

CLINICAL TRIAL PROTOCOL

Study Title:	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
Brief Study Title:	The Symptomatic Cerebral Cavernous Malformation Trial of REC-994 (SYCAMORE)
Study Number:	REC-994-201
Investigational Product:	REC-994
Phase of Development:	2
Study Type:	Part 1: Safety, efficacy, and pharmacokinetics Part 2: Long-term safety and efficacy
Sponsor:	Recursion Pharmaceuticals, Inc. 41 South Rio Grande St. Salt Lake City, UT 84101 USA (385) 269-0203
Responsible Medical Officer	Recursion Pharmaceuticals, Inc.
Protocol Version	Version 6.0
Date	22 September 2023

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1 SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by:

{See appended electronic signature page}

Date

{See appended electronic signature page}

Date

INVESTIGATOR'S AGREEMENT

I have read the REC-994-201 protocol and agree to conduct the study as outlined and in accordance with GCP. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

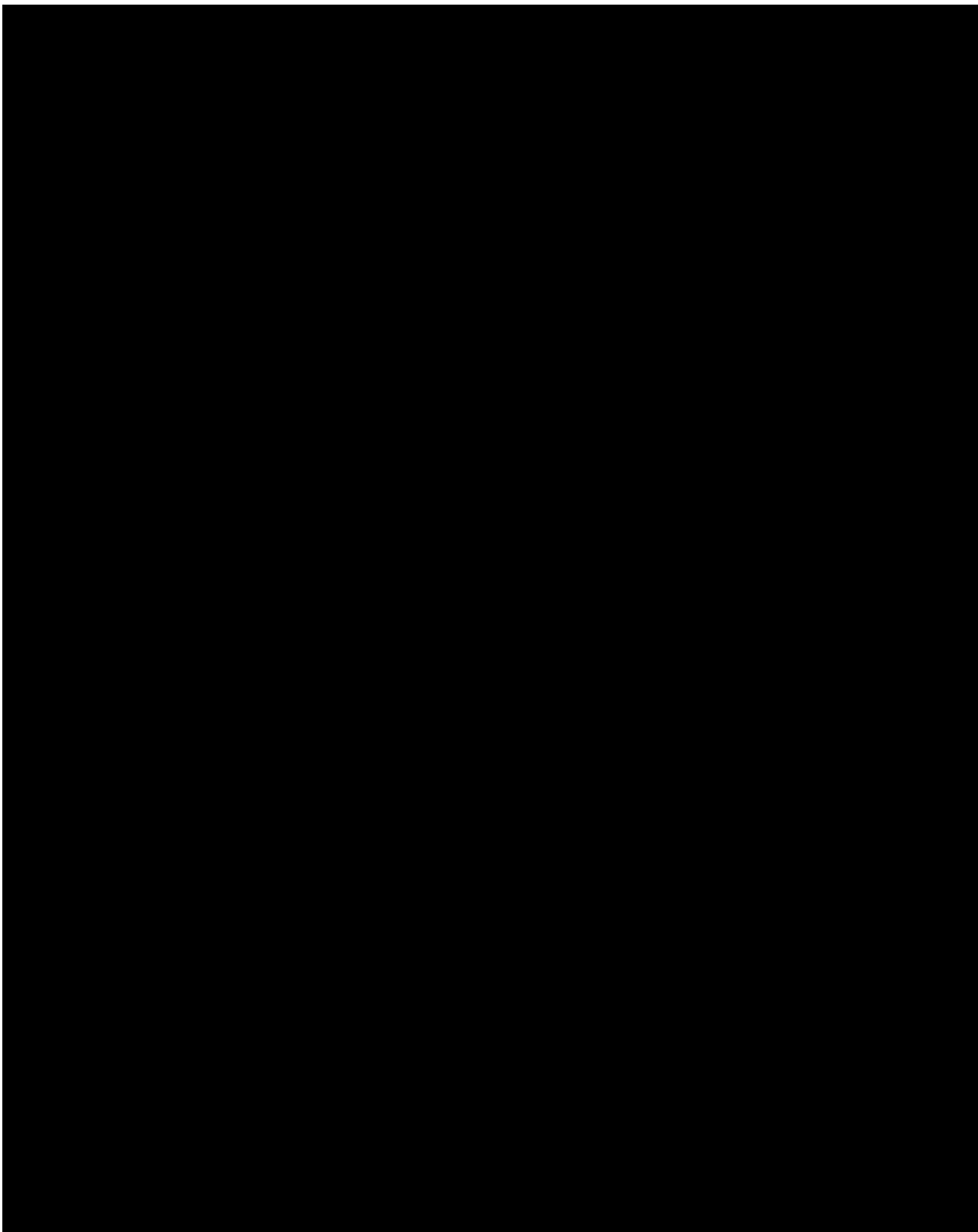
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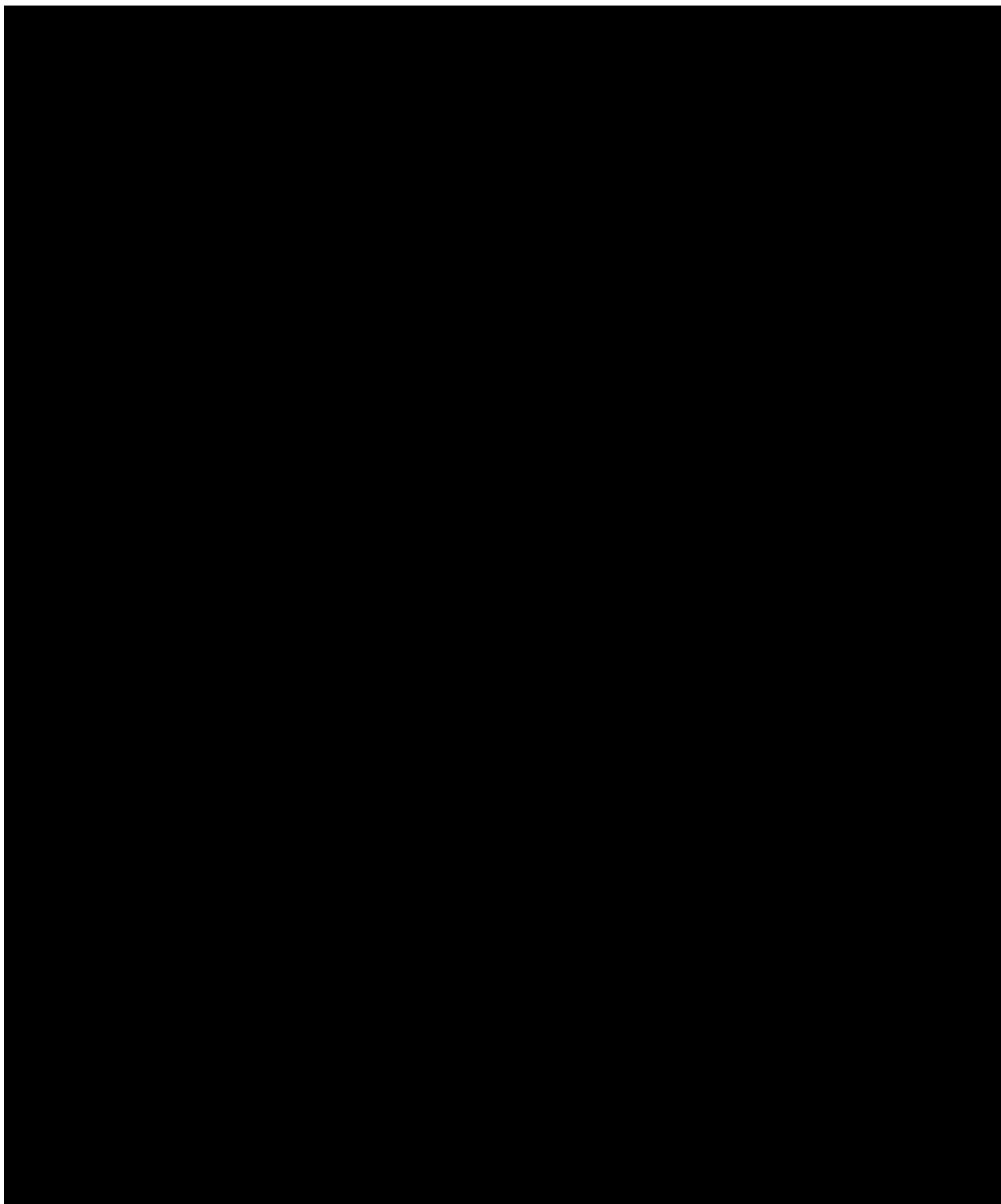
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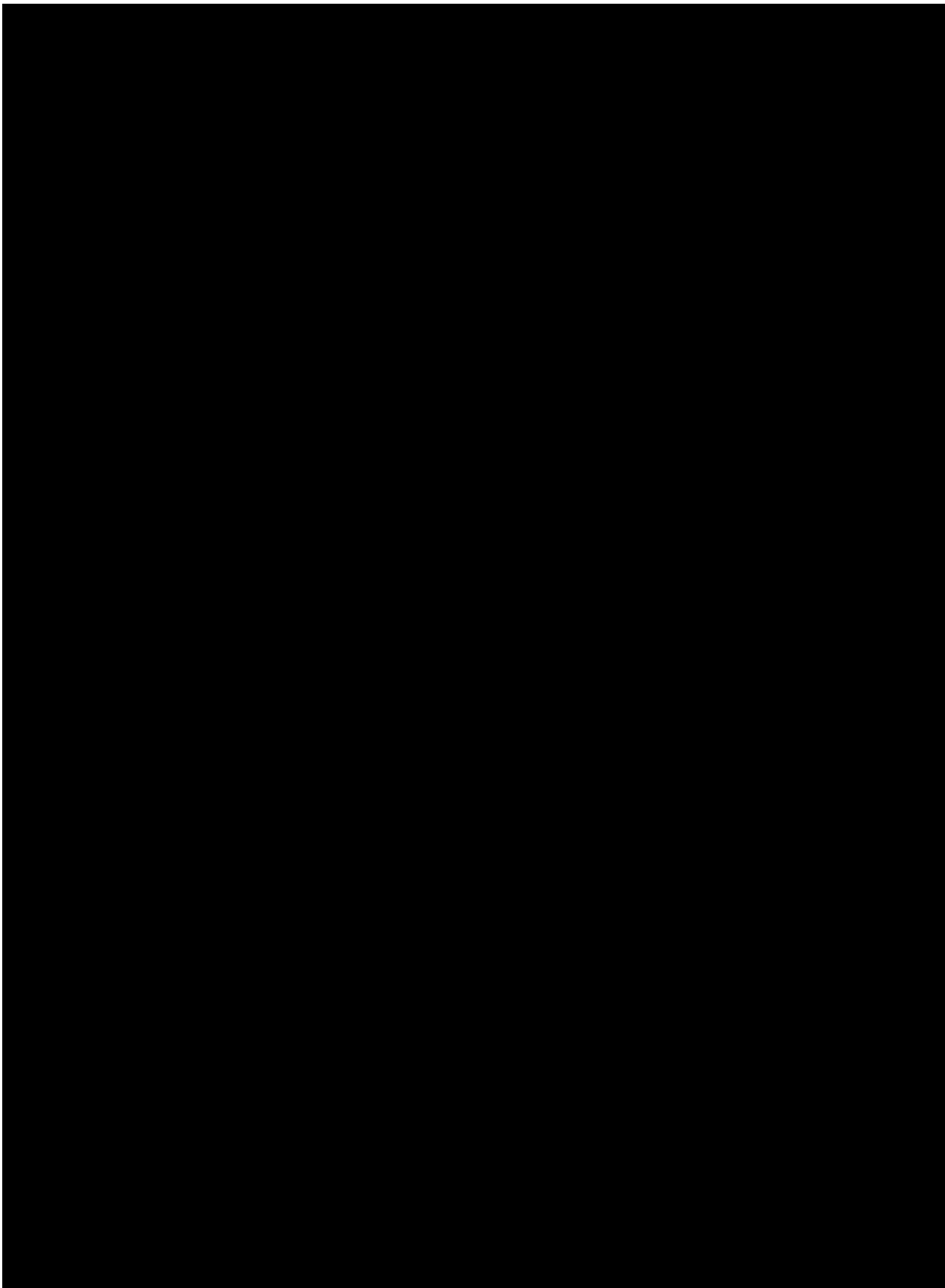
Role in Study	Name	Address and Telephone Number
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PROTOCOL AMENDMENT HISTORY

The following amendments have been made to this protocol since the date of preparation:







2 SYNOPSIS

Study Title	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	
Brief Study Title	The Symptomatic Cerebral Cavernous Malformation Trial of REC-994 (SYCAMORE)	
Study Number	REC-994-201	
Study Phase and Study Type	Phase 2 Part 1: Safety, efficacy, and pharmacokinetics (PK) Part 2: Long-term safety and efficacy	
Study Population	Part 1: Participants with symptomatic CCM, male or female, 18 years of age or older Part 2: Participants who completed the [REDACTED] visit for Part 1 and who remain eligible for extended dosing with REC-994	
Objectives and Endpoints	Part 1:	
	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- or CT-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] • Clinical Global Impression (CGI) • Patient Global Impression (PGI) • Number of seizures per month (participant diary) • Number of headaches per month (participant diary) • Number of MRI- or CT-confirmed symptomatic hemorrhagic events
	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	
	Part 2:	
	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: (see Section 14.2 for definition of Baseline) - mRS - SMSS ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED] ■ [REDACTED]

	• CGI-I • PGI-I • Number of MRI- or CT-confirmed symptomatic hemorrhagic events • Number of MRI- or CT-confirmed cerebral hemorrhagic events
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 () and () compared to placebo in participants with symptomatic CCM over a treatment period of (). 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 Part 1 of the study will consist of 3 periods: • Screening () • Treatment Period () • Follow-up Period () <u>Screening Period</u> During the Screening Period (approximately ()), participants will undergo assessments as described in the Schedule of Assessments for Part 1 (SOA/Part 1; Table 6) to ensure they meet the Inclusion and Exclusion Criteria of the study. Medical history will be reviewed, including a 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). <u>Treatment Period</u> Approximately () participants who have met the Inclusion and Exclusion Criteria for Part 1 will be enrolled in the study. Participants will be randomized () to receive () doses of study drug: REC-994 () or REC-994 () or placebo for the remainder of Part 1 of the study. Pre- and post-dosing safety monitoring performed during the study will include vital signs, ECGs, physical examination, neurologic evaluation, laboratory assessments, 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 (to establish baseline values) and at study visits during the Treatment Period (to assess changes from baseline): • SMSS (to assess baseline participant-reported disease severity)

On Study 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 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, respectively, 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 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 [REDACTED] treatment period will remain on study for regular scheduled assessments.

Assessments to be conducted at the respective study visits are described in the SOA/Part 1 (Table 6).

End of Part 1 Treatment / Follow-up Period

Prior to the Part 1 [REDACTED] End-of-Treatment 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 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 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 safety follow-up visit ([REDACTED]). For subjects 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.

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.

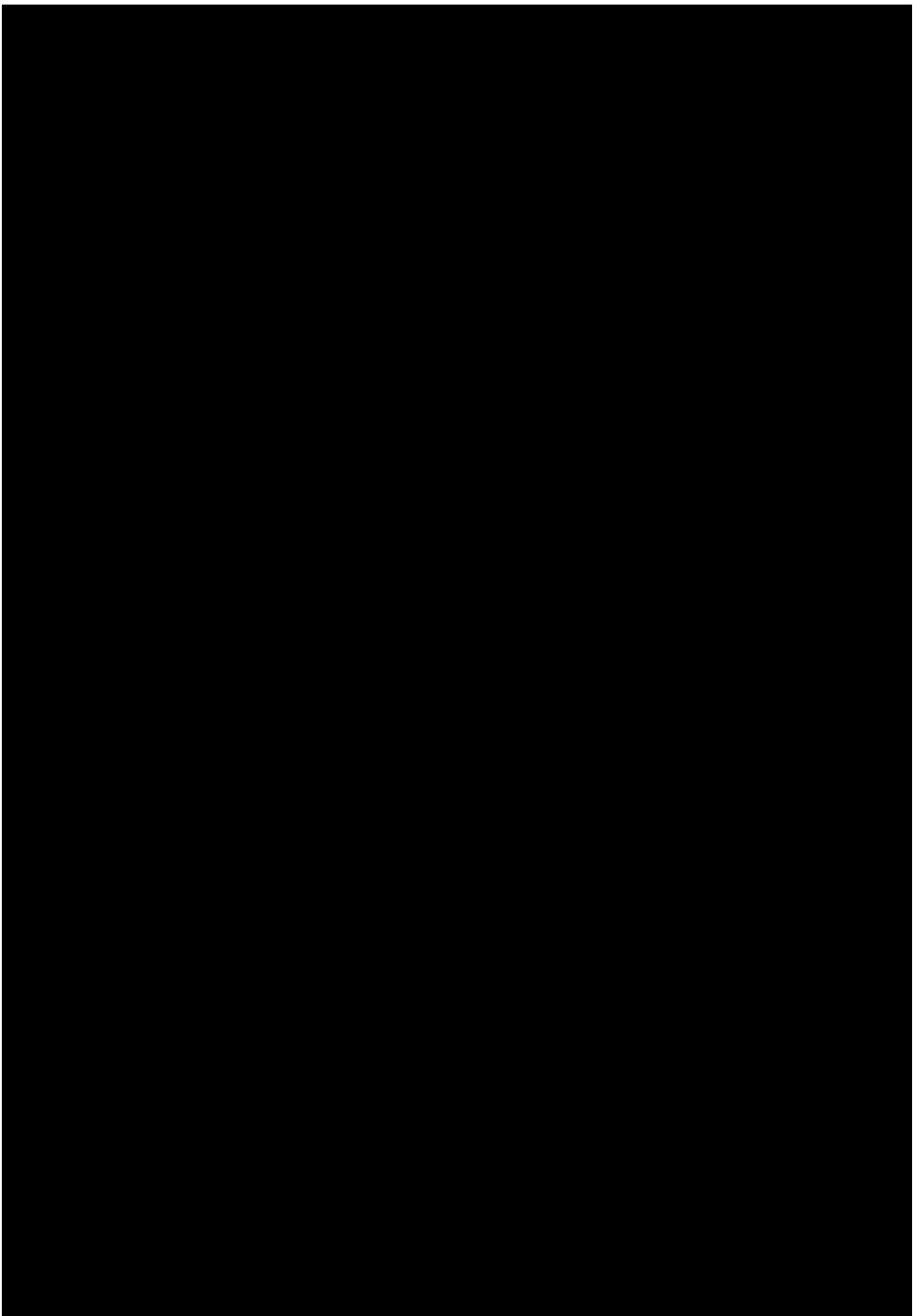
At the [REDACTED] Part 1 End-of-Treatment visit, safety monitoring will include vital signs, ECGs, physical examination, neurologic evaluation, laboratory assessments, assessment of AEs, and review of concomitant medications. Final efficacy assessments for Part 1 will also be performed, including MRI. For details, see the SOA/Part 1 (Table 6).

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.

Part 2

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, 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. <u>LTE Eligibility Visit (LTE Day 1)</u> 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 (Table 7). 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. <u>LTE Treatment Period</u> Participants will receive [REDACTED] doses of REC-994 [REDACTED] or REC-994 [REDACTED] 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] 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]. 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. 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 (Table 7); MRIs will be performed at the [REDACTED] visits and also for subsequent visits occurring [REDACTED] <u>LTE Follow-up Period</u> 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 EoS visit will occur within [REDACTED] following the 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 1 month later for an End-of-Study/Follow-up visit. For subjects 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.
Study Overview Diagram	

Number of Participants (planned)	Approximately [REDACTED] participants will be randomized for participation in Part 1 of the study. Only participants completing Part 1 are eligible for participation in Part 2.
Investigational Product, Dosage, and Mode of Administration	REC-994 [REDACTED] tablets for [REDACTED] Active Substance: REC-994 (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl [C ₉ H ₁₈ NO ₂]) Manufacturer: [REDACTED]
Reference Therapy, Dosage, and Mode of Administration	Placebo tablets for [REDACTED] Substance: Microcrystalline cellulose, National Formulary (NF); lactose monohydrate, NF; magnesium stearate (vegetable source), NF; and Opadry™ II 85F18422 white. Opadry™ II is non-compendial ingredient and released per manufacturer's specifications. Manufacturer: [REDACTED]
Duration of Study	The duration of participation for each participant in Part 1 is up to [REDACTED], as follows: • Screening ([REDACTED]), • Treatment Period ([REDACTED]) • Follow-up Period ([REDACTED], only for participants who do not proceed to Part 2) Participants who proceed to Part 2 will move directly from the Part 1 [REDACTED] End-of-Treatment Visit into dosing for Part 2. Total study duration for participants who complete Part 1 ([REDACTED]) and Part 2 is open-ended subject to Sponsor's discretion, as follows: • Screening ([REDACTED]), • Treatment Period for Part 1 ([REDACTED]) plus Part 2 ([REDACTED]) • Follow-up Period ([REDACTED]) All participants will have a follow-up visit 1 month after their last dose of study drug for final safety monitoring regardless of whether they end participation early in either Part 1 or Part 2 of the study, complete Part 1 and do not proceed to Part 2 of the study, or complete Part 2 of the study.
Selection Criteria: Part 1	Inclusion Criteria To participate in Part 1 of the study, the participant must meet ALL of the following criteria at the time of enrollment: 1. Be male or female 18 years of age or older with anatomic CCM lesions demonstrated by brain MRI 2. Have symptomatic CCM, defined as having clinical signs and symptoms consistent with CCM lesion neuroanatomical location and manifested by mRS score greater than or equal to 1 3. Have provided written informed consent to participate in the study 4. Females must be either: • of non-childbearing potential (defined as having undergone surgical sterilization or being postmenopausal [ie, greater than 50 years old with amenorrhea for ≥ 12 months]) OR • using at least two of the following acceptable methods of contraception during the study and for up to 24 weeks after the last administration of study drug:

	a. Double-barrier method (e.g., condom plus spermicide, condom plus diaphragm with spermicide) b. Stable use of hormonal contraceptive treatment c. Intrauterine Device (IUD) d. Monogamous relationship with a vasectomized partner e. Abstinence for 8 weeks prior to and throughout the study 5. Men who are sexually active must use the following forms of medically acceptable birth control during the study drug treatment period and for 24 weeks after the last administration of study drug: a. Vasectomy with medical assessment of surgical success OR b. Consistent use of a condom with partner also using either stable hormonal contraceptive or IUD. Sperm donation is prohibited during the study and for up to 24 weeks after the last administration of study drug. 6. Have NOT participated in a clinical study utilizing an investigational agent within 28 days or within 5 half-lives (if known) of the investigational drug (whichever is longer) prior to Screening 7. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, and other study procedures. Exclusion Criteria To participate in Part 1, the participant must meet NONE of the following at the time of enrollment: 1. Have symptoms deemed by the study Investigator to be caused exclusively by irreversible neuronal damage from prior stroke or neurosurgical instrumentation 2. Have a history of cranial irradiation or surgical/radiosurgical treatment of the primary symptomatic CCM lesion as determined by the study Investigator 3. DELETED: Exclusion criterion 3 removed in Amendment 2 4. Be pregnant or breast feeding 5. Be unable or unwilling to participate in MRI assessments (e.g., claustrophobia, metal implant, or implanted cardiac pacemaker) 6. Have liver dysfunction or active liver disease as defined by baseline serum transaminases >2x upper limit of normal (ULN) 7. Have moderately or severely impaired renal function (estimated glomerular filtration rate [eGFR] <60ml/min/1.73m²), active renal disease or have previously received a kidney transplant 8. Have had a previous diagnosis of skeletal muscle disorders (myopathy) of any cause or have a baseline creatine kinase level >5x ULN 9. Have a history of alcohol or substance abuse within 1 year prior to screening for study participation, or is currently using alcohol, drugs of abuse, or any prescribed or over-the-counter medication in a manner, which, in the opinion of the Investigator, indicates abuse 10. Have any clinically significant laboratory abnormality or illness which, in the opinion of the Investigator, could interfere with the conduct or interpretation of the study or put the participant at risk
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	11. Have had an intracerebral hemorrhage within 3 months of screening or any brain surgery within 6 months of screening (not including the primary symptomatic CCM lesion [Exclusion criteria #2])
Selection Criteria: Part 2	Inclusion Criteria To participate in Part 2 of the study, the participant must meet ALL the following criteria at the time of enrollment: 1. Have provided written informed consent to participate in Part 2; this will occur at or before the [REDACTED] End-of-Treatment visit Part 1 (or as soon as possible thereafter [up to 14 days]). Part 2 consent should be obtained prior to any Part 1 [REDACTED] assessments to be used as an assessment for Part 2. 2. Have completed the Part 1 [REDACTED] End-of-Treatment and, in the opinion of the Investigator, is an appropriate candidate for continued participation. Participants who terminate Part 1 prematurely will not be eligible to participate in Part 2. 3. Females must be either of non-childbearing potential as confirmed in Part 1, or continue to use acceptable methods of contraception during the treatment period and for 24 weeks after the last administration of study drug 4. Men who are sexually active must continue the use the following forms of medically acceptable birth control during the study drug treatment period and for 24 weeks after the last administration of study drug NOTE: Sperm donation is prohibited during the study and for up to 24 weeks after the last administration of study drug. 5. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, and other study procedures. Exclusion Criteria To participate in Part 2, the participant must meet NONE of the following at the time of enrollment: 1. Be pregnant or breastfeeding 2. Be unable or unwilling to participate in MRI assessments (e.g., claustrophobia or metal implant) 3. Have any previously identified clinically significant laboratory abnormality or illness which, in the opinion of the Investigator, could interfere with the conduct or interpretation of the study or put the participant at risk
Safety Assessments	The primary purpose of Part 1 is to evaluate the safety and tolerability of REC-994. The safety of study drug (REC-994 and placebo) will be evaluated by clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis), 12-lead ECGs, vital sign measurements, physical examinations, neurological examinations, and ongoing assessment of AEs. Any events of intracerebral hemorrhage (ICH), whether or not they are symptomatic, will be recorded as an AE. • Pre-treatment emergent AEs will be those recorded after informed consent is signed up to the time of the first administration of study drug. • Treatment-emergent adverse events (TEAEs) will be those recorded from the time of the first administration of study drug to the last dose of study drug taken by the participant during this study. • Post-treatment emergent AEs will be those recorded from the last dose of study drug taken by the participant through the last study-associated visit.

