HEALEY ALS Platform Trial - Regimen B Verdiperstat

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REGIMEN-SPECIFIC APPENDIX [B]

FOR VERDIPERSTAT (BHV-3241)

Regimen-Specific Appendix Date: 02 December 2021

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SIGNATURE PAGE

I have read the Regimen-Specific Appendix (RSA) entitled, Verdiperstat (BHV-3241) in Participants with Amyotrophic Lateral Sclerosis (ALS) dated July 15, 2021 (Version 5.0.) 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
ALP	Alkaline Phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire
Anti-TPO	Anti-Thyroid Peroxidase
AUC	Area Under the Curve
BHV-3241	Verdiperstat
BID	Twice daily
°C	Degrees Celsius
CBC	Complete blood count
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ER	Extended Release
°F	Degrees Fahrenheit
FVC	Forced Vital Capacity
GRAS	Generally recognized as safe
HDPE	High-density polyethylene
HHD	Hand Held Dynamometry
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio

IB	Investigator Brochure
ICF/IC	Informed Consent Form
ICH	International Council on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web-Based Response System
LPLV	Last participant last visit
MAD	Modification of Diet in Renal Disease
mg	Milligram
MPO	Myeloperoxidase
MSA	Multiple System Atrophy
NADPH	Nicotinamide adenine dinucleotide phosphate
NfL	Neurofilament Light Chain
NOEL	No-Observed-Effect-Level
NOX	NADPH oxidase
NRF2	Nuclear factor erythroid 2–related factor 2
OLE	Open-Label Extension
PD	Pharmacodynamic
PET	Positron emission tomography
P-gp	P-glycoprotein
PK	Pharmacokinetic
PMA	Phorbol-12-myristate-13-acetate
PP	Polypropylene
QD	Once Daily
QTcF	Corrected QT Interval by Fridericia
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
RSA	Regimen-specific appendix
SAD	Single Ascending Dose
SAE	Serious Adverse Event

SI	Site Investigator
SOA	Schedule of Activities
SOD	Superoxide dismutase
SVC	Slow Vital Capacity
T3	Triiodothyronine
T4	Thyroxine
TSPO	Translocator Protein
TPO	Thyroid Peroxidase
TSH	Thyroid Stimulating Hormone
TSPO	Translocator Protein
USB	Universal Serial Bus
USP	US Pharmacopoeia
VC	Vital Capacity
WOCBP	Women of Childbearing Potential

REGIMEN-SPECIFIC APPENDIX (RSA) SUMMARY

Regimen-Specific Appendix [B]

For verdiperstat (also known as BHV-3241).

Rationale and RSA Design

The proposed study is based on cumulative preclinical and clinical studies that implicate myeloperoxidase (MPO) activity in the onset and progression of neurodegenerative diseases and suggest treatment with verdiperstat at a dosage of 600 mg twice daily (BID) has the potential to slow neurodegeneration in Amyotrophic Lateral Sclerosis (ALS).

Allocation to Treatment Regimens

Participants must first be screened under the Master Protocol before they are randomized to an RSA. As soon as pre-defined criteria for futility for the RSA are met, or the target number of randomized participants for the RSA has been reached, enrollment will stop in the RSA.

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 in the US.

Treatment Duration

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

Follow-up Duration

At the conclusion of the 24-week placebo-controlled 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 verdiperstat in the open-label extension (OLE) phase of the study.

The OLE portion of the study will continue until verdiperstat is approved and available in the United States, or Biohaven Pharmaceuticals terminates development of verdiperstat for ALS. At the completion of the OLE, a Follow-up Safety Call should be conducted approximately 28 days after the last dose of study drug.

For participants who early terminate from the placebo-controlled phase, 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.

For participants who early terminate from the OLE, 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 Final visit should be conducted. At the Follow-up Safety Call, information on clinical status should be collected.

Total Planned Trial Duration

For participants completing only the placebo-controlled Treatment Period of the study, the planned amount of time for participation in the trial is 34 weeks, or about 8 months. This duration assumes a 6-week screening window, a 24-week placebo-controlled treatment period, and a 28-day safety follow-up period for those participants who do not enter the OLE. Participants will complete approximately 10 study visits during the placebo-controlled period of the study.

SCHEDULE OF ACTIVITIES – 24-WEEK PLACEBO-CONTROLLED PHASE

As per the Schedule of Activities (SOA) below, visits must occur every 4 weeks and will be alternatively 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]**	**Baseline**	**Week 2[2]**	**Week 4[18,19]**	**Week 8[18,19]**	**Week 12**	**Week 16[18,19]**	**Week 20**	**Week 24 or Early Term. Visit[3,18]**	**Follow-up Safety Call[3,4]**
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		-42 to -1 Days	-41 to 0 Days	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	28±7 days after last dose
Written Informed Consent – Placebo-controlled Period[5]	**Master**	X	X									
Written Informed Consent - OLE	**Regimen**								X			
Inclusion/Exclusion Review	**Master**	X	X[6]									
ALS & Medical History	**Master**	X										
Demographics	**Master**	X										
Physical Examination	**Master**	X										
Neurological Exam	**Master**	X										
Vital Signs[7]	**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	
12-Lead ECG	**Regimen**	X					X				X	

Activity	Master Protocol or Regimen-Specific	Master Protocol Screening[1]	Regimen Specific Screening[1]	Baseline	Week 2[2]	Week 4[18,19]	Week 8[18,19]	Week 12	Week 16[18,19]	Week 20	Week 24 or Early Term. Visit[3,18]	Follow-up Safety Call[3,4]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		-42 to -1 Days	-41 to 0 Days	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	28±7 days after last dose
Clinical Safety Labs[8]	**Master**	X		X		X	X		X		X	
Verdiperstat (BHV-3241specific PD biomarkers[10]	**Regimen**			X		X	X		X		X	
PK Blood Collection[10]	**Regimen**			X		X	X		X		X	
Biomarker Blood Collection	**Master**			X			X		X		X	
Biomarker Urine Collection	**Master**			X			X		X		X	
DNA Collection[11](optional)	**Master**			X								
CSF Collection (optional)	**Master**			X					X[17]			
Concomitant Medication Review	**Master**	X	X	X		X	X	X	X	X	X	
Concomitant Medication Review	**Regimen**				X							
Adverse Event Review[9]	**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[21]	**Regimen**			X								
Voice Recording[12]	**Regimen**			X		X	X		X		X	
Uninstall Smartphone App	**Master**										X	
Assignment to the Regimen	**Master**	X										
Randomization within the Regimen	**Master**		X									
Administer/Dispense Investigational product	**Regimen**			X[13]		X	X		X		X[14]	

Activity	Master Protocol or Regimen-Specific	Master Protocol Screening[1]	Regimen Specific Screening[1]	Baseline	Week 2[2]	Week 4[18,19]	Week 8[18,19]	Week 12	Week 16[18,19]	Week 20	Week 24 or Early Term. Visit[3,18]	Follow-up Safety Call[3,4]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone
		-42 to -1 Days	-41 to 0 Days	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	28±7 days after last dose
Study Drug Accountability/Compliance	**Master**				X[2,22]	X	X	X[22]	X	X[22]	X	
Dose Escalation	**Regimen**			X[15]	X[15]							
Exit Questionnaire	**Master**										X	
Vital Status Determination	**Master**										X[16]	

[1] Master Protocol Screening procedures must be completed within 42 days to 1 day prior to the Baseline Visit. The Regimen-Specific Screening Visit and Baseline Visit should be combined if possible.
[2] At the end of Week 2, an assessment of compliance and tolerance to this dose titration schedule will be conducted. The assessment will be conducted by phone. If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 5.3.2).
[3] Participants will only have a Follow-Up Safety Call at this time if they *do not* continue into the OLE or if they discontinue prior to Week 24. Participants who continue into OLE will have a Follow-Up Safety Call after their last dose of study drug during the OLE phase.
[4] Participants who continue into the OLE and then early terminate will be asked to complete an Early Termination Visit and Follow-Up Safety Call as described in the body of this RSA.
[5] During the Master Protocol Screening Visit, participants will be consented via the Master Protocol informed consent form (ICF). After a participant is randomized to a regimen, participants will be consented a second time via the RSA ICF.
[6]At the Regimen Specific Screening Visit, participants will have regimen-specific inclusion and exclusion criteria assessed, if applicable.
[7] Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate and temperature. Height is measured at Master Protocol Screening Visit only.
[8] Clinical safety labs include hematology (CBC with differential), complete chemistry panel, thyroid function (TSH) and urinalysis. Serum pregnancy testing will occur in women of child-bearing potential at the Master Protocol Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy.
[9] Adverse events that occur after signing the master protocol consent form will be recorded.
[10] Myeloperoxidase protein and activity, and plasma concentrations of verdiperstat will be measured. For each sample, the time of the last verdiperstat or matching placebo dose prior to sample collection, time of the last meal prior to sampling and time of the PD/PK sample collection should be reported on the CRF.

