Statistical Analysis Plan for Study M19-148

A Randomized, Double-Blind, Placebo-Controlled Proof-of-Concept Study to Assess the Safety and Efficacy of Elezanumab in Acute Ischemic Stroke

Date: 08 May 2024

Version 3.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for elezanumab (ABT-555) Study M19-148: A Randomized, Double-Blind, Placebo-Controlled Proof-of-Concept Study to Assess the Safety and Efficacy of Elezanumab in Acute Ischemic Stroke.

The analyses of pharmacokinetic and pharmacodynamic fluid biomarkers will not be covered in this SAP.

This is the second version of the SAP. If applicable, the SAP will be updated to include changes to analyses implemented in protocol amendments and/or analyses that are different from the latest version of the protocol. Details will be outlined in Section 13.0. The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

The objective is to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of elezanumab in subjects with acute ischemic stroke.

This study will assess the proof-of-concept of the use of elezanumab in the improvement of neurologic function in patients with acute ischemic stroke.

2.2 Study Design Overview

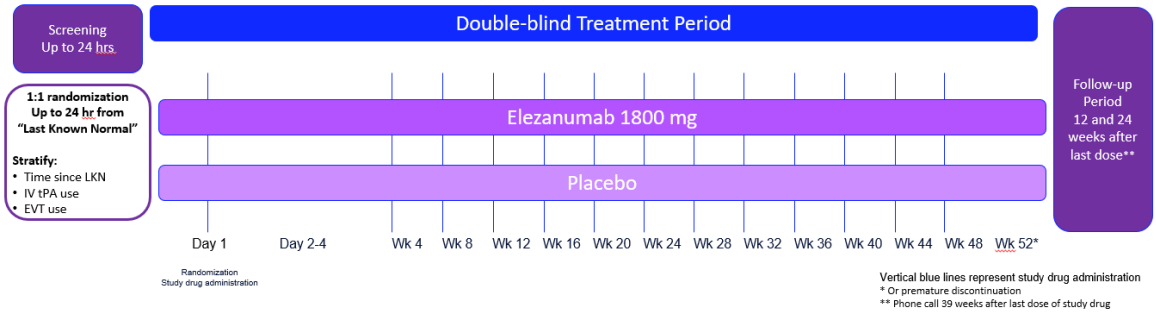
This is a 52-week, Phase 2a, randomized, double-blind, parallel-group, placebo-controlled, multicenter proof-of concept study to evaluate the safety and efficacy of elezanumab in subjects with acute ischemic stroke.

Administration of blinded study drug must be initiated as soon as possible but no later than 6 hours after randomization and done every 4 weeks thereafter through Week 48 for a total of 13 doses. The final double-blind Treatment Period study visit will be at Week 52. Subjects will have 2 post-treatment follow-up visits at 12 and 24 weeks after last dose of study drug, and a final follow-up phone call 39 weeks (~5 half-lives) after last dose of study drug.

Final efficacy analyses will be performed after the last subject completes the Week 52 visit and after an interim database lock. Final safety analyses will be performed following completion of the post-treatment period and final database lock.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



EVT endovascular therapy; hr(s) hour(s); IV intravenous; LKN last known normal; tPA tissue plasminogen activator; Wk week

2.3 Treatment Assignment and Blinding

Subjects will be randomized to elezanumab or placebo in a 1:1 ratio. Randomization will be stratified by intravenous (IV) tissue plasminogen activator (tPA) use (yes/no), treatment with endovascular therapy (EVT) (yes/no), and by time since "last known normal" (≤ 11 hours or > 11) at the time of randomization.

The primary analysis of efficacy endpoints will be performed after the last subject completes the Week 52/Premature discontinuation visit. At this time, an interim database lock will occur, the randomization will be loaded into the database and the Data and Statistical Sciences department at AbbVie will perform the statistical analysis. Final safety analyses and post-treatment efficacy analyses will be performed following completion of the post-treatment period and database lock.

Study sites and subjects will remain blinded through the duration of the study.

2.4 Sample Size Determination

The primary efficacy endpoint is the monthly-adjusted, model-based area under the curve (AUC) of the National Institutes of Health Stroke Scale (NIHSS) total score during the Treatment Period. Approximately [redacted] subjects will be randomized to elezanumab [redacted] mg or placebo in a [redacted] ratio. Assuming the true difference in AUC is [redacted], this sample size is sufficient to show a [redacted] difference in AUC (with the elezanumab group having a lower, i.e., better, AUC) between treatment and placebo with a posterior probability of > [redacted]%. This sample size was calculated based on simulations and included a [redacted]% mortality rate for the population under [redacted] years of age, [redacted]% mortality rate for the population greater than or equal to [redacted] years of age, and an additional [redacted]% discontinuation rate.

The number and proportion of missing assessments (due to missed visits or study drug discontinuation) will be monitored on an ongoing basis and if the proportion of missing assessments is higher than planned, additional subjects may be randomized.

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is the NIHSS total score during the Treatment Period. The primary analysis will be a comparison of a model-based AUC of the NIHSS total score between elezanumab and placebo.

3.2 Secondary Endpoint

The secondary endpoint is the proportion of subjects with a favorable outcome based on the modified Rankin Scale (mRS) at Week 52. A favorable outcome is defined as having an mRS score of 0, 1, or 2 at the specified time point.

3.4 Safety Endpoints

Safety evaluations include adverse event (AE) monitoring, serious adverse event (SAE) monitoring, adverse events of special interest (AESI) monitoring, physical examinations, neurologic examinations, vital sign measurements, clinically significant magnetic resonance imaging (MRI) abnormalities, electrocardiogram (ECG) variables, Columbia-Suicide Severity Rating Scale (C-SSRS) assessments, and clinical laboratory testing (hematology, chemistry, and urinalysis) as measures of safety and tolerability for the entire study duration.

3.5 Other Endpoints

Brain MRI scans will be obtained for all subjects at Baseline (collected between 2-4 days after randomization) and follow-ups (Week 4 and Week 52). Images will be analyzed to assess infarct (ischemic core and penumbra) and presence of microstructural damage related to myelin loss and axonal destruction.

4.0 Analysis Sets

The following population sets will be used for the analyses.

The Full Analysis Set (FAS) includes all randomized subjects who receive any study drug. Subjects will be grouped according to treatment as randomized. The FAS will be used for all efficacy, demographic, and baseline analyses.

The Safety Analysis Set consists of all subjects who receive any study drug. Subjects will be included in the analysis according to the study drug that they actually receive regardless of the randomized treatment assigned as defined below.

If a subject was randomized to treatment X, but received treatment Y during the entire study, this subject will be included in the Y treatment group for analysis purposes. If a subject receives both treatments but one > 50% of the time, the subject will be included in that treatment group. If a subject receives both treatments an equal percentage of the time, the subject will be analyzed in the treatment group to which they were randomized.

5.0 Subject Disposition

The total number of subjects who were screened (Overall only), enrolled (randomized), and treated will be summarized.

A summary of subject accountability overall and by country/investigator will be provided where the number of subjects in each of the following categories will be summarized for each treatment group and overall:

- Subjects randomized in the study
- Subjects who took any study drug (Safety Analysis Set)
- Subjects who completed study drug
- Subjects who prematurely discontinued study drug
- Subjects who completed the study
- Subjects who prematurely discontinued study
- Subjects in each efficacy analysis set (FAS, MMIAS)

For end of study participation, the number and percentage of subjects who completed study drug and the study and those who prematurely discontinue with associated reasons will be summarized overall and by treatment group.

