Biohaven Pharmaceuticals

Protocol BHV4157-201

A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of BHV4157 in Adult Subjects with Spinocerebellar Ataxia

Statistical Analysis Plan

Version 4.0 Addendum

Date: March 27, 2020

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Signature Page

Protocol Title:	A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of BHV4157 in Adult Subjects with Spinocerebellar Ataxia
Sponsor:	Biohaven Pharmaceuticals
Protocol Number:	BHV4157-201
Document Version/Date:	V04.0/Addendum/27Mar2020
Author: [redacted]	Signature [redacted] Date:___

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatories:

[redacted]

1 INTRODUCTION

This document is an addendum to the statistical analysis plan (SAP), version 2.0, dated 6 September 2017 for protocol BHV4157-201, which is a Phase 2b/3, randomized, double-blind, placebo-controlled trial of BHV4157 in adult subjects with spinocerebellar ataxia (SCA). Reference the protocol (version 7.0, 8 July 2019) and the original SAP (version 2.0, 6 September 2017) for additional detail on the trial design and plan for statistical analysis. The purpose of this document is to provide more detail to items that are not specifically discussed in the original SAP, make corrections to the SAP, as well as include a statistical plan for any additional ad hoc analyses of interest.

[redacted]

[redacted]

3 COMPUTING ENVIRONMENT

Section 4.2.2 of the SAP referred to specific versions of the coding dictionaries; however, medical history and adverse events (AEs) are coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock, and prior/concomitant medications are coded using the most current version of the World Health Organization Drug Dictionary (WHO-DD) at the time of database lock.

4 ANALYSIS SETS

BHV4157 cohort: Subjects that took at least one dose of BHV4157 and provided at least one post-baseline total SARA score.

- The analysis of the FAS cohort will take into account both the dosing break between phases (Randomization and Extension) and the dosing break prior to the Expanded Extension.

- The analysis of the ITT cohort will take into account the dosing break between phases (Randomization and Extension) but not the dosing break prior to the Expanded Extension.

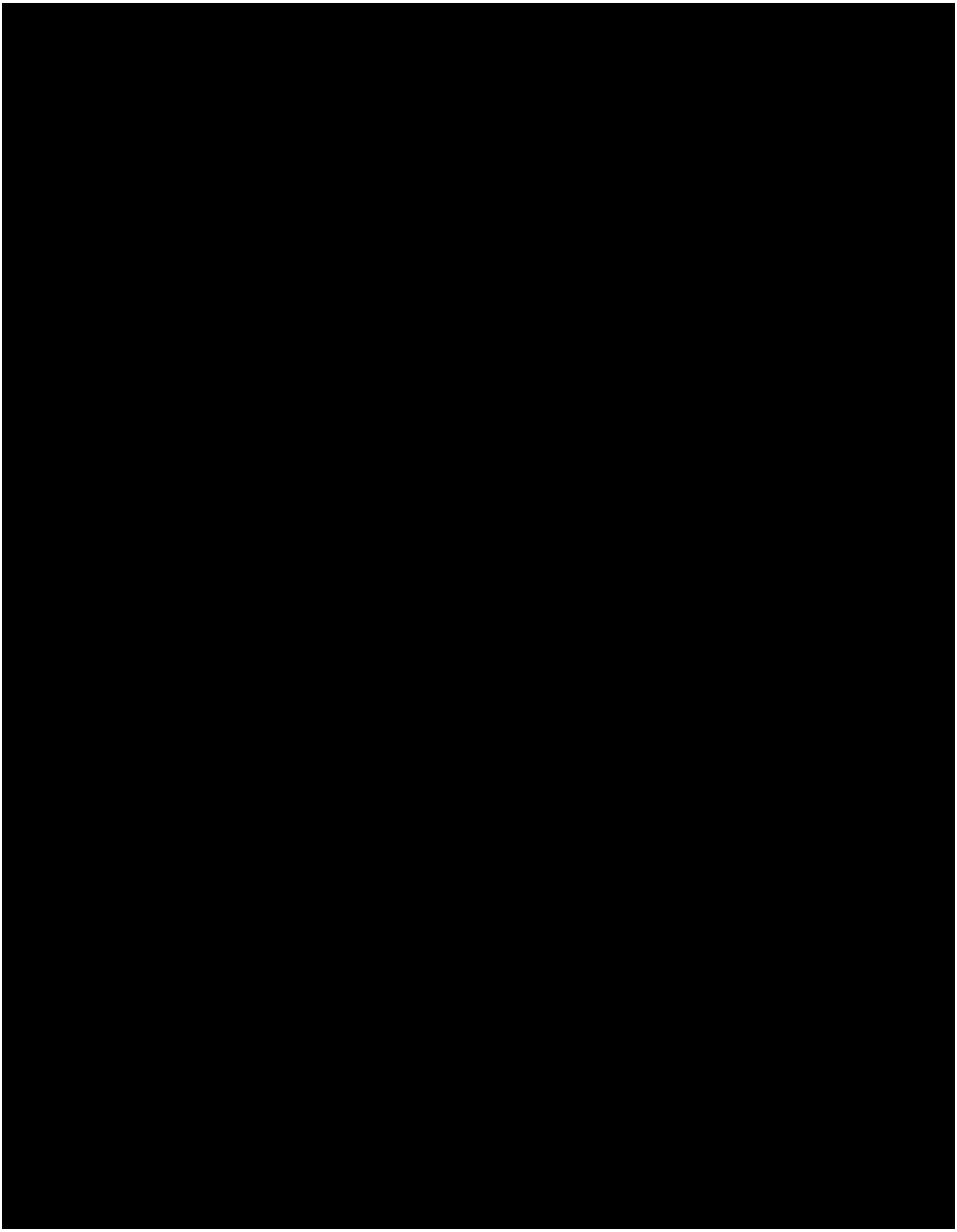
5 VISIT WINDOWS

[redacted]

On-treatment data for efficacy analyses are considered as any visit that occurs within 7 days (inclusive) of the post-final study treatment dose. The Final Study Visit is considered as any visit that occurs between 8 and 21 days post-final study treatment dose.

On-treatment data for safety analyses are considered as any visit or AE recorded within 30 days (inclusive) post-final study treatment dose.

[redacted]



8 SUBJECTS IDENTIFIED FOR NARRATIVES

A safety narrative will be prepared for each subject who received at least one dose of troriluzole and experienced the following events (regardless of relationship to study drug):

- All deaths on-treatment and post-treatment through the end of the study
- SAEs on-treatment, which includes up to 30 days after the last dose of study drug; SAEs that occur > 30 days (i.e., during the follow-up period) will be included per the clinical judgment of the Biohaven medical monitor
- All premature discontinuations of study drug due to AEs (either identified through "action taken" or "end of treatment status")
- The following on-treatment events of special interest:
  - Neutropenia based on laboratory results and defined as minimum absolute neutrophil count < 500 per mm^3
  - LFT abnormalities:
    - ALT or AST > 3x ULN
    - ALT or AST > 3x ULN, and serum total bilirubin ≥ 2x ULN
  - Interstitial lung disease Standardized MedDRA Query (SMQ) including eosinophilic pneumonia

These select events are described in the current version (v3) of the Biohaven Safety Narrative Scope for BHV4157 (troriluzole). Because select events may be subject to change, updates to the list of

events or selection algorithms after database lock may be described in a Note to File (NTF) rather than amending the SAP.