[11] The DNA sample can be collected after baseline if a baseline sample is not obtained or the sample is not usable.
[12] In addition to study visits outlined in the SOA, participants may be asked to complete twice weekly voice recordings at home. During weeks when a participant is doing a voice recording in-clinic, he or she would only do one other voice recording at home that week.
[13] Administer first dose of investigational product (IP) only after Baseline Visit procedures are completed. Participants should take the first dose of IP while in the office/clinic on the day of the Baseline visit and stay at the clinic for approximately 30 minutes post-dose for observation.
[14] Investigational product will only be dispensed at this visit if the participant continues in the OLE.
[15] From start to end of Week 1, participants will ingest either 300 mg QD of verdiperstat or matching placebo QD. From start to end of Week 2, participants will ingest either 300 mg BID of verdiperstat or matching placebo BID. Starting with Week 3 and continuing to Week 24, participants will ingest either 600 mg BID of verdiperstat or matching placebo BID.
[16] Vital status, defined as a determination of date of death or death equivalent or date last known alive, will be determined for each randomized participant at the end of the placebo-controlled portion of their follow-up (generally the Week 24 Visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant's last visit (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.
[17] If the CSF collection cannot happen at the Week 16 Visit for logistical reasons such as scheduling, it can happen at the Week 24 Visit.
[18] Participants should be instructed to skip the morning dose of study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.
[19] Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic or other reason.
[20] If required due to pandemic-related restrictions, Forced Vital Capacity (FVC) performed by a Pulmonary Function Laboratory evaluator or with a study-approved home spirometer, or sustained phonation using a study approved method may be used for eligibility (Master Protocol Screening ONLY).
[21] Two smartphone apps should be installed on the participant's phone, one to collect the voice recordings and one to collect home spirometry.
[22] Drug accountability will not be done at phone visits. A drug compliance check in must be held during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.

SCHEDULE OF ACTIVITIES – REGIMEN-SPECIFIC OPEN-LABEL EXTENSION PHASE (OPTIONAL)

Open Label Extension (Optional)										
Activity	**Week 24 Visit**	**Week 2[1]**	**Week 4[11]**	**Week 8[11]**	**Week 12**	**Week 16[10,11]**	**Week 20**	**Week 24**	**Week 28[10,11] and Q12 weeks**	**Follow-up Safety Call[3,4]**
	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Phone	Clinic	Phone
	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	112 ±7 days	140±3 days	168±3 days	Q12 weeks ±14 days	28±7 days after last dose
Vital Signs[5]	X		X	X		X			X	
Slow Vital Capacity	X		X	X		X			X	
Home Spirometry			X	X		X			X	
Muscle Strength Assessment	X									
ALSFRS-R	X		X	X	X	X	X	X	X	
ALSAQ-40	X								X[14]	
CNS bulbar Function Scale	X			X		X			X	
12-Lead ECG	X		X						X[13]	
Clinical Safety Labs[6]	X		X	X		X			X	
Biomarker Blood Collection	X					X			X[12]	
Verdiperstat (BHV-3241specific PD biomarkers[7]	X					X			X[12]	
PK Blood Collection[7]	X					X			X[12]	
Biomarker Blood Collection	X					X			X[12]	
Biomarker Urine Collection	X					X			X[12]	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	
Adverse Event Review	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	X		X	X		X			X	
Administer/Dispense Investigational product	X[8]		X	X		X			X[15]	
Drug Accountability/Compliance	X	X[16]	X	X	X[16]	X	X[16]	X[16]	X	
Dose Escalation		X[9]								

[1] At the end of Week 2, an assessment of compliance and tolerance to this dose titration schedule will be conducted. The assessment will be conducted by phone. If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 5.3.2).
[2] The last visit for the open-label extension will be at Week 52. Participants who withdraw consent or terminate early (prior to Week 52) from the study will be asked to be seen for an in-person Early Termination Visit and should have the same procedures as the Week 52 visit.
[3] Participants who continue into the OLE and then early terminate will be asked to complete an Early Termination Visit and Follow-Up Safety Call as described in the body of this RSA.
[4] Participants will have a Follow-up Safety Call approximately 28 days after the last dose of study drug. At this call, information on clinical status should be collected.
[5] Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate and temperature.
[6] Clinical safety labs include hematology (CBC with differential), complete chemistry panel, liver function tests, thyroid function (TSH) and urinalysis. Serum pregnancy testing will occur in women of child-bearing potential at the Master Protocol Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy.
[7] Myeloperoxidase protein and activity, and plasma concentrations of verdiperstat will be measured. For each sample, the time of the last verdiperstat dose prior to sample collection, time of the last meal prior to sampling, and time of the PD/PK sample collection should be reported on the CRF.
[8] Administer first dose of investigational product (IP) only after Week 24 procedures are completed. Participants should take the first dose of IP while in the office/clinic on the day of the Week 24 visit and stay at the clinic for approximately 30 minutes post-dose for observation.
[9] From start to end of Week 1, participants will ingest 300 mg QD of verdiperstat QD. From start to end of Week 2, participants will ingest 300 mg BID of verdiperstat BID. Starting with Week 3 and continuing to Week 52, participants will ingest 600 mg BID of verdiperstat BID.
[10] Participants should be instructed to skip the morning dose of study drug on the day of the study visit – at OLE Weeks 16, 28 and 52. Study drug should not be taken until after study visit procedures are complete.
[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.
[12] Biomarker Blood Collection, Biomaker Urine Collection and all regimen-specific samples will occur at OLE Weeks 16, 28 and 52 only.
[13] 12-Lead ECG is performed at OLE Weeks 4 and 52 only
[14] The ALSAQ-40 is performed at OLE Weeks 28 and 52 only
[15] Investigational product is not administered at the participant's final in-clinic visit at the completion of the OLE.
[16] Drug accountability will not be performed at phone visits. A drug compliance check-in must be held during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.

1 INTRODUCTION REGIMEN B: VERDIPERSTAT (BHV-3241)

1.1 Verdiperstat Background Information

Biohaven Pharmaceuticals, Inc [Biohaven] is developing a new drug, verdiperstat (also known as BHV-3241), for the treatment of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS).

Verdiperstat is a first-in-class, potent, selective, brain-permeable, irreversible myeloperoxidase (MPO) enzyme. MPO is one of the most abundant enzymes in activated myeloid cells, including microglia [1]. It is a lysosomal enzyme that plays essential roles in immune surveillance and host defense. In disease, innate immune system activation leads to MPO-induced pathological oxidative stress and further inflammation that contribute to cellular injury [1]. Increasing evidence suggests MPO is involved several neurodegenerative diseases [1],[2].

The proposed study is based on cumulative nonclinical, clinical, and neuroimaging studies that implicate MPO activity in the onset and progression of neurodegenerative diseases and suggest treatment with verdiperstat has the potential to slow neurodegeneration. The high unmet need for an effective treatment, together with the available data, provide a compelling rationale for the development of verdiperstat as a treatment for ALS.

Summaries of relevant findings from nonclinical and clinical studies conducted with verdiperstat are provided. Please refer to the Investigator Brochure [3] for additional information.

1.1.1 Primary Pharmacodynamics

1.1.1.1 *In Vitro Pharmacology*

Verdiperstat inhibitory potency was characterized in biochemical and cellular assays. In the biochemical assay, which was based on the physiological enzymatic activity of MPO (using chloride and hydrogen peroxide as substrates and hypochlorous acid as product), verdiperstat inhibited human MPO with an IC_{50} of 630 nmol/L. In cellular assays, MPO is not active in cellular systems unless the cells expressing the enzyme are activated, which can be accomplished by using phorbol-12-myristate-13-acetate (PMA), which promotes both an oxidative burst and extracellular release of MPO. Using PMA-activated neutrophils from human donors, verdiperstat was measured to have IC_{50} of 88 nmol/L; and using PMA-activated rat peritoneal leukocytes (primarily neutrophils), it had similar potency with an IC_{50} of 100 nmol/L.

1.1.1.2 *In Vivo Pharmacology*

- Verdiperstat efficiently inhibited MPO activity in vivo during acute rat peritonitis.
- Verdiperstat shows the ability to reduce neurodegeneration and microglial activation in MSA animal models, suggesting a potential therapeutic effect in other neurodegenerative patients.

1.1.2 Secondary Pharmacodynamics

- Verdiperstat is 14 times more potent at human MPO than at human thyroid peroxidase (TPO).

- No significant interactions were observed for any other of the over 150 targets tested, resulting in a selectivity of more than 15- to 150-fold.

1.1.3 Safety Pharmacology

A battery of safety pharmacology studies was performed with verdiperstat to examine potential effects on the cardiovascular, nervous, respiratory, renal, and gastrointestinal functions in accordance with the International Conference on Harmonization (ICH) S7A and ICH S7B guidelines for safety pharmacology studies. Please refer to the Investigator's Brochure (IB) for additional information.

- Verdiperstat had no significant effects on central nervous system, gastrointestinal, or respiratory function in rats.

- Verdiperstat had no effects on arterial blood pressure or electrocardiograms (ECGs) in telemetry studies in rats and dogs. Verdiperstat increased heart rate by 46% compared to baseline 15 minutes after administration of 600 µmol/kg (152 mg/kg) in rats.