	Changes from baseline to [REDACTED] in clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis), standard digital ECGs, vital signs, TEAEs, and serious adverse events (SAEs, including deaths and withdrawals) will be evaluated. All participants who receive at least one dose of study drug will be included in the Part 1 analyses of safety. The primary purpose of Part 2 is to evaluate long-term safety and tolerability of REC-994, which will include ongoing assessment of AEs, clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis), 12-lead ECGs, vital sign measurements, physical examinations, and neurological examinations.
Efficacy Assessments	A secondary objective for Part 1 is to assess the efficacy of REC-994. The endpoints will be change from baseline to [REDACTED] for SMSS, mRS score, [REDACTED] score, CGI/PGI scale, participant-recorded diary number of seizures per month, participant-recorded diary number of headaches per month, and number of symptomatic hemorrhagic events (based on clinical and MRI or CT evidence). [REDACTED] All participants having at least one efficacy assessment after randomization will be included in the Part 1 analyses of efficacy. Long-term efficacy assessments in Part 2 include the same variables as Part 1: mRS, SMSS, [REDACTED], CGI-I/PGI-I, number of symptomatic hemorrhagic events (MRI or CT), number of MRI- or CT-confirmed cerebral hemorrhagic events, [REDACTED]. [REDACTED]
Pharmacokinetics Assessments	Plasma concentrations of REC-994 will be assessed during Part 1 of the study; no PK assessments will be performed for Part 2. Extended PK sampling will be performed at the [REDACTED] visit at 0 (pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, and 5 hours after administration of study drug. Participants will also return to the clinic the next day for PK sampling at 24 hours following initial administration of study drug at the [REDACTED] visit. Participants enrolled under Protocol REC-994-201 Versions 1-3 who underwent extended PK sampling at Study Day 1 are not required to undergo repeated PK sampling at [REDACTED]. Trough (pre-dose) and T_{max} (1.5 hours post dose) samples will be collected at [REDACTED] (T_{max} only) and at [REDACTED] to monitor exposure; these data may be used for population PK analyses. Individual and summary pharmacokinetic parameters to be determined include, but are not limited to, area under the curve from time zero (pre-dose) to the dosing interval time (area under the curve [AUC_{0-tau}]), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and pre-dose concentration (C_{trough}). Population PK parameters may be summarized in a separate report.

Sample Size	
Statistical Methods	Data from Part 1 will constitute the primary analyses of the study and will be performed upon database lock after the last participant enrolled in Part 1 has completed the last study visit of Part 1. Statistical analysis details will be provided in the Statistical Analysis Plan (SAP). Part 1 The Part 1 primary objective is safety and tolerability as assessed by the following endpoints: number, severity, and relatedness of AEs; number, severity, and relatedness of SAEs; number, severity, and relatedness of AESIs; and number of AEs leading to study drug discontinuation. The secondary objective for safety and tolerability will be assessed by the following endpoints: clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis), 12-lead ECGs, vital sign measurements, physical examinations, and neurological examinations. Safety and tolerability will be summarized by treatment group in terms of the number and percentage of AEs. All TEAEs will be coded in accordance with The Medical Dictionary for Regulatory Activities (MedDRA) in terms of preferred term (PT) and system organ class (SOC). The frequency and severity of AEs will be summarized by randomized treatment group; in particular, TEAEs, SAEs and deaths, AEs leading to cessation or suspension of randomized treatment will be presented. AEs by relationship to study treatment will also be summarized by the MedDRA SOC and PT. Laboratory data, physical examination, neurological examination, vital signs, and 12-lead ECG data will be summarized descriptively by treatment group over time, including displays of change from baseline. Values outside normal ranges will be identified and summarized by treatment groups. Incidence of abnormal physical examination and neurological findings will also be summarized. Details regarding data displays will be specified in the SAP.

	Part 2
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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
aPTT	Activated partial thromboplastin clotting time
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC ₀₋₂₄	Area under the plasma concentration-time curve from time zero to 24 hours
AUC _{0-t}	Area under the curve from time zero (pre-dose) to the last quantifiable timepoint
AUC _{0-inf}	Area under the plasma concentration-time curve from time zero to infinity
β-hCG	Beta human chorionic gonadotropin
■	■
BUN	Blood urea nitrogen
CCM	Cerebral cavernous malformation
■	■
CGI	Clinical Global Impression
CI	Confidence interval
cKO	Conditional knock-out
CL/F	Relative total clearance
C _{max}	Maximum concentration of drug in plasma
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computerized tomography
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EDC	Electronic data capture
FAS	Full Analysis Set
FoxO1	Forkhead box protein O1
GCP	Good Clinical Practice

26

Abbreviation or Specialist Term	Explanation
ROS	Reactive oxygen species
████	████████████████
SAE	Serious adverse event
SAP	Statistical analysis plan
SMSS	SymptoMScreen
SOC	System organ class
SOD	Superoxide dismutase
SS	Safety Set
SWI	Susceptibility-weighted imaging
$T_{1/2}$ ($t_{1/2}$)	elimination half-life
TEAE	Treatment-emergent adverse events
$T_{\max}$ ($t_{\max}$)	time to reach highest observed (peak) concentration in plasma following drug administration
ULN	Upper limit of normal
US(A)	United States of America
V_z/F	Apparent volume of distribution
WBC	White blood cells

5 INTRODUCTION

REC-994 is a redox-cycling nitroxide compound capable of reducing reactive oxygen species (ROS) and is being advanced for the treatment of patients with symptomatic CCM.

5.1 Cerebral Cavernous Malformation

Cerebral cavernous malformation 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 (*CCM1*), oncostatin M (*CCM2*), or programmed cell death 10 (*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 ROS, such as superoxide anions or hydroxyl radicals, during mitochondrial metabolism and their scavenging by antioxidant enzymes, such as superoxide dismutase-2 (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 subject 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, a protein complex that helped to limit apoptosis in response to oxidative stress ([Whitehead, 2009](#)).

5.2 REC-994

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, 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, ie, in the skin after ultraviolet 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. 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](#); and unpublished results).

5.2.1 [REDACTED]

5.2.2 REC-994 – Other Clinical Studies

REC-994 has been tested in humans for several indications, all related to the reduction of ROS.

- Mitos Pharmaceuticals tested tempol (MTS-01) in human clinical studies as a topical agent to treat radiation-induced dermatitis (NCT01324141) and radiation-induced alopecia (NCT00801086).
- Matrix Biomed proposed conducting a clinical study with tempol for the treatment of radiation-induced mucositis, nephrotoxicity, and ototoxicity (NCT03480971).
- OT-551 is the cyclopropyl ester prodrug of tempol-H, the reduced form of tempol which is also a metabolite of REC-994. Othera Pharmaceuticals has conducted 2 clinical studies evaluating the efficacy of OT-551 to treat geographic atrophy in age-related macular degeneration. In a Phase 2 study, 10 participants received a 0.45% solution of OT-551 three times daily via topical administration to the eye for 2 years (Wong, 2010). OT-551 was well tolerated with no adverse effects reported. In a larger Phase 2 study (Sternberg, 2010), 137 participants received either a 0.30% or 0.45% solution of OT-551 topically to the eye 4 times daily for 18 months; no significant adverse effects were reported. One of the major metabolites of tempol, tempol-H, showed no evidence of ocular toxicity when administered directly to the eye.

5.3 Non-Clinical Summary

Details regarding the non-clinical profile of REC-994, including summaries of pharmacology and toxicology studies conducted by Recursion, are provided in the Investigator's Brochure (IB). These data indicate that no neurobehavioral effects or change to respiratory parameters were observed with use of REC-994 in animal models, and that REC-994 is not expected to elicit off-target pharmacodynamic effects at the doses proposed for this clinical study.

In the cardiovascular safety pharmacology study, [REDACTED]

Overall, results in toxicology studies performed with REC-994 are supportive of the safe use of REC-994 in humans. The primary toxicities observed in chronic rat and dog studies [REDACTED]

[REDACTED] These observations were seen in only a few animals and occurred generally within 30 to 40 minutes after dose administration and lasted approximately 30 minutes, after which animals were fully recovered. These findings were sporadic in nature and occurred only at doses and exposures significantly higher than will be observed in humans.

Table 1 presents C_{max} exposure multiples at no observable adverse effect level (NOAEL) dose levels in the chronic rat and dog studies relative to human exposure at a [REDACTED] dose. [REDACTED]

[REDACTED] Recursion therefore believes that the NOAEL doses identified in the chronic rat and dog toxicity studies support dosing up to [REDACTED] in the proposed Phase 2 study design.

Table 1 Exposure Multiples for REC-994 Following [REDACTED] Administration Based on Systemic C_{max} in Animals and Humans

Study		NOAEL Dose	C _{max} (ng/mL)	AUC _{0-t} (ng*hr/mL)	Exposure Multiple ^a
6-month Rat ^b	M	100 mg/kg	[REDACTED]	[REDACTED]	[REDACTED]
	F	100 mg/kg			
9-month Dog ^b	M	75 mg/kg			
	F	75 mg/kg			
[REDACTED]		[REDACTED]			

Abbreviations: AUC_{0-t}: area under the curve from time zero (pre-dose) to the last quantifiable timepoint; C_{max}: maximum concentration of drug in plasma; F: female; M: male; [REDACTED] NOAEL: no observable adverse effect level.

^a Exposure multiple = (C_{max} in animals) ÷ (C_{max} in humans at proposed clinical dose).

^b Data reported in table are from the NOAEL doses from the 6-month rat (Study RPG-19-002) and 9-month dog (Study RPG-19-001) studies

^c [REDACTED]

The potential genotoxicity of REC-994 was evaluated in a complete battery of Good Laboratory Practice-compliant genotoxicity studies as described in International Council for Harmonisation (ICH) S2(R1) which included an [REDACTED]

Based on the overall data from these studies, REC-994 is not considered to pose a genotoxic risk.

In summary, results in toxicology studies performed with REC-994 are supportive of the safe use of REC-994 in humans in CCM participants up to [REDACTED] daily.

Recent data not summarized in the IB are presented below.

5.3.1 In Vivo Efficacy

The ability of REC-994 to improve lesion burden, surface area, and volume was evaluated in CCM1 and CCM2 conditional knock-out (cKO) mice.

Study animals were randomly assigned to receive vehicle, 1-, 2.5-, or 10-mM REC-994 in drinking water starting at postnatal day 5 (P5). Drinking water with REC-994 was first given to nursing mothers starting at day P5 to enable drug exposure in the pups. Once pups were weaned, they were supplied with the same drinking water with or without REC-994 until euthanasia. CCM1 and CCM2 cKO animals were euthanized at 3 and 5 months of age for MRI analysis, respectively. MRI analysis was used to determine total lesion numbers, area, and volume in treated and control mice.

Dosing of REC-994 in the drinking water was well tolerated by all study animals including nursing mothers and their pups, along with weaned animals for both CCM1 and CCM2 cKO animals. All groups, including vehicle treated, experienced some animal deaths, but these numbers were low (1 to 3) and evenly distributed between groups.

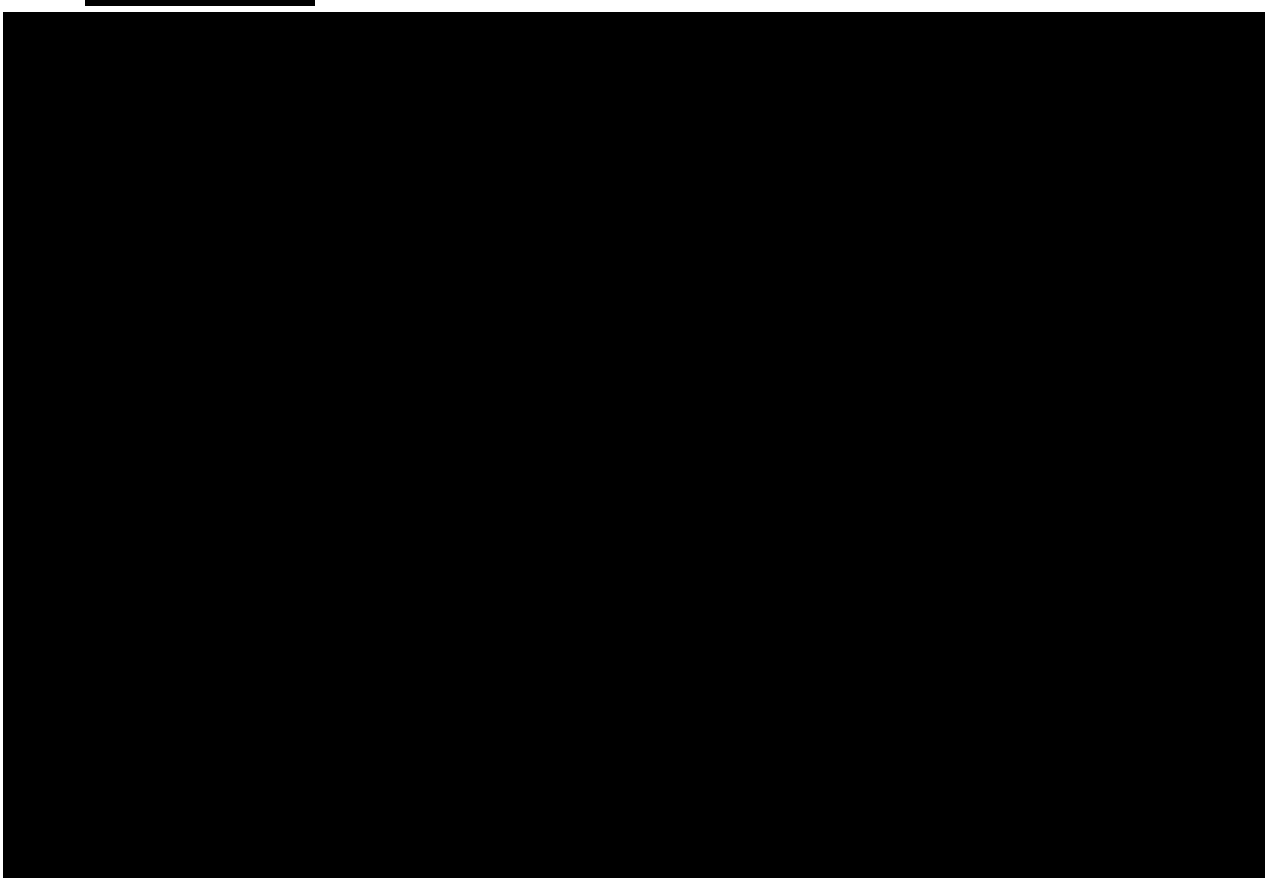
CCM1 cKO animals treated with 1 mM showed an increase in total brain lesions compared to controls but no changes in lesion areas or volumes. However, CCM1 cKO animals treated with 10 mM REC-994

showed statistically significant decreases in total lesions, lesion surface areas, and volumes when compared to vehicle treated controls.

CCM2 cKO animals were treated for 5 months. Treated animals did not show a statistically significant difference in total lesions, areas, or volumes compared to vehicle controls. However, similar to results published in [Gibson, 2015](#), mice treated with 10 mM REC-994 showed a trend of marginal rescue of lesion numbers. Also, as previously reported ([Gibson, 2015](#)), treatment with 10 mM REC-994 decreased the quantity of smaller lesions in CCM2 cKO mice compared to vehicle treated animals.

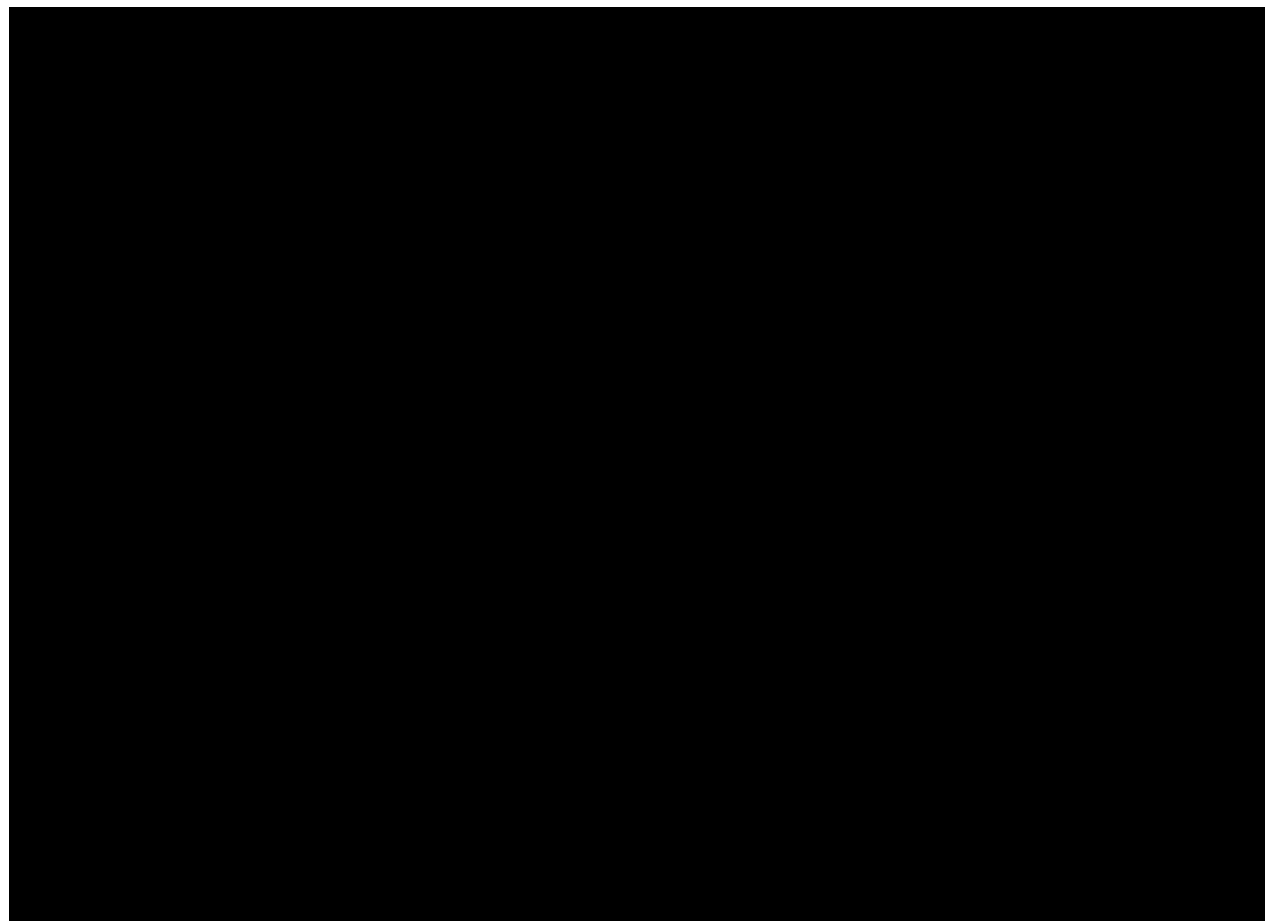
Mice given REC-994 in the drinking water for one week at 1-, 2.5-, or 10-mM had total average plasma concentrations of REC-994 (over 24 hours) of 80, 313, and 2580 nM respectively. These values translate to unbound average concentrations of 35.2 nM (6.06 ng/ml), 137 nM (23.6 ng/ml), and 1137 nM (196 ng/mL), respectively, given the measured REC-994 free fraction of 44% in mouse plasma.

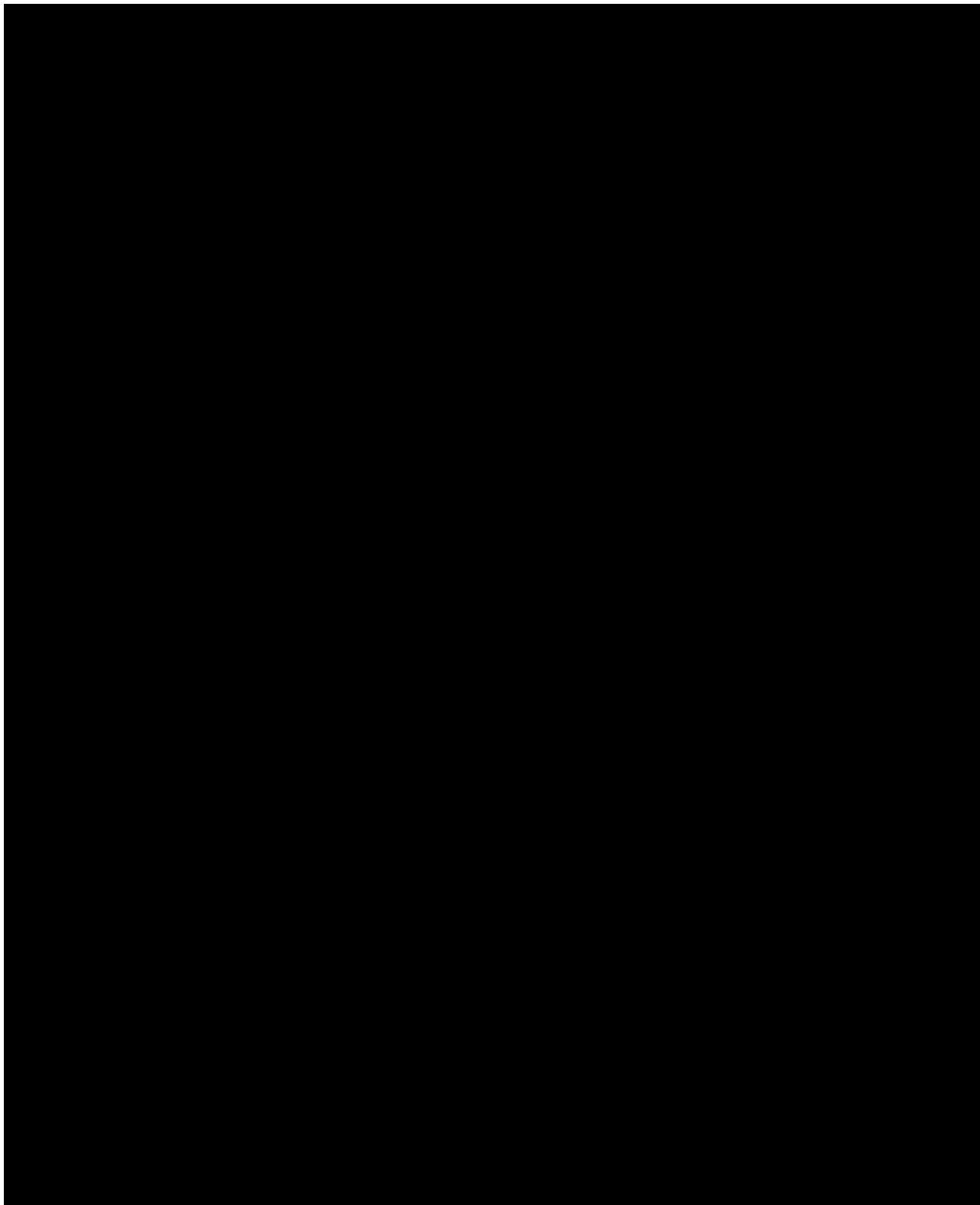
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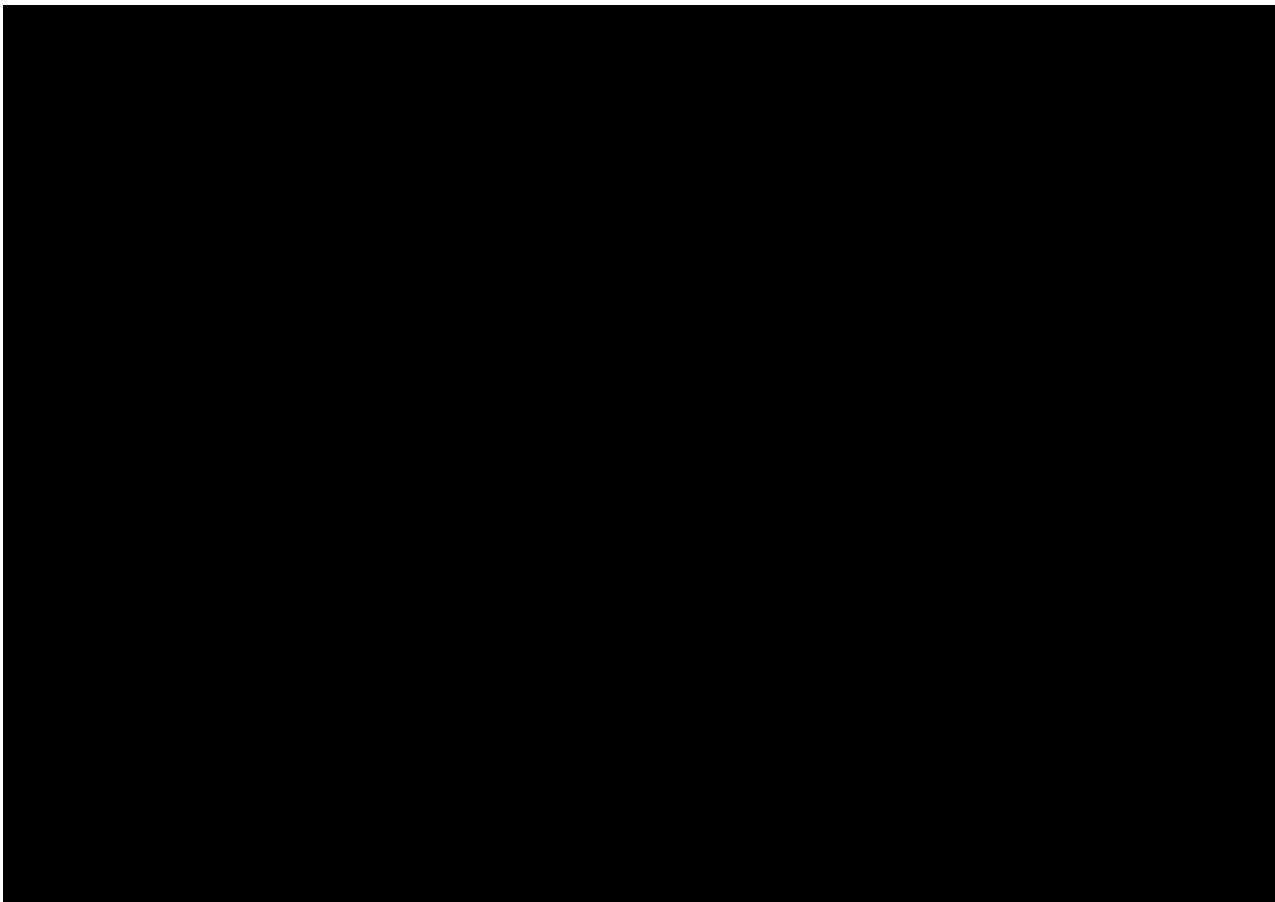


