will be kept at 15 to 25 ºC in a secure, limited-access, controlled storage area. Only authorized personnel will have access to the IP. The study personnel at each site will be responsible for the correct storage and handling of the IP.
Each bottle will be labelled with the protocol number, storage information, warning language (i.e., as required by local legislation for IP), dosing and storage instructions.
The Investigator is responsible for recording the receipt and use of all IP supplied, and for ensuring the supervision of the storage and allocation of these supplies. Full accountability will be performed for all used and unused IP.

5.4 Drug Returns and Destruction

At each in person visit the steps outlined in Manual of Procedures must be followed for study drug accountability and compliance, as well as study drug return and destruction.

Prior to study drug destruction, all used and unused IP requires a second accountability verification to be completed by a different study team member, and both verifications should be documented on the study destruction logs. No study drug may be destroyed on-site until written

approval is provided by the study monitoring team. Sites should follow their local drug destruction policies.

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

Participants will take 45 mg capsules of active IP/placebo BID (1 capsule in the morning and 1 capsule in the afternoon, approximately 7 to 10 hours after the morning dose); total daily dose (TDD) of 90 mg. Capsules should be swallowed whole with a drink of water (or other liquid) or swallowed whole with substances of other consistencies as appropriate (e.g. applesauce), and can be taken irrespective of meals. For delivery via gastrostomy tube, the capsule can be opened and the contents diluted in 20-30mL of water and mixed. The prepared solution should be used immediately. Flushing with water is recommended to minimize clogging of the gastrostomy tubing after administration.
All participants receiving study intervention are intended to receive the same fixed-dose regimen, in terms of dose and daily (BID) frequency, according to the study schedule. There will be a titration period leading up to the proposed dose whereby at the baseline visit participants will initiate pridopidine/placebo at 45 mg QD and then increase to 45 mg BID after 2 weeks.

5.6 Justification for Dose

The dosage of pridopidine (45 mg BID) was selected on the basis of three large HD clinical studies (HART, MermaiHD, and PRIDE-HD) and has been shown to be safe and well-tolerated in >1300 participants. Pridopidine 45 mg BID showed potential beneficial clinical effects in the PRIDE-HD study, including potential sustainable effects based on the long-term open-label study, and is therefore anticipated to provide efficacy with low safety and tolerability risks. *In vivo* target engagement was demonstrated by a positron emission tomography (PET) imaging study in humans. At 45 mg BID, pridopidine shows near to complete (~90%) S1R binding ([^{18}F]fluspidine) (Figure 1).

5.7 Dosage Changes

After the 2-week up-titration period, participants who are unable to tolerate a BID schedule will be allowed to stay in the study at the lower dose QD schedule for 1 additional week. After 1 additional week of study intervention on the QD schedule, the dose will be increased to a BID dose schedule. If the participant cannot tolerate the second increase to a BID dose schedule, they will be allowed to continue on QD for the remainder of the study.

If a participant meets the ECG Monitoring Rule for a second time, the participant may decrease to QD dosing for the remainder of the study, as long as the Monitoring Rule is not met for a third time.

5.8 Participant Compliance

Responsible study personnel will dispense the study drug. Participants will be requested to return any unused IP including empty packaging and used bottles at each study visit. Treatment compliance will be assessed at in clinic study visits through bottle counts and will be

documented and summarized by a drug-dispensing log for each participant. During phone visits, drug compliance check-in will be held to ensure participant is taking drug per dose regimen and to note any report of missed doses.Participants will be counseled on the importance of taking the IP as directed at all study visits. If poor compliance continues, (i.e., multiple missed doses resulting in less than 80% overall compliance), discontinuation of the participant from the trial should be considered and discussed with the Medical Monitor.

5.9 Overdose

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

- Overdose of the IP, where 'overdose' is defined as a participant ingesting more than 3 times the intended dose
- Suspected abuse/misuse of the IP
- Inadvertent or accidental exposure to the IP
- Medication error involving IP (with or without participant exposure to the IP, e.g., name confusion)

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

5.10 Prohibited Medications

Excluded Medications:

Class	Drugs
Antipsychotics	Clozapine, haloperidol, mesoridazine, thioridazine, pimozide, chlorpromazine, perphenazine, risperidone, zuclopenthixol, and sulpiride.
Antiarrhythmic	Disopyramide, procainamide, flecainide, propafenone, amidiarone, dofetilide, ibutilide, and sotalol
Others	Astemizole, terfenadine, azithromycin, erythromycin, moxifloxacin, pentamidine, sparfloxacin, clarithromycin, chloroquine, halofantrine, bepridil, cisapride, domperidone, droperidol, levomethadyl, sevoflurane, anagrelide, budipine, fluconazole, levofloxacin, lidoflazine, ondansetron, probucol, terodiline, vandetanib, tramadol, tamoxifen, atomoxetine, tolterodine

