

Recursion Pharmaceuticals, Inc.

REC-994-201

**Two-Part Study of REC-994 in the Treatment of Adults with
Symptomatic Cerebral Cavernous Malformation (CCM)**

**Part 1: A Phase 2 Randomized, Double-Blind, Placebo-Controlled
Clinical Trial to Evaluate the Safety, Efficacy and
Pharmacokinetics of Two Doses of REC-994**

**Part 2: A Long-Term Blinded Extension Clinical Trial to Evaluate
Long-Term Safety Tolerability and Efficacy of REC-994**

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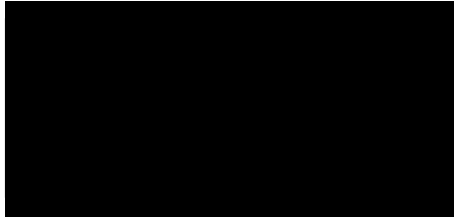
Statistical Analysis Plan – Primary Analysis

FINAL Version 2.0

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1 List of Abbreviations

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ALD	Above the limit of detection
ALQ	Above the limit of quantification
AST	Aspartate aminotransferase
AUC _{0-t}	Area under the curve from time 0 to the last measurable observed concentration
AUC _{0-tau}	Area under the curve within a dosing interval
AUC _{0-inf}	Area under the curve from time 0 extrapolated to infinity
AUC _{extrap}	Percentage of area under the curve from time 0 extrapolated to infinity due to extrapolation
β-hCG	Beta human chorionic gonadotropin
BLD	Below the limit of detection
BLQ	Below the limit of quantification
BUN	Blood urea nitrogen
CBC	complete blood count
CCM	Cerebral cavernous malformation
██████	██
CFB	Change from baseline
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CI	Confidence interval
CL/F	Apparent total body clearance
C _{max}	Maximum observed plasma concentration
C _{trough}	Observed concentration at the end of the dosing interval, determined directly from the concentration-time data
CTMS	Clinical trial management system
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
ERM	Ezrin, Radixin, and Moesin
EoS	End of Study
EoT	End of Treatment
FAS	Full analysis set
FoxO1	Forkhead box protein O1
FSH	Follicle stimulating hormone
HMVEC-D	Human dermal microvascular endothelial cells
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LTE	Long-term extension
MAR	Missing at random
MCID	Minimum Clinical Important Difference
MedDRA	Medical dictionary for regulatory activities
██████	██
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
MPD	Major protocol deviation
██████	██
NII	Non-improver imputation

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2 Introduction

This statistical analysis plan (SAP) should be read in conjunction with the study protocol amendment version 6.0 (22SEP2023) and the case report forms version 7.0 (09JAN2024).

The purpose of this SAP is to define the scope and provide detailed descriptions of the statistical methods for the primary analysis of data from the protocol REC-994-201:

A Two-Part Study of REC-994 in the Treatment of Adults with Symptomatic Cerebral Cavernous Malformation (CCM);

Part 1: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of Two Doses of REC-994;

Part 2: A Long-Term Blinded Extension Clinical Trial to Evaluate Long-Term Safety Tolerability and Efficacy of REC-994.

The primary analysis includes all data collected from Part 1 of the study as well as the safety and MRI data collected from the long-term extension (LTE) Part 2. The SAP will be finalized prior to the database lock after the last participant completes the last study visit of Part 1 (██████████ EoS visit for participants not participating Part 2 or ██████████ EoT visit for Part 2 participants), which is the cutoff date of the primary analysis.

Any deviation from this SAP will be substantiated by sound statistical rationale and will be documented in the final clinical study report for primary analysis.

The efficacy data, safety data, and other study endpoints collected from the LTE Part 2 will be analyzed at the end of the Part 2 study. Details for the Part 2 analysis will be provided in a separate SAP. The final database lock will occur upon completion of the last participant's end of study (EoS) visit.

Cerebral cavernous malformation (CCM) is characterized by vascular malformations in the brain and spinal cord comprising closely clustered, enlarged capillary channels with a single layer of endothelium without mature vessel wall elements ([Lampugnani, 2017](#)). These malformations (or lesions) are highly permeable and this leakiness can lead to a variety of clinical symptoms including seizures, progressive neurologic impairment, and a risk of death due to hemorrhagic stroke. CCM is caused by inherited or acquired loss-of-function mutations in the genes Krev interaction trapped protein 1 (KRIT1, also labeled CCM1), oncostatin M (OSM, also labeled CCM2), or programmed cell death 10 (PDCD10, also labeled CCM3) in endothelial cells lining the cavernous capillary cavities. CCM has been identified as an orphan disease.

Oxidative stress is linked to the molecular and cellular associations related to CCM diseases, including weakening of cell-cell junctions, increased integrin activation, and loss of quiescence ([Fidalgo, 2012](#)). An imbalance between the generation of reactive oxygen species (ROS), such as superoxide anions or hydroxyl radicals, during mitochondrial metabolism and their scavenging by antioxidant enzymes, such as SOD2, causes oxidative stress. Specifically, experiments in CCM1 knockout murine fibroblasts demonstrated that the expression of the stress responsive transcription factor FoxO1 and the protective scavenger protein, SOD2 were both reduced ([Fidalgo, 2012](#)). These fibroblasts were participant to increased DNA damage and cell death in response to oxidative stress. An additional study showed that CCM3 promoted activation of Ezrin, Radixin,

and Moesin (ERM), a protein complex that helped to limit apoptosis in response to oxidative stress ([Whitehead, 2009](#)).

REC-994 (also known as tempol) is among the most potent of the nitroxides in protecting cells and tissues from the damaging effects of ROS ([Wilcox, 2010](#)). REC-994 reduces ROS by functioning as a superoxide scavenger to reduce superoxide in a species independent manner. REC-994 has demonstrated the ability to protect lipids, deoxyribonucleic acid (DNA), or proteins from oxidative damage, and has interacted with other antioxidants to promote their ability to reduce oxidized lipids ([Wilcox, 2010](#)).

The multiple antioxidant actions of nitroxides have been widely studied in diverse animal models, tissues, and cell models of oxidative stress. Nitroxides prevented oxidative damage in many cellular or organ systems, i.e., in the skin after ultraviolet (UV) radiation, in cells after X-irradiation, and in tissues after incubation in a high glucose-containing medium ([Wilcox, 2010](#)).

REC-994 was found to correct a high dimensional morphological phenotype in CCM2 deficient human dermal microvascular endothelial cells (HMVEC-D). The potential of REC-994 as a therapy for CCM was discovered using in vitro cell models and further established in multiple rodent models of the disease. REC-994 was evaluated in two independent chronic, mouse models of CCM disease caused by endothelial cell specific deletion of CCM1 or CCM2, genes causative of disease in humans. Chronic treatment of endothelial-specific CCM1 or CCM2 deficient mice for 5-months yielded a significant reduction in lesions by MRI ([Gibson, 2015](#) & unpublished results).

3 Study Objectives and Endpoints

The primary analysis for this study will focus on Part 1 objectives and endpoints described in [Section 3.1](#) with the scope and details described in this SAP.

Details for evaluating Part 2 objectives and endpoints ([Section 3.2](#)) will be provided in a separate SAP for LTE Part 2.

3.1 Part 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Safety and tolerability	• Number, severity, and relatedness of adverse events (AEs) • Number, severity, and relatedness of serious AEs (SAEs) • Number, severity, and relatedness of AEs of special interest (AESI) • Number of AEs leading to study drug discontinuation
Secondary	
Safety and tolerability	• Clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis) • 12-lead electrocardiograms (ECGs) • Vital sign measurements • Physical examinations • Neurological examinations
Efficacy • Neurologic disability • Patient-reported outcomes • Clinician assessment • Patient assessment • Disease-associated symptoms • MRI-related	• Change from Baseline to [REDACTED] in modified Rankin scale (mRS) • Change from Baseline to [REDACTED] in SymptoMScreen (SMSS) • Change from Baseline to [REDACTED] in [REDACTED] • [REDACTED] total score and subscale scores • [REDACTED] improvement status in total score and subscale scores • Clinical Global Impression (CGI) • Patient Global Impression (PGI) • Number of seizures per month (participant diary) • Number of headaches per month (participant diary) • Number of symptomatic hemorrhagic events • Total cerebral lesion volume • Total hemosiderin ring size in diameter
Pharmacokinetics (PK)	• Plasma concentrations of REC-994 • Plasma PK parameters including, but not limited to, C_{max}, T_{max}, AUC_{tau}, and C_{trough}
Exploratory	
[REDACTED]	

3.2 Part 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
Long-term safety and tolerability	Same safety and tolerability assessments as in Part 1: • Ongoing assessment of AEs • Clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis) • 12-lead ECGs • Vital sign measurements (blood pressure, heart rate, temperature, respiratory rate) • Physical examinations • Neurological examinations
Secondary	
Long-term efficacy	Same efficacy variables as in Part 1: • Change from Baseline in: – mRS – SMSS  • CGI-I • PGI-I • Number of symptomatic hemorrhagic events • Total cerebral lesion volume • Total hemosiderin ring size in diameter

4 Investigational Plan

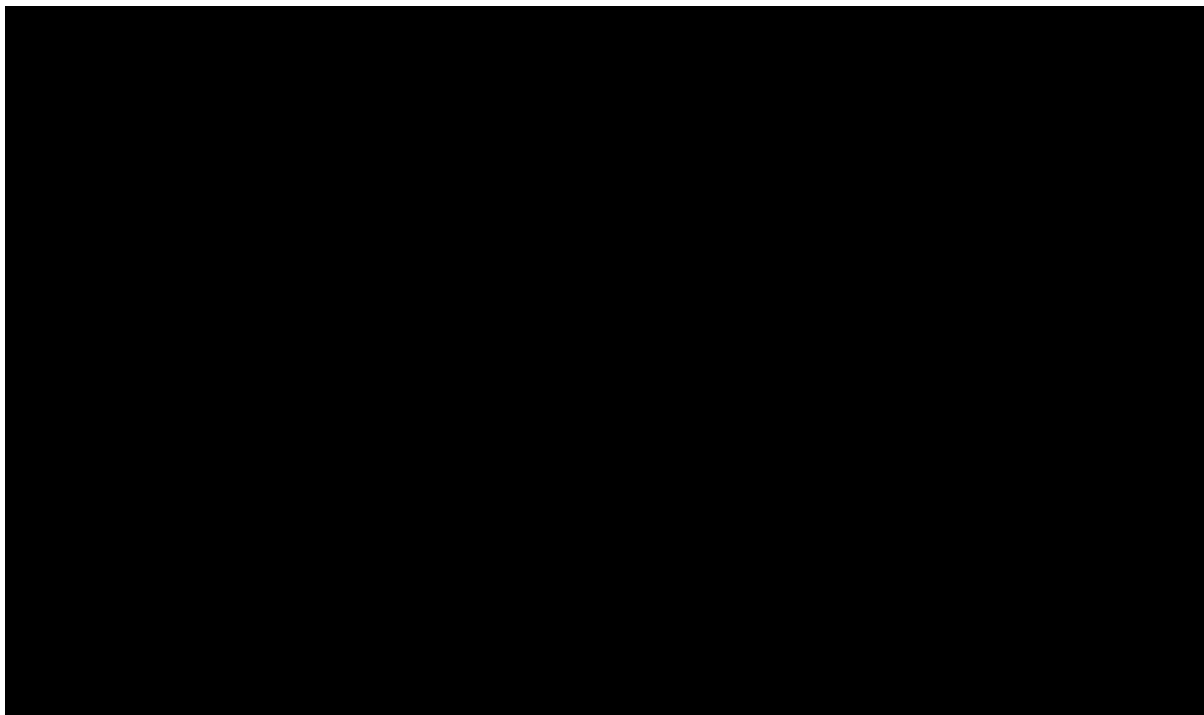
4.1 Overall Study Design

This is a multi-center study being conducted in two parts. Part 1 is a randomized, double-blind, placebo-controlled trial to investigate the safety, efficacy, and PK of daily doses of REC-994 ([REDACTED]) and [REDACTED] compared to placebo in participants with symptomatic CCM over a treatment period of [REDACTED]. Part 2 is an optional, double-blind, long-term extension (LTE) study of daily doses of REC-994 for participants completing Part 1 of the study.

Part 1 of the study will consist of 3 periods:

- Screening ([REDACTED])
- Treatment Period ([REDACTED])
- Follow-up Period ([REDACTED]).
 - Participants not participating in the LTE Part 2 study will discontinue study drug at the [REDACTED] visit and will then return in [REDACTED] for an End-of Study Visit.
 - For participants participating in the long-term extension, the End-of-Treatment Study Visit ([REDACTED]) will also represent the First Visit for the LTE Part 2.

An overview of the study design for Part 1 is presented in **Table 1** [Table 1](#).

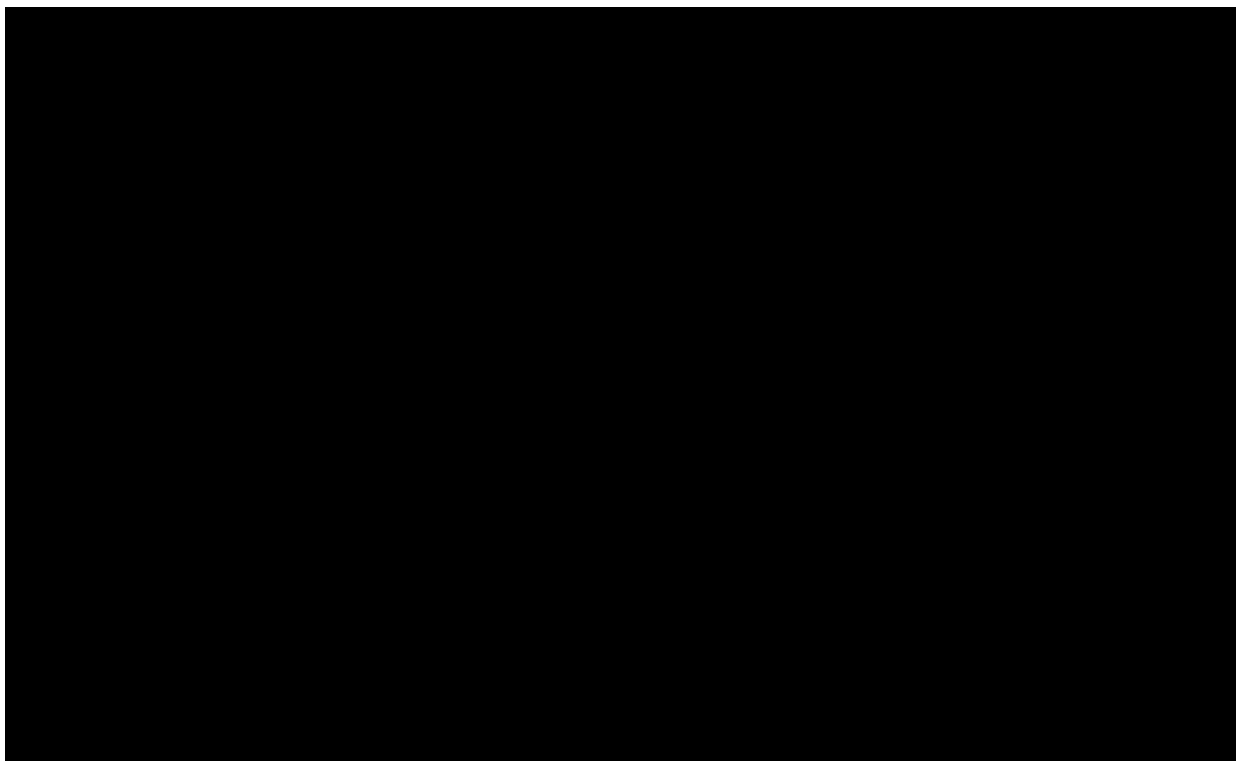


Part 2 is an optional blinded LTE study of REC-994 for participants who have successfully completed [REDACTED] of treatment in Part 1 and are eligible for extended treatment with REC-994.

Part 2 of the study will consist of 3 periods:

- LTE Eligibility Visit: LTE Day 1 (coincident with the [REDACTED] visit of Part 1 or as soon as possible thereafter [up to 14 days]).
- LTE Treatment Period: LTE Day 1 (Part 1 [REDACTED]) through the end of treatment, which is open-ended and subject to Sponsor discretion. Day 1 of Part 2 is coincident with the [REDACTED] visit of Part 1; participants who are eligible and enter Part 2 will receive their first LTE dose at this visit.
- LTE Follow-up Period: [REDACTED] following the EoT visit or [REDACTED] after the decision to terminate Study REC-994-201, whichever is sooner.

An overview of the study design for Part 2 is presented in [Table 2](#).



4.1.1 Screening Period: Part 1

During the Screening Period (approximately [REDACTED]), participants will undergo assessments as described in the Schedule of Assessments ([Appendix 14.1.1](#)) to ensure they meet the Inclusion and Exclusion Criteria of the study. Medical history will be reviewed, including detailed review of the participant's CCM history. In addition, the following assessments will be performed:

- mRS (to assess neurological disability)
- Baseline seizure frequency (assessed by use of a daily e-diary)
- Baseline headache frequency (assessed by use of a daily e-diary)
- MRI to confirm anatomic definition of CCM, identify target lesions (up to 10), and assess baseline imaging endpoints, including evidence of prior hemorrhage.
- A blood sample will be obtained from participants who agree to undergo genotyping. Full genome analysis will be performed with a focus on regions of interest in CCM-associated genes (including but not limited to, KRIT1, CCM2, PDCD10).

4.1.1.1 Rescreening: Part 1

Individual assessments can be repeated once within the designated screening window following discussion and agreement with the Medical Monitor.

For those participants who screen fail, or whose screening period has elapsed, they may rescreen once. All procedures should be repeated except for genotyping. Participants who rescreen will only receive a new screening number if they exceed the screening window and are re-screened in full (e.g., not just retested for a single analyte).