- In the dog cardiovascular telemetry study, verdiperstat affected only heart rate, which was increased by a maximum of 52% at the mid dose and by a maximum of 84% at the high dose at 1-2 hours. The no-observed-effect level (NOEL) for cardiovascular effects was therefore 90 µmol/kg, giving a C_{plasma} of 49.8 µmol/L.

- Hemodynamic effects of verdiperstat were evaluated in telemetered dogs following acute administration of 3.5, 8, 18, and 45 mg/kg. At the three lower doses, there were no major effects compared to vehicle on mean arterial pressure, heart rate, myo-cardiac contractility, cardiac output, or total peripheral resistance. At 178 µmol/kg, with a C_{plasma} of 100 µmol/L, verdiperstat increased heart rate. In addition, aortic blood flow was slightly increased and total peripheral resistance and stroke volume were slightly decreased. The cardiovascular response evoked by a rapid orthostatic tilt following oral administration of verdiperstat at 5, 18, and 45 mg/kg was evaluated. Administration of 45 mg/kg verdiperstat caused a significant increase in heart rate at pre-tilt for up to 2 hours post-dosing, whereas no relevant variations were observed on arterial blood pressure. No incidents of orthostatic hypotension were observed following administration of verdiperstat at any of the doses tested.

1.2 Verdiperstat Rationale

Oxidative stress

Based on extensive supportive evidence from human ALS and animal models, oxidative stress is thought to promote neurodegeneration in ALS and other disorders [4]. MPO catalyzes generation cytotoxic oxidizing and nitrosylating compounds, e.g., hypochlorous acid and peroxynitrite [5] [6] which are strongly implicated in the pathophysiology of ALS. This is because biological macromolecules undergo oxidative damage by reactive oxygen and nitrogen species (ROS/RNS), which leads to organelle dysfunction and neuronal death. Free radical scavengers and other antioxidants are obvious treatment approaches but have had disappointing effects in clinical trials. Advances in ROS/RNS biology explain the failure of such antioxidants and suggest more mechanistic strategies for reducing oxidative stress. ROS/RNS are not merely toxic metabolic waste products. Rather, they are part of complex cellular signaling networks that include ROS/RNS producing enzymes (MPO, NADPH oxidase [NOX], xanthine oxidase), ROS targets (NF-κB mediated inflammatory pathways, inflammasomes), and ROS-metabolizing enzymes (SOD and NRF2-regulated antioxidant pathways). Deregulation of ROS/RNS pathways contributes to other known neurodegenerative disease mechanisms, i.e., microglial activation and neuroinflammation. Thus, it may be advantageous to inhibit ROS/RNS producing enzymes, such as MPO, thereby reducing oxidative stress and inflammation in a physiologic manner. The general relevance of this strategy is supported by preliminary data that suggest inhibiting NOX reduces microglial activation and may have other benefits in an ALS model [7].

Neuroinflammation

Based on extensive supportive evidence from human ALS and animal models, neuroinflammation is also thought to be an important mediator of neurodegeneration in ALS and other disorders [8], [9]. Microglia, the primary innate immune cells of the brain, are central players that drive neuroinflammation. In disease, resting microglia are activated or transformed into a pathological "M1" phenotype that is characterized by secretion of pro-inflammatory cytokines and ROS/RNS as well as an ameboid morphology and phagocytic properties similar to peripheral macrophages. Modulating microglial activation is a promising and common therapeutic strategy for neurodegenerative diseases, including ALS. However, it is unclear how to determine the optimal molecular target for intervention in this dynamic, in vivo process from studies in disease models.

Positron emission tomography (PET) imaging of translocator protein (TSPO) is a state-of-the-art method for assessing pathological neuroinflammation in human disease states Because TSPO is highly expressed in activated microglia, signal from TSPO-specific radioligands, such as [^{11}C]-PBR28, is interpreted as a measure of microglial activation. [^{11}C]-PBR28 PET signal is dynamic, responsive to treatment, and potentially predictive of benefit on clinical outcome measures. Thus, [^{11}C]-PBR28 PET is a valuable pharmacodynamic biomarker for anti-inflammatory therapies that can demonstrate central target engagement and provide proof of mechanism of action in human neurodegenerative disorders [10]. Cross-sectional and longitudinal [^{11}C]-PBR28 PET studies in participants with ALS show that [^{11}C]-PBR28 signal is increased in ALS but

stable over at least 6 months of disease progression. Corresponding sample size and power calculations suggest [^{11}C]-PBR28 PET is a sensitive biomarker allowing for efficient signal detection in smaller, early phase studies. Several such studies are ongoing to assess investigational treatments in ALS, however none of these treatments has yet demonstrated the ability to decrease [^{11}C]-PBR28 uptake. By contrast, MPO inhibition is the only approach that has demonstrated the ability to decrease [^{11}C]-PBR28 uptake in human neurodegenerative disease, highlighting the therapeutic relevance of this target for ALS.

Additional

MPO may also play a role in increasingly recognized disease mechanisms mediated by peripheral myeloid cells, including those that migrate into the brain as well as those that remain in the periphery [8], suggesting relevance of MPO as a therapeutic target at both sites. For example, circulating immune cell numbers (particularly neutrophils) appear to correlate with ALS disease progression measured by ALSFRS-R. And, MPO^+ neutrophils seem to contribute to distal motor axon and muscular pathology in human ALS autopsy tissue and in an ALS animal model.

1.2.1 Dosage Selection and Justification

The dosage of verdiperstat selected for evaluation in this study is 600 mg BID. This dosage was selected based on cumulative experience, including nonclinical toxicology and safety/tolerability, pharmacokinetic, pharmacodynamic, and preliminary efficacy data from phase 1 and phase 2 studies.

Nonclinical toxicology: The program for verdiperstat is comprehensive and supports oral administration in the clinic for chronic treatment. The following studies were included in the toxicology program: single and repeat-dose toxicity in rats and dogs, genotoxicity, reproductive toxicity, phototoxicity, and safety pharmacology. The verdiperstat 600 mg BID dosage is anticipated to produce pharmacokinetic exposures below limits set based on nonclinical toxicology data.

Clinical studies: As of January 2021, approximately 490subjects have received verdiperstat in completed and ongoing studies. In the phase 1 studies (5 completed studies) in healthy subjects, treatment with multiple dosages of up to 900 mg BID was generally safe and well tolerated. In the completed phase 2 studies in participants with Parkinson's disease and Multiple System Atrophy (MSA), treatment at dosages of up to 600 mg BID for 8-12 weeks was generally safe and well tolerated. In the phase 2 studies, the 600 mg BID dosage decreased MPO activity in plasma, providing evidence of peripheral target engagement; reduced TSPO binding on brain PET imaging, providing evidence of central target engagement and proof of mechanism (decreased microglial activation/neuroinflammation); and demonstrated favorable, dose-dependent trends on clinical efficacy measures at 12 weeks in subjects with MSA.

A phase 3 study in patients with MSA is ongoing and currently is still blinded. In this study, approximately 336 subjects have received verdiperstat or placebo. Subjects are randomized 1:1

to receive verdiperstat or placebo, 600 mg BID, for 48 weeks with the option to continue in the study for an additional 48 weeks of open-label treatment with verdiperstat. Please refer to the Investigator's Brochure [3] for additional information.

2 STUDY OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective:
To evaluate the efficacy of verdiperstat as compared to placebo on ALS disease progression.

Secondary Efficacy Objective:

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

Safety Objective:

- To evaluate the safety of verdiperstat for ALS.

Exploratory Efficacy Objective:

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

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

Secondary Efficacy Endpoints:

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

Safety Endpoints:

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

Exploratory Efficacy Endpoints:

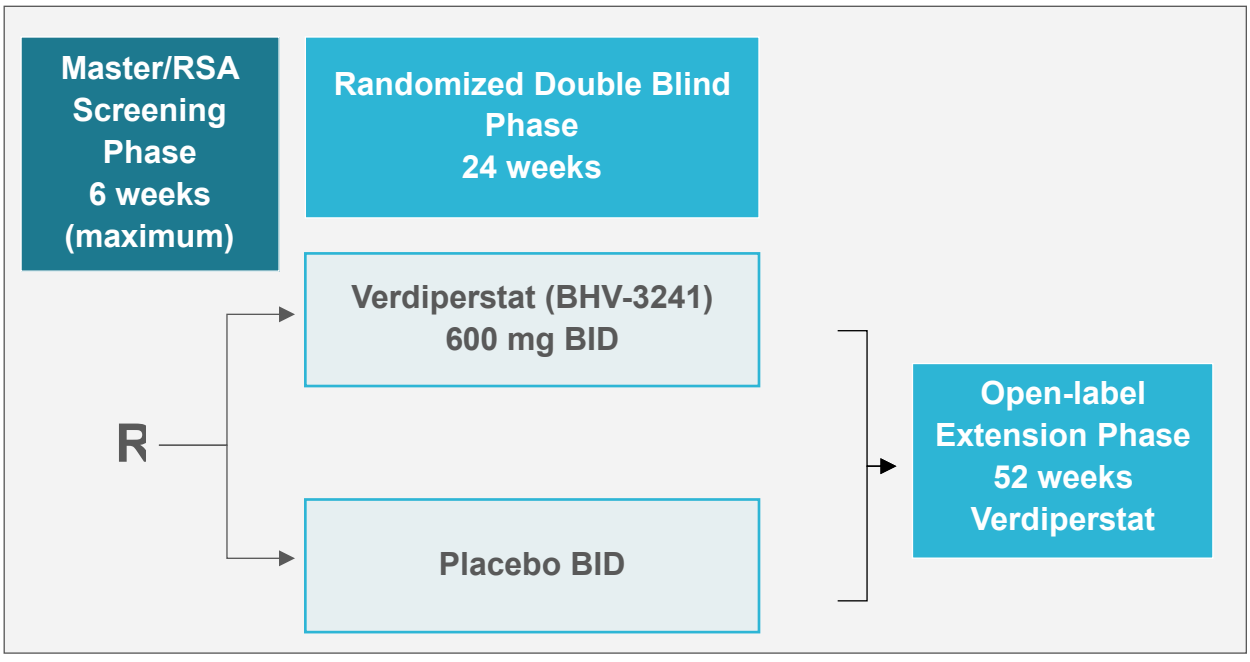
- Changes in quantitative voice characteristics.
- Changes in biofluid biomarkers of neurodegeneration.

- Changes in patient reported outcomes.
- Changes in verdiperstat PK and PD biomarkers.
- Change in respiratory function as assessed by home spirometry.

3 RSA DESIGN

This study is a multicenter, randomized, double-blind, 2-arm placebo-controlled parallel-group study designed to evaluate the efficacy and safety of verdiperstat in a population of participants with ALS. The study is planned to consist of a Screening phase lasting a maximum of approximately 6 weeks (42 days) and a randomized double-blind treatment phase of approximately 24 weeks (see Figure 1). It is anticipated that the Randomization phase will include a dose titration period of approximately 2 weeks followed by a full dosage period of approximately 22 weeks. Participants completing 24 weeks of treatment with verdiperstat or placebo will be eligible to continue to an Open-label Extension Phase (OLE) which will include an additional 52 weeks of dosing. Approximately 160 participants in total are planned to be randomized in a 3:1 ratio to receive either verdiperstat 600 mg BID, or matching placebo BID. The assessments for each visit are outlined in the Schedule of Activities (SoA).

Figure 1. Regimen Specific Appendix Schematic



3.1 Scientific Rationale for RSA Design

This RSA is designed to correspond with the design of the Master Protocol and the goals of that study.

3.2 End of Partipation 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

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

3.3 End of Regimen Definition

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

The end of the OLE period in a Regimen occurs when all participants who initiated open-label study drug 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 160 participants will be randomized into this Regimen.

4.2 Additional RSA Inclusion and Exclusion Criteria

To be randomized to an RSA, participants must meet the Master Protocol eligibility criteria. In addition, participants meeting all the following inclusion and exclusion criteria will be allowed to enroll in this Regimen.

4.2.1 RSA Inclusion Criteria

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

4.2.2 RSA Exclusion Criteria

- Participants who are taking strong inhibitors of CYP1A2 (i.e., ciprofloxacin, enoxacin, fluvoxamine, zafirlukast) for chronic/long-term use defined as more than two weeks.

- Participants who are taking strong inhibitors of CYP3A4 (i.e., conivaptan, itraconazole, ketoconazole, posaconazole, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, and certain antiviral agents [cobicistat, danoprevir, ritonavir, elvitegravir, indinavir, lopinavir, paritaprevir, ombitasavir, dasabuvir, saquinavir, tipranavir, nelfinavir]) for chronic/long-term use defined as more than two weeks. Note: Topical antifungal use is not exclusionary. Participants should not consume large quantities of grapefruit juice (more than 8oz per day) on a regular basis.

There are RSA-specific requirements that apply to Master Protocol exclusion criteria #6. For further details of contraceptive requirements for this RSA, please refer to Section 5.8.2.

*Guidance regarding CYP1A2 and CYP3A4 has been updated in Protocol Section 5.8 Drug-Drug Interactions and Prohibited Medications, however this exclusion criteria has **not** been modified as all participants have been enrolled.*

4.3 Treatment Assignment Procedures

Each participant who meets all eligibility criteria for the RSA will be randomized to receive either verdiperstat or matching placebo for approximately 24 weeks of treatment. Participants who complete the 24-week blinded Treatment Period will be eligible to continue treatment with open-label verdiperstat for an additional 52 weeks.

5 INVESTIGATIONAL PRODUCT

The Investigational Product (IP) should be stored in a secure area according to local regulations. It is the responsibility of the Site Investigator (SI) to ensure that the IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the IP is verdiperstat 300 mg extended release (ER) tablets and matching placebo tablets.

5.1 Investigational Product Manufacturer

Biohaven Pharmaceuticals, Inc. is the manufacturer of verdiperstat.

5.2 Labeling, Packaging, and Resupply

5.2.1 Labeling

Container(s) of investigational product will bear a label containing (at a minimum) the name of the study drug, lot and/or batch number and appropriate storage conditions (15°-25°C [59°-77°F] [see USP controlled room temperature] in a tightly closed container, protected from light).

The drug product is presented as verdiperstat Extended Release (ER) Tablets that are reddish-beige, film coated and oval (300 mg strength). The tablets each consist of 300 mg of verdiperstat drug substance as free base, and generally recognized as safe (GRAS) excipients for oral dosage forms including hydroxypropyl methyl cellulose, microcrystalline cellulose, hydroxypropyl cellulose, sodium stearyl fumarate and orange color. Matching placebo tablets contain microcrystalline cellulose and sodium stearyl fumarate and are film-coated with OPADRY® (mixture of hypromellose, polyethylene glycol and titanium dioxide) and iron oxide to give reddish-beige color. The tablets are packed in high-density polyethylene (HDPE) bottles. The bottles are induction sealed and closed with child resistant polypropylene (PP) screw caps.

All investigational products should be kept in a secure area with limited access under appropriate storage conditions: 15°-25°C (59°-77°F) (see USP controlled room temperature) in a tightly closed container, protected from light.

Excursions outside this storage temperature range should be reported as per the Pharmacy Manual Instructions.

5.2.2 Acquisition and Preparation

Initially, after informed consent is obtained at the Screening Visit, the SI or designee will enter the participant into the study and obtain a participant number assignment. After completion of Screening evaluations, all eligible participants will be randomized, in a 3:1 ratio to receive either verdiperstat (600 mg BID) or matching placebo, using an EDC.

5.2.3 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.

5.3 Study Medication/Intervention, Administration and Duration, and Titration

All participants will be randomized to receive verdiperstat 600 mg BID or matching placebo BID. Participants should take the study drug twice a day; dosing in the morning and evening approximately 12 hours apart.

The tablets should be swallowed whole with a drink of water (or other liquid) or swallowed with substances of other consistencies as appropriate (e.g., apple sauce). The tablets should not be split, chewed, or crushed.

Study medication can be taken without regard to meals.

5.3.1 Administration and Duration

Day 1/first dose:

Participants should be administered the Day 1/first dose of study medication (300 mg QD or matching placebo QD) while in the office/clinic on the day of the Regimen-Specific Baseline visit after all visit assessments are complete. Participants should stay at the office/clinic for monitoring for approximately 30 minutes post-dose.

Dose titration period:

From the beginning to the end of Week 1 participants should ingest either 300 mg QD of verdiperstat or matching placebo QD. From the beginning to the end of Week 2, participants should ingest either 300 mg BID of verdiperstat or matching placebo BID.

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

Full dose period:

Starting with the beginning of Week 3 and throughout the remainder of the study, participants should ingest either 600 mg BID of verdiperstat or matching placebo BID.

At the Weeks 4, 8, 16, and 24 study visits, the morning dose of study medication should be held on the day of the study visit and administered in the clinic/office during the study visit, to collect one pre-dose (trough) PK and PD blood sample (see Section 8).

5.3.2 Dosage Modification

Participants will be instructed on the dosing regimen. If tolerability issues are experienced during the dosage titration period with the 300 mg QD and/or 300 mg BID doses (or matching placebo), the titration schedule may be extended (e.g., up titration to the next dosage level delayed by an additional week). Potential tolerability issues may include sudden, clinically significant changes from baseline in symptoms of presyncope, syncope, orthostatic hypotension, or falls that are not otherwise explained. The SI must consult with the Medical Monitor if he or she believes that a change to the dosage titration schedule is warranted; and, the SI must document any such changes to the dosage titration schedule.

