PROTOCOL TITLE: Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BHV-3241 in Subjects with Multiple System Atrophy (M-STAR Study)

NCT NUMBER: NCT03952806

DATE: 20-Jan-2021

DRUG:	BHV-3241
STUDY NUMBER:	BHV3241-301
PROTOCOL TITLE:	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BHV-3241 in Subjects with Multiple System Atrophy (M-STAR Study)
IND NUMBER:	107,398
EudraCT NUMBER:	2019-001100-38
SPONSOR:	Biohaven Pharmaceuticals, Inc 215 Church Street New Haven, CT 06510 USA
ORIGINAL PROTOCOL DATE:	19 Dec 2018
VERSION NUMBER:	V07
VERSION DATE:	20 Jan 2021

SUMMARY OF CHANGES

Version Number	Brief description summary of changes	Date
Version 01 –Original Draft	Not Applicable	19 Dec 2018
Version 02	Administrative updates, refinement of inclusion criteria, and assessment schedule prior to EC submission.	15 Jan 2019
Version 03	Modification of Primary and Secondary Objectives and Endpoints, addition of PGI-S, refinement of eligibility criteria and dose modification guidelines, addition of Week 48 phone call, addition of Benefit/Risk section, administrative clarifications/updates.	18 Apr 2019
Version 03.1	UK country specific amendment-modifications per request of MHRA	22 Nov 2019
Version 03.2	France country specific amendment-modifications per request of ANSM	02 Dec 2019
Version 03.3	Germany country specific amendment-modifications per request of BfArM	18 Dec 2019
Version 04	Only submitted to US sites-Modification of UMSARS analysis per FDA, further refinement of eligibility criteria and clarification of prohibited/restricted concomitant medications /timing of required washout for prohibited medications to address limitations in this rare disease population of very ill patients with multiple comorbidities, specification of option to Rescreen patients, incorporation of Administrative Letters 1, 2 and 3 to update CCI medical monitor information and clarify IP storage temperature and excursion reporting, and administrative clarifications/updates.	20 Nov 2019
Version 05	Consolidation of country specific protocol versions 3.1, 3.2, and 3.3 with version 4.0.	31 Jan 2020
Version 06	Due to restrictions intended to minimize COVID-19 public health emergency and resurgence potential hazards to study participants, that impact conduct of study assessments and visits, certain provisions were added/implemented to allow alternatives to in-person study visits if needed, including remote safety visits (incorporating COVID-19 Risk Reduction Addendum-US) and expansion of window for Week 48 visit to proactively account for any visits that may be delayed. In addition, sample size was increased to proactively account for potential loss of subjects due to COVID-19 and to increase the power to 90%. Addition of Open-Label Extension to provide participants who complete the double-blind portion of the study with access to treatment with open-label BHV-3241.	16 Jul 2020
Version 07	Addition of CCI and clarification of eligibility criteria related to Open Label Extension phase of study and correction of typographical error in Section 4.5.2 to correspond to text correctly presented in Table 2 Schedule of Assessments and Events – Open Label Phase, Footnote 1.	20 Jan 2021

BHV3241-301

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BHV-3241 IN SUBJECTS WITH MULTIPLE SYSTEM ATROPHY (M-STAR STUDY)

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BHV-3241 are the confidential and proprietary information of Biohaven Pharmaceuticals, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Biohaven Pharmaceuticals, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Biohaven Pharmaceuticals, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about BHV-3241 and the study.

Principal Investigator Name (printed) _____ Signature _____

Date _____ Site Number _____

STUDY SUMMARY (SYNOPSIS)

Title: Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BHV-3241 in Subjects with Multiple System Atrophy (M-STAR Study)

Rationale: Multiple-system atrophy (MSA) is an adult-onset, fatal neurodegenerative disease that is characterized pathologically by olivopontocerebellar and striatonigral atrophy, neurodegenerative changes affecting the central autonomic nervous system, and the presence of glial cytoplasmic inclusions (GCIs) containing fibrilized α-synuclein protein in oligodendrocytes. The formation of GCIs is associated with oxidative stress, neuroinflammation, loss of neurotrophic support, and ultimately neuronal cell death.

Myeloperoxidase (MPO) is an enzyme that generates cytotoxic oxidants and acts as a key driver of oxidative and neuroinflammatory processes that underlie neurodegeneration. The levels of MPO are significantly increased in activated immune cells, such as microglia, in brains from MSA patients, and these elevations in MPO are believed to promote neurodegeneration. By inhibiting MPO activity, thereby reducing the generation of cytotoxic oxidizing species, BHV-3241 has the potential to slow the progression of neurodegeneration in MSA.

In a mouse model of MSA, treatment with BHV-3241 was found to have neuroprotective effects, including the following: suppression of microglial activation (neuroinflammation); reduction of alpha-synuclein pathology; neuroprotection in several brain regions affected in MSA, including substantia nigra and striatal projection neurons; and beneficial effects on motor function.

The proposed Phase 3 study is based on cumulative preclinical and clinical studies that implicate MPO activity in the onset and progression of neurodegenerative diseases, including MSA, suggesting treatment with BHV-

	3241 has the potential to slow neurodegeneration in MSA. The purpose of this Phase 3 study is to demonstrate the efficacy of BHV-3241 in the treatment of MSA and characterize its safety/tolerability profile.
Target Population:	Male and female patients, ≥40 to ≤80 years of age, with a diagnosis of possible or probable MSA according to consensus clinical criteria (Gilman, 2008), including subjects with either MSA subtype, MSA-Parkinsonism (MSA-P) or MSA-Cerebellar (MSA-C).
Number of Subjects:	Approximately 325 randomized subjects. Randomization will be stratified by disease subtype of either MSA-P vs. MSA-C, diagnostic category of either possible MSA vs. probable MSA, and country.
Objectives:	**Primary Objectives** • To evaluate the efficacy of BHV-3241, compared to placebo, as measured by a change from baseline in a modified Unified MSA Rating Scale (UMSARS), consisting of a subset of items from Part I and Part II, at Week 48. • To assess the safety and tolerability of BHV-3241, relative to placebo, in subjects with MSA. **Key Secondary Objectives** • To evaluate the efficacy of BHV-3241, compared to placebo, as measured by the Clinical Global Impression of Improvement (CGI-I) score at Week 48. • To evaluate the impact of BHV-3241 on quality of life, compared to placebo, as measured by a change from baseline in the motor subscale of the MSA-Quality of Life (MSA-QoL) scale at Week 48. • To evaluate the impact of BHV-3241 on quality of life, compared to placebo, as measured by a change from baseline in the non-motor subscale of the MSA- QoL scale at Week 48. • To evaluate the efficacy of BHV-3241, compared to placebo, as measured by a change from baseline in the UMSARS Part I and Part II total score at Week 48. **Other Secondary Objectives** • To assess the impact of BHV-3241, relative to placebo, as measured by a change from baseline at Week 48 in the following instruments: ▪ Patient Global Impression of Severity (PGI-S),

- Clinical Global Impression of Severity (CGI-S),
- UMSARS Part III,
- UMSARS Part IV.

CCI

[redacted]

CCI [redacted]

Study Design: BHV3241-301 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-arm study designed to assess the efficacy and safety of BHV-3241 in subjects with MSA (MSA-C or MSA-P). The study design schematic is presented in Figure 1. The study is planned to consist of a Screening period of a maximum of approximately 6 weeks; and a randomized double-blind treatment phase of approximately 48 weeks, which will include a dose titration period of approximately 2 weeks, and a full dose period of approximately 46 weeks. Approximately 325 subjects are planned to be randomized in a 1:1 ratio to receive either BHV-3241 600 mg BID, or matching placebo BID.

Eligible subjects will have the opportunity to continue in a 48-week open-label extension phase (once it is open for recruitment at their study site).

Figure 1: Study Schematic

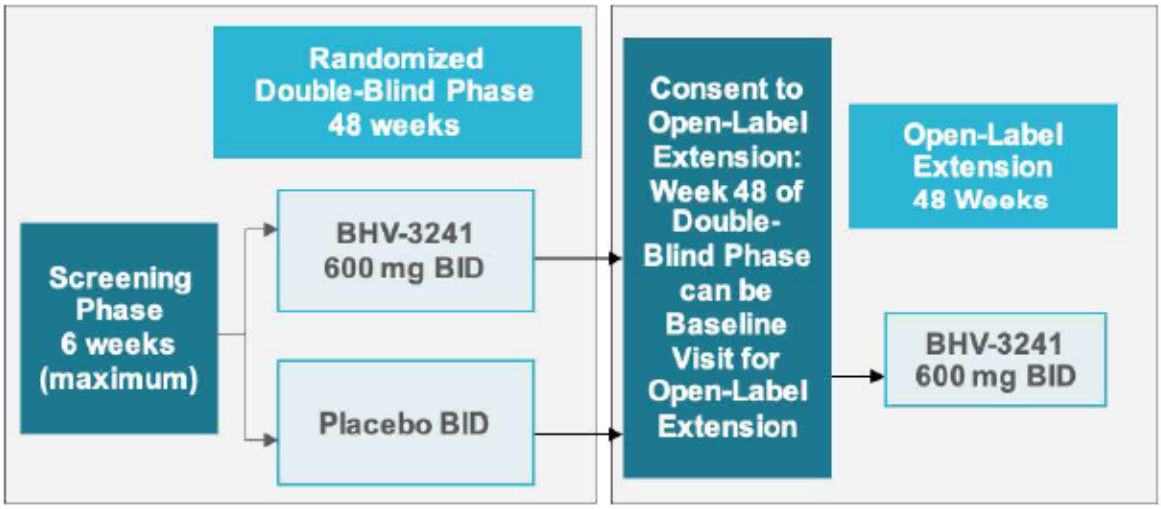


TABLE OF CONTENTS

SUMMARY OF CHANGES 2
CONFIDENTIALITY AND INVESTIGATOR STATEMENT 3
STUDY SUMMARY (SYNOPSIS) 4
TABLE OF CONTENTS 8
LIST OF TABLES 10
LIST OF FIGURES 10
LIST OF ABBREVIATIONS 11
1 INTRODUCTION AND RATIONALE 15
1.1 Background 15
1.1.1 Multiple System Atrophy (MSA) 15
CCI
1.1.3 BHV-3241 16
CCI
1.1.5 Clinical Adverse Event Profile 29
1.1.6 Potential Risk to Fetal Development 35
1.2 Study Rationale 35
1.2.1 Study Design Rationale 35
1.3 Dose Selection 36
1.4 Benefit-Risk 37
2 STUDY OBJECTIVES 40
2.1 Primary 40
2.2 Secondary 40
CCI
3 STUDY ENDPOINTS 42
3.1 Primary 42
3.2 Secondary 42
4 STUDY PLAN 43
4.1 Study Design and Duration 43
4.2 Study Schematic 43
4.3 Schedule of Assessments 44
4.3.1 COVID-19 Public Health Emergency 44
4.3.2 Screening Phase 54
4.3.3 Randomization Phase 54
4.4 End of Treatment 55
4.5 Post Study Access to Therapy/Open-Label Extension Phase 56
4.5.1 Open-Label Extension Phase Eligibility Criteria 56
4.5.2 Open-Label Extension Phase Procedures 57
5 POPULATION 58
5.1 Number of Subjects 58
5.2 Inclusion Criteria 58
5.3 Exclusion Criteria 60
5.4 Prohibited and Restricted Concomitant Medication 65
5.4.1 Other Restrictions and Precautions 67
5.5 Woman of Childbearing Potential (WOCBP) 68

5.6 Deviation from Inclusion/Exclusion Criteria 69
6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES 69
6.1 Study Materials 69
6.2 Eligibility and Safety Assessments 69
6.2.1 Medical and Psychiatric History 69
6.2.2 Safety Assessments 69
6.2.3 Clinical Outcome Assessments 73
6.3 Other Assessments 76
CCI
6.3.2 Pharmacokinetic Assessments 77
CCI
CCI
6.3.5 CSF Collection (Optional) 79
6.4 Early Discontinuation from the Study 79
7 STUDY DRUG MANAGEMENT 81
7.1 Description of Study Drug 81
7.1.1 Investigational Product 81
7.1.2 Packaging, Shipment and Storage 81
7.2 Dose and Administration 82
7.2.1 Method of Assigning Patient Identification 82
7.2.2 Selection and Timing of Dose and Administration 83
7.2.3 Dose Modifications 84
7.3 Blinding and Unblinding 85
7.4 Treatment Compliance 86
7.5 Destruction and Return of Study Drug 86
8 ADVERSE EVENTS 86
8.1 Serious Adverse Events 87
8.1.1 Definition of Serious Adverse Event (SAE) 87
8.1.2 Definition of Terms 87
8.1.3 Classification of Adverse Events 88
8.1.4 Collection and Reporting Serious Adverse Events 89
8.1.5 Overdose 91
8.1.6 Pregnancy 91
8.1.7 Potential Drug Induced Liver Injury (DILI) 92
8.1.8 Adverse Event of Special Interest-Thyroid Function 92
8.2 Non-serious Adverse Events 93
8.2.1 Collection and Reporting of Non-Serious Adverse Events 93
8.2.2 Laboratory Test Abnormalities 93
9 STATISTICS 94
9.1 General Procedures 94
9.2 Sample Size 94
9.3 Populations for Analysis 94
9.4 Statistical Methods 95
9.4.1 Demographic and Baseline Characteristics 95
9.4.2 Primary Endpoint(s) 95
9.4.3 Secondary Endpoint(s) 96

9.4.4 Extension Phase Analysis 96
9.4.5 Adjustment for Multiplicity 96
9.4.6 Missing Data 96
9.4.7 Analysis of Safety 97
9.5 Schedule of Analyses 97
10 ETHICS AND RESPONSIBILITIES 97
10.1 Good Clinical Practice 97
10.2 Data Monitoring Committee 98
10.3 Institutional Review Board/Independent Ethics Committee 98
10.4 Informed Consent 99
10.5 Case Report Forms 100
10.6 Records Management and Retention 100
10.7 Source Documentation 101
10.8 Study Files and Record Retention 101
11 AMENDMENTS 101
12 STUDY REPORT AND PUBLICATIONS 102
13 STUDY DISCONTINUATION 102
14 CONFIDENTIALITY 102
15 APPENDICES 103
15.1 APPENDIX I - Names of Study Personnel 103
16 REFERENCES CITED 104
CLINICAL PROTOCOL APPROVAL FORM 106

LIST OF TABLES

Table 1: Schedule of Assessments and Events - Randomized Double-blind Phase ... 47
Table 2: Schedule of Assessments and Events - Open-Label Extension Phase 51

LIST OF FIGURES

Figure 1: Study Schematic 7
Figure 2: Study Schematic 43

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AT	Aminotransferases
AUC	Area Under the Curve
AV	Atrioventricular
BE	Bioequivalence
BID	Twice a Day
BMI	Body Mass Index
BP	Blood Pressure
BID	Twice Daily
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
CCI	
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CHF NYHA	Congestive Heart Failure New York Heart Association
CK	Creatine Kinase
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CCI	
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CYP	Cytochrome P450
DA	Dopamine
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DMPK	Drug Metabolism and Pharmacokinetics
DSM-V	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Erectile Dysfunction
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
CCI	

ER	Extended Release
eTMF	Electronic Trial Master File
EU	European Union
°F	Degrees Fahrenheit
FAX	Facsimile
FLAIR	Fluid Attenuation Inversion Recovery
FSH	Follicle-Stimulating Hormone
GCIs	Glial Cytoplasmic Inclusions
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL	High-Density Lipoproteins
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICF/IC	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IDDM	Insulin-Dependent Diabetes Mellitus
IEC	Independent Ethics Committee
IM	Investigational Medicine
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web-Based Response System
Kg	Kilogram
L	Liters
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoproteins
MAD	Multiple-Ascending Dose
MDMA	3,4-Methylenedioxymethamphetamine
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

min	Minute
MINI	Mini International Neuropsychiatric Interview
mITT	Modified Intent to Treat
mL	Milliliter
mmHg	Millimeters Mercury
MMRM	Mixed Model for Repeated Measuring
CCI	[redacted]
MPO	Myeloperoxidase
MPOi	Myeloperoxidase Inhibition
CCI	[redacted]
MSA	Multiple System Atrophy
MSA-C	Multiple System Atrophy with Cerebellar Ataxia
MSA-P	Multiple System Atrophy with Parkinsonian Features
MSA-QoL	Multiple System Atrophy Quality of Life Scale
NAG	N-acetyl-B-D-glucosaminidase
NDA	New Drug Application
NfL	Neurofilament Light Chain
NO	Nitrous Oxide
NOEL	No-Observed-Effect-Level
NOAEL	No-Observed-Adverse-Effect-Level
OC	Orthostatic Challenge
OLE	Open-Label Extension
CCI	[redacted]
PCP	Phencyclidine
PD	Pharmacodynamic
P-gp	P-glycoprotein
PET	Positron Emission Tomography
PGI-S	Patient Global Impression of Severity
PID	Patient Identification Number
PK	Pharmacokinetic
PO	By Mouth, Orally
CCI	[redacted]
CCI	[redacted]
PVCs	Premature Ventricular Contractions
CCI	[redacted]
QC	Quality Control
QD	Once Daily
QTcF	Corrected QT Interval by Fridericia
ROD	Relative Optical Density
RPR	Rapid Plasma Reagin

SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAERF	Serious Adverse Event Report Form
SAP	Statistical Analysis Plan
SCr	Serum Creatinine
SD	Standard Deviation
CCI	[redacted]
S-STS	Sheehan Suicidality Tracking Scale
T3	Triiodothyronine
T4	Thyroxine
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TH	Tyrosine Hydroxylase
TIA	Transient Ischemic Attack
T_{max}	Time when C_{max} is reached
TMF	Trial Master File
TPO	Thyroid Peroxidase
TSH	Thyroid Stimulating Hormone
TSPO	Translocator Protein
ULN	Upper Limit of Normal
UMSARS	Unified Multiple System Atrophy Rating Scale
USPI	United States Package Insert
WBC	White Blood Count
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Background

Biohaven Pharmaceuticals, Inc [Biohaven] is developing a new drug, BHV-3241, also known as Verdiperstat, for the treatment of multiple system atrophy (MSA). BHV-3241 is an irreversible inhibitor of the myeloperoxidase (MPO) enzyme that generates cytotoxic oxidizing and nitrosylating compounds. The proposed study is based on cumulative preclinical, clinical, and neuroimaging studies that implicate MPO activity in the onset and progression of neurodegenerative diseases, including MSA, suggesting treatment with BHV-3241 has the potential to slow neurodegeneration in MSA. The high unmet need for an effective treatment, together with the available data, provide a compelling rationale for the development of BHV-3241 as a treatment for MSA.

1.1.1 Multiple System Atrophy (MSA)

MSA is an orphan disease (Orphan number: ORPHA102 [www.orpha.net]) that is an adult-onset, fatal neurodegenerative disease [1]. Onset of MSA usually occurs during the sixth decade of life, and invariably leads to death after an average of 6 to 10 years from symptom onset, with the causes of death commonly being bronchopneumonia, urosepsis, and sudden death. No disease modifying treatment currently exists, only symptomatic and palliative approaches are available [1].

The defining neuropathology of MSA on post-mortem examination includes variable degrees of olivopontocerebellar atrophy and striatonigral degeneration, which reflect the presence of ataxia and parkinsonism, respectively, during life. In addition, neurodegenerative changes affect the central autonomic nervous system, including the hypothalamus, noradrenergic and serotoninergic brain-stem nuclei, dorsal nucleus of the vagus nerve, nucleus ambiguus, intermediolateral columns of the spinal cord, and Onuf nucleus. The defining molecular and cellular neuropathology of MSA is the widespread presence of glial cytoplasmic inclusions (GCIs) containing fibrilized α-synuclein protein in oligodendrocytes [2-4]. MSA is thus considered an α-synucleinopathy, like Parkinson's disease and dementia with Lewy bodies, although it has very distinct pathological and clinical features.

MSA is a sporadic disease of unknown etiology. Although the pathophysiological mechanisms underlying MSA remain unclear, evidence from preclinical models and post-mortem studies suggests that the formation of GCIs is associated with oxidative stress, neuroinflammation, loss of neurotrophic support, and ultimately neuronal cell death.

MSA is characterized clinically by progressive autonomic failure, parkinsonian features, and cerebellar and pyramidal features in various combinations [1]. Patients with MSA are divided into 2 subtypes based on their predominant symptoms: 1) MSA-P patients have predominantly parkinsonian features; and 2) MSA-C patients have cerebellar ataxia as the predominant symptom. Based on the revised criteria for the diagnosis of MSA that were established at a consensus conference in 2007 [5], the diagnosis of MSA includes 3 categories: 1) Definite MSA; 2) Probable MSA; and 3) Possible MSA. As the predominant features of MSA may change over time, the designation of MSA-P or MSA-C for a given patient may change during the

course of the disease. Approximately 60-80% of MSA patients in Europe and North America have the MSA-P subtype [6], whereas 65-85% of MSA patients in Japan and Korea have the MSA-C subtype [7,8].

MSA has an estimated point prevalence of 3.4 to 4.9 cases per 100,000, increasing to 7.8 per 100,000 among persons older than 40 years of age [9]. Cases of MSA-P outnumber cases of MSA-C by 2:1 to 4:1 in most countries [10-12], with MSA-C being more prevalent in Japan [13] and likely influenced by genetic and epigenetic factors.

CCI

1.1.3 BHV-3241

BHV-3241 is an irreversible, mechanism-based MPO inhibitor that is hypothesized to suppress the generation of cytotoxic oxidizing and nitrosylating compounds, thereby slowing the progression of MSA-associated neurodegeneration. The enzyme, MPO, is an oxidative heme

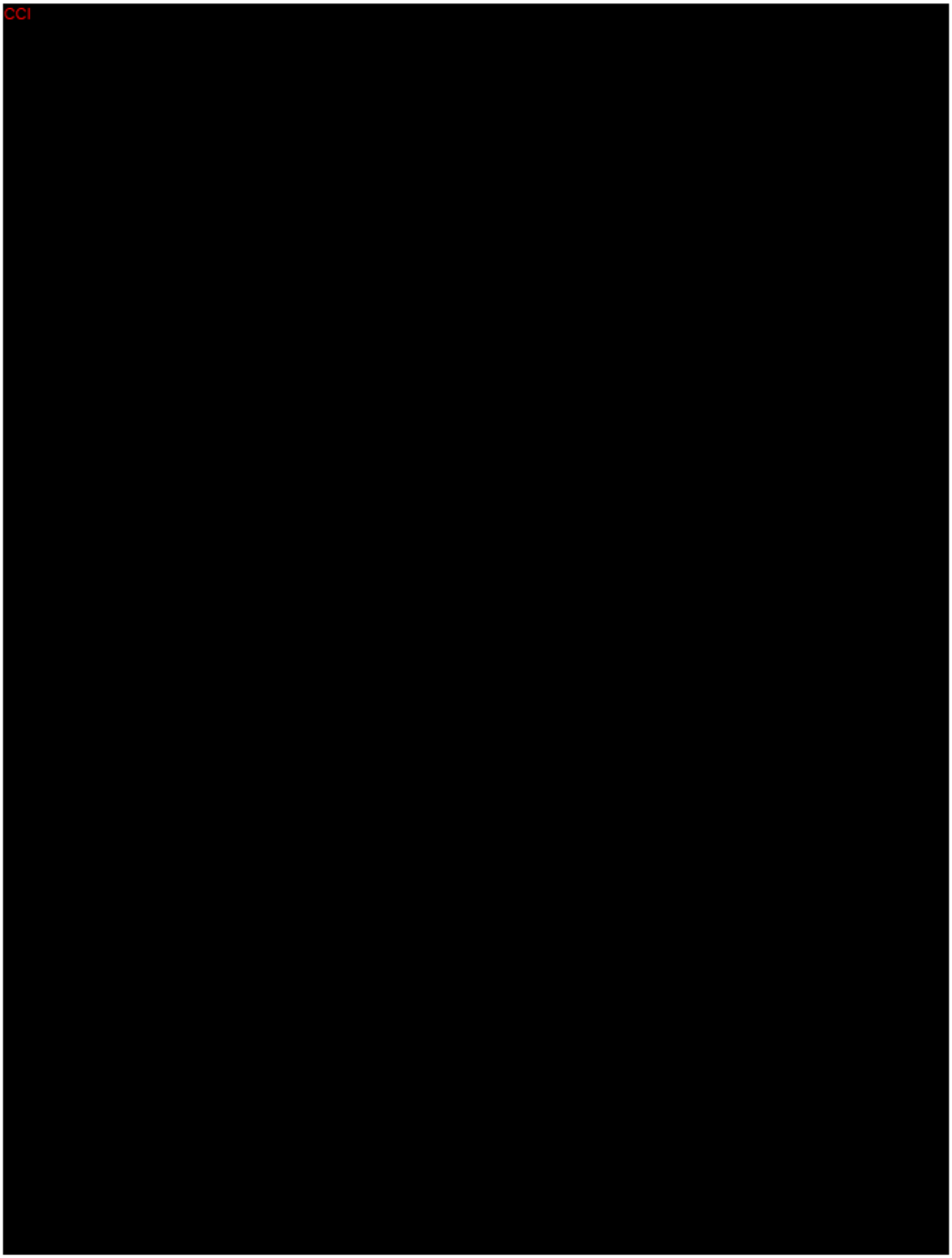
protein released primarily by activated neutrophils, but is also expressed in phagocytic cells, including microglia, and leads to the production of hypochloric acid, a potent oxidant. MPO oxidizes nitrite to reactive nitrogen species and converts tyrosine to tyrosyl radical, a reactive intermediate that promotes o,o'-dityrosine formation and initiates lipid peroxidation.