6.0 Study Drug Duration and Compliance

For the Safety Analysis Set, extent of exposure will be summarized for each treatment group. Extent of exposure will be summarized as duration of treatment and number of infusions. Duration of treatment is defined for each subject as last dose date minus first dose date + 28. A gap in treatment due to missed infusions will not be considered in the calculation of study drug duration. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each unique treatment duration interval (28, 29 to 56, 57 to 84, 85 to 112, 113 to 140, 141 to 168, 169 to 196, 197 to 224, 225 to 252, 253 to 280, 281 to 308, 309 to 336, 337 to 364, > 364) will be summarized.

The number and percentage of subjects who received each number of infusions from 1 to 13 will be summarized.

Because the treatment is administered by the site, compliance will not be summarized.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the FAS by treatment group and overall. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight (by sex and overall), height, and body mass index (BMI). Categorical demographic variables include sex, ethnicity, race, age (< 70, 70 - < 80, ≥ 80), weight (< 60 or ≥ 60 kg), BMI (< 25 or ≥ 25 kg/m^2), country (United States, Non-US), nicotine user (current, former, never, unknown for each type), and alcohol user (current, former, never, unknown).

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class (SOC) and preferred term) will be summarized overall and by treatment group for the FAS. The SOC will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

The following stratification factors related to the current stroke will be summarized with the number and percentage of subjects in each category:

- Time since last known normal (≤ 12 hours between last known normal and study drug initiation, > 12 hours between last known normal and study drug initiation) based on the stroke history eCRF. Randomization is stratified by time from last known normal to randomization transaction (≤ 11 hours or > 11 hours) for operational purposes. Time from last known normal to study drug initiation will be used for analysis purposes.
- Treatment with tPA (Yes, No) based on the prior and concomitant medications and supplements eCRF.
- Treatment with EVT (Yes, No) based on the prior and concomitant procedures eCRF.
- Treatment with EVT and/or tPA (Yes, No) based on the eCRFs noted above. Yes indicates treatment with either or both EVT and tPA, and No indicates treatment with neither.

Additionally, the number and percentage of subjects with baseline NIHSS total score categories of < 15, and ≥ 15, and the number and percentage of subjects with reperfusion as measured by the modified Thrombolysis in Cerebral Infarction (mTICI)[2] score (< 2B, ≥ 2B) as reported by the central reader will be summarized by treatment group. Baseline NIHSS total score will also be summarized continuously.

Time between last known normal and study drug initiation will be summarized both as a continuous variable and a categorical variable (0 - 6 hours, > 6 - 12 hours, > 12 - 18 hours, > 18 - 24 hours, > 24 hours).

Discharge destination, time from last known normal to discharge post-stroke in days, and stroke subtype based on the Stroke History eCRF will be summarized.

7.3 Prior and Concomitant Medications

The number and percentage of subjects taking prior and concomitant medications will be summarized separately by generic name based on the World Health Organization (WHO) Drug Dictionary. A prior medication is defined as any medication taken prior to the date of the study drug initiation. A concomitant medication is defined as any medication that started prior to the date of study drug initiation and continued to be taken after study drug initiation or any medication that started on or after the date of study drug initiation, but not after the date of the last dose of study drug plus 39 weeks (273 days).

7.4 MRI

The MRI parameters from images obtained at Days 2 - 4 (defined as Baseline) will be summarized categorically with the number and percentage of subjects by treatment group as observed. The following will be summarized:

- Number and percentage of subjects with cerebral infarct location at Baseline, based on the categories of gray matter only (cortical and/or subcortical gray matter), white matter only (subcortical white matter), both (cortical and/or subcortical gray matter, and white matter), and other (none of the above)
- Number and percentage of subjects with cerebral infarct location at Baseline in the left hemisphere only, right hemisphere only, or both
- Number and percentage of subjects with cerebral infarct location at Baseline, based on the categories cortical, subcortical white matter, subcortical gray matter, other
- Vessel occlusion location at Baseline, based on the categories extracranial ICA, intracranial ICA or T lesion, MCA-M1, MCA-M2, MCA-M3, other
- mTICI score at Baseline, based on the categories 0, 1, 2a, 2b, 3

8.0 Efficacy Analyses

8.1 General Considerations

All efficacy analyses will be conducted in the FAS. Where noted, some analyses may additionally be conducted in the MMIAS. Because this is a small, exploratory, proof of concept study, p-values will not be presented. Where statistical models are noted, appropriate point estimates and 95% confidence intervals will be presented.

The primary analysis of efficacy endpoints will be performed after all ongoing subjects have completed the Treatment Period and an interim lock has been performed. This will be the final analysis for the efficacy endpoints during the Treatment Period. Post treatment efficacy analyses will be completed following the final database lock.

Generally, "Baseline" refers to the last non-missing observation before the first administration of study drug. Where noted, Day 2-4 or Week 4 may be used as baseline. Unless otherwise specified, categorical variables will be summarized with the number and percentage of subjects in each category. Responder analyses will be presented with the number and percentage of subjects in each category, the difference in proportion of responders between the 2 treatment groups, and the 95% confidence interval for the difference based on Wald confidence limits, unless otherwise specified. Continuous variables will be analyzed using Mixed-Effect Model for Repeat Measures (MMRM) method. The dependent variable will be the visit value and baseline (pre-dose, Day 2-4 or Week 4, depending on the endpoint) will be included as one of the timepoints in the repeated measures. For analyses of change from baseline (pre-dose, Day 2-4 or Week 4, depending on the endpoint), this will be derived from a contrast of the group-level least squares (LS) means from the MMRM.

Unless otherwise specified, any subject who is randomized based on a wrong stratum will be analyzed according to the actual stratum the subject belongs to based on the eCRFs as noted in Section 7.2.

8.2 Handling of Missing Data

Missing data will be imputed using the following methods for the efficacy analyses:

- Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who does not have evaluation during a specific visit window as a non-responder for that visit. Unless otherwise noted, this will be the primary approach for accounting for missing data in responder analyses.
- Generalized linear mixed model (GLMM): The model will include a logit link function to compare the probability of having responder between treatment groups of each visit of Day 2-4, Week 4, Week 8, Week 12, Week 24, Week 36, Week 52, and will include baseline NIHSS as a covariate and time from last known normal and initiation of first dose (≤ 12 hours, > 12 hours), tPA use (Y/N), EVT use (Y/N), visit, and treatment group as fixed effects. An unstructured variance covariance matrix will be used. The compound symmetry variance covariance matrix will be used if the model does not converge with unstructured matrix. The GLMM model relies on a missing at random (MAR) assumption.
- As Observed (AO): The AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study.
- MMRM: The repeated measures analysis will be conducted using a mixed model including observed measurements at all visits. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factors at randomization, and the continuous fixed covariates of baseline measurement, unless otherwise noted. An unstructured variance-covariance matrix will be used; if the model does not converge, then a compound symmetry variance-covariance matrix will be used. Denominator degrees of freedom will be computed using the Kenward-Roger method. Parameter estimation is based on the assumption of data being missing at random and using the method of restrictive maximum likelihood. MMRM will be the primary approach in the analysis of continuous

variables unless otherwise noted. The MMRM model relies on a missing at random (MAR) assumption.

For all analyses related to the mRS, if a subject has a value of 6 (dead), this will be carried forward to future visits in the analysis. This will be applied to all mRS analyses, including the responder analysis as observed.