A by-subject listing of safety narrative subject identifiers will be presented for all screened subjects with the select events as described above

9 AD HOC ANALYSES

Additional analyses of interest not specified directly in the SAP were analyzed using the FAS. These analyses were performed on the following data cuts:

- Randomization Phase: locked data through Extension Phase Week 48

[redacted]

- Extension Week 48: locked data through Extension Phase Week 48

[redacted]

Randomization Phase

[redacted]

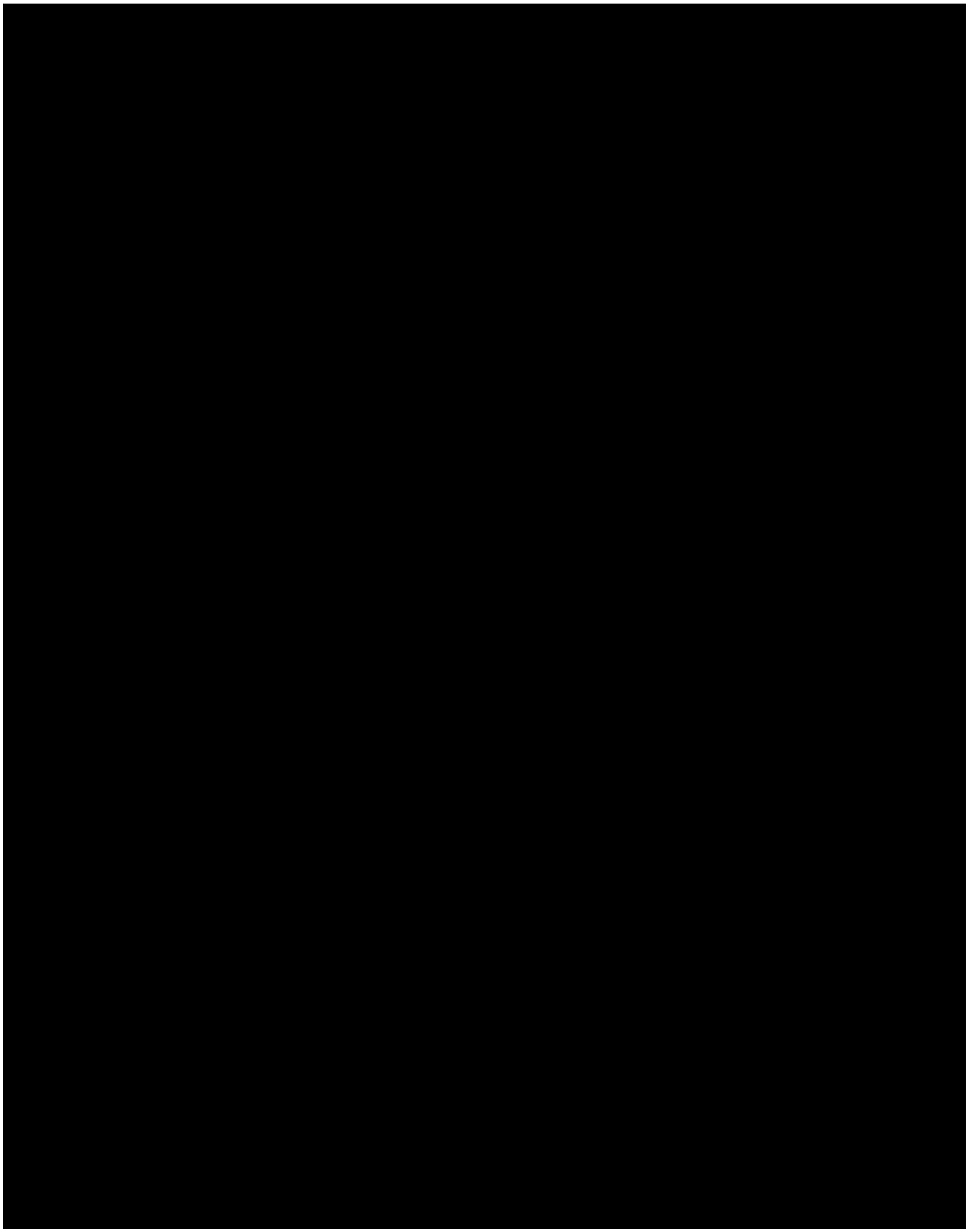
[redacted]

[redacted]

[redacted]

Extension Phase – Week 48

[redacted]

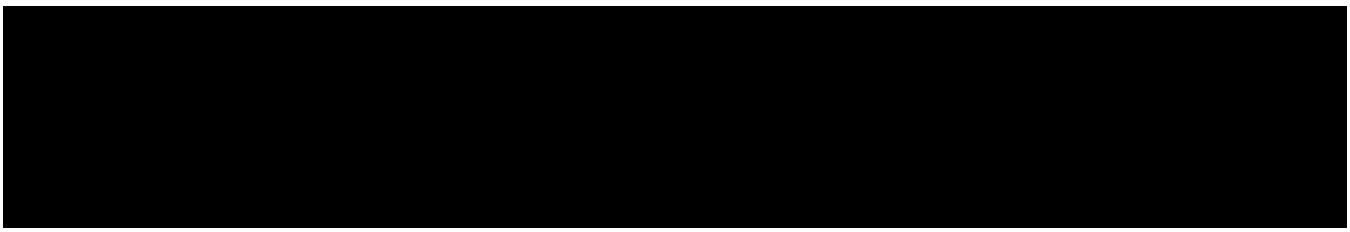


[redacted]

10 UPDATES TO ANALYSES SPECIFIED IN THE SAP

The following updates were made to the SAP (v2) specified analyses:

[redacted]



11 ADVERSE EVENTS

Treatment-related AEs are defined as any AE considered unlikely related, possibly related, or related. This is an update to Section 4.8.2 of the SAP (v2.0) where AEs related to treatment were only inclusive of those considered definitely related, probably related, or possibly related. This has been updated to match the options in the Case Report Form (CRF).