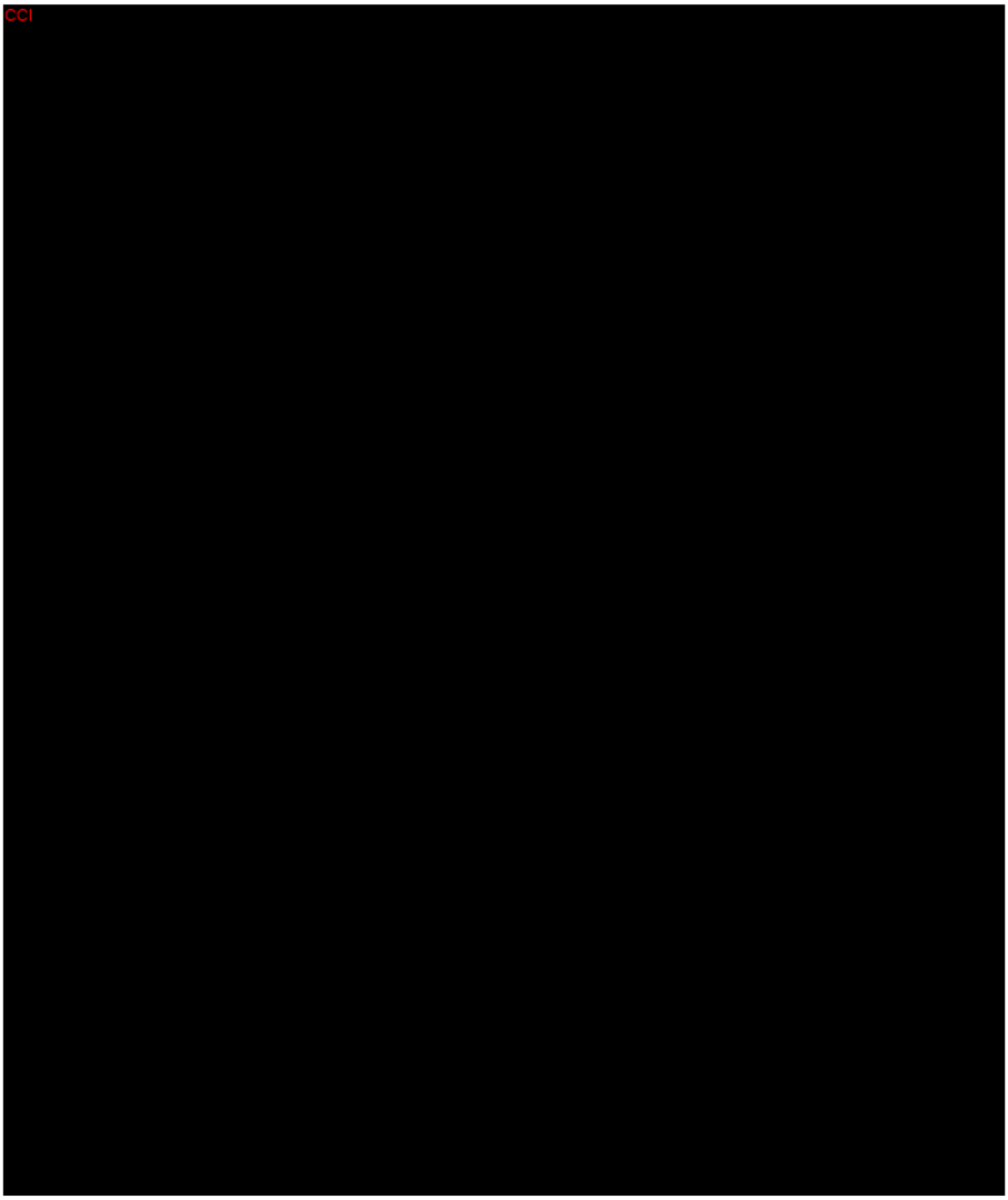
1.1.3.1 Pre-Clinical Studies

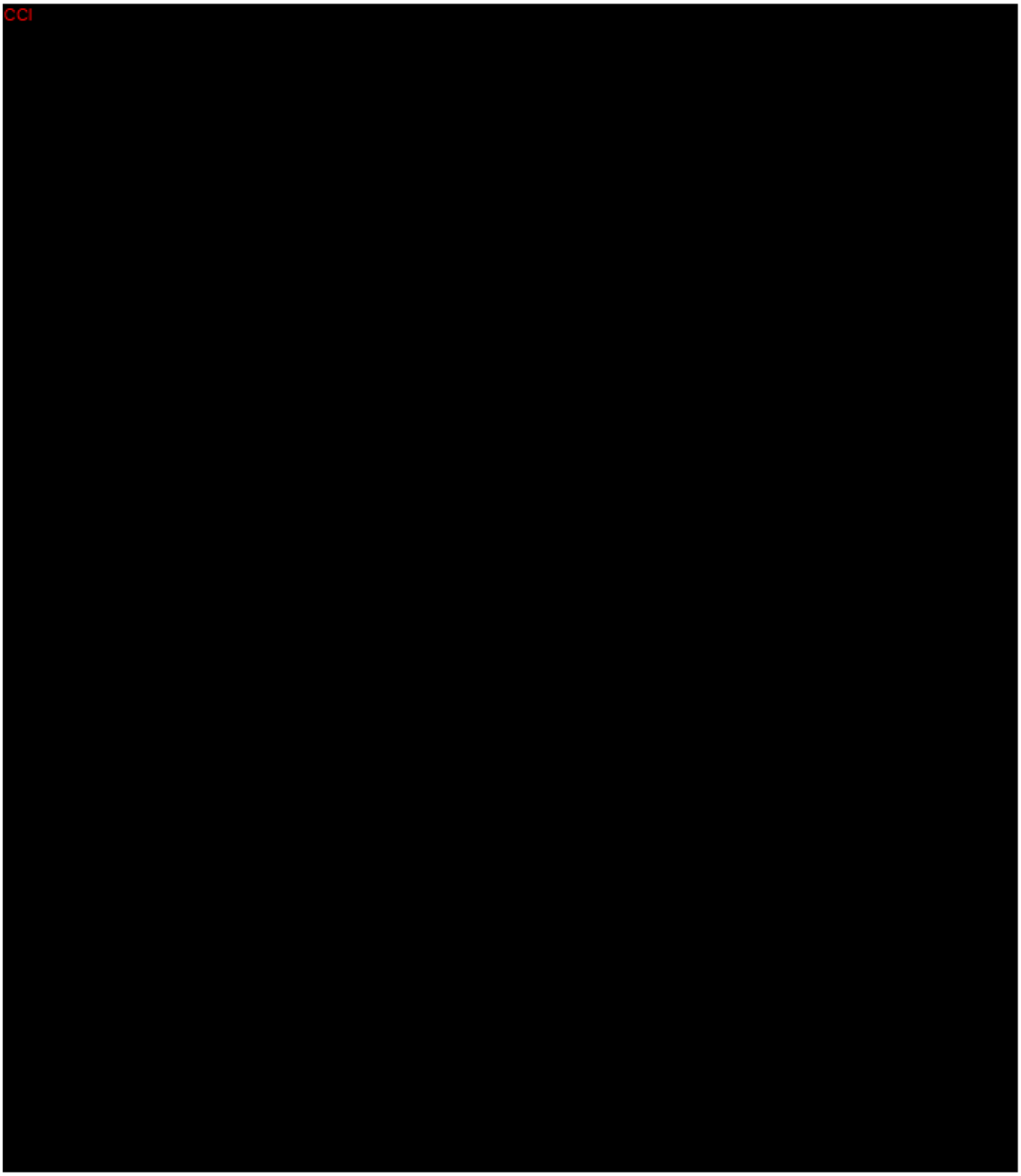
Summaries of relevant findings from pre-clinical studies conducted with BHV-3241 are provided. Please refer to the Investigator Brochure for additional information.

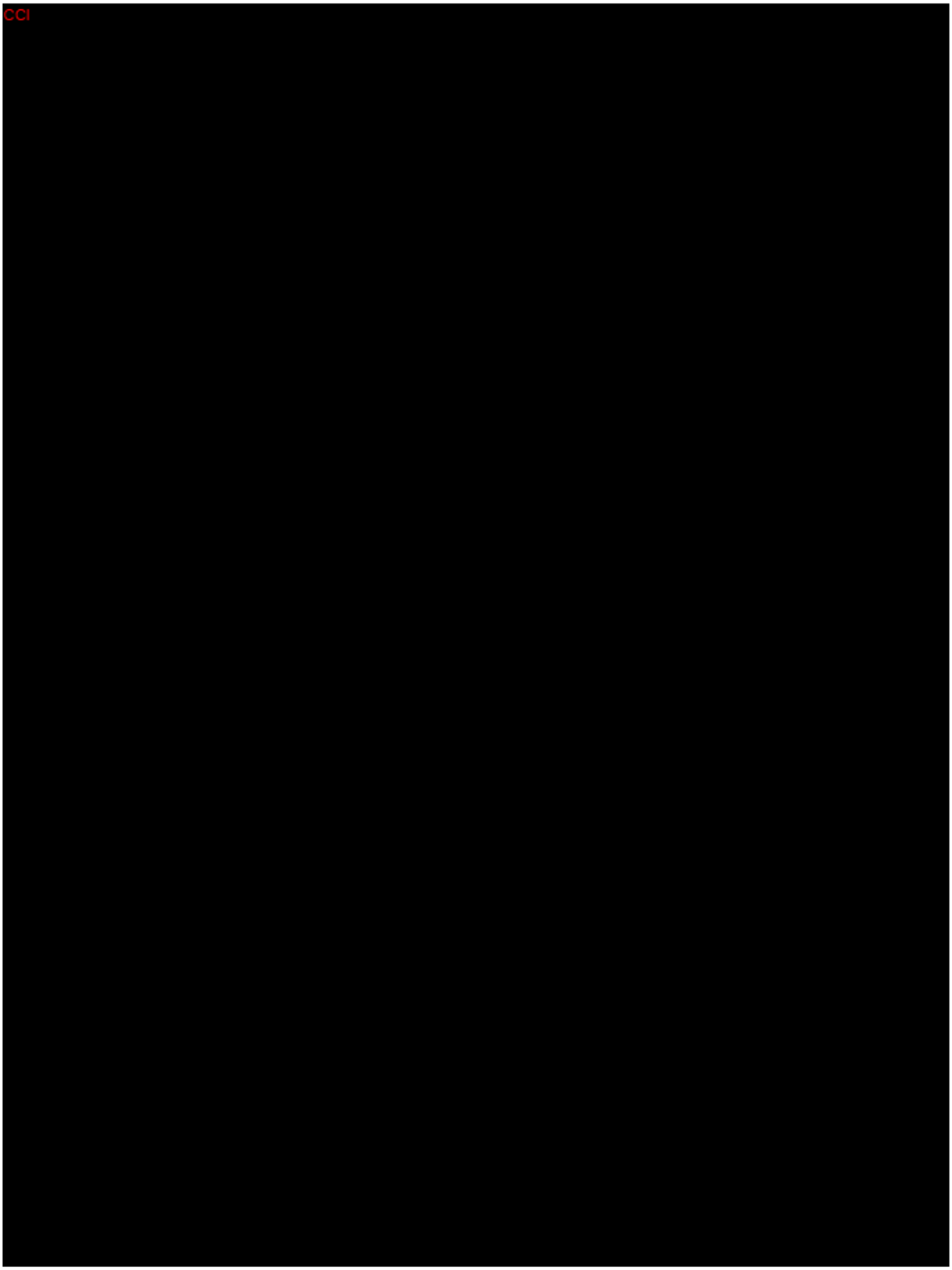
1.1.3.1.1 Primary Pharmacodynamics

CCI


CCI


CCI


CCI


CCI

CCI

[redacted]

1.1.3.2 Clinical Experience

To date, seven clinical studies (four Phase 1 studies in healthy subjects; two Phase 2 studies in subjects with Parkinson's disease; and one Phase 2 study in subjects with MSA) have been conducted with BHV-3241, with approximately 234 subjects having received BHV-3241 in these clinical studies. Refer to the Investigator Brochure for detailed information on these studies.

1.1.3.2.1 BHV-3241 Phase I

Refer to the Investigator Brochure for detailed information on the Phase 1 studies.

CCI

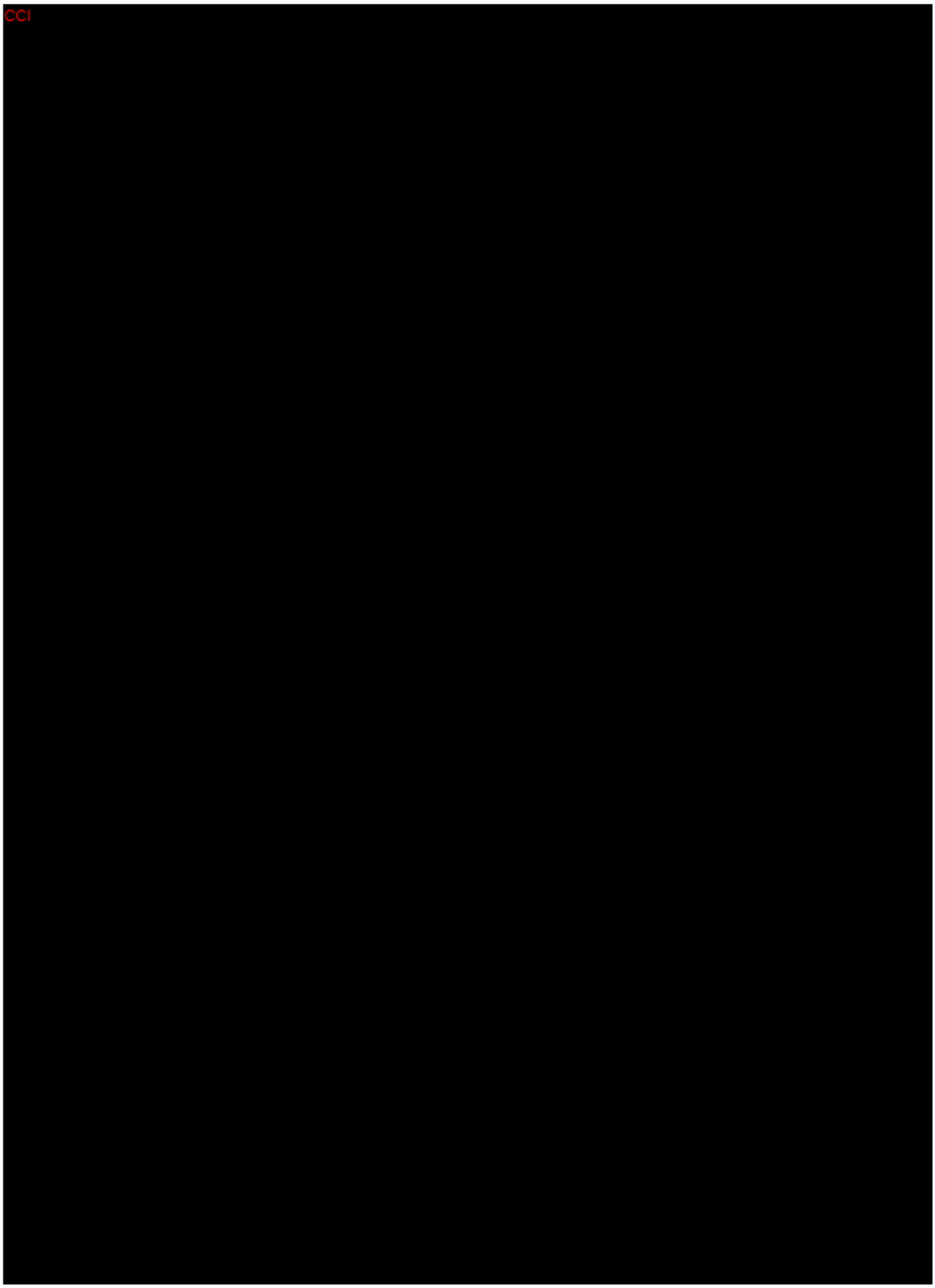
[redacted]

CCI

[redacted]

CCI

[redacted]


CCI

CCI

1.1.3.2.2.3 *Study D0490C00023*

This Phase 2 12-week, multicenter, randomized, parallel-group study in patients with MSA was designed to assess the effect on safety, tolerability, pharmacokinetics, microglial activation (assessed by PET imaging), biomarker effects, and efficacy of two dosages of BHV-3241 (300 mg and 600 mg BID). Recruited subjects were male and female, 30 to 80 years of age, inclusive, at Screening, who met the criteria for diagnosis of probable or possible MSA according to consensus clinical criteria. 59 subjects were actually randomized and treated (19, BHV-3241 300 mg BID; 20, BHV-3241 600 mg BID; and 20, placebo BID); and 46 subjects completed the study (14, BHV-3241 300 mg BID; 17 BHV-3241 600 mg BID; and 15 placebo BID).

CCI

PET imaging: BHV-3241 treatment at either dosage (300 mg or 600 mg) had no statistically significant effect on microglial activation, based on change in the regional total distribution volume from baseline to Week 12 (ΔV_T) measured by PET imaging of radioligand [^{11}C] PBR28 binding to translocator protein. Importantly, the lack of statistically significant difference between BHV-3241 treatment arms and placebo arms on [^{11}C] PBR28 binding to TSPO is not inconsistent with a potential treatment effect in MSA. The relatively large treatment effect size in Study D0490C00004 in patients with Parkinson's disease was used to determine the sample size for this study in patients with MSA, and may have been an overestimate. In addition, there are known issues with this PET imaging technique, including heterogeneous and non-specific binding and signal-to-noise ratio.

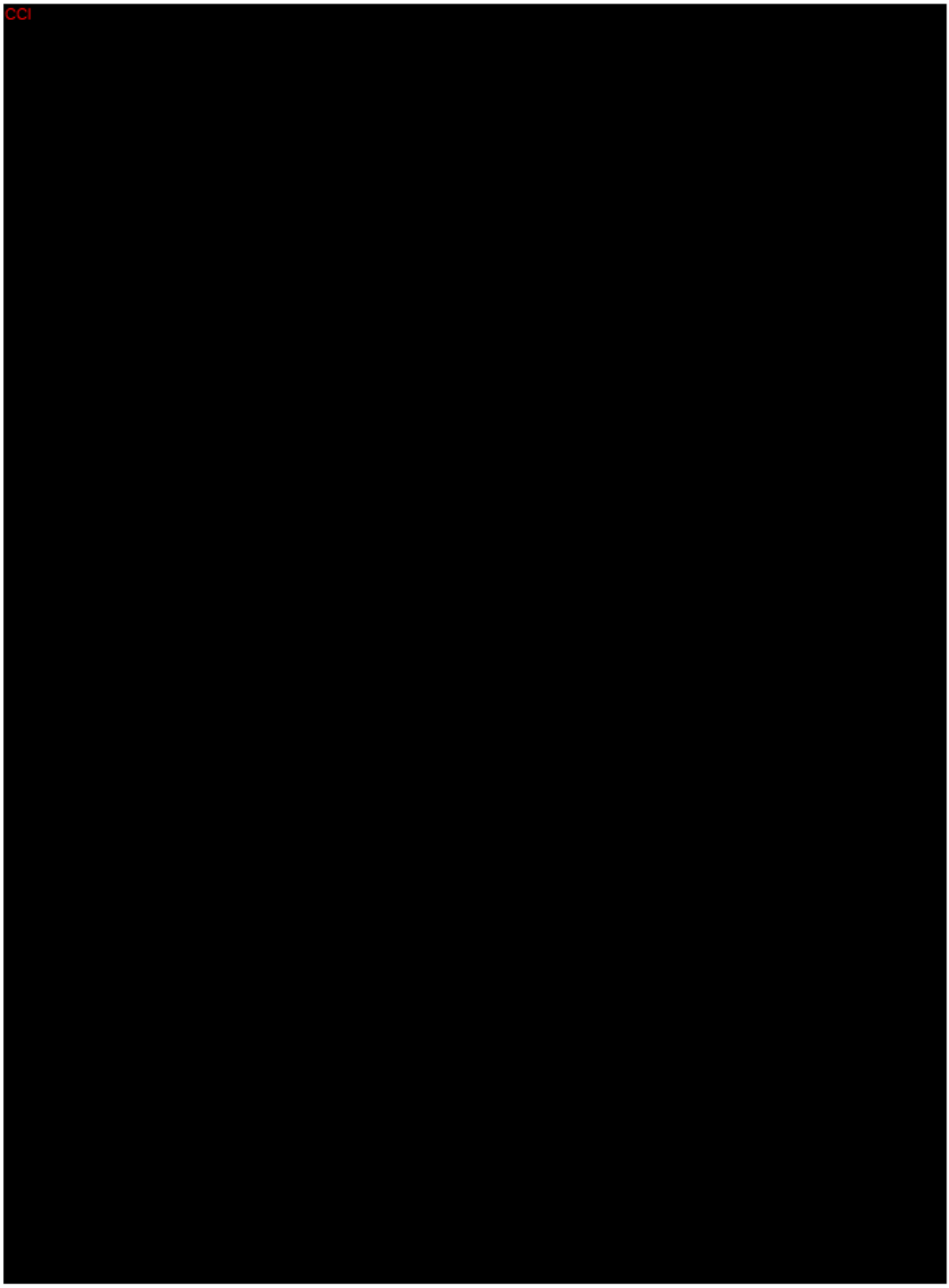
Plasma MPO activity: BHV-3241 treatment for 12 weeks (at doses of either 300 mg BID or 600 mg BID) showed statistically significant reductions in measures of MPO activity in plasma. For specific MPO activity (MPO activity/MPO protein), there were statistically significant reductions of approximately 10% between baseline and post-dose assessments at Week 12, for the BHV-3241 300 mg BID and BHV-3241 600 mg BID treated groups (p=0.0138 and p=0.0003, respectively). Pairwise comparisons between the BHV-3241 treated groups and placebo were statistically significant (p=0.0166 and p=0.0026 for the 300 mg BID and 600 mg BID groups, respectively). These clinical trial results support the intended mechanism of action of BHV-3241.