During the full dose period of the study, it is anticipated that all participants will receive either verdiperstat 600 mg BID or matching placebo BID. If participants have difficulty tolerating verdiperstat 600 mg BID or matching placebo BID dosing, the SI may permit the participants to switch to verdiperstat 300 mg BID or matching placebo BID dosing (and document this change in the participant's records). Potential tolerability issues may include those listed above as well as clinically significant laboratory abnormalities (i.e., thyroid and renal function) that are not otherwise explained. Down titration to verdiperstat 300 mg BID or matching placebo BID will only be allowed to address tolerability issues and only with Medical Monitor approval. If a participant is down titrated to the 300 mg BID dose, they may be allowed to retry the 600 mg BID dose (re-challenge), if deemed appropriate by the SI and Medical Monitor. Only two re-challenges are allowed. Any such changes must be documented. If a switch to verdiperstat 300 mg BID or matching placebo BID dosing does not result in acceptable tolerability, then dosing should be discontinued.

Dosage modification should be considered if a participant experiences one of the following:

a. Clinically significant changes in frequency and/or severity from baseline in symptoms of presyncope, syncope, orthostatic hypotension, and/or falls that are not explained by disease progression or intercurrent illness and not able to be adequately treated with symptomatic pharmacological and non-pharmacological treatments, based on the judgement of the SI.

b. Development of Grade 3 or Grade 4 hypothyroidism. Re-challenge may be attempted, if warranted, when improved to less than or equal to Grade 2 (inclusive of treatment with thyroxine replacement therapy, see Section 9.1).

c. Development of a greater than or equal to Grade 3 toxicity or an intolerable side effect attributed to verdiperstat based on the judgement of the SI. Re-challenge may be attempted, if warranted, when symptoms improve to less than or equal to Grade 1.

5.4 Drug Holiday

Other dosage reductions or holidays may be determined by the SI who should consult with the Medical Monitor. If a participant experiences an AE for which the SI believes a dose reduction or holiday is warranted, then the SI may temporarily suspend dosing (dose holiday) until such time as he/she feels it is safe for the participant to return to the assigned dose. Any such modifications to the dosage regimen should be noted in the eCRF. If greater than seven days, then a discussion with the Medical Monitor must take place and is required. If a participant is off study drug for more than 14 consecutive days, the participant should re-escalate using the titration paradigm described in section 5.3.1.

5.5 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 study drug 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.

If the participant loses the ability to swallow while enrolled in Regimen B, the participant will no longer be able to take the study drug as directed. If this occurs the participant will discontinue study drug and will be asked to complete the 6-month study under ITT.

5.6 Justification for Dosage

The dosage of verdiperstat proposed for evaluation in this ALS platform trial regimen is 600 mg BID. This dosage selection was based on cumulative clinical and nonclinical experience with verdiperstat, including nonclinical toxicology, safety and efficacy data in multiple system atrophy and Parkinson's disease patients. Please refer to the Investigator's Brochure [3] for additional information.

5.7 Overdose

An overdose is defined as the accidental or intentional administration of any dose of the product that is considered both excessive and medically important. All occurrences of overdose as defined above (suspected or confirmed and irrespective of whether or not it involved

verdiperstat) must be communicated to the Healey Center and Biohaven Pharmaceutical or a specified designee within 24 hours of the SI becoming aware of the updated information and be fully documented as an SAE. An SAE is reported for overdose when the SI feels the overdose was excessive and medically important. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

5.8 Drug-Drug interactions and Prohibited Medications

5.8.1 Effect of other drugs on verdiperstat metabolism

Verdiperstat drug-drug interactions have been evaluated in clinical DDI studies. One recently conducted study evaluated the effect of fluvoxamine (a strong CYP1A2 inhibitor) on concomitantly administered verdiperstat [11]. Fluvoxamine increased the AUC of verdiperstat 2.2-fold and the Cmax by 68%, indicating that verdiperstat is a moderately sensitive CYP1A2 substrate. Therefore, interactions are expected to occur when verdiperstat is given concurrently with agents that affect CYP1A2. In order to minimize any potential safety risks:
:

- Strong inhibitors of CYP1A2 (i.e., ciprofloxacin, enoxacin, fluvoxamine) could potentially increase verdiperstat levels and **should be excluded** for both chronic/long-term and acute/short-term use.

- Moderate inhibitors of CYP1A2 (i.e., methoxsalen, mexiletine) could potentially increase verdiperstat levels and should be used with caution for chronic/long-term (>2 weeks) use, based on the clinical judgement of the SI.

- Moderate inducers of CYP1A2 (i.e., phenytoin, rifampin, ritonavir, and teriflunomide) could reduce verdiperstat levels and should be used with caution for chronic/long-term (>2 weeks) use, based on the clinical judgement of the SI.

An additional clinical DDI study, which was recently conducted, tested the effect of itraconazole (a strong CYP3A4 inhibitor) on concomitantly administered verdiperstat [12]. Itraconazole did not have a clinically significant impact on verdiperstat exposure, indicating that verdiperstat is not a sensitive CYP3A4 substrate in vivo. Therefore, there are no recommended DDI-based restrictions to concomitant administration of CYP3A4 inhibitors or inducers with verdiperstat.

5.8.2 Effect of verdiperstat on the metabolism of other drugs:

A clinical DDI study was recently conducted to evaluate the effect of verdiperstat on concomitantly administered midazolam (a sensitive CYP3A4 substrate) [13]. Verdiperstat moderately reduced the exposure of midazolam and a ~2.5-fold increase of hydroxy-Metabolite/Parent ratio confirmed metabolic induction as the mechanism for midazolam exposure decrease. These results support the conclusion that verdiperstat is a moderate CYP3A4

inducer. Therefore, interactions are expected to occur when verdiperstat is given concurrently with agents that are principally metabolized by CYP3A4.

Drugs principally metabolized by CYP3A4 (i.e., atorvastatin, buspirone,, ethinylestradiol [hormonal contraceptives], quetiapine, telithromycin, quinidine, verapamil, warfarin, zileuton) should be used with caution, based on the clinical judgement of the SI. Note: The effectiveness of certain estrogen-containing oral hormonal contraceptives may potentially be reduced. Women of childbearing potential (WOCBP) who use estrogen-containing oral hormonal contraceptives must use alternative and/or additional barrier methods of birth control while participating in this RSA. Procedures for documenting alternative and/or additional methods of birth control will be detailed in the Manual of Procedures.

In vitro, verdiperstat markedly induced human CYP2B6 at 50 μmol/L, but not at 1 mol/L [14]. The verdiperstat dosage of 600 mg BID measured in previous studies generated a steady state, geometric mean C_{max} level of 4.15 μmol/L [CV: 41.6%]). Thus, verdiperstat is unlikely to cause significant enhancements in the clearance of coadministered drugs through CYP2B6 inductive processes at therapeutic verdiperstat concentrations.

Nonetheless, interactions may theoretically occur when verdiperstat is given concurrently with agents that are principally metabolized by CYP2B6. Verdiperstat induction of CYP2B6 may reduce exposures of CYP2B6 substrates, leading to potential loss of efficacy. Therefore, in order to minimize any potential safety risks:

- Drugs principally metabolized by CYP2B6 (i.e., bupropion, cyclophosphamide, efavirenz, ifosfamide, methadone) should be used with caution, based on the clinical judgement of the SI.

5.9 Verdiperstat Known Potential Risks and Benefits

ALS is an adult-onset, fatal neurodegenerative disease. No disease modifying treatment currently exists, only symptomatic and palliative approaches are available. Verdiperstat is an irreversible inhibitor of the MPO enzyme that promotes oxidative stress and neuroinflammation. The high unmet need for an effective treatment for ALS, together with the available preclinical and clinical data with verdiperstat, provide a compelling and favorable overall benefit-risk assessment for the development of verdiperstat at the 600 mg BID dosage as a treatment for ALS. The safety monitoring in the planned clinical study will minimize the potential risks to study participants.

5.9.1 Known Potential Risks

Preclinical and clinical studies have demonstrated an acceptable safety and tolerability profile for verdiperstat but do suggest specific potential risks. The present study includes general and specific safety procedures anticipated to minimize any potential risks.

General procedures will include frequent safety assessments by SIs, thorough evaluations and review of AEs and SAEs on an ongoing basis to monitor for any safety signals or trends by the

Sponsor and Medical Monitor, and Data Safety Monitoring Board review of the benefit-risk of the study for participants.

5.9.1.1 *Thyroid*

In preclinical studies, reversible histopathological changes in the thyroid gland and reversible thyroid hormone changes were observed. In clinical studies, verdiperstat has been associated with laboratory changes indicative of decreased thyroid function. Specifically, there have been increases over time in mean TSH levels and some decreases over time in mean free T4 and mean free T3 levels relative to placebo. Most participants did not have thyroid function test values outside the normal range, and the abnormalities that occurred were mild. Changes in thyroid function tests associated with verdiperstat returned toward baseline levels during the period of observation following discontinuation of verdiperstat.

In aggregate, clinically significant thyroid function abnormalities were rare or infrequent with verdiperstat. The present study will involve monitoring of thyroid function. Thyroid function test abnormalities indicating clinically significant thyroid hormone deficiency are readily treatable with thyroid hormone replacement (see Section 9.1).