4.1.2 Treatment Period: Part 1

Approximately [REDACTED] participants who have met the Inclusion and Exclusion Criteria for Part 1 will be enrolled in the study.

Participants will be randomized [REDACTED] to receive daily [REDACTED] doses of study drug: REC-994 [REDACTED] or REC-994 [REDACTED] or placebo for the remainder of Part 1 of the study.

Pre- and post-dosing safety monitoring will include vital signs, electrocardiograms (ECGs), physical examination, neurologic evaluation, laboratory assessments and assessment of AEs, and review of concomitant medications. Participants will use a daily e-diary to record dosing, and information about seizures and headaches.

The following assessments will be performed on Day 1 of Part 1 (to establish baseline values for Part 1) and at study visits during the Part 1 Treatment Period (to assess changes from baseline):

- SMSS (to assess baseline participant-reported disease severity)

[REDACTED]

On Study Part 1 Day 1, the Investigator will complete a Clinical Global Impression-Severity (CGI-S) and the participant will complete a Patient Global Impression-Severity (PGI-S) to, respectively, assess the severity of the participant's disease at the time of study entry.

At study visits during the Part 1 Treatment Period, the Investigator will complete a Clinical Global Impression-Improvement (CGI-I) and the participant will complete a Patient Global Impression-Improvement (PGI-I) to assess changes in the severity of the participant's disease following initiation of treatment with study drug.

At [REDACTED], participants will return to the investigative site for follow-up safety and efficacy evaluations. The [REDACTED] Visit will include a follow-up MRI. Blood will be collected on Part 1 Day 1 to evaluate peak REC-994 concentrations, at [REDACTED] for peak and trough REC-994 PK, and at [REDACTED] for extended PK. Participants enrolled under Protocol REC-994-201 Versions 1-3 who underwent extended PK sampling at Day 1 are not required to undergo repeated PK sampling at [REDACTED]. Participants who discontinue from study treatment during the 12-[REDACTED] treatment period will remain on study for regular scheduled assessments ([Appendix 14.1.1](#)).

4.1.3 End of Treatment / Follow-up Period: Part 1

Prior to the Part 1 [REDACTED] End-of-Treatment (EoT) visit, potential participation in the optional Part 2 extension study should be discussed with participants. Participants not participating in Part 2 will discontinue treatment with study drug at the [REDACTED] visit and will return to the investigative site in [REDACTED] for the End-of-Study (EoS) Visit during which follow-up safety and efficacy testing will be conducted. Participants who discontinue from study treatment during the [REDACTED] treatment period in Part 1 will have an Early Termination (ET) visit conducted within [REDACTED] of their last dose of study drug and will be encouraged to remain on the study to complete assessments through [REDACTED], and the follow-up visit ([REDACTED]). For participants who terminate early, an MRI will be conducted if the termination is due to a symptomatic hemorrhage or ≥ 3 months has passed since the last MRI.

Participants who choose to continue into Part 2 and provide signed informed consent will be evaluated for Part 2 eligibility at the Part 1 [REDACTED] visit. For these participants, signed consent should be obtained prior to performing any Part 1 [REDACTED] assessments. At the [REDACTED] Part 1 End-of-Treatment visit, safety monitoring will include vital signs, ECGs, physical examination, neurologic evaluation, laboratory assessments, assessment of AEs, and review of concomitant medications. Final efficacy assessments for Part 1 will also be performed, including MRI. For details, see the SOA/Part 1 ([Appendix 14.1.1](#)).

Following completion of this visit, participants who are eligible for Part 2 will receive REC-994 at doses of either [REDACTED] or [REDACTED] beginning on LTE Day 1 as described below for Part 2.

4.1.4 LTE Eligibility Visit (LTE Day 1): Part 2

Eligibility for Part 2 will be determined during the Part 1 [REDACTED] visit (or as soon as possible thereafter [up to 14 days]). Participants who consent and are eligible for Part 2 will be dosed on the same day (i.e., this will become LTE Day 1). Assessments performed at the Part 1 [REDACTED] visit will serve as the baseline assessments for Part 2 except as noted in the SOA/Part 2 ([Appendix 14.1.2](#)). Participants who do not consent and/or initiate dosing in Part 2 within 14 days of the Part 1 [REDACTED] visit will not be eligible for participation in the LTE unless approved by the Sponsor.

4.1.5 LTE Treatment Period: Part 2

Participants will receive [REDACTED] doses of REC-994 from [REDACTED] (LTE Day 1) through the end of study treatment (as determined by the Sponsor).

Treatment in Part 2:

- Participants randomized to receive REC-994 in Part 1 will continue to receive the same dose they received in Part 1 during Part 2.
- Participants randomized to receive placebo in Part 1 will be randomized [REDACTED] to receive [REDACTED] [REDACTED] doses of either REC-994 [REDACTED] or REC-994 [REDACTED] during Part 2.

During Part 2, dose decreases for tolerability may occur from REC-994 [REDACTED] to [REDACTED]. Participants who cannot tolerate REC-994 [REDACTED] will be discontinued from treatment. Thus, participants who are not able to tolerate study drug will be unblinded to treatment and those who are receiving [REDACTED] will be discontinued from treatment but will remain on study for regular

scheduled assessments as described in Section 4.1.6. Once the primary analysis in Part 1 of the study has been completed, Part 2 participants may be switched to a single, unblinded dose level for the remainder of the study at the discretion of the Sponsor. Doses will be switched at the participant's next scheduled visit upon approval by the Sponsor.

At [REDACTED], participants will return to the investigative site for follow-up safety and efficacy evaluations.

Participants will continue to use a daily e-diary to record dosing and information about seizures and headaches. Safety monitoring and efficacy assessments will be performed as outlined in the SOA/Part 2 ([Appendix 14.1.2](#)); MRIs will be performed at the [REDACTED] visits and also for subsequent visits occurring [REDACTED].

4.1.6 LTE Follow-up Period: Part 2

Participants who complete Part 2 will return to the investigative site [REDACTED] after receiving the last dose of study drug for a Part 2 End-of-Study visit during which follow-up safety and efficacy testing will be conducted. The Part 2 EoS visit will occur within [REDACTED] following the Part 2 EoT visit or [REDACTED] after the decision to terminate Study REC-994-201, whichever is sooner. For participants who terminate Part 2 early for any reason, a Part 2 Early Termination visit will be conducted as soon as possible, and participants will be asked to return [REDACTED] later for an End-of-Study/Follow-up visit. For participants who terminate early, an MRI will be conducted if the termination is due to a symptomatic hemorrhage or if ≥ 3 months has passed since the last MRI.

4.2 Treatments

4.2.1 Treatment Assignment: Part 1

Participants will be randomized [REDACTED] to study drug during Part 1 of the study:

- REC-994 [REDACTED] [dosed as: REC-994 [REDACTED] + matching placebo [REDACTED]] or
- REC-994 [REDACTED] [dosed as: REC-994 [REDACTED]] or
- Placebo [REDACTED] [dosed as: matching placebo [REDACTED]].

4.2.2 Treatment Assignment: Part 2

Participants who are eligible for Part 2 will receive daily dosing of REC-994 as follows:

- Participants randomized to receive REC-994 in Part 1 will continue to receive the same dose they received in Part 1 during Part 2.
- Participants randomized to receive placebo in Part 1 will be randomized [REDACTED] to receive [REDACTED] doses of either REC-994 [REDACTED] or REC-994 [REDACTED] during Part 2.

During Part 2, dose decreases for tolerability may occur from REC-994 [REDACTED] to [REDACTED], and all Part 2 participants may be switched to a single, unblinded dose level after completion of Part 1. See [Section 4.1.5](#) for details of dose decreases and treatment switch in Part 2.

5 General Statistical Considerations

All data collected from Part 1 of the study as well as the safety and MRI data collected from LTE Part 2 will constitute the primary analysis of the study. This primary analysis will be performed after the database lock of Part 1 (after the last participant enrolled in Part 1 has completed the last study visit of Part 1). This SAP describes the details and scope for the primary analysis.

Two separate analyses will be provided for the primary analysis.

- Part 1 analysis - includes data collected from Part 1 of the study:
 - For participants not participating in LTE Part 2, use
 - all adverse event (AE) data with event start date up to [REDACTED] after [REDACTED] EoT;
 - all efficacy and other safety data collected up to scheduled [REDACTED] EoS.
 - For participants continuing in LTE Part 2, use
 - all AE data with event start date prior to the LTE Day 1 visit;
 - all efficacy and other safety data collected up to scheduled [REDACTED] EoT.
- Combined Part 1 and Part 2 analysis – includes MRI and safety data collected from Part 1 and LTE Part 2:
 - For participants not participating in LTE Part 2, use same data as described for the Part 1 analysis above.
 - For participants continuing in LTE Part 2, use
 - all safety data collected up to [REDACTED] after the last dose in LTE Part 2;
 - all MRI data collected from scheduled visits in Part 1 and LTE Part 2.

All data collected from LTE Part 2 will be analyzed separately at final database lock after the last participant has completed the last study visit of Part 2. The details for analyzing Part 2 data will be described separately in an LTE Part 2 SAP.

Unless otherwise specified, for the Part 1 analysis, participant characteristics, disposition, demographics data, prior and concomitant medication, medical history, and the safety summary statistics will be presented by individual treatment groups (REC-994 [REDACTED], REC-994 [REDACTED], Placebo), REC-994 combined (pooled) group, and overall. Drug exposure and all efficacy analyses will be presented by treatment groups and REC-994 pooled group. Efficacy summary tables will also include a column for the overall group. Drug compliance data will be presented by individual treatment groups (REC-994 [REDACTED], REC-994 [REDACTED], Placebo).

For the combined Part 1 and Part 2 analysis, unless otherwise specified, participant disposition and the safety summary statistics will be presented by REC-994 [REDACTED], REC-994 [REDACTED], placebo re-randomized to REC-994 [REDACTED], placebo re-randomized to REC-994 [REDACTED], and overall. Summary of MRI data will be presented by REC-994 [REDACTED], REC-994 [REDACTED], placebo re-randomized to REC-994 [REDACTED], and placebo re-randomized to REC-994 [REDACTED].

All safety analyses will be based on the Safety Analysis Set (SS) by actual treatment received. Baseline characteristics, demographics, and all efficacy analyses will be based on the Full analysis

set (FAS) by randomized treatment group. All summarized data will be listed, unless otherwise specified.

Continuous, quantitative, variable summaries will include the number of participants (n) with non-missing values, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum, unless otherwise specified.

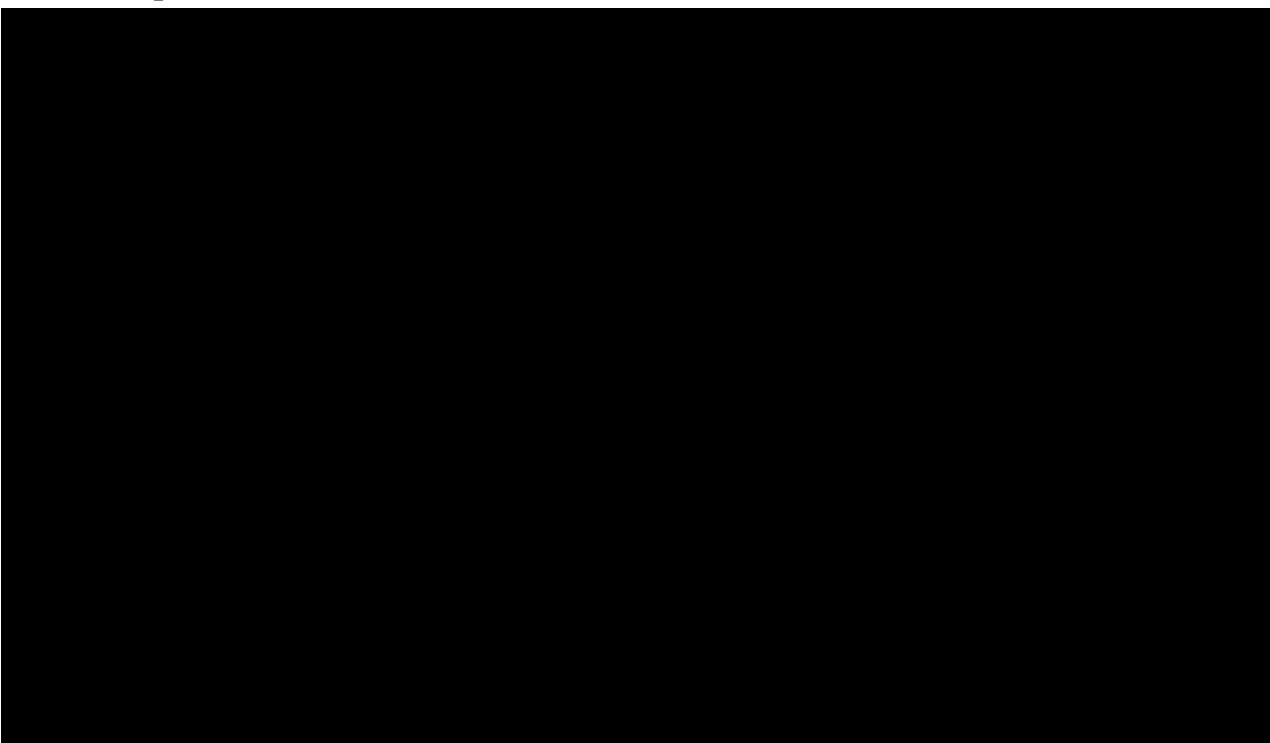
Categorical and qualitative variable summaries will include the frequency and percentage of participants in the particular category. The denominator for all percentages will be the number of participants in that treatment group within the analysis set of interest, unless otherwise specified.

All analyses will be performed using SAS® Software version 9.4 or later.

For AEs, medical history and concomitant medications reported on a per-participant basis, the denominator for the percentage calculation will be the number of participants at risk in each treatment group. A participant will be considered at risk if the participant is in the analysis set and in the subgroup of interest.

Confidence intervals will be presented as 2-sided 95% CIs, to one level of precision greater than the data reported, unless otherwise stated. All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001 it will be displayed as “< 0.0001”.

5.1 Sample Size



5.2 Randomization and Blinding

On Study Day 1, eligible participants will be randomized [REDACTED] to receive [REDACTED] dosing with study drug: REC-994 [REDACTED] ([REDACTED] REC-994 [REDACTED] and [REDACTED] matching placebo) or REC-

994 [REDACTED] ([REDACTED] REC-994 [REDACTED]) or placebo ([REDACTED] matching placebo [REDACTED]). Participants and investigational site staff will remain blinded to treatment assignment for both Part 1 and Part 2 unless the sponsor decided to switch Part 2 to a single, unblinded dose level based on the primary analyses of Part 1.

- The eligible participants randomized to receive placebo in Part 1 will be automatically re-randomized [REDACTED] by IRT system to receive REC-994 [REDACTED] or [REDACTED] during Part 2, to maintain the blind on treatment assignment until primary analysis.
- Participants randomized to receive REC-994 in Part 1 will continue to receive the same dose they received in Part 1 during Part 2.

During the study, if there is a medical emergency where knowledge of IP is critical to the subject's management, the blind may be broken by the investigator.

Once the primary analysis in Part 1 of the study has been completed, Part 2 participants may be switched to a single, unblinded dose level for the remainder of the study at the discretion of the Sponsor. Doses will be switched at the participant's next scheduled visit upon approval by the Sponsor.

5.3 Analysis Sets

All analysis sets will be defined separately for the primary analysis and LTE Part 2 analysis. The analysis sets defined in Section 5.3 is for primary analysis only. The analysis sets for Part 2 analyses will be defined in a separate SAP for LTE Part 2.

5.3.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all participants randomly assigned to a treatment group on Day 1 of Part 1 and have at least one efficacy assessment after randomization in Part 1. In this set, treatment will be assigned based on the treatment to which participants are randomized, regardless of which treatment they actually received. The FAS will be used for all demographics, baseline characteristics, and efficacy analysis for Part 1 as well as the MRI data for the combined Part 1 and Part 2 analysis.

5.3.2 Safety Analysis Set

The Safety analysis set (SS), as treated, will include all participants randomized on Day 1 of Part 1 who have received at least 1 dose of REC-994 or placebo, irrespective of randomization. In this set, treatment will be assigned based on the actual treatment participants receive. The SS will be used for prior and concomitant medication, extent of exposure, doses taken/missed, drug compliance and safety analysis for Part 1 as well as safety analysis for the combined Part 1 and Part 2 data.

5.3.3 Per Protocol Analysis Set

The Per protocol analysis set (PPS) will include all participants randomized on Day 1 of Part 1 meeting the study eligibility criteria, having at least one efficacy assessment after randomization, and completing the study without a major protocol deviation (MPD) that impacts the efficacy evaluation. In this set, treatment will be assigned based on the treatment to which participants are randomized.

5.3.4 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKS) will include participants who have received at least 1 dose of study drug and have at least one post baseline evaluable PK sample. Where participants experience issues which may affect exposure to study drug (eg. emesis, dosing errors, etc.), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK population on a case-by-case basis. All participants excluded from the PK population will be documented in the data listings.

5.3.5

5.4 General Data Handling Strategy

The data handling strategy for definition of study day and baseline, missing data, unscheduled visits, and analysis interval defined in Section 5.4 is for primary analysis only.

The data handling strategy for Part 2 data will be described separately in an LTE Part 2 SAP.

5.4.1 Definition of Study Day

Study day is defined as the number of days from the date of first dose of study drug in Part 1. Day 1 of Part 1 is the date of first dose. For assessments or events on or after the date of first dose, study day is calculated as the date of interest minus date of first dose plus 1 day. For assessments/events before the date of first dose, study day is calculated as the date of interest minus date of first dose.

The date of last dose for a participant is the actual last dose date if available.