The COVID-19 pandemic is interfering with the conduct of many ongoing trials, with potential impact on treatment duration and the collection, analysis and the interpretation of clinical trial data. Some protocol-specified visits in this clinical trial may be impacted due to COVID-19 infection or logistical restrictions during the pandemic. For example, some scheduled visits may be missed due to self-quarantine or local government restrictions on travel; some visits may also be delayed or canceled due to healthcare resource constraints during the pandemic. These missed visits will be recorded in the database. The probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic can be reasonably assumed to be unrelated to the unobserved values conditional on the observed data. Therefore, for the purpose of statistical analysis, it is reasonable to assume that these missing data are missing at random (MAR) and the statistical models that require MAR assumption are appropriate. In some cases, sensitivity analyses may be performed to assess the impact of missing data and the robustness of the conclusion.

8.3 Primary Efficacy Endpoint and Analyses

8.3.1 Primary Efficacy Endpoint

The primary endpoint is the National Institutes of Health Stroke Scale (NIHSS) total score during the Treatment Period.

8.3.2 Handling of Missing Data for the Primary Efficacy Endpoint

Missing data will not be imputed for the primary analysis, which will be based on an MMRM model.

8.3.3 Primary Efficacy Analysis

The primary efficacy analysis will be based on the monthly-adjusted area under the curve (AUC) derived from an MMRM. The dependent variable is the NIHSS total score during the Treatment Period. The model will include the stratification factors of tPA use (Y/N), EVT use (Y/N), time since last known normal (≤ 12 hours, > 12 hours based on time between last known normal and study drug initiation), main effects of treatment group and visit, and the treatment-by-visit interaction. The REPEATED statement will be used for visit with blocks in the covariance matrix identified by subject nested within treatment group. The unstructured covariance structure will be used to estimate the within subject variance-covariance; if the model does not converge with this variance-covariance structure, then compound symmetry will be used.

The monthly-adjusted AUC of NIHSS total score for each treatment group will be obtained using the trapezoidal method where i treatment group (placebo, elezanumab) and j visit during the Treatment Period {Day 1, Day 2-4, Week 4, Week 8, Week 12, Week 24, Week 36, Week 52}:

$$AUC_i \quad \frac{1}{13} \sum_{j=Stabil.(Day\ 2\ \ 4)}^{Week\ 52} \frac{(Week\ Number_j \quad Week\ Number_{j\ \ 1})}{4} \frac{1}{2}(LS\ Mean_{i,j} + LS\ Mean_{i,j\ \ 1})$$

The AUC for each treatment group, as well as the difference in AUCs (placebo minus elezanumab) and their respective standard errors and confidence intervals will be presented.

The posterior probability that the difference in AUCs being greater than 0.6 based on the observed data will be presented.

The attributes of the estimand corresponding to the primary efficacy objective are summarized in Table 1.

Table 1. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Objective

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
NIHSS total score AUC	Elezanumab 1800 mg or placebo IV Q4W (13 doses)	NIHSS total score at each visit	FAS	Missing data due to intercurrent events (e.g., premature discontinuation of study drug, lost to follow-up, death, COVID-19) will be handled using MMRM with MAR assumption	Difference in monthly-adjusted AUC between treatment groups

8.3.4 Additional Analyses of the Primary Efficacy Endpoint(s)

A line graph by treatment group of the LS means with 95% confidence intervals derived from the primary MMRM model will be produced.

The analysis of the primary endpoint will be repeated based on the MMIAS.

The NIHSS total score will be summarized continuously at Baseline and each visit including Post-Treatment with the number of observations, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

The change from baseline in the NIHSS total score will be summarized based on the MMRM noted in Section 8.3.3. Change from baseline to specified time points (Day 2-4, Week 4, Week 8, Week 12, Week 24, Week 36, Week 52) will be derived from a contrast of the group-level least squares (LS) means. The visit means, standard error, and 95% confidence interval, as well as the between-group difference, standard error, 95% confidence interval, and effect size will be presented for each visit during the Treatment Period.

The number and percentage of responders for the NIHSS total score will be summarized based on a responder definition of improvement (decrease) from Day 1 of at least 4 points

and at least 8 points improvement at visits Day 2-4, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, and Week 52, as well as a responder definition of NIHSS total score 0 at the specified time point.

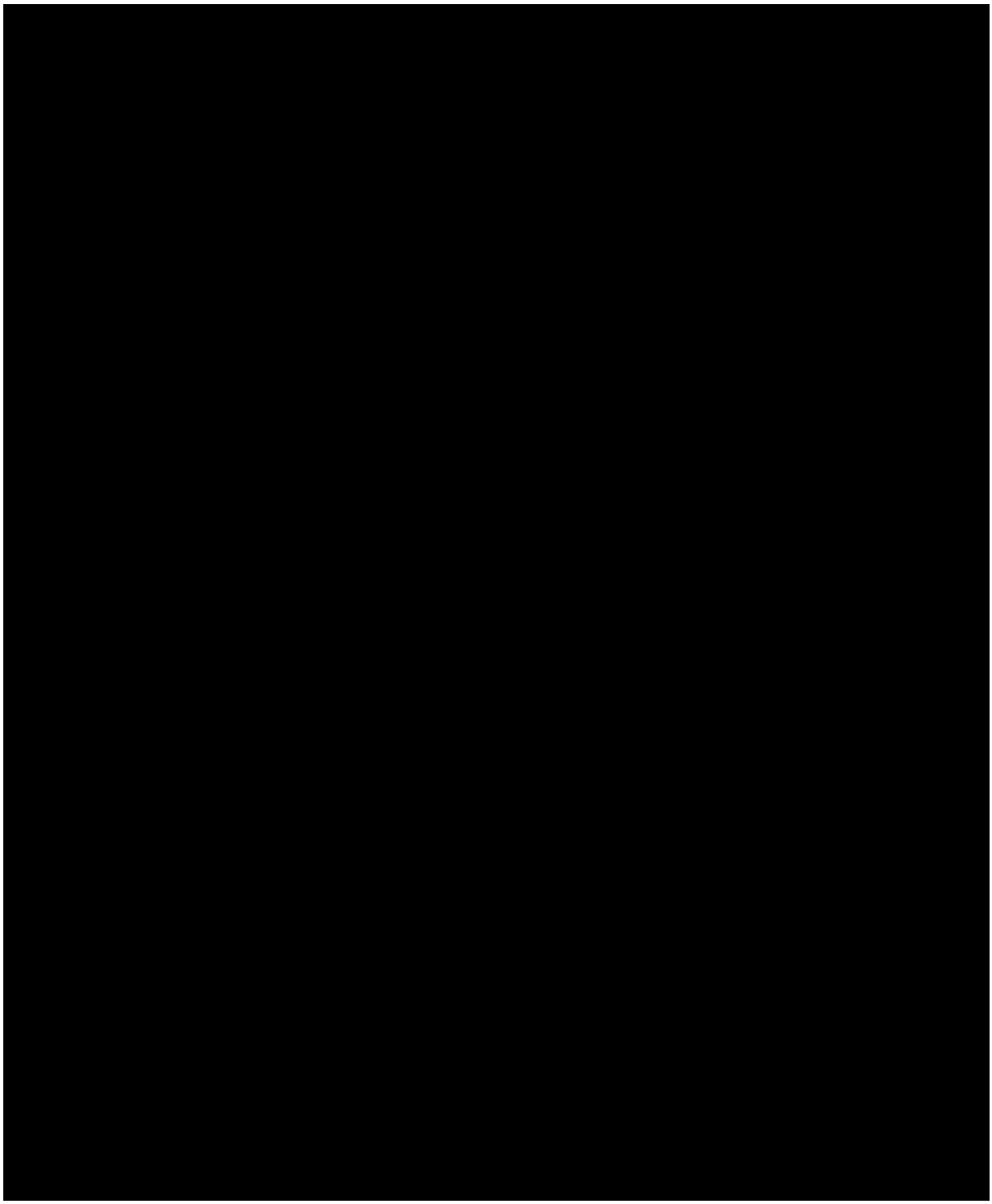
The plot of the cumulative distribution function of the NIHSS total score at Weeks 12, 24, and 52 will be produced based on the data as observed.