5.9.1.2 *Renal*

Reversible renal findings were observed in the 1-month preclinical studies in female rats at high doses, and no renal changes were noted in the 6-month study. In clinical studies, verdiperstat has been associated with decreases in mean uric acid levels over time relative to placebo. A variable proportion of participants receiving verdiperstat have had plasma uric acid levels below the lower limit of normal. Decreases in uric acid levels associated with verdiperstat have tended to return toward baseline following the discontinuation of dosing. Indices of renal function have not shown any abnormalities associated with verdiperstat. The mechanism of the changes in uric acid levels is unclear but could include decreased uric acid production or decreased renal tubular reabsorption. Hypouricemia is thought to be a biochemically defined disorder with no known clinical significance.

In aggregate, clinically significant renal events associated with decreases in uric acid levels have not been observed with verdiperstat. The present study will continue to monitor for indices of renal function.

5.9.1.3 *Cardiovascular*

Increases in heart rate were observed in dogs during the preclinical studies. However, verdiperstat had no effect on blood pressure or on ECG parameters at any dose. Two studies evaluating cardiovascular response to orthostatic tilt in dogs were also performed; no incidences of orthostatic hypotension were observed following administration of verdiperstat.

The first SAD clinical study [15] was discontinued on the basis of AEs that included syncope associated with brief sinus pauses detected on cardiac telemetry. Two of the cases of syncope were associated with orthostatic testing. There was not a relationship between these events and

verdiperstat concentrations. There was no evidence of direct proarrhythmic or other cardiotoxic effects. It was considered that events of syncope may have represented an exaggerated physiological response to study procedures, involving syncope of neurocardiogenic origin. However, an effect of verdiperstat could not be ruled out. A second SAD study [16] was conducted with 2 modifications designed to reduce the risk of syncope: (1) the exclusion of participants with a history of recurrent presyncope and/or syncope in connection with orthostatic challenge, and (2) fractionated dosing. In this second SAD study, there were no episodes of presyncope or syncope, and no clinically relevant findings involving vital signs or ECG parameters. Subsequent clinical studies have used ER formulations and there have been no cases of syncope in participants receiving verdiperstat. There have been some AEs potentially related to syncope (e.g., dizziness, orthostatic hypotension). Overall, there have been no clinically relevant findings involving vital signs or ECGs, with the exception of some decreases in the mean RR interval observed in the verdiperstat 600-mg BID group in the safety/tolerability study conducted in participants with Parkinson's disease [17].

In the clinically concluded Phase 1 study (BHV3241-101), the effect of verdiperstat on ECG parameters was evaluated in 14 healthy volunteers. Preliminary analyses of continuous ECG recordings (Holter monitors) demonstrated that verdiperstat may have had an effect on heart rate, but no clinically relevant effects on the QTcF, PR, or QRS intervals.

In the ongoing, blinded Phase 3 study in subjects with MSA (BHV3241-301) and Phase 2/3 study in subjects with ALS, cardiovascular events have been reported. Independent Data Monitoring Committees are responsible for reviewing unblinded study data from each study on a regular basis in order to safeguard the interests of the enrolled study subjects and for monitoring the benefit-risk profile of the blinded clinical study.

In aggregate, the clinical data do not show clear evidence of significant cardiovascular abnormalities associated with administration of verdiperstat ER formulations. However, an effect of verdiperstat cannot be ruled out, and cardiovascular TEAEs and parameters, including vital signs and ECGs, will continue to be monitored in this study.

5.9.1.4 *Liver*

Minimally non-adverse, increased alanine aminotransferase and slight (adaptive) histopathological effects in the liver were observed in rats during the preclinical studies; these are likely related to enzyme induction (e.g., CYP2B1 induction). In the MAD study [18], several participants, including those receiving verdiperstat and placebo, had increases in hepatic transaminases.

In the ongoing, blinded Phase 3 study in subjects with MSA (BHV3241-301), preliminary data indicate that 4 subjects (1.2%) discontinued the study due to elevations in liver enzymes. Of these, 3 subjects had elevations 5x upper limit of normal. All 4 subjects were asymptomatic, and the elevations in liver enzymes were isolated without increased bilirubin levels. Elevated levels returned to normal in a few weeks.

In aggregate, the clinical data show a possible association of asymptomatic and reversible liver enzyme increases with verdiperstat. The present study will involve monitoring of liver function tests.

5.9.2 Known Potential Benefits

The rationale for the proposed study is based on cumulative preclinical and clinical studies that implicate MPO activity in the onset and progression of neurodegenerative diseases and suggest treatment with verdiperstat has the potential to reduce oxidative stress and neuroinflammation (microglial activation).

6 REGIMEN SCHEDULE

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
- Blood samples for PK and PD analyses
- Smartphone installation and removal
- Voice recording

Modifications to Regimen Schedule

Designated visits in the Schedule of Activities (i.e. Week 4, Week 8, and Week 16) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic 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 (Week 8 and 16 only)
- Voice Recording
- CNS Bulbar Function Scale (Week 8 and 16 only).

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

Blood samples for PK and PD analyses and the Week 8 ECG (Week 8 only) are **not** collected during the remote visits by the home health agency and this should be recorded as such in the applicable source documentation and EDC.

6.1 Placebo-Controlled Period

6.1.1 Verdiperstat Regimen Specific Screening Visit

This visit will take place in-person after the Master Protocol randomization to a regimen. There are no additional procedures specific for the verdiperstat RSA other than what is being done at the Master Protocol.

Participants may be required to reconsent to the regimen if new procedures or information 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.

6.1.2 Baseline Visit

This visit will take place in-person after the Regimen-Specific Screening Visit. The following procedures will be performed for the regimen schedule:

- ALSAQ-40
- CNS Bulbar Function Scale
- Collection of plasma samples for verdiperstat PD biomarkers (MPO protein and activity) and a plasma PK sample
- Install Smartphone App
- Home Spirometry
- Voice Recording
- Dispense IP
- Remind participant to bring IP to the next visit

After all Baseline procedures are completed, administer a single 300 mg tablet of verdiperstat or placebo. Participants should stay at the clinic for approximately 30 minutes for observation.

Participants should be instructed:

- To ingest either 300 mg QD of BHV-3241 or matching placebo QD for the rest of Week 1.
- To ingest either 300 mg BID of BHV-3241 or matching placebo BID starting at the beginning of Week 2.
- Participants should take the study drug twice a day; dosing in the morning and evening approximately 12 hours apart.

6.1.3 Week 2 Telephone Visit

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

- Collection of concomitant medication information.
- An assessment of compliance (i.e. whether participant has stopped taking study drug) and tolerance to this dose titration schedule.
  - If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 5.3.2).
- Participants should be instructed:
  - Starting at the beginning of Week 3, to ingest either 600 mg BID of verdiperstat or matching placebo BID and continue taking this dosage through the remainder of the 24-week Treatment Period.

6.1.4 Week 4 Visit

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

This visit will take place in-person 28 ± 7 days after the Baseline Visit. The following procedures will be performed for the regimen schedule:

- Collection of plasma samples for verdiperstat PD biomarkers (MPO protein and activity) and a plasma PK sample
- Voice Recording
- Dispense IP
- Remind participant to bring study drug to the next visit

6.1.5 Week 8 Visit

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

This visit will take place in-person 56 ± 7 days after the Baseline Visit. The following procedures will be performed for the regimen schedule:

- Home Spirometry
- CNS Bulbar Function Scale
- 12-Lead ECG
- Collection of plasma samples for verdiperstat PD biomarkers (MPO protein and activity) and a plasma PK sample
- Voice recording
- Dispense IP
- Remind participant to bring IP to the next visit

6.1.6 Week 12 Telephone Visit

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

6.1.7 Week 16 Visit

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

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

- 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.
- Home Spirometry
- CNS Bulbar Function Scale
- Collection of plasma samples for verdiperstat PD biomarkers (MPO protein and activity) and a plasma PK sample
- Voice Recording
- Dispense IP
- Remind participant to bring IP to the next visit

6.1.8 Week 20 Telephone Visit

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

6.1.9 Week 24 Visit or Early Termination Visit

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

The Week 24 Visit will take place in-person 168 ± 7 days after the Baseline Visit. The following procedures will be performed at either the Week 24 Visit or the Early Termination Visit for the regimen schedule:

- Home Spirometry
- ALSAQ-40
- CNS Bulbar Function Scale
- Collection of plasma samples for verdiperstat PD biomarkers (MPO protein and activity) and a plasma PK sample
- Voice Recording
- Uninstall Smartphone App
- Dispense IP (only if continuing in OLE)
- Remind participant to bring IP to the next visit

For participants rolling into the OLE, all participants should be instructed to follow the dose escalation scheme.

- After all Week 24 procedures are completed, administer a single 300 mg tablet of verdiperstat. Participants should stay at the clinic for approximately 30 minutes for observation.
- Dispense study drug to last for the next 4 weeks.
- Participants should be instructed:
  - To ingest 300 mg QD of BHV-3241 for the rest of Week 1.
  - To ingest 300 mg BID of BHV-3241 starting at the beginning of Week 2. Participants should take the study drug twice a day; dosing in the morning and evening approximately 12 hours apart.
    - If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 5.3.2).
  - To ingest 600 mg BID of BHV-3241 starting at the beginning of Week 3 and through the remainder of the 52-week OLE. Participants should take the study drug twice a day; dosing in the morning and evening approximately 12 hours apart.