12 LABORATORY DATA

In addition to AEs of special interest (i.e., interstitial lung disease), specified in Section 4.8.2 of the SAP (v2.0), the following on-treatment events are of special interest:

- Neutropenia based on laboratory results and defined as the minimum absolute neutrophil count $< 0.5 \times 10^9$/L

- Liver function test abnormalities:
    - ALT or AST > 3x ULN
    - ALT or AST > 3x ULN and serum total bilirubin ≥ 2x ULN

13 REFERENCES

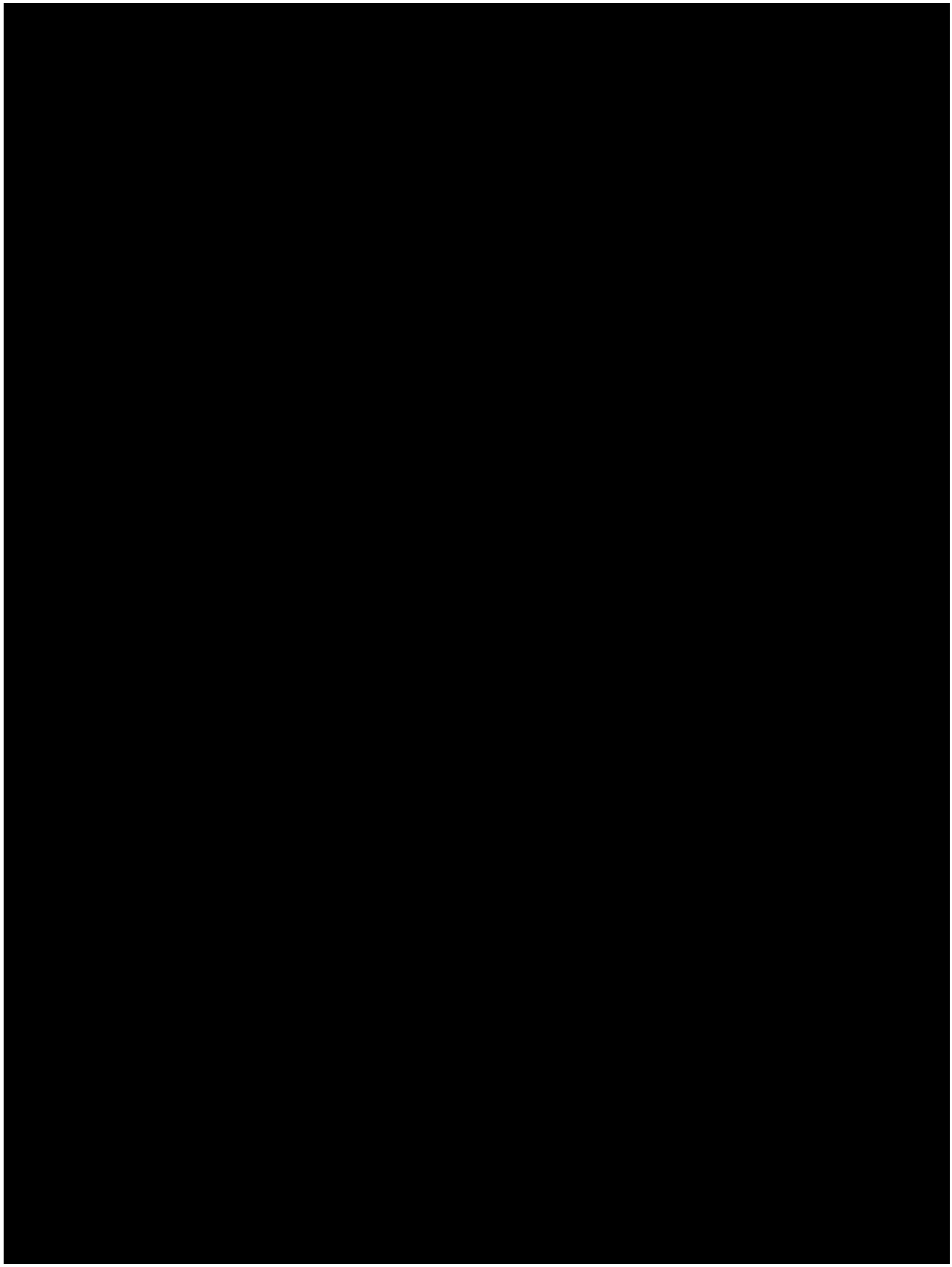
Abbreviated SAP BHV4157-201, Subjects with Spinocerebellar Ataxia with BHV-4157 Compared to a Natural History Cohort, Version 1, Biohaven Pharmaceutical Holding Company Limited, 2017.

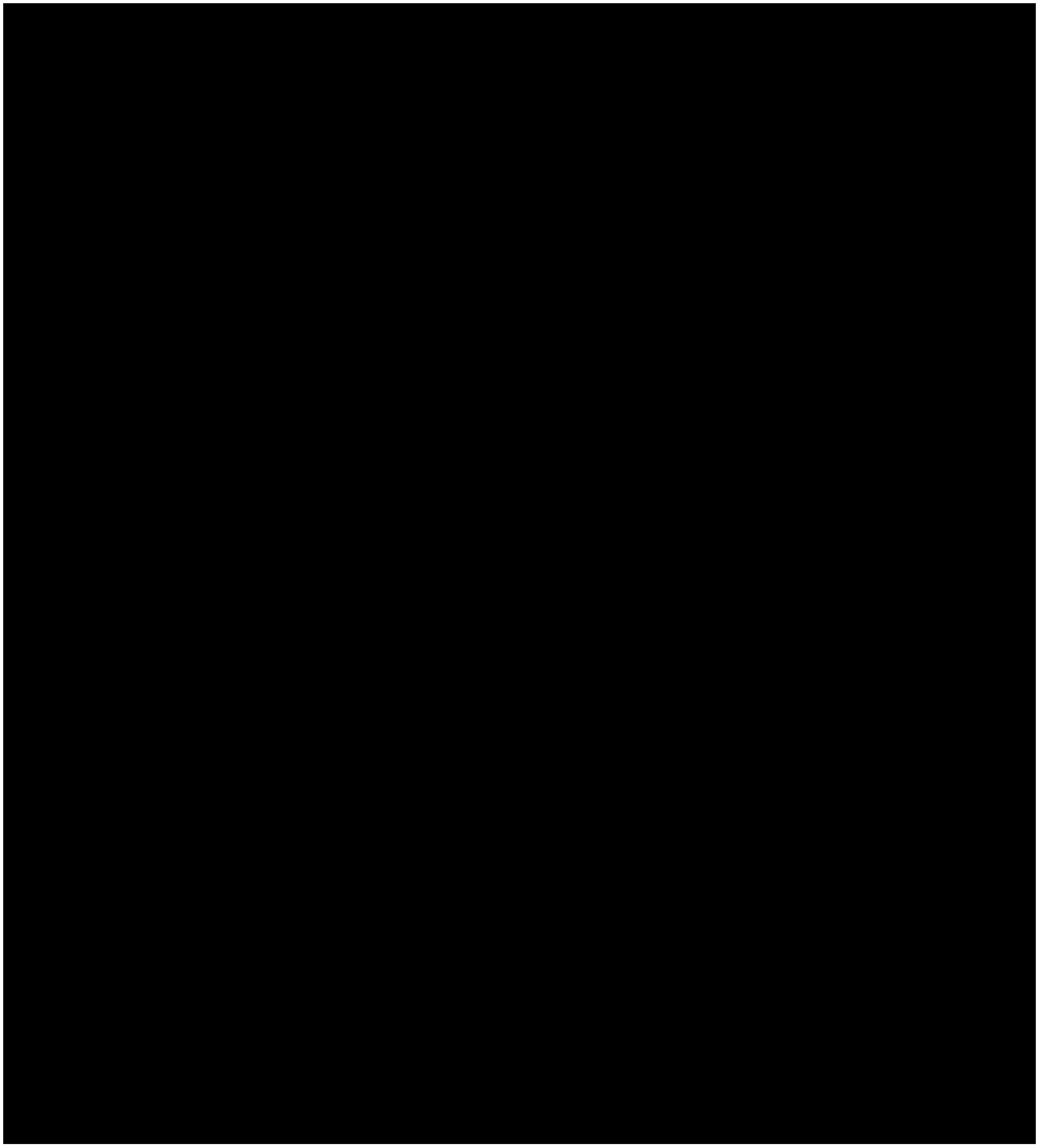
Ashizawa T, Figueroa KP, Perlman SL, Gomez CM, Wilmot GR, Schmahmann JD, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. Orphanet J Rare Dis 2013;8:177. doi: 10.1186/1750-1172-8-177