PK: MSA subjects treated with BHV-3241 300 mg BID for 12 weeks had the following steady state, geometric mean exposures: AUC of 21.2 µmol h/L (CV: 49.0%) and C_{max} of 2.38 µmol/L (CV: 46.4%). MSA subjects treated with BHV-3241 600 mg BID for 12 weeks had the following steady state, geometric mean exposures: AUC of 39.5 µmol*h/L (CV: 43.8%) and C_{max} of 4.15 µmol/L (CV: 41.6%).

Safety/Tolerability: BHV-3241 treatment was generally safe and well-tolerated in MSA subjects at doses of 300 mg and 600 mg BID.

CCI

[redacted]


CCI

CCI

[redacted]

1.1.5 Clinical Adverse Event Profile

To date, approximately 234 subjects have received BHV-3241 in seven clinical studies: four Phase 1 studies in healthy subjects, a Phase 2 PET imaging study in subjects with Parkinson's disease (Study D0490C00004), a Phase 2 safety and tolerability study in subjects with Parkinson's disease (Study D0490C00005), and a Phase 2 PET imaging study in subjects with MSA (Study D0490C00023). In the Phase 1 studies, treatment with multiple doses of up to 900 mg BHV-3241 BID was generally safe and well tolerated. In the Phase 2 studies in subjects with Parkinson's disease and MSA, treatment with BHV-3241 at doses of up to 600 mg BID for 8-12 weeks was generally safe and well tolerated.

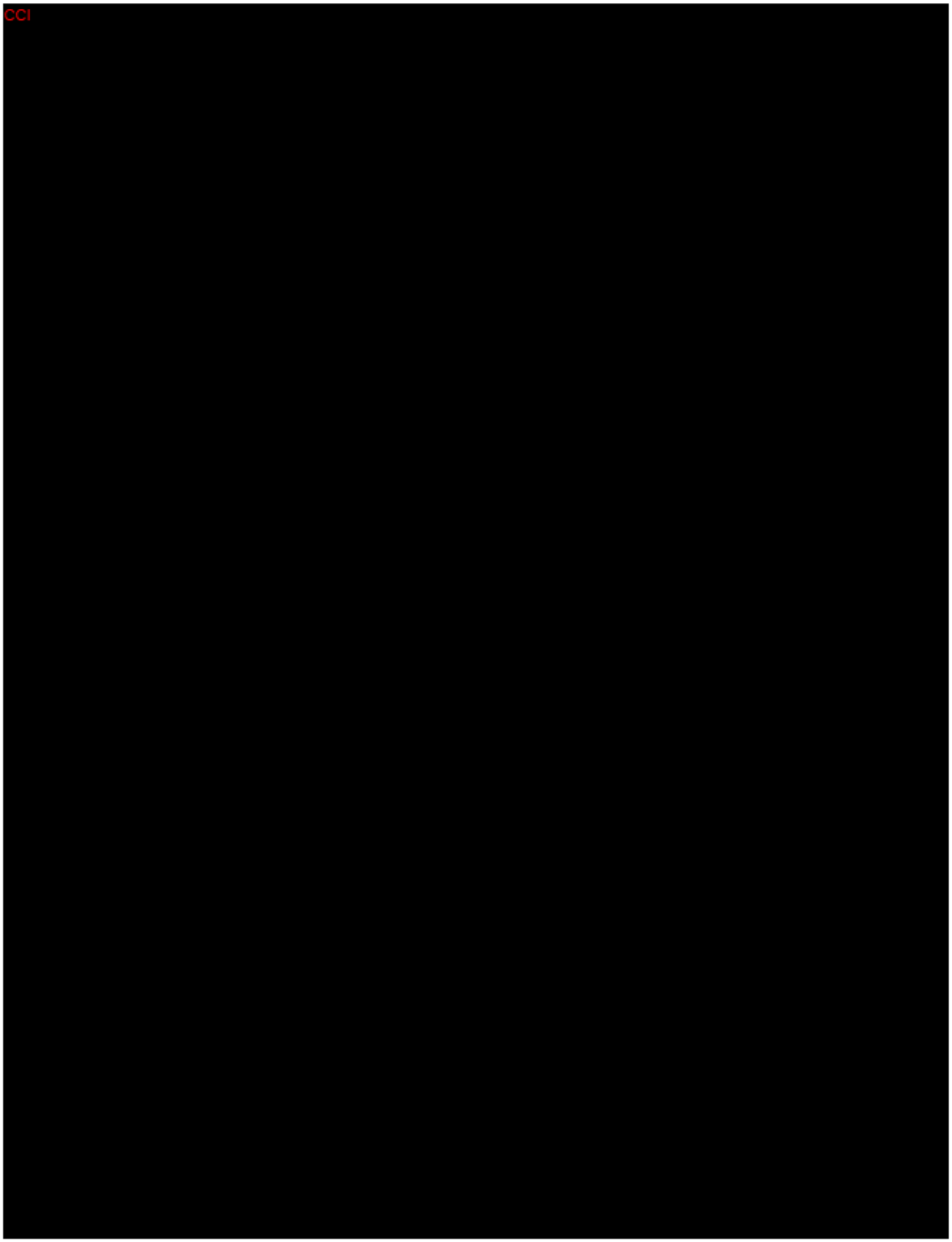
1.1.5.1 BHV-3241 Phase 1 Studies

To date, 4 Phase 1 studies have been conducted with BHV-3241. Key safety-related findings from these studies are presented below.

CCI

[redacted]

CCI



CCI

[redacted]

1.1.5.2 BHV-3241: Phase 2 Clinical Adverse Event Profile

To date, 3 Phase 2 studies have been conducted with BHV-3241. Key safety-related findings from these studies are presented below.

CCI

[redacted]

1.1.5.2.3 Study D0490C00023

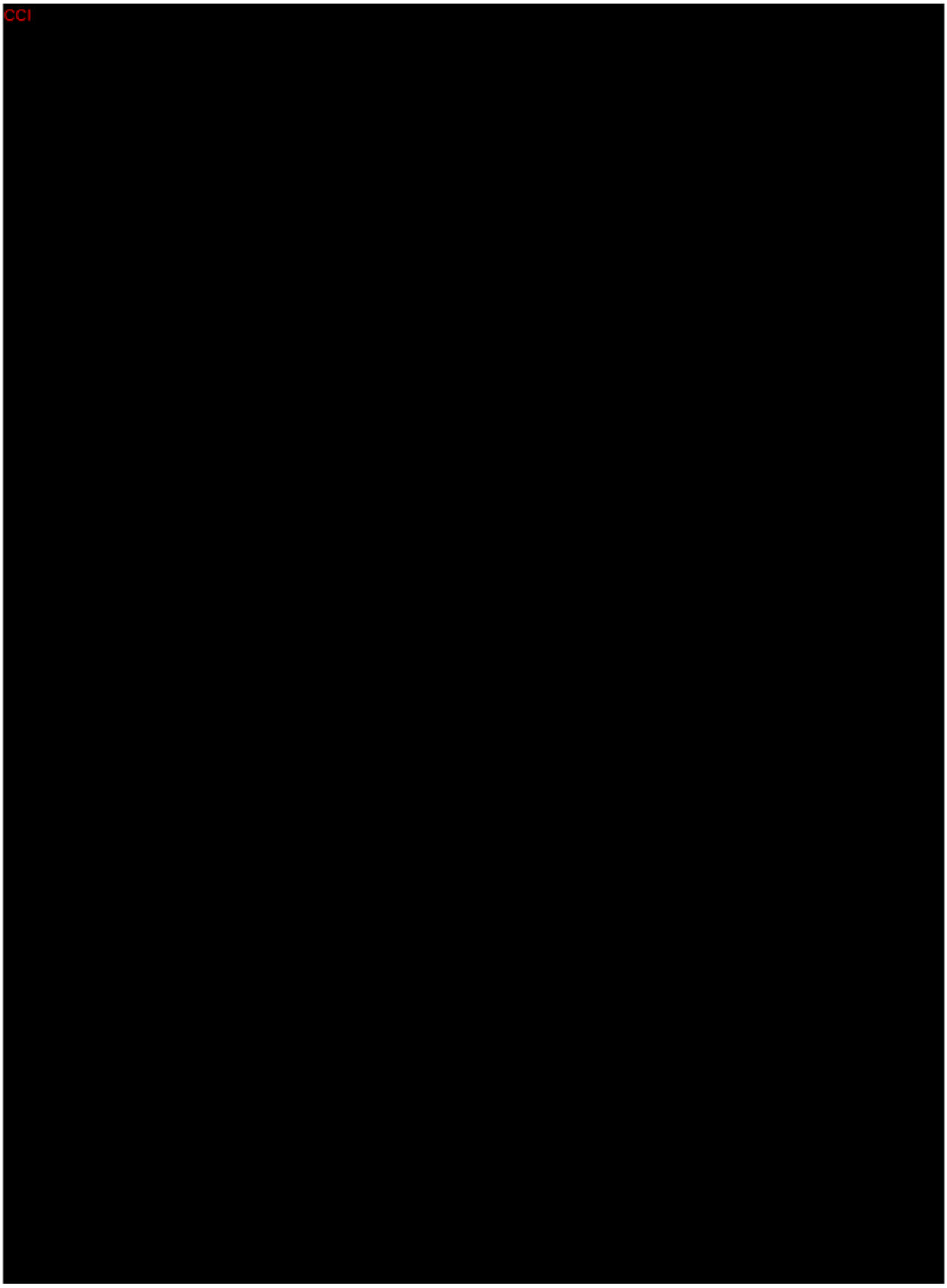
In this study in MSA patients, treatment with BHV-3241 (600 mg BID and 300 mg BID) for 12 weeks was generally safe and well tolerated. There were 2 deaths in this study due to AEs of MSA disease progression (BHV-3241 600 mg) and choking on food (placebo); both events were considered severe and judged not related to BHV-3241. Three subjects experienced SAEs. One subject in the BHV-3241 300 mg treated group had an SAE of fractured right hip that was considered severe, judged not related to study drug, and led to discontinuation. Two subjects had SAEs of MSA disease progression and choking which led to death (see above). Four subjects, 3 receiving BHV-3241 300 mg and 1 receiving placebo, discontinued the study due to AEs. The AEs that led to discontinuation of treatment with BHV-3241 300 mg included mild-to-moderate balance disorder, syncope, feeling jittery, and epistaxis in 1 subject; fractured right hip (severe) in a second subject; and dysphagia (severe) in a third subject. The subject receiving placebo discontinued from the study due to general discomfort (moderate) and headache (mild). All of the events leading to discontinuation, except for epistaxis and hip fracture, were considered by the Investigator- to be related to study drug administration. The overall incidence of TEAEs was similar across the treatment groups, ranging from 78.9% to 84.2%. The most common AE was urinary tract infection, reported with a higher incidence in the BHV-3241 300- mg group (26.3%) than in the BHV-3241 600 mg (15.0%) or placebo (15.8%) groups. Fatigue was reported with a similar incidence in the BHV-3241 300 mg (15.8%) and 600 mg (15.0%) groups, but with a lower incidence in the placebo group (5.3%). Orthostatic hypotension was more frequent among subjects in the BHV-3241 600 mg group (15.0%) than in the BHV-3241 300 mg (5.3%) and placebo (0) groups. Similarly, falls and presyncope events were more frequent among subjects in the BHV-3241 600 mg group (20.0% and 10.0%, respectively) than in the BHV-3241 300 mg (5.3% for both events) and placebo

(5.3% and 0, respectively) groups. The majority of AEs reported in this study were mild (63.2% of events in both the placebo and BHV-3241 300 mg groups and 60.0% of events in the BHV-3241 600 mg group). Severe TEAEs were reported in 1 subject each in the BHV-3241 600 mg (5.0%) and placebo (5.3%) groups and in 4 subjects in the BHV-3241 300 mg group (21.1%). The severe TEAEs in the BHV-3241 300 mg group were dysphagia, thermal burn, hip fracture, and headache; and the severe AE in the BHV-3241 600 mg group was MSA (worsening). Choking was the severe AE in the placebo group. The majority of AEs were judged unrelated to study treatment by the Investigators, ranging from 70.0% to 73.7% across the treatment groups. Treatment-related AEs were reported in 6 (31.6%) subjects in the BHV-3241 300 mg group, 5 (25.0%) subjects in the BHV-3241 600 mg group, and 4 (21.1%) subjects in the placebo group.

Laboratory values that met potentially clinically significant (PCS) criteria were infrequent in this study. Of 17 subjects with PCS laboratory values, 7 received placebo, 6 received BHV-3241 300 mg BID, and 4 received BHV-3241 600 mg BID. Three (16.7%) subjects in the BHV-3241 300 mg group had potentially clinically significant TSH levels: 1 subject had low TSH at the early termination (0.18 uIU/mL) and follow-up (0.33 uIU/mL; reference range: 0.34-5.6) visits; 1 other subject had high TSH at Weeks 2, 3, 4, 8, and 12 (ranging from 6.58 to 9.33 uIU/mL); and the third subject had high TSH beginning at Week 4 (9.11 uIU/mL) and decreasing at Week 8 (7.43 uIU/mL) and Week 12 (6.28 uIU/mL). One (5.3%) subject in the BHV-3241 600 mg BID group had high TSH at Week 12 (9.31 uIU/mL) and the Follow-up visit (7.25 uIU/mL). Two (11.1%) subjects in the BHV-3241 300 mg BID group and 1 (5.3%) subject in the BHV-3241 600mg BID group had high urine protein.

There were no clinically significant differences in ECG results between either of the BHV-3241 groups and placebo.

CCI


CCI

CCI

[redacted]

1.1.6 Potential Risk to Fetal Development

On the basis of the reproductive and developmental toxicity studies described above, women of childbearing potential (WOCBP) may be included in the clinical trials provided they are not pregnant or lactating at admission and sufficient contraceptive protection is used. There is a potential risk of drug-drug interactions with hormonal contraceptive methods sensitive to induction of CYP3A4 with BHV-3241. Consequently, study Investigators should keep this potential of reduced hormonal contraceptive effectiveness in mind for women using contraceptive control medicines and devices containing estrogen/progesterone. Estrogen and progesterone hormonal contraceptives as a sole method of contraception are prohibited.

1.2 Study Rationale

1.2.1 Study Design Rationale

The purpose of this Phase 3 study is to demonstrate the efficacy of BHV-3241 in the treatment of MSA and characterize its safety/tolerability profile.

The study is a randomized, double-blind, 2-arm, placebo-controlled, parallel-group study in subjects with MSA treated with BHV-3241 for 48 weeks. If absolutely necessary due to the COVID-19 public health emergency, treatment duration may be longer, with an expanded Week 48 visit window up to a maximum treatment duration of 60 weeks, as detailed in the Schedule of Assessments and Events tables (Table 1, Table 2). Under these circumstances, the sponsor medical monitor (or designee) should be consulted and must approve the request to extend the treatment duration.

During the randomized double-blind treatment phase, the use of placebo control will facilitate the identification of a treatment effect related to administration of BHV-3241. The use of placebo is justified because there is no current standard therapy for MSA and subjects in this study will be allowed to continue their background symptomatic treatments for MSA (with the exception of excluded medications). The population includes subjects with MSA (MSA-P and MSA-C). Both have the same underlying disease process and the same rate of disease progression as measured by clinical rating scales (i.e., UMSARS). Moreover, both subtypes are equally likely to benefit from MPO inhibition by BHV-3241 and demonstrated the potential to be responsive to treatment with BHV-3241 in the previous Phase 2 study in MSA subjects (Study D0490C00023).

Subjects who are completing or have completed Week 48 of the randomized double-blind treatment phase may be offered the opportunity to enroll in an Open-Label Extension (OLE) phase, in which subjects will receive open-label treatment with BHV-3241 for approximately 48 weeks. Enrollment into the OLE phase for all subjects is contingent on the Investigator's

judgement that open-label treatment offers an acceptable risk-benefit profile for each individual.

The primary outcome variable in this study is a modified UMSARS score comprised of a subset of items from the UMSARS (UMSARS I: Activities of Daily Living & UMSARS II: Motor Examination). The UMSARS is a clinical rating scale that has been developed and validated for measuring functional impairment in MSA over 48 weeks. It is the standard outcome variable used in longitudinal natural history studies and interventional studies. The key secondary outcome variables are the Clinical Global Impression of Improvement (CGI-I) and MSA-Quality of Life (MSA-QoL) motor and non-motor subscales, which assess complementary aspects of disability in MSA and have also previously been validated in MSA studies to monitor disease progression, as well as the UMSARS Part I and Part II total score at Week 48. CCI [redacted] Pharmacokinetic parameters and PD effects, such as MPO activity, are also included.

1.3 Dose Selection

The dose selected for evaluation in this Phase 3 BHV-3241-301 study is 600 mg BID. This dose selection was based on cumulative clinical and nonclinical experience with BHV-3241, including nonclinical toxicology and safety and efficacy data in MSA subjects.

The nonclinical toxicology program for BHV-3241 is comprehensive and supports oral administration in the clinic for chronic treatment. Included in the toxicology program are: single and repeat-dose toxicity studies in rats and dogs, genotoxicity studies, reproductive toxicity studies, phototoxicity studies, and safety pharmacology studies. BHV-3241 doses in the present study are predicted to produce pharmacokinetic exposures below the exposure limits set on the basis of nonclinical toxicology data.

To date, approximately 234 subjects have received BHV-3241 in seven clinical studies: four Phase 1 studies, a Phase 2 PET imaging study in subjects with Parkinson's disease (Study D0490C00004), a Phase 2 safety and tolerability study in subjects with Parkinson's disease (Study D0490C00005), and a Phase 2 PET imaging study in subjects with MSA (Study D0490C00023). In the Phase 1 studies, treatment with multiple doses of up to 900 mg BHV-3241 BID was generally safe and well tolerated. In the Phase 2 studies in subjects with Parkinson's disease and MSA, treatment with BHV-3241 at doses of up to 600 mg BID for 8-12 weeks was generally safe and well tolerated.

The selected dose of BHV-3241 administered 600 mg BID is based on the findings in the Phase 1 and 2 studies regarding safety and tolerability of BHV-3241 at 600 mg BID; CCI [redacted] and the dose-dependent favorable trends on clinical efficacy measures in the Phase 2 study in MSA. Taken together, the safety, tolerability, PK, and PD data generated in clinical studies with BHV-3241,

along with the preclinical pharmacology, PK, and safety data, support the further evaluation of BHV-3241 in MSA patients in a Phase 3 study.

1.4 Benefit-Risk

Benefit-Risk Assessment

The current benefit-risk analysis is based on the available data with BHV-3241 from preclinical studies (in rats and dogs) and clinical studies (in healthy subjects, Parkinson's disease subjects and MSA subjects). It is considered that the benefits of evaluating BHV-3241 as a potential treatment for MSA outweigh the risks.

Preclinical studies safety and toxicology studies are described in Section 1.1.3.1.3 and Section 1.1.3.1.5, respectively. Safety pharmacology studies were performed assessing the central nervous, respiratory, cardiovascular and gastrointestinal systems. A comprehensive toxicology data package has been developed on BHV-3241 including single dose toxicity, repeat-dose toxicity (including chronic toxicity in rats and dogs), genetic toxicity, reproductive and developmental toxicity, and special toxicity.

The clinical experience with BHV-3241 is described in detail in Section 1.1.3.2. The adverse event profile observed in these clinical studies with BHV-3241 is described in Section 1.1.5. To date, seven clinical studies (four Phase 1 studies in healthy subjects; two Phase 2 studies in subjects with Parkinson's disease; and one Phase 2 study in subjects with MSA) have been conducted with BHV-3241, with approximately 234 subjects having received BHV-3241 in these clinical studies.

Exposure

The exposure limits for BHV-3241 in clinical studies have previously been a C_{max} of 40 µmol/L and an AUC(0-24) of 180 µmol•h/L, based on the histopathological findings in the thyroid gland in the rat 6-month study. In the Phase 2b study (D0490C00023), MSA subjects treated with BHV-3241 600 mg BID for 12 weeks had the following steady state, geometric mean exposures: AUC of 39.5 µmol•h/L (CV: 43.8%) and C_{max} of 4.15 µmol/L (CV: 41.6%). Thus, the exposures of BHV-3241 in planned clinical trials are projected to be below the NOAEL.

Safety and Tolerability in Clinical Studies

In the Phase 1 studies, BHV-3241 has been generally well tolerated when administered through titration as multiple doses up to 900 mg BID. In the Phase 2 studies in subjects with Parkinson's disease and MSA, treatment with BHV-3241 at doses of up to 600 mg BID for 8 to 12 weeks was generally safe and well tolerated.

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 MSA and suggest treatment with BHV-3241 has the potential to slow neurodegeneration in MSA.

In particular, in a Phase 2b study, subjects with MSA were randomized to receive BHV-3241 300 mg BID, BHV-3241 600 mg BID, or placebo for 12 weeks. The BHV-3241 groups exhibited numerical, but not statistically significant, improvements compared to the placebo group that were dose-related, based on changes in the Unified MSA Rating Scale scores from baseline to Week 12. Placebo-treated subjects worsened by 4.6 points, while BHV-3241 treated subjects showed less worsening of 3.7 points at the 300-mg dose and 2.6 points at the 600-mg dose, suggesting a dose-response relationship. BHV-3241 treatment for 12 weeks (at doses of 300 mg BID and 600 mg BID) showed statistically significant reductions in measures of MPO activity in plasma. These results support the intended mechanism of action of BHV-3241 and potential for efficacy in MSA.

Potential Risks

Preclinical and clinical studies have demonstrated an acceptable safety and tolerability profile for BHV-3241 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 Investigators, 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 DMC review of the benefit-risk of the study for subjects.

Thyroid

In preclinical studies, reversible histopathological changes in the thyroid gland and reversible thyroid hormone changes were observed. In clinical studies, BHV-3241 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 subjects 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 BHV-3241 returned toward baseline levels during the period of observation following discontinuation of BHV-3241.

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.

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, BHV-3241 has been associated with decreases in mean uric acid levels over time relative to placebo. A variable proportion of subjects receiving BHV-3241 have had plasma uric acid levels below the lower limit of normal. Decreases in uric acid levels associated with BHV-3241 have tended to return toward baseline following the discontinuation of dosing. Indices of renal function have not shown any abnormalities associated with BHV-3241. 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.

The present study will involve monitoring of uric acid levels and indices of renal function.

Cardiovascular

Increases in heart rate were observed in dogs during the preclinical studies. However, BHV-3241 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 BHV-3241.

The first SAD clinical study (D0490C00001) 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 BHV-3241 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 BHV-3241 could not be ruled out. A second SAD study was conducted with 2 modifications designed to reduce the risk of syncope: (1) the exclusion of subjects 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 subjects receiving BHV-3241. 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 BHV-3241 600-mg BID group in the safety/tolerability study conducted in subjects with Parkinson's disease (D0490C00005).

In aggregate, the clinical data do not show clear evidence of significant cardiovascular abnormalities associated with administration of BHV-3241 ER formulations at the doses used. The present study will involve monitoring of vital signs, including orthostatic measurements, and ECGs.

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 (D0490C00002), several subjects, including those receiving BHV-3241 and placebo, had increases in hepatic transaminases. However, in subsequent studies there have been no clinically relevant findings involving hepatic function.

In aggregate, the clinical data do not show a clear association of hepatic abnormalities with BHV-3241. The present study will involve monitoring of liver function tests.

Overall Benefit-Risk Assessment

MSA is an adult-onset, fatal neurodegenerative disease. No disease modifying treatment currently exists, only symptomatic and palliative approaches are available. BHV-3241 is an irreversible inhibitor of the MPO enzyme that promotes oxidative stress and neuroinflammation. The high unmet need for an effective treatment for MSA, together with the available preclinical and clinical data with BHV-3241, provide a compelling and favorable overall benefit-risk assessment for the development of BHV-3241 at the 600 mg BID dose as a treatment for MSA. The safety monitoring in the planned clinical study will minimize the potential risks to study subjects.