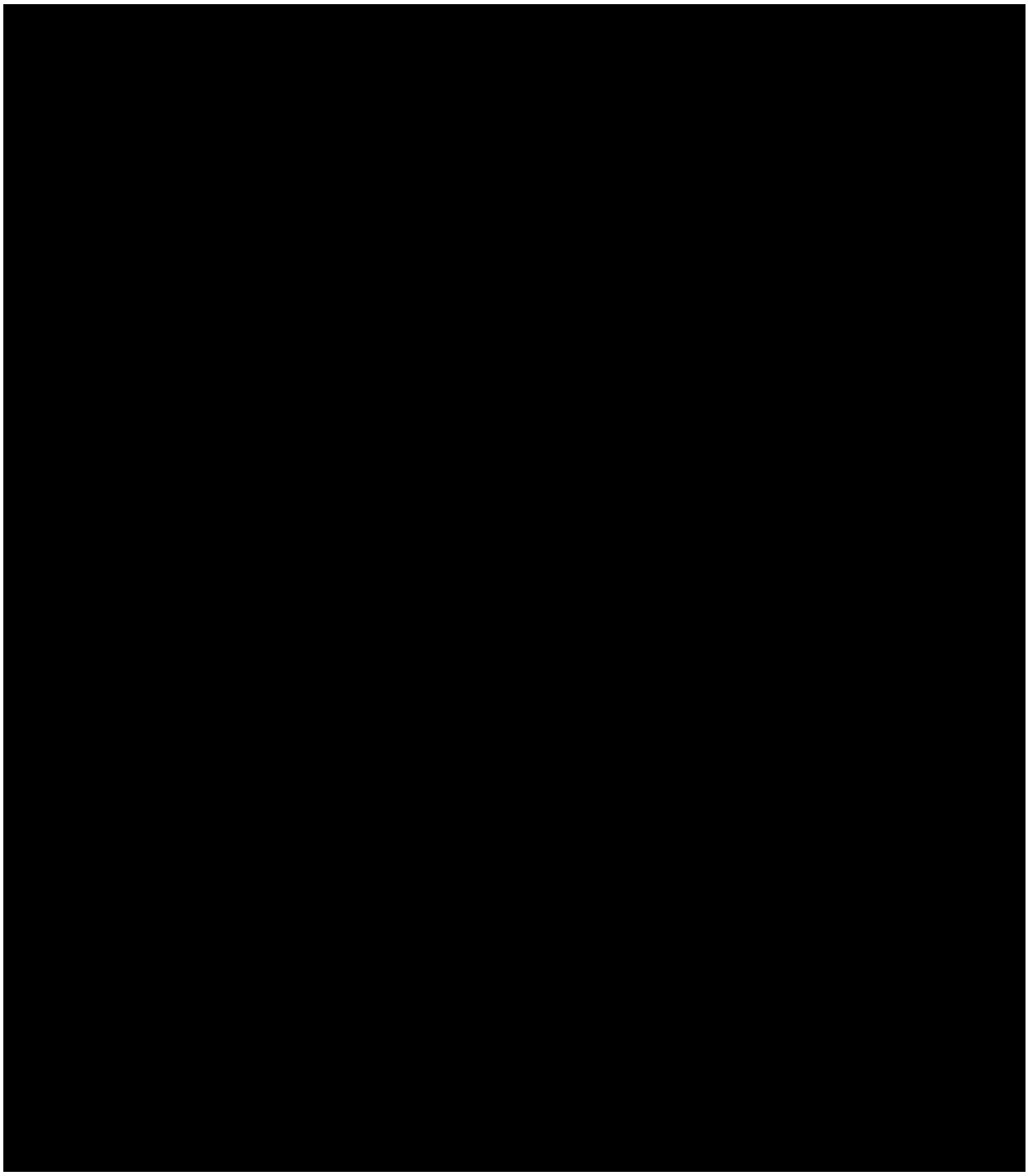
8.4 Secondary Efficacy Analyses

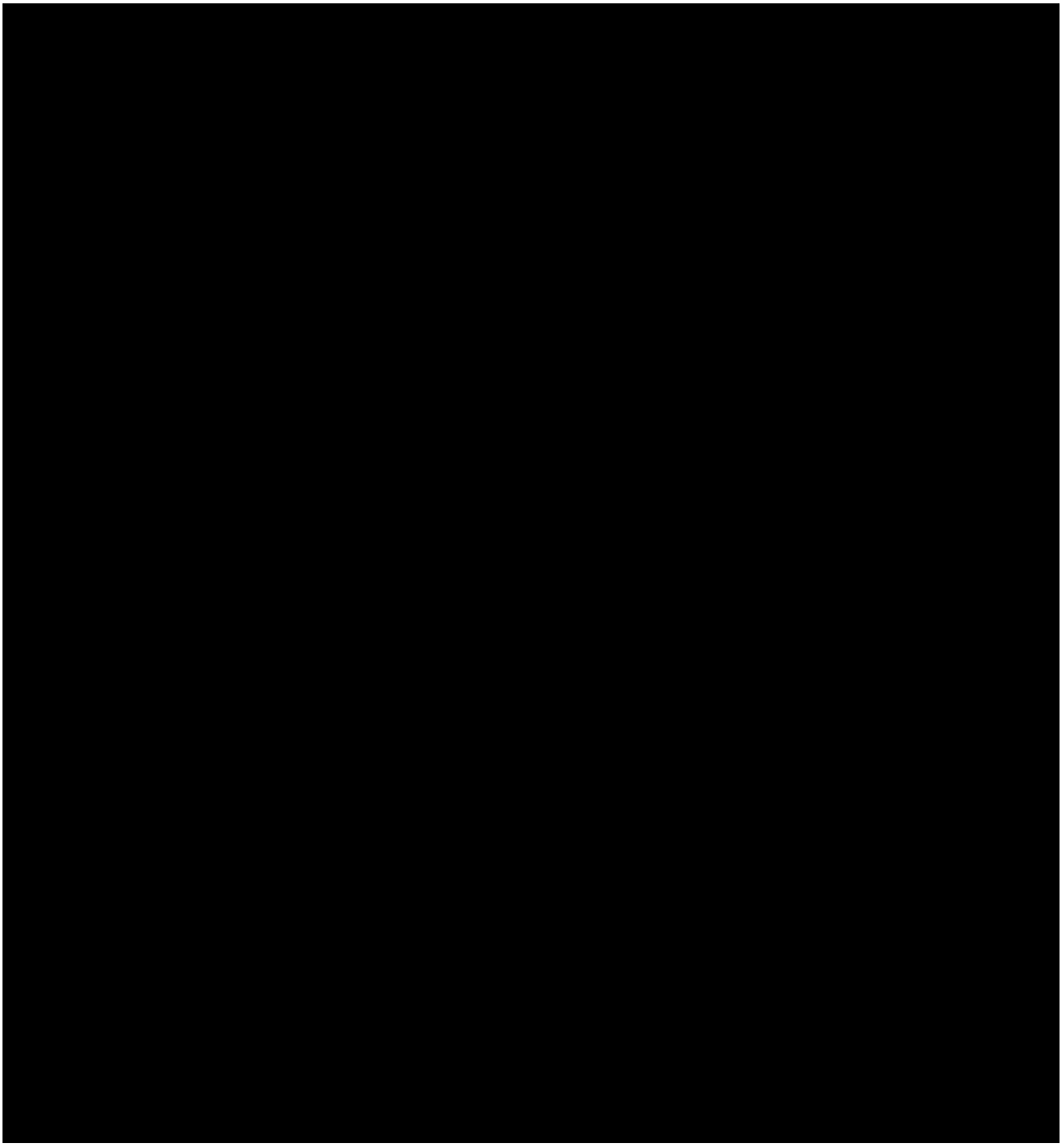
The point estimate of the responder rate, odds ratio, and corresponding 95% confidence intervals will be derived from a generalized linear mixed model (GLMM) with a logit link function to compare the probability of having responder between treatment groups of each visit of Week 4, Week 8, Week 12, Week 24, Week 36, Week 52. The model will include time from last known normal and initiation of first dose (≤ 12 hours, > 12 hours), tPA use (Y/N), EVT use (Y/N), visit, treatment group as fixed effects, and visit as the random effect by subject. An unstructured variance covariance matrix will be used. The compound symmetry variance covariance matrix will be used if the model does not converge with unstructured matrix.