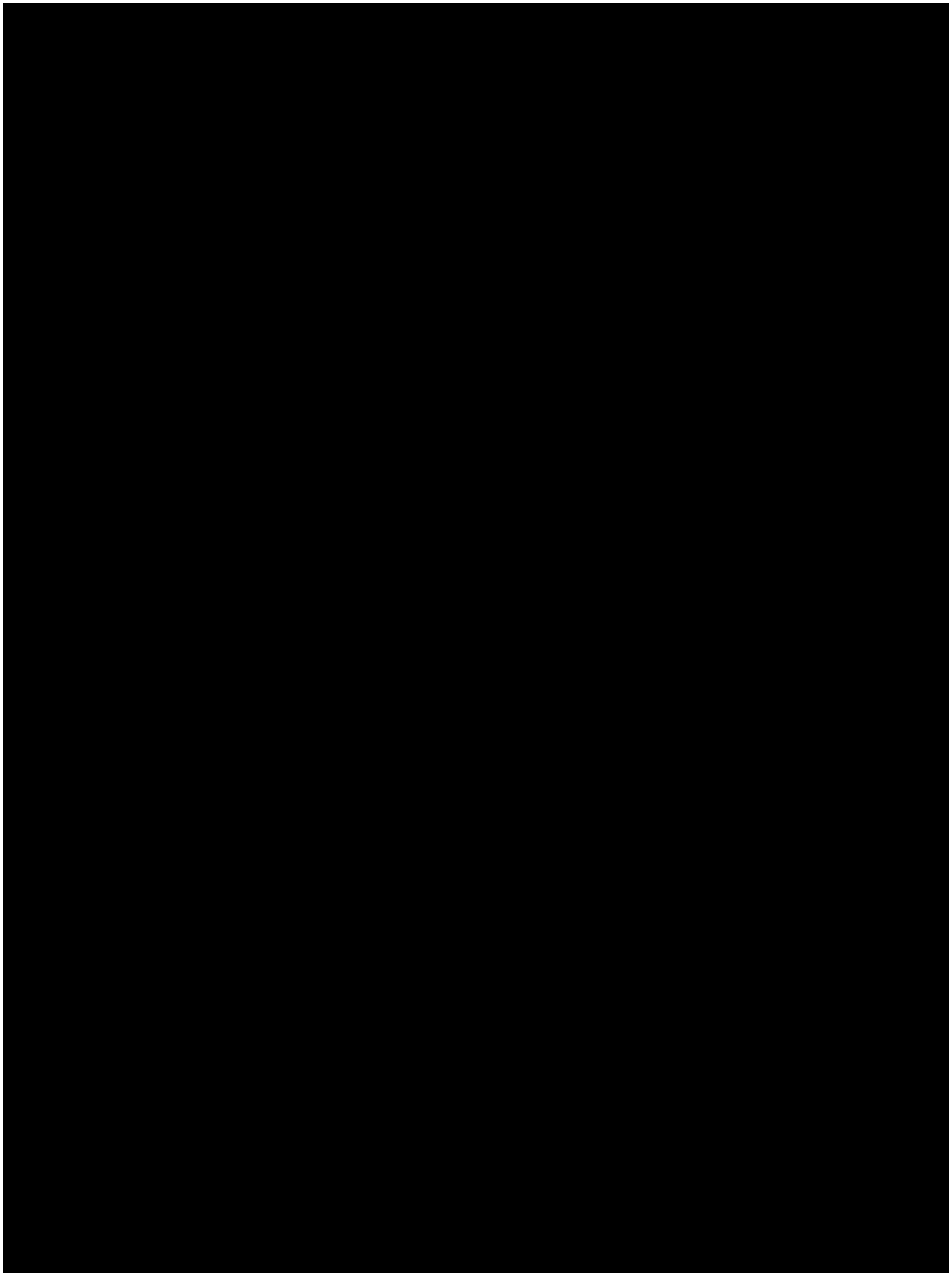
Protocol BHV4157-201, A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of BHV-4157 in Adult Subjects with Spinocerebellar Ataxia, Version 7, Biohaven Pharmaceutical Holding Company Limited, 2017.

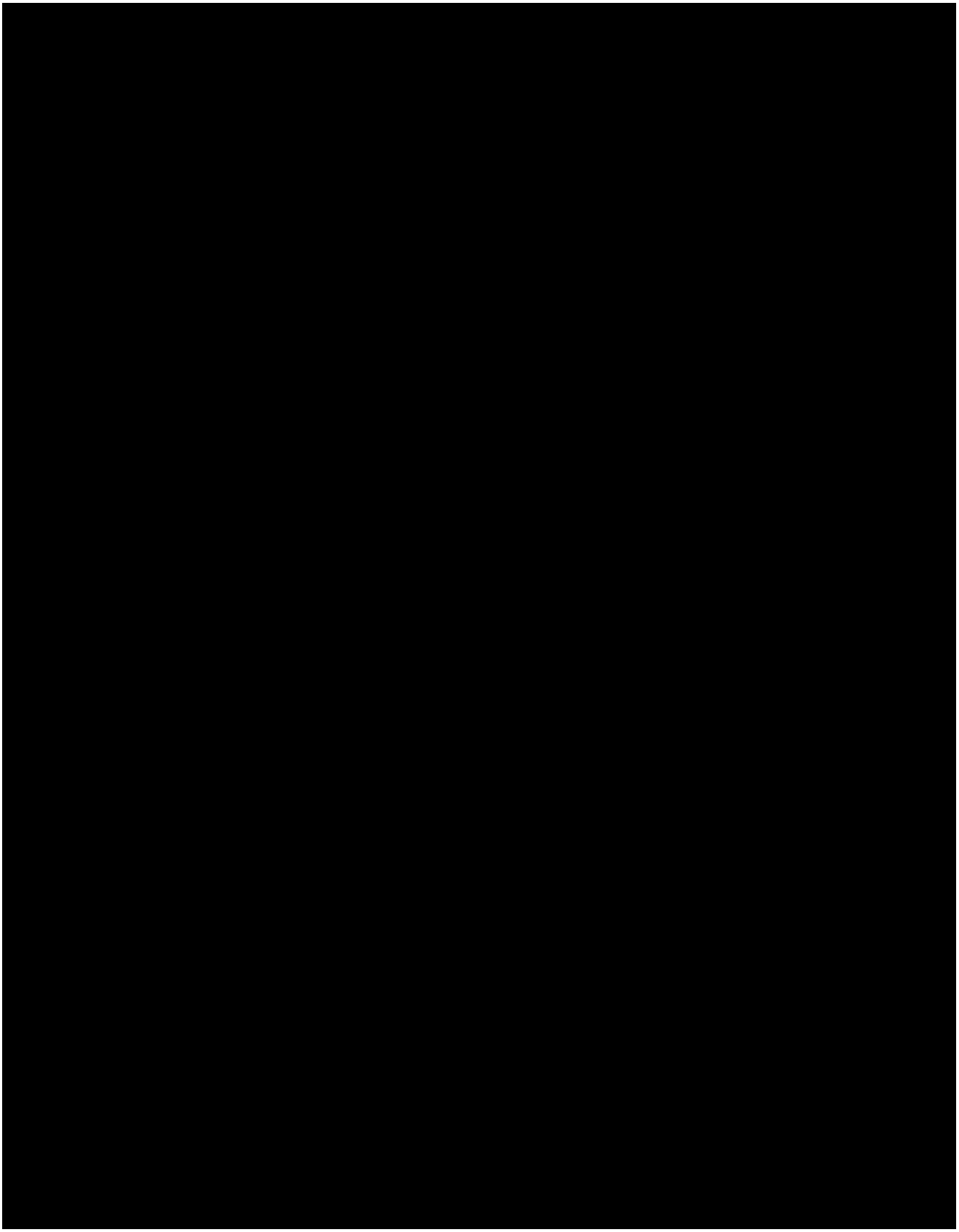
SAP BHV4157-201, A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of BHV-4157 in Adult Subjects with Spinocerebellar Ataxia, Version 2, Biohaven Pharmaceutical Holding Company Limited, 2017.