For the Part 1 analysis, the date of last dose is the last day a participant received study drug during Part 1 and is recorded on the EoT page in the eCRF. For participants who do not yet have a Part 1 EoT page completed either because they are ongoing in Part 1 or they discontinued prior to [REDACTED] with EoT visit missing, the date of last dose is the latest dose date recorded in the eDiary. For participants who have completed Part 1 and are continuing on in LTE Part 2, the last dose date in Part 1 is the latest treatment date recorded in the eDiary that is prior to the first dose in the Part 2 LTE period.

For the combined Part 1 and Part 2 analysis, the date of the last dose for ongoing participants in LTE Part 2 is the latest treatment date recorded in the eDiary. For participants who have completed LTE Part 2 or terminated early, the last dose date is recorded on the Part 2 LTE EoT page in the eCRF. If the Part 2 LTE EoT visit is missing or if the last dose date is missing on the LTE Part 2 EoT page, then the last dose date is the latest treatment date recorded in the eDiary. For participants not participating in LTE Part 2, the above definition for the Part 1 analysis will be used.

5.4.2 Definition of Baseline

For efficacy assessments not assessed during screening period (██████ SMSS, ██████, ██████, CGI-S, and PGI-S), the assessment at Day 1 of Part 1 will be defined as the baseline value.

The baseline of seizure and headache frequencies will be based on non-missing e-Diary data collected during the Screening Period and standardized to [REDACTED]. Please refer to [Section 5.4.4](#) for further details.

For safety and MRI data, data collected from Part 1 [REDACTED] visit will serve as baseline value for Part 2.

All safety data will be evaluated as reported and no imputation of missing values will be done unless otherwise stated. [REDACTED]

Change from baseline at [REDACTED] in total lesion volume and total hemosiderin ring size:
For treatment comparison using Wilcoxon Rank Sum test, Last Observation Carry Forward (LOCF) will be implemented for any missing post-baseline observations.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, then assume the date of first dose of study drug;
- UK-UKN-YYYY: If the year is prior to the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, then assume the date of first dose of study drug;
- UK-UKN- UNKN: Assume date of first dose of study drug.

If the imputed start date is after the non-missing end date, the start date will be imputed to the end date.

Missing stop dates for concomitant medications data will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- UK-UKN-YYYY: Assume 31-DEC-YYYY;
- UK-UKN- UNKN: Assume ongoing and leave it missing.

TEAEs:

For the purpose of inclusion in TEAE tables, incomplete AE start and end dates will be imputed separately for the Part 1 analysis and combined Part 1 and Part 2 analysis as follows:

Part 1 analysis:

Incomplete onset dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the date of first dose, assume 01-MMM-YYYY. If the month and year are the same as the month and year for the date of first dose, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the month and year are the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.
- DD-UNK-YYYY/UK-UNK-YYYY: If the year is different from the year of the date of first dose, assume 01-JAN-YYYY of the collected year. If the year is the same as the date of first dose year, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the year is the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.

Incomplete end dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UNK-YYYY/UK-UNK-YYYY: Assume 31-DEC-YYYY.

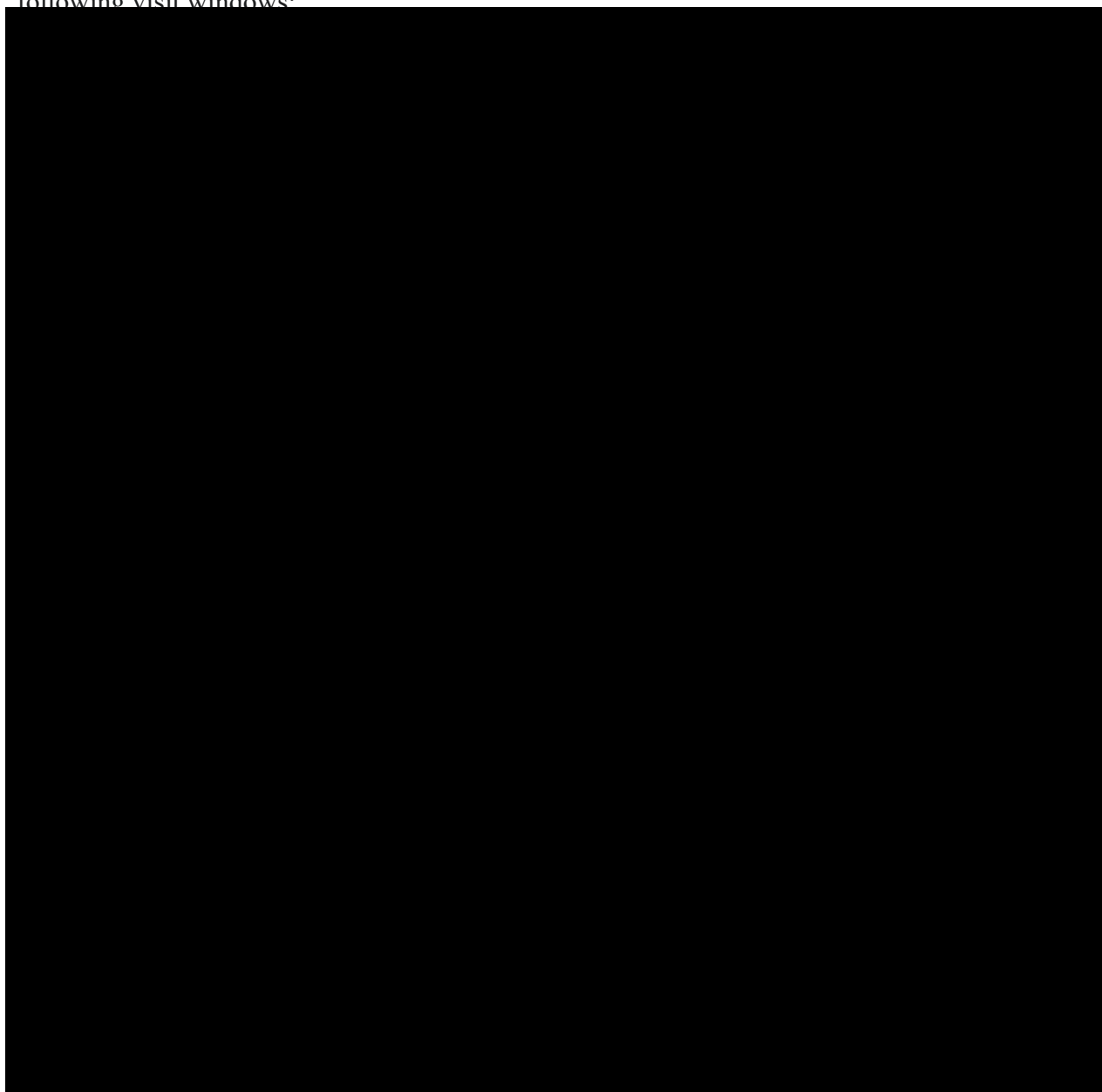
The missing onset dates will be imputed as the date of first dose of study drug. The missing end date will be imputed as the participant's last visit date.

Combined Part 1 and Part 2 analysis:

For participants not participating in LTE Part 2 or participants in "REC-994 [REDACTED] to REC-994 [REDACTED]" and "REC-994 [REDACTED] to REC-994 [REDACTED]" treatment sequences, the incomplete / missing AE onset / end dates will be imputed the same as Part 1 analysis.

For participants in "placebo to REC-994 [REDACTED]" and "placebo to REC-994 [REDACTED]" treatment sequences, the incomplete / missing AE onset / end dates will be imputed by using LTE Day 1 as the date of first dose for imputation rules described for the Part 1 analysis above.

Efficacy data and safety data (i.e., clinical laboratory tests, vital signs, ECG, and physical, neurological, and focused physical examinations) collected at unscheduled visits or early termination visits post baseline, will be mapped to analysis visit window, according to the following visit windows:



█ [REDACTED]

5.4.4 Analysis Interval

For the diary data used to produce the seizure and headache endpoints, the analysis intervals specified in **Table 3** will be used to collapse the daily data into [REDACTED] intervals.

[REDACTED]

6 Subject Disposition

6.1 Disposition

All participants who provide informed consent for Part 1 of the study will be included in the summary. Participant disposition data will be summarized separately in Part 1 analysis and combined Part 1 and Part 2 analysis for all enrolled participants.

For the Part 1 analysis, the number of participants screened in Part 1, number of screen failures in Part 1, number of randomized participants in Part 1, number of participants who completed the Part 1 study treatment/study, number of participants who discontinued the Part 1 study treatment/study, classified by primary reason for discontinuation, will be summarized descriptively by frequency and percentage, as applicable. Percentages will be based on the number of participants randomized in Part 1.

For the combined Part 1 and Part 2 analysis, the number of participants who were randomized to REC-994 (██████ or ██████) in either Part 1 or LTE Part 2, number of participants who completed the Part 1 study treatment/study, number of participants who participated in the LTE Part 2, number of participants who discontinued the Part 1/Part 2 study treatment/study, classified by primary reason for discontinuation, will be summarized descriptively by frequency and percentage, as applicable. Percentages for the Part 1 summary will be based on the number of participants randomized to REC-994 (██████ or ██████) in either Part 1 or LTE Part 2. Percentages for the Part 2 summary will be based on the number of participants continuing in Part 2.

Reasons for study treatment discontinuation include: withdrew consent, protocol deviation, adverse event, death, disease progression or lack of efficacy, lost to follow-up, withdrawn due to PI, withdrawn due to sponsor or sponsor terminates, pregnancy, non-compliance, clinically significant intracerebral hemorrhage, other.

Reasons for study discontinuation include: withdrew consent, protocol deviation, adverse event, death, disease progression or lack of efficacy, lost to follow-up, withdrawn due to PI, withdrawn due to sponsor or sponsor terminates, pregnancy, non-compliance, clinically significant intracerebral hemorrhage, other.

A disposition listing will be prepared for Part 1 analysis.

6.2 Protocol Deviations

All protocol deviations (both major and non-major) will be entered and tracked within the PPD Clinical Trial Management System (CTMS) by the study team throughout the conduct of the study in accordance with the Study Deviation Rules Document. The Study Deviation Rules Document contains all potential protocol deviations, classified by CTMS activity subtype (also referred to as protocol deviation category), and whether the deviation is major or not. A major deviation is any deviation that affects primary efficacy and safety assessments (as applicable), the safety or mental integrity of a participant, or the scientific value of the study.

Data will be reviewed prior to closure of the database to ensure all major deviations are captured and properly categorized.

Major protocol deviations (MPD) will be summarized by category and deviation code for FAS by randomized treatment groups in Part 1 analysis only.

A by-participant listing will be provided for the MPD.

7 Demographics and Baseline Characteristics

7.1 Demographics

Descriptively summary of demographics will be provided for FAS in Part 1 analysis only. A by-participant data listing will be provided. The following characteristics will be summarized as continuous variables:

- Age at time of enrollment (years)
- Baseline body weight (kg)
- Baseline height (cm)
- Baseline body mass index (BMI, kg/m²).

The following characteristics will be summarized as categorical variables:

- Age (years): < 65, ≥ 65
- Sex
- Race
- Ethnicity

7.2 Medical History

The summary of medical history, CCM medical history, and past CCM history will be provided for FAS in Part 1 analysis only.

7.2.1 General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 27.0 or higher, depending on when the Part 1 study is completed). The number and percentage of participants with medical history results will be summarized by system organ class and preferred term. A by-participant listing of medical history, including start date, end date and condition and event of medical history will be generated.

7.2.2 CCM Medical History

CCM medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 27.0 or higher, depending on when the Part 1 study is completed). The number and percentage of participants with CCM medical history results will be summarized by system organ class and preferred term. A by-participant listing of CCM medical history, including start date, end date and condition and event of CCM history will be generated.

7.2.3 Past Cerebral Cavernous Malformation (CCM) History

Past cerebral cavernous malformation history will be summarized descriptively. A by-participant listing, including age at diagnosis, symptoms/findings triggered testing that led to the CCM diagnosis, information on: seizures, disease related headaches, speech abnormalities/abnormal body movements, stroke, brain hemorrhage (age event started, estimated number of times symptoms occurred), diagnostic information: EEG, brain scan, MRI, CT/CAT scan (age at time of most recent test) and clinical trial information, other than this one (how long ago participant completed participation) will be generated.

7.3 Genotyping

Genotyping results at Screening, if available, will be provided in a by-participant listing.

8

8.1

8.1.1

8.1.2

ns

8.2

8.2.1

8.2.1.1

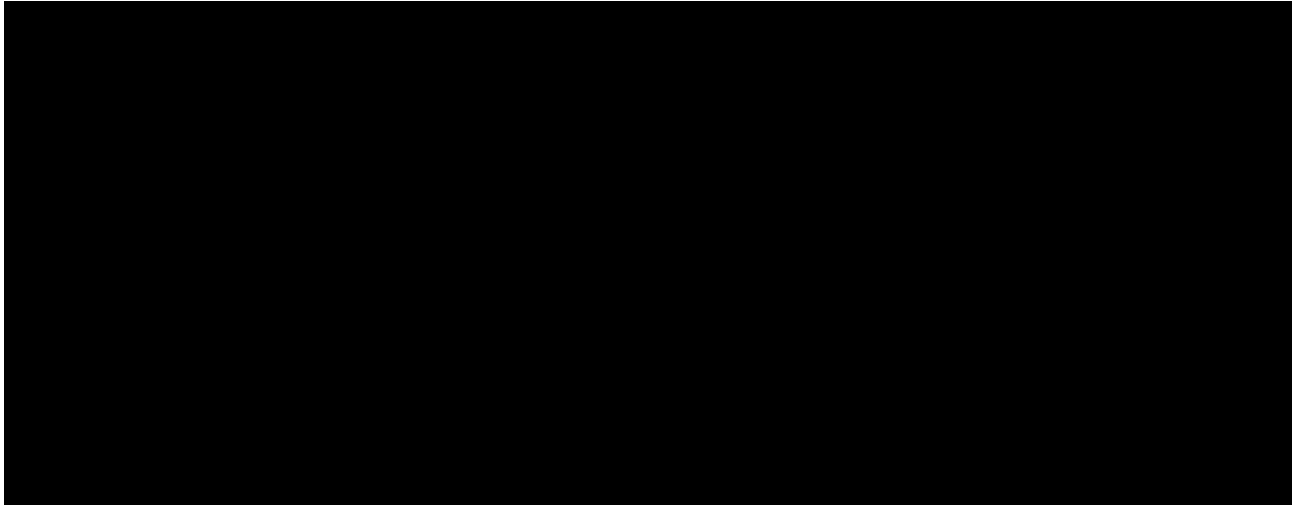
[REDACTED]

8.2.1.2

[REDACTED]

8.2.2

[REDACTED]



9 Efficacy Analysis

9.1 General Consideration

The efficacy endpoints will be summarized and analyzed for Part 1 data only except for MRI related endpoints.

9.2 Primary Efficacy Analysis

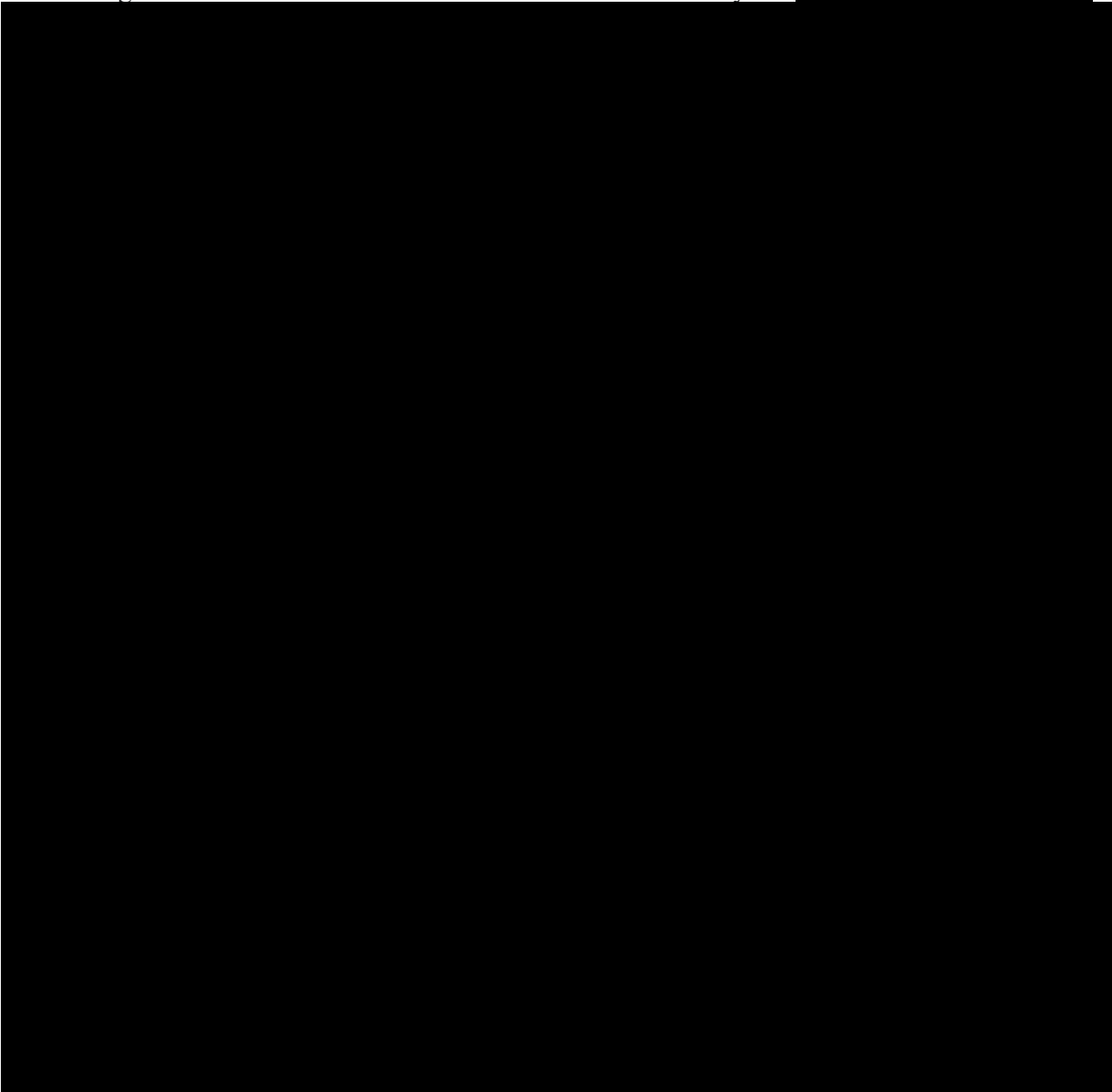
There are no primary efficacy endpoints to be assessed.