5.4.1

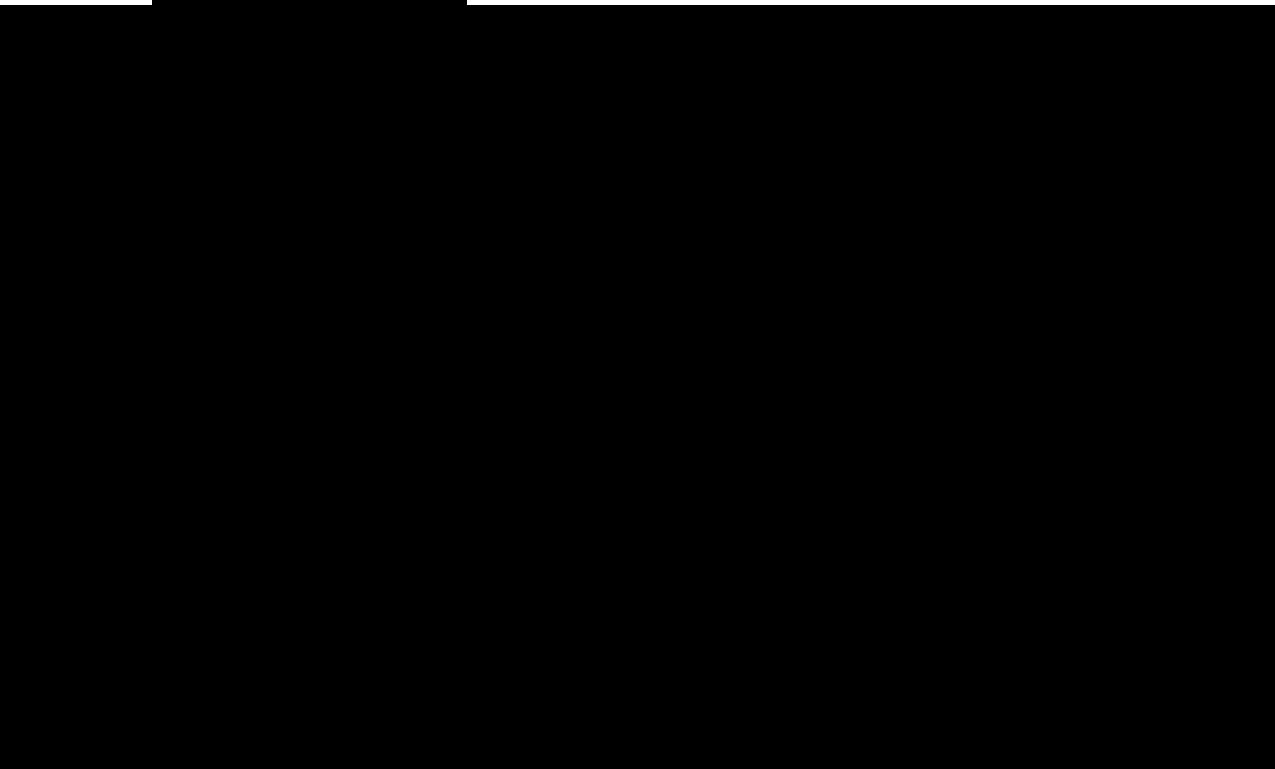








5.4.2



REC-994 is a superoxide scavenger. Results from nonclinical and human clinical studies have demonstrated the beneficial effects of REC-994 in supporting endothelial function and vascular tone in the context of pathological states, as well as neuronal protection from ischemia and neuroinflammation in the context of ischemia and diseases of the brain.

5.6 Rationale for Dose and Route of Administration

Hence, the [REDACTED] dose levels chosen for this study are expected to be safe and well tolerated.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 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- or CT-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] • Clinical Global Impression (CGI) • Patient Global Impression (PGI) • Number of seizures per month (participant diary) • Number of headaches per month (participant diary) • Number of MRI- or CT-confirmed symptomatic hemorrhagic events
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]	

6.2 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: (see Section 14.2 for definition of baseline) – mRS – SMSS • CGI-I • PGI-I • Number of MRI- or CT-confirmed symptomatic hemorrhagic events • Number of MRI- or CT-confirmed cerebral hemorrhagic events

For details regarding assessments of efficacy, see Section 12. For details regarding assessments of safety, see Section 11.

7 INVESTIGATIONAL PLAN

7.1 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 (██████) and ██████ compared to placebo in participants with symptomatic CCM over a treatment period of ██████. 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:

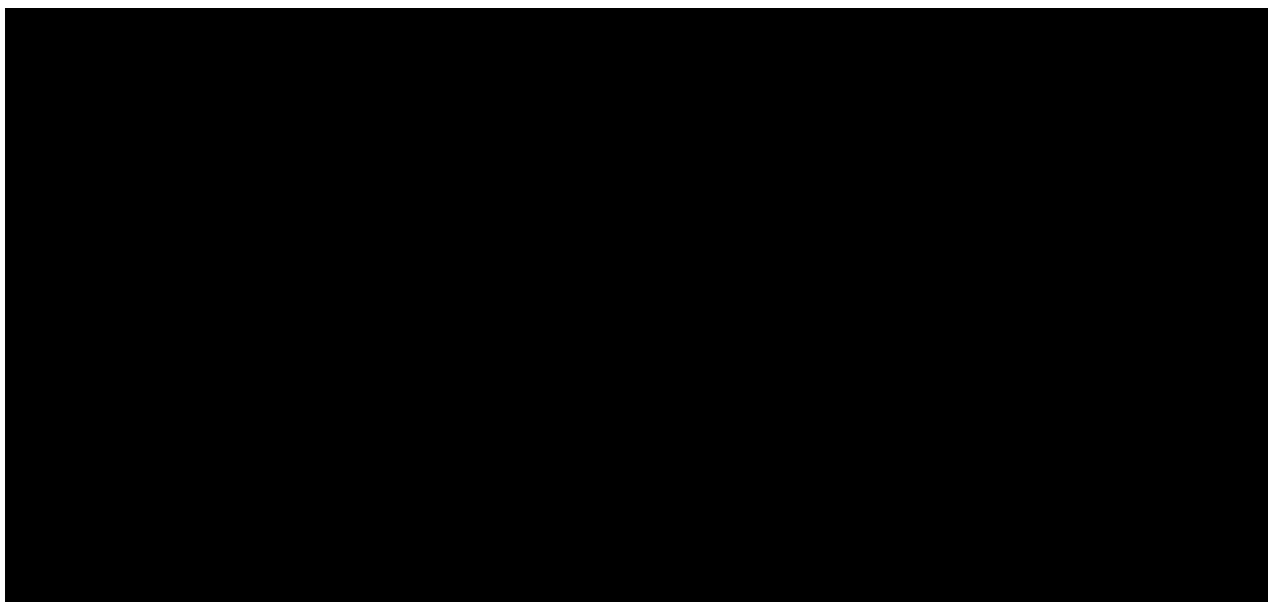
- Screening (████████████████████)
- Treatment Period (████████████████████)
- Follow-up Period (████████████████████)

Part 2 is an optional blinded LTE study of REC-994 for participants who have successfully completed ██████ 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 ██████ visit of Part 1 or as soon as possible thereafter [up to 14 days]).
- LTE Treatment Period: LTE Day 1 (Part 1 ██████) through the end of treatment, which is open-ended and subject to Sponsor discretion. Day 1 of Part 2 is coincident with the ██████ visit of Part 1; participants who are eligible and enter Part 2 will receive their first LTE dose at this visit (see Section 10.2).
- LTE Follow-up Period: ██████ following the EoT visit or ██████ after the decision to terminate Study REC-994-201, whichever is sooner.

An overview of the study design is presented in [Figure 1](#) and [Figure 2](#).



7.1.1 Part 1: Screening Period

During the Screening Period (approximately [REDACTED]), participants will undergo assessments as described in the Schedule of Assessments (SOA) for Part 1 (Table 6) to ensure they meet the Inclusion and Exclusion Criteria of the study. Medical history will be reviewed, including a 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*).

7.1.1.1 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).

7.1.2 Part 1: Treatment Period

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 [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 performed during the study will include vital signs, ECGs, physical examination, neurologic evaluation, laboratory assessments, 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 (to establish baseline values) and at study visits during the Treatment Period (to assess changes from baseline):

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

[REDACTED]
[REDACTED]
[REDACTED]

On Study 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 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, respectively, 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 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 [REDACTED] treatment period will remain on study for regular scheduled assessments (Table 6).

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

Prior to the Part 1 [REDACTED] End-of-Treatment 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 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 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], the safety follow-up visit ([REDACTED]). For subjects 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 (Table 6).

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.

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

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 (Table 7). 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.

7.1.5 Part 2: LTE Treatment Period

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 7.1.6. 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 (Table 7); MRIs will be performed at the [REDACTED]

7.1.6 Part 2: LTE Follow-up Period

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 EoS visit will occur within [REDACTED] following the 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 subjects 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.

7.2 Number of Participants

Approximately [REDACTED] participants will be randomized for Part 1 of the study with approximately [REDACTED] participants randomized to each treatment group. Only participants completing Part 1 are eligible for participation in Part 2.

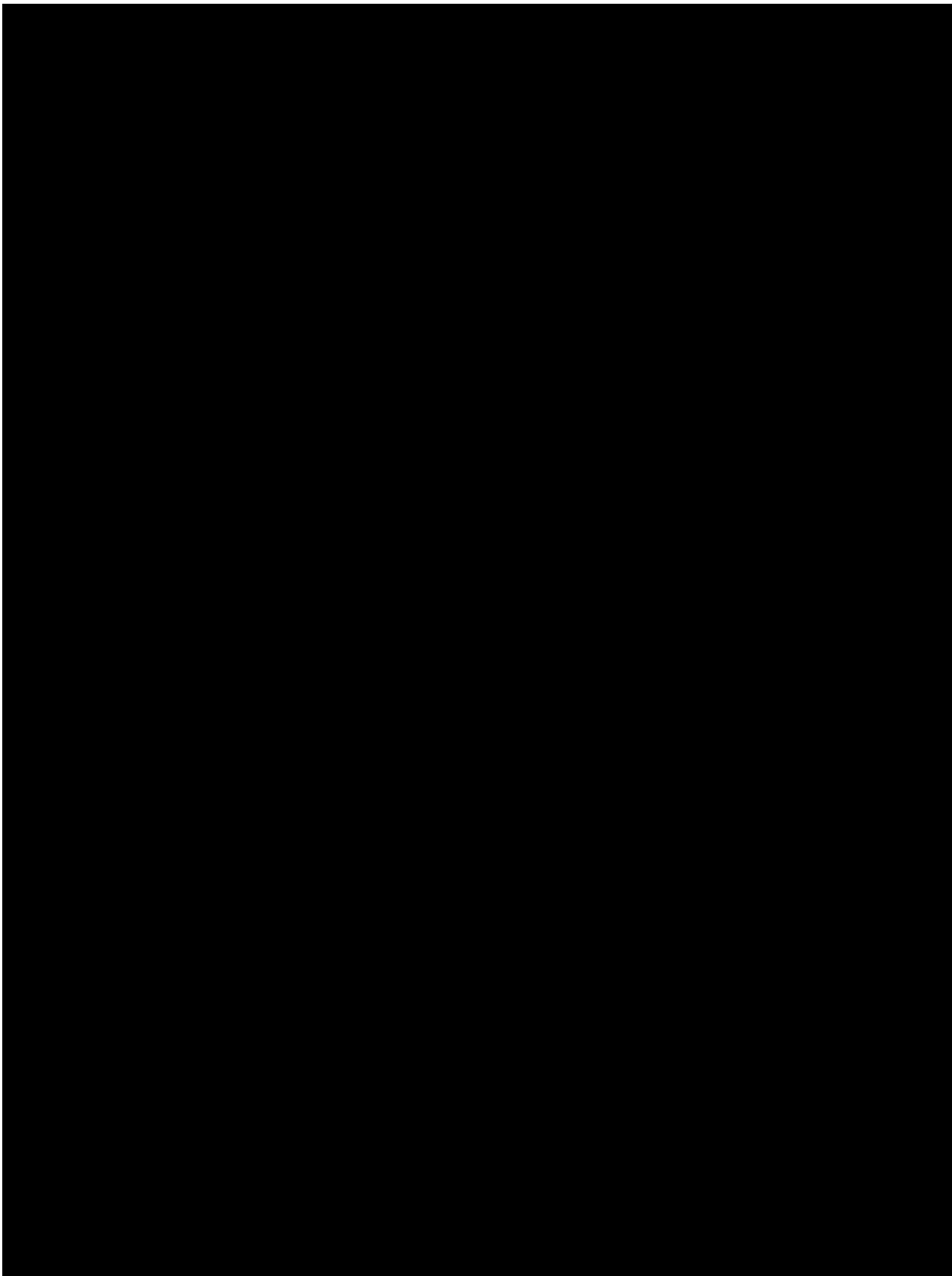
7.3 Treatment Assignment

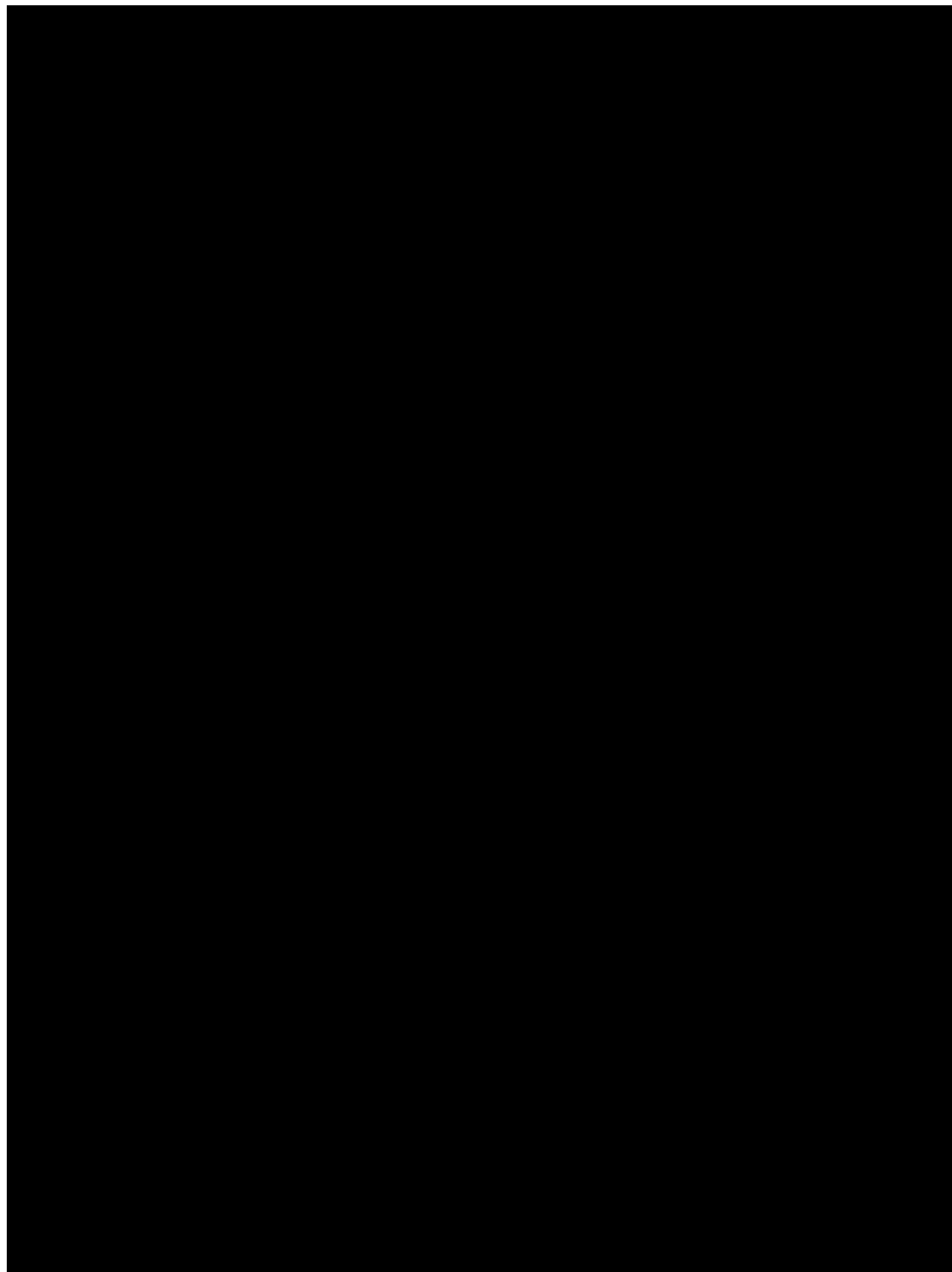
Participants will be randomized [REDACTED] to study drug during Part 1 of the study:

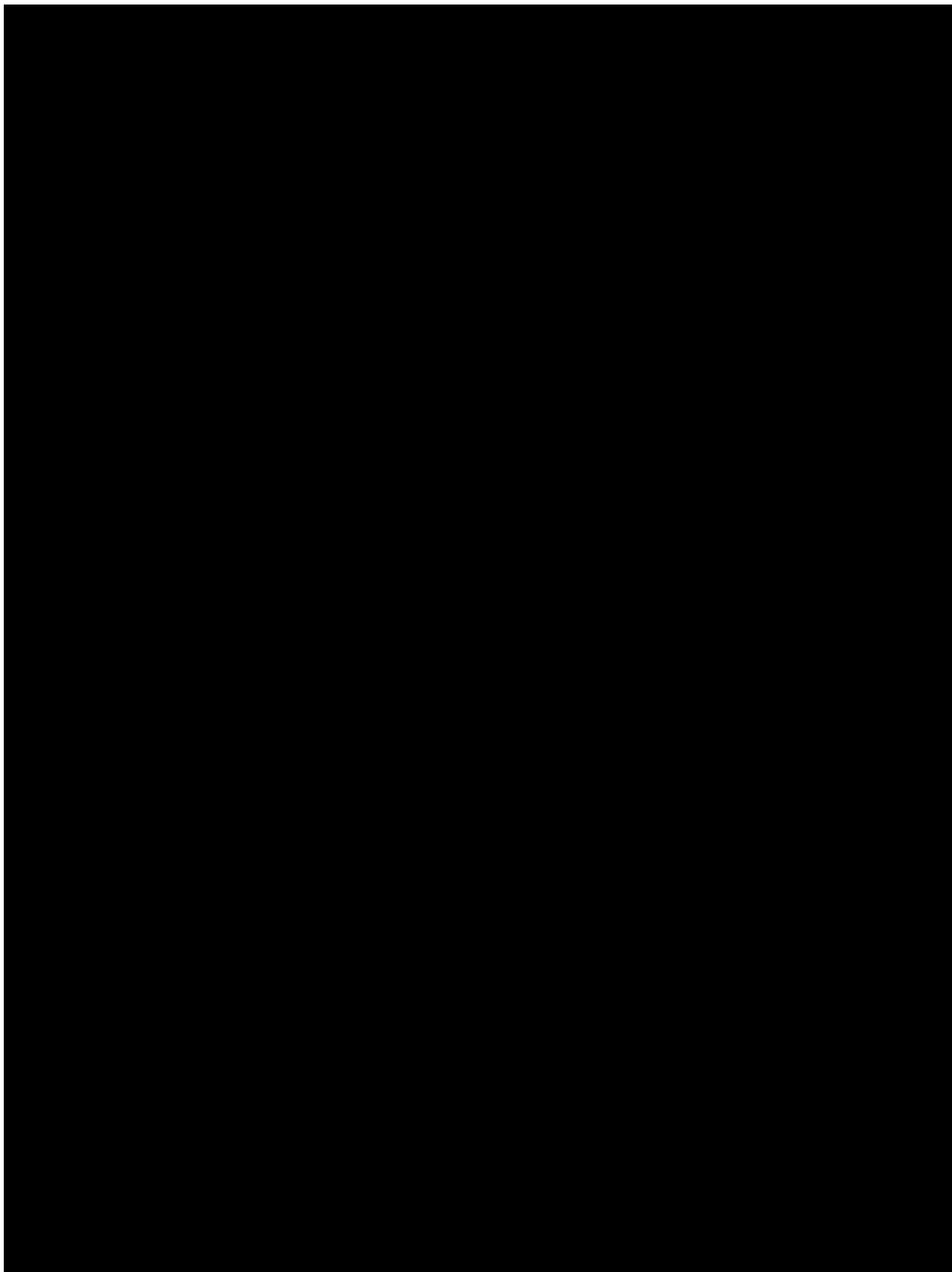
- REC-994 [REDACTED] [dosed as: REC-994 [REDACTED] + matching placebo [REDACTED]] or
- REC-994 [REDACTED] [dosed as: REC-994 [REDACTED]] or
- Placebo [REDACTED] [dosed as: matching placebo [REDACTED]].

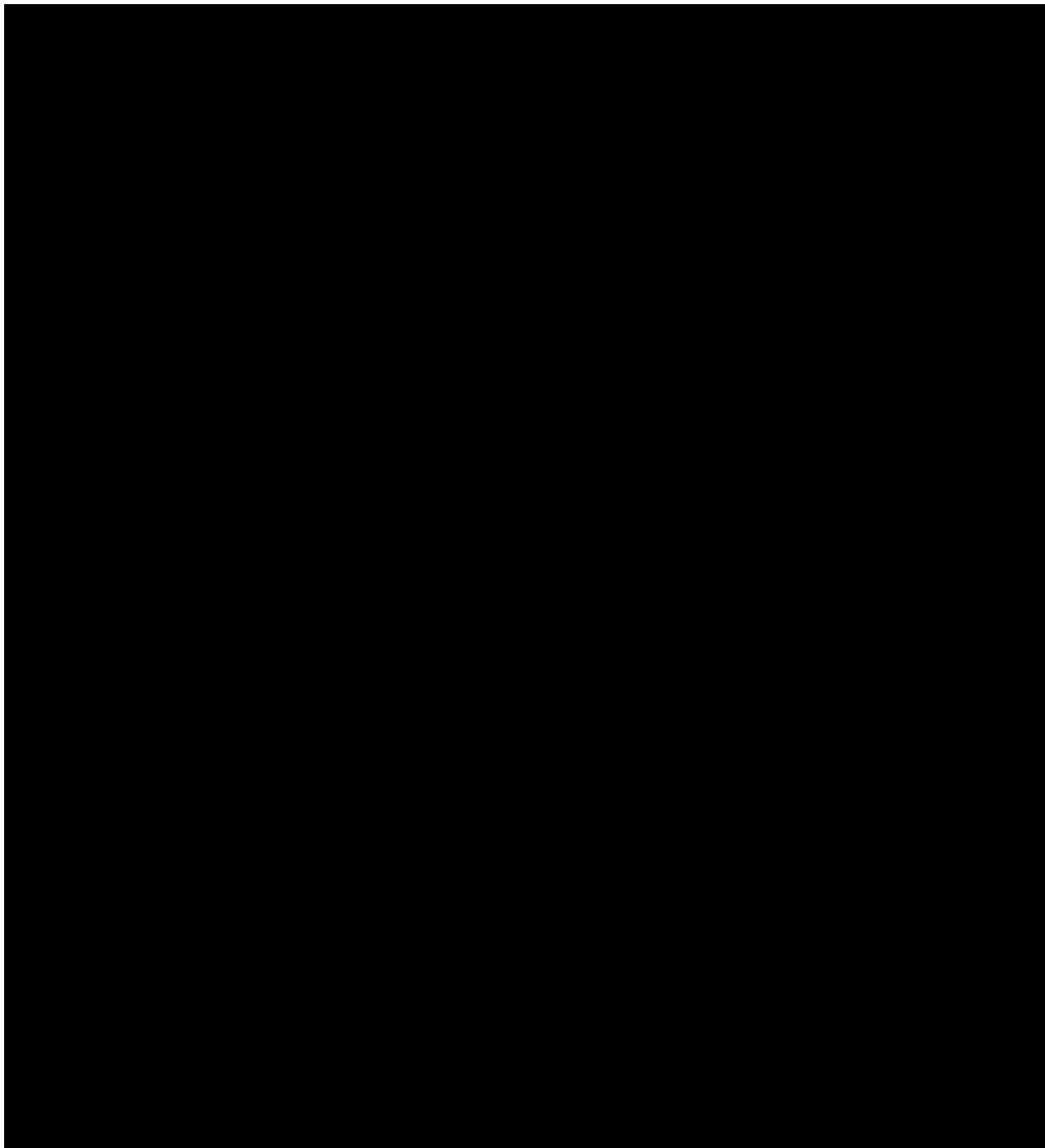
Participants who are eligible for Part 2 will receive daily dosing of REC-994 as follows:

- 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.