Appendix









Biohaven Pharmaceuticals

Protocol BHV4157-201

A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of BHV-4157 in Adult Subjects with Spinocerebellar Ataxia

Statistical Analysis Plan

Final Version 2.0
Date: September 6, 2017

SIGNATURE PAGE

Protocol Title:	A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of BHV-4157 in Adult Subjects with Spinocerebellar Ataxia
Sponsor:	Biohaven Pharmaceutical Holding Company Limited
Protocol Number:	BHV4157-201
Document Version/Date:	V1.0/09Jun2017: Original SAP V2.0/06Sep2017: Promoted PGI-C to a secondary endpoint; [redacted] dded new analyses on liver function; and other administrative updates.

Author:

[redacted]

[redacted]

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

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Sponsor Signatories:

[redacted]

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[redacted]

[redacted]

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic class
BCVA	Best-corrected visual acuity
[redacted]	[redacted]
BQL	Below limit of quantification
BUN	Blood urine nitrogen
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CPK	Creatine phosphokinase
CSR	Clinical study report
ECG	Electrocardiogram
[redacted]	[redacted]
[redacted]	[redacted]
ERG	Electroretinography
FAS	Full analysis set
HbA1C	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
IOP	Intraocular pressure
GGT	Gamma-glutamyl transferase
ICH	International Conference on Harmonisation
[redacted]	[redacted]
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LogMAR	Logarithm of the minimum angle of resolution
LSMeans	Least square means
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures

Abbreviation	**Definition**
MMSE	Mini Mental State Exam
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetic
PP	Per protocol set
PT	Preferred term
QD	Quaque die (once daily)
S-STS	Sheehan-Suicidality Tracking Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SARA	Scale for the Assessment and Rating of Ataxia
SCA	Spinocerebellar ataxia
SD	Standard deviation
[redacted]	[redacted]
SMQ	Standardized MedDRA query
SOC	System organ class
TSH	Thyroid-stimulation hormone
[redacted]	[redacted]
ULN	Upper limit of normal
[redacted]	[redacted]
WHO-DD	World Health Organization-Drug Dictionary

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

This document presents the statistical analysis plan (SAP) for Biohaven Pharmaceuticals, Protocol BHV4157-201: A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of BHV-4157 in Adult Subjects with Spinocerebellar Ataxia.

This SAP is based on Amendment 4 to the final protocol dated July 27, 2017. It contains the analysis details and methodology to answer the study objectives, including planned summary tables, by-subject listings, and figures, which will provide the basis for the results section of the clinical study report (CSR). Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

1.2. Objectives of Statistical Analysis

Primary Objective

- To compare the efficacy of BHV-4157 (140 mg once daily) versus placebo on ataxia symptoms in subjects with spinocerebellar ataxia (SCA) after 8 weeks of treatment as measured by the total score on the Scale for the Assessment and Rating of Ataxia (SARA)

Secondary Objectives

- To assess of the safety and tolerability of BHV-4157 in subjects with SCA
- To compare efficacy of BHV-4157 with placebo on patient impression of benefit via use of the Patient Global Impression of Change (PGI-C)

[redacted]

2. STUDY DESIGN

2.1. Synopsis of Study Design

BHV4157-201 is a Phase IIb/III, multicenter, randomized, double-blind, 2-arm placebo-controlled parallel-group study designed to assess safety, tolerability, and efficacy signals in a population of subjects with SCA.

Subjects who are determined to be eligible for the study will enter the Randomization Phase. Dosing will continue for 8 weeks. Subjects will return to the clinic 2 weeks after discontinuing study medication for a follow-up safety visit (see Figure 1). In addition, subjects completing the Randomization Phase will be offered 48 weeks of open-label treatment given the principle investigator believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Extension Phase will not be required to wash-out of drug or complete the follow-up safety visit, but instead should continue dosing as specified in the Extension Phase.

Subjects entering the Extension Phase will have their first Extension visit 4 weeks after the Week 8 Randomization Phase visit. If there is a delay of two weeks or more in dosing between the Randomization Phase and the Extension Phase, then subjects will be required to complete an Extension baseline visit. Thereafter, subjects will undergo visits every fourth week through Week 12 of this phase. Then subjects will undergo visits every 12 weeks up to Week 48 of this phase. All subjects will undergo a post study drug termination visit two weeks after the last dose of study drug in the Extension Phase.

2.2. Randomization Methodology

Subjects will be randomized to receive placebo once daily (QD) or BHV-4157 (140 mg QD).

2.3. Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician. The unblinded biostatistician, or designee, will be unblinded to the randomized treatment assignments. A PK and interactive web response system (IWRS) randomization manager may also be unblinded. Except as noted above, members of the Biohaven research team will remain blinded.