For participants NOT rolling into the OLE:

A Follow-up Safety Call should be scheduled approximately 28 days after last dose of study drug to collect clinical status information.

6.1.10 Follow-Up Safety Call

Participants will have a Follow-Up Safety Call 28+7 days after their last dose of study drug. Only those participants NOT continuing on in the Open Label Extension will have the Follow-Up Safety Call following 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*)

6.1.11 Process for Early Terminations

Participants who early terminate from the study and do not complete the protocol per ITT 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. The Follow-Up Safety Call should be completed approximately 28±7 days after the last dose of study drug. If the participant terminates early 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±7 days after the last dose of IP.

If the Early Termination Visit occurs approximately 28±7 days after the last dose of study drug, the information from 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±7 days of the last dose of study drug, the Follow-Up Safety Call should occur approximately 28±7 days after the last dose of study drug and the Early Termination Visit will be completed after the Follow-Up Safety Call.

6.1.12 Criteria for Participant Termination

Participants MUST discontinue the IP (and non-investigational product at the discretion of the SI) for any of the following reasons:

- Withdrawal of informed consent (participant's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the SI or sponsor, indicates that continued participation in the study is not in the best interest of the participant

- Disease progression, which, in the opinion of the SI or sponsor, indicates that continued participation in the study is not in the best interest of the participant
- Pregnancy
- Termination of the study by the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

All participants who discontinue study treatment earlier than Week 24 should comply with protocol specified Early Termination procedures as appropriate, outlined in the Schedule of Activities.

An exception to the requirement for End of Treatment procedures is when a participant withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

6.2 Open Label Extension (OLE)

Participants who have completed the placebo-controlled portion of the trial on drug, will be eligible to continue in the Open Label Extension. The OLE of the study will continue until verdiperstat is approved and available in the United States, or Biohaven Pharmaceuticals terminates development of verdiperstat for ALS.

Modifications to OLE Schedule

Designated visits in the Schedule of Activities for the OLE (i.e. Week 4, Week 8, Week 16, Week 28, and Week 40) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic 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 Manaul of Procedures.

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

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

Blood samples for Week 16 PK and PD analysis and the Week 4 and 28 ECGs are **not** collected during the remote visits by the home health agency and this should be recorded as such in the applicable source documentation and EDC.

6.2.1 Week 2 Telephone Visit - OLE

This visit (via telephone) will take place 14 ± 3 days after the Week 24 visit. The procedures listed in the SoA should be performed including:

- Assess and document AEs and concomitant medications, including Key Study Events (see section 10.3 of Master Protocol)
- Assess compliance and tolerance to this dose titration schedule
  - If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 5.3.2).
- Instruct participants on appropriate dosing
  - Starting at the beginning of Week 3, to ingest 600 mg BID of verdiperstat and continue taking this dose through the remainder of the 52-week OLE
- Remind participant to bring in IP to the next visit

6.2.2 Week 4 Visit – OLE

This visit will take place in-person 28 ± 10 days after the Week 24 Visit of the placebo-controlled portion of the trial. The procedures listed in the SoA should be performed and participants should be provided with 4 weeks of drug and instructions for dosing.

6.2.3 Week 8 Visit - OLE

This visit will take place in-person 56 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The procedures listed in the SoA should be performed and participants should be provided with 8 weeks of drug and instructions for dosing.

6.2.4 Week 12 Telephone Visit – OLE

This visit will take place 84 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial via telephone. The procedures listed in the SoA should be performed.

6.2.5 Week 16 Visit – OLE

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

This visit will take place in-person 112 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The procedures listed in the SoA should be performed and participants should be provided with 12 weeks of drug and instructions for dosing.

6.2.6 Week 20 Telephone Visit – OLE

This visit will take place in-person 140 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The procedures listed in the SoA should be performed.

6.2.7 Week 24 Telephone Visit – OLE

This visit will take place 196 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial via telephone. The procedures listed in the SoA should be performed.

6.2.8 Week 28 Visit and Q12 Weeks – OLE

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

This visit will take place in-person 196 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. The procedures listed in the SoA should be performed and participants should be provided with 8 weeks of drug and instructions for dosing. Following the Week 28 OLE Visit, visit will occur every 12 weeks ± 14 days.

7 OUTCOME MEASURES AND ASSESSMENTS

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

7.1 Voice Analysis

Voice samples will be collected twice per week, using an app installed on either an android or iOS based smartphone. The app characterizes ambient noise, then asks 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 patient self-report health status patient-reported outcome. The ALSAQ-40 consists of forty questions that are specifically used to measure the subjective well-being of patients with ALS and motor neuron disease.

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

7.3 Center for Neurologic Study Bulbar Function Scale

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

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

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

7.4 Home Spirometry

Remote/home-based forced vital capacity will be measured with the MIR Spirobank Smart spirometer. Instructions for use will be provided to the participant. The participant will perform the vital capacity maneuver at home 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

8.2 Pharmacokinetic Assessments

Blood samples for PK analysis should be collected at Baseline and Weeks 4, 8, 16, and 24 in the Treatment Phase, and at Weeks 16, 28, and 52 for participants who are in the OLE. Participants who discontinue early from study medication are not required to have PK samples collected at the early discontinuation visit.

A PK sample should be collected pre-dose at the Baseline visit.

At Weeks 4, 8, 16, and 24 in the Treatment Phase, and at Weeks 4, 16, 28, 40, and 52 in the OLE, the morning dose of study drug should be held and administered in the clinic/office during the study visit, so that one pre-dose (trough) PK sample can be collected. For each sample, the time of the last dose of study drug prior to sample collection, time of the last meal, and time of collection of the PK samples should be reported on the CRF.

8.3 Pharmacodynamic Biomarker Assessments

Blood samples for PD biomarker analysis and verdiperstat-specific PD analysis should be collected at Baseline and Weeks 4, 8, 16, and 24 in the Treatment Phase, and at Weeks 16, 28 and 52 for participants who are in the OLE. Participants who discontinue early from study medication are not required to have PD samples collected at the early discontinuation visit.

PD biomarkers should be collected along with the PK samples, so that one pre-dose PD sample is collected at each specified visit. For each sample, the time of the last dose of study drug prior to sample collection and time of the PD sample collection should be reported on the CRF. The verdiperstat-specific PD biomarkers that will be analyzed are MPO protein and MPO activity. Uric Acid will be collected and results remain blinded throughout the duration of the trial

9 SAFETY AND ADVERSE EVENTS

9.1 Adverse Events of Special Interest – Thyroid Function

Reversible changes in thyroid function tests were observed during the preclinical studies and clinical studies with verdiperstat. Based on prior trials, a small percentage of participants may be expected to develop mild (subclinical) hypothyroidism generally with serum TSH < 10 mIU/L. Laboratory monitoring of thyroid function will be performed and documented throughout this study. Site Investigators should review TSH levels and note the trend over time. The Central Laboratory will flag any TSH $\geq$ ULN, and T3 and free T4 analysis should be performed.

Any significant abnormal findings should be discussed with the study Medical Monitor and may be followed up as per local practice (e.g., investigations and consultation with endocrinologist). In cases of suspected hypothyroidism, repeat thyroid function tests should be measured and levothyroxine replacement therapy should be considered. Initiation of treatment is at the discretion of the SI.

Potential initiation of levothyroxine (T4) replacement therapy may be considered according to the following guidelines:

- For a serum TSH between 5 and 10, levothyroxine 0.05 mg daily (50 mcg) is a reasonable dose to prescribe.
- For a serum TSH between 10 and 20, levothyroxine 0.075 mg daily (75 mcg) is a reasonable dose to prescribe.
- For a serum TSH greater than 20, many physicians would feel more comfortable having an endocrinologist treat such participants.

If signs/symptoms of hypothyroidism (i.e. adverse event, initiation of levothyroxine) and/or significant changes in thyroid function develop, collection of follow up clinical chemistry samples and/or unscheduled study visits may be warranted. It is recommended to wait for 5 or 6 half-lives (5 – 6 weeks) to retest thyroid function. Serum T3, free T4 and TSH should be monitored in such participants, and the serum TSH assesses whether therapy is adequate.

If there are clinically significant issues with tolerability that are not able to be treated adequately with levothyroxine replacement therapy, the SI may consider modifications to the dosage regimen. Consultation with the Medical Monitor is required. Modifications may include reducing the dose of verdiperstat /matching placebo to 300 mg BID or taking a dose holiday. Any such modifications to the dosage regimen should be noted in the CRF.

10 REGIMEN-SPECIFIC STATISTICAL CONSIDERATIONS

10.1 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 with only one deviation. This regimen will not include interim analyses for early success. As such, unless this regimen is stopped early for futility, it will enroll to the maximum sample size. At the final analysis, the treatment will be considered success relative to the shared control group if the posterior probability of superiority is greater than 98.0%. This value was selected by simulation to control the overall one-sided Type I error rate across the null scenarios to less than 2.5%. Results are based on 5000 simulations per scenario.