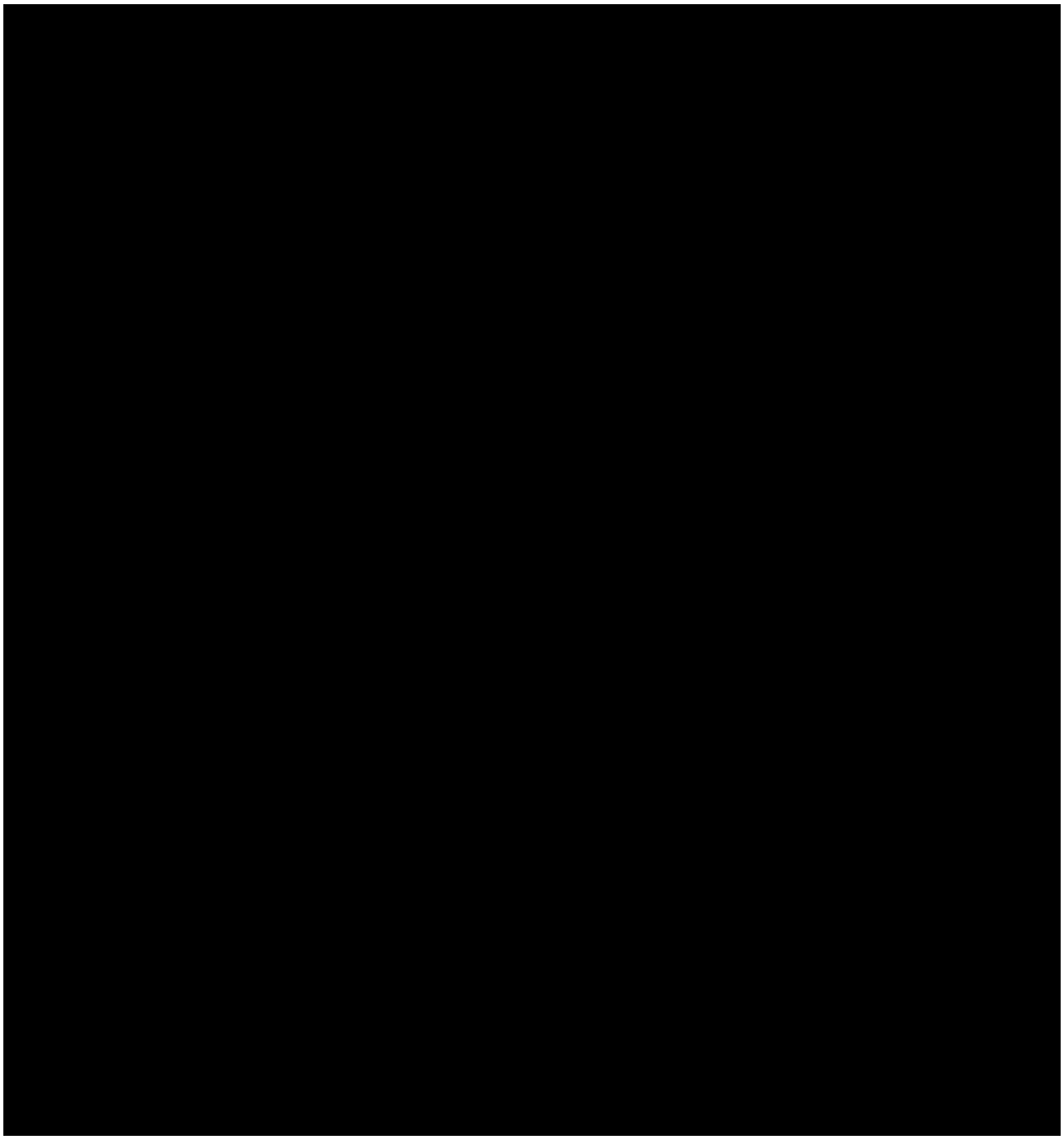
8.4.1 Additional Analyses of the Secondary Efficacy Endpoint

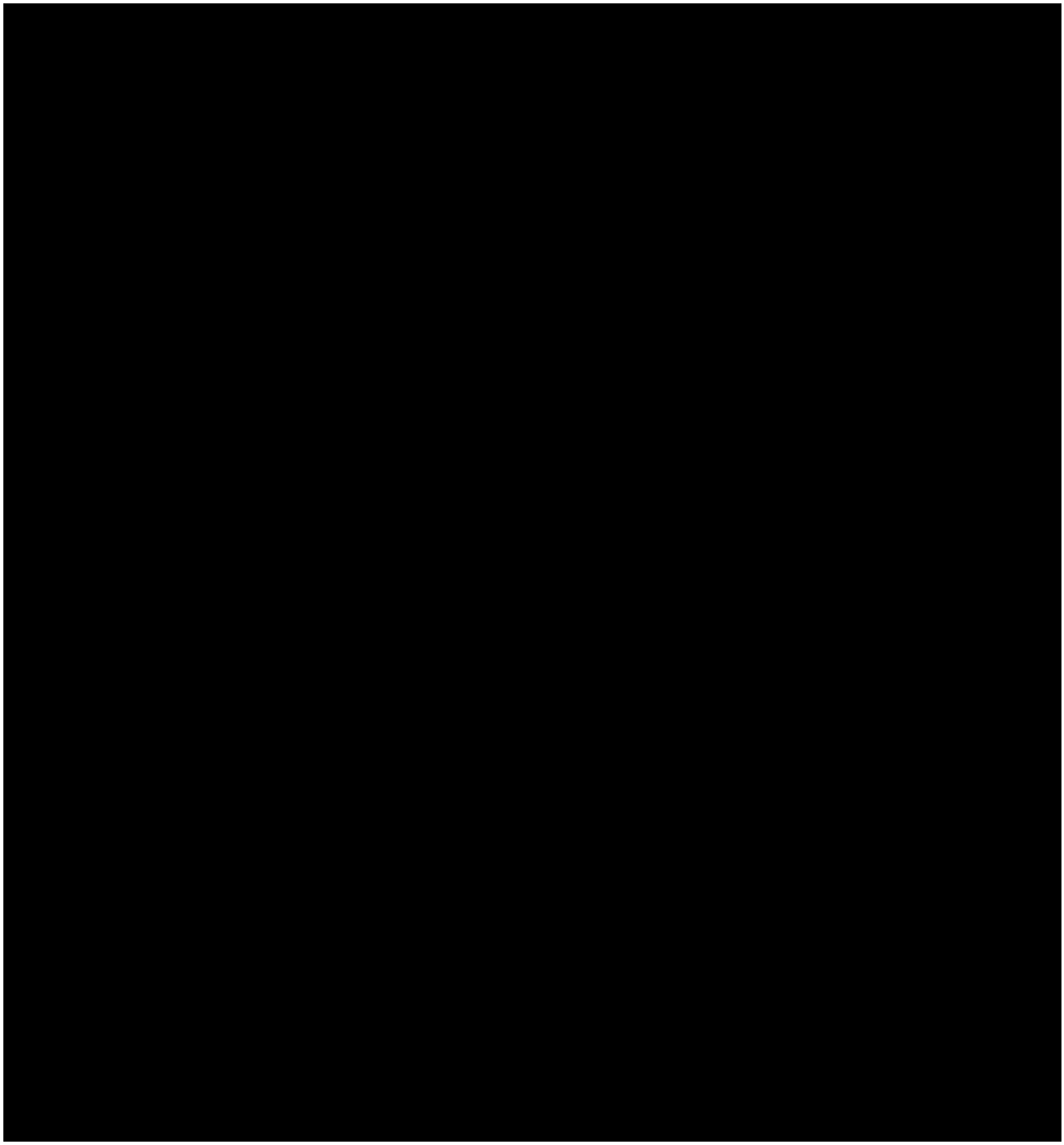
The analysis of the secondary endpoint will be repeated based on the MMIAS.