9.3 Secondary Efficacy Analysis

9.3.1 SymptoMScreen Score (SMSS)

The SMSS questionnaire is a self-assessment tool ([Green, 2017](#); [Fitzgerald 2019](#); [Kister, 2020](#)) originally developed for measuring symptom severity in participants with multiple sclerosis. It assesses 12 critical neurologic questions that are also commonly affected in participants with CCM: mobility, hand function/dexterity, spasticity and stiffness, pain, sensory symptoms, bladder control, fatigue, vision, dizziness, cognition, depression and anxiety. The questionnaire consists of 12 items assessed on a seven-point Likert scale ranging from 0 (not at all affected) to 6 (total limitation). The total score ranges from 0 to 72, with higher scores indicating more severe symptom endorsement. See [Appendix 14.2](#) for the detail of the SMSS questionnaire.

The changes from baseline on SMSS total score will be analyzed



9.3.2 modified Rankin Scale (mRS) Score

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered an acute stroke. The scale runs from 0-5, corresponding to no symptoms at all (0) to severe (5). ([Van Swieten, 1998](#)) Assessments will be made at Screening and throughout the treatment period. See [Appendix 14.3](#) for the calculation detail of mRS scores.

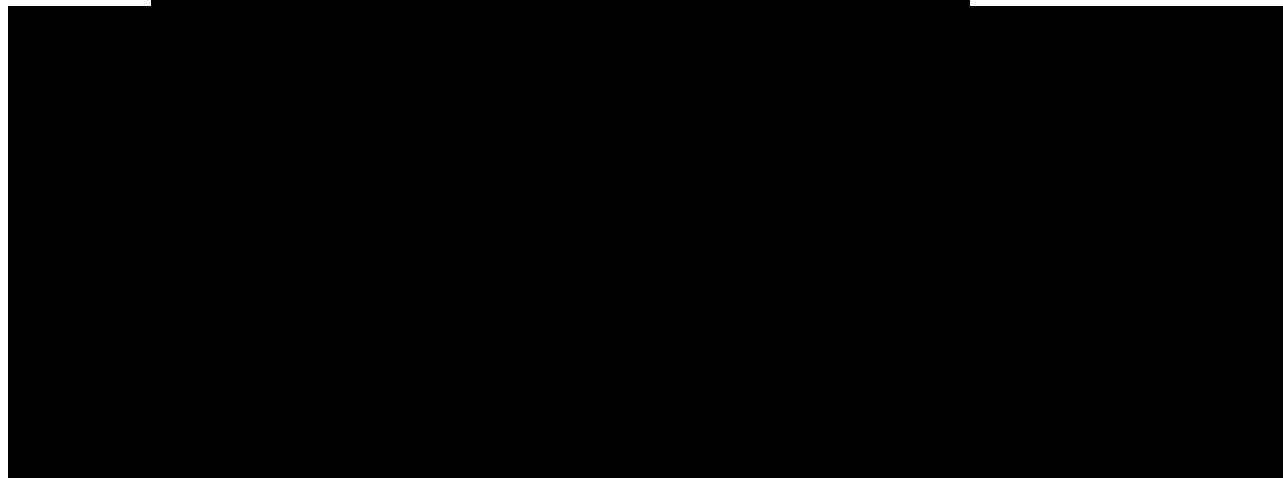


Categorical summary of mRS score at each scheduled visit will be provided.

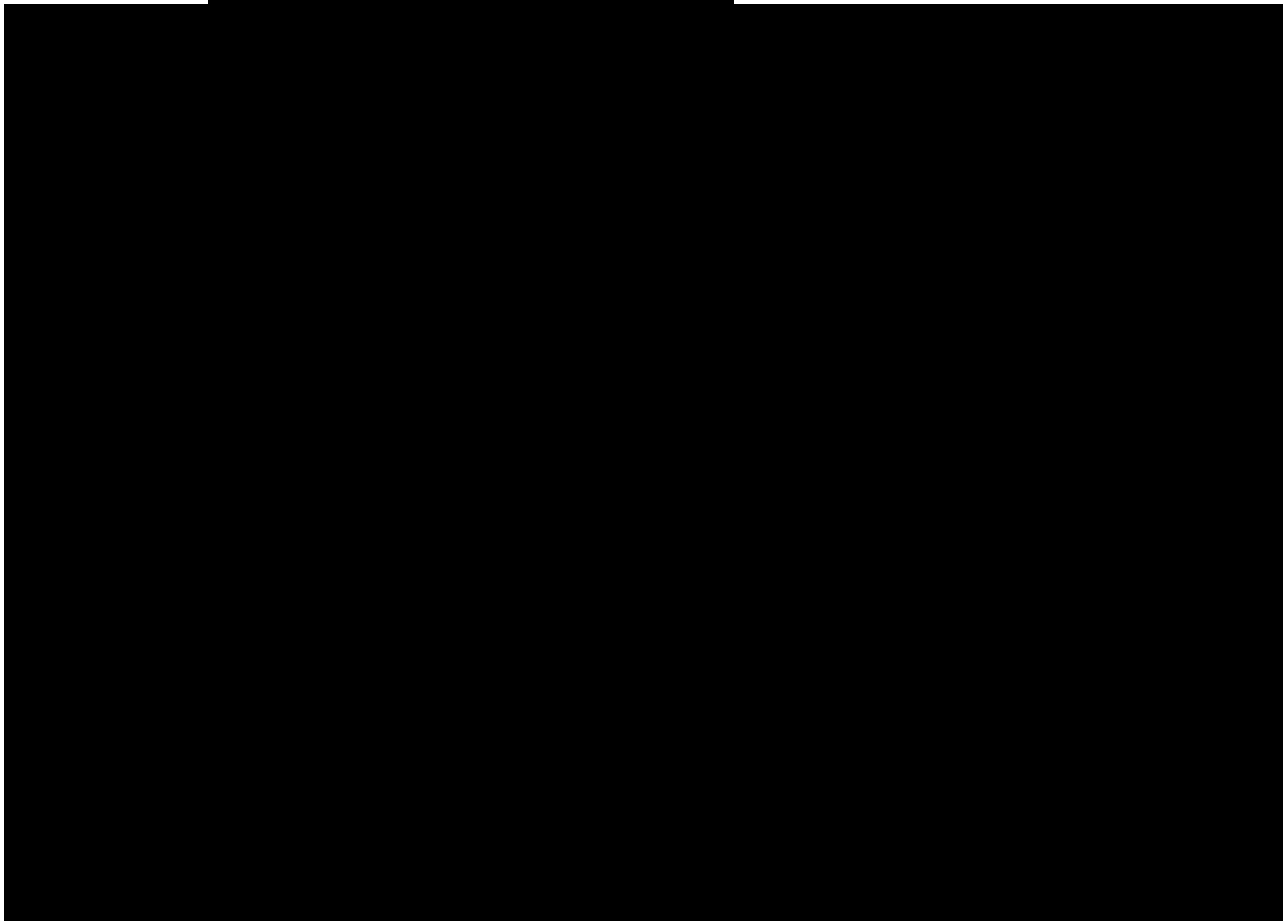
A stacked bar chart showing the proportion of participants with mRS scores of 0, 1, 2, 3, and ≥ 4 for each scheduled visit will be presented by randomized treatment group and REC-994 pooled group.

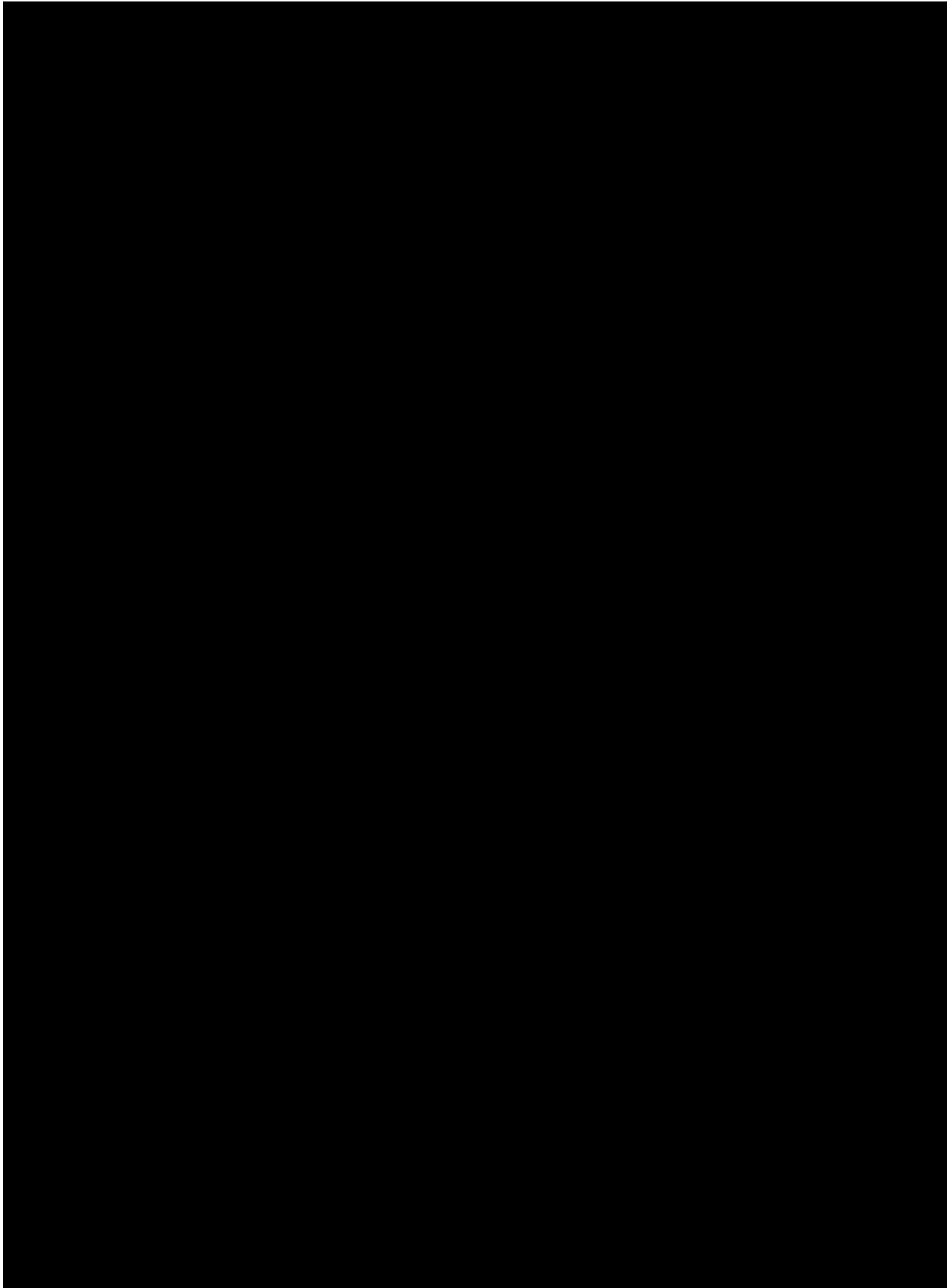
A by-participant listing will be provided.

9.3.3



9.3.3.1





[REDACTED]

9.3.3.2

[REDACTED]

9.3.3.3

[REDACTED]

9.3.4 Clinical/Patient Global Impression (CGI/PGI) Scales

The measure comprises 2 companion components: CGI/PGI-Severity (CGI-S and PGI-S) that will be assessed at baseline (Part 1 Day 1) and CGI/PGI-Improvement (CGI-I and PGI-I) that will be assessed by scheduled visits during the study. The CGI-S/CGI-I scores will be assessed by the investigator and the PGI-S/PGI-I scores will be assessed by the participants.

The CGI-S assessed at baseline will be graded to a 1 to 7 scale: 1 = Normal, not at all ill; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients.

The investigator will provide an estimation of the change in the participant's overall status following initiation of study drug on Part 1 Study Day 1. CGI-I will be recorded at each subsequent investigative site visit and will be graded to a 1 to 7 scale: 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, 7 = Very much worse.

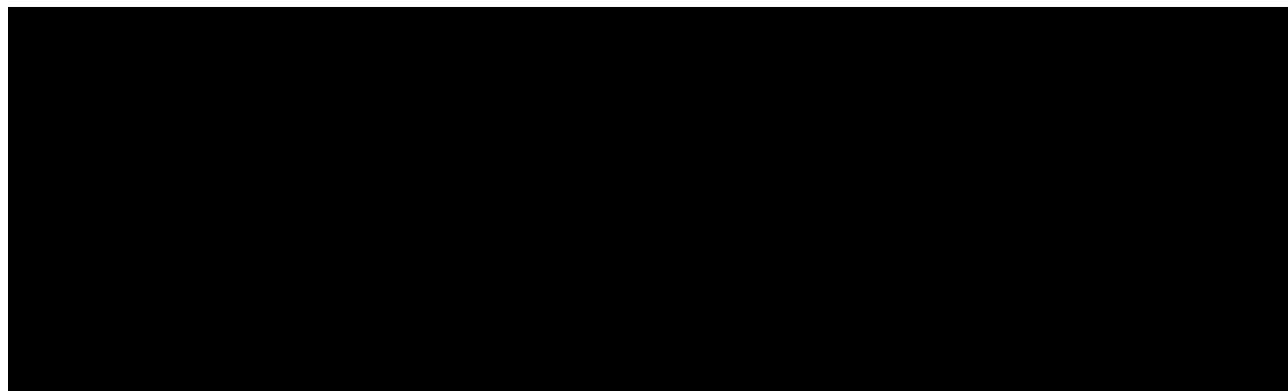
The PGI-S assessed at baseline will be graded to a 1 to 7 scale: 1 = Not present, 2 = Very mild, 3 = Mild, 4 = Moderate, 5 = Moderately severe, 6 = Severe, 7 = Extremely severe.

PGI-I will be recorded at each subsequent visit and graded to a 1 to 7 scale: 1 = Very much better, 2 = Much better, 3 = Somewhat better, 4 = No change, 5 = Somewhat worse, 6 = Much worse, 7 = Very much worse. See Appendix 14.5 for detail of CGI-S/CGI-I and PGI-S/PGI-I questionnaire.

CGI-I scale scores will also be categorized as: "Improved" = Very much improved + Much improved + Minimally improved, "No Change" = No change, and "Worse" = Minimally worse + Much worse + Very much worse and summarized by visit.

PGI-I scale scores will also be categorized as: “Improved” = Very much better + Much better + Somewhat better, “No change” = No change, and “Worse” = Somewhat worse + Much worse + Very much worse and summarized by visit.

The CGI-S/PGI-S scale score assessed at baseline will be summarized descriptively by randomized treatment groups and REC-994 pooled group.



Categorical summary of CGI-S/CGI-I and PGI-S/PGI-I scale score at each scheduled visit will be provided.

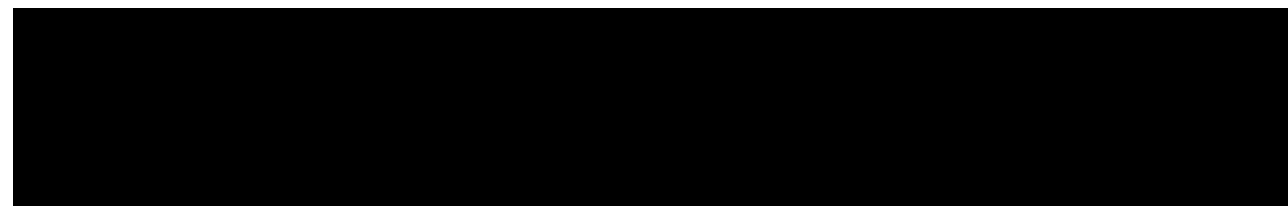
A cross tabulation with number of participants at each CGI-S/PGI-S baseline score level and each corresponding CGI-I/PGI-I post-baseline score level, will be presented by scheduled visits and repeated for each randomized treatment group and REC-994 pooled group.

A stacked bar chart will be provided for the proportions of participants in each improvement category (improved, no change, and worse) over scheduled visits for randomized treatment groups and REC-994 pooled group.

9.3.5 Seizure Frequency

All participants will record the occurrence of seizures in daily e-Diary regardless of the occurrence of any seizure events or not, during the screening period and throughout the study. Participants with a history of seizures prior to entering the screening period of the study will provide an estimate of seizure frequency over the month prior to screening.

For the analysis of seizure frequency, the baseline total number of seizure count during the screening period (up to 60 days from eDiary consent date to the day prior to Part 1 Day 1) will be normalized to a 30-day seizure frequency rate by summing the number of observed seizures during screening, dividing by the days with reported seizure diary data during screening, and multiplying by 30.



The planned number of daily entry during baseline will be derived as the date of Part 1 Day 1 – eDiary consent date. For each post-baseline analysis interval (i.e., [REDACTED]), the planned number of daily entry is 30. For participants continuing in the LTE Part 2, the planned number of daily entry for [REDACTED] is the date of LTE Day 1 – Day 331. For participants who discontinue the study early during Part 1, the planned number of daily entry for the last month is study discontinued date – the start date of the last month + 1.

The compliance rate for daily entry (%) during each analysis interval will be derived as actual number of daily entry in the analysis interval divided by planned number of daily entry in the analysis interval, and multiplying by 100.