2 STUDY OBJECTIVES

2.1 Primary

- To evaluate the efficacy of BHV-3241, compared to placebo, as measured by a change from baseline in a modified Unified MSA Rating Scale (UMSARS), consisting of a subset of items from Part I and Part II, at Week 48.
- To assess the safety and tolerability of BHV-3241, relative to placebo, in subjects with MSA.

2.2 Secondary

Key Secondary

- To evaluate the efficacy of BHV-3241, compared to placebo, as measured by the Clinical Global Impression of Improvement (CGI-I) score at Week 48.
- To evaluate the impact of BHV-3241 on quality of life, compared to placebo, as measured by a change from baseline in the motor subscale of the MSA-Quality of Life (MSA-QoL) scale at Week 48.
- To evaluate the impact of BHV-3241 on quality of life, compared to placebo, as measured by a change from baseline in the non-motor subscale of the MSA- QoL scale at Week 48.

- To evaluate the efficacy of BHV-3241, compared to placebo, as measured by a change from baseline in the UMSARS Part I and Part II total score at Week 48.

Other Secondary

- To assess the impact of BHV-3241, relative to placebo, as measured by a change from baseline at Week 48 in the following instruments:
  - Patient Global Impression of Severity (PGI-S),
  - Clinical Global Impression of Severity (CGI-S),
  - UMSARS Part III,
  - UMSARS Part IV.

CCI

[redacted]

3 STUDY ENDPOINTS

3.1 Primary

- Change from baseline in a modified UMSARS score, based on a subset of items from Part I and II, at Week 48 (see Section 9.4.2).
- The frequency of unique subjects with: serious adverse events; adverse events leading to discontinuation; adverse events judged to be related to study medication; clinically significant ECG abnormalities and clinically significant laboratory abnormalities.

3.2 Secondary

Key Secondary

- The CGI-I score at Week 48
- Change from baseline in the MSA-QoL motor subscale at Week 48
- Change from baseline in the MSA-QoL non-motor subscale at Week 48
- Change from baseline in UMSARS Part I and II total score at Week 48

Other Secondary

- Change from baseline at Week 48 on the following instruments:
  - PGI-S,
  - CGI-S,
  - UMSARS Part III,
  - UMSARS Part IV.

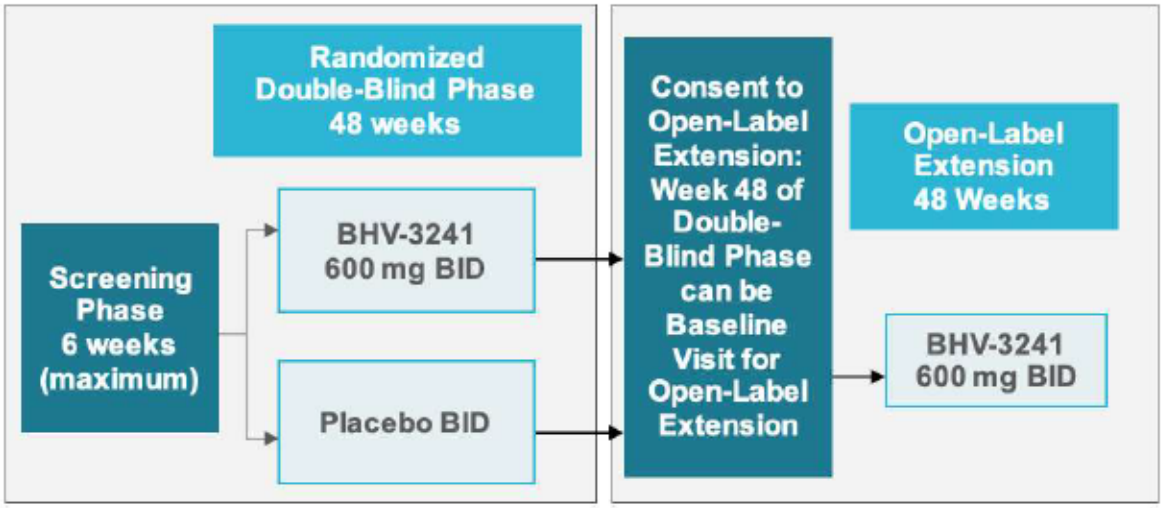
4 STUDY PLAN

4.1 Study Design and Duration

BHV3241-301 is a Phase 3, multicenter, randomized, double-blind, 2-arm placebo-controlled parallel-group study designed to evaluate the efficacy and safety of BHV-3241 in a population of patients with MSA (MSA-C and MSA-P). The study is planned to consist of a Screening phase lasting a maximum of approximately 6 weeks and a randomized double-blind treatment phase of approximately 48 weeks, per Figure 2. It is anticipated that the Randomization phase will include a dose titration period of approximately 2 weeks followed by a full dose period of approximately 46 weeks. Approximately 325 subjects in total are planned to be randomized in a 1:1 ratio to receive either BHV-3241 600 mg BID, or matching placebo BID. It is anticipated that subjects will be assessed at clinic visits, per the Schedule of Assessments & Events (Table 1). In addition, subjects who are completing or have completed Week 48 of the double-blind treatment phase may be offered the opportunity to enroll in an Open-Label Extension phase, in which subjects will receive open-label treatment with BHV-3241 for approximately 48 weeks. (Table 2)

4.2 Study Schematic

Figure 2: Study Schematic



4.3 Schedule of Assessments

4.3.1 COVID-19 Public Health Emergency

In both the double-blind phase and OLE phase of the study, every effort should be made to conduct protocol-specified in-person study visits as planned and as close to the date of the scheduled visit as possible. However, due to the COVID-19 public health emergency, in order to minimize potential risks to the safety of study participants and study site personnel and to comply with government and local health care institution guidance and restrictions, study participants may be unable to attend study scheduled protocol required visits in person (e.g., shelter in place restrictions, study site policy that clinical research visits must be delayed). Under these circumstances, if a study participant is unable to attend an in person protocol-required evaluation at the study site at the scheduled time, the site Investigator should discuss the appropriate course of action and specific requirements for remote safety visits on a case by case basis with the Sponsor Medical Monitor (or designee), based on the specific study visit, the clinical status of the participant, consideration of their compliance to study medication, previous lab results and other risk factors.

Potential courses of action include expansion of the visit window, conduct of a remote [via phone or telemedicine video] visit, focusing on safety assessments during remote visits, including study drug compliance, concomitant medication review, adverse event monitoring, Sheehan Suicidality Tracking Scale, UMSARS Part I and Time to Event Measures, performing safety labs via local labs or in-home phlebotomy vendors, and shipping study medication to study participants, if needed. Vital signs, physical exams, and clinician-rated outcome measures (e.g., UMSARS Part II, CGI-I/S) will not be conducted remotely. ECGs may be conducted at a local health facility other than the study site, with subsequent submission to CCI (central ECG vendor). Screening, Baseline and Week 48 visits must be conducted in person and lab analyses should be conducted by CCI central lab.

For on-treatment study visits (not Screening, Baseline or Week 48), if the COVID-19 public health emergency prevents study subjects from being able to have blood and urine lab samples collected at the study site for shipment to CCI central lab for analysis, the samples may be collected at locations other than the study site (local lab, primary care practice, in-home phlebotomy service) and may be analyzed by a local lab. The study site will collect any local lab results for review and entry into the eDC eCRF. The safety lab samples collected and analyzed in these cases of remote assessments will be limited to safety labs specified by the Sponsor (see Section 6.2.2.4). Pharmacokinetic and CCI will not be collected.

4.3.1.1 Criteria for Temporary Interruption of Investigational Product (IP)

The visit windows for collection of BHV3241-301 protocol-required safety labs during the COVID-19 emergency, and the criteria for temporary interruption of IP due to inability to monitor patient safety via lab analyses are as follows:

- Week 4 or Week 4-Extension safety labs-need to be conducted within a 10 day window of Week 4 or Week 4-Extension. If not, need to temporarily interrupt IP until labs are conducted.

- Week 12 or Week 12-Extension safety labs-need to be conducted within a 8-week window of Week 12-Extension (assuming no clinically significant lab abnormalities at Week 8 or Week 8-Extension). For subjects who did not have Week 8 or Week 8 -Extension labs conducted, but who had Week 4 or Week 4-Extension labs conducted with no clinically significant lab abnormalities, then Week 12 or Week 12-Extension labs need to be conducted within a 4 week window of Week 12 or Week 12-Extension. If not, need to temporarily interrupt IP until labs are conducted.

- Week 24 or Week 24-Extension safety labs-need to be conducted within a 12-week window of Week 24 or Week 24-Extension (assuming no clinically significant lab abnormalities at Week 12 or Week 12-Extension). If not, need to temporarily interrupt IP until labs are conducted.

4.3.1.2 Week 18 Assessment

If a subject has not been assessed at an in person visit at Week 12 or Week 12-Extension, checking in with the subject remotely (by phone or video) between Week 12 or Week 12-Extension and Week 24 or Week 24-Extension (at approximately the Week 18 or Week 18-Extension timepoint) and obtaining safety labs is strongly encouraged. These labs may be conducted using the CCI central lab Unscheduled Visit lab kit or they may be collected at a location other than at the study site (e.g., at a local lab or in the study participant's home via visiting phlebotomy service) and may be analyzed by a local lab.

4.3.1.3 Shipment of Study Medication to Study Participants

In these cases of remote assessments, when an in-person study visit is not possible due to the COVID-19 public health emergency, overnight shipment of study medication from the site to the study participant via certified and trackable courier under ambient conditions (following Remote Visit Workaround Guidelines provided to sites), is permissible, if acceptable to the study site's institution. Confirmation that the study drug shipment was received by the study participant should be retained as documentation, e.g., tracking confirmation printout from the courier, written documentation of contact with the subject (by phone, email, text), subject signature on packing list, etc.

4.3.1.4 Remote Monitoring/Source Data Verification

The on-site review and verification of study source documents by the Sponsor and its representatives may be affected by COVID-19 public health emergency restrictions limiting access to the study site. If it is specifically allowed according to health authority, IRB/EC and data protection agency regulations, remote source data verification may be conducted through Remote Monitoring, with study documents accessed electronically without breaking study participant confidentiality, according to CCI standard operating procedure.

Table 1: Schedule of Assessments and Events - Randomized Double-blind Phase

Visit	Screening	Baseline (Pre-dose)	2[a]	3	3-1	4	5	6	7[9]	
Day (Visit procedures conducted within a +/- 3 day window, unless otherwise specified)	Maximum of 42 days (-42 to -1)	1	14	29	57	85	169	253	337 (+/- 7 days)	
Week		0	2	4	8	12	24	36	48 (Early D/C) [9]	Week 48 Phone Call (if applicable)[10]
Eligibility Assessments										
Informed Consent (subject and caregiver)	X									
Inclusion/Exclusion Criteria	X	X								
Medical History	X									
Demographic Data	X									
Concomitant Medication review	X	X	X	X		X	X	X	X	X
Safety Assessments										
Physical Examination*	X	X	X	X		X	X	X	X	
Physical Measurements[1]	X	X							X	
Vital Signs[2]	X	X	X	X		X	X	X	X	
ECG (12-lead)	X	X	X	X		X	X	X	X	
Laboratory Tests	X	X	X	X	X	X	X	X	X	
Pregnancy Test[3]	X	X		X		X	X	X	X	
Sheehan Suicidality Tracking Scale	X	X	X	X		X	X	X	X	
Adverse Event Reporting										
Monitor for Nonserious AEs		X	X	X		X	X	X	X	X
Monitor for SAEs	X	X	X	X		X	X	X	X	X

Visit	Screening	Baseline (Pre-dose)	2[a]	3	3-1	4	5	6	7[9]	
Day (Visit procedures conducted within a +/- 3 day window, unless otherwise specified)	Maximum of 42 days (-42 to -1)	1	14	29	57	85	169	253	337 (+/- 7 days)	
Week		0	2	4	8	12	24	36	48 (Early D/C)[9]	Week 48 Phone Call (if applicable)[10]
Efficacy Assessments										
Unified MSA Rating Scale Parts I-IV*	X	X		X		X	X	X	X	
Clinical Global Impression of Severity (CGI-S)		X		X		X	X	X	X	
Clinical Global Impression of Improvement (CGI-I)				X		X	X	X	X	
Patient Global Impression of Severity (PGI-S)		X		X		X	X	X	X	
MSA Quality of Life		X					X		X	
CCI										
Time-to-event measures of disease progression		X		X		X	X	X	X	X[10]
Other Assessments										
CCI										
Lumbar Puncture[5]		X							X	
Pharmacokinetic Assessments										
Blood PK Sampling[6]		X		X		X	X	X	X	
CCI										

Visit	Screening	Baseline (Pre-dose)	2[a]	3	3-1	4	5	6	7[9]	
Day (Visit procedures conducted within a +/- 3 day window, unless otherwise specified)	Maximum of 42 days (-42 to -1)	1	14	29	57	85	169	253	337 (+/- 7 days)	
Week		0	2	4	8	12	24	36	48 (Early D/C)[9]	Week 48 Phone Call (if applicable)[10]
CCI										
Clinical Drug Supplies										
Randomize		X								
Dispense Study Drug		X		X		X	X	X		
Study Drug Compliance Assessment[8]		X	X[a]	X		X	X	X	X	

Under regular circumstances, visits are to be completed in-person, unless otherwise specified. Some visits can be conducted remotely, as needed, due to COVID-19 restrictions. See Protocol Section 4.3.1, COVID-19 Public Health Emergency, for further details and requirements regarding conduct of remote visits due to COVID-19.

[a] The Week 2 assessment should generally be conducted at the study site. Per Investigator judgement, additional evaluations/procedures may be conducted at this timepoint as appropriate.

*Including neurologic exam as a component of general physical exam and UMSARS

[1] Height at Screening and Week 48; weight at Screening, Baseline, and Week 48.

[2] Subjects should be seated and resting for approximately 5 minutes prior to vital sign measurements - temperature, blood pressure, and heart rate. Tilt table may be used, if available.

[3] Serum pregnancy test will be conducted in WOCBP (see section 5.5) at all scheduled visits. Urine pregnancy test will be performed on WOCBP (in addition to serum) at Baseline (within 24 hours prior to first dose).

CCI

CCI

[redacted]

[6] One PK sample should be collected pre-dose and one PK sample should be collected post-dose. The time of the last BHV-3241/placebo dose prior to the sample collection and time of the PK sample collection and time of most recent meal should be reported on the CRF. At Weeks 4, 12, 24, 36 and 48, 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) and one post-dose PK sample can be collected. The post-dose sample should be collected within a time window of approximately 2 to 4 hours. Collection of PK samples is not required at the Early Discontinuation visit.

CCI

[redacted]

[8] Subjects should take the first dose of investigational product (IP) while in the office/clinic on the day of the Baseline visit and stay at the clinic for ~4 hours for observation. From start to end of Week 1, subjects will ingest either 300 mg QD of BHV-3241 or matching placebo QD. From start to end of Week 2, subjects will ingest either 300 mg BID of BHV-3241 or matching placebo BID. Starting with Week 3 and for the remainder of the double-blind portion of the study, subjects will ingest either 600 mg BID of BHV-3241 or matching placebo BID.

[9] The Week 48 assessments/procedures should be conducted as an in person visit at the study site. Every effort should be made to conduct the Week 48 visit and maintain a +/- 7 day window. However, due to the COVID-19 public health emergency, if absolutely necessary, in order to minimize potential risks to study participant safety and to comply with governmental and local institutional guidance (e.g., study site has a policy that an in person clinical research visit must be delayed), the Week 48 visit window may be expanded up to an additional 12 weeks (maximum treatment duration of 60 weeks). However, every attempt should be made to conduct the visit as close as possible to the date that the visit is due. Under these circumstances, the Investigator should discuss the specific circumstances of these cases with the sponsor medical monitor (or designee), who must approve the request to extend the treatment duration, prior to any modification of the visit window. If the Week 48 visit window is modified, participants should have safety assessments evaluated remotely (e.g., via phone) and safety labs conducted (at a local lab) at the time of the scheduled Week 48 visit.

Subjects who discontinue from study medication prior to Week 48 will have an Early Discontinuation visit. Depending on the reason for the early discontinuation (e.g., declining patient status), some procedures, for example, PK samples, PD samples, lumbar puncture, may not be conducted at this visit. Conduct of all procedures, if possible, is encouraged.

[10] For subjects who discontinue study medication early (prior to Week 48), the site should contact the subject by phone call at approximately Week 48 to collect information on clinical status (including Time to Event measures of disease progression, and if applicable, AEs, SAEs).

Table 2: Schedule of Assessments and Events - Open-Label Extension Phase

Visit	Baseline Ext[1] (Pre-dose)	Abbreviated Drug Dispensation Visit[2]	2 Ext (phone)	3 Ext[7] (can be remote)	4 Ext[7] (can be remote)	5 Ext	6 Ext	7 Ext	8 Ext[8]
Day (Visit procedures conducted within a +/- 7 day window, unless otherwise specified)	1		14	29	57	85	169	253	337
Week	0		2 Ext	4 Ext	8 Ext	12 Ext	24 Ext	36 Ext	48 Ext /Early Discontinuation[8]
Eligibility Assessments									
Informed Consent (subject)	X	X							
Medical History	X								
Concomitant Medication review	X	X				X	X	X	X
Safety Assessments									
Physical Examination[3]	X					X	X	X	X
Physical Measurements[4]	X								X
Vital Signs[5]	X	X				X	X	X	X
ECG (12-lead)	X			X if visit is conducted in person	X if visit is conducted in person	X	X	X	X
Laboratory Tests	X			X	X	X	X	X	X
Pregnancy Test[6]	X			X	X	X	X	X	X
Sheehan Suicidality Tracking Scale	X		X			X	X	X	X
Adverse Event Reporting									
Monitor for Nonserious AEs and SAEs	X	X	X	X	X	X	X	X	X

Visit	Baseline Ext[1] (Pre-dose)	Abbreviated Drug Dispensation Visit[2]	2 Ext (phone)	3 Ext[7] (can be remote)	4 Ext[7] (can be remote)	5 Ext	6 Ext	7 Ext	8 Ext[8]
Day (Visit procedures conducted within a +/- 7 day window, unless otherwise specified)	**1**		**14**	**29**	**57**	**85**	**169**	**253**	**337**
Week	**0**		**2 Ext**	**4 Ext**	**8 Ext**	**12 Ext**	**24 Ext**	**36 Ext**	**48 Ext /Early Discontinuation[8]**
Efficacy Assessments									
Unified MSA Rating Scale Parts I-IV[3] (if visit is conducted remotely [by phone], only conduct Part I)	X					X	X	X	X
MSA Quality of Life	X					X	X	X	X
Time-to-event measures of disease progression	X					X	X	X	X
Dispense Study Drug	X	X				X	X	X	
Study Drug Compliance Assessment	X		X			X	X	X	X

Under regular circumstances, visits are to be completed in-person, unless otherwise specified. Some visits can be conducted remotely, as needed, due to COVID-19 restrictions. See Protocol Section 4.3.1, COVID-19 Public Health Emergency, for further details and requirements regarding conduct of remote visits due to COVID-19.

[1] Baseline visit for the OLE Phase is only required if there is an extended break (≥4 weeks) in dosing between the double-blind and OLE Phases. Otherwise, the double-blind Week 48 visit will take the place of the Baseline-Extension visit. Subjects should take the first dose of IP while in the office/clinic on the day of the Baseline-Extension visit and stay at the clinic for ~ 4 hours for observation. From start to end of Week 1-Extension, subjects will ingest 300 mg QD of BHV-3241. From start to end of Week 2-Extension, subjects will ingest 300 mg BID of BHV-3241. Starting with Week 3-Extension and for the remainder of the OLE, subjects will ingest 600 mg BID of BHV-3241.

[2] Abbreviated visit only needed for patients who completed dosing in the double-blind phase <4 weeks prior to entering the OLE Phase. The double-blind Week 48 Visit serves as the Baseline-Extension visit. This visit is primarily to dispense study drug. Subjects should take the first dose of IP while in the office/clinic on the day of the Baseline-Extension visit and stay at the clinic for ~4 hours for observation. From start to end of Week 1, subjects will ingest 300 mg QD of BHV-3241. From start to end of Week 2, subjects will ingest 300 mg BID of BHV-3241. Starting with Week 3 and for the remainder of the OLE, subjects will ingest 600 mg BID of BHV-3241.

[3] Including neurologic exam as a component of general physical exam and UMSARS.

[4] Height and weight.

[5] Subjects should be seated and resting for approximately 5 minutes prior to vital sign measurements - temperature, blood pressure, and heart rate. Tilt table may be used, if available.

[6] Serum pregnancy test will be conducted in WOCBP (see section 5.5) at all scheduled visits. Urine pregnancy test will be performed on WOCBP (in addition to serum) at Baseline-Extension (within 24 hours prior to first dose of open-label BHV-3241).

[7] Week 4-Extension and Week 8-Extension are primarily to collect lab tests and, if conducted in the clinic/study site, to conduct an ECG. If the patient attends the visit at the clinic/study site, an assessment of adverse events, conduct of an ECG and collection of samples for lab analyses will be completed. If a participant prefers to not attend the visit at the clinic/study site, the lab samples can be collected/conducted at a local laboratory/location and a telephone call to confirm these were collected, as well to assess any adverse events, will take place.

[8] Subjects who discontinue from study medication prior to Week 48-Extension will have an Early Discontinuation visit

4.3.2 Screening Phase

The purpose of the Screening phase is to ensure that the appropriate subjects are entered into the trial and remain stable during the pre-treatment period. It is estimated that approximately 360 subjects will enter the Screening phase of the trial. The Investigator will determine that the subject meets eligibility criteria and will collect demographic and medical data presenting a full characterization of the subject. All attempts should be made to obtain medical and pharmacy records to confirm the subject's medical and medication treatment history. During Screening, Biohaven (or designee) may review relevant clinical information to confirm the diagnosis and subtype of MSA, for study eligibility and stratification prior to randomization.

Screening will range from a minimum of 1 day to a maximum of 42 days. Please refer to the Schedule of Assessments & Events (Table 1) for Screening procedure details.

If initial Screening lab sample results do not meet protocol-specified eligibility criteria and the Investigator determines that a repeat sample may meet the range required for eligibility, a repeat lab sample may be collected (one repeat collection/analysis allowed).

Rescreening: After obtaining Sponsor approval, a subject who does not meet protocol required eligibility criteria during Screening but who may potentially become eligible (e.g., logistical reasons such as exceeding screening window to accommodate time required for adjustment/stability of concomitant medication, washout of prohibited medication or repeat procedures to allow for recheck/confirmation of an abnormality that may meet the required range in a reasonable amount of time), may be entered as a Screen Failure in IWRS and then rescreened one time (entered as a Screen Failure and Rescreen in IWRS and eCRF). If the Sponsor approves Rescreening for a subject, instructions will be provided to the site regarding the specific Screening procedures/evaluations that will need to be repeated for Rescreening, as this is dependent on the amount of time elapsed.

4.3.3 Randomization Phase

Subjects who are determined to be eligible for the study will be randomized into the trial. It is estimated that approximately 325 subjects will be randomized and assigned to receive BHV-3241 (600 mg BID) or matching placebo (BID) in a 1:1 ratio, with randomization stratified by disease subtype of either MSA-P vs. MSA-C, diagnostic category of either possible MSA vs. probable MSA, and country.

Subjects 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 Baseline visit. Subjects should stay at the office/clinic for monitoring for approximately 4 hours.