Participants who use the above medications while enrolled in Regimen D of the HEALEY ALS Platform Trial increase their risk of QT prolongation and torsades. If participants inadvertently use these medications while they are on IP, the Medical Monitor should be notified and a single 12-lead ECG should be collected within 3-14 days of initiating the new prohibited co-medication, or higher dose, to test for QTcF prolongation meeting the Monitoring or Stopping Rules.

If there is a clinical indication for any medication specifically prohibited during the study, the Medical Monitor will be notified and engaged in consultation as to how to address.

5.11 Pridopidine Known Potential Risks and Benefits

5.11.1 Known Potential Risks

QT prolongation:
In the PRIDE-HD trial of 408 participants, the cardiac effects of pridopidine were evaluated in people with HD at doses up to 112.5 mg BID for 52 weeks. Although low, there was a higher overall incidence of AE-reports of QT prolongation in pridopidine-treated participants compared to placebo-treated participants: 1.5% in pridopidine-treated participants vs 0% in placebo-treated participants. However, there was no evidence of a dose response in QT-related AEs (QT prolongation AEs: 0 in placebo, 2 in 45 mg BID, 0 in 67.5 mg BID, 1 in 90 mg BID and 2 in 112.5 mg BID; total 5/327=1.5%). Using the PRIDE-HD data, a cardiac exposure-response model was developed utilizing ECG data paired with PK samples collected for up to a year. Only ECGs that were paired with PK samples (n=3071) were used to develop the cardiac exposure-response model, which was based on 2753 ECGs from pridopidine-treated participants and 763 from placebo-treated participants.

A concentration-dependent effect of pridopidine on the QTcF interval was observed in this study, with a slope of 0.012 ms per ng/mL (90% CI: 0.0109 to 0.0127 ms per ng/mL).

At 45 mg BID, the predicted QT effect (ΔΔQTcF) in participants with HD was 6.6 ms (with an upper bound of the 90% CI 8 ms), which is not clinically meaningful. Pridopidine 45 mg BID is the dose to be tested in the HEALEY ALS Platform Trial. Although this was not a clinically meaningful QT effect, as there is no prior experience with pridopidine in the ALS patient population, we plan to include additional safety monitoring and risk mitigation measures.

5.11.2 Potential Benefits

Loss of function mutations in S1R cause neurodegenerative diseases such as ALS (Al-Saif, Al-Mohanna, and Bohlega 2011; Watanabe et al., n.d.; Izumi et al. 2018) and distal hereditary motor neuropathies (dHMN) (Gregianin et al. 2016; Li et al. 2015), suggesting restoration of S1R function could be beneficial in these motor neuron diseases. Denervation at the neuromuscular junction (NMJ) is considered one of the earliest events in ALS disease progression (Fischer et al. 2004). Using *in vitro* ALS models, pridopidine was shown to restore NMJ function (percent of contracting ALS $SOD1^{G93A}$ myotubes) to wild-type (WT) levels (Ionescu et al. 2019).

Additionally, pridopidine has been shown to exert neuroprotection via activation of the S1R in numerous preclinical models including ALS, HD, PD, and AD, where it promotes pro-survival pathways, promotes neurite growth and spine density, restores abnormalities in calcium signaling (Ryskamp et al. 2017), and restores mitochondrial function (Geva et al. 2016; Ionescu et al. 2019; Francardo et al. 2019; Kusko et al. 2018). This body of preclinical data, generated from multiple labs using a diverse set of models, in addition to the results of the PRIDE-HD study, and combined with the genetics, suggests that pridopidine possesses potential neuroprotective effects and may, therefore, have therapeutic effects in ALS.

6 REGIMEN SCHEDULE

6.1 Placebo-Controlled Period

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

- Home Spirometry
    - Note: Home spirometry should be collected within the visit window but will occur while the participant is not in the clinic (at home or other remote location).
- ALSAQ-40
- CNS Bulbar Function Scale (CNS-BFS)
- CNS-Lability Scale (CNS-LS)
- Additional ECG monitoring
- PK analysis of pridopidine and metabolite plasma exposure
    - All blood samples should be collected after the ECG, or at least one hour prior to the ECG
- Smartphone installation and removal
- Voice Recording

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

1. The site staff sends copy of the informed consent form to the participant.
2. The participant reads through the consent form but does not sign.
3. The Site Investigator, or other study staff member approved and delegated to obtain informed consent, contacts the participant and reviews the informed consent form with the participant.
4. The participant signs the informed consent form and returns the original signed consent form back to the site.
5. Once received at the site, the individual who consented the participant signs the informed consent form.