The monthly seizure frequency rate will be derived by summing the number of observed seizures during an analysis interval (see definition in 5.4.4), dividing by the days with reported seizure diary data in the analysis interval, and multiplying by 30. If there is a consecutive 7-day missing seizure diary data or less than 15 days of seizure diary data entry during a post-baseline analysis interval, the monthly seizure rate will be treated as missing.

The planned number of daily entry, actual number of daily entry, compliance rate of daily entry (%), observed monthly seizure frequency rate and change from baseline in monthly frequency rate will be summarized descriptively by randomized treatment groups and REC-994 pooled group for each analysis interval. The number and percentage of participants excluded from the monthly seizure frequency rate calculation will be summarized for each post-baseline analysis interval by the reason for exclusion (i.e., consecutive 7-day missing seizure diary data or less than 15 days of seizure diary data entry during a post-baseline analysis interval).

A plot of mean ($\pm$ SD) and change from baseline ($\pm$ SD) on monthly seizure frequency rate will be provided by randomized treatment groups and REC-994 pooled group.

9.3.6 Headache Frequency

All participants will record the occurrence of headaches in daily e-Dairy regardless of the occurrence of any headache events or not, during screening period and throughout the study. Participants with a history of headaches prior to entering the screening period of the study will provide an estimate of headache frequency over the month prior to screening.

The analysis of headache frequency will follow the same method as seizure frequency, described in [Section 9.3.5](#).

9.3.7 MRI Assessments of Cerebral Lesions

Magnetic resonance imaging (MRI) will be used to evaluate the number, size and rate of change of cerebral CCM lesions, as well as evidence of hemorrhage. MRIs will be performed at Screening, [REDACTED] Computerized tomography (CT) scans may be used to confirm hemorrhagic events.

MRI endpoints will be summarized and analyzed separately for Part 1 data alone, combined Part 1 and Part 2 data, and Part 2 data alone based on FAS.

9.3.7.1 Symptomatic Cerebral Hemorrhagic Events

Symptomatic cerebral hemorrhagic events will be recorded in the Adverse Event (AE) eCRF page. A review of the AE Preferred Terms (PTs) coded by MedDRA will be performed by qualified individuals to determine the PTs to include in the summary and analysis of symptomatic cerebral hemorrhagic events as described below. The following PT terms are used for symptomatic cerebral hemorrhagic events:

- Brain oedema
- Brain stem haemorrhage
- Cerebral haemorrhage
- Cerebral infarction
- Cerebral microhaemorrhage
- Cerebrovascular accident
- Vasogenic cerebral oedema

Part 1 analysis:

Symptomatic cerebral hemorrhagic events collected from the AE eCRF page will be included in Part 1 analysis if the event start date is on or after the start date of randomized Part 1 study drug (Day 1):

- up to [REDACTED] after the last dose of Part 1 study (see [5.4.1](#) for definition of the last dose date) for participants not participating Part 2 or discontinued during Part 1 of the study.
- prior to LTE Day 1 for participants continuing in LTE Part 2.

The number and percentage of participants with symptomatic cerebral hemorrhagic events onset during Part 1 of the study will be summarized descriptively by treatment groups and REC-994 pooled group.

[REDACTED]

A by-participant listing will be provided for symptomatic cerebral hemorrhagic events onset during Part 1.

Combined Part 1 and Part 2 summary:

Symptomatic cerebral hemorrhagic events with event start date on or after the start date of randomized Part 1 study drug (Day 1) up to [REDACTED] after the last dose of study (see 5.4.1 for definition of the last dose date) will be included in combined Part 1 and Part 2 summary.

For the combined Part 1 and Part 2 summary, the number and percentage of participants with symptomatic cerebral hemorrhagic events onset during the study will be summarized descriptively by REC-994 [REDACTED], REC-994 [REDACTED], placebo re-randomized to REC-994 [REDACTED], and placebo re-randomized to REC-994 [REDACTED].

A by-participant listing will be provided for symptomatic cerebral hemorrhagic events onset during Part 1 and Part 2 of the study.

9.3.7.2 Cerebral anatomy and CCM Lesion (Volume and Hemosiderin Ring Size)

The number of targeted cerebral lesions, corresponding volumetric measurement for each targeted lesion, and corresponding hemosiderin ring size of each target lesion are collected by MRI at [REDACTED] until the end of study.

Part 1 analysis:

Descriptive statistics for the total lesion volume (sum of all target lesions volume), the total hemosiderin ring size (sum of all target lesions hemosiderin ring size) will be provided for observed values, change and percentage change from baseline at each visit in Part 1.

Boxplots with a trend line connecting the median value at each visit will be presented for observed value, change and percentage change from baseline respectively on total lesion volume and total hemosiderin ring size by treatment groups and REC-994 pooled group.

A waterfall plot of change and percentage change from baseline at [REDACTED] for total lesion volume and total hemosiderin ring size will be presented with color differentiation of treatment groups.

The treatment difference in changes from baseline at [REDACTED] of total cerebral lesion volume and total hemosiderin ring size will be assessed by Wilcoxon Rank Sum test using 1-sided Type I error of 0.025. Specifically, each active treatment group and REC-994 pooled group will be compared to placebo group. The p-values will be presented along with Hodges-Lehmann estimates and corresponding 2-sided 95% CI for the difference. For any missing post-baseline data, Last Observation Carry Forward (LOCF) will be implemented.

[REDACTED]

A by-participant listing will be provided for Part 1 MRI data. A by-participant, by-lesion listing will be provided for total lesion volume and total hemosiderin ring size respectively with observed values, change and percentage change from Part 1 baseline (see definition in [Section 5.4.2.1](#)).

Combined Part 1 and Part 2 analysis:

Descriptive statistics (observed value, change and percentage change from baseline) for total lesion volume and total hemosiderin ring size, respectively, will be provided by all scheduled visits in Part 1 and Part 2 using Part 1 baseline value (see definition in [Section 5.4.2.1](#)) for the following treatment groups:

- REC-994 [REDACTED]
- REC-994 [REDACTED]
- Placebo re-randomized to REC-994 [REDACTED]
- Placebo re-randomized to REC-994 [REDACTED]

[REDACTED] similar to SMSS, with the treatment sequences REC-994 [REDACTED] to REC-994 [REDACTED] and [REDACTED] group to REC-994 [REDACTED] included as the treatment effect. The principal comparison will be REC-994 [REDACTED] vs. REC-994 [REDACTED] at all scheduled visits in Part 1 and Part 2.

A by-participant listing will be provided for the combined Part 1 and Part 2 MRI data. A by-participant, by-lesion listing will be provided for total lesion volume and total hemosiderin ring size respectively with observed values, change and percentage change from Part 1 baseline.

Part 2 data alone summary:

Descriptive statistics (observed value, change and percentage change from baseline) for total lesion volume and total hemosiderin ring size will be provided respectively by all scheduled visits in LTE Part 2 using Part 2 baseline value (see definition in [Section 5.4.2.2](#)) for the treatment groups described in combined Part 1 and Part 2 analysis above.

9.4 Other Efficacy Endpoints

9.4.1 [REDACTED]

[REDACTED]

9.4.2

[REDACTED]

10 Safety Analysis

Safety and tolerability will be assessed by adverse events, clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis), 12-lead ECGs, vital sign measurements, physical examinations, neurological examinations, ongoing assessment of AEs, and review of concomitant medications. Any events of intracerebral hemorrhage (ICH), whether or not they are symptomatic, will be recorded as an AE.

Safety data will be summarized separately in Part 1 analysis and combined Part 1 and Part 2 analysis by treatment groups (described in Section 5) for SS. Inclusion criteria for safety data has been described in Section 5.

For Part 1 safety analysis, the baseline is defined as the last available assessment prior to the first dose of the study treatment. (see Part 1 baseline definition in 5.4.2.1)

For Part 2 safety analysis, the baseline is defined separately for different treatment sequences, as:

- For "REC-994 [REDACTED] to REC-994 [REDACTED]" and "REC-994 [REDACTED] to REC-994 [REDACTED]" treatment sequences, the Part 1 baseline (see definition in Section 5.4.2.1) will be used.
- For the "placebo to REC-994 [REDACTED] or [REDACTED]" treatment sequences, Part 2 baseline (see definition in Section 5.4.2.2) will be used.

AEs will be summarized by treatment groups in terms of the number and percentage of individuals with a particular adverse event and the total number of such events in each treatment arm. AEs will be coded in accordance with MedDRA in terms of lowest level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT) and system organ class (SOC). Laboratory data, physical examination, vital signs, and electrocardiogram data will be summarized descriptively by treatment groups over time, including displays of change from baseline, as applicable.

10.1 Adverse Events

Adverse event (AE) verbatim terms will be coded into a MedDRA term and classified by System Organ Class (SOC) and Preferred Term (PT) for all applicable summaries (see Section 10.1.1). All TEAEs, treatment-related TEAEs, serious TEAEs and TEAEs of special interest (AESI) will be summarized by PT alone. The MedDRA version 27.0 or higher will be used, depending on when the Part 1 study is completed. Results will be displayed in order by Common Terminology Criteria for Adverse Events (CTCAE) Grade (if applicable) then in decreasing frequency by SOC in the total group and in decreasing frequency by PT (within each SOC) in the total group, and then in REC-994 pooled, REC-994 [REDACTED], REC-994 [REDACTED], and placebo treatment groups.

Part 1 analysis:

Treatment-emergent adverse events (TEAEs) are defined as AEs with a start date on or after the start date of randomized Part 1 study drug (Day 1) or if a pre-existing condition worsens in severity or becomes serious, after receiving the first dose of study drug:

- up to [REDACTED] after the last dose of Part 1 study for participants not participating in LTE Part 2 or discontinued during Part 1 of the study;

- prior to LTE Day 1 for participants continuing in LTE Part 2.

Combined Part 1 and Part 2 analysis:

TEAEs have the same definition as Part 1 analysis for participants not participating in LTE Part 2.

For participants in treatment sequences “REC-994 [REDACTED] to REC-994 [REDACTED]” and “REC-994 [REDACTED] to REC-994 [REDACTED]”, TEAEs are defined as AEs with a start date on or after the start date of randomized Part 1 study drug (Day 1) or if a pre-existing condition worsens in severity or becomes serious, after receiving the first dose of study drug, up to [REDACTED] after the last dose of LTE Part 2 study.

For participants in treatment sequences “placebo to REC-994 [REDACTED]” and “placebo to REC-994 [REDACTED]” TEAEs are defined as AEs with a start date on or after the LTE Day 1 or if a pre-existing condition worsens in severity or becomes serious, after receiving the first dose of study drug in LTE Part 2, up to [REDACTED] after the last dose of Part 2 study. See [Section 5.4.1](#) for the date of last dose definition.

Where dates are missing or partially missing, an AE will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE is not a TEAE. See [Section 5.4.3](#) for missing/incomplete date imputation rules.

10.1.1 Incidence of Adverse Events

For the Part 1 analysis, an overall summary of AEs and separate summaries of TEAEs will include the number and percentage of participants and the number of events by treatment groups, REC-994 pooled group, and overall, unless otherwise mentioned.

Summaries of AEs for the Part 1 analysis will include:

- Overall summary of the number and percentage of participants with at least one:
 - AE
 - TEAE/treatment-related TEAE,
 - serious TEAE/treatment-related serious TEAE,
 - TEAE leading to study drug discontinuation/treatment-related TEAE leading to study drug discontinuation,
 - TEAE leading to study drug interruption/treatment-related TEAE leading to study drug interruption,
 - TEAE leading to study discontinuation/treatment-emergent TEAE leading to study discontinuation,
 - TEAE with CTCAE Grade $\geq$ 3/treatment-related TEAE with CTCAE Grade $\geq$ 3,
 - TEAE leading to death/treatment-related TEAE leading to death,
 - TEAE of special interest/treatment-related TEAE of special interest.
- TEAEs by System Organ Class (SOC) and Preferred Term (PT);
- TEAEs by PT alone;
- Treatment-related TEAEs by SOC and PT;
- Treatment-related TEAEs by PT alone;

- TEAEs by maximum severity CTCAE Grade (1, 2, 3, 4, and 5), SOC and PT;
- TEAEs by maximum severity CTCAE Grade (1 or 2, 3 to 5), SOC and PT;
- Treatment-related TEAEs by maximum severity CTCAE Grade (1, 2, 3, 4, and 5), SOC and PT;
- Serious TEAEs by SOC and PT;
- Serious TEAEs by PT alone;
- Treatment-related serious TEAEs by PT alone;
- TEAEs leading to study drug interruption by SOC and PT;
- Treatment-related TEAEs leading to study drug interruption by SOC and PT;
- TEAEs leading to study drug discontinuation by SOC and PT;
- TEAEs leading to death by SOC and PT;
- TEAEs of special interest by PT alone.

For the combined Part 1 and Part 2 analysis, the number and percentage of participants and the number of events will be provided by REC-994 [REDACTED], REC-994 [REDACTED], placebo re-randomized to REC-994 [REDACTED], and placebo re-randomized to REC-994 [REDACTED]. Summaries of AEs will include:

- Overall summary of the number and percentage of participants with at least one:
 - AE
 - TEAE/treatment-related TEAE,
 - serious TEAE/treatment-related serious TEAE,
 - TEAE leading to study drug discontinuation/treatment-related TEAE leading to study drug discontinuation,
 - TEAE leading to study drug interruption/treatment-related TEAE leading to study drug interruption,
 - TEAE leading to study discontinuation/treatment-emergent TEAE leading to study discontinuation,
 - TEAE with CTCAE Grade $\geq$ 3/treatment-related TEAE with CTCAE Grade $\geq$ 3,
 - TEAE leading to death/treatment-related TEAE leading to death,
 - TEAE of special interest/treatment-related TEAE of special interest.
- TEAEs by System Organ Class (SOC) and Preferred Term (PT);
- Treatment-related TEAEs by SOC and PT;
- TEAEs by maximum severity CTCAE Grade (1 or 2, 3 or 4, 5), SOC and PT;
- Serious TEAEs by SOC and PT.

For each participant and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (treatment-related) will be attributed and used in the by-causality summaries. If severity or causality is missing, a conservative approach for AE assessment (taking into account the worst case) will be followed. Missing severity will be assumed to be “Grade 3 – Severe”.

The following by participant listings will be presented: AEs, serious AEs, and AEs of special interest.

10.1.2 Relationship of Adverse Events to Study Drug

Causality of AEs will be classified by the investigator as “Related” and “Not Related”. Treatment-related TEAEs will be summarized. Missing relationship will be assumed to be “Related”.

10.1.3 Adverse Events of Special Interest

Adverse events associated with hepatobiliary disorders are of special interest in this study. Liver AEs will be assessed by monitoring hepatic transaminases, bilirubin, and clinical jaundice.

An SAE will be added to the clinical database if potential drug-induced liver injury, defined as follows ([FDA, 2009](#)), is confirmed by medical review:

- Treatment-emergent ALT or AST $>3 \times$ upper limit of normal (ULN) in combination with total bilirubin $>2 \times$ ULN

OR

- Treatment-emergent ALT or AST $>3 \times$ ULN in combination with clinical jaundice

All cases of potential drug-induced liver injury are considered SAEs.

A by-participant listing of adverse events of special interest will be presented by treatment groups.

10.2 Clinical Laboratory Evaluations

Laboratory assessments including hematology, serum chemistry, coagulation, and urinalysis will be conducted as specified in the Schedule of Assessments ([Appendix 14.1.1](#)). Central laboratories will be used in this study for all clinical laboratory assessments (hematology, clinical chemistry, coagulation, and urinalysis).

The detailed lab collected is presented in the subsection below.

For the Part 1 analysis, continuous laboratory parameters (hematology, chemistry, coagulation) will be summarized descriptively for observed values, changes from baseline, and percentage change from baseline by scheduled visits in Part 1 of the study.

Continuous laboratory results (hematology, chemistry, coagulation) will also be categorized as low, normal, and high based on normal reference ranges, as applicable. A summary of the incidence of abnormal, high or low values will be provided by treatment groups at each scheduled visit in Part 1. Frequency summaries (shift tables) of shift from baseline to the worst post-baseline value by category of low, normal, high, will be provided for hematology, chemistry, and coagulation parameters for which normal ranges exist.

For Part 1 safety analysis, a participant will be defined as having a treatment-emergent laboratory abnormality if any of the following conditions are satisfied for a specific laboratory parameter:

- Laboratory result within the normal range at baseline and either a result below the lower limit of the normal range or above the upper limit of the normal range at any post-baseline time point:

- on or up to [REDACTED] after the last dose of study treatment in Part 1 for participants not participating in LTE Part 2.
- prior to LTE Day 1 for participants continuing in LTE Part 2.
- Laboratory result below the lower limit of the normal range at any post-baseline time point:
 - on or up to [REDACTED] after the last dose of study treatment in Part 1 for participants not participating in LTE Part 2.
 - prior to LTE Day 1 for participants continuing in LTE Part 2.

A by-participant, by-parameter, by-visit, listing of each laboratory category (hematology, chemistry, coagulation) will be provided for Part 1 lab data, with sample collection date, observed value, change from baseline value and percentage change from baseline value, treatment-emergent abnormal values identified, lab normal ranges, and any comments, where available.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with “L” for values below the lower limit of the clinical reference range and “H” for values above the upper limit of the clinical reference range.

By-participant, by-parameter, by-visit, listings of hematology, chemistry, and coagulation results will be provided separately for the combined Part 1 and Part 2 lab data.

10.2.1 Hematology

Hematology parameters include complete blood count, platelet count, hemoglobin, and hematocrit. The following values will also be determined or calculated: mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

10.2.2 Serum Chemistry

The following parameters will be measured:

- **Comprehensive metabolic panel:** sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, BUN/creatinine ratio, glucose, albumin, calcium, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, indirect (calculated) and direct bilirubin, and total protein. Estimated creatinine clearance will also be determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ([Levey, 2009](#)).
- **Other chemistry tests:** creatine kinase, amylase, lipase, magnesium, inorganic phosphorus, total cholesterol, high-density lipoprotein, low-density lipoprotein (calculated), triglycerides, lactate dehydrogenase, gamma-glutamyl transferase (GGT), and uric acid. Thyroid-stimulating hormone will also be measured.