Dose titration period: For the rest of Week 1, subjects will ingest either 300 mg QD of BHV-3241 or matching placebo QD. From start to end of Week 2, subjects will ingest either 300 mg BID of BHV-3241 or matching placebo BID. Subjects should take the study drug twice a day; dosing in the morning and evening approximately 12 hours apart. If there is a delay in dosing, the interval between two doses should be no less than 6 hours.

An end of Week 2 assessment of compliance and tolerance to this dose titration schedule will be conducted. Per Investigator judgement, additional evaluations/procedures may be conducted at this timepoint as appropriate. If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 7.2.3).

Full dose period: Starting with Week 3 and for the remainder of the study, subjects will ingest either 600 mg BID of BHV-3241 or matching placebo BID. Subjects should take the study drug twice a day; dosing in the mornings and evenings approximately 12 hours apart.

At Weeks 4, 12, 24, 36 and 48, the morning dose of study medication should not be taken on the day of the study visit until it is administered by site personnel during the study visit, so that one pre-dose (trough) and one post-dose PK sample can be collected approximately 2-4 hours post-dose (see Section 6.3.2).

The tablets should be swallowed whole with a drink of water. The tablets should not be split, chewed, or crushed.

Study medication can be taken without regard to meals, however, the last mealtime prior to collection of PK samples should be obtained.

If subjects have difficulty tolerating BHV-3241 600 mg BID, then the dose may be adjusted (see Section 7.2.3).

There is a +/- 3 day visit and procedure window during the study, unless otherwise specified. Please refer to the Schedule of Assessments & Events (Table 1) for details on procedures.

4.4 End of Treatment

Patients will have a Week 48/Early Discontinuation visit when they either complete the study at Week 48 or discontinue from study medication early (prior to Week 48). The Week 48/Early Discontinuation assessments/procedures should be conducted as an in person visit at the study site. Every effort should be made to conduct the Week 48 visit and maintain a +/- 7 day window. However, due to the COVID-19 public health emergency, if absolutely necessary, in order to minimize potential risks to study participant safety and to comply with governmental and local institutional guidance (e.g., study site has a policy that an in person clinical research visit must be delayed), the Week 48 visit window may be expanded beyond the +/- 7 day window up to an additional 12 weeks (maximum treatment duration of 60 weeks). However, every attempt should be made to conduct the visit as close as possible to the date that the visit is due. Under these circumstances, the Investigator should discuss the specific circumstances of these cases with the sponsor medical monitor (or designee), who must

approve the request to extend the treatment duration, prior to any modification of the visit window.

If the Week 48 visit window is modified, participants should have safety assessments evaluated remotely (e.g., via phone) and safety labs conducted (at a local lab) at the time of the scheduled Week 48 visit.

For subjects who discontinue early, depending on the reason for early discontinuation (e.g., declining patient status), some procedures (for example, PK samples, PD samples, lumbar puncture), may not be conducted at this visit. Conduct of all procedures, if possible, is encouraged. If possible, the subjects who discontinue from study medication prior to Week 48 should be contacted by a follow up phone call at the approximate time of their Week 48 visit, to collect information on clinical status (including Time to Event measures of disease progression, and if applicable, AEs, SAES).

4.5 Post Study Access to Therapy/Open-Label Extension Phase

The OLE Phase is an optional 48 week open-label treatment phase following the double-blind phase of the study.

4.5.1 Open-Label Extension Phase Eligibility Criteria

The Investigator will be responsible for evaluating the participant's status, the participant's risk-benefit profile, the consent of the participant and the integrity of the trial, to determine whether a study participant is appropriate and eligible to continue participation in the optional OLE Phase, based on clinical judgement, the restricted and prohibited medication criteria specified in protocol section 5.4, the discontinuation criteria guidance specified in protocol section 6.4 and review of the following criteria:

- Completion of the 48 week Double-Blind randomized phase of the study. Participants who early-terminated from the double-blind phase of the trial or who discontinued the study medication for any reason will not eligible for enrollment in the OLE phase. All participants must have their Week 48 visit in-person prior to enrolling in the OLE phase. Due to COVID-19, the timing of this visit may be delayed.
- Study participants must be:
  - able to continue to swallow whole study medication tablets
  - willing and able to continue to
    - adhere to the study drug regimen
    - to participate in all protocol specific assessments, and
    - to comply with the study visit schedule.
- Provide informed consent to participate in the OLE phase. All subjects who enter the OLE phase will sign a new informed consent form.

4.5.2 Open-Label Extension Phase Procedures

When a site is open for recruitment to the OLE Phase, participants completing the double-blind treatment phase who choose to participate in the OLE phase and are eligible to continue, must consent to the OLE phase and directly enter the OLE phase starting at Week 48 visit of the double-blind treatment phase. The Week 48 visit will serve as the Baseline-Extension visit in the OLE phase for participants who move directly from the double-blind treatment phase to the OLE. Thereafter, participants will undergo visits at Week 2-Extension, Week 4-Extension, Week 8-Extension, Week 12-Extension, and then every 12 weeks of the OLE phase as outlined in Table 2 (Schedule of Assessments & Events- Extension Phase).

A participant who has completed the double-blind treatment phase of the study prior to the OLE phase of the study being approved and open for recruitment at the study center where they are participating, can reconsent and start the OLE phase as long as the investigator determines that open-label treatment offers an acceptable risk-benefit profile for the participant. Once the study site is open for recruitment for the OLE, study participants who previously completed the double-blind phase of the study will have up to approximately 12 weeks (from the date of OLE opening at the site) to enroll and complete the OLE Baseline-Extension Visit, regardless of their date of double-blind phase completion.

For participants who have been off of the study drug for less than 4 weeks, the subject should attend an Abbreviated Drug Dispensation Visit at the investigative site, when medical and/or medication changes will be reviewed prior to dispensing open-label BHV-3241. In this case, for these participants, the Week 48 visit will also serve as the Baseline-Extension visit in the OLE Phase. Thereafter, participants will undergo visits at Week 2-Extension, Week 4-Extension, Week 8-Extension, Week 12-Extension, and then every 12 weeks of the Extension Phase as outlined in Table 2 (Schedule of Assessments & Events- Extension Phase).

For participants who will have been off of the study drug for greater than or equal to 4 weeks, these participants should be re-assessed and re-consented by the Investigator during an OLE Baseline-Extension Visit. From the date that the OLE is open for recruitment at their investigative site, these participants will have up to approximately 12 weeks to complete the OLE Baseline-Extension Visit. Thereafter, participants will undergo visits at Week 2-Extension, Week 4-Extension, Week 8-Extension, Week 12-Extension, and then every 12 weeks of the Extension Phase as outlined in Table 2 (Schedule of Assessments & Events-Extension Phase).

Dose Titration: Subjects entering the OLE phase of the study will receive open-label active BHV-3241 and will follow the same dose titration schedule as the titration in the double-blind phase of the study, to ensure that all participants safely continue from either active BHV-3241 or placebo to open-label BHV-3241.

Subjects should be administered the Day 1/first dose of open-label BHV-3241 (300 mg QD) while in the office/clinic on the day of the Baseline-Extension visit. Subjects should stay at the office/clinic for monitoring for approximately 4 hours.

For the rest of Week 1-Extension of the OLE phase, subjects will ingest one tablet of BHV-3241 (300 mg) per day in the morning for one week. From start to end of Week 2-Extension, subjects will ingest 300 mg BID of BHV-3241. Subjects should take one 300 mg tablet of BHV-3241 twice a day (600 mg per day); in the mornings and evenings, approximately 12 hours apart. If there is a delay in dosing, the interval between two doses should be no less than 6 hours.

An end of Week 2-Extension assessment of compliance and tolerance to this dose titration schedule will be conducted. Per Investigator judgement, additional evaluations/procedures may be conducted at this timepoint as appropriate. If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 7.2.3).

Starting with Week 3-Extension and for the remainder of the OLE phase of the study (additional 46 weeks), subjects will ingest 600 mg BID of BHV-3241. Subjects should take two 300 mg tablets of BHV-3241 twice a day (1200 mg per day); in the mornings and evenings, approximately 12 hours apart.

Subjects who were taking a reduced dose of 300 mg BID (one tablet twice a day) of the blinded study medication due to tolerability issues when they completed the double-blind phase of the protocol, may continue taking 300 mg BID during the OLE.

5 POPULATION

5.1 Number of Subjects

Approximately 325 subjects are expected to be randomized in this study.

5.2 Inclusion Criteria

1. **Informed Consent**

    a. Subjects must provide a written signed and dated informed consent form/forms (IRB/EC specific) in accordance with regulatory and institutional guidelines, prior to the initiation of any protocol required procedures. Only patients with the capacity to understand the nature, significance and scope of the clinical trial interventions and to express their wishes accordingly may provide consent to participate in the study.

    b. Caregivers must be willing to sign and date an IRB/EC-approved written informed consent form that outlines the caregiver expectations and responsibilities in this study (see Inclusion criterion 3k), in accordance with regulatory and institutional guidelines, as appropriate.

2. **Age and Sex**

    a. Male and female subjects between the ages of ≥40 to ≤80 years at time of Screening.

3. **Target Population**

a. Diagnosis of probable or possible MSA according to consensus clinical criteria (Gilman et al 2008), including subjects with MSA of either subtype (MSA-P or MSA-C).

b. Able to ambulate without the assistance of another person, defined as the ability to take at least 10 steps. Use of assistive devices (e.g., walker or cane) is allowed.

c. Anticipated survival of at least 3 years at the time of Screening, as judged by the Investigator.

d. A brain MRI scan (conducted within the 14 days prior to Baseline/Day 1, approximately) that does not rule out a diagnosis of MSA.

e. Able to tolerate MRI.

f. Body mass index (BMI) $\leq$ 40 kg/m^2 at Screening.

g. Able to swallow tablets whole and anticipated to be able to do so throughout the duration of the study.

h. Willing and able to adhere to the study drug regimen.

i. Willing and able to perform all protocol-specified assessments and comply with the study visit schedule.

j. Able to read, understand, and speak local language fluently to ensure comprehension of informed consent and protocol-specified assessments.

k. Must have reliable caregiver to accompany subject to study visits, with the same caregiver completing caregiver assessments at Baseline, Week 24 and Week 48/Early Discontinuation, when possible. Caregiver must be able to read, understand, and speak local language fluently to ensure comprehension of informed consent and protocol-specified assessments. Caregiver must also have frequent contact with subject (at least 3 hours per week at one time or different times) and be willing to monitor the subject's health and concomitant medications throughout the study.

l. If subject is receiving treatment for MSA, the doses must have been stable for at least 30 days prior to Baseline/Randomization and medications present at Baseline expected to remain relatively stable during the study period. This may include medications commonly used for Parkinson's disease (e.g., coenzyme Q10, levodopa/carbidopa, levodopa/benserazide, fava bean extract, a dopamine agonist, catechol-0-methyltransferase inhibitor, amantadine) or those for autonomic dysfunction (e.g., ephedrine, midodrine, fludrocortisone, octreotide, desmopressin, oxybutynine, droxidopa).

m. Stable on other chronic medications and supplements for at least 30 days prior to Baseline/Randomization and expected to remain relatively stable during the study period.

n. Women of child bearing potential (WOCBP) [see protocol section 5.5] and fertile men (including those vasectomized for less than 6 months) with female partners who are WOCBP (not surgically sterile and not postmenopausal) [see protocol section 5.5] must agree to use highly effective birth control, including two methods of contraception, for the duration of the study (i.e., beginning 30 days prior to Baseline/Randomization and extending to 30 days for women and 90 days for men **after** the last dose of study drug). The two methods of contraception should include:

   i. one barrier method (e.g. diaphragm with spermicide, condom with spermicidal gel, cervical cap);

   ii. and one other method that could include hormonal contraceptives (e.g. oral contraceptives, injectable contraceptives, contraceptive implant, patch) used for at least 4 weeks prior to sexual intercourse (Section 5.5);

o. WOCBP must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within approximately 24 hours prior to dosing at Baseline/Randomization.

5.3 Exclusion Criteria

1. **Target Disease Exceptions**

   a. Subjects having advanced disease, defined by the presence of one or more of the following on the UMSARS Part I:

      i. Speech impairment, as assessed by a score greater than or equal to 3, Question 1;

      ii. Swallowing impairment, as assessed by a score of greater than or equal to 3 on Question 2;

      iii. Falling more frequently than once per week, as assessed by a score of greater than or equal to 3 on Question 8; or

CCI [redacted]

2. **Medical History Exclusions**

   a. Any condition that would interfere with the subject's ability to comply with study instructions, place the subject at unacceptable risk, and/or confound the interpretation of safety or efficacy data from the study, as judged by the Investigator.

b. Diagnosis of neurological disorders, other than MSA, including (but not limited to) the following:

   i. Idiopathic Parkinson's disease or another form of parkinsonism (e.g., dementia with Lewy bodies, drug-induced, post-encephalitic, vascular), which has not subsequently revised to a diagnosis of MSA,

   ii. Any other neurodegenerative disease (e.g., Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis, prion disease),

   iii. Any other clinically significant neurological disorder (e.g., history of stroke, history of head injury with loss of consciousness for at least 15 minutes within the past 20 years, history of seizure disorder, brain tumor, or other space-occupying lesion).

c. History of or Screening brain MRI scan indicative of significant abnormality, including (but not limited to) the following: prior hemorrhage or infarct greater than 1 cm^3; 3 or more lacunar infarcts; cerebral contusion; encephalomalacia; aneurysm; vascular malformation; subdural hematoma; hydrocephalus; space-occupying lesion (e.g., abscess or brain tumor).

d. Contraindication to MRI examination for any reason.

e. For those participating in the optional CSF sub-study, contraindication to undergoing an LP including, but not limited to: inability to tolerate an appropriately flexed position for the time necessary to perform an LP; infection at the desired LP site; taking antiplatelet/anticoagulant medications that cannot be discontinued for a short period of time prior to performing the LP; degenerative arthritis of the lumbar spine; suspected non-communicating hydrocephalus or intracranial mass; prior history of spinal mass or trauma.

f. Presence of clinically significant thyroid disease with abnormal free T4 levels and TSH >10 mIU/L (despite treatment) at Screening, confirmed by repeat.

g. Within 1 year prior to Screening or between Screening and Baseline (Day -1), any of the following: myocardial infarction; hospitalization for congestive heart failure; hospitalization for, or symptoms of, unstable angina; or syncope not related to MSA.

h. Diagnosis of clinically significant psychiatric disorder including (but not limited to) the following: any psychotic disorder, severe bipolar or unipolar depression, prior history of suicidal thoughts or behavior that are believed to represent a current safety risk.

i. History of substance use disorder (drug or alcohol) in the last 12 months, with the exception of nicotine, as defined by DSM-V criteria.

j. History or presence of gastrointestinal or other disease known to interfere with absorption, distribution, metabolism, or excretion of drugs, or a history of surgery known to interfere with absorption or excretion of drugs (i.e., gastric bypass).

k. History of any other clinically significant disease (e.g., autoimmune, cardiovascular, endocrine, gastrointestinal, hematological, hepatic, immunological, infectious, neurological, pulmonary, psychiatric, or renal) that, based on the judgment of the Investigator, is clinically unstable, is likely to deteriorate during the course of the study, could put the patient at risk because of participation in the study, could affect the subject's ability to complete the study, or could influence the study results.

l. History of human immunodeficiency virus infection.

m. Hematologic or solid malignancy diagnosis within 5 years prior to Screening. [Note: Subjects with a history of localized skin cancer, basal cell or squamous cell carcinoma, may be enrolled in the study as long as they are cancer free prior to randomization. Subjects with other localized cancers (without metastatic spread) who have previously completed their course of treatment more than 5 years prior to Screening, are not currently receiving treatment and have been in remission may be enrolled only if, in the opinion of the Investigator, there is no expectation for recurrence or further cancer treatment during the study period. Antihormonal therapy (e.g., tamoxifen) is allowed if the subject's cancer is in remission and the subject is on stable maintenance therapy to reduce their risk of recurrence.]

n. Any major surgery within 4 weeks of Screening.

o. Blood transfusion within 4 weeks of Screening.

p. History of brain surgery for Parkinsonism (i.e., deep-brain stimulation).

q. History of stem-cell treatment.

r. Women who are pregnant or breastfeeding.

s. Subjects or prisoners who are involuntarily detained or incarcerated for treatment of either a psychiatric or physical illness must not be enrolled into the study.

t. Any medical condition, based on the judgement of the Investigator, that would confound the ability to adequately assess safety and efficacy outcome measures

3. **Physical and Laboratory Test Findings**

a. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population.

b. Clinically significant abnormality on 12-lead ECG prior to study drug administration beyond what is consistent with the target population, confirmed by repeat.

c. QTcF (Fridericia) interval ≥ 470 msec during the Screening/Baseline period or uncontrolled arrhythmia or frequent premature ventricular contraction (PVCs) (>

5/minute) or Mobitz Type II second or third degree atrioventricular (AV) block or left bundle branch block, or right bundle branch block with a QRS duration ≥ 150 msec or intraventricular conduction defect with a QRS duration ≥ 150 msec or evidence of acute or sub-acute myocardial infarction or ischemia or other ECG findings that, in the Investigator's opinion, would preclude participation in the study.

d. Abnormal free T4 levels and TSH > 10 mIU/L (despite treatment) at Screening, confirmed by repeat.

e. Total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2 times the upper limit of normal (ULN), confirmed by repeat. If the patient is diagnosed as having Gilbert's syndrome, the patient can be discussed with the Medical Monitor.

f. Pathologic renal findings at Screening as defined by the presence of either of the following criteria:

   i. Estimated glomerular filtration rate (eGFR) according to the re- expressed abbreviated (four-variable) Modification of Diet in Renal Disease (MDRD) Study equation < 30 ml/min/ 1.73m2; The MDRD estimation is calculated as follows: eGFR (mL/min/1.73m2) = 175 x (standardized Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if Black). [Scr: Standardized serum creatinine];

   ii. Creatinine ≥ 2mg/dL

g. Hematologic abnormalities at Screening:

   i. Hemoglobin < 10 g/dL; or

   ii. WBC < 3.0 x 103/mm3; or

   iii. Platelet count < 100,000/mm3; or

   iv. Neutrophils, Absolute ≤ 1000/mm^3

h. Hemoglobin A1C ≥7.5%, confirmed by repeat.

i. Urine drug screen positive for a drug of abuse, for which the patient does not have a valid prescription and is suspected of abusing, in the judgement of the Investigator.

   Note: urine drug screen positive for cannabis is exclusionary unless the Investigator and Medical Monitor agree that the subject can abstain from use for the duration of the study, or if the subject has a valid medical prescription.

j. Human Immunodeficiency Virus (HIV) positive at Screening (indicated by positive confirmatory Western Blot);

k. HBsAg or HCV positive at Screening;

l. For WOCBP, positive serum β-hCG which is indicative of pregnancy and not false positive at Screening or a positive urine pregnancy test at Baseline.

4. **Prohibited and Restricted Treatments and/or Therapies (can be washed out during Screening)**

a. Participation in another clinical trial for an investigational agent and having taken at least one dose of study medication, unless confirmed as having been on placebo, is excluded within 90 days or 5 half-lives (whichever is longer) prior to Baseline/Randomization. The end of a previous investigational trial is defined as the date of the last dose of an investigational agent.

b. Dopamine antagonists, including metoclopramide and antipsychotic medications are excluded.

i. Quetiapine and clozapine are allowed if the doses are stable for at least 30 days prior to Baseline/Randomization

c. Inhibitors of CYP1A2 - Strong inhibitors of CYP1A2 (i.e., ciprofloxacin, enoxacin, fluvoxamine, zafirlukast) could potentially increase BHV-3241 levels and are excluded for chronic/long-term (> 2 weeks) use. Strong inhibitors of CYP1A2 for acute/short-term use should be avoided, if possible, or used with caution, based on the clinical judgement of the investigator. Moderate inhibitors of CYP1A2 (i.e., methoxsalen) could potentially increase BHV-3241 levels and should be used with caution for chronic/long-term use, based on the clinical judgement of the investigator.

d. Inducers of CYP1A2 - Strong inducers of CYP1A2 (i.e., phenytoin, rifampin) could reduce BHV-3241 levels and should be used with caution, based on the clinical judgement of the investigator.

e. Inhibitors of CYP3A4 - Strong inhibitors of CYP3A4 (i.e., conivaptan, grapefruit juice, itraconazole, ketoconazole, posaconazole, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, and antiviral agents [cobicistat, danoprevir, ritonavir, elvitegravir, indinavir, lopinavir, paritaprevir, ombitasvir, dasabuvir, saquinavir, tipranavir, nelfinavir]) could potentially increase BHV-3241 levels and are excluded for chronic/long-term (> 2 weeks) use. Strong inhibitors of CYP3A4 for acute/short-term use should be avoided, if possible, or used with caution, based on the clinical judgement of the investigator. Moderate inhibitors of CYP3A4 (i.e., aprepitant, cimetidine, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, imatinib, tofisopam, verapamil) could potentially increase BHV-3241 levels and should be used with caution for chronic/long-term use, based on the clinical judgement of the investigator.

f. Inducers of CYP3A4 – Strong inducers of CYP3A4 (i.e., carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort) could reduce BHV-3241 levels and should be used with caution, based on the clinical judgement of the investigator.

g. Drugs principally metabolized by CYP2B6 (i.e., bupropion, cyclophosphamide, efavirenz, ifosphamide, methadone, and sorafenib) should be used with caution, based on the clinical judgement of the investigator.

h. Drugs principally metabolized by CYP3A4 (i.e., clarithromycin, erythromycin, ethinylestradiol [hormonal contraceptives], telithromycin, quinidine, theophylline, tizanidine, verapamil, warfarin, zileuton, and zolmitriptan) should be used with caution, based on the clinical judgement of the investigator. Note: hormonal contraceptive effectiveness may potentially be reduced; thus dose adjustment, use of alternative and/or additional methods of birth control is required for WOCBP.

i. Chronic/long-term (> 2 weeks) use of immunomodulatory medications is excluded, including the following: azathioprine, chlorambucil, cyclophosphamide, fingolimod (and other S1P receptor modulators), ibudilast, methotrexate, montelukast, mycophenolate mofetil, tacrolimus, sirolimus (rapamycin), and monoclonal antibodies or related biological agents (i.e., abatacept, adalimumab, anakinra, basiliximab, belimumab, canakinumab, certolizumab, daclizumab, etanercept, infliximab, natalizumab, ocrelizumab, tocilizumab, rituximab, trastuzumab, and ustekinumab).

   NOTE: Aspirin, and nonsteroidal anti-inflammatory medications, are allowed

5.4 Prohibited and Restricted Concomitant Medication

During the course of the study (from Baseline/Randomization to end of treatment), patients should stay on their usual medication regimes (i.e. those not excluded by the protocol) at relatively stable doses.

Use of the following medications is prohibited or restricted as follows. Subjects receiving such medications chronic/long-term at enrollment should undergo a 4 week washout period prior to Baseline/Randomization unless otherwise noted or medically contraindicated:

1. Any other investigational agent is prohibited (requires minimum washout of 90 days or 5 half-lives [whichever is longer], prior to Baseline/Randomization)

2. Dopamine antagonists, including metoclopramide and antipsychotic medications are prohibited.

   a. Quetiapine and clozapine are allowed if the doses are stable for at least 30 days prior to Baseline/Randomization

3. Inhibitors of CYP1A2 - Strong inhibitors of CYP1A2 (i.e., ciprofloxacin, enoxacin, fluvoxamine, zafirlukast) could potentially increase BHV-3241 levels and are prohibited for chronic/long-term (> 2 weeks) use. Strong inhibitors of CYP1A2 for acute/short-term use should be avoided, if possible, or used with caution, based on the clinical judgement of the investigator. Moderate inhibitors of CYP1A2 (i.e., methoxsalen) could potentially increase BHV-3241 levels and should be used with caution for chronic/long-term use, based on the clinical judgement of the investigator.