Modifications to Regimen Schedule

Designated visits in the Schedule of Activities (i.e. 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 or other reason. 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 Manual of Procedures (MOP).

If a remote visit is scheduled, the ECG must still be conducted in-clinic within the visit window, and all other procedures can be collected via telemedicine (or phone if telemedicine is not available) as described in the MOP.

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

- Home Spirometry (Week 8 and 16 only)
- Voice Recording
- CNS-BFS
- CNS-LS

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

6.1.1 Regimen Screening/Baseline Visit

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

- ALSAQ-40
- CNS-BFS
- CNS-LS
- Install Smartphone Apps
- Home Spirometry
- Voice Recording
- Collect blood sample prior to the first dose of IP
- Dispense IP to participant, and administer first dose after all Baseline procedures have been completed, with the exception of the post-dose ECG
- ECG
    - Screening Visit – administer **triplicate ECG** to determine eligibility
    - Baseline - administer post-dose **single** ECG 1-2 hours after the first dose of IP is administered
        - Note: if the participant is taking Nuedexta, the Nuedexta dose should be taken within 6 hours prior to the pre dose ECG. If participant has taken Nuedexta outside of this window, the ECG should still be completed and a protocol deviation recorded. Refer to the MOP for additional guidance.
- Remind participant to bring study drug to the next visit

6.1.2 Week 2 Telephone Visit

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

- Participant will be reminded to up-titrate to 45mg/placebo BID of IP following an assessment of tolerability of 45 mg/placebo QD dose

6.1.3 Week 4 Visit

If a participant's visit occurs in the morning, the participant should be instructed not to take the morning dose at home, and the morning dose should be administered in-clinic 1-2 hours prior to the post-dose ECG. If a participant's visit occurs in the afternoon, the participant should be instructed to take the morning dose immediately upon waking in the morning, and the second dose should be administered in-clinic 1-2 hours prior to the post-dose ECG.

These visits will take place on Day 28 ± 7. The following procedures will be performed for the regimen schedule:

- Administer **single** ECG 1-2 hours **AFTER** IP is administered
    - Note: if the participant is taking Nuedexta, the Nuedexta dose should be taken within 6 hours prior to the ECG. If participant has taken Nuedexta outside of this window, the ECG should still be completed and a protocol deviation recorded. Refer to the MOP for additional guidance.
- Plasma collection **AFTER** ECG
    - All blood samples should be collected after the ECG is performed. If the blood samples cannot be collected after the ECG due to scheduling constraints, blood samples should be collected at least one hour prior to the ECG.
- Voice Recording
- Remind participant to bring study drug to the next visit

6.1.4 Week 8 Visit

These visits will take place on Day 56 ± 7 days. The following procedures will be performed for the regimen schedule:

- Home Spirometry
- CNS-BFS
- CNS-LS
- Voice Recording
- Dispense IP
- Remind participant to bring in study drug to the next visit

6.1.5 Week 12 Telephone Visit

This visit will take place 84 ± 3 days after the Baseline Visit via telephone.

6.1.6 Week 16 Visit

This visit will take place in-person 112 ± 7 days after the Baseline Visit. The following procedures will be performed:

- Home Spirometry
- CNS-BFS
- CNS-LS
- Voice Recording
- Dispense IP
- Document participant's willingness to participate in the OLE
    - If OLE consent is not obtained at Week 16, it may be obtained at Week 24.
- Remind participant to bring in study drug to the next visit

6.1.7 Week 20 Telephone Visit

This visit will take place 140 ± 3 days after the Baseline Visit via telephone.

6.1.8 Week 24 Visit or Early Termination Visit

<u>Participants Not Enrolling into the OLE</u>

Only a pre-dose ECG is required at this visit for participant who are not enrolling into the OLE.

If a participant's visit occurs in the morning, the participant should be instructed not to take the morning dose at home, and the morning dose should be administered in-clinic after the pre-dose ECG. If a participant's visit occurs in the afternoon, the participant should be instructed to take the morning dose immediately upon waking in the morning, and the second dose should be taken after the pre-dose ECG.