10.2.3 Coagulation

Coagulation parameters include prothrombin time/international normalized ratio and activated partial thromboplastin clotting time (aPTT).

10.2.4 Urinalysis

A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, WBCs, and pH (to be captured in the database). Microscopic analysis will only be performed when results are 2+ or greater for blood, protein, or WBCs.

Dipstick and microscopy urinalysis results in Part 1 will be listed separately by scheduled visits.

10.2.5 Pregnancy Testing

Pregnancy tests will be performed for all female participants of childbearing potential. A serum pregnancy test will be performed at Screening, [REDACTED] and [REDACTED] (EoS) visits. A urine pregnancy test will be performed at Day 1, [REDACTED] (EoT) and Early Termination (ET).

Pregnancy test results (serum, urine) in Part 1 will be listed by scheduled visits.

10.3 Vital Sign Measurements

Vital signs including temperature, respiratory rate, heart rate, and blood pressure (measured after participant has been seated for at least 5 minutes) will be collected at each visit. At visits on [REDACTED] [REDACTED] vital signs will be collected pre-dose. In addition, blood pressure and heart rate will be collected with each PK sample with the same time points as the serial blood samples described in [Section 11.2](#).

Weight will be measured at Screening and [REDACTED] (and at ET, as appropriate) before dosing (where applicable) with shoes off. Height will be measured at Screening and at [REDACTED] with shoes off.

Vital sign results will be summarized and listed for the Part 1 analysis only.

The observed value, change from baseline, and percentage change from baseline will be summarized for vital sign parameters (heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and temperature) by treatment groups and visit/timepoint (for observed and change from baseline values).

A by participant listing of vital signs measurements collected at scheduled visit will be provided by visit, including raw values, change from baseline values and percentage change from baseline values. In addition, a by participant listing of vital sign measurements collected at the same time as the PK samples will be presented by visit and timepoint.

10.4 Physical, Neurological and Focused Physical Examinations

Physical, neurological, and focused physical examinations are performed according to the Schedule of Assessments ([Appendix 14.1.1](#)).

Physical examination, includes the following body systems:

- Skin
- Head, eyes, ears, nose, and throat (HEENT)
- Respiratory
- Cardiovascular
- Gastrointestinal
- Endocrine metabolic
- Neurological
- Blood lymphatic
- Musculoskeletal.

Neurological examination, includes the following:

- Mental status
- Gait
- Cerebellar
- Cranial nerve exam
- Motor exam
- Reflex exam
- Sensations exam.

Physical and neurological data will be listed for the Part 1 analysis only.

By-participant, by visit listings will be presented for all physical, neurological and focused physical examination results, reported as Normal or Abnormal.

10.5 Electrocardiogram (ECG)

All standard digital ECGs will be performed in triplicate after the participant has been supine for at least 5 minutes. The average of the triplicates will be used in the analysis.

All ECG results will be summarized and listed for the Part 1 analysis only.

Summary statistics of observed values, changes from baseline and percentage change from baseline will be provided by treatment groups and visit for:

- Heart rate (beats/min)
- PR Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- Corrected QTc (QTcF).

In addition, QTcF will be summarized, by treatment groups and visit, according to the following categories:

Observed values: ≤ 450 msec; 451-480 msec; 481-500 msec; ≥ 500 msec

Change from baseline values: < 30 msec; ≥ 30 msec - < 60 msec; ≥ 60 msec.

A by-participant listing of all ECG assessments will be produced.

11 Pharmacokinetics (PK)

The pharmacokinetic analysis will be performed by PPD Clinical Pharmacology using standard noncompartmental methods with Phoenix[®] WinNonlin[®] Version 8.3 or higher (Certara USA, Inc., Princeton, NJ).

All PK listings and individual concentration-time profiles will be presented using the Safety Set. PK parameter tables, mean figures and all statistical analyses will be presented using the PK Analysis Set. No extraneous PK data collected as part of a protocol deviation will be summarized.

11.1 Data Handling

Data rounding specifications for PK data are documented in the PK TLF shells.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics. For PK analysis, all BLQ values will be treated as zero, with the exception of BLQ values observed between 2 quantifiable concentrations, which will be set to missing.

Missing concentrations will be excluded from all calculations and PK analyses.

11.2 Plasma Concentrations

Serial blood samples will be collected at the following time points for PK assessment:

- Part 1 (Subjects randomized to Protocol Amendment 1 – 3 and who had PK collection samples):
 - Day 1: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours following initial administration of study drug
 - Day 2: 24 hours following initial administration of study drug on Day 1
 - [REDACTED]: Pre-dose (0, C_{trough}) and T_{max} (1.5 hours post-dose)
 - A single PK sample will be collected prior to discharge from any subject who discontinues the study early.
- Part 1 (Subjects randomized to Protocol Amendment 4 and above and who had PK collection samples):
 - [REDACTED] Pre-dose (0, C_{trough}) and T_{max} (1.5 hours post-dose)
 - [REDACTED]: 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, and 5 hours following initial administration of study drug. A 24 hour sample (pre-dose) following the [REDACTED] dose will also be collected.
 - A single PK sample will be collected prior to discharge from any subject who discontinues the study early.

The sample collection windows are as follows:

- Part 1
 - Day 1 - 0 hour: Within 1 hour pre-dose
 - Day 1 - 0.5, 1, 1.5, and 2 hours post dose: ±5 minutes
 - Day 1 - 3, 4, 5, 6, and 8 hours post dose: ±10 minutes
 - Day 2 - 24 hours postdose: ±10 minutes

- [REDACTED]: C_{trough} (within 1 hour pre-dose) and T_{max} (1.5 hours) (± 5 minutes).

For purposes of this SAP, “extensive PK” is defined as 3 or more samples taken on Day 1 (Protocol Amendment v.1 – v. 3) or [REDACTED] followed by a PK sample 24 hours after dose. If only a sample is collected 24 hours after Day 1 or [REDACTED] this will be considered a pre-dose concentration and summarized in box plots (see below).

Individual plasma concentrations will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) by part, treatment, visit and nominal time point.

Individual plasma concentrations on extensive PK collection days will be plotted by actual time after last dose on both linear and semilogarithmic scales. Extensive PK collection days in Part 1 were as follows:

- Subjects who were randomized to Protocol Amendment v.1 – v.3 extensive PK was collected on Day 1.
- Subjects who were randomized after Protocol Amendment v4.0 extensive PK was collected in [REDACTED]

Arithmetic mean plasma concentrations from the nominal time after dose on extensive PK collection days will be plotted by part, treatment, and nominal time on both linear and semi-logarithmic scales. Non-extensive PK data collected will be summarized in box plots, with individual data overlaid. One box plot will show pre-dose concentrations by month/day and dose and the other box plot will show post-dose concentration by month/day and dose; and single point on the box plot will indicate the arithmetic mean.

During the study subjects may have obtained per-protocol PK collections in the transition from Protocol Amendment v.1 – v.3 to Protocol Amendment v.4.0. All subjects with extensive PK collections taken on Day 1 and/or [REDACTED] will be included in the summary tables and figures. A listing of each subject and when they received extensive PK will be provided; if a subject did not receive extensive PK, it will be noted in this listing.

11.3 Plasma Pharmacokinetic Parameters

Plasma concentration-time data will be analyzed by non-compartmental analysis using Phoenix[®] WinNonlin[®] Version 8.3 or higher (Certara USA, Inc., Princeton, NJ) or SAS[®] Software version 9.4 or later.

The following PK parameters will be calculated for REC-994, where data permits:

C_{max}	Maximum observed plasma concentration.
C_{trough}	Observed plasma concentration at the end of the dosing interval, determined directly from the concentration-time data.
T_{max}	Time of maximum observed concentration.

AUC ₀₋₂₄	AUC from time 0 to the time 24 hours postdose. In instances where the actual last sample collection time is prior to 24 hours, AUC _{0-t} may be used in place of AUC ₀₋₂₄ .
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Actual sampling times will be used for the estimation of all plasma PK parameters, and all concentrations will be included in the analysis. Concentrations collected outside of the predefined sampling windows will be excluded from the calculation of summary statistics. For AUC₀₋₂₄ and C_{max}, only subjects who had all extensive PK samples taken on Day 1 and/or [REDACTED] will be evaluated. If the subject had extensive PK samples on both occasions, they will be evaluated for each instance and included in the summaries.

Plasma PK parameters will be presented in data listings and summarized by part, day, and visit separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) by treatment. T_{max} will be summarized using number of observations, median, minimum, and maximum only.

12 Changes in the Planned Analysis

Per the protocol, the primary analysis is for Part 1 of the study. Since the primary analysis will also include safety and MRI data from Part 2, Part 1 analysis and combined Part 1 and Part 2 analysis will constitute the primary analysis.

[REDACTED]. However, for this study, lesion volume and hemosiderin ring size are more appropriate endpoints to track the changes in disease status. For MRI data analysis, lesion number will not be summarized or analyzed. Instead, the hemosiderin ring size will be included and analyzed using the same method as described for total lesion volume. Further, total lesion volume and hemosiderin ring size will be considered as secondary efficacy endpoints instead of exploratory endpoints per the protocol, because of their importance in tracking disease status.

Per the protocol, the number of seizures/headaches during the treatment period will be assessed using the generalized estimation equations (GEE) approach based on Negative Binomial (NB) distribution. However, the frequency data has excess zeros which cause issues with the original NB distribution assumption. Therefore, a zero-inflated Negative Binomial model is proposed for analysis of seizure/headaches frequency data.

[REDACTED]

Per the protocol, PPS will be used for selected efficacy endpoints. No efficacy analyses will be repeated for the PPS.

Per the protocol, complete blood count (CBC) (including differential count) will be collected and analyzed as hematology parameters. However, when the CBC test panel was set-up in central lab, sponsor confirmed that these differential counts analytes are not reportable. Hence, the differential counts data are not collected and will not be included in the lab data summary.

13 References

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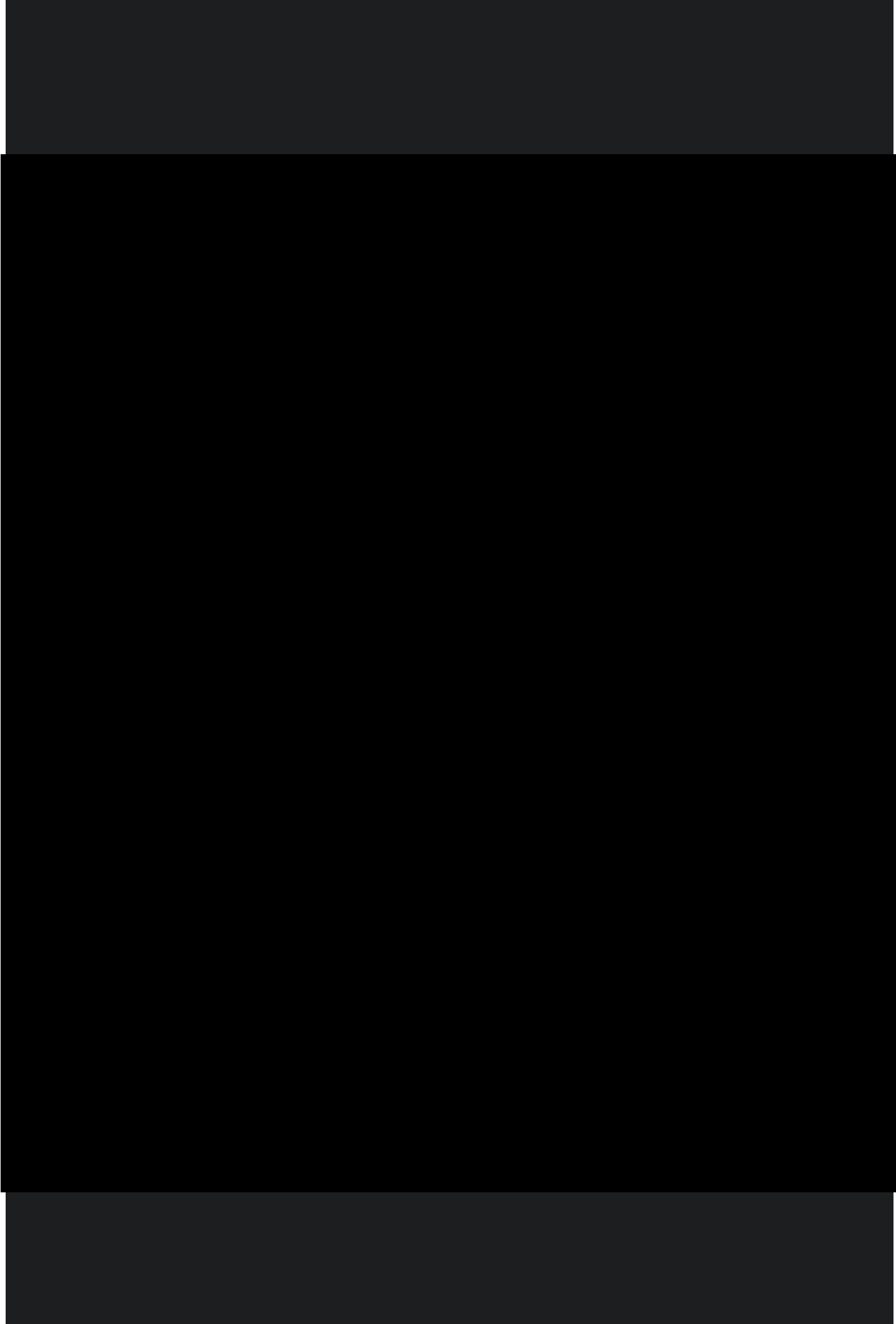
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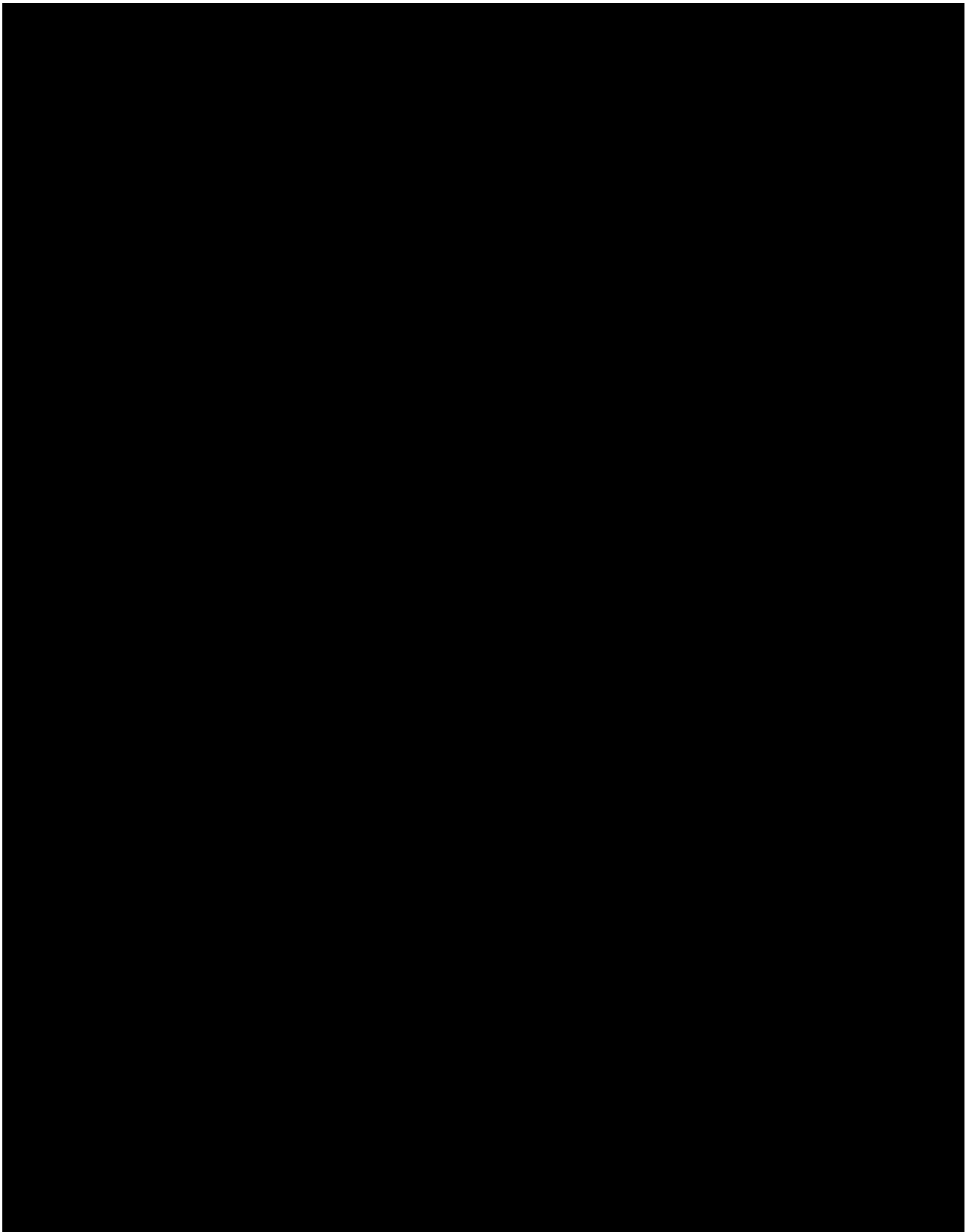
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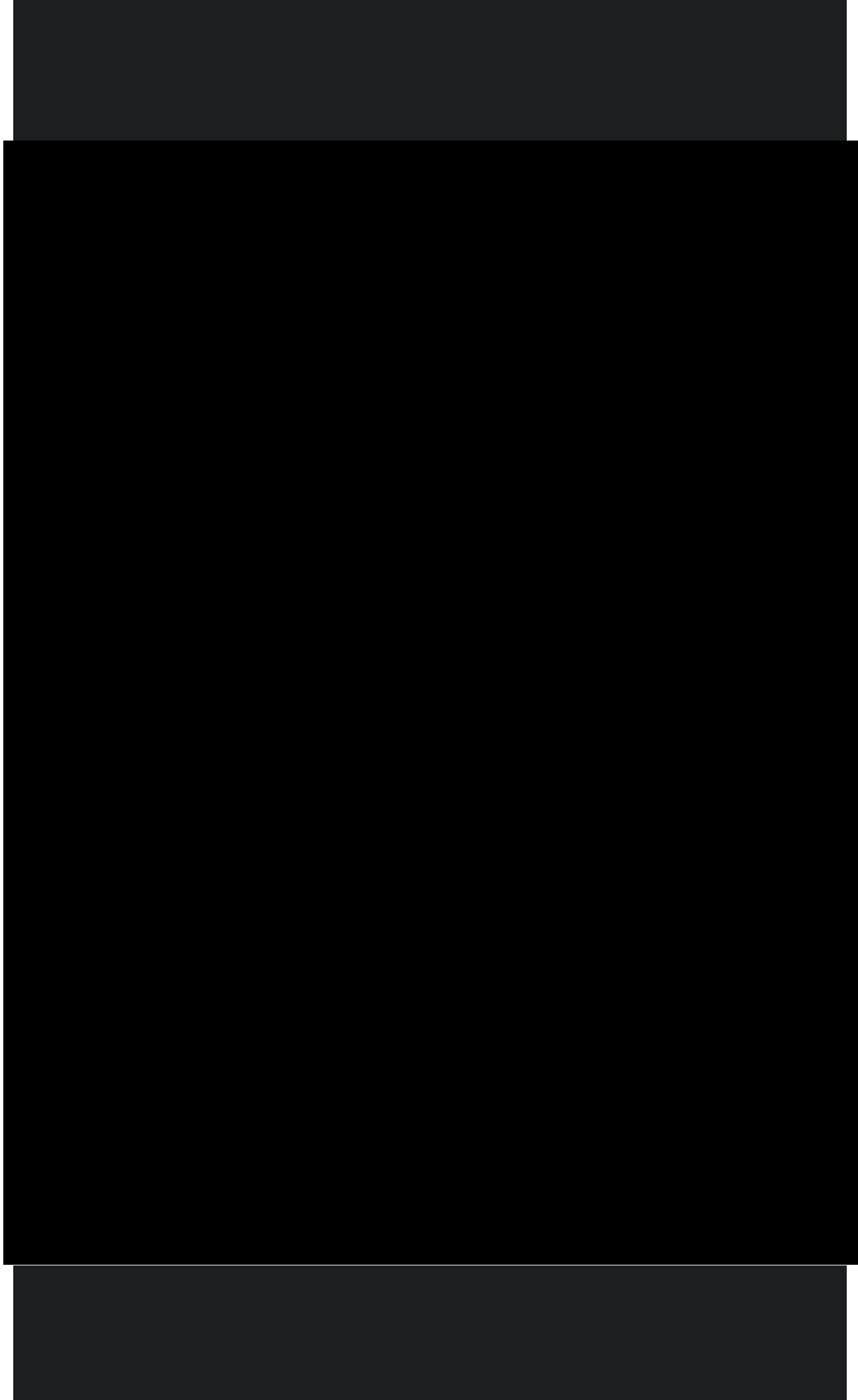
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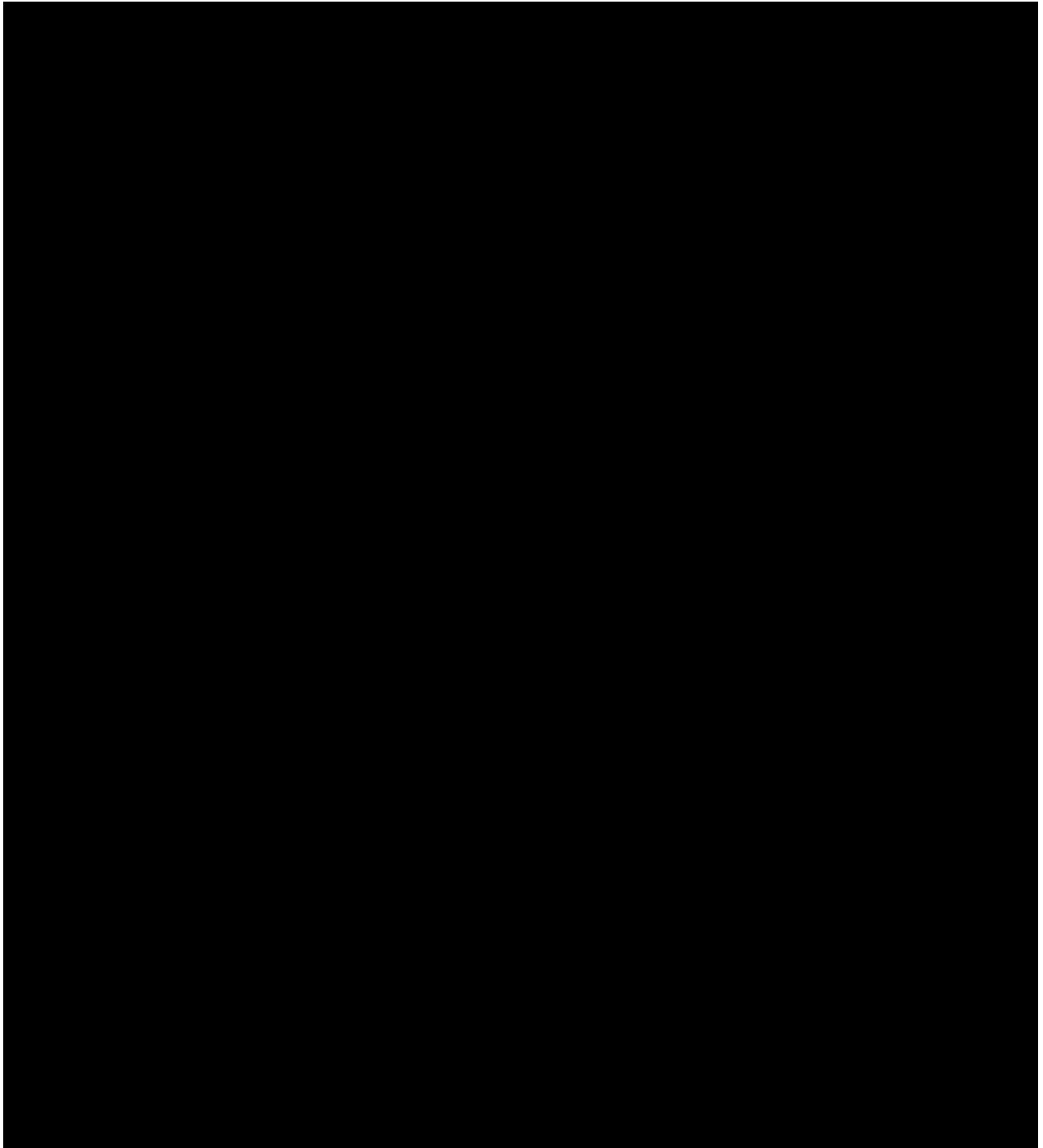
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14.2 SymptoMScreen Score (SMSS)