4. Inducers of CYP1A2 - Strong inducers of CYP1A2 (i.e., phenytoin, rifampin) could reduce BHV-3241 levels and should be used with caution, based on the clinical judgement of the investigator.

5. Inhibitors of CYP3A4 - Strong inhibitors of CYP3A4 (i.e., conivaptan, grapefruit juice, itraconazole, ketoconazole, posaconazole, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, and antiviral agents [cobicistat, danoprevir, ritonavir, elvitegravir, indinavir, lopinavir, paritaprevir, ombitasvir, dasabuvir, saquinavir, tipranavir, nelfinavir) could potentially increase BHV-3241 levels and are prohibited for chronic/long-term (> 2 weeks) use. Strong inhibitors of CYP3A4 for acute/short-term use should be avoided, if possible, or used with caution, based on the clinical judgement of the investigator. Moderate inhibitors of CYP3A4 (i.e., aprepitant, cimetidine, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, imatinib, tofisopam, verapamil) could potentially increase BHV-3241 levels and should be used with caution for chronic/long-term use, based on the clinical judgement of the investigator.

6. Inducers of CYP3A4 – Strong inducers of CYP3A4 (i.e., carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort) could reduce BHV-3241 levels and should be used with caution, based on the clinical judgement of the investigator.

7. Drugs principally metabolized by CYP2B6 (i.e., bupropion, cyclophosphamide, efavirenz, ifosphamide, methadone, and sorafenib) should be used with caution, based on the clinical judgement of the investigator.

8. Drugs principally metabolized by CYP3A4 (i.e., clarithromycin, erythromycin, ethinylestradiol [hormonal contraceptives], telithromycin, quinidine, theophylline, tizanidine, verapamil, warfarin, zileuton, and zolmitriptan) should be used with caution, based on the clinical judgement of the investigator. Note: hormonal contraceptive effectiveness may potentially be reduced; thus dose adjustment, use of alternative and/or additional methods of birth control is required for WOCBP.

9. Chronic (> 2 weeks) use of immunomodulatory medications, including the following: azathioprine, chlorambucil, cyclophosphamide, fingolimod (and other S1P receptor modulators), ibudilast, methotrexate, montelukast, mycophenolate mofetil, tacrolimus, sirolimus (rapamycin), and monoclonal antibodies or related biological agents (i.e., abatacept, adalimumab, anakinra, basiliximab, belimumab, canakinumab, certolizumab, daclizumab, etanercept, infliximab, natalizumab, ocrelizumab, tocilizumab, rituximab, trastuzumab, and ustekinumab) is prohibited.

   NOTE: Aspirin and nonsteroidal anti-inflammatory medications are allowed.

The above medications, if used for the short-term treatment of intercurrent illness, are allowed if needed, at the discretion of the Investigator, provided they are not otherwise prohibited as noted above.

The generic name (where possible), start date, end date and dosing information for any medication (prescriptions or non-prescription) taken by the subject within 1 month prior to study enrollment and up to the subject's last study visit/discontinuation will be recorded in the concomitant medication electronic case report form.

5.4.1 Other Restrictions and Precautions

Medications prescribed by another physician: In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medication, either non-prescription or prescription therapy prescribed by another physician, without prior consultation with the Investigator.

Physical rehabilitation: Participation in physical rehabilitation programs is permitted if these have been ongoing prior to starting the study and are planned to continue throughout the duration of the study. Change in a subject's physical rehabilitation programs during study participation should be limited in an attempt to maintain a stable regimen, whenever possible, as clinically appropriate.

CCI [redacted]

Elective medical procedures: Subjects should not undergo any elective medical procedures without prior consultation with the Investigator. An elective procedure (e.g., minor surgery, dental surgery, orthopedic surgery) that might require hospitalization or anesthesia should be deferred until after the study, when clinically appropriate.

5.5 Woman of Childbearing Potential (WOCBP)

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as:

- Amenorrhea greater than or equal to 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

  NOTE: FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to one year.

The requisite drug interaction studies to determine the interaction of BHV-3241 with oral contraceptives have not been completed to date. It is therefore not possible to determine the efficacy of oral contraceptives as an effective method of contraception for WOCBP who are participating in this study. Since hormonal contraceptive effectiveness may be reduced, estrogen and progesterone hormonal contraceptives as a sole method of contraception are therefore prohibited.

It is required that all WOCBP use two methods of contraception to avoid pregnancy for the duration of the study (i.e., beginning at 30 days prior to baseline) through 30 days **after** the last dose of investigational product in such a manner that risk of pregnancy is minimized. The two methods should include one barrier method (e.g., diaphragm with spermicidal gel, condom with spermicidal gel, cervical cap) and one other method. The other method could include hormonal contraceptives (e.g., oral contraceptives, injectable contraceptives, patch, or contraceptive implant) used since at least 4 weeks prior to sexual intercourse.

Any male who has a female partner of WOCBP must avoid pregnancy while participating in this study. If male subjects are sexually active and not vasectomized for at least 6 months, and if the subject's female partner is not surgically sterile or is not postmenopausal, then the following accepted methods of contraception should be used throughout the study and for 90 days after the last study drug administration:

- Simultaneous use of male condom with spermicidal gel, and for the female partner, hormonal contraceptives (e.g., birth control pills, implants, patch, depot injection, used since at least 4 weeks) or intra-uterine contraceptive device placed since at least 4 weeks before sexual intercourse;

  OR

- Simultaneous use of male condom, and for the female partner cervical cap or diaphragm with intravaginally applied spermicide.

5.6 Deviation from Inclusion/Exclusion Criteria

Any significant event that does not comply with the inclusion exclusion criteria, study conduct, or study procedures will be documented as a deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Deviations will be reported to the IRB/EC at the frequency required by the IRB/EC. No protocol exceptions related to Inclusion/Exclusion criteria will be granted by the Sponsor.

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

Biohaven will provide the IP, which will include BHV-3241 300 mg ER tablets and matching placebo tablets.

Sites will also be provided with a Regulatory binder, IWRS Manual, CSF collection manual and CCI Imaging Manual. Source document creation is the responsibility of the site. Instructions on all specimens collected will be provided by a central laboratory.

All sites will use an Electronic Data Capture (EDC) tool to submit study data. Electronic Case Report Forms (eCRFs) will be prepared for all data collections.

Sites will be provided with a study protocol and any amendments.

The Investigator will be required to have a centrifuge (preferably refrigerated), a secure locked cabinet or similar (for drug storage), as well as freezer (-20C or -70 to -80C; see CCI lab manual and CSF Sub-study Collection and Processing manual for specific instructions regarding storage of lab samples), appropriate containers and dry ice for shipment and storage of blood, plasma and urine samples. The same centrifuge and freezer at a site should be used consistently for preparation and storage of samples from study subjects. Sufficient dry ice, when indicated, should be utilized to allow samples to arrive at their designated laboratory in a frozen state.

6.2 Eligibility and Safety Assessments

6.2.1 Medical and Psychiatric History

A full medical history will be obtained at Screening. This will include, but is not limited to, smoking history, cardiovascular disease, patient history of MSA and other medical and psychiatric history.

6.2.2 Safety Assessments

Safety and tolerability will be evaluated by report of AEs and by evaluation of abnormalities and clinically significant changes in physical examinations, ECGs, vital signs, Sheehan Suicidality Tracking Scale (S-STS), and laboratory tests.

6.2.2.1 Vital Signs and Physical Measurements (Height and Weight)

Vital sign measurements (temperature, blood pressure, and heart rate) will be recorded at every in-person visit as specified in the Schedule of Assessments & Events (Table 1 and Table 2). Subjects should be seated and resting for approximately 5 minutes prior to performing vital sign measurements (tilt table may be used, if available).

Height will be recorded at Screening and Week 48 and/or early discontinuation. Body weight will be recorded at Screening, Baseline, and Week 48 and/or early discontinuation. In the OLE phase, height and weight will be recorded at Baseline-Extension and Week 48-Extension/Early Discontinuation. The following guidelines will aid in the standardization of these measurements:

1. The same scale should be used to weigh a given subject throughout the study;

2. Scales should be calibrated and zeroed per site guidelines.

6.2.2.2 Physical Exam

Subjects will undergo a complete physical exam at each in-person study visit. The physical exam should include at least the following components: HEENT (head, eyes, ears, nose, and throat), neck, lymph nodes, lungs, cardiovascular, abdomen, skin, musculoskeletal and neurologic evaluation by the Principal Investigator or a medically qualified delegate. If a subject is discontinued for any reason, an attempt should be made to conduct a final physical exam.

6.2.2.3 Electrocardiogram (ECG)

A 12-Lead ECG will be recorded at Screening, Baseline, Week 2, 4, 12, 24, 36, and 48, Baseline-Extension, Week 4-Extension (if in person visit is conducted), Week 8-Extension (if in person visit is conducted), Week 12-Extension, 24-Extension, 36-Extension and 48-Extension and/or early discontinuation, as specified in the Schedule of Assessments & Events (Table 1 and Table 2) and as medically necessary. If a subject is discontinued for any reason, an attempt should be made to conduct a final ECG.

6.2.2.4 Laboratory Assessments

Laboratory testing will be conducted at Screening, Baseline, and Weeks 2, 4, 8, 12, 24, 36, and 48, Baseline-Extension, Week 4-Extension, Week 8-Extension, Week 12-Extension, Week 24-Extension, Week 36-Extension, Week 48-Extension and/or early discontinuation, as specified (and as medically necessary), to include the following (Refer to Schedule of Assessments & Events [Table 1 and Table 2]):

a. Hematology: hemoglobin, hematocrit, platelets, CBC with differential and absolute neutrophil count, RBC count and indices. At Screening and prior to lumbar puncture: INR, PT and partial PT.

b. Serum Chemistry: sodium, potassium, chloride, calcium, magnesium, ALT, AST, LDH, ALP, GGT, phosphorus, bicarbonate, CPK, total protein, albumin, total bilirubin (if greater than 2 mg/dl bilirubin will be fractionated), glucose, creatinine, BUN, uric acid. TSH, free T3 and free T4. Also, anti-TPO antibodies at Baseline, Week 2, Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, Baseline-Extension, Week 4-Extension, Week 8-Extension, Week 12-Extension, Week 24-Extension, Week 36-Extension, Week 48-Extension and whenever TSH is outside of normal range. Additionally, at Screening: total cholesterol, LDL, HDL, triglycerides, folate, HbA1c, P-Amylase or Lipase; Estimated glomerular filtration rate (eGFR)

c. Urinalysis (collect urine specimen just prior to obtaining weight): macroscopic examination, pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, creatinine, glucose, and occult blood. If blood, protein, or leukocytes are positive, microscopic examination will be performed on abnormal findings;

d. Serum pregnancy test will be conducted on WOCBP (per section 5.5) at Screening, Baseline, and Weeks 4, 12, 24, 36 and 48, Baseline-Extension, Week 4-Extension, Week 12-Extension, Week 24-Extension, Week 36-Extension, Week 48-Extension and early discontinuation. Urine pregnancy tests will be performed (as well as serum) at Baseline and Baseline-Extension (prior to dosing) on WOCBP and at the discretion of the Investigator. FSH is to be conducted on postmenopausal women at Screening to confirm postmenopausal status (see Section 5.5).

e. At Screening Only: HBsAg, HCV (reflex HCV-RNA after a positive HCV Ab), HIV antibody detection, and rapid plasma reagin (RPR). Reflex testing will be done for any positive RPR.

f. At Screening, Baseline and Baseline-Extension Only: Urine Drug Screen for cannabis (medical and recreational), amphetamines (including MDMA/ecstasy), cocaine, barbiturate, PCP, benzodiazepines, tricyclic antidepressants, and/or opiates. Reflex confirmatory testing will be conducted on all positive urine drug screen samples.

g. At Screening Only: Urine alcohol level.

h. For those participating in the optional CSF sub-study, analysis conducted by local lab of cell counts (white blood cells and red blood cells [with reflexed differential if either of the counts is abnormal], CSF protein and CSF glucose.

If initial Screening lab sample results do not meet protocol-specified eligibility criteria and the Investigator determines that a repeat sample may meet eligibility criteria, repeat lab samples may be collected (one repeat collection/analysis allowed).

If lab samples are collected and analyzed by a local lab rather than CCI central lab, due to COVID-19 restrictions preventing a study participant from attending an in person visit at the study site, the following safety lab analyses should be ordered:

- TSH
- Free T3
- Free T4
- Anti-TPO antibodies
- Hematology panel- Hematology: hemoglobin, hematocrit, platelets, CBC with differential and absolute neutrophil count, RBC count and indices
- Chemistry Panel-Direct Bili REFLEX, Indirect Bili REFLEX, Serum Chemistry: sodium, potassium, chloride, calcium, magnesium, ALT, AST, LDH, ALP, GGT, phosphorus, bicarbonate, CPK, total protein, albumin, total bilirubin (if greater than 2 mg/dl bilirubin will be fractionated), glucose, creatinine, BUN, uric acid
- Urinalysis Panel with Urine Creatinine- macroscopic examination, pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, creatinine, glucose, and occult blood. If blood, protein, or leukocytes are positive, microscopic examination will be performed on abnormal findings.
- Serum pregnancy test for all WOCBP.

Clinically significant laboratory abnormalities will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017)[18]. For those not available in CTCAE, according to Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017)[19].

6.2.2.5 Sheehan Suicidality Tracking Scale (Sheehan-STS)

The Sheehan STS (S-STS) is a prospective, clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors [20,21]. The S-STS will be completed on a paper form at the site at Screening, Baseline and each study visit, including Week 48, Baseline-Extension, Week 2-Extension, Week 12-Extension, Week 24-Extension, Week 36-Extension, Week 48-Extension, or early withdrawal. At Screening, the recall period for completing the S-STS is 6 months prior; at all other visits, the recall period for completing the S-STS is since the last visit (two separate versions will be provided). Subjects who have a S-STS score > 0 should be evaluated by the Investigator. If the Investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented and the Investigator should evaluate if the patient should be discontinued from the study.

6.2.3 Clinical Outcome Assessments

Each of the Clinician Reported Outcome (ClinRO) measures described below should be performed by an appropriately qualified individual. Specific qualification requirements for raters will be documented and appropriate training will be provided through didactic, video certification, and/or online training. Whenever possible, for any individual subject, each of these assessments should be performed by the same rater throughout the course of the study.

The Patient Reported Outcome (PRO) measures described below should be directly presented to the patient on paper. As a back-up option, each of the PRO measures may be administered as Clinician Reported Outcome measures where allowable by the assessment author/developer—meaning that the assessments will be presented to the patient verbally by a qualified member of the site staff, who will record the responses collected from the subject—in order to promote consistent quality, standardization, and minimize burden on the study subject. Caregivers should not complete the PRO measures on behalf of patients.

For any individual subject, each of the caregiver assessments should be completed by the same caregiver throughout the course of the study, when possible. Caregiver facing scales should be directly presented to the caregiver on paper. As a back-up option, each of the caregiver measures may be administered as Clinician Reported Outcome measures where allowable by the assessment author/developer-meaning that the assessments will be presented to the caregiver verbally by a qualified member of the site staff, who will record the responses collected from the caregiver-in order to promote consistent quality, standardization, and minimize burden on the caregiver. Caregivers must be willing to sign and date an IRB/EC-approved written informed consent form in accordance with regulatory and institutional guidelines, as appropriate. Caregiver information will be recorded on the CRF.

The UMSARS should be the first ClinRO completed, whenever possible. The MSA-QoL and/or PGI-S should be the first PROs completed, whenever possible.

6.2.3.1 Unified Multiple System Atrophy Rating Scale (UMSARS)

The UMSARS is a clinician-rated scale comprised of four parts [22]. Part I, Historical Review, is an assessment of functioning across various areas. Part II is a Motor Examination. Part III is an Autonomic Examination, and includes supine and standing vital signs, orthostatic change, and orthostatic symptoms. Tilt table may be used, if available. Part IV is a Global Disability Scale. Note: The UMSARS will be used to collect data in this study. However, the primary outcome variable for the study will be a modified UMSARS, composed of a subset of items from UMSARS Part I and Part II, with the items selected based on feedback from Health Authorities, expert opinion, and analysis of data from previous clinical trials in MSA.

The UMSARS is assessed during the Screening phase to determine eligibility for study entry and will subsequently be administered at Baseline, and Weeks 4, 12, 24, 36 and 48, Baseline-Extension, Week 12-Extension, Week 24-Extension, Week 36-Extension, Week 48-Extension and/or early discontinuation.

If the UMSARS is administered remotely (by phone/video) due to COVID-19 remote visit allowances, only Part I should be conducted and entered in the eCRF.

6.2.3.2 *Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I)*

The CGI-S scale is a clinician-rated scale measuring the severity of the patient's illness. It is scored on a 7- point scale ranging from 1 (normal, not ill at all) to 7 (among the most extremely ill patients). The CGI-S will be administered at Baseline and Weeks 4, 12, 24, 36 and 48 and/or early discontinuation. The CGI-S will not be administered during the OLE.

The CGI-I scale is a clinician-rated scale measuring the change in the patient's clinical status from a specific point in time. It is scored on a 7- point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. The CGI-I should be assessed relative to the CGI-S at the Week 0 (Day 1) visit as the reference. The CGI-I will be administered at Weeks 4, 12, 24, 36 and 48 and/or early discontinuation. The CGI-I will not be administered during the OLE.

Notation in the subject's study records should substantiate the CGI ratings. For any individual subject, these assessments should be performed by the same rater throughout the study.

6.2.3.3 *MSA Quality of Life Scale (MSA-QoL)*

The MSA-QoL is a patient-rated scale that was designed to measure health-related quality of life specifically in MSA [23]. It assesses activities of daily living and has subscales for motor, nonmotor, and emotional/social domains.

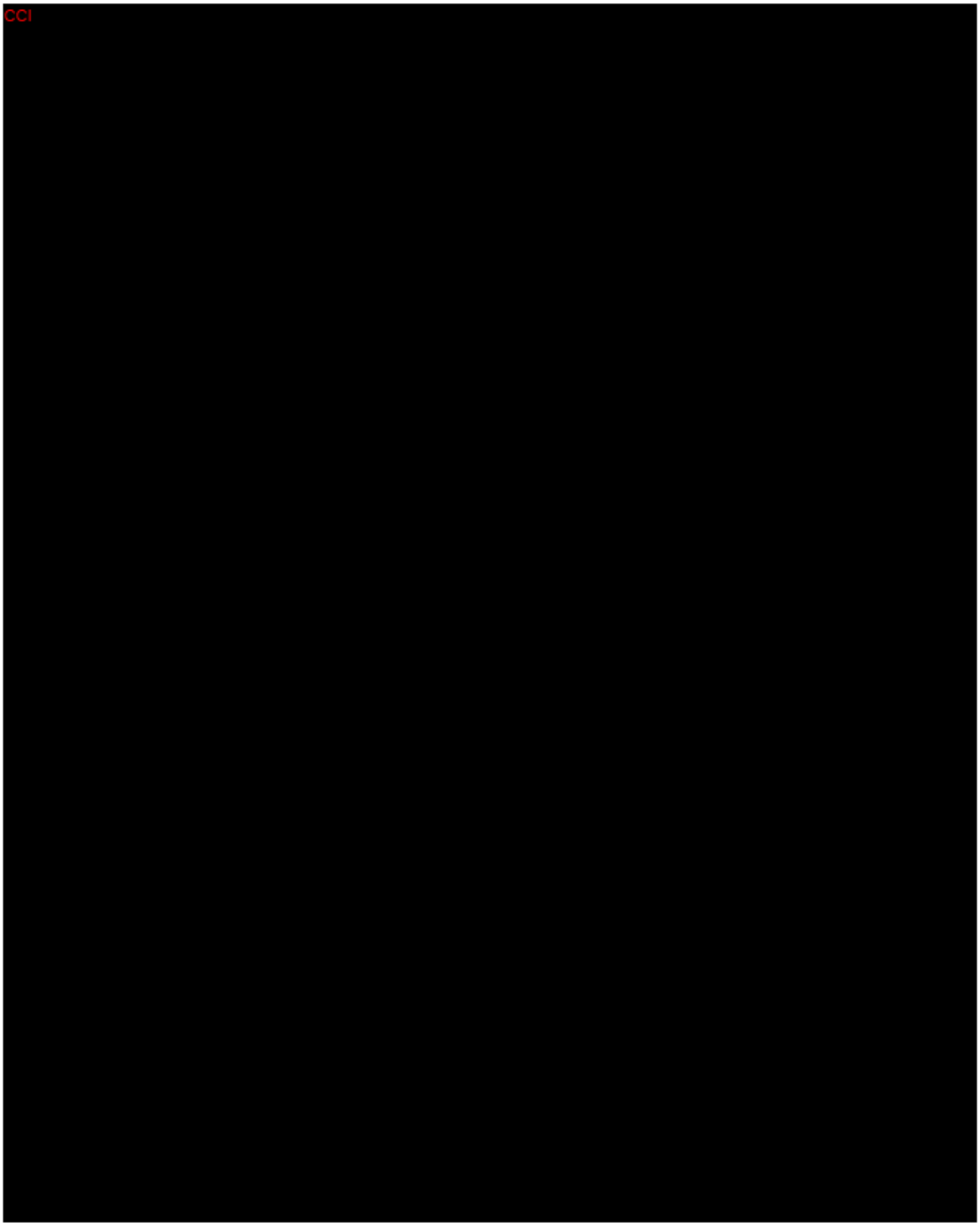
The MSA-QoL will be administered at Baseline, Week 24 and 48, Baseline-Extension, Week 12-Extension, Week 24-Extension, Week 36-Extension, Week 48-Extension and/or early discontinuation.

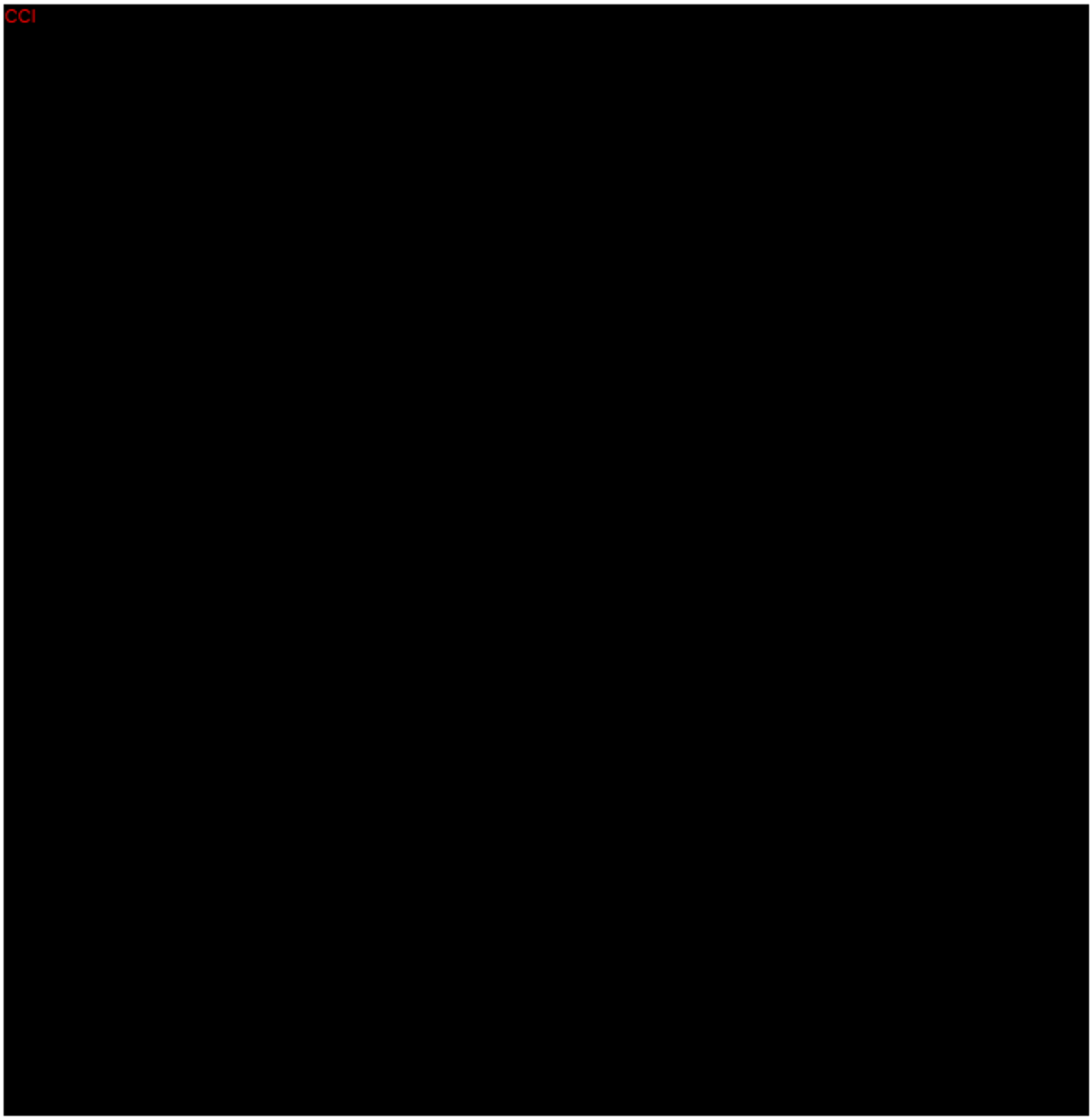
6.2.3.4 *Patient Global Impression of Severity (PGI-S)*

The PGI-S is a patient-rated scale and will be administered at Baseline and Weeks 4, 12, 24, 36 and 48 and/or early discontinuation. The patient will rate how they perceive the severity of their illness. The PGI-S will not be administered during the OLE.