8 SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1 Part 1 Selection Criteria

8.1.1 Inclusion Criteria

In order to participate in Part 1 of the study, the participant must meet ALL of the following criteria at the time of enrollment:

1. Be male or female 18 years of age or older with anatomic CCM lesions demonstrated by brain MRI
2. Have symptomatic CCM, defined as having clinical signs and symptoms consistent with CCM lesion neuroanatomical location and manifested by mRS score greater than or equal to 1
3. Have provided written informed consent to participate in the study
4. Females must be either:

- of non-childbearing potential (defined as having undergone surgical sterilization or being postmenopausal [i.e., greater than 50 years old with amenorrhea for ≥ 12 months])

OR

- using at least two of the following acceptable methods of contraception during the study and for up to 24 weeks after the last administration of study drug:
 - a. Double-barrier method (e.g., condom plus spermicide, condom plus diaphragm with spermicide)
 - b. Stable use of hormonal contraceptive treatment
 - c. Intrauterine Device (IUD)
 - d. Monogamous relationship with a vasectomized partner
 - e. Abstinence for 8 weeks prior to and throughout the study
5. Men who are sexually active must use the following forms of medically acceptable birth control during the study drug treatment period and for 24 weeks after the last administration of study drug:
 - a. Vasectomy with medical assessment of surgical successOR
 - b. Consistent use of a condom with partner also using either stable hormonal contraceptive or IUD.Sperm donation is prohibited during the study and for up to 24 weeks after the last administration of study drug.
 6. Have NOT participated in a clinical study utilizing an investigational agent within 28 days or within 5 half-lives (if known) of the investigational drug (whichever is longer) prior to Screening.
 7. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, and other study procedures.

8.1.2 Exclusion Criteria

To participate in Part 1, the participant must meet NONE of the following at the time of enrollment:

1. Have symptoms deemed by the study Investigator to be caused exclusively by irreversible neuronal damage from prior stroke or neurosurgical instrumentation
2. Have a history of cranial irradiation or surgical/radiosurgical treatment of the primary symptomatic CCM lesion as determined by the study Investigator
3. DELETED: Exclusion criterion 3 removed in Amendment 2
4. Be pregnant or breast feeding
5. Be unable or unwilling to participate in MRI assessments (e.g., claustrophobia, metal implant, or implanted cardiac pacemaker)
6. Have liver dysfunction or active liver disease as defined by baseline serum transaminases $>2\times$ upper limit of normal (ULN)

7. Have moderately or severely impaired renal function (estimated glomerular filtration rate [eGFR] $<60\text{ml/min/1.73m}^2$), active renal disease or have previously received a kidney transplant
8. Have had a previous diagnosis of skeletal muscle disorders (myopathy) of any cause or have a baseline creatine kinase level $>5\times$ ULN
9. Have a history of alcohol or substance abuse within 1 year prior to screening for study participation, or is currently using alcohol, drugs of abuse, or any prescribed or over-the-counter medication in a manner, which, in the opinion of the Investigator, indicates abuse
10. Have any clinically significant laboratory abnormality or illness which, in the opinion of the Investigator, could interfere with the conduct or interpretation of the study or put the participant at risk
11. Have had an intracerebral hemorrhage within 3 months of screening or any brain surgery within 6 months of screening (not including the primary symptomatic CCM lesion [Exclusion criteria #2]).

8.2 Part 2 Selection Criteria

8.2.1 Inclusion Criteria

In order to participate in Part 2 of the study, the participant must meet ALL of the following criteria at the time of enrollment:

1. Have provided written informed consent to participate in Part 2; this will occur at or before the [REDACTED] End-of-Treatment visit Part 1 (or as soon as possible thereafter [up to 14 days]). Part 2 consent should be obtained prior to any Part 1 [REDACTED] assessments to be used as an assessment for Part 2.
2. Have completed the Part 1 [REDACTED] End-of-Treatment and, in the opinion of the Investigator, is an appropriate candidate for continued participation. Participants who terminate Part 1 prematurely will not be eligible to participate in Part 2.
3. Females must be either of non-childbearing potential as confirmed in Part 1, or continue to use acceptable methods of contraception during the treatment period and for 24 weeks after the last administration of study drug
4. Men who are sexually active must continue the use the following forms of medically acceptable birth control during the study drug treatment period and for 24 weeks after the last administration of study drug.
5. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, and other study procedures.

NOTE: Sperm donation is prohibited during the study and for up to 24 weeks after the last administration of study drug.

8.2.2 Exclusion Criteria

To participate in Part 2, the participant must meet NONE of the following at the time of enrollment:

1. Be pregnant or breastfeeding
2. Be unable or unwilling to participate in MRI assessments (e.g., claustrophobia or metal implant)
3. Have any previously identified clinically significant laboratory abnormality or illness which, in the opinion of the Investigator, could interfere with the conduct or interpretation of the study or put the participant at risk

8.3 Withdrawal Criteria

8.3.1 Removal from Therapy or Assessment

Study medication may be discontinued at the discretion of the Investigator in consultation with the participant in the following instances:

- Unacceptable AEs or toxicity, as defined in Section 11 of the protocol, or toxicity that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered to not be in the participant's best interest
- Participant's request to discontinue for any reason
- Participant's non-compliance
- Pregnancy during the study
- Dosing is interrupted for more than 4 weeks for any reason
- Discontinuation of the study at the request of the Sponsor, a regulatory agency, or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The reason for study medication discontinuation must be documented. In the case of discontinuation due to an AE, SAE, or laboratory toxicity, the event that led to discontinuation must be specified and recorded on the AE electronic case report form (eCRF).

Participants who discontinue from study treatment during the [REDACTED] treatment period in Part 1 (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the [REDACTED] assessments) will have a Part 1 Early Termination visit conducted within [REDACTED] of their last dose of study drug. Participants will be encouraged to remain on the study and complete assessments through [REDACTED]; i.e., following the Early Termination visit participants will continue with visits as per the SOA, and be asked to complete a safety follow-up visit ([REDACTED] visit). Participants who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable. For subjects who terminate early, an MRI will be conducted if the termination is for symptomatic hemorrhage or if ≥ 3 months has passed since the last MRI.

For participants who terminate Part 2 participation early, a Part 2 Early Termination visit will be conducted as soon as possible, and participants will be asked to return 1 month later for an End-of-Study/Follow-up visit. For subjects who terminate early, an MRI will be conducted if the termination is for symptomatic hemorrhage or if ≥ 3 months has passed since the last MRI. At the time the Sponsor decides to terminate the study, participants will complete the EoT visit within 2 weeks of the decision to terminate the study; if a participant's last [REDACTED] visit occurred within 3 months of the decision to terminate the study, it may serve as the EoT visit. The EoS visit will occur at least [REDACTED] following the EoT visit or [REDACTED] after the decision to terminate Study REC-994-201, whichever is sooner.

If a participant discontinues dosing due to an SAE, the SAE should be followed as described in Section 11.2.1.5.

If a participant develops symptoms (e.g., new seizure, new headache or new or progressive neurologic deficit) possibly related to a clinically significant intracerebral hemorrhage, a brain MRI or CT scan should be performed as soon as possible to evaluate for new hemorrhage or new CCM lesions. Modified Rankin Scale and [REDACTED] assessments should be performed as soon as possible after the onset of

symptoms. Study drug should be stopped pending assessment by the investigator, in consultation with the Sponsor or Medical Monitor. Following review of the imaging reports, assessment of the participant's clinical condition, and consideration of the participant's prior CCM history, the Investigator will make a determination regarding the participant's continued participation in the study. Prior to discontinuing the participant from the study, the Investigator will confer with the Sponsor or Medical Monitor.

If a female study participant or the female partner of a male study participant becomes pregnant during the participant's participation in this clinical study, site staff must notify the Sponsor within 24 hours of learning of the pregnancy using the Pregnancy Reporting Form. For female study participants, study drug must be temporarily discontinued. A positive urine pregnancy test should be confirmed by a serum pregnancy test and if pregnancy is confirmed, female study participants will be permanently discontinued from study drug dosing immediately (see Section 11.3 for reporting and follow-up of pregnancy). Note that pregnancy only becomes an AE/SAE if there is an abnormal outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring.

8.3.2 Withdrawal from Study

Participants considering withdrawing from the study should be informed that they can discontinue treatment or withdraw from the study at any time without having to justify the reason for doing so and without jeopardizing their future medical care by the physician or institution. Participants must be discontinued from study treatment and withdrawn from the study under the following circumstances:

- Participant or participant's legally authorized representative requests discontinuation from the study
- Investigator advises that the participants safety and/or well-being could be compromised by further participation
- Sponsor request, for example, due to suspicion of fraud, multiple enrollments in clinical studies, lack of compliance

For participants who are withdrawn from the study, every effort should be made to conduct the assessments scheduled to be performed during the Early Termination Visit (see SOA Part1 and 2, [Table 6](#) and [Table 7](#)).

In all cases, prior to the Investigator discontinuing the participant from the study, the Investigator will confer with the Sponsor or Medical Monitor.

If a participant withdraws, or is withdrawn, from the study, the principal reason leading to the decision for withdrawal must be recorded in the appropriate section of the eCRF. The reasons for withdrawal from the study will be coded as:

- AE (serious or non-serious; related or unrelated to study procedures / medication, as assessed by the Investigator)
- Disease progression or lack of efficacy
- Non-compliance (participant fails to comply with protocol requirements)
- Withdrawal of consent by participant
- Lost to follow-up
- Discretion of Investigator (the Investigator determines that continuation in the study would be detrimental to a participant's well-being)
- Discretion of Sponsor
- Female participant becomes pregnant

- Clinically significant intracerebral hemorrhage
- Other (specify)

For participants withdrawing due to AE(s), the Investigator should review the potential relationship of the AE to the study/study medication and record their assessment on the eCRF. If a participant withdraws due to an AE, the AE should be followed as described Section 11.2.

8.3.3 Replacement of Participants

Participants discontinuing from study drug or withdrawing from the study will not be replaced.

8.4 Study Termination

The duration of Part 2 of the study is open-ended, and the study will be terminated at the Sponsor's discretion.

The study may also be terminated at the discretion of the Investigator, Sponsor, or Sponsor's Medical Monitor for any reason at any time. In addition, for reasonable cause, either the Investigator or the IRB/IEC may terminate the study at their center.

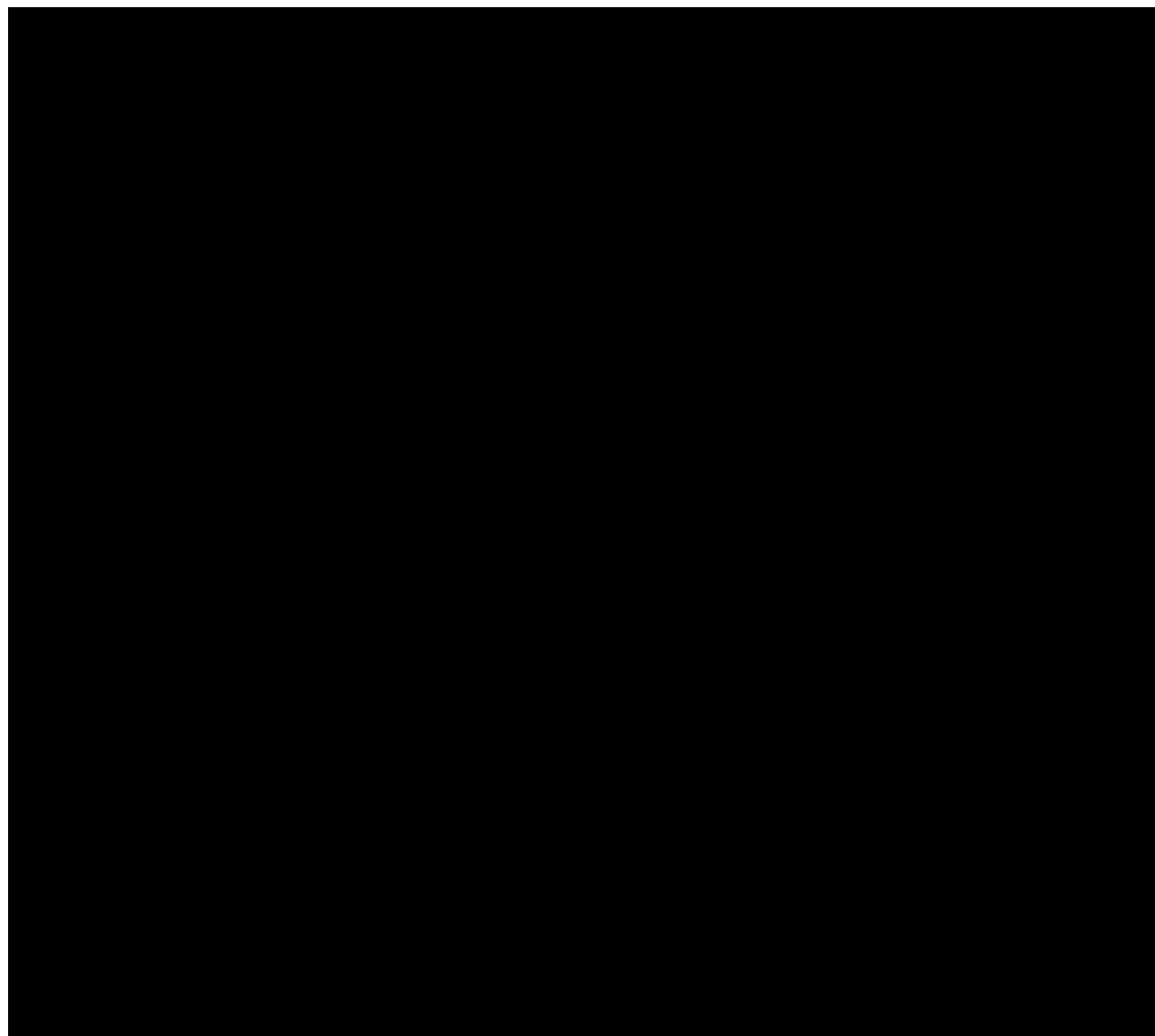
Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Administrative decision by the Investigator
- New toxicological or pharmacological findings or safety issues that alter the risk-benefit assessment
- Participant or Investigator noncompliance
- Unsatisfactory participant enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Decision by the Sponsor to discontinue development of REC-994 or modify the plan for its development
- Decision by a regulatory authority

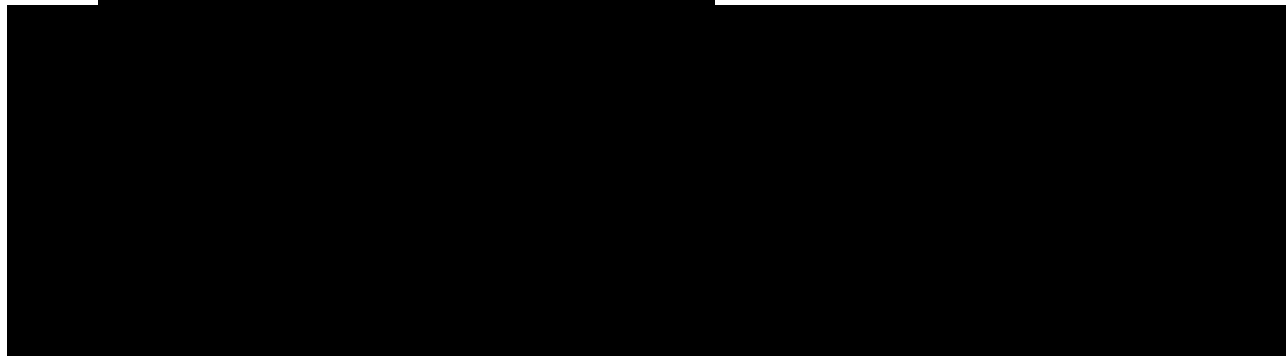
If the study is stopped, participants who are terminated early will be followed according to withdrawal criteria and procedures described in Section 8.3.1.

9 TREATMENT OF PARTICIPANTS

9.1



9.2



9.3

9.4 Randomization and Blinding

After obtaining informed consent, participants will be screened for Part 1 according to the inclusion and exclusion criteria. Participants who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study. On Study Day 1, participants will be randomized [REDACTED] to receive [REDACTED] dosing with study drug: REC-994 [REDACTED] or REC-994 [REDACTED] or placebo. Both participants and medical staff administering the study drug will be blinded to treatment assignment.

Eligibility for Part 2 will be determined during the Part 1 [REDACTED] visit (or as soon as possible thereafter [up to 14 days]). Signed consent for Part 2 must be obtained before any Part 2 Day 1 (i.e., Part 1 [REDACTED]) assessment is performed. Participants who consent and are eligible for Part 2 will be dosed on the same day (i.e., this will become LTE Day 1).

Treatment in Part 2 will be 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 daily [REDACTED] doses of either REC-994 [REDACTED] or REC-994 [REDACTED] during Part 2.

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.

10 [REDACTED]

10.1 [REDACTED]

[REDACTED]

10.2 [REDACTED]

[REDACTED]

10.3 [REDACTED]

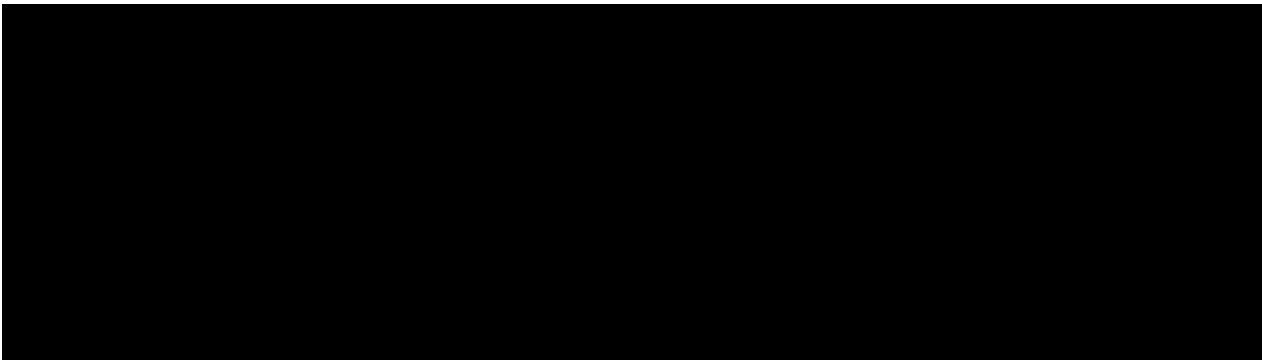
[REDACTED]

10.4 [REDACTED]

[REDACTED]

10.5 Administration

Randomized participants will receive their first [REDACTED] dose of study drug at the investigative site on Day 1. Participants will maintain daily [REDACTED] dosing with study drug throughout the treatment period. On the scheduled visit days for Part 1 [REDACTED], participants should not take their morning dose at home; the dose will be taken at the investigative site. The dose on the day after the Part 1 [REDACTED] visit will be taken following completion of the 24-hour PK sampling (for participants enrolled in Protocol REC-994-201 Versions 4 and higher).



10.6 Study Drug Accountability

The Investigator is responsible for the control of the study drug under investigation. Adequate records of the receipt and disposition of the study drug must be maintained as directed by the Sponsor. All records and study drug supplies must be available for inspection by the monitor at every monitoring visit.

10.7 Study Drug Handling and Disposal

Procedures for disposal of unused study drug at the end of the study will be specified by the Sponsor.

11 ASSESSMENT OF SAFETY

11.1 Safety Parameters

The safety of study drug (REC-994 and placebo) will be evaluated by 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 as specified in the SOAs (Table 6 and Table 7). Any events of intracerebral hemorrhage (ICH), whether or not they are symptomatic, will be recorded as an AE.

- Pre-treatment emergent AEs will be those recorded after informed consent is signed up to the time of the first administration of study drug.
- Treatment-emergent adverse events (TEAEs) will be those recorded from the time of the first administration of study drug to the last dose of study drug taken by the participant during this study.
- Post-treatment emergent AEs will be those recorded from the last dose of study drug taken by the participant through the last study-associated visit.

Changes from baseline to [REDACTED] in clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis), standard digital ECGs, vital signs, and TEAEs, and serious adverse events (SAEs, including deaths and withdrawals) will be evaluated for Part 1 analyses. Change from baseline to EoT will be applied to study Part 2. Baseline for Part 2 analyses will be based on Part 1 Day 1 or Part 2 LTE Day 1 (Part 1, [REDACTED]) as appropriate.

All participants who receive at least one dose of study drug will be included in the analyses of safety.

11.1.1 Vital Signs

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 as outlined in the SOAs (Table 6 and Table 7). Where applicable, vital signs will be collected pre-dose. In addition, blood pressure and heart rate will be collected with each PK sample.

11.1.2 Weight and Height

Weight will be measured as outlined in the SOAs (Table 6 and Table 7). Height will be measured at Screening at Part 1.

11.1.3 Physical Examination and Neurological Examination

A full physical examination will be performed at [REDACTED]. A focused physical exam (including head, eyes, ears, nose, and throat, respiratory, cardiovascular, and any other relevant organ systems) will be performed on other Study Visits as outlined in the SOAs (Table 6 and Table 7). Symptom-targeted physical examination will occur at any time during the study if indicated by AEs or if deemed necessary by the Investigator.

A neurological examination will be conducted during the study as outlined in the SOAs (Table 6 and Table 7). The full neurological examination will cover the following: cranial nerves, muscle strength and tone, reflexes, coordination, sensory function, and gait. Any unfavorable findings not present at screening, or worsened from the baseline assessment and considered by the investigator as clinically significant, occurring at any point in the study will be documented in the eCRF as an AE. Abbreviated neurological

examinations will evaluate any symptoms or systems found to be abnormal and/or unstable, or to investigate any reported or observed AEs.

11.1.4 Electrocardiogram (ECG)

All standard digital ECGs will be performed in triplicate after the participant has been supine for at least 5 minutes. Occasions on which ECGs are to be performed are specified in the SOAs (Table 6 and Table 7). Heart rate, PR duration, QRS duration, QT duration, QTcF (Fridericia's correction formula), and the investigator's overall interpretation will be recorded in the eCRF.

11.1.5 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. Wherever possible, confirmation of initial liver-related laboratory abnormalities should be performed in a timely fashion.

Potential drug-induced liver injury is an SAE and is defined as (FDA, 2009):

- Treatment-emergent alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$

OR

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

All cases of potential drug-induced liver injury are considered SAEs and require immediate reporting (Section 11.2.1.5).

11.1.6 Laboratory Assessments

Laboratory assessments including hematology, serum chemistry, coagulation, and urinalysis will be conducted as specified in the SOAs (Table 6 and Table 7). All blood and urine specimens will be sent to the study-specified Central Laboratory for analysis and testing. Details on sample collection, handling, storage, and shipping will be described in The Study Laboratory Manual.

The clinical laboratory tests should include, but are not limited to:

- **Hematology:** Complete blood count (including differential 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.
- **Coagulation:** prothrombin time/international normalized ratio and activated partial thromboplastin clotting time (aPTT).
- **Comprehensive metabolic panel:** sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, BUN/creatinine ratio, glucose, albumin, calcium, alkaline phosphatase, AST, 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 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, and uric acid. Thyroid-stimulating hormone will also be measured.
- **Urinalysis:** A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, white blood cells (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.

- **Pregnancy Testing:** Follicle stimulating hormone will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum levels must be ≥ 40 mIU/mL to be considered postmenopausal. If the participant was determined to be post-menopausal in Part 1, FSH does not need to be repeated and future pregnancy tests may be omitted.

Any female participant who does not meet the criteria for non-childbearing is considered to be of childbearing potential. Pregnancy tests will be performed for all female participants of childbearing potential. A serum pregnancy test will be performed during Part 1 at Screening, [REDACTED] and [REDACTED] (End of Study) and during Part 2 at End of Treatment, End of Study, and Early Termination. A urine beta human chorionic gonadotropin (β -hCG) test will be performed during Part 1 at Day 1 prior to receiving the first dose of study drug, at [REDACTED] (End of Treatment), and at the Investigator's discretion at an Early Termination Visit. During Part 2, a urine β -hCG test will be performed at the LTE Eligibility Visit and at [REDACTED]. If the urine β -hCG test is reported as positive, the result will be confirmed with a serum pregnancy test.

In case of unexplained or unexpected clinical laboratory test values, the tests will be repeated as soon as possible and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate which of these deviations after treatment are clinically significant. These clinically significant deviating laboratory results will then be recorded as AEs and the relationship to the treatment will be indicated.

11.2 Adverse and Serious Adverse Events

11.2.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a participant during the study; the event does not necessarily have a causal relationship with the treatment.

This includes events that occur after obtaining consent and throughout the duration of the study, including the follow-up off-study medication period. For example,

- Pre- or post-treatment complications that occur as a result of protocol mandated procedures (e.g., invasive procedures such as venipuncture) during or after screening (before the administration of study drug)
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical study, will also be considered an AE.

A subset of AEs may meet serious criteria. The definition of an SAE and reporting procedures for SAEs are detailed in Section 11.2.1.5. The definitions below apply to both AEs and SAEs.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the participant was screened in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).

Events and symptoms related to CCM (e.g., headache) will be monitored as trial endpoints and thus will not be recorded as AEs, unless individual events qualify as SAEs (see Section 11.2.1.5). One exception is

intracerebral hemorrhage, which is to be recorded as an AE regardless of whether the event is serious or nonserious.

The following are not considered to be AEs:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure or the complication that occurs as a result of the procedure is an AE
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for planned elective surgery, social and/or convenience admissions for example, a preexisting condition that is deemed clinically stable)
- Overdose without clinical sequelae (see below)
- Any medical condition or clinically significant laboratory abnormality with an onset date before signed consent is not an AE; it is considered to be pre-existing and should be documented on the medical history eCRF.

For this protocol, an overdose is any dose of investigational drug given to a patient or taken by a patient that exceeds by 2 times the dose described in the protocol (e.g., [REDACTED]). There is no information regarding overdose with REC-994. Any overdose, with or without associated AEs, must be promptly reported to the CRO's Medical Monitor. The overdose event does not need to be recorded as an AE in the eCRF. If an AE is associated with the overdose, the AE should be recorded on the relevant AE/SAE sections in the eCRF.

All AEs that occur after any participant has been enrolled, before treatment, during treatment, or through study discontinuation, whether or not they are related to the study, must be recorded on the AE page of the eCRF.

11.2.1.1 Documentation of Adverse Events

All participants will be queried, using non-leading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms should be identified as 1 overall event or diagnosis. All AEs for randomized participants will be recorded in the eCRF and the participant's source documents. The following data should be documented for each AE:

- Description of the event
- Classification of "serious" or "not serious"
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given.

11.2.1.2 Adverse Event Severity

The Investigator must determine and record the severity of all serious and non-serious AEs. The severity of an AE should be determined according to the definitions in [Table 9](#). Clinically significant laboratory tests should be recorded as AEs in the participant's source documents and eCRF.