8.6 Efficacy Subgroup Analyses

Subgroup analysis of the change from baseline in NIHSS total score will be conducted for the following subgroups at Day 2-4, Week 4, Week 12, Week 24, and Week 52:

- Age (< 70, 70 - < 80, ≥ 80 years at time of randomization)
- Sex (male, female)
- NIHSS total score at baseline (< 15, ≥ 15)
- Time since last known normal based on actual study drug initiation time (≤ 12 hours, > 12 hours)
- tPA use (Yes, No)
- EVT use (Yes, No)
- Either tPA +/- EVT use (Yes, No)

This will be based on an ANCOVA as observed, with change from baseline as the dependent variable and including treatment and the stratification factors (except for the subgroup analysis corresponding to that stratification term, in which case that particular term will not be included in the model) as main effects and baseline NIHSS as a covariate. This will be based on the subsets for each subgroup separately, at the following time points: Day 2-4, Week 4, Week 12, Week 24, Week 52.

The number and percentage of responders based on the modified Rankin Scale (mRS 0-2) will be repeated for the subsets above using a non-responder imputation at Week 4, Week 12, Week 24, Week 52. The difference between treatment groups and corresponding 95% CI for the difference based on the Wald method will be produced.

A forest plot of each of the subgroups will be presented for each analysis at the time points Week 4, Week 12, Week 24, Week 52 based on the same outputs used in the tables.

8.7 Biomarker Analyses

Biomarker variables neurofilament light (NFL), glial fibrillary acidic protein (GFAP), interleukin 6 (IL6) and repulsive guidance molecule a (RGMa) will be summarized for all

time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum, and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized as observed. The within-group and between-group LS means, SE, and 95% confidence intervals will be presented based on an ANCOVA with baseline as a covariate and treatment as a main effect.

9.0 Safety Analyses

9.1 General Considerations

Safety data will be summarized for the Safety Analysis Set as described in Section 4.0. Safety summaries will be presented by treatment group.

"Baseline" refers to the last non-missing observation before the first administration of study drug.

9.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA SOCs and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

9.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset that is on or after the first dose date. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized.

9.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any serious treatment-emergent AE related to study drug according to the investigator
- Any treatment-emergent AE leading to discontinuation of study drug
- Any treatment-emergent AE leading to death
- Any treatment-emergent AE of special interest
- All deaths

An overview of treatment-emergent AEs of special interest will also be presented, including the above categories and for each of the AESI SMQ/CMQs noted in Appendix B.

9.2.3 Treatment-Emergent Adverse Events by SOC and PT

Treatment-emergent adverse events and corresponding subject numbers will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the elezanumab group.

Recurrent stroke events based on the embolic and thrombotic events SMQ provided in Appendix B will be tabulated and listed.

9.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format. Listing of all adverse events for subjects experiencing death will be produced.

9.2.5 Adverse Events of Special Interest

Treatment-emergent adverse events of special interest will be summarized by SOC and PT and by maximum severity and will be based on standardized MedDRA queries (SMQs) or company MedDRA queries (CMQs). Infusion reactions are considered to be adverse events of special interest for elezanumab and will be display by each category provided in Appendix B.

Detailed information about the search criteria is provided in Appendix B.

9.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) asl well as minimum value, maximum value, and final value, with the number of non-missing observations, mean and standard deviation, median, minimum, and maximum.

Mean change from baseline to each applicable post-baseline visit will be summarized for PT, aPTT, total cholesterol, and triglycerides, with the number of observations, baseline mean, and visit mean. The mean change from baseline, standard error, and 95% confidence interval will be presented within each treatment group and between treatment group difference (active vs. placebo) based on an ANCOVA with baseline as a covariate and treatment as a main effect.

Changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline to minimum and maximum value (based on normal range), will be created. A similar shift table will be provided to summarize shifts from baseline to the final post-baseline value. Listing of subjects with lab abnormalities meeting CTC Criteria Grade 3 or 4 will be provided.

Laboratory abnormalities will be evaluated based on Potentially Clinically Significant (PCS) criteria (Appendix C). For each laboratory PCS criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria.

The following criteria will be used to assess for potential hepatotoxicity. The number and percentage of subjects meeting each of the following criteria will be summarized by treatment group, and a listing of ALT, AST, TBL, and alkaline phosphatase at each time for all subjects that met any of the criteria below at any time will be produced.

- ALT ≥ 3 × ULN, ≥ 5 × ULN, ≥ 10 × ULN, ≥ 20 × ULN
- AST ≥ 3 × ULN, ≥ 5 × ULN, ≥ 10 × ULN, ≥ 20 × ULN
- TBL ≥ 1.5 × ULN, ≥ 2 × ULN
- ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN
- ALT ≥ 3 × ULN and TBL ≥1.5 × ULN
- ALT ≥ 3 × ULN and TBL ≥ 2 × ULN

- Alkaline phosphatase ≥ 1.5 × ULN

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions simultaneously, will be provided: ALT ≥ 3 × ULN or AST ≥ 3 × ULN. that is associated with an increase in bilirubin ≥ 2 × ULN and alkaline phosphatase < 2 × ULN.

9.4 Analysis of Vital Signs and Weight

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, and body temperature, as well as weight will be summarized.

Each vital sign variable will be summarized for all time points (starting with Baseline) for the pre-infusion value with the number of non-missing observations, mean and standard deviation, median, minimum and maximum.

Mean change from baseline to each applicable post-baseline visit based on the pre-infusion value will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented within each treatment group and between treatment group difference (elezanumab vs. placebo) based on an ANCOVA with baseline as a covariate and treatment as a main effect.

The pre-infusion and post-infusion means will be calculated for each infusion visit (time point) for subjects who have both values. The change from pre-infusion to post-infusion mean, standard error, and 95% confidence interval will be presented for within each treatment group and between treatment groups (elezanumab vs. placebo) based on an ANCOVA with baseline as a covariate and treatment as a main effect.