<u>Participants Enrolling into the OLE</u>

A pre-dose and post-dose ECG are required for participants who enroll into the OLE. The SI should confirm the mean QTcF following the pre-dose triplicate ECG. If the mean QTcF is >450 ms for men and >470 ms for women, then participant will not be eligible to continue into the OLE.

If a participant's visit occurs in the morning, the participant should be instructed not to take the morning dose at home. A pre-dose triplicate ECG should be collected prior to administration of the first dose of OLE IP in-clinic. A single post-dose ECG should then be collected 1-2 hours after administration of the first dose of OLE IP.

If a participant's visit occurs in the afternoon, the participant should be instructed to take the morning dose immediately upon waking in the morning, and a pre-dose triplicate ECG should be collected prior to administration of the first dose of OLE IP in-clinic (which will be the 2nd daily dose).

A single post-dose ECG should then be collected 1-2 hours after administration of the first dose of OLE IP.

This visit will take place on Day 168 ± 7. The following procedures will be performed at either the Week 24 Visit or the Early Termination Visit:

- Home Spirometry
- ALSAQ-40
- CNS-BFS
- CNS-LS
- **Triplicate** ECG monitoring **BEFORE** IP administration
- Administer **single** ECG 1-2 hours **AFTER** IP is administered (only for participants enrolling into the OLE)
    - Note: if the participant is taking Nuedexta, the Nuedexta dose should be taken within 6 hours prior to the pre-dose ECG. If participant has taken Nuedexta outside of this window, the ECG should still be completed and a protocol deviation recorded. Refer to the MOP for additional guidance.
- Plasma PK collection
    - **after** the pre-dose ECG for participants NOT participating in the OLE
    - **after** the post-dose ECG for participants participating in the OLE
    - All blood samples should be collected after the ECG is performed. If the blood samples cannot be collected after the ECG due to scheduling constraints, blood samples should be collected at least one hour prior to the ECG.
- Voice Recording
- Uninstall Smartphone App
- Dispense IP [See note below.]
- Remind participant to bring investigational product to the next visit (only if continuing in OLE)

Note: Drug is only dispensed at this visit if the participant is continuing in the OLE.

6.1.9 Follow-Up Safety Call

Participants will have a Follow-Up Safety Call 28±3 days after their last dose of IP. Only those participants NOT continuing on in the Open Label Extension will have the Follow-Up Safety Call at the end of their participation in the placebo-controlled portion of the trial. The following procedures will be performed:

- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)

6.1.10 Process for Early Terminations

A research participant may choose to discontinue their participation at any time for any reason. The SI or designee will encourage the participant to follow the study protocol under intent-to-treat principle and follow the study visits, off treatment, up to the week 24 visit. If a participant decides to discontinue IP, but will complete the protocol, an in-person Early Termination Visit and Follow-Up Safety Call is not necessary.

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. If a participant is not able to be seen in-person, safety assessments and others that can be conducted remotely should be performed.

The in-person Early Termination Visit should be scheduled as soon as possible after a participant early terminates. 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. If the participant early terminates during the OLE period, all assessments that are intended for collection at the OLE 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 the Early Termination Visit occurs approximately 28±3 days after the last dose of IP, 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±3 days after the last dose of IP and the Early Termination Visit will be completed after the Follow-Up Safety Call.

6.2 Open Label Extension

Participants who completed the placebo-controlled portion of the trial on drug, will be eligible to continue in the OLE as outlined in the SOA. Participants will first be asked about their desire to continue in the OLE at the Regimen-Specific Screening Visit. They will also be asked to *re-confirm* whether they want to continue in the OLE at the Week 16 Visit of the placebo-controlled period. In the OLE, pridopidine will be provided by Prilenia Therapeutics, until the primary results of the 24 week double-blind portion of the study are available, or they terminate development of pridopidine for ALS.

To preserve the blind, all participants in the OLE, regardless of whether they were in the active or placebo arm of the study initially will need to initiate the OLE at a QD dose and then up-titrate to BID after 2 weeks.

Modifications to OLE Schedule

Designated visits in the Schedule of Activities for the OLE (i.e. Week 8, 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 or other reason. If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP.