Investigators seeking further guidance on assessment of intensity may consult the Common Terminology Criteria for Adverse Events, version 5.0 (information, including a searchable spreadsheet) can be found at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_60.

Table 9 Grading of Adverse Event Severity

Classification	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life-threatening consequences: urgent intervention required
Grade 5	Death related to an adverse event

11.2.1.3 Adverse Event Causality

Every effort should be made by the Investigator to assess the relationship of the AE, if any, to the study drug. Causality should be classified using the categories presented in [Table 10](#).

Table 10 Classifications for Adverse Event Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, i.e., there is a plausible biological mechanism for the event to be related to the investigational study drug, and/or the event re-appeared on re-exposure to the investigational study drug. Temporal proximity between the use of the drug and the appearance of the AE is not in itself sufficient as a basis for asserting that the use of the drug resulted in the occurrence of the AE.
Not Related	The event is related to an etiology other than the investigational study drug (the alternative etiology must be documented in the study participant's medical record).

11.2.1.4 Study Drug Action Taken

The Investigator, or designee, will classify the study drug action taken with regard to the AE. The action taken should be classified according to the categories shown in [Table 11](#).

Table 11 Classifications for Study Drug Action Taken with Regard to an Adverse Event

Classification	Definition
Dose Not Changed	Study drug dose not changed in response to an adverse event
Drug Interrupted	Study drug administration interrupted in response to an adverse event
Dose Decreased	Study drug dose decreased in response to inability to tolerate higher dose of study drug.
Drug Withdrawn	Study drug administration permanently discontinued in response to an adverse event
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as when the investigational treatment had been completed before the adverse event began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

Adverse Event Outcome

An AE should be followed until the Investigator has determined and provided the final outcome. The outcome should be classified according to the categories shown in [Table 12](#).

Treatment Given

The Investigator will ensure adequate medical care is provided to participants for any AEs, including clinically significant laboratory values. In addition, the Investigator will describe whether any treatment was given for the AE.

- "Yes" is used if any treatment was given in response to an AE and may include treatments such as other medications, hospitalization, surgery, or physical therapy. Any medications administered should be documented on the concomitant medication eCRF.
- "No" indicates the absence of any kind of treatment for an AE.

Table 12 Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an adverse event with no residual signs or symptoms
Recovered/Resolved with Sequelae	Resolution of an adverse event with residual signs or symptoms
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an adverse event, such that it remains ongoing
Fatal	Outcome of an adverse event is death. "Fatal" should be used when death is at least possibly related to the adverse event
Unknown	Outcome of an adverse is not known (e.g., a participant is lost to follow-up)

11.2.1.5 Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., screening, treatment, or follow-up), and at any dose of the investigational product, comparator, or placebo, that fulfils one or more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization (rehospitalizations for the same AE within one week of discharge will not be considered as a new admission)
- Results in persistent or significant disability or incapacity in conducting activities of daily living for at least 28 days
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above

SAEs (related and unrelated) will be collected from the signing of the informed consent form (ICF) until the final study visit. If clinical site personnel become aware of an event fulfilling the criteria of an SAE, the Investigator or clinical site personnel must notify Recursion Pharmaceuticals, Inc. Pharmacovigilance within 24 hours, regardless of assessment of relationship to the study drug. The site should report SAEs via the AE eCRF in the electronic data capture system (EDC) AND email a completed SAE report form to Recursion Pharmaceuticals Pharmacovigilance at safety@recursionpharma.com within 24 hours of awareness.

In addition, notification must be provided by the Investigator to the IRB.

If the Investigator becomes aware of an AE occurring after a participant has completed participation in the study that meets the criteria of an SAE AND is determined to be likely to be related to study drug, the SAE must also be reported to the Sponsor as a post-study event no later than 24 hours after the Investigator or any site staff becomes aware of the event.

SAEs deemed by the Investigator to be related to study drug that continue beyond the participant's participation in the study should be followed until the SAE is resolved or the Investigator determines the SAE is stable and requires no additional follow-up.

Recursion Pharmaceuticals, Inc. is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

11.3 Pregnancy

If a study participant or the partner of a male study participant becomes pregnant during the participant's participation in this clinical study, site staff must notify the Sponsor within 24 hours of learning of the pregnancy.

A female clinical study participant must be instructed to stop taking the study drug until the pregnancy is confirmed by a serum pregnancy test. If the test confirms the pregnancy, the participant will be discontinued from the study.

Female participants who become pregnant

The Investigator will make arrangements for the participant to be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. The investigator should follow up with the subject regarding any congenital anomalies diagnosed at 2 months following the birth of the child. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 11.2.1.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Male participants with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. The investigator should follow-up with the subject regarding any congenital anomalies diagnosed at 2 months following the birth of the child. Any termination of the pregnancy will be reported including fetal status (presence or absence of anomalies) and indication for the procedure.

NOTE: Pregnancy itself is not an AE/SAE. The event only becomes an AE/SAE if there is an abnormal outcome, a spontaneous abortion or still birth, an elective termination for medical reasons, or a congenital anomaly in the offspring.

12 ASSESSMENT OF EFFICACY

There is no standardized tool for assessing functional outcome in CCM studies. Most published natural history studies of patients with CCM have focused on presentation, diagnosis, management approaches and follow-up for prominent symptoms (headache, seizures, intracerebral hemorrhage, focal neurological deficit).

Since there is NO standardized tool for assessing functional outcome in CCM studies, there are no primary efficacy endpoints to be assessed in Part 1 or Part 2. This study will employ several tools to better understand potential effectiveness of REC-994 in participants with symptomatic CCM. The tools represent the following categories:

Non-specific assessments previously used in neurology intervention studies.

- mRS [REDACTED] (status and prediction of disability following acute stroke)
- CGI-S/CGI-I and PGI-S/PGI-I (global assessments of baseline severity and improvement following initiation of treatment with study drug)
- SMSS [REDACTED] (non-specific patient-reported outcomes)

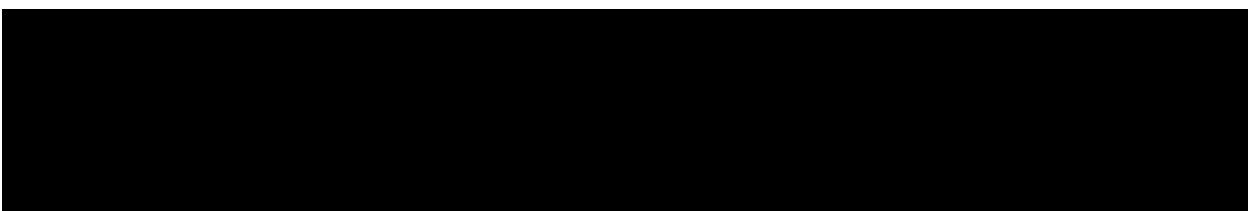
Clinical signs and symptoms previously associated with CCM in clinical studies

- Disease-associated [REDACTED]
- Disease-associated symptoms (seizures, headaches, symptomatic intracerebral hemorrhage)

Imaging outcomes

- MRI- or CT-assessed changes in cerebral anatomy and CCM lesions

While these tools, as a group, are likely to provide evidence of a response or lack of response to interventional treatment, there remains an unmet need for a CCM-specific functional outcome assessment tool. The tool should be broadly inclusive of symptoms and meaningful concerns of patients with CCM and be sensitive to changes (positive or negative) in functional outcomes following therapeutic interventions.



Efficacy assessments will be conducted during the screening period and at various Study Visits, as specified in the SOAs (Table 6 and Table 7). Efficacy endpoints for Part 1 of the study are listed in Section 6.1 and efficacy endpoints for Part 2 are listed in Section 6.2 .

12.1 Efficacy Assessments

12.1.1 SymptoMScreen Score (SMSS)

The SMSS questionnaire is a self-assessment tool (Green, 2017; Fitzgerald, 2019; Kister, 2020) originally developed for measuring symptom severity in patients with multiple sclerosis. It assesses 12 critical

neurologic domains that are also commonly affected in patients 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 these 12 items assessed on a seven-point Likert scale ranging from 0 (no at all affected) to 6 (total limitation). The total score ranges from 0 to 72, with higher scores indicating more severe symptom endorsement.

The SMSS total score was found to correlate with clinical disability, patient-perceived physical and psychological impact, and work productivity (as assessed by the Expanded Disability Status Scale, 29-item Multiple Sclerosis Impact Scale, and Working Productivity and Impairment Questionnaire, respectively) ([Green, 2017](#)).

The SMSS is being used in this study as a non-disease specific patient-reported outcome measure. Assessments will be made at Screening and throughout the treatment period. A copy of the instrument is provided in [Appendix 21.1](#).

12.1.2 Modified Rankin Scale (mRS) Score

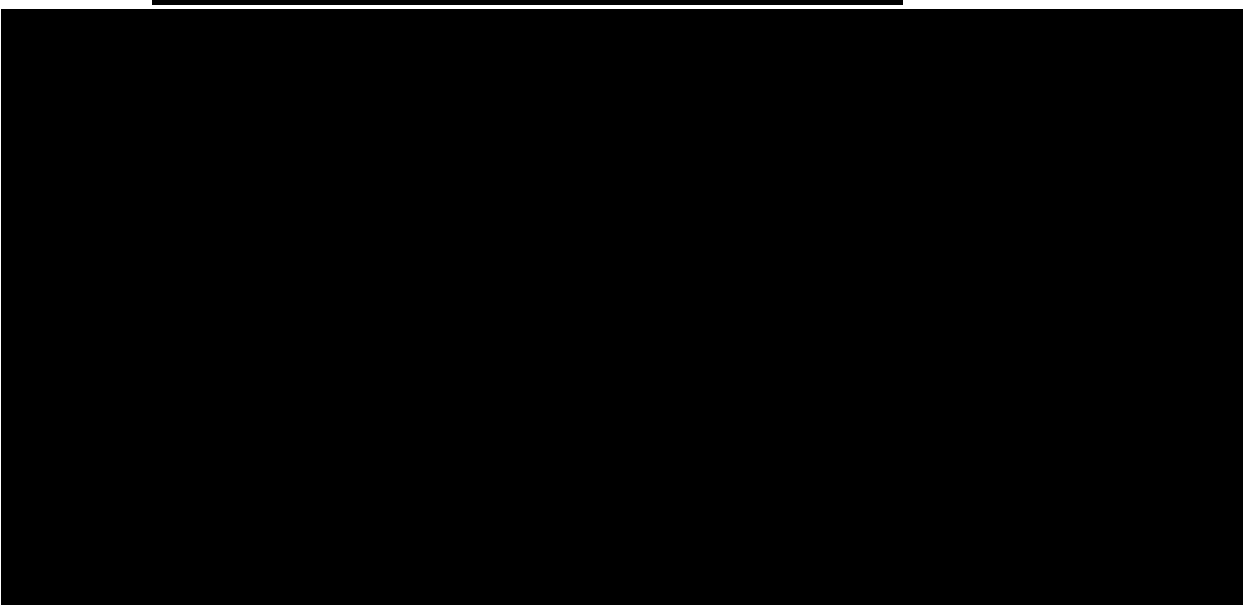
The modified Rankin Scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered an acute stroke. The mRS has been used widely in both secondary prevention and acute stroke studies, including most of the thrombolysis studies and all of the thrombectomy studies ([Broderick, 2017](#)).

The degree of disability is usually assessed by an independent observer and is scored according to a standardized scale. The scale runs from 0-5, corresponding to no symptoms at all (0) to severe (5) ([Van Swieten, 1998](#)). A recognized limitation of the mRS has been the subjective determination between categories and the reproducibility of the score by examiners and patients. ([Broderick, 2017](#)) To reduce variability, a structured interview format will be used to determine mRS scoring ([Wilson, 2002](#)).

Assessments will be made at Screening and throughout the treatment period by a certified rater. The interviewer should complete the structured interview then assign the appropriate mRS grade.

A copy of the instrument is provided in [Appendix 21.2](#).

12.1.3



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

The CGI Scale was originally designed to provide a clinician-rated view of a patient's global functioning before and after the initiation of study medication in clinical studies across psychiatric disease states. (Guy, 1976). Use of the Scale has been extended to multiple therapeutic areas assessing the effects of various treatments. Advantages of the Scale include the simplicity in administration and the extensive clinical study experience.

The measure comprises 2 companion components:

- a severity assessment performed on Study Day 1 (baseline) to provide a general summary assessment of the participant's CCM disease at the time of study entry and
- an improvement assessment that is performed during the Treatment Period at the time of study visits throughout both parts of study to provide an assessment of the change (improvement or worsening) in the participant's CCM disease after initiating treatment with study drug.

The Investigator and the participant will provide independent assessments at Baseline (CGI-S and PGI-S, respectively) and during treatment (CGI-I and PGI-I, respectively) (Table 6 and Table 7). The same individual should perform the assessment at all timepoints.

A copy of the instrument is provided in Appendix 21.4.

12.1.5 Seizure Frequency

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. All participants will provide daily Seizure Frequency Diaries through the Screening Period and throughout both parts of the study. If a participant is unable to complete the diary, the participant's caregiver will be able to complete the diary on their behalf.

12.1.6 Headache Frequency

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. All participants will provide daily Headache Frequency Diaries through the Screening Period and throughout both parts of the study. If a participant is unable to complete the diary, the participant's caregiver will be able to complete the diary on their behalf.

12.1.7

12.1.8

12.1.9

12.1.10 MRI and CT Assessments of Cerebral Lesions

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

Conventional MRI is able to accurately detect symptomatic cavernous malformations, which are surrounded by a ring of hypointensity due to hemosiderin deposits from recurring microhemorrhages. T2-weighted Gradient Recalled Echo (GRE) MRI displays CCM hemosiderin-filled brain tissue with a very distinct hypointensity. GRE MRI is an important assessment tool since it capable of identifying all CCM lesions while providing enhanced delineation. Susceptibility-weighted imaging (SWI) is a MRI technique that enhances image contrast by using the susceptibility differences between tissues. It is created by combining both magnitude and phase in the gradient echo data. SWI is sensitive to both paramagnetic and diamagnetic substances which generate different phase shift in MRI data ([Akers, 2017](#)).

Quantitative susceptibility mapping (QSM) images are reconstructed from GRE data and enable assessments of lesional temporal rates of change ([Mouchtouris, 2015](#)). MRI-QSM will be performed at a subset of investigational sites. The MRI Study Manual will provide details regarding equipment standardization, collection, processing, and analysis of images.

MRIs will be performed at as outlined in the SOAs ([Table 6](#) and [Table 7](#)). Routine MRI sequences will include T1-weighted pre- and post-contrast images, gradient echo T2*-weighted imaging, SWI and T2*-weighted images performed at 3 Tesla. Additional details regarding acquisition parameters will be specified in the MRI Manual associated with this study.

A local radiologist will perform the baseline radiographic assessment, and initial determination for inclusion will be made by the Investigator. The baseline radiographic assessment will be reviewed by a central reader; any differences between local and central review will be documented. Target CCM lesions (up to 10) to be followed during the course of the study will be identified by the central reviewer *a priori*, i.e., before the first dose of study drug. If more than 10 CCM lesions are present, the number (per hemisphere) and location of all other CCM lesions will be documented by the central reader.

To assess the efficacy of REC-994 in this study, total CCM lesion volume and number by MRI will be measured by a blinded independent central reviewer. Details regarding analysis of data from MRI procedures will be specified in the SAP associated with the study.

13 PHARMACOKINETIC ASSESSMENTS

13.1 Pharmacokinetic Sampling

Pharmacokinetic parameters of REC-994 following [REDACTED] will be measured in plasma during Part 1 of the study as described below. No pharmacokinetic assessments will be performed for Part 2.

- Plasma concentrations of REC-994 will be assessed at the [REDACTED] visit at 0 (pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, and 24 hours post-dose. Leftover PK samples from the [REDACTED] visit may be used for [REDACTED]. Participants enrolled under Protocol REC-994-201 Versions 1-3 who underwent extended PK sampling at Study Day 1 are not required to undergo repeated PK sampling at [REDACTED].
- Pre-dose (0, C_{trough}) and T_{max} (1.5 hours post-dose) samples will be collected at Study Visits at [REDACTED] (T_{max} sample only), [REDACTED] to monitor exposure; these data may be used in population PK analyses.
- A single PK sample will be collected prior to discharge from any participant who discontinues the study early.
- Pharmacokinetic parameters to be assessed at [REDACTED] include, but are not limited to:
 - maximum observed plasma concentration (C_{max})
 - time to maximum plasma concentration (T_{max})
 - area under the curve from time zero (pre-dose) to the dosing interval time (24 h, AUC_{0-tau})

14 STATISTICAL METHODS

The following provides an overview of the planned statistical methods for analysis and reporting. A separate SAP will be written to document in more detail the planned methods. If there are differences between the protocol and the SAP, the SAP will supersede the protocol.

14.1 Analysis Sets

All analysis sets will be defined separately for Part 1 and 2.

14.1.1 Full Analysis Set

The Full Analysis Set (FAS) will be defined as all participants randomly assigned to a treatment group having at least one efficacy assessment after randomization. In this set, participants will be grouped based on the randomized treatment, irrespective of the actual treatment received. The FAS will be used for all demographics, baseline characteristics, and efficacy analysis.

14.1.2 Safety Analysis Set

The Safety Set (SS), as treated, will include all randomized participants 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 set will be used for all safety analyses.

14.1.3 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPS) will include all randomized participants meeting the study eligibility criteria, at least one efficacy assessment after randomization, completing the study without major protocol deviation that impacts the efficacy evaluation, and with a treatment compliance rate of 80% to 120%. The PPS will be used for selected efficacy endpoints.

14.1.1 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKS) will include participants who have received at least 1 dose of study drug and had at least one post baseline evaluable PK sample to support accurate estimation of at least 1 PK parameter.

14.1.2 [REDACTED]

[REDACTED]

The details and any additional analysis sets may be described in the Statistical Analysis Plan (SAP).

14.2 General Issues for Statistical Analysis

In general, participant characteristics, demographics data, and safety summary statistics will be presented by treatment group, combined REC-994 group, and overall. Data will be presented separately for Part 1 and Part 2.

Continuous, quantitative, variable summaries will include the number of participants (N) with non-missing values, mean, standard deviation, median, minimum, and maximum, unless otherwise specified. Categorical and qualitative variable summaries will include the frequency and percentage of participants in the particular category.

Definition of Baseline:

- Part 1:
 - For efficacy assessments not assessed during screening period (██████ SMSS, ██████ ██████ CGI, and PGI), Day 1 assessment will be defined as the baseline value.
 - For safety and other efficacy assessments, the baseline is defined as the last available assessment prior to the first dose of the study treatment.
 - The baseline of seizure and headache frequencies will be based on non-missing eDiary data collected during screening period and standardized to 28 days.
- Part 2:
 - For safety analysis, the baseline for all participants is defined as LTE Day 1 (i.e., ██████ visit of Part 1), irrespective of their treatment groups.
 - For efficacy analysis, the baseline is defined as the LTE Day 1 for participants who are on REC-994 in Part 1 and continue their treatment in Part 2. For participants who are on placebo and re-randomized into active REC-994 in Part 2, two baseline definitions are applied. The main analysis will be using LTE Day 1 as the baseline and the sensitivity analysis will be using Part 1 baseline defined above for Part 2.

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

14.3 Participant Characteristics and Disposition

All participants who provide informed consent will be accounted for in these analyses.

The number of screened participants, number of screen failures, number of randomized participants, number of participants who completed the study treatment/study, number of participants who discontinued the study treatment/study, classified by reason of discontinuation, and the number of participants in each analysis set will be summarized. Corresponding by-participant listings will be prepared.

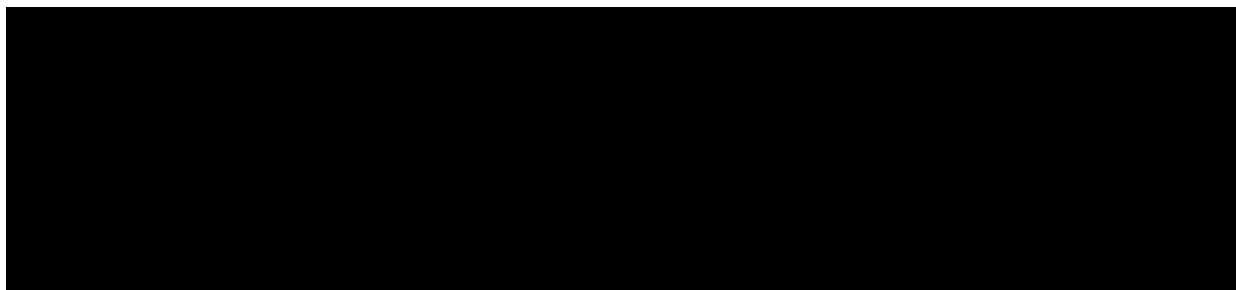
14.4 Statistical Analysis Plan for Efficacy, Safety and Pharmacokinetics Evaluation

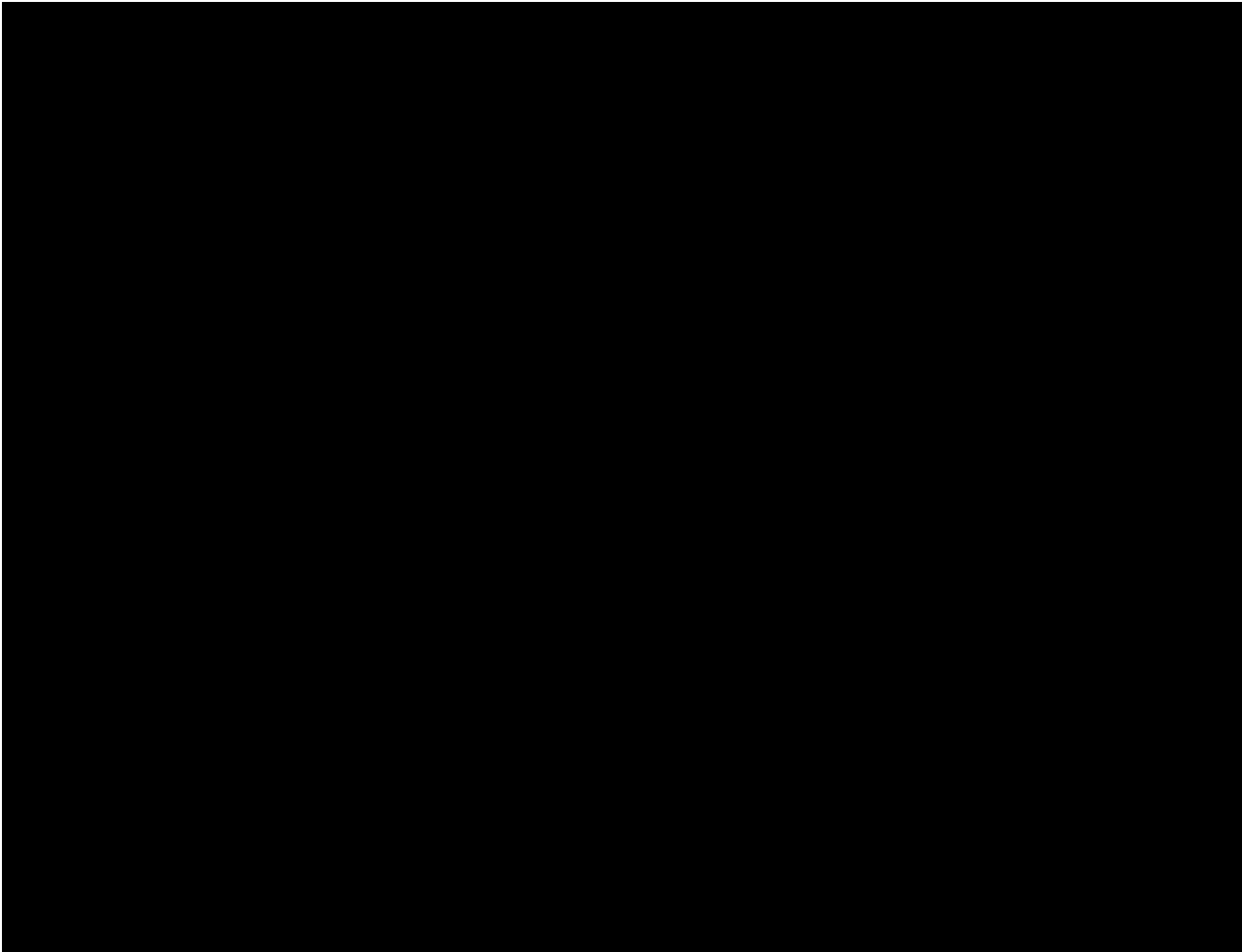
Data from Part 1 will constitute the primary analyses of the study and will be performed upon database lock after the last participant enrolled in Part 1 has completed the last study visit of Part 1. Data from part 2 will be analyzed separately at final database lock after the last participant has completed the last study visit of Part 2.

Statistical analysis details will be provided in Statistical Analysis Plan. Any deviation from the SAP will be reported in the “Changes in Planned Analysis” section in the Clinical Study Report (CSR).