Vital sign variables will be evaluated based on potentially clinically significant (PCS) criteria (Appendix C). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCS criteria.

9.5 Other Safety Analyses

9.5.1 Analysis of ECG Parameters

The proportion of subjects with Normal, Abnormal - not clinically significant and Abnormal - clinically significant electrocardiogram (ECG) readings will be summarized at each visit ECG is performed for each treatment group and all subjects overall. Listings will be provided to summarize subject-level ECG data for subjects meeting PCS criteria.

9.5.2 Analysis of Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a systematically administered instrument developed to track suicidal adverse events across a treatment study. At Day 2-4 the C-SSRS will be administered to collect prior to study entry. At all other visits, the C-SSRS will collect experience since the last visit. Affirmative responses on the C-SSRS will be summarized for the initial screening and each subsequent visit for each treatment group and all subjects overall.

Each summary will include the number and percentage of subjects with one or more affirmative responses to each of the 5 suicidal ideation questions, each of the 6 suicidal behavior questions, any of the 5 suicidal ideation questions, any of the 6 suicidal behavior questions, any suicidal ideation or behavior question, and the self-injurious behavior without suicidal intent. A listing will also be prepared that includes all subjects with 1 or more affirmative responses.

9.5.3 MRI

The MRI safety parameters will be summarized categorically with the number and percentage of subjects by treatment group as observed. The following will be summarized:

- Midline shift at each visit (Yes, No) and for those with Yes, Midline shift size ($< 3, \geq 3$)

- Hemorrhagic transformation (Yes, No), and for those with Yes, categories of HI-1, HI-2, PH-1, PH-2
- Vasogenic edema present at each visit (Yes, No, Questionable, Not evaluable)

10.0 Other Analyses

10.1 Post-Stroke Rehabilitation Questionnaire

The number and percentage of subjects with rehabilitation will be summarized as observed by treatment group for each of the types of rehab.

The number of hours of rehabilitation use in the last 4 weeks prior to the assessment will be summarized continuously as observed by treatment group for each of the types of rehab (inpatient, outpatient, home) at Week 4, Week 8, Week 12, Week 24, Week 36 and Week 52.

11.0 Interim Analyses

No interim analyses of efficacy variables for the purposes of stopping the study early due to futility or efficacy are planned for this study.

11.1 Data Monitoring Committee

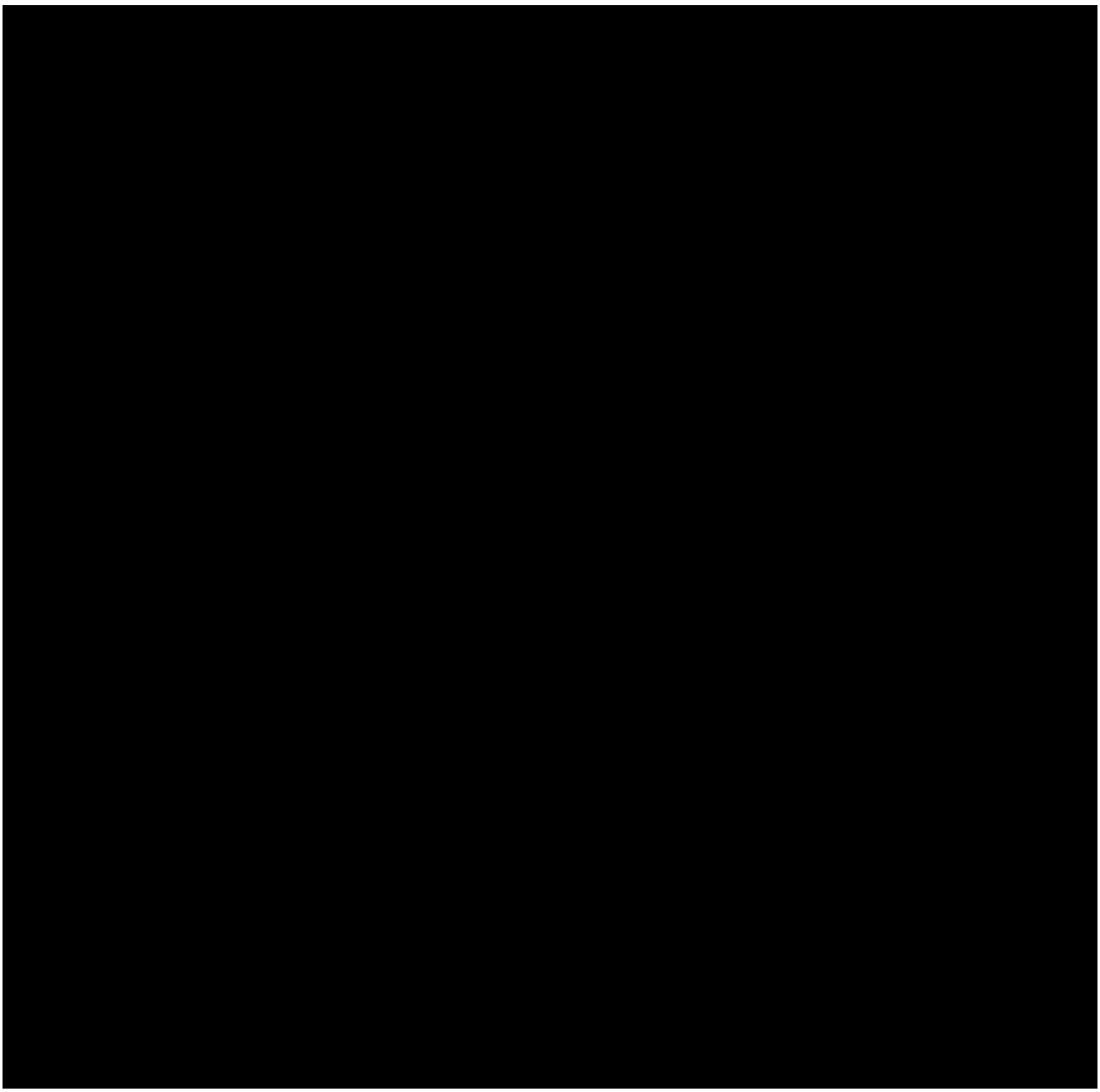
An external data monitoring committee (DMC) composed of persons independent of AbbVie and with relevant expertise in their field will review unblinded data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