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

- Home Spirometry
- CNS-BFS
- CNS-LS
- ALSAQ-40

6.2.1 Week 2 OLE Telephone Visit

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

- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Drug Compliance Check-In (Participant should increase dose from QD to BID)
- Remind participant to bring investigational product to the next visit

6.2.2 Week 4 OLE Visit

If a participant's visit occurs in the morning, the participant should be instructed not to take the morning dose at home, and the morning dose should be administered in-clinic 1-2 hours prior to the post-dose ECG. If a participant's visit occurs in the afternoon, the participant should be instructed to take the morning dose immediately upon waking in the morning, and the second dose should be administered in-clinic 1-2 hours prior to the post-dose ECG.

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
- Collect Home Spirometry
- Administer ALSFRS-R questionnaire
- Administer single ECG 1-2 hours **AFTER** IP is administered
    - Note: if the participant is taking Nuedexta, the Nuedexta dose should be taken within 6 hours prior to the post-dose ECG. If participant has taken Nuedexta outside of this window, the ECG should still be completed and a protocol deviation recorded. Refer to the MOP for additional guidance.
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable

    - All blood samples should be collected after the ECG is performed. If the blood samples cannot be collected after the ECG due to scheduling constraints, blood samples should be collected at least one hour prior to the ECG.
- 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
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

6.2.3 Week 8 OLE Visit

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

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

6.2.4 Week 12 OLE Telephone Visit

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

- Administer ALSFRS-R questionnaire
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Drug Compliance Check-In
- Remind participant to bring investigational product to the next visit

6.2.5 Week 16 OLE Visit

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

6.2.6 Week 20 OLE Telephone Visit

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

- Administer ALSFRS-R questionnaire
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Drug Compliance Check-In
- Remind participant to bring investigational product to the next visit

6.2.7 Week 24 and Q12 Weeks OLE Visit

If a participant's visit occurs in the morning, the participant should be instructed not to take the morning dose at home, and the morning dose should be administered in-clinic after the pre-dose ECG. If a participant's visit occurs in the afternoon, the participant should be instructed to take the morning dose immediately upon waking in the morning, and the second dose should be taken after the pre-dose ECG.

The Week 24 OLE Visit will take place in-person 196 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. Following the Week 24 OLE Visit, visits will occur every 12 weeks ± 14 days as applicable. The following procedures will be performed:

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

- CNS Lability Scale
- Administer ECG **BEFORE** IP is administered (at Week 24 and Final OLE Visit only)
    - Note: if the participant is taking Nuedexta, the Nuedexta dose should be taken within 6 hours prior to the post-dose ECG. If participant has taken Nuedexta outside of this window, the ECG should still be completed and a protocol deviation recorded. Refer to the MOP for additional guidance.
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
    - All blood samples should be collected after the ECG is performed. If the blood samples cannot be collected after the ECG due to scheduling constraints, blood samples should be collected at least one hour prior to the ECG.
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Collect urine sample for biomarker analyses
- Collect blood sample for biomarker analyses
- Dispense investigational product to participant
- Perform investigational product compliance
- Remind participant to bring investigational product to the next visit

7 OUTCOME MEASURES AND ASSESSMENTS

For all assessments listed below, please refer to the Manual of Procedures for detailed instructions.

7.1 Voice Analysis

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

The voice analysis app is only available in English, therefore participants who do not speak English should not complete the voice recording. Caregivers cannot provide language assistance when the participant is completing the voice recording.

7.2 ALSAQ-40

The Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ-40) is a participant 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 participants with ALS and motor neuron disease. Higher scores indicate a decrease in quality of life.

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

7.3 Center for Neurologic Study Bulbar Function Scale

The Center for Neurologic Study Bulbar Function Scale (CNS-BFS) is a participant 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 (Smith et al, 2018). The CNS-BFS consists of three domains (swallowing, speech, and salivation), which are assessed with a 21-question, self-report questionnaire. Higher scores indicate greater bulbar dysfunction.

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

Instructions on administering the questionnaire during a phone or telemedicine visit will be included in the MOP.

7.4 CNS-Lability Scale

The Center for Neurologic Study Lability Scale (CNS-LS) is a participant self-report scale that has been developed for use as an endpoint in clinical trials and as a clinical measure for evaluating emotional lability. The CNS-LS is a short (seven-question), self-report questionnaire, designed to be completed by the participant, that provides a quantitative measure of the perceived frequency of PBA episodes. Higher scores indicate greater emotional lability. A CNS-LS score of 13 or higher may suggest PBA.

For all in person visits, participants will be handed the questionnaire and asked to write their answers themselves. Caregivers can also help, if needed. During telephone visits, site staff will administer and record data for this scale.