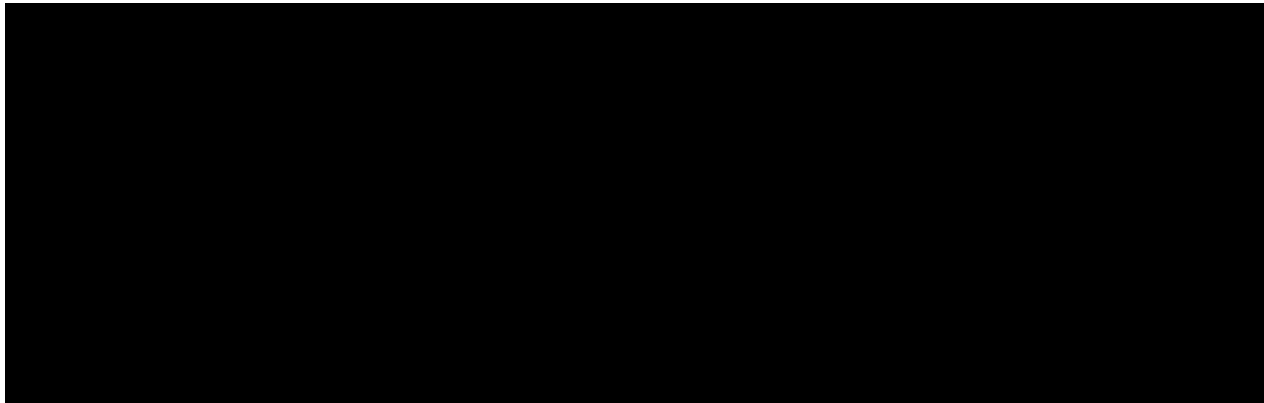
14.4.1 Efficacy Evaluation

14.4.1.1 Part 1 Efficacy Evaluation





14.4.1.2 Part 2 Efficacy Evaluation



14.4.2 Safety Evaluation

Safety and tolerability will be assessed by AEs, clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis), 12-lead ECGs, vital sign measurements, physical examinations, and neurological examinations and summarized by treatment group in terms of the number and percentage of individuals with a particular AE, the total number of such events in each treatment arm. AEs will be coded in accordance with MedDRA in terms of preferred term and system organ class. The number, severity, and relatedness of AEs will be summarized by treatment group; in addition, SAEs, AEs leading

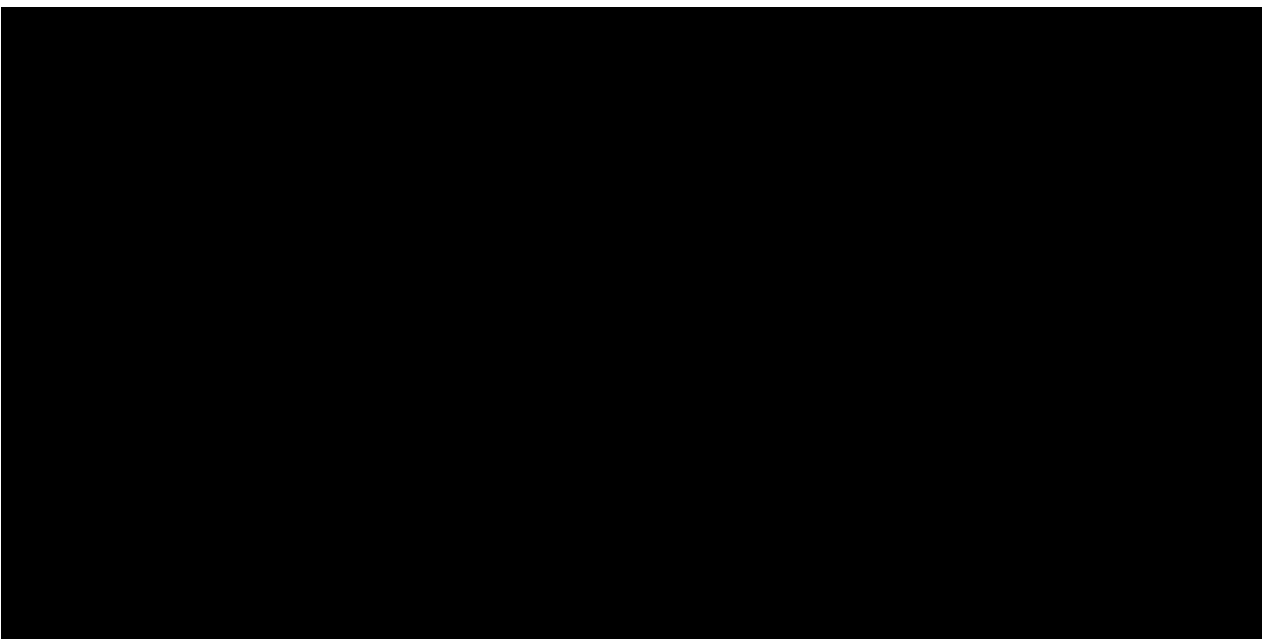
to withdrawal, and/or cessation or suspension of treatment and AEs leading to death will be presented. Laboratory data, physical examination, neurological examinations, vital signs, and ECG data will be summarized descriptively by treatment group over time, including displays of change from baseline. Values outside of the normal ranges will be identified and summarized by treatment group. Details regarding data displays will be specified in the SAP.

14.4.3 Pharmacokinetic Evaluation

Plasma concentrations of REC-994 will be listed and summarized by treatment, time point, and visit, and displayed graphically. Standard pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max}) will be estimated using non-compartmental analysis. PK parameters will be listed and summarized by treatment and visit. The details of the pharmacokinetic analysis will be further described in the SAP.

PK data from this study may be used for population PK modeling. The analyses, if conducted, will be reported separately from the CSR. Results from [REDACTED] will be summarized separately from the CSR.

14.5 Determination of Sample Size



15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study will be conducted according to the relevant regulatory requirements. The eCRF entries will be verified with the source documentation.

Regulatory authorities, the IRB, and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

An explanation will be given for all missing, unused, and spurious data in the relevant sections of the CSR.

15.1 Case Report Form

The Study Data Management Plan will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process. Furthermore, the Study Data Management Plan will describe the data flow and timelines within the study.

Data captured electronically will be immediately saved to a central database and changes tracked to provide an audit trail. When the PI has signed the eCRF electronically as per eCRF instructions, then the subject's data will be locked.

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture system unless otherwise directed. The electronic case report form casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a non-electronic data capture vendor system (e.g., central laboratory). The Inclusion/Exclusion Criteria and Enrollment electronic case report forms should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form Completion Guidelines provided by the Sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the electronic data capture system as data discrepancies are identified by the study monitor or CRO Monitor who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g., data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the PI of the data entered into the electronic data capture system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Recursion), the Investigator applies their electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents.

15.2 Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Recursion Pharmaceuticals, Inc. will visit the investigational study site to:

- Determine the adequacy of the facilities and
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Recursion Pharmaceuticals, Inc. or its representatives. This

will be documented in a Clinical Study Agreement between Recursion Pharmaceuticals, Inc. and the Investigator.

During the study, a monitor from Recursion Pharmaceuticals, Inc. or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s),
- Confirm that facilities remain acceptable,
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed,
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (e.g., clinic charts),
- Record and report any protocol deviations not previously sent to Recursion Pharmaceuticals, Inc. and
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Recursion Pharmaceuticals, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.3 Audits and Inspections

Authorized representatives of Recursion Pharmaceuticals, Inc., a regulatory authority, an IEC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Recursion Pharmaceuticals, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact Recursion Pharmaceuticals, Inc. immediately if contacted by a regulatory agency about an inspection.

15.4 Institutional Review Board (IRB)

The Investigator must obtain IRB approval for the investigation. Copies of the initial IRB approval and all materials approved by the IRB for this study, including the participant consent form and recruitment materials, must be maintained by the Investigator, and be made available for inspection.

16 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Recursion Pharmaceuticals, Inc. may conduct a quality assurance audit. See Section [15.3](#) for more details regarding the audit process.

17 ETHICS

17.1 Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Recursion Pharmaceuticals, Inc. before he or she can enroll any participant into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Recursion Pharmaceuticals, Inc. will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki ([World of Medical Association, 2013](#)) and are consistent with ICH/GCP ([ICH E6, 2016](#)), applicable regulatory requirements and Recursion Pharmaceuticals, Inc.'s policy on bioethics.

17.3 Written Informed Consent

The Investigator(s) at each center will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

The participant's signed and dated informed consent must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed informed consent form. A copy of the signed informed consent form must be given to the participant.

18 DATA HANDLING AND RECORDKEEPING

18.1 Inspection of Records

Recursion Pharmaceuticals, Inc. will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

18.2 Retention of Records

An Investigator shall retain all documentation relating to the study for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

If it becomes necessary for Recursion Pharmaceuticals, Inc., or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

19 PUBLICATION POLICY

By signing this clinical study protocol, the Investigator reaffirms to the Sponsor that he or she will maintain in confidence all information furnished to him or her or resulting from this study. The Investigator and designees will only divulge such information as may be necessary to the IRB, the members of the staff, and the participants who are involved in this study.

20 LIST OF REFERENCES

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21 APPENDICES

21.1 SymptoMScreen questionnaire (SMSS)

REC-0000994-201: SymptomScreen

Subject Number:		Visit Date:		Study Visit:	
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Please circle **one number that best describes how each CCM symptom has affected your everyday life activities**. For example, if it takes you longer to type or text, your hand function may have a 'mild limitation' (circle '2'), but if you gave up typing or texting completely, your hand function may have a 'severe limitation' (circle '4').

	0 – not affected at all	1 – very mild limitation/ I make minor adjustments	2 – mild limitation/ I make frequent adjustments	3 – moderate limitation/ I reduced my daily activities	4 – severe limitation/ I gave up some activities	5 – very severe limitation/ I'm unable to do many daily activities	6 – total limitation/ I'm unable to do most daily activities
Walking	0	1	2	3	4	5	6
Hand function/Dexterity Poor hand coordination, tremors	0	1	2	3	4	5	6
Spasticity & Stiffness Muscle cramping or muscle tightness	0	1	2	3	4	5	6
Bodily Pain Aching, tenderness	0	1	2	3	4	5	6
Sensory Numbness, tingling or burning	0	1	2	3	4	5	6
Bladder Control Urinary urgency, urinary frequency	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Vision Blurry vision, double vision	0	1	2	3	4	5	6
Dizziness Feeling off balance, 'spinning'/vertigo	0	1	2	3	4	5	6
Cognitive function Memory, concentration problems	0	1	2	3	4	5	6
Depression Depressed thoughts, low mood	0	1	2	3	4	5	6
Anxiety Feelings of stress, panic attacks	0	1	2	3	4	5	6

Adapted from: R Green, J Kalina, R Ford, K Pandey, I Kister. SymptoMScreen: A Tool for Rapid Assessment of Symptom Severity in MS Across Multiple Domains Appl Neuropsychol Adult. 2017;24:183-189. License: <https://creativecommons.org/licenses/by/4.0/legalcode>

REC-0000994-201 SymptomScreen v1.0

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21.2 modified Rankin Scale (mRS)

REC-994-201: Modified Rankin Scale

SCREENING

Subject Number:	
Visit Date:	
Study Visit:	

Structured Interview for the Modified Rankin Scale Screening

The Modified Rankin Scale (mRS) (van Swieten, et al., 1988) is widely used as a functional outcome measure in stroke.

The purpose of the Structured Interview is to assign patients to mRS grades in a systematic way. The interview consists of five sections corresponding to the levels of disability on the mRS (see Table).

Use the best source of information available. Information can be obtained from the patient and/or a person who is familiar with the daily routine of the patient.

Proceed through the questionnaire in the sequence provided, i.e., Section 1, Section 2, etc. For each section, ask about current activities. If there are currently no problems or limitations in a particular activity, check the "No" box and move to the next item.

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

Based on: Wilson JTL, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. Stroke. 2002;33:2243-6.

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REC-994-201: Modified Rankin Scale

SCREENING

Subject Number:	
Visit Date:	
Study Visit:	

1	CONSTANT CARE	YES	NO
Constant care means that someone needs to be available at all times. Care may be provided by either a trained or an untrained caregiver. The patient will usually be bedridden and may be incontinent			
1.1S	Does the person require constant care?	[5]	
If “yes”, score 5 and discontinue interview			

2	ASSISTANCE TO ATTEND TO BODILY NEEDS/ FOR WALKING	YES	NO
Assistance includes physical assistance, verbal instruction, or supervision by another person.			
2.1S	Is assistance required for eating? <i>[Eating without assistance: food and implements may be provided by others.]</i>	[4]	
2.2S	Is assistance required for using the toilet? <i>[Using toilet without assistance: reaching the toilet/commode; undressing sufficiently; cleaning self; dress and leaving.]</i>	[4]	
2.3S	Is assistance required for routine daily hygiene? <i>[Routine hygiene: washing face, doing hair, cleaning teeth/fitting false teeth. Implements may be provided by others; this should not be considered assistance]</i>	[4]	
2.4S	Is assistance required for walking? <i>[Walking without assistance: Able to walk indoors around house or ward, may use any aid (e.g., stick/cane, walking frame/walker), however not requiring physical help or verbal instruction or supervision from another person.]</i>	[4]	
If “yes” is answered to one or more questions, score 4 and discontinue interview			

3	ASSISTANCE TO LOOK AFTER OWN AFFAIRS	YES	NO
Assistance includes physical assistance, verbal instruction, or supervision by another person.			
3.1S	Is assistance required for preparing a simple meal? <i>[For example, able to prepare breakfast or a snack.]</i>	[3]	
3.2S	Is assistance essential for basic household chores? <i>[For example, finding and putting away clothes, clearing up after a meal. Exclude chores that do not need to be done every day, such as using a vacuum cleaner.]</i>	[3]	
3.3S	Is assistance essential for looking after household expenses?	[3]	
3.4S	Is assistance essential for local travel? <i>[Individual may drive or use public transport to get around. Ability to use a taxi is sufficient, provided they can phone for it themselves and instruct the driver.]</i>	[3]	
3.5S	Is assistance essential for local shopping? <i>[Local shopping: at least able to buy a single item]</i>	[3]	
If “yes” is answered to one or more questions, score 3 and discontinue interview			

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REC-994-201: Modified Rankin Scale

SCREENING

Subject Number:	
Visit Date:	
Study Visit:	

4	USUAL DUTIES AND ACTIVITIES
Mark responses based on the ability of the patient to perform the activity and not whether the patient actually performs the activity currently. Please use your judgement to decide whether the person can actually do something before recording a response. The set of questions in Section 4 is about how the patient usually spends his/her day. It is important to consider present circumstance, not activities anticipated to occur in the future (e.g., returning to school or work).	

4.1	SCHOOL	YES	NO
4.1.1S	Prior to entering the study, was the subject studying as a student?		Go to 4.2
4.1.2S	If “yes,” was the subject limited in performing activities of a student?	[2]	Go to 4.2
4.1.2.1S	If limited, please describe		
	<i>Subject was taking less than a full schedule</i>		
	<i>Subject was not able to participate in student activities at all</i>		
If “yes” is answered to Question 4.1.2S, <u>score 2</u>			

4.2	WORK	YES	NO
4.2.1S	Prior to entering the study, was the subject working or seeking work? <i>[Work refers to paid employment and does not include voluntary work (which can be included under ‘social and leisure activities’).]</i>		Go to 4.3
4.2.2S	If “yes,” was the subject limited in working or seeking work?	[2]	Go to 4.3
4.2.2.1S	If limited, please describe		
	<i>Had reduced level of work, e.g., full-time to part-time or changed level of responsibility</i>		
	<i>Was no longer able to work</i>		
If “yes” is answered to Question 4.2.2S, <u>score 2</u>			

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REC-994-201: Modified Rankin Scale

SCREENING

Subject Number:	
Visit Date:	
Study Visit:	

4.3	FAMILY RESPONSIBILITIES	YES	NO
Refers to the patient's ability to look after others. Probe using specific examples such as "babysitting, looking after your partner, your parents, your children or dependent others."			
4.3.1S	Prior to entering the study, was the subject looking after family at home? (If this was <u>not</u> a major role for the subject prior to entering the study, indicate 'No' and go to 4.4)		Go to 4.4
4.3.2S	If "yes," was the subject limited in looking after family at home?	[2]	Go to 4.4
4.3.2.1S	If limited, please describe		
	<i>Reduced responsibility for looking after family.</i>		
	<i>Currently unable to look after family.</i>		
If "yes" is answered to Question 4.3.2S, <u>score 2</u>			

4.4	SOCIAL & LEISURE ACTIVITIES	YES	NO
This refers to any specific free-time activities which the person did or does for pleasure. Social and leisure activities include hobbies and interests. Includes activities outside the home or at home. <u>Activities outside the home</u> : going to the pub/bar, restaurant, club, church, cinema, visiting friends, going for walks. <u>Activities at home</u> : involving "active" participation including knitting, sewing, painting, games, reading books, home improvements.			
4.4.1S	Prior to entering the study, did the subject have regular leisure-time activities?		Go to 4.5
4.4.2S	If "yes," was the subject limited in performing regular leisure-time activities?	[2]	Go to 4.5
4.4.2.1S	If limited, please describe		
	<i>Participates less, but at least half the prior activity level.</i>		
	<i>Participates much less, less than half the prior activity level.</i>		
	<i>Rarely or unable to participate in activities.</i>		
If "yes" is answered to Question 4.4.2S, <u>score 2</u>			

REC-994-201: Modified Rankin Scale

SCREENING

Subject Number:	
Visit Date:	
Study Visit:	

4.5	FAMILY & FRIENDSHIPS	YES	NO
It is important to query about changes in mood, personality changes or other behavioral changes that might lead to changes in interactions with family and friends. Problems with relationships include difficulties in relationships with people at home, loss of friendships or increase in isolation. Changes in the subject may include: communication problems, quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable behavior.			
4.5.1S	Prior to entering the study, was the subject having difficulties with family relationships or friendships?	[2]	Go to 5
4.5.1.1S	If having difficulties, please describe		
	<i>Occasional episodes – less than weekly</i>		
	<i>Frequent episodes – once a week or more, but tolerable</i>		
	<i>Constant disruption – daily & intolerable</i>		
If “yes” is answered to Question 4.5.1S, <u>score 2</u>			

If one or more questions in Section 4 is answered “yes,” <u>score 2</u>. Even if a question in Section 4 is answered “yes,” proceed to Section 5 and answer all questions. However, do not score responses to individual questions.

REC-994-201: Modified Rankin Scale

SCREENING

Subject Number:	
Visit Date:	
Study Visit:	

5	OTHER SYMPTOMS
Mark responses based on the <u>ability</u> of the patient to perform the activity and not whether the patient actually performs the activity currently. Please use your judgement to decide whether the person can actually do something before recording a response. These can be any symptoms or problems reported by the patient or found on neurological examination. It is important to exclude common problems and complaints not due to a prior stroke.	

		YES	NO
5.1S	<u>At the time of entry into the study, does the subject have any of the following symptoms?</u> [If yes, also enter in "CCM Past History" on electronic Case Report Form.] [Please answer all]		
5.1.1S	Difficulty reading or writing?	[1]	
5.1.2S	Difficulty speaking or finding the right word?	[1]	
5.1.3S	Problems with balance or coordination?	[1]	
5.1.4S	Visual problems?	[1]	
5.1.5S	Numbness (face, arms, legs, hands, feet)?	[1]	
5.1.6S	Loss of movement (face, arms, legs, hands, feet)?	[1]	
5.1.7S	Difficulty with swallowing?	[1]	
5.1.8S	Other symptoms? (Please list below)	[1]	
		[1]	

Answer all questions. If one or more questions is answered "yes", score 1
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REC-994-201: Modified Rankin Scale

SCREENING

Subject Number:	
Visit Date:	
Study Visit:	

Assigning a grade on the Modified Rankin Scale

1. Examine the responses.
2. Rankin categories are given in brackets beside specific responses.
3. The overall rating is the most severe (highest numerical) disability category indicated by the subject's answers.

NOTE: Rankin 5 is the highest disability category and Rankin 0 is the lowest disability category. If the subject has no limitations or symptoms, then the Rankin grade is 0.

Rankin Grade =	
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REC-994-201: Modified Rankin Scale

TREATMENT PERIOD

Subject Number:	
Visit Date:	
Study Visit:	

Structured Interview for the Modified Rankin Scale Treatment Period

The Modified Rankin Scale (mRS) (van Swieten, et al., 1988) is widely used as a functional outcome measure in stroke.

The purpose of the Structured Interview is to assign patients to mRS grades in a systematic way. The interview consists of five sections corresponding to the levels of disability on the mRS (see Table).

Use the best source of information available. Information can be obtained from the patient and/or a person who is familiar with the daily routine of the patient.

Proceed through the questionnaire in the sequence provided, i.e., Section 1, Section 2, etc. For each section, ask about current activities. If there are currently no problems or limitations in a particular activity, check the "No" box and move to the next item.

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

Based on: Wilson JTL, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. Stroke. 2002;33:2243-6.

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REC-994-201: Modified Rankin Scale

TREATMENT PERIOD

Subject Number:	
Visit Date:	
Study Visit:	

1	CONSTANT CARE	YES	NO
Constant care means that someone needs to be available at all times. Care may be provided by either a trained or an untrained caregiver. The patient will usually be bedridden and may be incontinent			
1.1T	Does the person require constant care?	[5]	
If “yes”, score 5 and discontinue interview			

2	ASSISTANCE TO ATTEND TO BODILY NEEDS/ FOR WALKING	YES	NO
Assistance includes physical assistance, verbal instruction, or supervision by another person.			
2.1T	Is assistance required for eating? <i>[Eating without assistance: food and implements may be provided by others.]</i>	[4]	
2.2T	Is assistance required for using the toilet? <i>[Using toilet without assistance: reaching the toilet/commode; undressing sufficiently; cleaning self; dress and leaving.]</i>	[4]	
2.3T	Is assistance required for routine daily hygiene? <i>[Routine hygiene: washing face, doing hair, cleaning teeth/fitting false teeth. Implements may be provided by others; this should not be considered assistance]</i>	[4]	
2.4T	Is assistance required for walking? <i>[Walking without assistance: Able to walk indoors around house or ward, may use any aid (e.g., stick/cane, walking frame/walker), however not requiring physical help or verbal instruction or supervision from another person.]</i>	[4]	
If “yes” is answered to one or more questions, score 4 and discontinue interview			

3	ASSISTANCE TO LOOK AFTER OWN AFFAIRS	YES	NO
Assistance includes physical assistance, verbal instruction, or supervision by another person.			
3.1T	Is assistance required for preparing a simple meal? <i>[For example, able to prepare breakfast or a snack.]</i>	[3]	
3.2T	Is assistance essential for basic household chores? <i>[For example, finding and putting away clothes, clearing up after a meal. Exclude chores that do not need to be done every day, such as using a vacuum cleaner.]</i>	[3]	
3.3T	Is assistance essential for looking after household expenses?	[3]	
3.4T	Is assistance essential for local travel? <i>[Individual may drive or use public transport to get around. Ability to use a taxi is sufficient, provided they can phone for it themselves and instruct the driver.]</i>	[3]	
3.5T	Is assistance essential for local shopping? <i>[Local shopping: at least able to buy a single item]</i>	[3]	
If “yes” is answered to one or more questions, score 3 and discontinue interview			

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REC-994-201: Modified Rankin Scale

TREATMENT PERIOD

Subject Number:	
Visit Date:	
Study Visit:	

4	USUAL DUTIES AND ACTIVITIES
Mark responses based on the ability of the patient to perform the activity and not whether the patient actually performs the activity currently. Please use your judgement to decide whether the person can actually do something before recording a response. The set of questions in Section 4 is about how the patient usually spends his/her day. It is important to consider present circumstance, not activities anticipated to occur in the future (e.g., returning to school or work).	

4.1	SCHOOL	YES	NO
4.1.1T	Currently, is the subject studying as a student?		Go to 4.2
4.1.2T	If “yes,” is the subject limited in performing activities of a student?	[2]	Go to 4.2
4.1.2.1T	If limited, please describe		
	<i>Subject is taking less than a full schedule</i>		
	<i>Subject is not able to participate in student activities at all</i>		
If “yes” is answered to Question 4.1.2T, score 2			

4.2	WORK	YES	NO
4.2.1T	Currently, is the subject working or seeking work? <i>[Work refers to paid employment and does not include voluntary work (which can be included under ‘social and leisure activities’).]</i>		Go to 4.3
4.2.2T	If “yes,” was the subject limited in working or seeking work?	[2]	Go to 4.3
4.2.2.1T	If limited, please describe		
	<i>Has reduced level of work, e.g., full-time to part-time or changed level of responsibility</i>		
	<i>Is no longer able to work</i>		
If “yes” is answered to Question 4.2.2T, score 2			

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REC-994-201: Modified Rankin Scale

TREATMENT PERIOD

Subject Number:	
Visit Date:	
Study Visit:	

4.3	FAMILY RESPONSIBILITIES	YES	NO
Refers to the patient's ability to look after others. Probe using specific examples such as "babysitting, looking after your partner, your parents, your children or dependent others."			
4.3.1T	Currently, is the subject looking after family at home?		Go to 4.4
4.3.2T	If "yes," is the subject limited in looking after family at home?	[2]	Go to 4.4
4.3.2.1T	If limited, please describe		
	<i>Reduced responsibility for looking after family.</i>		
	<i>Currently unable to look after family.</i>		
If "yes" is answered to Question 4.3.2T, score 2			

4.4	SOCIAL & LEISURE ACTIVITIES	YES	NO
This refers to any specific free-time activities which the person did or does for pleasure. Social and leisure activities include hobbies and interests. Includes activities outside the home or at home. <u>Activities outside the home</u> : going to the pub/bar, restaurant, club, church, cinema, visiting friends, going for walks. <u>Activities at home</u> : involving "active" participation including knitting, sewing, painting, games, reading books, home improvements.			
4.4.1T	Currently, does the subject have regular leisure-time activities?		Go to 4.5
4.4.2T	If "yes," is the subject limited in performing regular leisure-time activities?	[2]	Go to 4.5
4.4.2.1T	If limited, please describe		
	<i>Participates less, but at least half the prior activity level.</i>		
	<i>Participates much less, less than half the prior activity level.</i>		
	<i>Rarely or unable to participate in activities.</i>		
If "yes" is answered to Question 4.4.2T, score 2			

REC-994-201 mRS-Treatment Period v3.0

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REC-994-201: Modified Rankin Scale

TREATMENT PERIOD

Subject Number:	
Visit Date:	
Study Visit:	

4.5	FAMILY & FRIENDSHIPS	YES	NO
It is important to query about changes in mood, personality changes or other behavioral changes that might lead to changes in interactions with family and friends. Problems with relationships include difficulties in relationships with people at home, loss of friendships or increase in isolation. Changes in the subject may include: communication problems, quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable behavior.			
4.5.1T	Currently, is the subject having difficulties with family relationships or friendships?	[2]	Go to 5
4.5.1.1T	If having difficulties, please describe		
	Occasional episodes – less than weekly		
	Frequent episodes – once a week or more, but tolerable		
	Constant disruption – daily & intolerable		
If “yes” is answered to Question 4.5.1T, score 2			

If one or more questions in Section 4 is answered “yes,” **score 2**.

Even if a question in Section 4 is answered “yes,” proceed to Section 5 and answer all questions. However, do not score responses to individual questions.