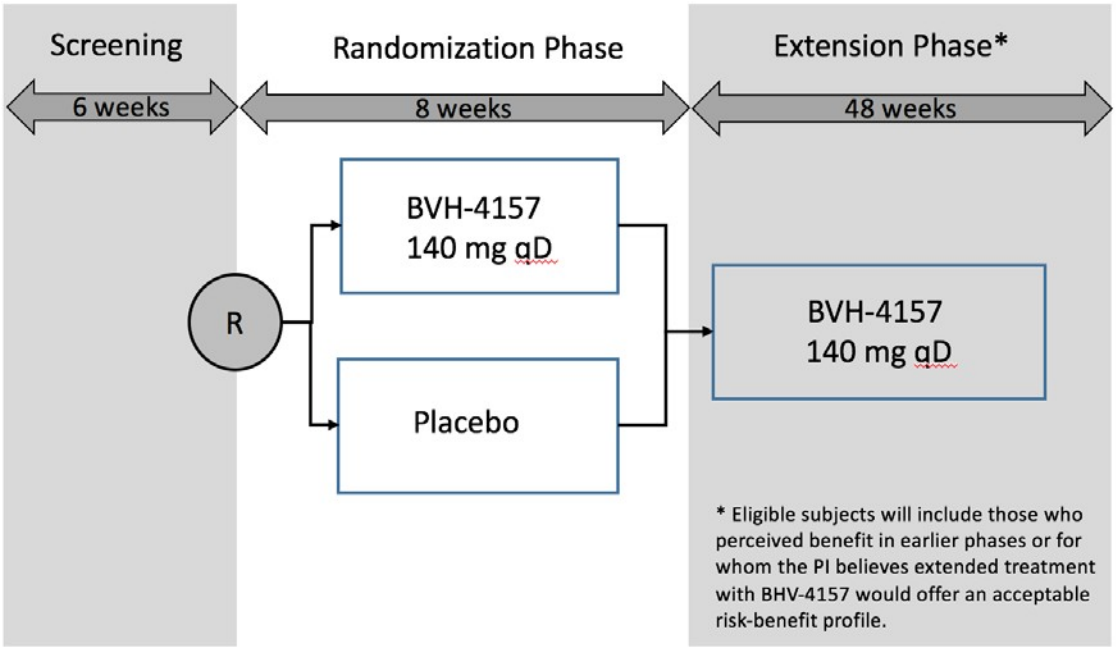


Figure 1: Study Schematic

R=Randomization

2.4. Efficacy, [redacted] Safety, and Other Variables

2.4.1. Efficacy Variables

Primary Endpoint

- Change from baseline to Week 8 in SARA total score

Secondary Endpoints

- Frequency and severity of adverse events (AEs) and discontinuation due to AEs
- Patient impression of benefit via use of PGI-C at Week 8

[redacted]

[redacted]

2.4.4. Safety and Other Variables

Safety assessments performed during the study include AEs, laboratory evaluations, physical examinations, vital signs and physical measurements, 12-lead electrocardiograms (ECGs), concomitant medications, and the Sheehan-Suicidality Tracking Scale (S-STS). [redacted].

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

Full Analysis Set (FAS): All randomized subjects with at least 1 dose of study treatment and a baseline and post-baseline total SARA score during the Randomization Phase.

Per Protocol (PP) Set: All FAS subjects without any major protocol deviations.

Safety Analysis Set: All subjects who received at least 1 dose of study treatment.

3.2. Protocol Deviations

Any significant event that does not comply with the inclusion/exclusion criteria, study conduct (e.g., inadequate informed consent, unreported SAEs), or study procedures (e.g., use of prohibited medications as defined by the protocol; improper breaking of the blind; overall non-compliance with study medication <80% for either the Randomization Phase or both phases, calculated prior to database lock) will be documented as a major deviation.

[redacted]

All protocol deviations will be presented in the data listings.

4. STATISTICAL METHODS

4.1. Sample Size Justification

The sample size for this study will be 120 randomized subjects to accommodate for dropouts and based on the rationale that follows.

[redacted] For this trial, conservatively assuming a TRUE underlying difference between treatments of 1.24 units and pooled SD=2.01, N=112 (56/group) has ~90% power to yield a statistically significant (alpha=0.05, 2-sided) difference between treatments in change from baseline to Week 8 in the total SARA score. This calculation is via 2-sample t-test, which is likely conservative compared to the planned repeated measures analysis planned for this trial to leverage the likely correlation of response between Weeks 4 and 8. [redacted]

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, [redacted] safety, and other parameters. For categorical variables, summary tabulations of the number and percentage within each category of the parameter will be presented. If applicable, a category for missing data will also be presented. For continuous variables, n, mean, median, SD, minimum and maximum values will be presented. The median, minimum, and maximum values will be presented with the same precision as the data. The mean will be presented with the precision of the data + 1 decimal place. The SD will be presented with the precision of the data + 2 decimal places.

Formal statistical hypothesis testing and summary statistics will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

4.2.2. Computing Environment

All statistical analyses will be performed using SAS statistical software (Version 9.2 or higher). Medical history and AEs will be coding using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1). Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD, Sep2016).

[redacted]

4.2.4. Adjustments for Covariates [redacted]

[redacted]

4.2.5. Multiple Comparisons/Multiplicity

Type 1 error will be controlled for the primary and secondary efficacy endpoints by testing them with a fixed sequence procedure. The primary endpoint, change from baseline in the total SARA score, will be tested at a two-sided alpha level of 0.05. If this test is significant, then a single secondary endpoint, PGI-C, will also be tested at a two-sided alpha level of 0.05. If the test of the primary endpoint is not significant, then the p-value for the secondary endpoint will be presented only for descriptive purposes, and no conclusions may be drawn from this result.

The multiplicity corrections discussed above apply only to analyses done on the FAS population. Any parallel analyses performed on the PP population are considered to be sensitivity analyses, and are not corrected for multiplicity.

[redacted]

4.2.7. Withdrawals, Dropouts, and Loss to Follow-up

Subjects who withdrew from the study were not replaced.

4.2.8. Missing, Unused, and Spurious Data

Unless otherwise noted, efficacy analyses will be based on observed data only. No missing data will be imputed. We expect the amount of data that will be lost in the 8-week double blind phase of this study to be small; most likely less than 10%.

For efficacy analyses, partial or missing dates will not be imputed. The relative study days, where determined, will be calculated for full dates only.

4.2.9. Visit Windows

The protocol-specified visit window is ± 2 days during the Randomization Phase and ± 7 days during the Extension Phase of the study. Observations collected within ± 1 week visit window during the Randomization Phase and ± 2 weeks visit window during the Extension Phase will be included in the analyses

[redacted]

Actual dates and times will be used for PK analysis rather than nominal days and times.

4.3. Planned Analyses

Data from the double-blind portion of the trial will be unblinded and analyzed after the last subject completes 8 weeks of treatment or discontinues from the Randomization Phase. Subjects who complete the Randomization Phase may be eligible for an open-label Extension Phase of the study. Data from the Extension Phase will be summarized after the last subject completes the last visit or discontinues from the Extension Phase.

4.4. Subject Disposition

A summary of subject disposition will be tabulated for all subjects by treatment group and overall for the Randomization and Extension Phases, separately, including:

- Number of subjects screened
- Number of screened subjects excluded from the study and reason for exclusion
- Number of subjects in each analysis population
- Number of subjects who entered the Randomization Phase
- Number of subjects who completed the Randomization Phase
- Number of subjects who prematurely withdrew from the Randomization Phase and reasons for withdrawal

- Number of subjects who entered the Extension Phase
- Number of subjects who completed the Extension Phase
- Number of subjects who withdrew from the Extension Phase and reasons for withdrawal

A by-subject listing of study completion information for both the Randomization and Extensions Phases, including the reason for withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Demographic information, medical and disease history, and Mini Mental State Exam (MMSE) results will be summarized by treatment group and overall, based on the Safety population. However, if a substantial difference exists between the number of subjects in the Safety and the FAS populations, then a separate similar summary will be provided for the FAS population.

Demographic and other baseline data will also be provided in by-subject data listings.