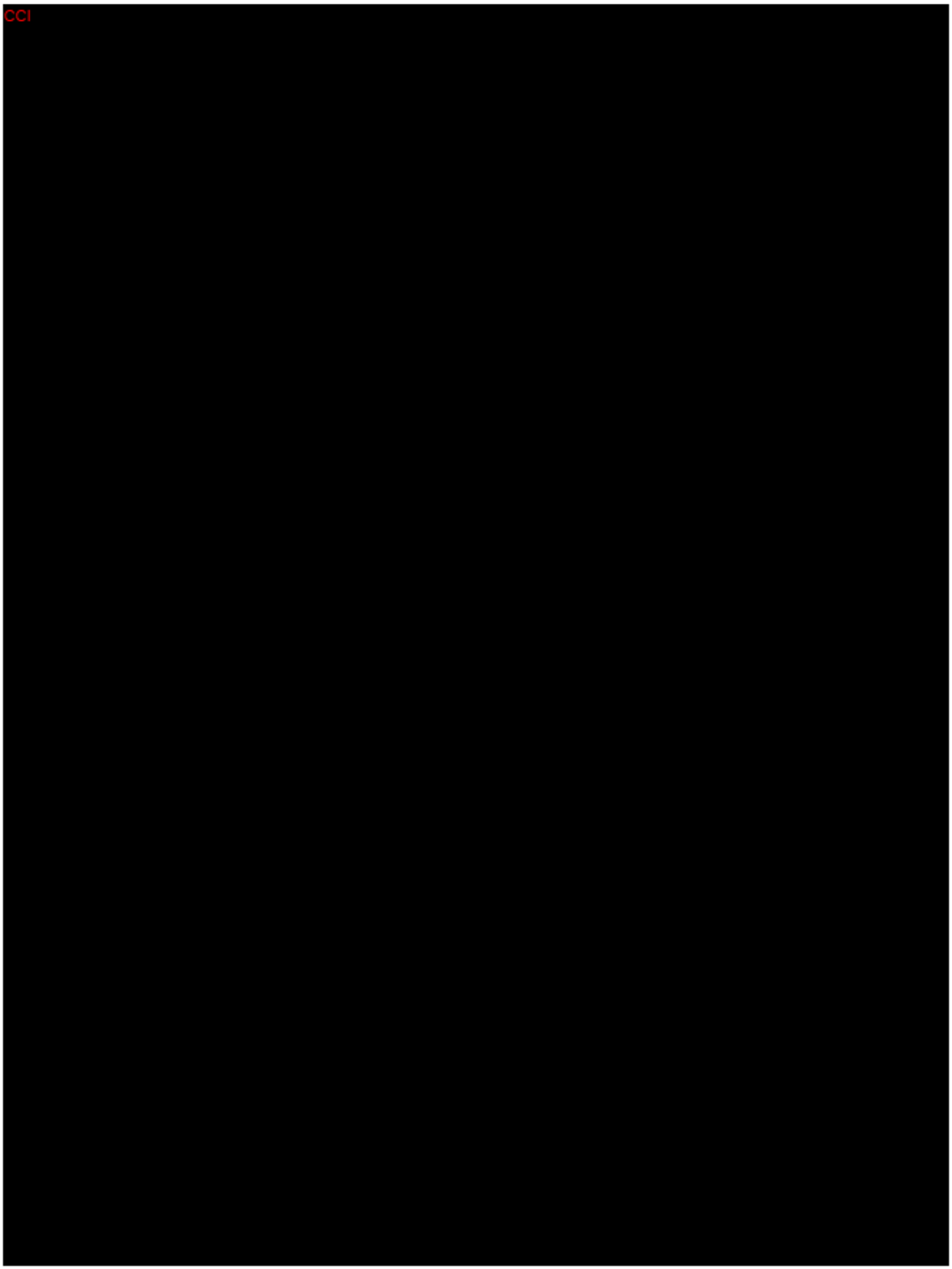
CCI

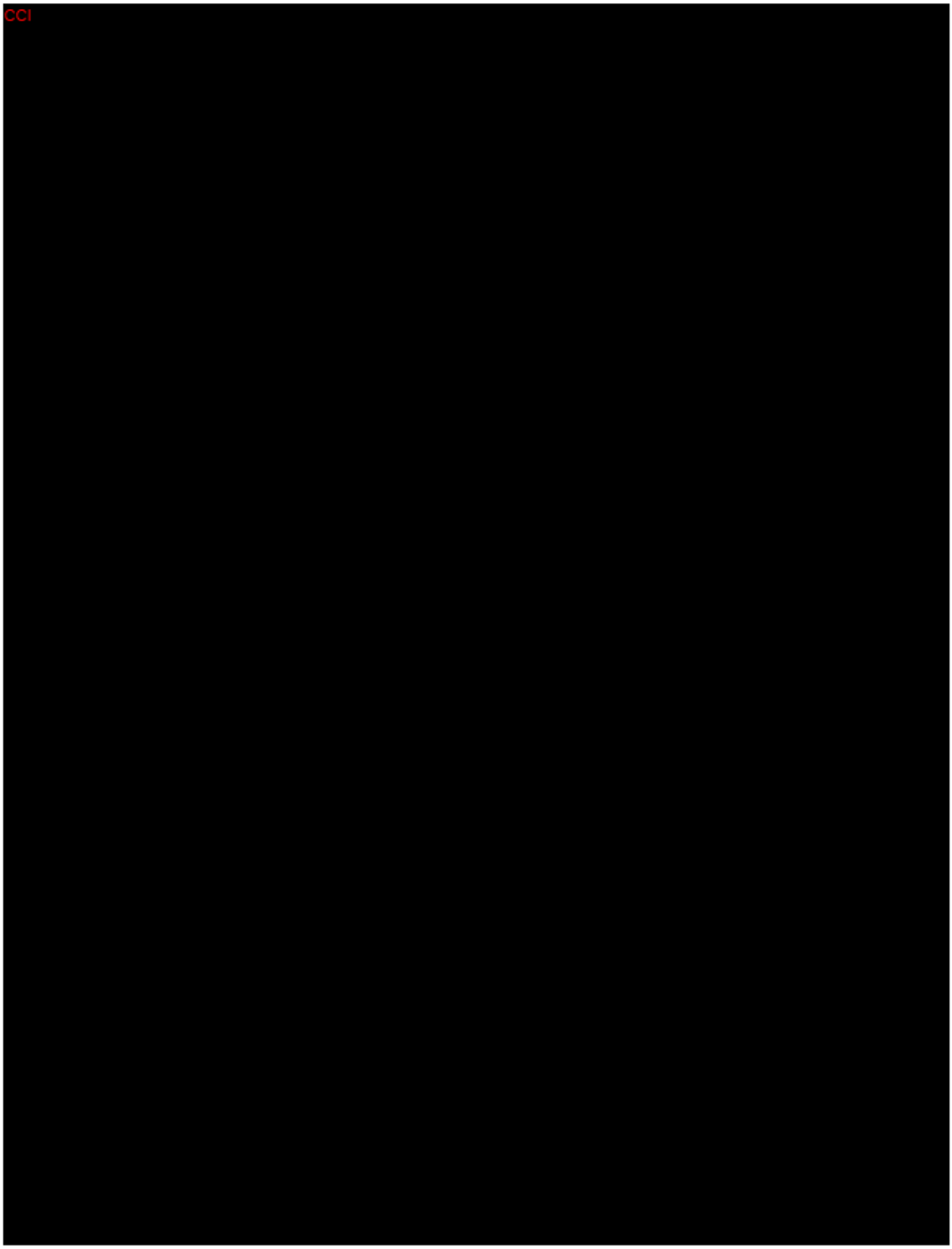
[redacted]


CCI



6.3 Other Assessments


CCI


CCI

6.4 Early Discontinuation from the Study

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), ECG, and laboratory abnormalities (confirmed by repeat if appropriate) or intercurrent illness which, in the opinion of the Investigator or sponsor, indicates that continued participation in the study is not in the best interest of the subject. This may include the following:

  i. Treatment-emergent ECG abnormalities

  (1) QTcF values that exceed an absolute QTcF value of 500 msec, or

  (2) QTcF prolongation that exceeds the baseline QTcF values by > 60 msec.

ii. Treatment-emergent hepatic laboratory abnormalities

(1) AST or ALT values > 8x ULN, or

(2) AST or ALT values > 5x ULN for more than 2 weeks, or

(3) AST or ALT values > 3x ULN and (TBL > 2x ULN or INR >1.5), or

(4) AST or ALT values > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

iii. Treatment-emergent renal laboratory abnormalities

(1) Serum creatinine values > 3x ULN, if SCr was normal at baseline, or

(2) Serum creatinine increase > 3x from baseline values, if SCr was not normal at baseline.

iv. Treatment-emergent thyroid laboratory abnormalities

(1) TSH values > 10x ULN despite appropriate treatment with thyroid hormone replacement (as outlined in Section **8.1.8**) and despite potential dose modification (as outlined in Section **7.2.3**).

- Disease progression, which, in the opinion of the Investigator or sponsor, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Biohaven Pharmaceuticals
- 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 subjects who discontinue study treatment earlier than Week 48 or Week 48-Ext should comply with protocol specified Early Discontinuation procedures as appropriate, outlined in the Schedule of Assessments & Events (Table 1, Table 2). Depending on the reason for the early discontinuation (e.g., declining patient status), some procedures, for example, PK samples, PD samples, lumbar puncture, may not be conducted at this visit. Conduct of all procedures, if possible, is encouraged. If possible, the subjects who discontinue from study medication prior to Week 48 should be contacted by a follow up phone call at the approximate time of their Week 48 visit, to collect information on clinical status (including Time to Event measures of disease progression and if applicable, adverse events, SAEs).

An exception to the requirement for End of Treatment procedures is when a subject 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).

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

An Investigational Product (IP), also known as Investigational Medicinal Product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

In this protocol, the IP is BHV-3241 300 mg tablets and matching placebo tablets.

The IP during the OLE phase of the study is BHV-3241 300 mg tablets.

7.1.2 Packaging, Shipment and Storage

The drug product is presented as BHV-3241 Extended Release (ER) Tablets that are reddish-beige, film coated and oval (300 mg strength). The tablets each consist of 300 mg of BHV-3241 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. 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] in a tightly closed container, protected from light).

Storage temperature excursions should be reported per Pharmacy Manual instructions. Temp-Tale USB monitors will be included in shipments of investigational medication to study sites and upon receipt, study personnel must retrieve, print and email the Temp-Tale monitor report in order to confirm that unacceptable excursions did not occur during shipment.

7.2 Dose and Administration

7.2.1 Method of Assigning Patient Identification

The Investigator or designee will need to access an Interactive Web-based Response System (IWRS) in order to register each subject. Initially, after informed consent is obtained at the Screening Visit, the Investigator or designee will enter the subject into the study and obtain a subject number assignment. After completion of Screening evaluations, all eligible subjects will be randomized, in a 1:1 ratio to receive either BHV-3241 (600 mg BID) or matching placebo. Randomization will be stratified by disease subtype of either MSA-P vs. MSA-C, diagnostic category of possible MSA vs. probable MSA, and country. Container assignments will be obtained by the Investigator (or designee) via the IWRS system.

Investigational sites will access the IWRS at each scheduled visit throughout the double-blind phase of the study (except for Weeks 2, 8 and 48) to track patient enrollment and dispense drug. Study medication will be assigned via the IWRS system; the system will assign specific container numbers for all blinded study drug to be dispensed to the subject. Once a container has been assigned it cannot be dispensed to another study subject.

After a subject has provided informed consent to participate in the OLE phase, the Investigator or designee will access the IWRS to register the subject's OLE participation and at each scheduled visit throughout the OLE phase of the study (except for Weeks 2-Ext, 4-Ext, 8-Ext and 48-Ext) to track patient enrollment and obtain container numbers of open-label BHV-3241 to be dispensed to the subject. Once a container has been assigned it cannot be dispensed to another study subject.

Sites will be responsible for recording the container numbers dispensed to the subject on the Drug Accountability Form provided in the Regulatory Binder, as well as ensure appropriate documentation of dispensation in the subject's medical record.

Once a subject completes the study, or if a subject is discontinued early from the study, the Investigator or designee must access the IWRS to document discontinuation of the patient from participation in the study.

Rescreening: If initial Screening lab sample results do not meet protocol-specified eligibility criteria and the Investigator determines that a repeat sample may meet the range required for eligibility, a repeat lab sample may be collected (one repeat collection/analysis allowed).

After obtaining Sponsor approval, a subject who does not meet protocol required eligibility criteria during Screening but who may potentially become eligible (e.g., logistical reasons such as exceeding screening window to accommodate time required for adjustment/stability of concomitant medication, washout of prohibited medication or repeat procedures to allow for recheck/confirmation of an abnormality that may meet the required range in a reasonable amount of time) may be entered as a Screen Failure in IWRS and eCRF and rescreened one time (entered as a Rescreen in IWRS and eCRF). If the Sponsor approves Rescreening for a

subject, instructions will be provided to the site regarding the specific Screening procedures/evaluations that will need to be repeated for Rescreening, as this is dependent on the amount of time elapsed.

7.2.2 Selection and Timing of Dose and Administration

All subjects will be randomized to receive BHV-3241 600 mg BID or matching placebo BID.

Subjects 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 Baseline visit. Subjects should stay at the office/clinic for monitoring for approximately 4 hours.

The tablets should be swallowed whole with a drink of water. The tablets should not be split, chewed, or crushed.

Study medication can be taken without regard to meals.

Dose titration period - Double-Blind Phase:

From the beginning to the end of Week 1 subjects should ingest either 300 mg QD of BHV-3241 or matching placebo QD. From the beginning to the end of Week 2, subjects should ingest either 300 mg BID of BHV-3241 or matching placebo BID. Subjects should take the study drug twice a day; dosing in the morning and evening approximately 12 hours apart.

At the end of Week 2, an assessment of compliance and tolerance to this dose titration schedule will be conducted. Per Investigator judgement, additional evaluations/procedures may be conducted at this timepoint as appropriate. If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 7.2.3).

Full dose period - Double-Blind Phase:

Starting with the beginning of Week 3 and throughout the remainder of the study, subjects should ingest either 600 mg BID of BHV-3241or matching placebo BID. Subjects should take the study drug twice a day; dosing in the morning and evening approximately 12 hours apart. At the Weeks 4, 12, 24, 36 and 48 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, so that one pre-dose (trough) and one post-dose PK sample can be collected approximately 2-4 hours post-dose (see Section 6.3.2).

Dose Titration Period - OLE Phase:

Subjects entering the OLE phase of the study will receive open-label active BHV-3241 and will

follow the same dose titration schedule as the titration in the double-blind phase of the study, to ensure that all participants safely continue from either active BHV-3241 or placebo to open-label BHV-3241.

Subjects should be administered the Day 1/first dose of open-label BHV-3241 (300 mg QD) while in the office/clinic on the day of the Baseline -Extension visit. Subjects should stay at the office/clinic for monitoring for approximately 4 hours.

For the rest of Week 1-Extension of the OLE phase, subjects will ingest one tablet of BHV-3241 (300 mg) per day in the morning for one week. From start to end of Week 2-Extension, subjects will ingest 300 mg BID of BHV-3241. Subjects should take one 300 mg tablet of BHV-3241 twice a day (600 mg per day); in the mornings and evenings, approximately 12 hours apart. If there is a delay in dosing, the interval between two doses should be no less than 6 hours.

An end of Week 2-Extension assessment of compliance and tolerance to this dose titration schedule will be conducted. Per Investigator judgement, additional evaluations/procedures may be conducted at this timepoint as appropriate. If tolerability issues are experienced with 300 mg QD or 300 mg BID dosing, the titration schedule may be modified (see Section 7.2.3).

Full Dose Period-OLE Phase:

Starting with Week 3-Extension and for the remainder of the OLE phase of the study (additional 46 weeks), subjects will ingest 600 mg BID of BHV-3241. Subjects should take two 300 mg tablets of BHV-3241 twice a day (1200 mg per day); in the mornings and evenings, approximately 12 hours apart.

Subjects who were taking a reduced dose of 300 mg BID (one tablet twice a day) of the blinded study medication due to tolerability issues when they completed the double-blind phase of the protocol, may continue taking that 300 mg BID during the OLE.

7.2.3 Dose Modifications

Subjects, along with their caregivers, will be instructed on the dosing regimen.

If tolerability issues are experienced during the dose 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 dose 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 Investigator must consult with the Medical Monitor if he or she believes that a change to the dose titration schedule is warranted; and, the Investigator must document any such changes to the dose titration schedule.

During the full dose period of the study, it is anticipated that all subjects will receive either BHV-3241 600 mg BID or matching placebo BID. If subjects have difficulty tolerating BHV-3241 600 mg BID or matching placebo BID dosing, the Investigator may permit the subject to switch to BHV-3241 300 mg BID or matching placebo BID dosing (and document this change in the subject'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 BHV-3241 300 mg BID or matching placebo BID will only be allowed to address tolerability issues and only with Medical Monitor approval. If a subject 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 Investigator and Medical Monitor. Only two re-challenges are allowed. Any such changes must be documented by the Investigator. If a switch to BHV-3241 300 mg BID or matching placebo BID dosing does not result in acceptable tolerability, then dosing should be discontinued.

Dose modification should be considered if a patient 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 MSA 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 Investigator,

b. Development of Grade 3 or Grade 4 hypothyroidism. Rechallenge may be attempted, if warranted, when improved to less than or equal to Grade 2 (inclusive of treatment with thyroxine replacement therapy. see Section 8.1.8).

c. Development of a greater than or equal to Grade 3 toxicity or an intolerable side effect attributed to BHV-3241 based on the judgement of the Investigator. Rechallenge may be attempted, if warranted, when symptoms improve to less than or equal to Grade 1.

7.3 Blinding and Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that patient may be broken by the treating physician. Before breaking the blind of an individual subject's treatment, the Investigator should have determined that the information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed without the need for unblinding, by assuming that the subject is receiving active product. Unblinding will be managed via the IWRS system. The clinical supply manager, pharmacokinetic and pharmacodynamic vendors, IWRS vendor, pharmacovigilance and DMC (if requested) roles may be unblinded before data are unblinded for the primary endpoint and all subjects complete the study. Except as noted above, other members of the Biohaven research team will remain blinded. In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

During the OLE phase, all participants will not be blinded and will be receiving active BHV-3241.

7.4 Treatment Compliance

Responsible study personnel will dispense the study drug. Accountability and compliance verification should be documented in the subject's study records. Subjects will be counseled on the importance of taking the study drug as directed at all study visits.

Overnight shipment of study medication under ambient conditions (via certified and tracked courier and following Remote Visit Workaround Guidelines provided to sites), from the study site to study participants is permissible when an in-person study visit is not possible due to the COVID-19 public health emergency and if acceptable to the study site's institution. The sponsor should be consulted prior to shipping drug. Confirmation that the study drug shipment was received by the study participant should be retained as documentation, e.g., tracking confirmation printout from the courier, written documentation of contact with the subject (by phone, email, text), subject signature on packing list, etc.

If poor compliance continues, (i.e., taking study drug differently than per Investigator instructions, multiple missed doses resulting in less than 80% overall compliance), discontinuation of the subject from the trial should be considered and discussed with the Sponsor.

7.5 Destruction and Return of Study Drug

All unused and/or partially used study drug can be sent back to the drug depot for destruction only after being inspected and reconciled by the responsible Study monitor or the sponsor's designee. If it is site policy to destroy study drug on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor or the Sponsor's designee.

8 ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example) symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

If a specific diagnosis or syndrome is identified by the Investigator, this should be recorded as the AE, rather than recording as separate AEs the individual signs/symptoms or clinically significant laboratory abnormalities known to be associated with, and considered by the Investigator to be a component of, the disease/syndrome.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

There are two types of AEs, Serious Adverse Events (SAEs) and Non-Serious AEs.

8.1 Serious Adverse Events

8.1.1 Definition of Serious Adverse Event (SAE)

A SAE is any event that meets any of the following criteria at any dose:

- Death;
- Life-threatening;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received BHV-3241:
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):
  - Intensive treatment in an emergency room or at home for allergic bronchospasm;
  - Blood dyscrasias or convulsions that do not result in inpatient hospitalization;
  - Development of drug dependency or drug abuse;
  - Potential drug induced liver injury (see section 8.1.7)

8.1.2 Definition of Terms

Mild: A mild AE is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A moderate AE is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Severe: A severe AE interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

The following hospitalizations are not considered SAEs in Biohaven clinical studies (but may be considered non-serious AEs):

- A visit to the emergency room or other hospital department <24 hours that does not result in an admission (unless considered “important medical event” or event that is life threatening);
- Elective surgery, planned prior to signing consent;
- Admissions as per protocol for a planned medical/surgical procedure;
- Routine health assessment requiring admission (i.e., routine colonoscopy);
- Admission encountered for another life circumstance that carries no bearing on health and requires no medical intervention (i.e., lack of housing, care-giver respite, family circumstances).

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

8.1.3 Classification of Adverse Events

The severity of all AEs must be recorded in the eCRF and on the SAE Form, if applicable. The severity or intensity of an AE refers to the extent to which it affects the subject’s daily activities. The severity of events should be graded as mild, moderate or severe.

The Investigator’s assessment of an AEs relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. The

relationship or association of the study drug in causing or contributing to the AE will be characterized as not related, unlikely related, possibly related or related for non-serious AEs and as not related or related for SAEs.

Disease related signs and symptoms, including those that are part of the diagnostic criteria for MSA, may be reported as AEs as follows:

- Disease related signs and symptoms that meet the definition of an SAE as outlined in Section 8.1.1 should be reported as SAEs.
- Disease related signs and symptoms not meeting the definition of an SAE, but representing untoward medical occurrences or changes in the condition that are medically significant should be reported as AEs.
- Disease related signs and symptoms may be medically significant if they
    - are uncommon and unexpected for the stage of the disease,
    - change significantly in their frequency or intensity,
    - lead to the initiation of a new therapy or modification of an existing therapy, or
    - are associated with meaningful sequelae.