The SMSS questionnaire consists of 12 items (provided below) assessed on a seven-point Likert scale ranging from 0 (not at all affected) to 6 (total limitation). The total score ranges from 0 to 72, with higher scores indicating more severe symptom endorsement.

Items assessed: Walking, Hand Function/Dexterity (Poor hand coordination, tremors), Spasticity & Stiffness (Muscle cramping or muscle tightness), Bodily Pain (Aching, tenderness), Sensory (Numbness, tingling or burning), Bladder Control (Urinary urgency, urinary frequency), Fatigue, Vision (Blurry vision, double vision), Dizziness (Feeling off balance, ‘spinning’/vertigo), Cognitive Function (Memory, concentration problems), Depression (Depressed thoughts, low mood), and Anxiety (Feelings of stress, panic attacks).

Answer	Score
Not affected at all	0
Very mild limitation/I make minor adjustments	1
Mild limitation/I make frequent adjustments	2
Moderate limitation/I reduced my daily activities	3
Severe limitation/I gave up some activities	4
Very severe limitation/I'm unable to do many daily activities	5
Total limitation/I'm unable to do most daily activities	6

14.3 Modified Rankin Scale (mRS) Score

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered an acute stroke. A list of structured interview questions and rules are used to determine participant mRS grades in a systematic way. The interview consists of five sections corresponding to the levels of disability on the mRS. The mRS runs from 0-5, corresponding to no symptoms at all (0) to severe (5). The following table provides the type of questions and structured interview rule used to derive each score.

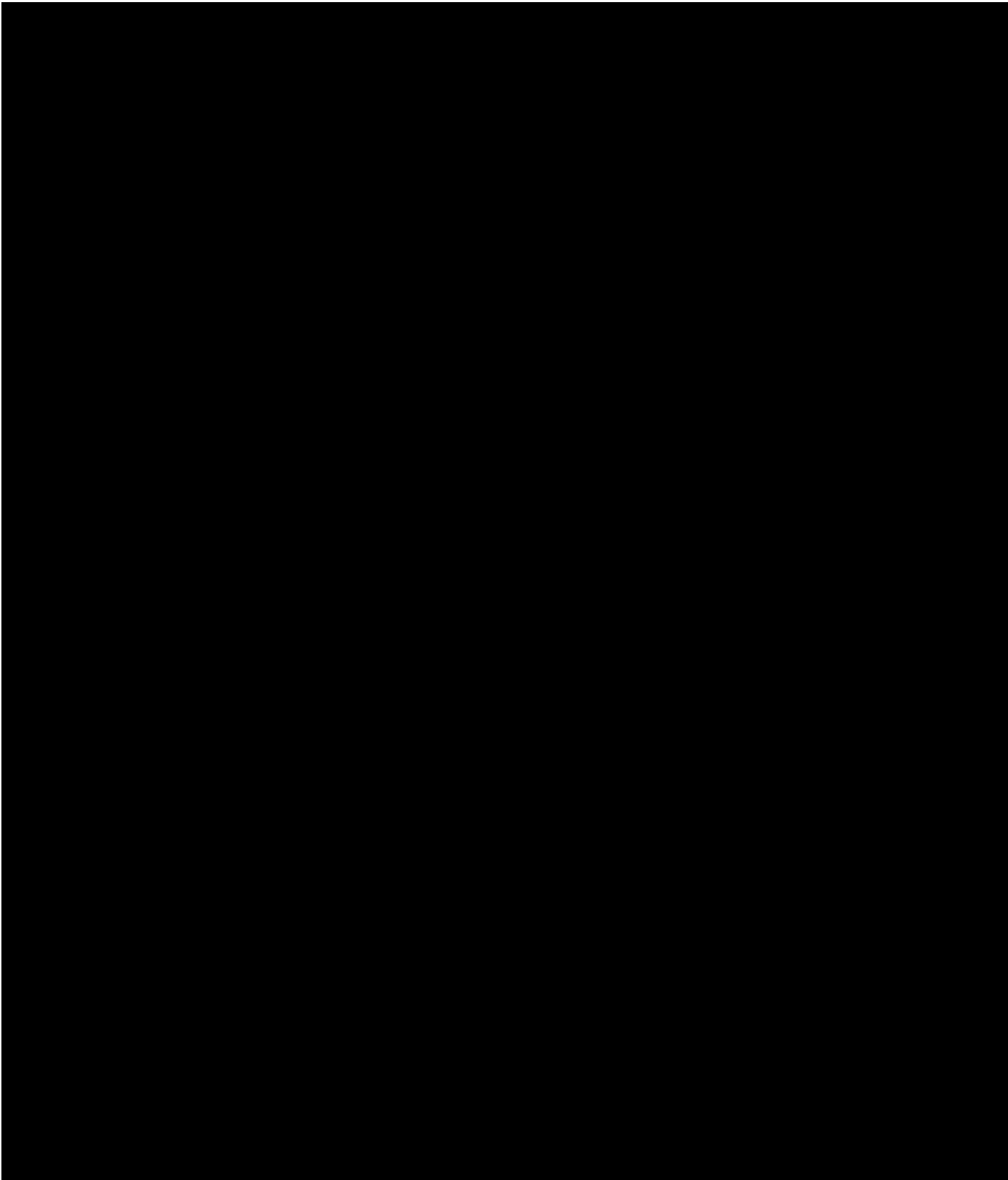
<u>Interview Topic</u>	<u>Interview Questions</u>	<u>Structured Interview Rule</u>	<u>Score</u>
Constant Care	Constant Care Required	If “yes”, score 5 and discontinue interview	5
Assistance to Attend Bodily Needs	Assist Required Eating Required Using Toilet Required Routine Hygiene Assist Required Walking	If “yes” is answered to one or more questions, score 4 and discontinue interview	4
Assistance To Look After Own Affairs	Assist Required Prep Meal Assist Essential Household Chore Assist Essential Manage Expenses Assist Essential Local Travel Assist Essential Local Shopping	If “yes” is answered to one or more questions, score 3 and discontinue interview	3
Usual Duties & Activities: School, Work, Family, Leisure, and Friendships	Limited Perform Student Activities Limited In Working / Seeking Work Limited in Looking After Family Limited In Leisure Activity Difficulty With Relationships	If “yes” is answered to any question then score 2 and discontinue interview	2
Other Symptoms	Difficulty Reading Or Writing Difficulty Speaking Finding Words Problems Balance or Coordination Visual Problems Numbness Loss of Movement Difficulty with Swallowing List of Other Symptoms	Answer all questions. If one or more questions is answered “yes”, score 1	1

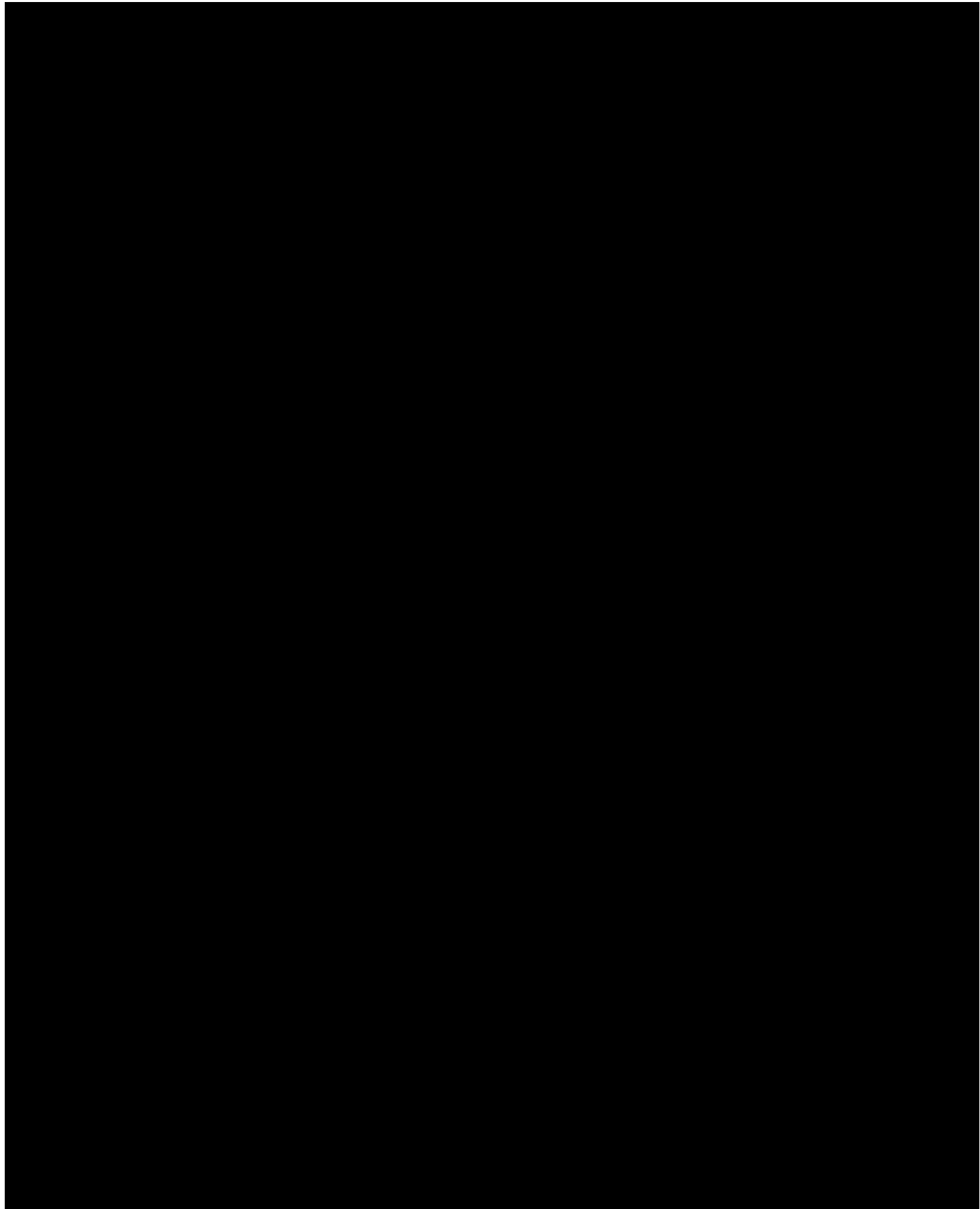
The Modified Rankin Scale definitions are provided below.