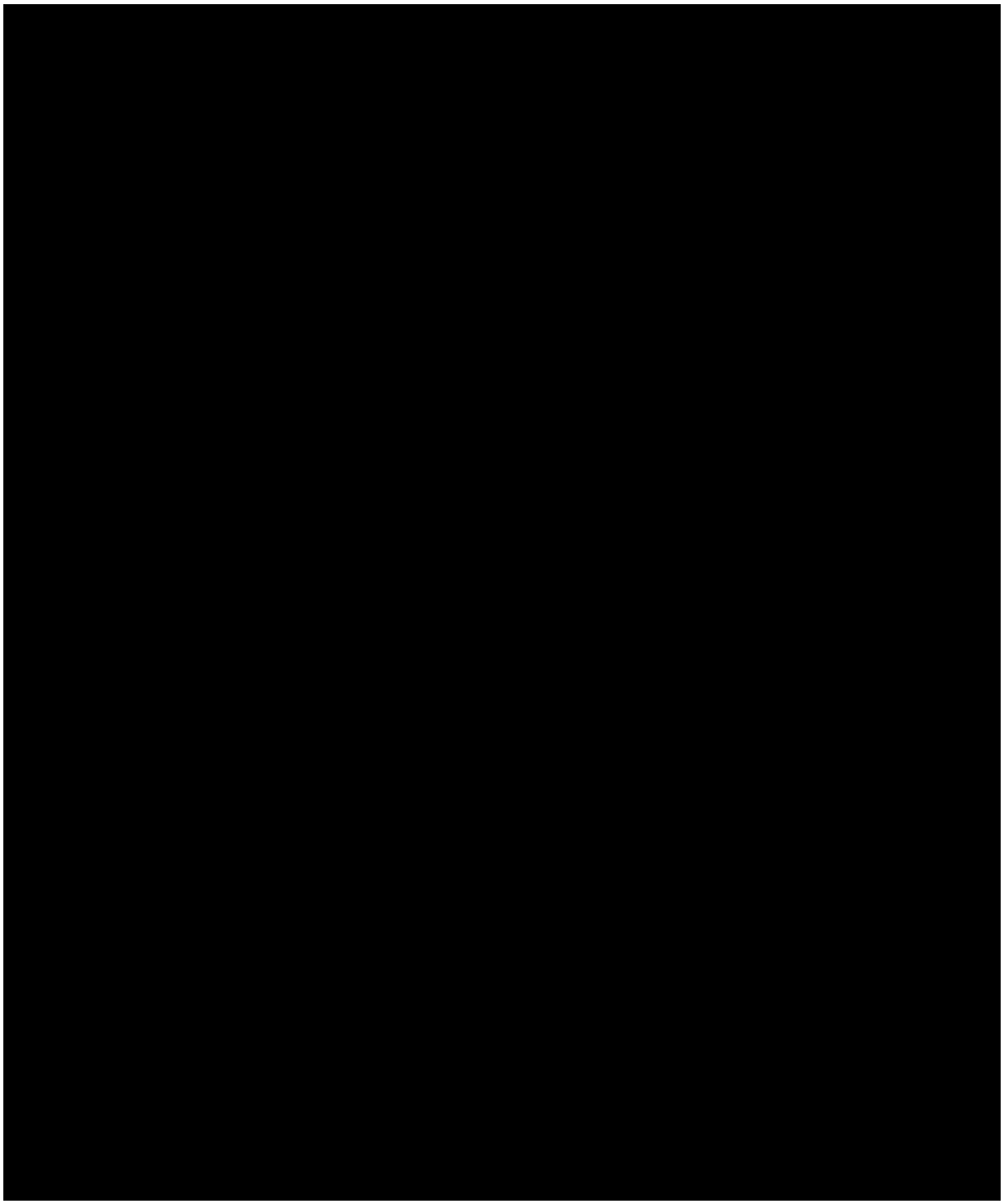
A separate DMC charter describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and general operations.

Since there are no efficacy analyses for early stopping, no alpha adjustment is needed.

12.0 Overall Type-I Error Control

No multiplicity adjustment will be performed for this exploratory, Phase 2a, proof-of-concept study.





13.1 Changes to Planned Analyses in the Protocol

There are no changes to the planned analyses described in the latest version of the protocol.

14.0 References

1. Mapi Research Trust, SIS V3.0, SIS-16, and SIS-16 Proxy Version Stroke Impact Scale Scaling and Scoring. May 2011.
2. Szende A, Williams A. Measuring self-reported population health: an international perspective based on EQ-5D. EuroQol Group Monographs Volume 1. SpringMed Publishing; 2004.
3. EuroQol Research Foundation. EQ-5D-5L user guide. 2019. Available from: https://euroqol.org/.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Definition of Adverse Events of Special Interest and Recurrent Stroke Events

Adverse Events of Special Interest (AESI) and recurrent stroke events will be identified using the following search criteria:

Area of Safety Interest	**Search Criteria**		
Infusion reactions	Type	Name	Code
	CMQ	Drug-induced rash	10000050
	SMQ	Hypersensitivity	20000214
	SMQ	Angiodema	20000024
	SMQ	Anaphylactic reaction	20000021
	CMQ	Injection site reaction	10000091
Recurrent stroke events	Type	Name	Code
	SMQ	Embolic and thrombotic events	20000081
	SMQ	Embolic and thrombotic events, arterial	20000082
	SMQ	Embolic and thrombotic events, venous	20000084
	SMQ	Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous	20000083

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

The criteria for Potentially Clinically Significant (PCS) laboratory findings are described in Table C-1, and the PCS criteria for vital sign findings are described in Table C-2.

Table C-1. Criteria for Potentially Clinically Significant Hematology, Chemistry Values

Variable Measured	Potentially Clinically Significant (PCS) Criteria	
	Very Low	**Very High**
Hematology		
Activated partial thromboplastin time prolonged (aPTT)	NA	> ULN
Hemoglobin	< 10.0 g/dL (6.2 mmol/L, 100 g/L)	> 4 gm/dL above ULN
INR	NA	> ULN
Lymphocyte count	< 500/mm^3 (0.5 × 10^9/L)	> 20,000/mm^3
Neutrophil count	< 1000/mm^3 (1.0 × 10^9/L)	NA
Platelet count	< 75,000/mm^3 (75.0 × 10^9/L)	NA
White blood cell (WBC)	< 2000/mm^3 (2.0 × 10^9/L)	> 100,000/mm^3
Chemistry		
Blood bilirubin	NA	> 1.5 × ULN
Cholesterol	NA	> 500 mg/dL (12.92 mmol/L)
Creatinine	NA	> 1.5 × ULN
Corrected Serum Calcium	< 7.0 mg/dL (1.75 mmol/L)	> 12.5 mg/dL (3.1 mmol/L)
Glucose	< 40 mg/dL (2.2 mmol/L)	> 250 mg/dL (13.9 mmol/L)
Gamma-glutamyl Transferase	NA	> 2.5 × ULN
Potassium	< 3.0 mmol/L	> 6.0 mmol/L
Sodium	< 130 mmol/L	> 155 mmol/L
Triglycerides	NA	> 500 mg/dL (5.7 mmol/L)
Uric acid	NA	> 10 mg/dL (0.59 mmol/L)
Albumin	< 2 g/dL (20 g/L)	NA
Phosphate	< 2.0 mg/dL (0.6 mmol/L)	NA
Enzymes		
Alanine aminotransferase (ALT)	NA	> 3.0 × ULN
Alkaline phosphatase	NA	> 2.5 × ULN
Aspartate aminotransferase (AST)	NA	> 3.0 × ULN
CPK	NA	> 5.0 × ULN

Note: A post baseline value must be more extreme than the baseline value to be considered a potentially clinically significant finding.

Table C-2. Criteria for Potentially Clinically Significant Vital Sign Values

Vital Signs Variables	Criterion	Potentially Clinically Significant (PCS) Value
Systolic blood pressure (mmHg)	Low	≤ 90 mm Hg and decrease ≥ 20 mm Hg from Baseline
	High	≥ 180 mm Hg and increase ≥ 20 mm Hg from Baseline
Diastolic blood pressure (mmHg)	Low	≤ 50 mm Hg and decrease ≥ 15 mm Hg from Baseline
	High	≥ 105 mm Hg and increase ≥ 15 mm Hg from Baseline
Heart rate (bpm)	Low	≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	≥ 120 bpm and increase ≥ 15 bpm from Baseline
Temperature	High	≥ 38.3°C and ≥ 1.1°C above baseline value
Post-infusion systolic blood pressure	High	> 160 mm Hg systolic and > 20 mm Hg above pre-infusion value
Post-infusion diastolic blood pressure	High	> 105 mm Hg diastolic and > 15 mm Hg above pre-infusion value