4.6. Efficacy Evaluation

Unless otherwise noted, all efficacy analyses will be conducted using the FAS and PP populations as outlined below. All efficacy data will be included in listings by subject, study medication, and visit (as applicable) for the Randomization and Extension phase, separately.

For the Randomization Phase, baseline is considered as the last visit prior to dosing (Visit 2 assessment); and for the Extension Phase, baseline is considered as the visit prior to Extension Visit 1:

- If less than 14 days elapsed between the Randomization and Extension Phases, then use the Visit 4 (Week 8) assessment during the Randomization Phase, or
- If 14 or more days elapsed between the Randomization and Extension Phases, then use the Repeat Baseline assessment at the beginning of the Extension Phase.

4.6.1. Primary Efficacy Endpoint

4.6.1.1. Scale for the Assessment and Rating of Ataxia (SARA)

The severity of ataxia is assessed with the SARA, an 8-item clinical rating scale from 0 (no ataxia) to 40 (most severe ataxia). The total score is derived as the sum of the individual items, which include gait (0-8), stance (0-6), sitting (0-4), speech disturbance (0-6), finger chase (0-4), nose-finger test (0-4), fast alternating hand movements (0-4), and heel-shin slide (0-4). Since the finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide are repeated on both the right and left side, the average of the right and left side assessments are used to derive the total score.

The primary endpoint is the difference between the BHV-4157 and placebo groups in the change from baseline to Week 8 in the total SARA score. The principal analysis will be carried out via a Mixed Model for Repeated Measures (MMRM). [redacted]

[redacted]

[redacted]

4.6.2. Secondary Efficacy Endpoint

4.6.2.1. Patient Global Impression of Change (PGI-C)

The patient's impression of benefit via the PGI-C will be summarized descriptively by post-baseline visit for the Randomization and Extension Phases, separately, including the number and percentage of subjects in each category:

- No change (or condition has gotten worse)
- Almost the same, hardly any change at all
- A little better, but no noticeable change
- Somewhat better, but the change has not made any real difference
- Moderately better, and a slight but noticeable change
- Better and a definitive improvement that has made a real and worthwhile difference
- A great deal better and a considerable improvement that has made all the difference at each post-baseline study visit

The significance of the difference between treatment groups in the PGI-C scores will be assessed via an exact Wilcoxon rank-sum test and p-values reported for the Randomization Phase only.

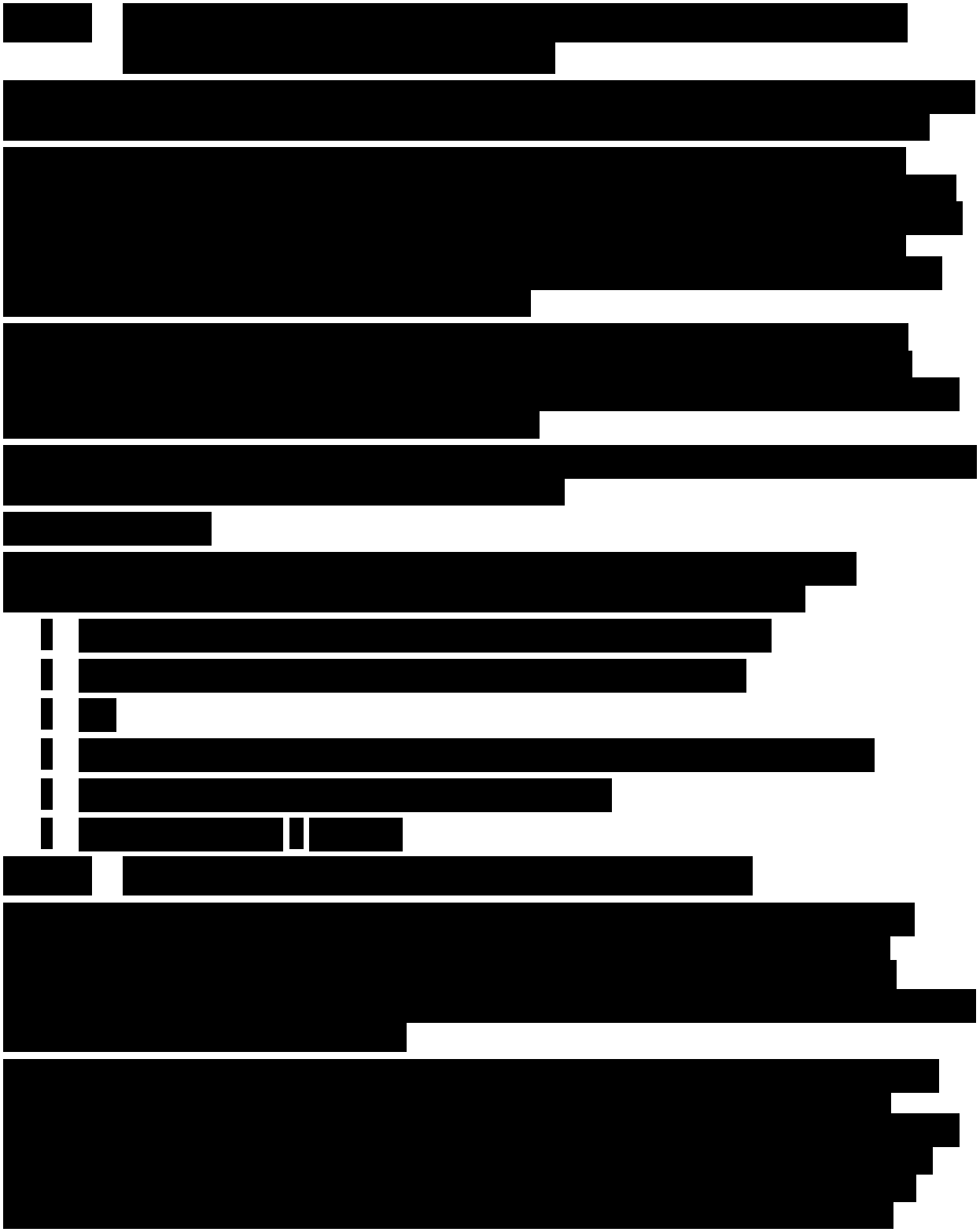
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

4.8. Safety and Other Analyses

Safety and other exploratory analyses will be conducted on the Safety Population. All safety and other data will be listed for the Randomization and Extension phase, separately.

Safety outcome measures include: extent of exposure, compliance to study treatment, adverse events, laboratory assessments, physical examinations, vital signs, ECGs, concomitant medications, and the S-STS questionnaire.

[redacted]

Baseline is considered as the last visit prior to dosing, either the Visit 1 or Visit 2 assessment, for the Randomization Phase. For the Extension Phase, baseline is considered as the visit prior to Extension Visit 1:

- If less than 14 days elapsed between the Randomization and Extension Phases, then use the Visit 4 (Week 8) assessment during the Randomization Phase, or
- If 14 or more days elapsed between the Randomization and Extension Phases, then use the Repeat Baseline assessment at the beginning of the Extension Phase.

4.8.1. Extent of Exposure and Compliance to Study Treatment

Subjects will receive placebo (QD) or BHV-4157 (140 mg QD) during the Randomization phase. Subjects who complete 8 weeks of treatment in the Randomization phase may be eligible for an open-label Extension phase of the study.