REC-994-201: Modified Rankin Scale

TREATMENT PERIOD

Subject Number:	
Visit Date:	
Study Visit:	

5	OTHER SYMPTOMS
Mark responses based on the ability of the patient to perform the activity and not whether the patient actually performs the activity currently. Please use your judgement to decide whether the person can actually do something before recording a response. These can be any symptoms or problems reported by the patient or found on neurological examination. It is important to exclude common problems and complaints not due to a prior stroke.	

		YES	NO
5.1T	<u>Currently, does the subject have any of the following symptoms?</u> [If yes and symptoms were not previously present, also enter in "Adverse Events" on electronic Case Report Form.] [Please answer all]		
5.1.1T	Difficulty reading or writing?	[1]	
5.1.2T	Difficulty speaking or finding the right word?	[1]	
5.1.3T	Problems with balance or coordination?	[1]	
5.1.4T	Visual problems?	[1]	
5.1.5T	Numbness (face, arms, legs, hands, feet)?	[1]	
5.1.6T	Loss of movement (face, arms, legs, hands, feet)?	[1]	
5.1.7T	Difficulty with swallowing?	[1]	
5.1.8T	Other symptoms? (Please list below)	[1]	
		[1]	

Answer all questions. If one or more questions is answered "yes", score 1
--

REC-994-201: Modified Rankin Scale

TREATMENT PERIOD

Subject Number:	
Visit Date:	
Study Visit:	

Assigning a grade on the Modified Rankin Scale

1. Examine the responses.
2. Rankin categories are given in brackets beside specific responses.
3. The overall rating is the most severe (highest numerical) disability category indicated by the subject's answers.

NOTE: Rankin 5 is the highest disability category and Rankin 0 is the lowest disability category. If the subject has no limitations or symptoms, then the Rankin grade is 0.

Rankin Grade =

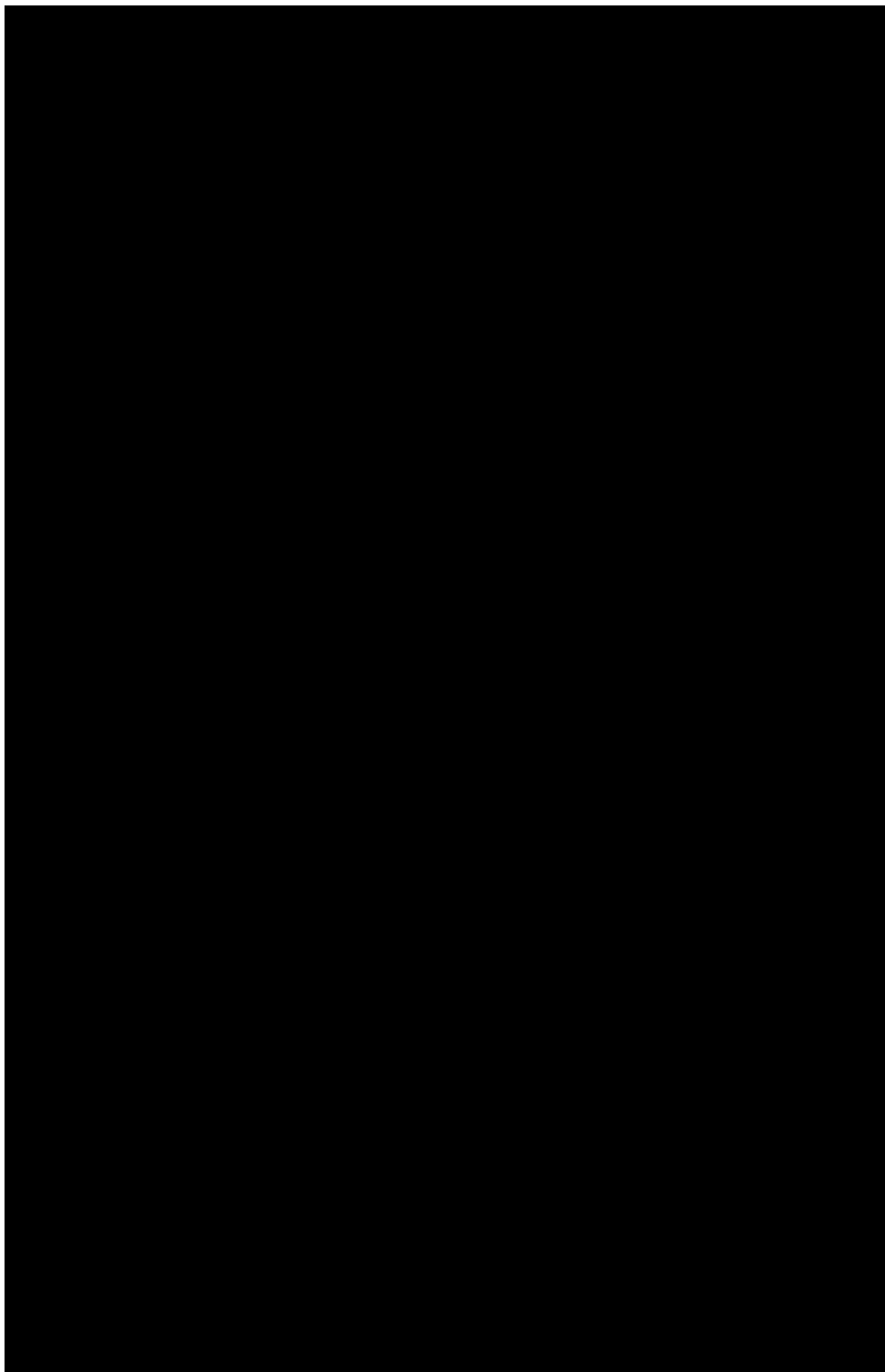
21.3

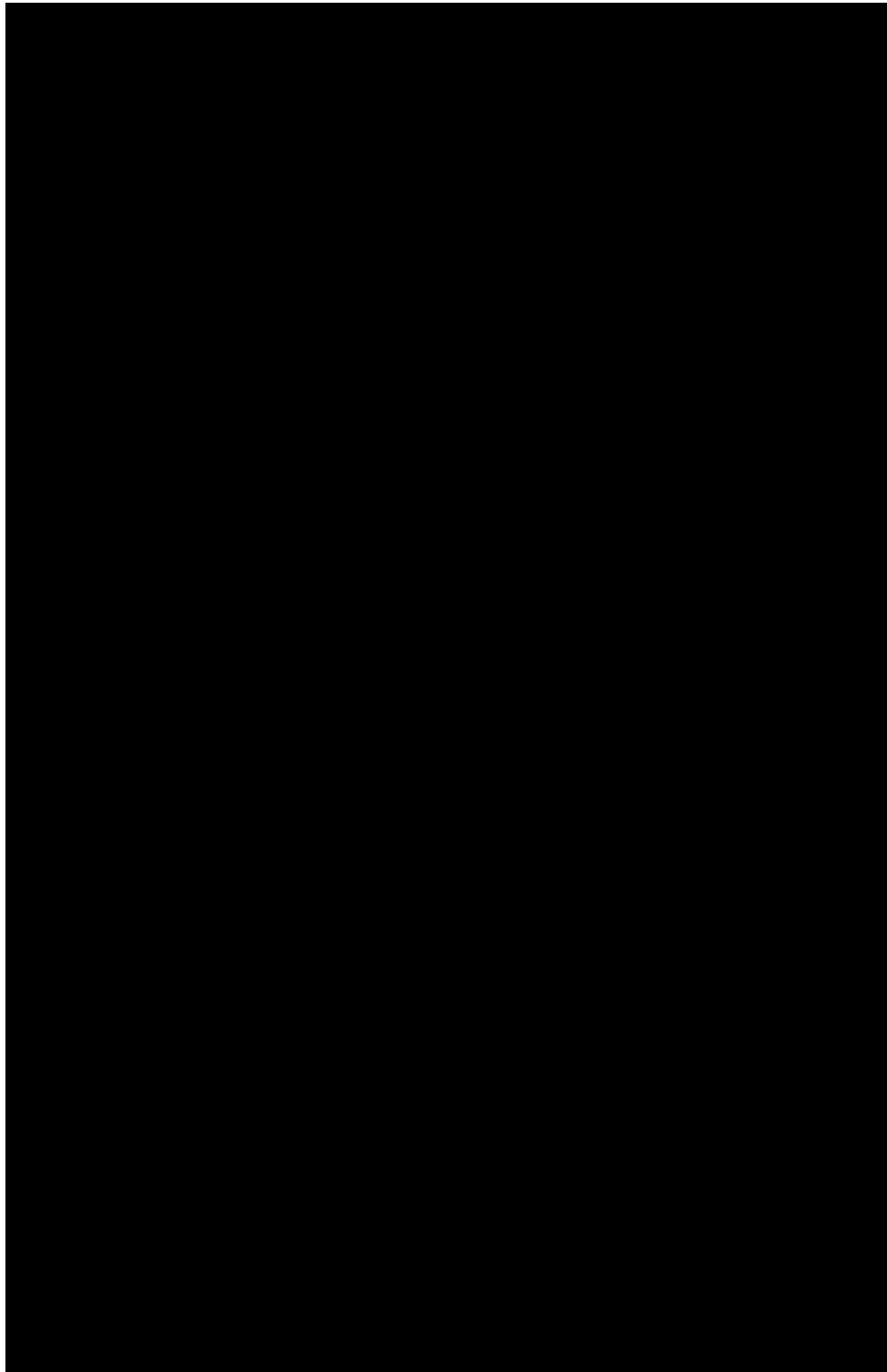


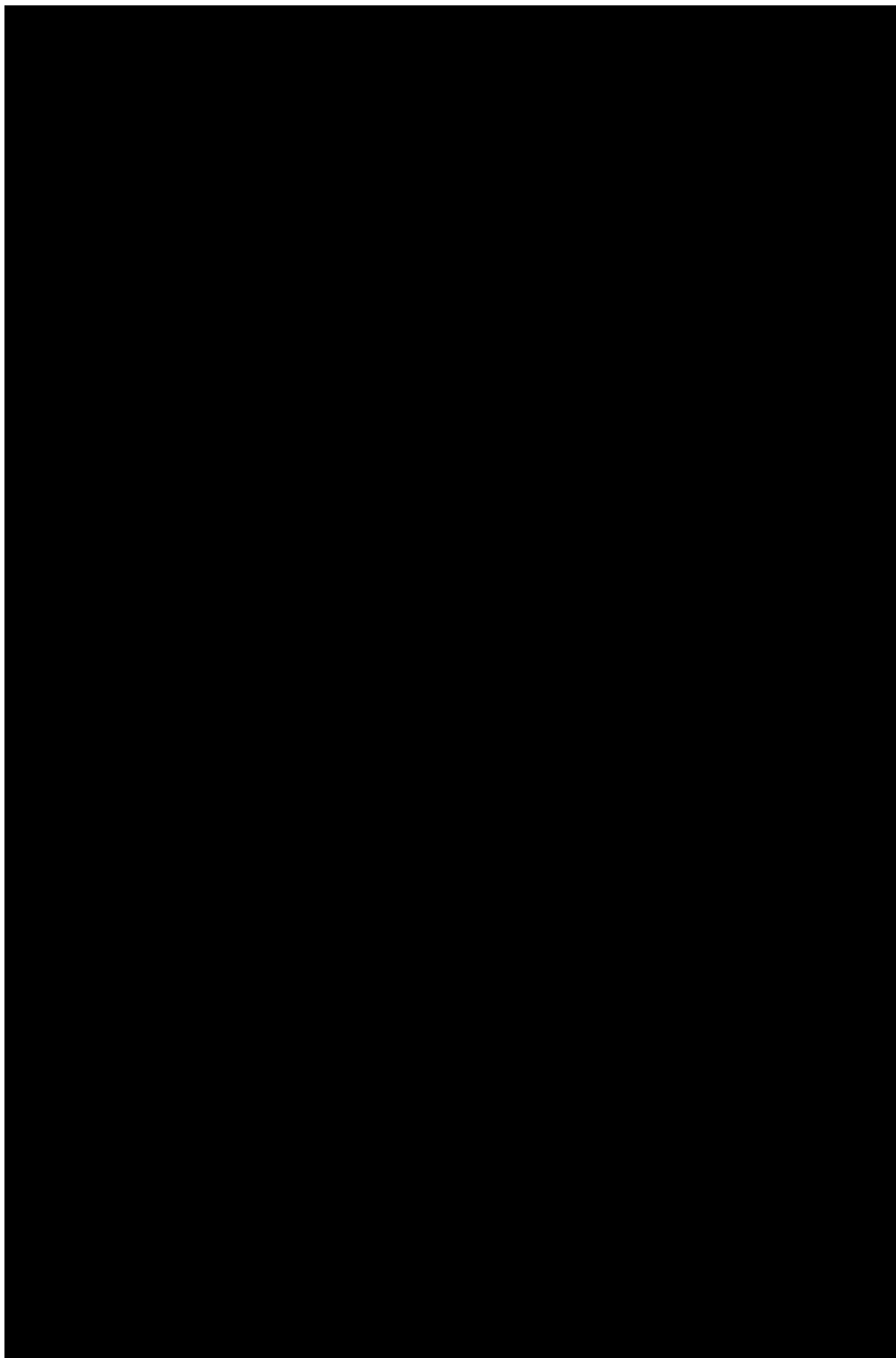












21.4 Clinical/Patient Global Impressions (CGI/PGI) Scale

Clinical Global Impressions – Severity Scale

As employed in this study, the Investigator will rate the overall status of the patient at Baseline.

The scale is listed below:

Please choose the response below that best describes the severity of the patient's condition at Baseline.

- 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

Clinical Global Impressions – Improvement (Change in Intensity/Severity) Scale

As employed in this study, the Investigator will provide an estimation of the change in the patient's overall status following initiation of study drug on Study Day 1. Impressions will be recorded at each subsequent investigative site visit.

Please choose the response below that best describes the overall change in the patient's OVERALL STATUS since beginning to take study drug

- 0 = Not Assessed
- 1 = Very much improved
- 2 = Much improved
- 3 = Minimally improved
- 4 = No change
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse

Patient Global Impressions – Severity Scale

As employed in this study, the patient will rate their overall status at Baseline.

The scale is listed below:

Please choose the response below that best describes the severity of your cerebral cavernous malformation (cavernous angioma) disorder right now.

- 1 = Not present
- 2 = Very mild
- 3 = Mild
- 4 = Moderate
- 5 = Moderately severe
- 6 = Severe
- 7 = Extremely severe

Patient Global Impressions – Improvement (Change in Intensity/Severity) Scale

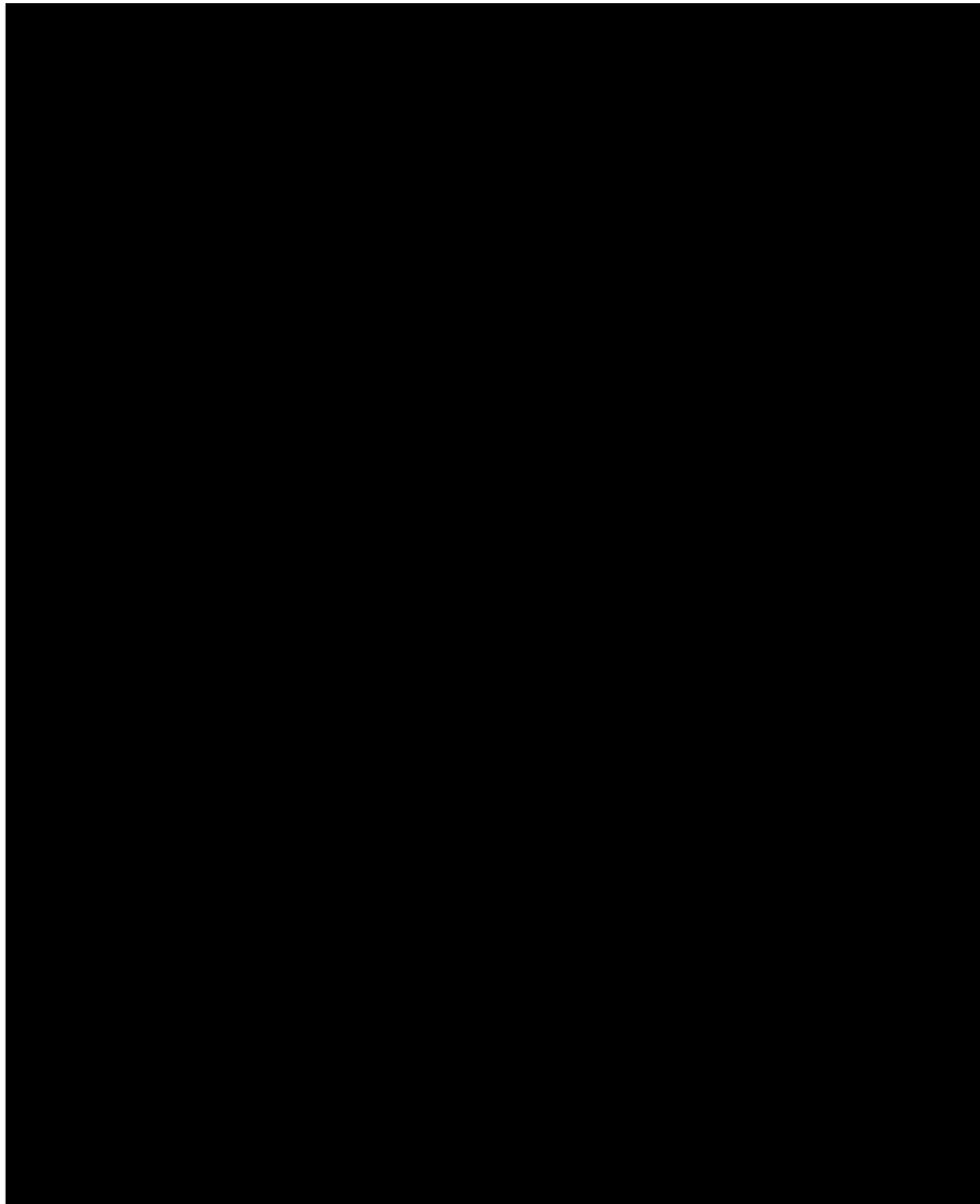
As employed in this study, the patient will provide an estimation of the change in their overall status following initiation of study drug on Study Day 1. Impressions will be recorded at each subsequent investigative site visit.

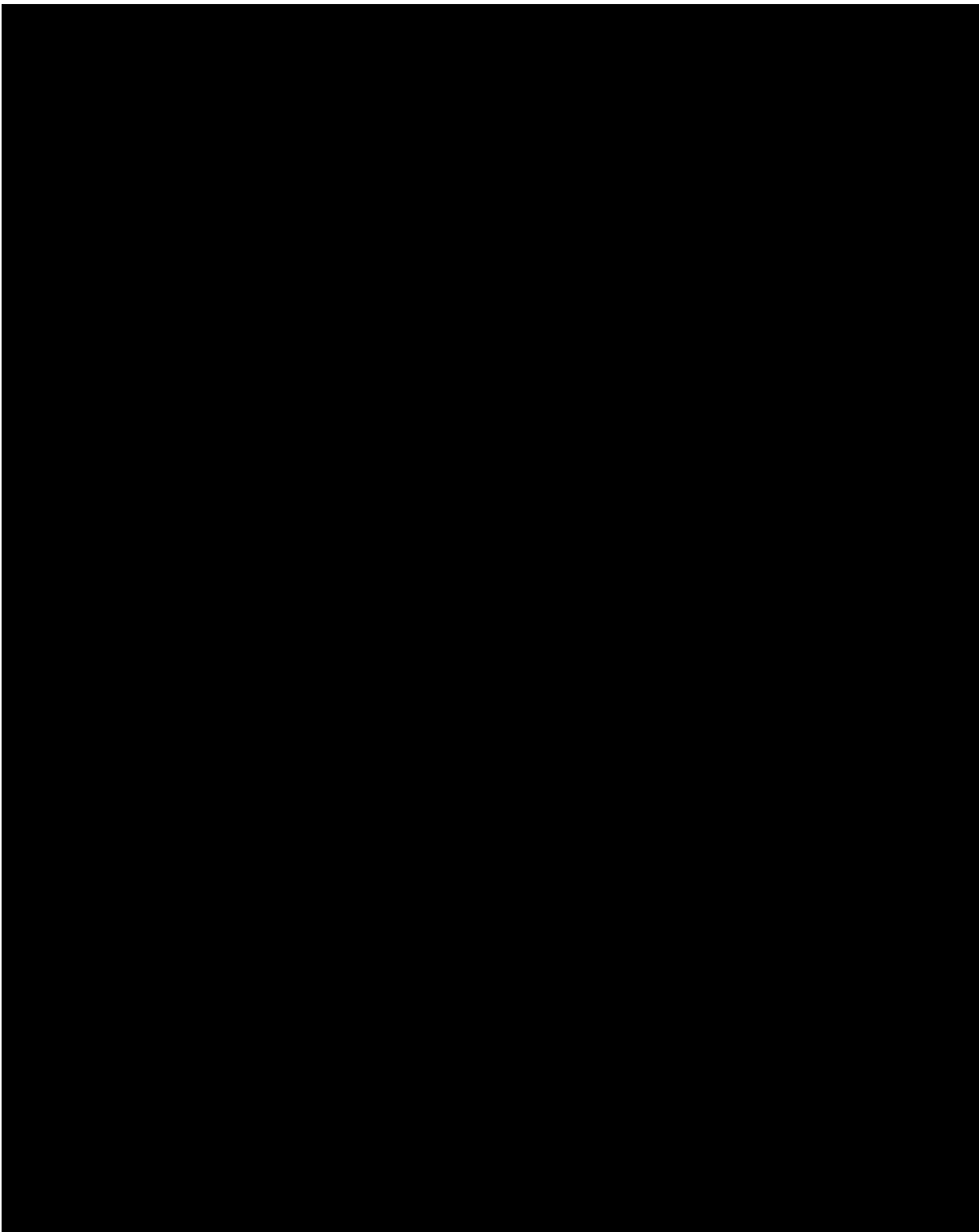
Please choose the response below that best describes how you feel overall since you started taking the study medication

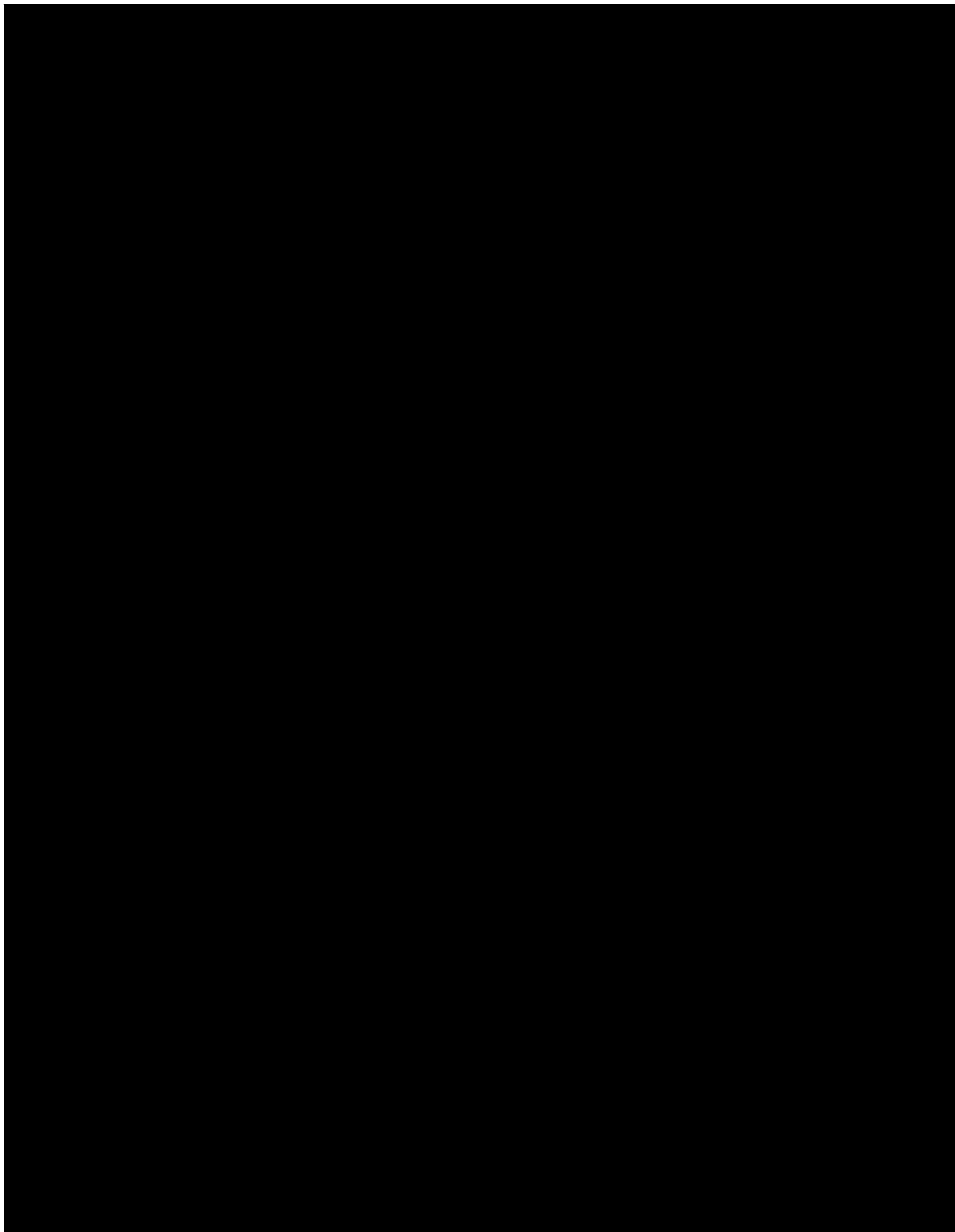
- 1 = Very much better
- 2 = Much better
- 3 = Somewhat better
- 4 = No change
- 5 = Somewhat worse
- 6 = Much worse
- 7 = Very much worse