10.2 Regimen Specific Operating Characteristics

Clinical trial simulation is used to quantify operating characteristics for this regimen given the difference from the default design. The simulation of virtual participants and the simulation scenarios are as described in Appendix I to the master protocol. We present here the operating characteristics for the regimen, according to the default design but with no opportunity to stop early for success. Futility is considered non-binding and as such, Table 10.2.1 shows null hypothesis scenarios and resulting Type I error with no futility stopping. We show null and alternative hypothesis scenarios inclusive of futility stopping in Tables 10.2.2 and 10.2.3. Table 10.2.2 shows operating characteristics under the base case assumptions and Table 10.2.3 shows operating characteristics for the various sensitivity scenarios.

This regimen will be one of the first three regimens to be enrolled in the platform and so there are no participants in the shared control from regimens already complete. The comparison to control will rely entirely upon concurrently randomized controls. Concurrently randomized controls will be defined according to Appendix I to the master protocol.

Table 10.2.1: Null Hypothesis Scenarios with No Early Futility Stopping

Sensitivity Scenario	Mean Duration (Months)	Mean N	Prob. Early Success	Prob. Total Success	Prob. Early Futility	Mean DRR
Null Treatment Effect (0% Slowing; Mort HR = 1.0)						
Base	15	160	0.000	0.020	0.000	1.007
Slower Accrual	27	160	0.000	0.023	0.000	1.007
Faster Accrual	11	160	0.000	0.023	0.000	1.008
Less Dropout	15	160	0.000	0.021	0.000	1.006
More Dropout	15	160	0.000	0.023	0.000	1.007
Reg. Start Same Time	18	160	0.000	0.025	0.000	1.005

Table 10.2.1: Null Hypothesis Scenarios with No Early Futility Stopping						
Sensitivity Scenario	**Mean Duration (Months)**	**Mean N**	**Prob. Early Success**	**Prob. Total Success**	**Prob. Early Futility**	**Mean DRR**
Reg. Start 3 Months Apart	11	160	0.000	0.025	0.000	1.017
ALSFRS-R Slower Less Var. Progress	15	160	0.000	0.022	0.000	1.006
ALSFRS-R Faster More Var. Progress	15	160	0.000	0.022	0.000	1.007
ALSFRS-R Lower Resid. Error	15	160	0.000	0.024	0.000	1.006
ALSFRS-R Higher Resid. Error	15	160	0.000	0.022	0.000	1.007
10% Mortality Rate	15	160	0.000	0.025	0.000	1.005
20% Mortality Rate	15	160	0.000	0.023	0.000	1.006

Table 10.2.2: Base Scenarios Operating Characteristics. Null and Alternative Hypotheses With Futility Stopping							
Scenario (% Slowing ALSFRS-R)	**HR Mort.**	**Mean Duration (Months)**	**Mean N**	**Prob. Early Success**	**Prob. Total Success**	**Prob. Early Futility**	**Mean DRR**
0%	**1**	14	155	0.000	0.020	0.290	1.049
25%	**.75**	15	160	0.000	0.615	0.008	0.747
30%	**.7**	15	160	0.000	0.776	0.002	0.694
35%	**.65**	15	160	0.000	0.888	0.001	0.642
30%	**1**	15	160	0.000	0.731	0.003	0.708
30%	**1.3**	15	160	0.000	0.683	0.004	0.722

Table 10.2.3: Base and Sensitivity Scenarios with Early Futility Stopping.						
Sensitivity Scenario	**Mean Duration (Months)**	**Mean N**	**Prob. Early Success**	**Prob. Total Success**	**Prob. Early Futility**	**Mean DRR**
Null Treatment Effect (0% Slowing; Mort HR = 1.0)						
Base	14	155	0.000	0.020	0.290	1.049
Slower Accrual	23	143	0.000	0.023	0.347	1.063
Faster Accrual	11	160	0.000	0.023	0.257	1.034
Less Dropout	14	155	0.000	0.021	0.280	1.047
More Dropout	14	155	0.000	0.023	0.271	1.047
Reg. Start Same Time	16	154	0.000	0.025	0.281	1.035
Reg. Start 3 Months Apart	10	160	0.000	0.025	0.219	1.043
ALSFRS-R Slower Less Var. Progress	14	155	0.000	0.022	0.283	1.049
ALSFRS-R Faster More Var. Progress	14	155	0.000	0.022	0.300	1.047
ALSFRS-R Lower Resid. Error	14	155	0.000	0.024	0.295	1.046
ALSFRS-R Higher Resid. Error	14	155	0.000	0.022	0.284	1.050
10% Mortality Rate	14	155	0.000	0.025	0.286	1.046
20% Mortality Rate	14	155	0.000	0.023	0.294	1.046
Alternative Common Treatment Effect (30% Slowing; Mort HR = .70)						
Base	15	160	0.000	0.776	0.002	0.694
Slower Accrual	27	160	0.000	0.771	0.005	0.695
Faster Accrual	11	160	0.000	0.762	0.002	0.694
Less Dropout	15	160	0.000	0.745	0.003	0.694
More Dropout	15	160	0.000	0.722	0.003	0.694
Reg. Start Same Time	18	160	0.000	0.782	0.002	0.691

Table 10.2.3: Base and Sensitivity Scenarios with Early Futility Stopping.						
Sensitivity Scenario	**Mean Duration (Months)**	**Mean N**	**Prob. Early Success**	**Prob. Total Success**	**Prob. Early Futility**	**Mean DRR**
Reg. Start 3 Months Apart	11	160	0.000	0.681	0.003	0.700
ALSFRS-R Slower Progress	15	160	0.000	0.754	0.003	0.693
ALSFRS-R Faster Progress	15	160	0.000	0.791	0.002	0.694
ALSFRS-R Lower Resid. Error	15	160	0.000	0.793	0.003	0.692
ALSFRS-R Higher Resid. Error	15	160	0.000	0.758	0.003	0.694
10% Mortality Rate	15	160	0.000	0.782	0.003	0.693
20% Mortality Rate	15	160	0.000	0.799	0.003	0.695
Alternative Treatment Effect No Mort. Benefit (30% Slowing; Mort HR = 1.0)						
Base (5% Mort. Rate)	15	160	0.000	0.731	0.003	0.708
10% Mort. Rate	15	160	0.000	0.695	0.004	0.721
20% Mort. Rate	15	160	0.000	0.602	0.007	0.749
Alternative Treatment Effect Worse Mort. (30% Slowing; Mort HR = 1.3)						
Base (5% Mort. Rate)	15	160	0.000	0.683	0.004	0.722
10% Mort. Rate	15	160	0.000	0.592	0.008	0.750
20% Mort. Rate	15	160	0.000	0.411	0.015	0.803

10.3 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.

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Appendix I: The Bulbar Function Scale (CNS-BFS)

BULBAR FUNCTION SCALE (CNS-BFS)						
SIALORRHEA	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	
1. Excessive saliva is a concern to me.	❍	❍	❍	❍	❍	
2. I take medication to control drooling.	❍	❍	❍	❍	❍	
3. Saliva causes me to gag or choke.	❍	❍	❍	❍	❍	
4. Drooling causes me to be frustrated or embarrassed.	❍	❍	❍	❍	❍	
5. In the morning I notice saliva on my pillow.	❍	❍	❍	❍	❍	
6. My mouth needs to be dabbed to prevent drooling.	❍	❍	❍	❍	❍	
7. My secretions are not manageable.	❍	❍	❍	❍	❍	
				TOTAL Sialorrhea Score: _____		
SPEECH	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	**Unable to Communicate by Speaking (6)**
1. My speech is difficult to understand.	❍	❍	❍	❍	❍	❍

2. To be understood I repeat myself.	❍	❍	❍	❍	❍	❍
3. People who understand me tell other people what I said.	❍	❍	❍	❍	❍	❍
4. To communicate I write things down or use devices such as a computer.	❍	❍	❍	❍	❍	❍
5. I am talking less because it takes so much effort to speak.	❍	❍	❍	❍	❍	❍
6. My speech is slower than usual.	❍	❍	❍	❍	❍	❍
7. It is hard for people to hear me.	❍	❍	❍	❍	❍	❍
				TOTAL Speech Score: _____		

SWALLOWING	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	
☐ Feeding tube is in place						
1. Swallowing is a problem.	❍	❍	❍	❍	❍	
2. Cutting my food makes it easier to chew and swallow.	❍	❍	❍	❍	❍	
3. To get food down I have switched to a soft diet.	❍	❍	❍	❍	❍	
4. After swallowing I gag or choke.	❍	❍	❍	❍	❍	

5. It takes longer to eat.	❍	❍	❍	❍	❍	
6. My weight is dropping because I can't eat normally.	❍	❍	❍	❍	❍	
7. Food gets stuck in my throat.	❍	❍	❍	❍	❍	
				TOTAL Swallowing Score: _____		
				OVERALL SCORE: _____		

Appendix II: 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.