For the Randomization phase, the extent of subject exposure to study treatment will be quantified as the number of days on study drug (placebo or BHV-4157) and measured from the time the subject received the first dose until the time the subject received the last dose, either at the end of 8 weeks of treatment or withdrawal from the Randomization phase.

For the Extension phase, the extent of subject exposure to study treatment will be quantified as the number of days on study drug (BHV-4157) and measured from the time the subject received the first dose of BHV-4157 until the time the subject received the last dose, either at the end of the study or withdrawal from the Extension phase.

The number of tablets taken will be summarized for both the Randomization and Extension phases, separately. Additionally, percent (%) compliance will be calculated and summarized as follows:

Randomization phase % compliance = number of tablets taken during the Randomization phase / (last dose date – first dose date + 1) × 100.

Extension phase % compliance = number of tablets taken during the Extension phase / (last dose date – first dose date + 1) × 100.

Overall % compliance = number of tablets taken during the study / [(last dose date – first dose date + 1) – (number of days with a dosing break in dosing between the Randomization and Extension phases)].

Study drug administration and compliance will be listed in subject data listings for the Randomization and Extension Phases, separately.

4.8.2. Adverse Events

Adverse eventss will be coded using MedDRA and displayed in tables and listings by system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE that developed, worsened, or became serious after first dose of test treatment.

Adverse events are summarized by subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given AE (SOC or PT).

The number and percentage of subjects with the following on-treatment AEs will be summarized by treatment group and overall for the Randomization and Extension Phases, separately.

- Treatment-emergent AEs,
- AEs related to treatment (definitely, probably, or possibly),
- SAEs,
- AEs with Grade 2 or greater severity,
- AEs leading to discontinuation, and
- Standardized MedDRA query (SMQ) of interstitial lung disease, including eosinophilic pneumonia

On-treatment AEs are AEs with a start date prior to 30 days after the last dose of study drug. For the Randomization Phase, treatment-emergent AEs will be assessed from the date of randomization until: 1) the first day of the Extension Phase or 2) if the subject did not continue into the Extension Phase, 30 days after the last dose of study drug. For the Extension Phase, treatment-emergent AEs will be assessed from the first day of the Extension Phase until 30 days after the last dose of study drug.

In the above tabulations, each subject will contribute only once (i.e., the most related occurrence or the most severe occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes. No formal hypothesis-testing analysis of AEs incidence rates will be performed.

All AEs occurring pre-treatment, during the Randomization phase, during the Extension phase, and throughout the entire study will be listed. Additional listings will be provided for the Randomization and Extension Phases, including deaths, SAEs, and AEs leading to withdrawal of study drug.

4.8.3. Laboratory Data

Clinical laboratory evaluations include:

- Hematology: hemoglobin, hematocrit, platelets, complete blood count with differential and absolute neutrophil count
- Serum Chemistry: sodium, potassium, chloride, calcium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), phosphorous, bicarbonate, creatine phosphokinase (CPK), total protein, albumin, total bilirubin (if greater than 2 mg/dl bilirubin will be fractionated), glucose, creatinine, blood urine nitrogen (BUN), uric acid, and pregnancy testing (for women of child-bearing potential). Additionally at screening, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, folate, hemoglobin A1c (HbA1C), P-Amylase, Lipase, thyroid-stimulation hormone (TSH), and T4
- Urinalysis: pH, specific gravity, protein, ketones, glucose, blood, and microscopic exam (completed only if any part of the urinalysis is not negative)
- Additional tests: human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody at screening

Clinical laboratory values will be expressed using conventional units. In the event of repeat values within the same analysis visit, the measurement closest to the target day for the analysis visit interval will be used.

On-treatment laboratory abnormalities are those with an assessment date after the date/time of first dose of study drug and within 30 days after the last dose of study drug. For the Randomization Phase, treatment-emergent laboratory abnormalities will be assessed from the date of randomization until: 1) the first day of the Extension Phase or 2) if the subject did not continue into the Extension Phase, 30 days after the last dose of study drug. For the Extension Phase, treatment-emergent lab abnormalities will be assessed from the first day of the Extension Phase until 30 days after the last dose of study drug.

The observed value and change from baseline will be summarized for each continuous laboratory parameter for the Randomization and Extension Phases, separately. In addition, the shift from baseline for laboratory abnormalities (low, normal, high) will be tabulated for the Randomization and Extension Phases, separately.

For the liver function tests, AST and ALT, the shift from baseline will be presented by visit and to the maximum observed abnormality for the Randomization and Extension Phases, separately. Additionally for ALT, the shift from baseline to the maximum observed treatment-emergent abnormality, regardless of phase, will be presented for subjects treated with BHV4157 only. The following categories will be used to summarize the shift from baseline based on the upper limit of normal (ULN) range:

- Normal
- >ULN to ≤ 3x ULN
- >3x ULN to ≤ 5x ULN
- >5x ULN

All laboratory data will be presented in data listings. Additional listings will be presented for all abnormal laboratory values for the Randomization and Extension Phases, separately. Subjects with a maximum value of ALT or AST >3x ULN and a maximum total bilirubin value >2x

ULN observed at any point during the entire study will also be presented in a listing. Note that these abnormalities do not need to occur on concurrent visits.

4.8.4. Physical Examinations

For each body system, the shift from baseline will be summarized as the number and percentage of subjects with each result (normal, abnormal, or physical examination not done) by visit for the Randomization and Extension Phases, separately.

4.8.5. Vital Signs and Physical Measurements

The observed value and change from baseline in vital signs will be summarized at each visit for the Randomization and Extension Phases, separately.

4.8.6. Electrocardiogram

The shift from baseline in ECG parameters will be summarized as the number and percentage of subjects with normal, abnormal, and clinically significant abnormal results by visit for the Randomization and Extension Phases, separately. Descriptive statistics for ECG interval data (e.g., QRS, PR, QT, QTcF), and ventricular heart rate will also be reported by visit for the Randomization and Extension Phases, separately.

4.8.7. Neurological Assessment

For each neurological site, the shift from baseline will be summarized as the number and percentage of subjects with each result (normal, abnormal, or neurological assessment not done) by visit for the Randomization and Extension Phases, separately.

4.8.8. Concomitant Medications

Concomitant medications will be coded using the WHO-DD. Results will be tabulated by Anatomic Therapeutic Class (ATC) and PT during the Randomization and Extension Phases, separately.

4.8.9. Sheehan-Suicidality Tracking Scale (S-STS)

The S-STS is a prospective, self-reported rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors. In the event the subject is unavailable, the S-STS clinician-administered rating scale will be completed that contains 6 yes/no questions.

Self-reported S-STS scores are calculated as follows:

- Ideation subscale score: Sum of scores (0 – 4) for Questions 2 – 11
- Behavior subscale score: Sum of scores (0 – 4) for Questions 1a, (highest of 12 or any row of 16), (highest of 14 or any row of 15), 17, and 20
- Total score: Sum of the ideation and behavior subscale scores

The self-reported S-STS ideation subscale, behavior subscale, and total score will be summarized as the change from baseline (i.e., <-1, -1, no change, 1, >1) at each visit in the Randomization and Extension phases, presented separately.

5. REFERENCES