21.5

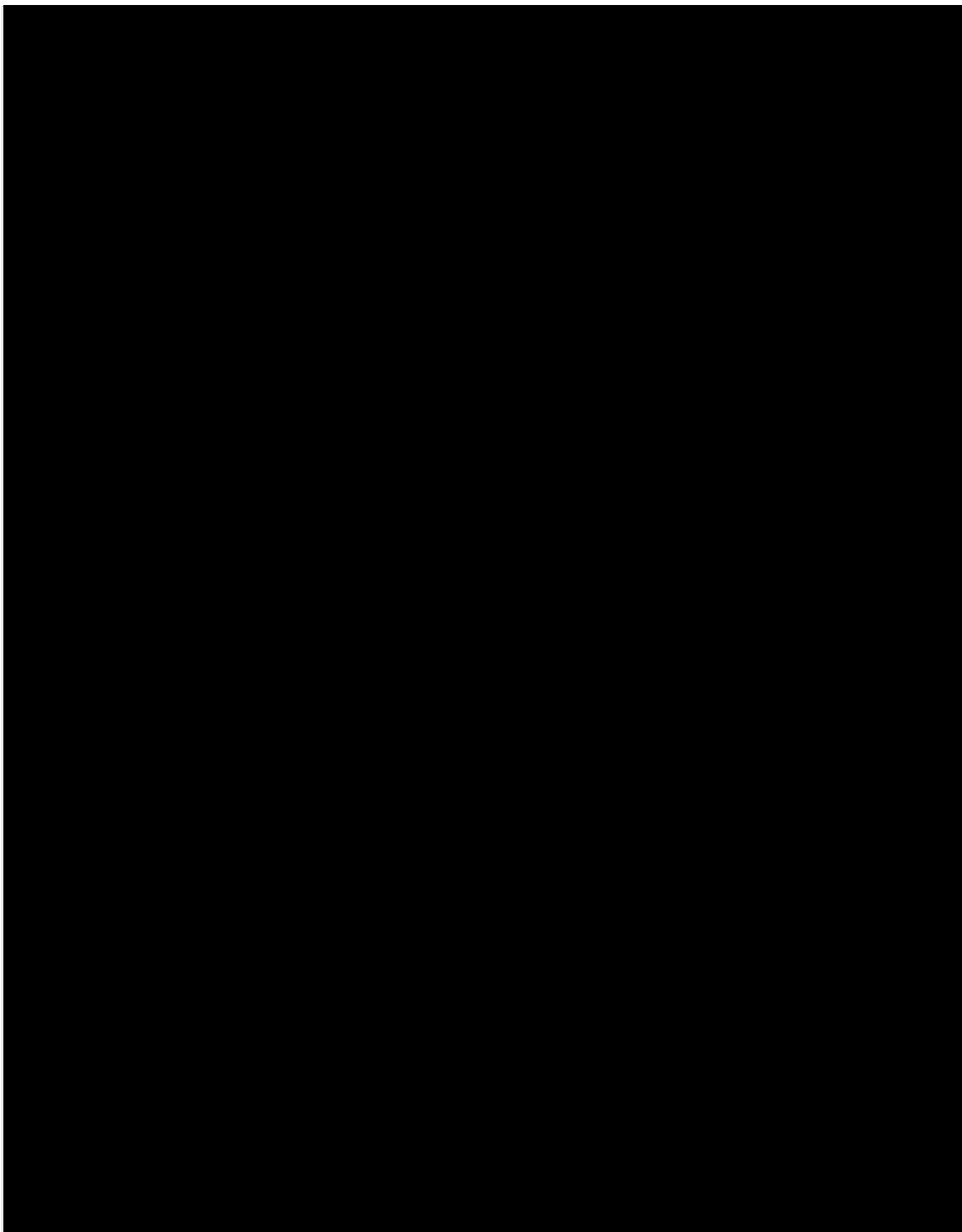


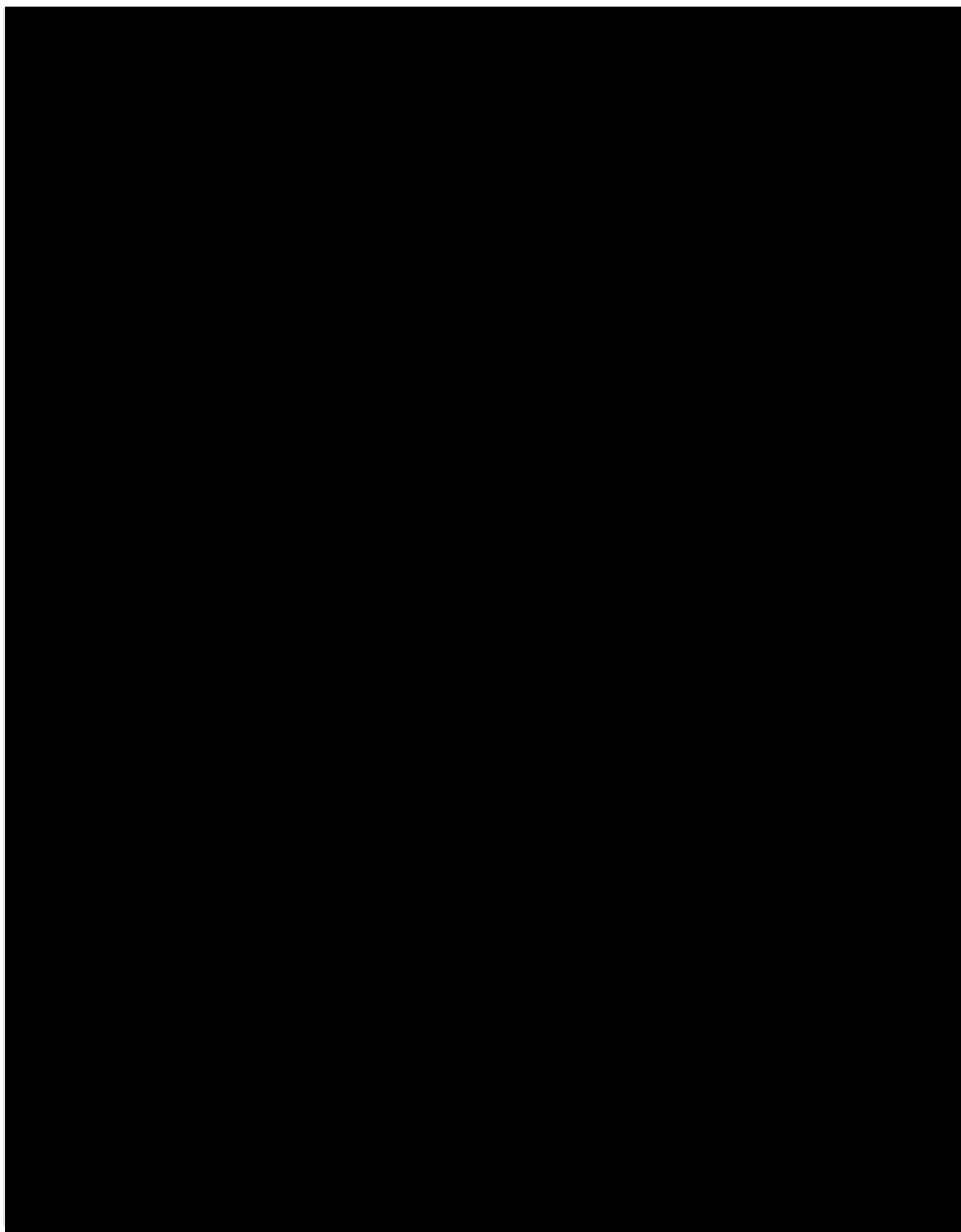


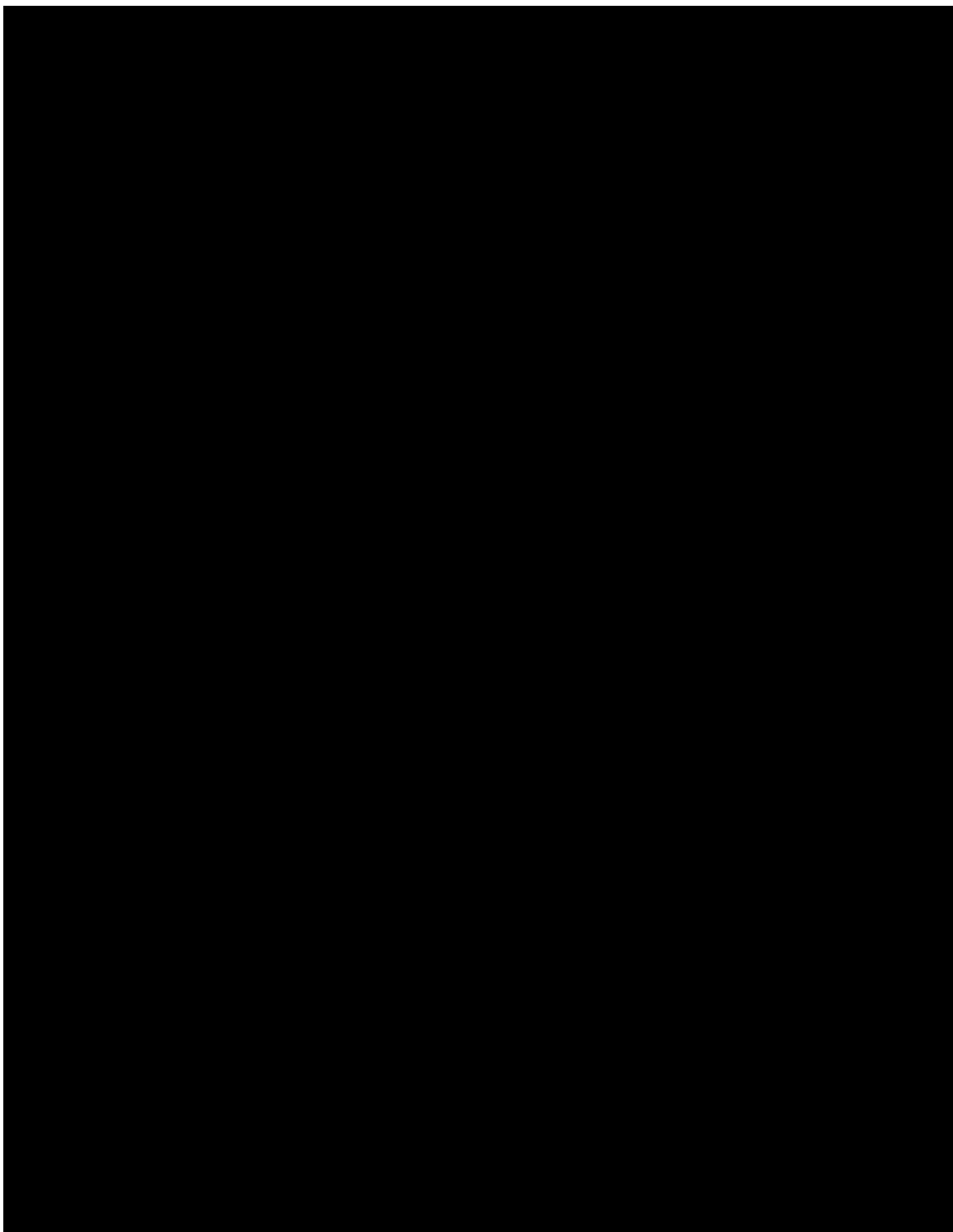


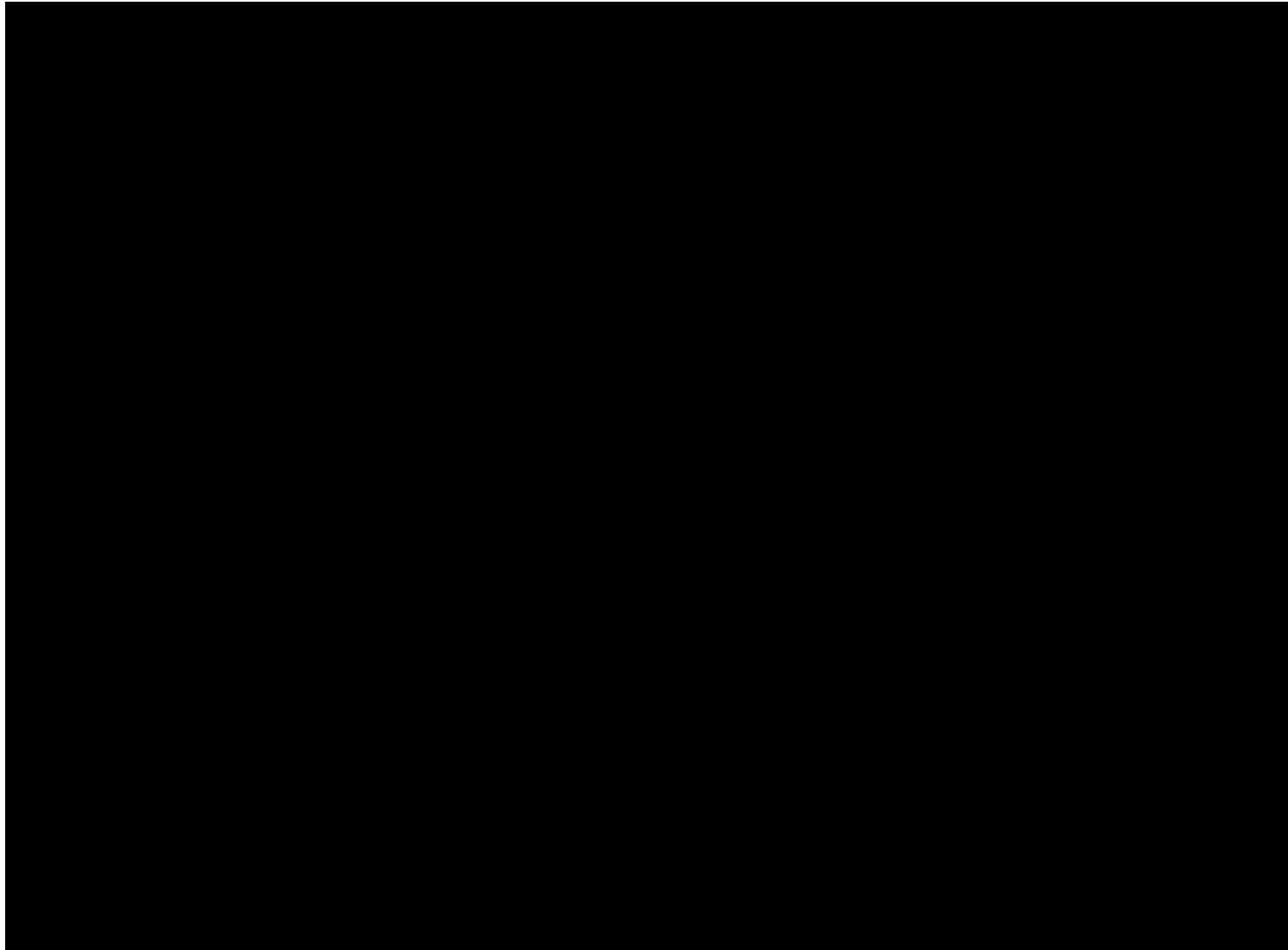


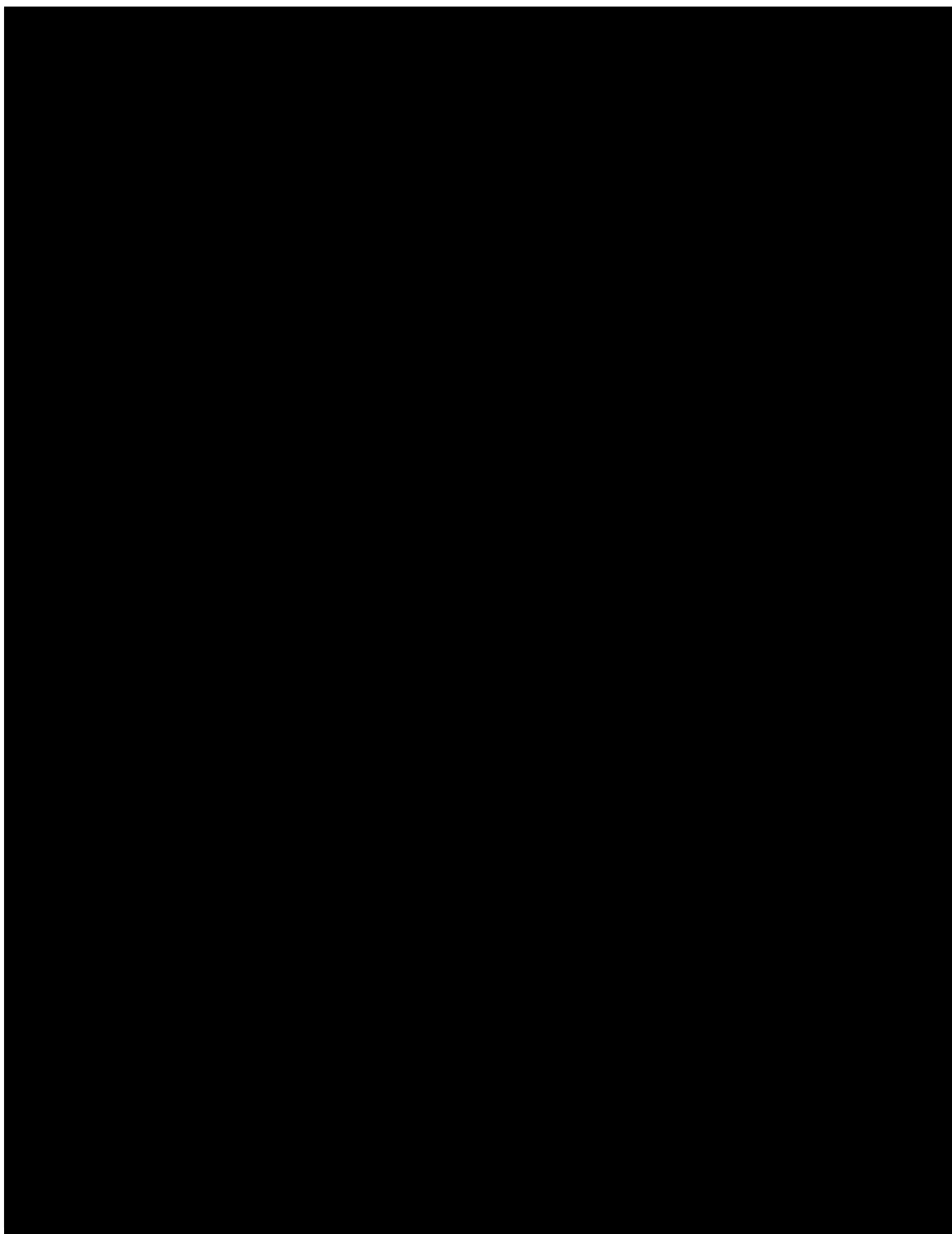
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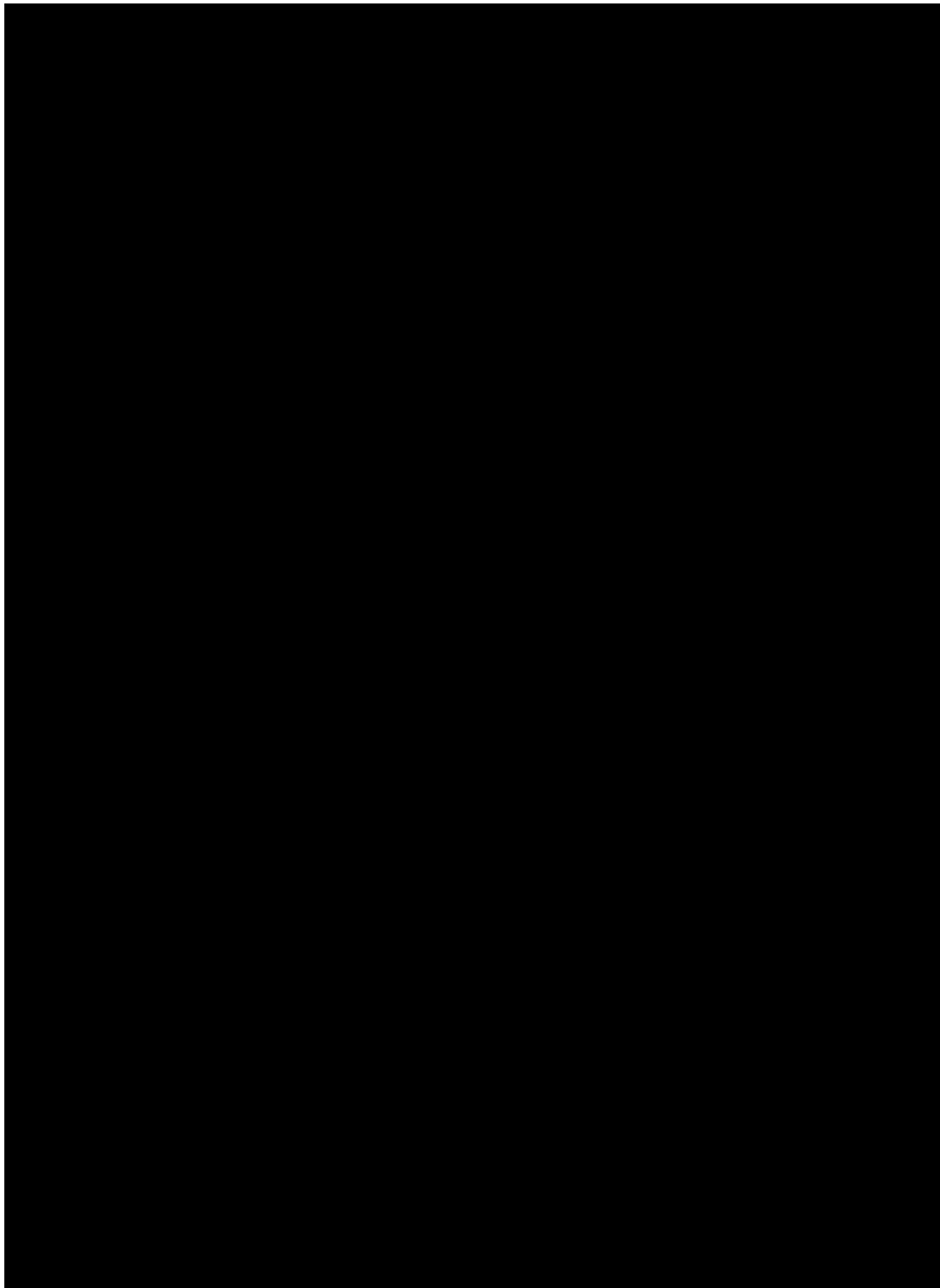


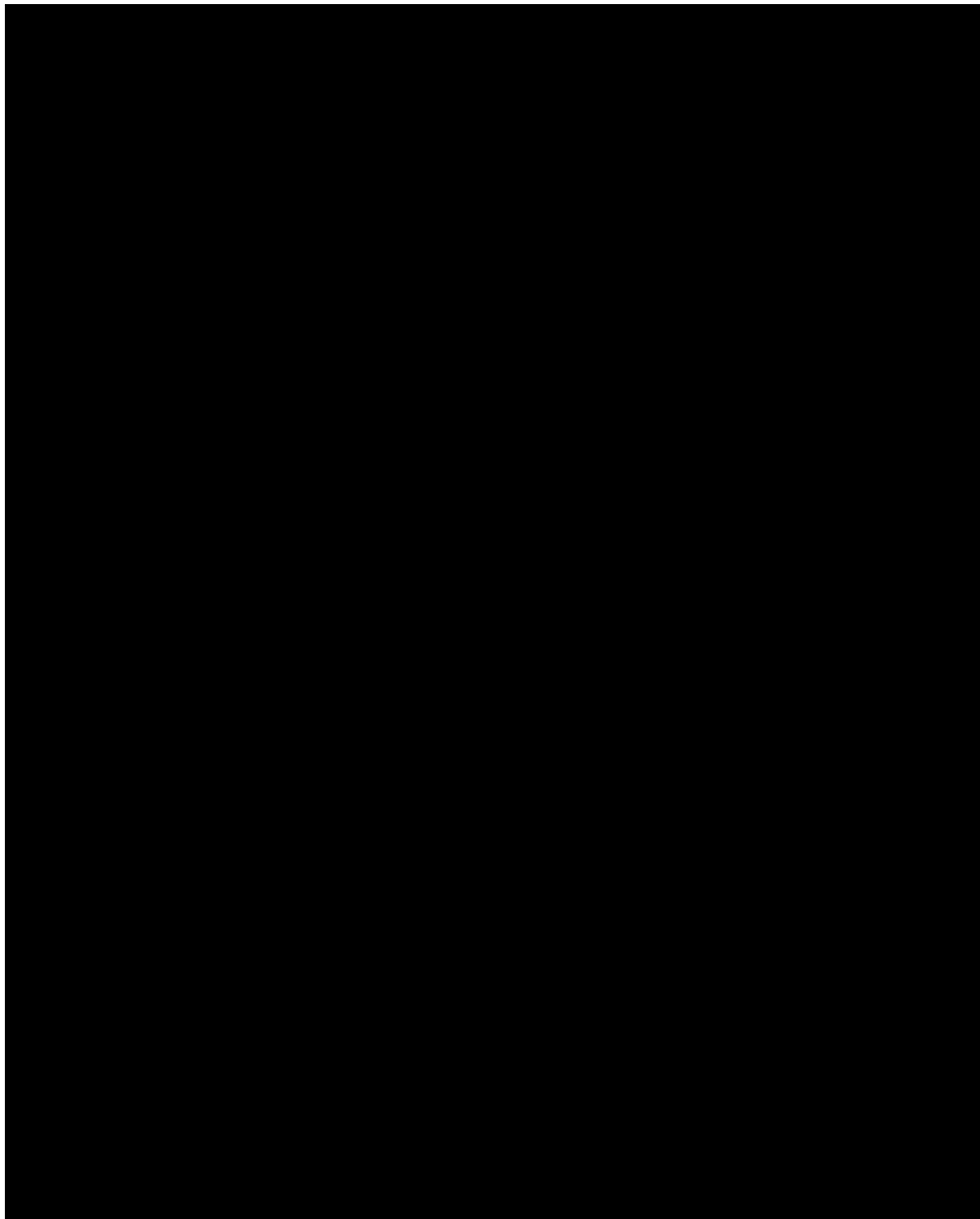












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Approval Task Verdict: Approved	 22-Sep-2023 20:16:13 GMT+0000
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Approval Task Verdict: Approved	 22-Sep-2023 20:32:08 GMT+0000
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