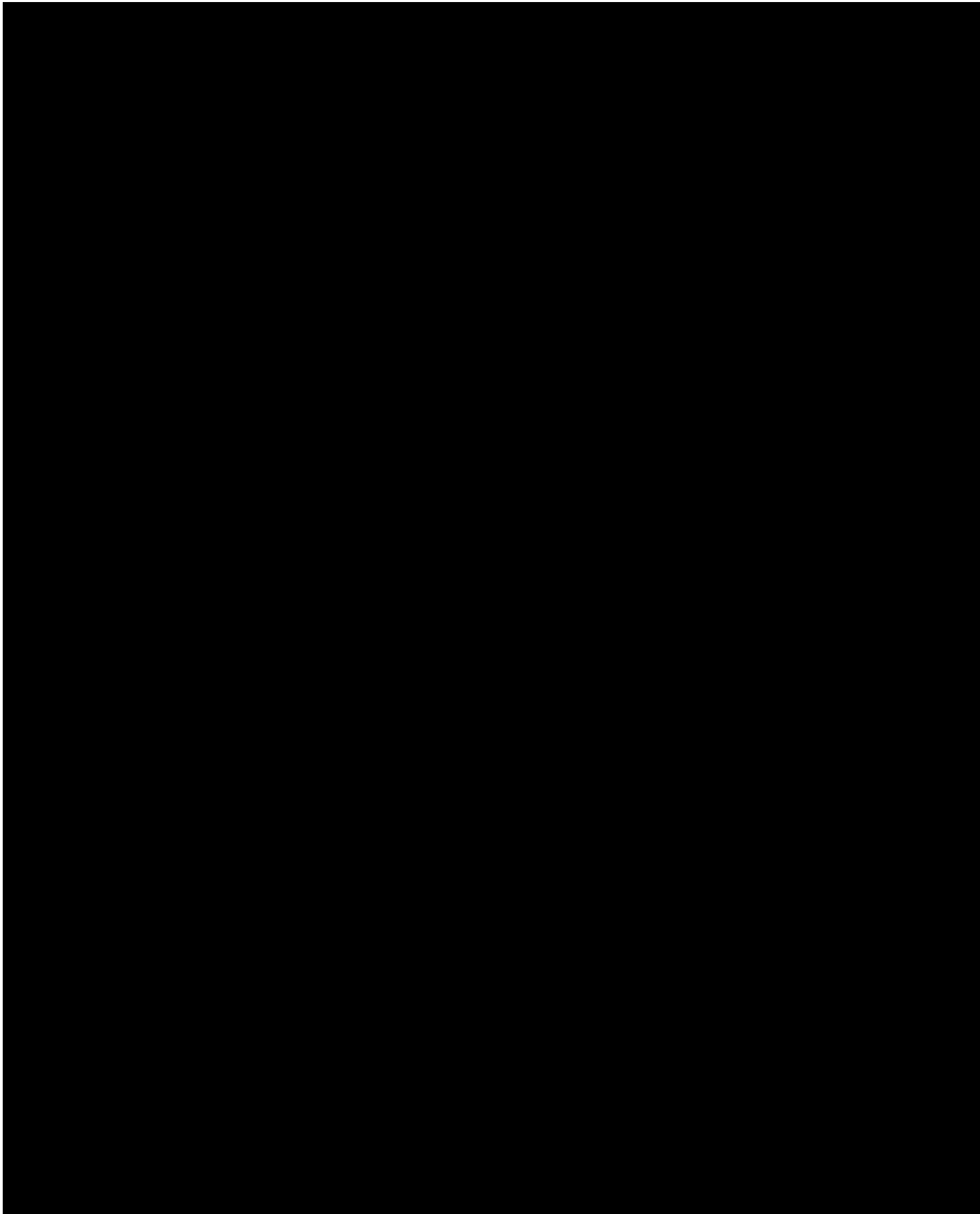
Score	Level of Disability	Functional Description	Section of Structured Interview
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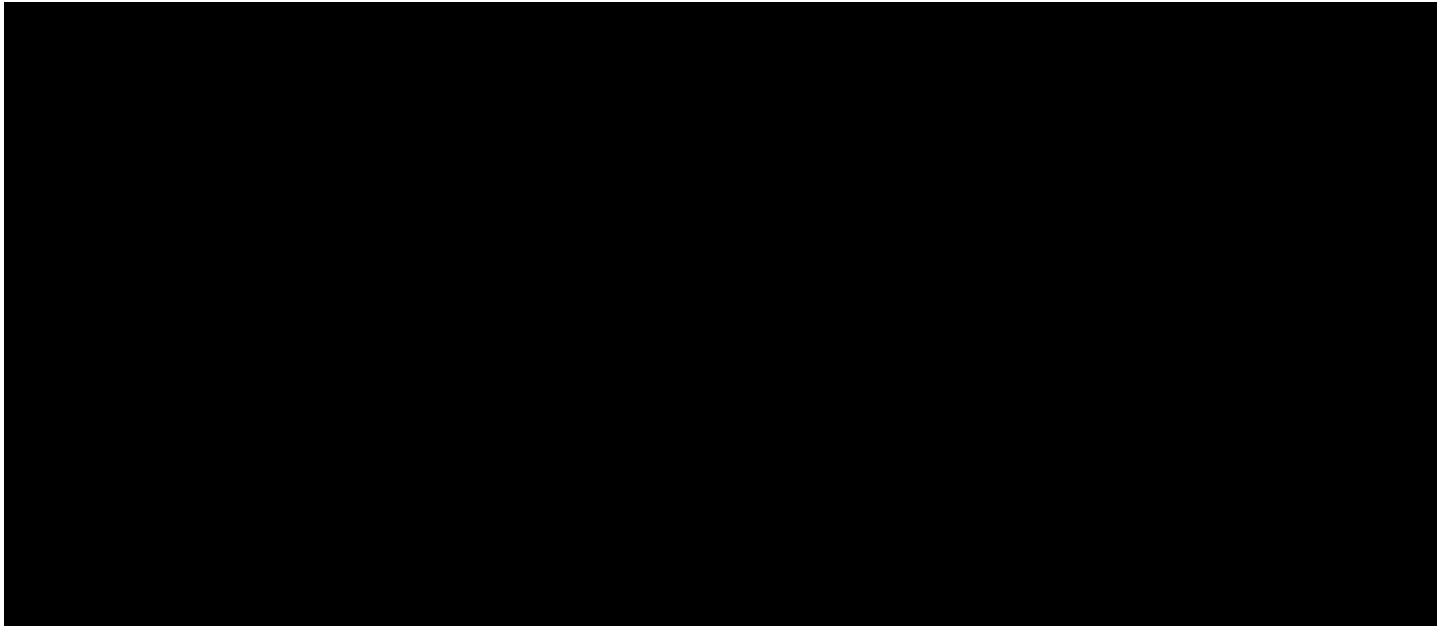
0	No Symptoms at all		
1	No significant disability	Despite symptoms: able to carry out all usual duties and activities.	Symptom checklist
2	Slight disability	Unable to carry out all previous activities, but able to look after own affairs without any assistance	Usual duties and activities
3	Moderate disability	Requiring some help, but able to walk without assistance.	Assistance to look after own affairs
4	Moderately severe disability	Unable to walk without assistance, and unable to attend to own bodily needs without assistance.	Assistance for bodily needs / walking
5	Severe disability	Bedridden, incontinent, and requiring constant nursing care and attention.	Constant care

14.4









14.4.2

[REDACTED]

[REDACTED]

14.5 Clinical/Patient Global Impression (CGI/PGI) Scales

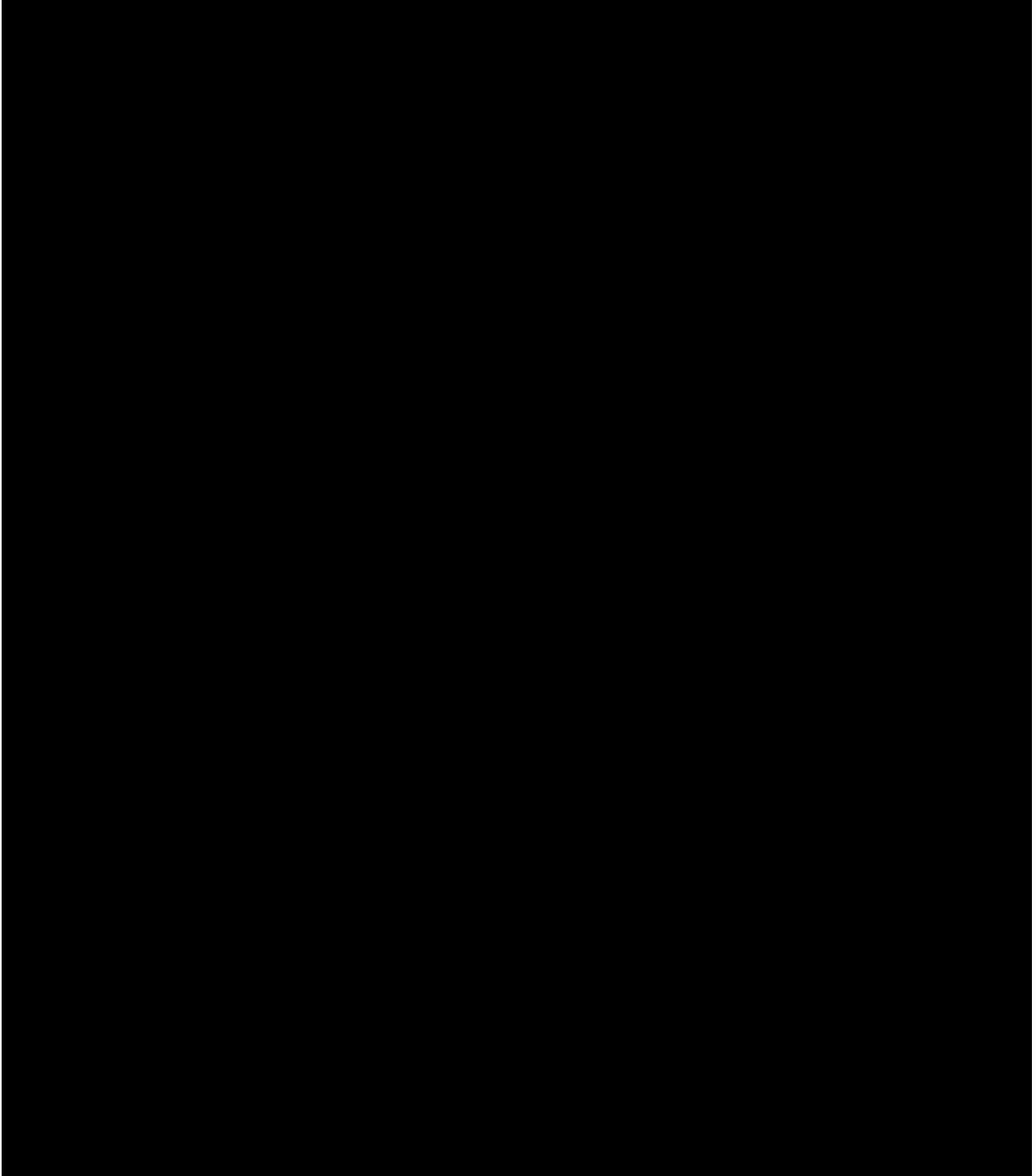
The Clinical/Patient Global Impression are measured via two components: CGI/PGI-Severity (CGI-S and PGI-S) is assessed at baseline and CGI/PGI-Improvement (CGI-I and PGI-I) is assessed periodically during the study. The scales below are used to assess baseline severity.

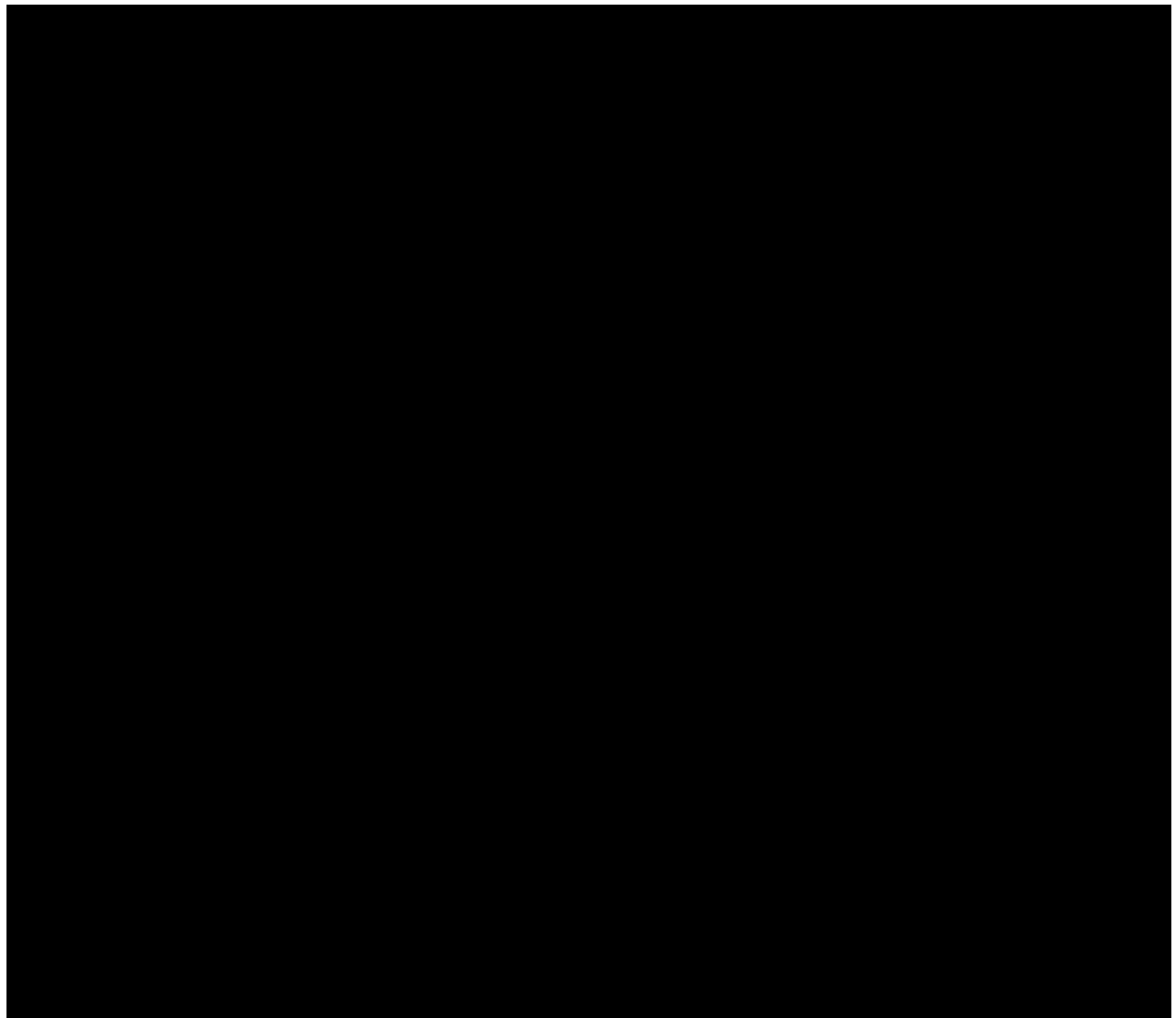
<u>CGI-S Assessment</u>	<u>Score</u>	<u>PGI-S Assessment</u>	<u>Score</u>
Normal, not at all ill	1	Not present	1
Borderline ill	2	Very mild	2
Mildly ill	3	Mild	3
Moderately ill	4	Moderate	4
Markedly ill	5	Moderately severe	5
Severely ill	6	Severe	6
Among the most extremely ill participants	7	Extremely severe	7

Clinical/Patient Global Impressions scales recorded post baseline are used to determine participant improvement. PGI and CGI Improvement is further categorized into categories of Improved, Not Improved & Worse. If a participant is not assessed (missing) by the investigator, then the CGI-I score is set to '0'.

<u>PGI-I/CGI-I</u>	<u>Score</u>	<u>PGI-I/CGI-I Categories</u>
Very much better/Very much improved	1	Improved
Much better/Much improved	2	
Somewhat better/Minimally improved	3	
No Change	4	No Change
Somewhat worse/Minimally Worse	5	Worse
Much worse/Much worse	6	
Very much worse/Very much worse	7	

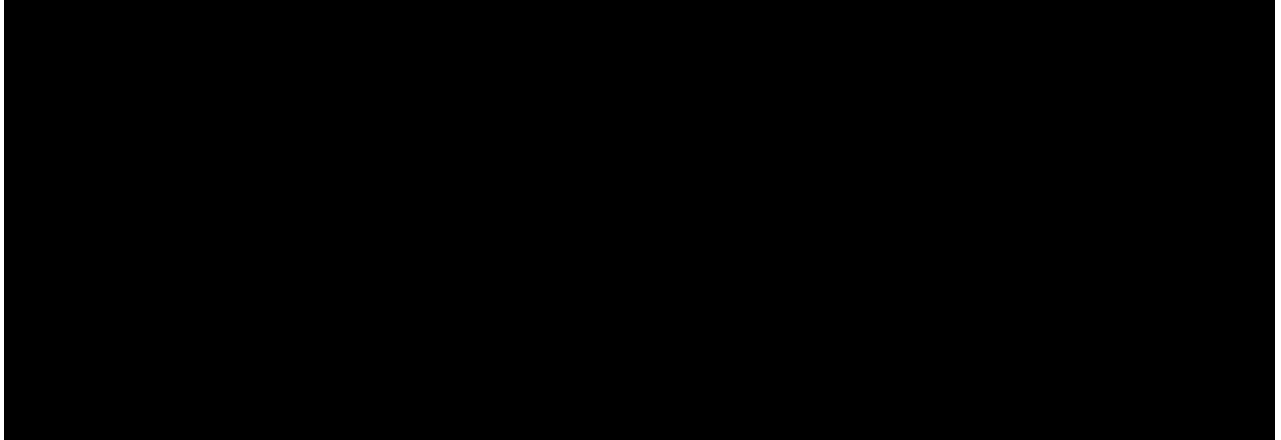
14.6







14.7



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Signing Complete	Security Checked	24 July 2024 22:16
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