8.1.4 Collection and Reporting Serious Adverse Events

Following the patient's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur during the Screening period and within 30 days of discontinuation of dosing. The Investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specific procedures.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the Investigator believes that an SAE is not related to the study drug, but is potentially related to the conditions of the study (such as a withdrawal of previous therapy or a complication related to study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs (whether related or not related to study drug), overdose, potential drug induced liver injury and pregnancies must be **reported immediately or no later than within 24 hours** of the Investigator awareness of the event to the [redacted] department.

The Investigator is responsible for reporting all SAEs and all Other Important Medical Events to CCI immediately upon observing or learning of the event. CCI will then immediately notify the Biohaven Medical Monitor of the event. The SAE form must then be submitted to CCI within one working day.

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term.

All SAEs should be followed to resolution or stabilization.

The Serious Adverse Event Report Form (SAERF) should be submitted to CCI by facsimile (FAX).

- **North America:** PPD
- **EU EMEA:** PPD

If site personnel do not have access to a FAX machine during the COVID-19 public health emergency, SAEs may be reported to CCI by email (encrypt the document before emailing) to PPD

Reports can be made by telephone via the Safety Hotline Number below if a SAERF cannot be immediately submitted.

- **North America:** PPD
- **EU EMEA:** PPD

Additionally, the Investigator, or designated staff, is responsible for entering the SAE information in the Electronic Data Capture (EDC) system (i.e.: event term, start stop dates, causality, severity).

The Investigator is responsible for submitting all applicable events to the IRB as per the IRB's reporting requirements.

For any questions relating to SAEs, please contact the Medical Monitor via telephone:

- **North America:** Dr. PPD PPD
- **EU EMEA:** Dr. PPD PPD

The Sponsor or specified designee/authorized representative will report suspected unexpected serious adverse reactions (SUSARs) in an expedited manner (without delay) to the Regulatory Authorities and Ethics Committees concerned, in accordance with Food and Drug

Administration Code of Federal Regulations (CFR) 21 CFR Parts 312 and 320, European Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on IPs for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor or specified designee/authorized representative shall notify the Investigator of the following information:

- Any AE that is both serious and unexpected and is suspected of being related to the use of the IP in this study or in other studies (i.e., SUSAR).

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

8.1.5 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 medically significant overdose (suspected or confirmed and irrespective of whether or not it involved BHV-3241) must be communicated to Biohaven or a specified designee within 24 hours of the Investigator becoming aware and be fully documented as an SAE. An SAE is reported for overdose when the investigator 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.

8.1.6 Pregnancy

If, following initiation of the IP, it is discovered that a study subject is pregnant or may have been pregnant at the time of the IP exposure, including during at least 6 half-lives after IP administration, the IP will be permanently discontinued in an appropriate manner (i.e., dose tapering, if necessary, for patient safety). Protocol-required procedures for study discontinuation and follow up will be conducted unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Sites should instruct patients to contact the Investigator if they become pregnant during the course of the study. The Investigator must immediately notify CCI of the event within 24 hours of the Investigator becoming aware of the information and the site must complete a Pregnancy Report Form. Follow up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must also be reported on a Pregnancy Report Form.

Any pregnancy that occurs in a female partner of a male study participant should also be reported to CCI

8.1.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of the initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs as per Section 8.1.4.

Potential drug induced liver injury is defined as:

- Aminotransferases (ALT or AST) elevation > 3 times the ULN;

  AND

- Total bilirubin (TBL) > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase);

  AND

- No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

If any potential DILI is identified and meets the criteria above, the Biohaven Medical Monitor should immediately be contacted for further instruction on dosing adjustments and whether the patient must discontinue from the trial and appropriate follow up requirements.

8.1.8 Adverse Event of Special Interest-Thyroid Function

Reversible changes in thyroid function tests were observed during the preclinical studies and clinical studies with BHV-3241. Physical examination and laboratory monitoring of thyroid function with serum triiodothyronine (free T3), thyroxine (free T4), TSH, and anti TPO antibodies will be performed and documented throughout this study. Any significant abnormal findings should be discussed with the study Medical Monitor and maybe 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 thyroxine replacement therapy should be considered. Initiation of treatment is at the discretion of the Investigator. Potential initiation of thyroxine replacement therapy may be considered according to the following guidelines:

- Mild TSH increase: 5.0 to 10 mU/L (assuming a normal TSH range of 0.4 to 4.9 mU/L) and unchanged free T4 (and/or free T3)
  - With clinical symptoms of hypothyroidism: Consider thyroxine treatment if confirmed at 2 consecutive occasions and not explained by concomitant illness/fever/infection/surgery

- No symptoms: Continue normal monitoring.

- TSH greater than the ULN and decreased free T4 (and/or free T3) below normal range:
  - Regardless of symptoms, consider initiation of thyroxine treatment if confirmed at 2 consecutive occasions and not explained by concomitant illness/fever/ infection/surgery (if severe symptoms, repeat sampling in 2 weeks).

If signs/symptoms of hypothyroidism and/or significant changes in thyroid hormone levels (free T3/free T4/TSH) develop, collection of follow up clinical chemistry samples and/or unscheduled study visits may be warranted.

Clinically significant laboratory abnormalities will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017)[18]. For those not available in CTCAE, according to Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017) [19].

If there are clinically significant issues with tolerability that are not able to be treated adequately with thyroxine replacement therapy, the Investigator may consider modifications to the dosage regimen. Consultation with the Medical Monitor is required. Modifications may include reducing the dose of BHV-3241/matching placebo to 300 mg BID or taking a dose holiday. Any such modifications to the dosage regimen should be noted in the CRF.

8.2 Non-serious Adverse Events

A non-serious adverse event is an AE not classified as a SAE.

8.2.1 Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the initiation of study drug.

Non-serious adverse events should be followed until conclusion or stabilization, or reported as SAEs if they become serious. Follow-up is required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at the end of study treatment.

8.2.2 Laboratory Test Abnormalities

The following laboratory test abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE;
- Any laboratory abnormality that required the patient to have the study drug discontinued or interrupted;
- Any laboratory abnormality that required the patient to receive specific corrective therapy.

9 STATISTICS

Detailed plans for analysis are summarized in a separate Statistical Analysis Plan (SAP) document. A summary of statistical aspects of the design and intended analysis is provided here.

9.1 General Procedures

Categorical variables are tabulated with counts and percentages. Continuous variables are summarized with univariate statistics (e.g., n, mean, standard error, median, minimum and maximum).

For the calculation of descriptive statistics of observed data, subjects must have a baseline value to be evaluable for endpoints based on values and changes from baseline over time.

Tabulations of the following endpoints present the number of unique subjects with an event: protocol deviations; non-study medications; adverse events; and laboratory abnormalities. Thus, for these endpoints, multiple occurrences of the same event are counted only once per subject.

9.2 Sample Size

The sample size for this study will be approximately 325 randomized subjects. Based on unpublished data from the Promesa study, studying EGCG (epigallocatechingallate) vs placebo[26] with a treatment duration of 48 weeks, the placebo group had a 4.88 point increase with a standard deviation of 4.85 in the modified UMSARS Part I and Part II total score. With an expected improvement of 40% at Week 48 for BHV-3241 compared to placebo, a total of 260 subjects (130 per group) provides 90% power based on a 2-sample, two-sided t-test. With a drop-out rate of ~20%, the study will randomize approximately 325 subjects.

9.3 Populations for Analysis

The population of interest, for all estimands, are subjects diagnosed with possible or probable MSA.

The following analysis sets are defined for this protocol:

Enrolled subjects: Subjects who signed an informed consent form and were assigned a Patient Identification number (PID).

Randomized subjects: Enrolled subjects who received a treatment assignment from the Interactive Web Response System (IWRS).

Treated/Safety: Enrolled subjects who received at least 1 dose of blinded study therapy (BHV-3241 or placebo).

Modified Intent to Treat (mITT) subjects: Randomized subjects that received at least one dose of blinded study therapy and provided a baseline and at least one post-baseline efficacy assessment.

Open-Label Extension Treated subjects: Enrolled subjects in the extension phase who received at least 1 dose of open-label study therapy (BHV-3241).

BHV-3241 Treated Participants: Enrolled subjects who received at least 1 dose of BHV-3241 (blinded or open-label).

9.4 Statistical Methods

9.4.1 Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics will be summarized by treatment group and for all treated subjects. A separate set of tabulations will be made for subjects enrolled but not randomized.

9.4.2 Primary Endpoint(s)

The primary endpoint is the change from baseline in the modified UMSARS score measured at the Week 48 visit. The items in the modified UMSARS will contain the following Part I items: Speech, Cutting Food and Handling Utensils, Dressing, Hygiene, Walking and Urinary Function. The following Part II items will also be included: Arising from Chair, Posture, and Gait. In the analysis of all items, the response categories of 0 and 1 will be combined into a single category before summing the individual items to derive the modified UMSARS.

The primary estimand, for the primary endpoint, will pursue a hypothetical strategy of estimating the effect of BHV-3241 relative to placebo had all subjects stayed on treatment. Using the mITT population, the summary will be the difference between placebo and BHV-3241 treated subjects at the Week 48 visit. The summary will be computed using a Mixed Model for Repeated Measures (MMRM) that will include fixed effect factors for treatment group, randomization strata (MSA-C or MSA-P, Possible or Probable MSA diagnosis, and country), visit, and the treatment group by visit interaction. Baseline modified UMSARS score will enter the model as a covariate, and subject will be a random effect. Intercurrent events that lead to discontinuation, or lack of data, will be handled by only using the-on treatment data. MMRM-based estimates (i.e., least-squares mean [LSM] with corresponding SD and 95% CI) of values and changes from baseline will be presented by treatment group and week. In addition, the LSM difference in change from baseline between treatment groups (BHV-3241 – placebo) at Week 48 with corresponding SD, 95% CI, and p-value from MMRM will also be presented. Since the estimate is calculated using a likelihood-based approach, the analysis is based on a Missing at Random (MAR) assumption. Sensitivity analyses will include multiple imputation of missing data using a copy increment from reference method.

Observed values and changes from baseline in the modified UMSARS scores will also be summarized using descriptive statistics over time by treatment group during the Randomization Phase.

Details of these analyses are provided in the SAP.

9.4.3 Secondary Endpoint(s)

The secondary endpoints, MSA-QoL motor subscale and non-motor subscale scores, UMSARS Part I and Part II total score, PGI-S, CGI-S, UMSARS Part III, and UMSARS Part IV are change-from-baseline endpoints and will be analyzed for mITT subjects using the same strategy as described for the primary estimand as the primary endpoint. The UMSARS Part I and Part II total score will exclude item 11 from Part I (sexual function).

The other secondary endpoint, the CGI-I, does not have a baseline value. The estimand for this endpoint will pursue a hypothetical strategy of estimating the effect of BHV-3241 relative to placebo had all subjects stayed on treatment. The analysis will use the mITT population. The population summary will be the difference in the CGI-I between placebo and BHV-3241 treated subjects at the Week 48 visit. The summary will be computed using an analysis of variance, that will include fixed effect factors for treatment group, baseline CGI-S score, and randomization strata (MSA-C or MSA-P, Possible or Probable MSA diagnosis and country). Intercurrent events will be handled by only using the on-treatment data.

Further details on the secondary analyses are provided in the SAP.

9.4.4 Extension Phase Analysis

CCI [redacted]

9.4.5 Adjustment for Multiplicity

Type-1 error will be controlled for the primary and key secondary efficacy endpoints by testing them with a gate-keeping procedure. The primary endpoint will be tested at a two-sided alpha level of 0.05. If this test is significant, then the key secondary efficacy endpoints will be tested using Hochberg's procedure. If the test of the primary endpoint is not significant, then the unadjusted p-values for the key secondary endpoints will be presented only for descriptive purposes.

No attempt will be made to adjust for multiplicity when testing the non-key secondary or CCI [redacted] endpoints. Any endpoints subjected to significance testing are evaluated at an unadjusted two-sided alpha level of 0.05.

9.4.6 Missing Data

If more than 10% of the subjects discontinue, then the missing data will be multiply imputed for the primary endpoint using a copy increment from reference method.

9.4.7 Analysis of Safety

The Investigators determine the intensity of AEs and the relationship of AEs to study therapy. The Investigators' terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available. AEs will be presented by system organ class and preferred term, ordered by the overall frequency of events. If a subject had an adverse event with different intensities over time, then only the greatest intensity is reported.

AEs are tabulated in all treated subjects. All deaths and SAEs are listed for enrolled subjects without regard to onset.

The frequencies of the following safety events are summarized by treatment group and overall for treated subjects: SAEs; all AEs, non-serious AEs; AEs by intensity; AEs by relatedness and clinically relevant laboratory abnormalities.

Graphical and tabular displays of on-treatment liver function test results are provided.

Safety will be presented separately for the double-blind phase and for the open-label extension phase, overall and by randomized arm.

9.5 Schedule of Analyses

The first scheduled unblinded analysis will be the primary analysis, which will be conducted after the last subject completes their Week 48 visit and the database has been locked. This will summarize all efficacy, safety, laboratory and other data collected through the entire study. In addition, data may be locked, blinded analyses conducted, and reports produced as required to support safety monitoring or regulatory requirements.

In addition to the above, a Data Monitoring Committee (see Section 10.2) will review efficacy and safety data on a periodic basis, with activities fully described in a DMC Charter.

A final analysis will be conducted at the end of the open-label extension phase.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP), International Conference on Harmonization guidelines, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

This study will be conducted in compliance with the protocol. The protocol, any amendments and the informed consent form(s) will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All serious breaches must be reported to Biohaven (or designee) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

10.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established for this study and its activities, processes and guidance for the oversight and adherence to DMC practices will be described in a separate DMC Charter. The DMC will be composed of at least 2 independent physicians and 1 independent statistician. In this study, the major responsibilities of the DMC will be to monitor the benefit/risk of BHV-3241, to assess whether there are unacceptable safety findings after administration of BHV-3241 that require modifying or stopping the study and potentially to adjudicate study drug-relatedness of SAEs and deaths that are unexpected and/or atypical for participants with MSA.

10.3 Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator brochure (if any) and any other written information provided to study subjects. The trial will not begin at a site until the Investigators have obtained the IEC favorable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed and dated by each subject prior to entering the trial or prior to performing any study procedure.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, the new version of the ICF must be approved by the IEC and subsequently, the subject/caregiver's consent to the revised ICF must be obtained.

The Principal Investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary.

10.4 Informed Consent

Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Biohaven (or designee) will provide the Investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Before the potential subject has undergone any study-related Screening procedures, the nature of the study and the potential risks associated with it will be explained to the subject, and the subject will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, the subject must read, sign and date an IRB/IEC approved written informed consent form. The signed and dated ICF will be retained at the Investigator's site, with a copy provided to the subject.

Any revisions to the protocol or ICF will be reviewed and approved by the IRB/IEC and subjects will be informed of ICF changes and document continuing consent by signing and dating the revised version of the ICF.

If informed consent is initially given by a patient's legal guardian or legally acceptable representative, and the patient subsequently becomes capable of making and communicating their informed consent during the study, then the consent must additionally be obtained from the patient.

The informed consent form must also include a statement that Biohaven and its representatives and regulatory authorities may have direct access to patient records.

The rights, safety, and well-being of study patients are the most important considerations and should prevail over interests of science and society.

10.5 Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation of each study patient. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

Electronic CRFs will be prepared for all data collections fields when EDC is being used.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator must retain a copy of the CRFs, including records of changes and corrections. If EDC is being used, signatures will be obtained electronically and a copy of the electronic CRFs will be provided (or the data from the CRFs) for future reference.

10.6 Records Management and Retention

In accordance with the principles of GCP and GLP, the study may be inspected by regulatory authorities, the Sponsor and CRO. The Sponsor (or specified designee) is entitled to access information about the status of the study and to review the original documents of the study.

The Investigator must retain all study records and source documents for the maximum required by the applicable regulations and guidelines, or institution procedures or for the period of time specified by the sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with this study if not within these guidelines.

Biohaven will notify the Investigators when the study files for this study are no longer needed.

If the Investigator withdraws from the study (i.e., retirement, relocation), the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to Biohaven.

It is the responsibility of the Investigator to ensure that the current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where the study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount of study drug received and placed in storage area;
- Label ID number or batch number or Kit number as specified for the protocol;

- Amount dispensed to and returned from each patient;
- Amount transferred to another area or site for dispensing or storage if applicable;
- Amount of drug lost or wasted;
- Amount destroyed at the site if applicable;
- Amount returned to sponsor, if applicable;
- Retained samples for bioavailability/bioequivalence, if applicable;
- Record of dates and initials of personnel responsible for IM dispensing and accountability.

10.7 Source Documentation

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent for all subjects on study.

If source documents are created to support the collection of study information, this must be retained with the other pertinent medical record for each patient for verification of data points, unless otherwise instructed by the Sponsor (or specified designee) to enter data directly on the CRF.

10.8 Study Files and Record Retention

The Sponsor does not require original documents that have already been scanned and entered into the eTMF system be forwarded to the Sponsor. Any original documents (i.e., 1572, signed financial disclosure, signed ICF, etc.) will be retained in the regulatory binder at the study site. The CRO will do a final TMF reconciliation to ensure all study files and regulatory documents have been correctly uploaded to the TMF prior to the close or termination of the study. Any materials or documents to support the clinical trial outside of the eTMF (i.e., rater training tapes) should be maintained by the CRO. The Sponsor will be contacted to determine whether the study documents/materials that are retained outside of the TMF will be forwarded to the Sponsor, destroyed or kept at the CRO or at another facility for a longer period of time at the Sponsor's expense.

11 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor (or specified designee). A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

12 STUDY REPORT AND PUBLICATIONS

The Sponsor (or specified designee) is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of the Sponsor is discussed in the Investigator's Clinical Research Agreement.

13 STUDY DISCONTINUATION

Both the Sponsor and the Principal Investigator reserve the right to terminate the study at the Principal Investigator's site at any time. Should this be necessary, the Sponsor (or specified designee) will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor (or specified designee). However, authorized regulatory officials, IRB/IEC personnel, the Sponsor and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by Subject numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

The Sponsor may approve the sharing of de-identified data from this study to be made available to researchers for the purpose of advancing the understanding of neurologic or psychiatric illness, rating scales, or trial methodology for the affected population. In any publication of this data, confidentiality of individual subjects will be protected.

15 APPENDICES

15.1 APPENDIX I - Names of Study Personnel

Sponsor:	Biohaven Pharmaceuticals, Inc. 215 Church Street New Haven, CT 06510
Medical Monitors and Medical Monitor Back-up:	**EU/EMEA:** PPD PPD PPD PPD CCI PPD Email: PPD Phone: PPD **North America:** PPD PPD PPD PPD CCI PPD Email: PPD Phone: PPD Back-ups: PPD PPD PPD PPD Biohaven Pharmaceuticals, Inc. PPD New Haven, Connecticut 06510 USA Email: PPD Phone: PPD PPD PPD PPD PPD Biohaven Pharmaceuticals, Inc. PPD New Haven, Connecticut 06510 USA Email: PPD Phone: PPD
Clinical Research Organization:	CCI PPD

16 REFERENCES CITED

1. Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med 2015;372:1375-6.

2. Ozawa T, Healy DG, Abou-Sleiman PM, et al. The alpha-synuclein gene in multiple system atrophy. Journal of neurology, neurosurgery, and psychiatry 2006;77:464-7.

3. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci U S A 1998;95:6469-73.

4. Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 1989;94:79-100.

5. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71:670-6.

6. Wenning GK, Geser F, Krismer F, et al. The natural history of multiple system atrophy: a prospective European cohort study. The Lancet Neurology 2013;12:264-74.

7. Yabe I, Soma H, Takei A, Fujiki N, Yanagihara T, Sasaki H. MSA-C is the predominant clinical phenotype of MSA in Japan: analysis of 142 patients with probable MSA. J Neurol Sci 2006;249:115-21.

8. Seo JH, Yong SW, Song SK, Lee JE, Sohn YH, Lee PH. A case-control study of multiple system atrophy in Korean patients. Mov Disord 2010;25:1953-9.

9. Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet 1999;354:1771-5.

10. Gilman S, May SJ, Shults CW, et al. The North American Multiple System Atrophy Study Group. J Neural Transm (Vienna) 2005;112:1687-94.

11. Kollensperger M, Geser F, Ndayisaba JP, et al. Presentation, diagnosis, and management of multiple system atrophy in Europe: final analysis of the European multiple system atrophy registry. Mov Disord 2010;25:2604-12.

12. Kim HJ, Jeon BS, Lee JY, Yun JY. Survival of Korean patients with multiple system atrophy. Mov Disord 2011;26:909-12.

13. Watanabe H, Saito Y, Terao S, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain : a journal of neurology 2002;125:1070-83.

14. Kaindlstorfer C, Sommer P, Georgievska B, et al. Failure of Neuroprotection Despite Microglial Suppression by Delayed-Start Myeloperoxidase Inhibition in a Model of

Advanced Multiple System Atrophy: Clinical Implications. Neurotoxicity research 2015;28:185-94.

15. Stefanova N, Georgievska B, Eriksson H, Poewe W, Wenning GK. Myeloperoxidase inhibition ameliorates multiple system atrophy-like degeneration in a transgenic mouse model. Neurotoxicity research 2012;21:393-404.

16. Jucaite A, Svenningsson P, Rinne JO, et al. Effect of the myeloperoxidase inhibitor AZD3241 on microglia: a PET study in Parkinson's disease. Brain 2015;138:2687-700.

17. Esparza Martin N, Garcia Nieto V. Hypouricemia and tubular transport of uric acid. Nefrologia 2011;31:44-50.

18. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50.)

19. DIADS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf2017.

20. Sheehan DV, Alphs LD, Mao L, et al. Comparative Validation of the S-STS, the ISST-Plus, and the C-SSRS for Assessing the Suicidal Thinking and Behavior FDA 2012 Suicidality Categories. Innovations in clinical neuroscience 2014;11:32-46.

21. Sheehan DV, Giddens JM, Sheehan IS. Status Update on the Sheehan-Suicidality Tracking Scale (S-STS) 2014. Innovations in clinical neuroscience 2014;11:93-140.

22. Wenning GK, Tison F, Seppi K, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord 2004;19:1391-402.

23. Schrag A, Geser F, Stampfer-Kountchev M, et al. Health-related quality of life in multiple system atrophy. Mov Disord 2006;21:809-15.

24. Pillas M, Selai C, Quinn NP, et al. Development and validation of a carers quality-of-life questionnaire for parkinsonism (PQoL Carers). Qual Life Res 2016;25:81-8.

25. Pillas M, Selai C, Schrag A. Rasch analysis of the carers quality of life questionnaire for parkinsonism. Mov Disord 2017;32:463-6.

26. Levin J, Maass S, Schuberth M, et al. The PROMESA-protocol: progression rate of multiple system atrophy under EGCG supplementation as anti-aggregation-approach. J Neural Transm (Vienna) 2016;123:439-45.

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BHV-3241 in Subjects with Multiple System Atrophy (MSA)

Study No: BHV3241-301

Draft Original Protocol Date: 18 Dec 2018

Protocol Version No: V07

Protocol Version Date: 20 Jan 2021

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.
- The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Signature Approval	Date
Author/Protocol Writer: PPD PPD PPD Biohaven Pharmaceuticals (I confirm, QC completed for required elements)		
Clinical Operations: PPD PPD PPD Biohaven Pharmaceuticals		
Biostatistics: PPD PPD PPD Biohaven Pharmaceuticals		
Medical Lead: PPD PPD PPD Biohaven Pharmaceuticals		
Regulatory Affairs: PPD PPD PPD Biohaven Pharmaceuticals		