7.5 Home Spirometry

Remote/home-based forced vital capacity will be measured with the MIR Spirobank Smart spirometer. Instructions for use will be provided to the participant. The participant will perform the vital capacity maneuver with real time video coaching (or phone coaching, if video is not available) by the evaluator. Three to five vital capacity maneuvers will be performed, consistent with the manner vital capacity is obtained in clinic.

8 BIOFLUID COLLECTION

8.1 Pharmacokinetic Sample

PK Collection

- Collect 4mL of blood in a 4mL K3EDTA tube at the allocated time-points.
- Invert the collection tube 8-10x
- Centrifuge the collected sample at 2000 x g for 15 min at 4˚C
- Aliquot 1mL of obtained plasma in the Primary and Back-up 3.6mL Cryo Vial
    - Note: The plasma should be transferred into the aliquot vials within 60 minutes (preferable immediately) of collection

9 REGIMEN-SPECIFIC STATISTICAL CONSIDERATIONS

9.1 Deviations from the Default Master Protocol Trial Design

The statistical design for this regimen will be in accordance with the default statistical design described in Appendix I of the Master Protocol, except that early success will not be permitted. Hence, as with the first 3 regimens, interim analyses for Regimen D will only allow stopping for early futility and not for early success.

9.2 Regimen-Specific Operating Characteristics

Clinical trial simulation is used to quantify operating characteristics for this regimen. Given that the statistical design for the regimen does not have any deviations from the design of the first three regimens, the simulation of virtual participants, simulation scenarios and operating characteristics are available in Appendix I to the master protocol.

9.3 Sharing of Controls from other Regimens

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

9.4 Secondary Efficacy Endpoints

If the primary analysis demonstrates significant slowing of decline in ALSFRS-R among participants randomized to pridopidine, then the following secondary hypotheses will be tested in the specified sequence with overall type I error rate controlled using a sequential closed-testing procedure:

1. Rate of change in ALSFRS-R bulbar subdomain (Q1-Q3) score among participants with bulbar dysfunction at baseline,
2. Rate of change in ALSFRS-R bulbar subdomain (Q1-Q3) score among all randomized participants,
3. Rate of change in the speech sub-score of the ALSFRS-R (Q1) among all randomized participants
4. Rate of change in SVC maximum percent of predicted among all randomized participants,
5. Rate of change in ALSFRS-R bulbar subdomain (Q1-Q3) score among participants with pre-baseline slope $\geq$0.75 points/month,
6. Time to onset of bulbar symptoms among participants free of bulbar dysfunction at baseline,
7. Rate of change in HHD percent change from baseline among all randomized participants,
8. Time to death or death equivalent

Analyses for each secondary hypothesis will use an ITT analysis sample that includes placebo participants from concurrently enrolling regimens. Analyses of ALSFRS-R bulbar subdomain,

CNS-BFS, HHD, and SVC will use shared-baseline linear mixed models that adjust for time since onset of weakness, pre-baseline slope, baseline riluzole use, baseline edaravone use, baseline Nuedexta use, and site of onset and their interactions with time since baseline, and include random intercepts and slopes by regimen and by participant with unstructured covariance at each level. Given low expected event rates, time to bulbar onset and time to death or death equivalent will use log-rank tests. Per protocol analyses will also be performed to evaluate the effects of pridopidine on participants complying with study regimen. Details of endpoint measures, analysis samples, statistical models, and the closed-testing procedure will be described in the regimen-specific statistical analysis plan.

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APPENDIX I: THE ALSAQ-40

ALSAQ-40

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you for completing this questionnaire.

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

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

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

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

APPENDIX III: THE LABILITY SCALE (CNS-LS)

Please select the number that describes the degree to which each item has applied to you DURING THE PAST WEEK.					
	Does not Apply 1	Rarely Applies 2	Occasionally Applies 3	Frequently Applies 4	Applies Most of the Time 5
1. There are times when I feel fine 1 minute, and then I'll become tearful the next over something small or for no reason at all.	❍	❍	❍	❍	❍
2. Others have told me that I seem to become amused very easily or that I seem to become amused about things that aren't funny.	❍	❍	❍	❍	❍
3. I find myself crying very easily.	❍	❍	❍	❍	❍
4. I find that even when I try to control my laughter, I am often unable to do so.	❍	❍	❍	❍	❍
5. There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts.	❍	❍	❍	❍	❍
6. I find that even when I try to control my crying, I am often unable to do so.	❍	❍	❍	❍	❍
7. I find that I am easily overcome by laughter.	❍	❍	❍	❍	❍

TOTAL: