COVER PAGE

Official Title:	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema Following Large Hemispheric Infarction
NCT Number:	NCT02864953
Document Date:	SAP Version 3.0: 11 Jul 2023

STATISTICAL ANALYSIS PLAN

CLINICAL PROTOCOL NUMBER: 252LH301

Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema Following Large Hemispheric Infarction

Protocol Version: 3.0, 3.1, and other country specific versions

Date of Protocol: February 11, 2022 and May 5, 2022

Date of Statistical Analysis Plan: June 21, 2023, Final Version 3.0

Sponsor: Biogen

Approved By:

[redacted], SMT Statistician, [redacted] Date

[redacted], [redacted] Date

[redacted] Date

Table of Contents

List of Tables

ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASPECTS	Alberta Stroke Program Early CT Score
AST	aspartate aminotransferase
BI	Barthel Index
BG	blood glucose
BUN	blood urea nitrogen
CMO	comfort measures only
CRO	contract research organization
DC	Decompressive Craniectomy
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5-level assessment of health outcomes
GCP	Good Clinical Practice
HCRUQ	HealthCare Resource Utilization Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
LHI	large hemispheric infarction
mITT	modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
mTICI	modified treatment in cerebral ischemia
NIHSS	National Institutes of Health Stroke Scale
PD	pharmacodynamic(s)
PE	physical examination
[redacted]	[redacted]
POC	Point-of-Care
rtPA	recombinant tissue plasminogen activator or thrombolysis
SAE	serious adverse event

SIS-16	Stroke Impact Scale 16 Questions
SOC	standard of care
TOAST	Trial of Org 10172 in Acute Stroke Treatment
ULN	upper limit of normal
US	United States
Zarit	Zarit Burden Interview

1 INTRODUCTION

This document provides details of the statistical analyses planned for 252LH301. This document defines all pre-planned analyses.

2 STUDY SYNOPSIS

This is a Phase 3 randomized, multicenter, placebo-controlled, double-blind study of subjects aged 18 to 85 with a large hemispheric infarction (LHI) and time from symptom onset to start of study drug infusion of ≤ 10 hours. The study allows standard of care (SOC) therapy including IV recombinant tissue plasminogen activator (rtPA), thrombectomy, mannitol, hypertonic saline, decompressive craniotomy (DC), and other treatments for LHI per local guidelines as determined by the Investigator. Following a 3-stage 72-hour continuous infusion of BIIB093 or matching placebo, subjects will receive efficacy and safety evaluations for 90 days. The primary efficacy assessment will be the mRS at Day 90. The study will be conducted as a single study in two parts. Part 1 of the study consists of the baseline visit, study drug infusion and efficacy and safety period through Study Day 90 (primary endpoint). Part 2 will be a LHI follow-up period from Day 91 to Month 12. Approximately 200 to 250 sites in 20 to 25 countries globally are planned.

The study is designed to determine whether BIIB093 improves functional outcomes measured by the modified Rankin scale (mRS) at Day 90 in the modified Intent-to-Treat Population ("mITT" Population; see Section 4), which is defined as those subjects aged 18 to 70 years (inclusive) who are randomized, receive study treatment, and who have at least 1 post-baseline mRS before or at the Day 90 visit. The study seeks to enroll approximately 688 subjects age 18 to 70 and approximately 80 subjects above 70 to 85, for a total of approximately 768 subjects. Since there is limited experience with thrombectomy in LHI patients, the number of subjects with thrombectomy performed prior to randomization is targeted at approximately 20% in the ≤70 year age group but may vary from this to reflect the evolving standard of care and stroke treatment guidelines. The number of subjects with thrombectomy performed prior to randomization is targeted at approximately 8% in the >70 year age group.

Subjects will be randomized to receive either BIIB093 or placebo in a 1:1 ratio. As part of randomization, for each age group (18 to 70 vs. >70 to 85), a minimization method will be used to achieve balance over the following baseline covariates: country, rtPA administration (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20). A buffered commercial formulation that provides greater control over drug product pH during administration and is therefore fully compatible with PVC and non-PVC infusion materials is planned to be introduced into this study. To investigate the safety of a commercial formulation, at least 90 subjects of the approximately 688 planned subjects aged 18 to 70 years will be dosed with the commercial formulation or matching placebo. The 1:1 randomization ratio between BIIB093 (clinical formulation or commercial formulation) and placebo remains unchanged. Therefore, approximately 45 or more subjects are expected to be dosed with BIIB093 commercial formulation. The overall sample size (n=768), dose and dosing regimen, schedule of assessments, and efficacy analysis will remain unchanged. Additional safety analyses by formulation will be performed. The PK, efficacy, and safety are not expected to be altered as the administered dose and infusion amount per unit time does not change.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 PART 1 Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To determine if BIIB093 improves functional outcome at Day 90 as measured by modified Rankin Scale (mRS) when compared with placebo in subjects with LHI.	Day 90 mRS score as a 5-category ordinal scale (the 5-category mRS combines mRS categories 0 and 1 and mRS categories 5 and 6).
Secondary Objectives	**Secondary Endpoints**
To determine if BIIB093 improves overall survival at Day 90 when compared with placebo in the modified intent-to-treat (mITT) population.	Time to all-cause death over the 90-day period.
To determine if BIIB093 improves functional outcome at Day 90 on the mRS dichotomized 0-4 vs. 5-6, when compared with placebo in the mITT population.	Proportion of subjects who achieved mRS 0-4 at Day 90.
To determine if BIIB093 reduces midline shift at 72 hours (or at time of DC or comfort measures only [CMO], if earlier) when compared with placebo in the mITT population.	Midline shift at 72 hours (or at time prior to DC or CMO, if earlier).
To evaluate the safety and tolerability of BIIB093 in subjects with LHI.	Incidence of adverse events (AEs), serious adverse events (SAEs), and clinically significant abnormal vital signs, 12-lead electrocardiogram (ECG) findings, and laboratory results (including those associated with blood glucose (BG) levels).
[redacted]	

[redacted]

3.2 PART 2 Objectives and Endpoints

Objectives	Endpoints
To evaluate long-term disability following LHI.	mRS score at Month 6 and Month 12 as a 5-category ordinal scale (the 5-category mRS combines mRS categories 0 and 1 and mRS categories 5 and 6)
To evaluate long-term outcome measures of clinical function, quality of life, and healthcare utilization	• EQ-5D-5L at Months 6 and 12 • BI score at Months 6 and 12 • SIS-16 at Months 6 and 12 • Zarit Burden Interview at Month12 • HealthCare Resource Utilization Questionnaire at Month 12
To assess the safety of BIIB093 in subjects with LHI during the follow-up period.	Incidence of SAEs

4 ANALYSIS POPULATIONS

All data from sites in ROW and China will be included in all analysis populations. The analysis populations include: Intent-to-Treat (ITT), mITT, Per-protocol, Age over 70, Safety, Safety age ≤70, and Safety age>70, [redacted].

4.1 Intent-to-Treat Population

The ITT Population for this study consists of all subjects randomized.

4.2 Modified Intent-to-Treat Population – Primary Population for Efficacy Assessments

The primary efficacy analysis will be performed in the mITT Population. The mITT population is defined as those subjects aged 18 to 70 years (inclusive) at the time of randomization who are randomized, receive any study drug, and who have at least 1 post-baseline mRS before or at Day 90 visit. The mITT analyses will be performed using the randomized treatment group.

4.3 Per-protocol Population

The per-protocol population is defined as subjects from the mITT population and

- had no violation of inclusion/exclusion criteria:
  - infarct size as determined by central imaging lab read in [80, 300] cm^3 or ASPECTS 1-5;
  - dosed within 11 hours from last known normal (LKN);
  - without intracerebral hemorrhage (ICH) at screening defined as without PH-1 or PH-2 by central imaging lab read;
- and had received at least 3.07 mg of BIIB093 or corresponding amount of placebo based on the infusion rate, infusion time period and concentration.

4.4 Age Over 70 Population

The Age over 70 Population comprises subjects over 70 years old at the time of randomization who have received any study treatment.

4.5 Safety Populations

The safety population is defined as all subjects who are enrolled and have received any portion of the infusion of study treatment (placebo or BIIB093 [clinical or commercial formulation]). The safety population age ≤70 is defined as subjects in the safety population with age ≤70. The safety population age>70 is defined as subjects in the safety population with age over 70. The safety analyses will be conducted based on the actual treatment received.

[redacted]

5 DESIGN CONSIDERATIONS

5.1 Sample Size Determination

The study will randomize approximately 768 subjects aged 18 to 85 years. Based on the observed Day 90 5-category mRS distributions of the BIIB093 group and the placebo group in the mITT population aged 18 to 70 years from the GAMES-RP Phase 2 trial, a sample size of 327 subjects aged 18 to 70 years per arm (total of 654 subjects) will have approximately 90% power using ordinal logistic regression to detect, with 5% significance (2-sided), an odds ratio of 1.595 in shifting the distributions of the 5-category mRS in the direction of lower disability. Assuming up to 5% of the sample will not be evaluable for the primary analysis, it is planned to randomize up to approximately 688 subjects to the population aged 18 to 70 years, inclusive. In addition, approximately 80 subjects aged >70 and up to 85 years (inclusive) will also be randomized for safety and [redacted] efficacy evaluations. Final sample size may be impacted by the potential interim sample size re-estimation (Section 6.6).

Of approximately 688 planned subjects aged 18 to 70 years, a target of at least 90 subjects will be dosed with the commercial formulation or matching placebo. The 1:1 randomization ratio between BIIB093 (clinical formulation or commercial formulation) and placebo remains unchanged. Therefore, approximately 45 or more subjects are expected to be dosed with BIIB093 commercial formulation. The sample size of 45 subjects dosed with commercial formulation will allow for a ≥90% chance to observe any AEs with an expected incidence of 5% or greater. The 95% confidence interval estimate of AE incidence of 5% is 0 to 11.4% (margin of error = 6.4%) and the 95% confidence interval estimate of AE incidence of 10% is 1.2% to 18.8% (margin of error = 8.8%).

5.2 Randomization

Randomization will be performed using interactive response technology (IRT). Subjects will be randomized to receive BIIB093 or placebo in a 1:1 ratio. As part of randomization, for each age group (18 to 70 vs. >70 to 85), a minimization method will be used to achieve balance over the following baseline covariates: country, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20). The number of subjects with thrombectomy performed prior to randomization is targeted at approximately 20% in the ≤70 year age group but may vary from this to reflect the evolving standard of care and stroke treatment guidelines. The number of subjects with thrombectomy performed prior to randomization is targeted at approximately 8% in the >70 year age group. To avoid any selection bias, the system will randomly assign a patient with 15% probability to the non-optimal treatment group. The detailed algorithm is documented in the randomization specification.

5.3 Blinding

The investigators, study site staff, subjects, and caregivers will be blinded to the subject treatment assignments for the duration of the trial (Parts 1 and 2). To ensure that efficacy and outcome assessors are blinded to study treatment, evaluators performing all efficacy and outcome evaluations will be blinded to knowledge of AEs and SAEs during the acute hospitalization phase of the study (should not have participated in the treatment during the acute hospitalization phase of the study nor review the subject's hospital records from this period including blood glucose (BG) levels, BG management, or carbohydrate intake).

The Sponsor and contract research organization (CRO) study management team will be fully blinded for Part 1 of the study. After Part 1 is completed and the clinical study database is locked, designated personnel at the Sponsor will be unblinded to the Part 1 data for the purposes of evaluating the Day 90 data. The Sponsor and CRO study management team responsible for all site interactions and data entry will remain blinded to individual treatment assignments during Part 2 of the study.

5.4 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) is established to assess the overall safety profile of BIIB093 during the study. The IDMC charter guides the overall governance plan for the IDMC. IDMC may recommend the Sponsor to terminate the study based on safety data or following the interim futility analysis if conducted. If the interim sample size re-estimation is performed, then the IDMC may recommend a sample size increase based on pre-set criteria in Section 6.6 and IDMC charter.

6 STATISTICAL ANALYSES FOR PART 1 DATA

The objectives of the study and the endpoints to be analyzed are listed in Section 3. The study database will be locked after the last subject completes the Day 90 visit and the endpoints for Part 1 of the study will be analyzed. A second database lock will be used to analyze the Part 2 endpoints after the last subject completes the month 12 visit or withdraws from the study (see Section 7).

6.1 Study Subjects

6.1.1 Accounting of Subjects

The summaries in this subsection will be based on the ITT population. Disposition of subjects will be summarized, and the summary data will include number (%) of subjects randomized and dosed, number (%) of subjects who completed the treatment/study Part 1, and number (%) of subjects who discontinued treatment and/or withdrew from study Part 1. For subjects who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal, and days on treatment and days on study will be summarized and listed. Number of subjects in each analysis population will be summarized. In addition, number of subjects dosed and number of subjects who completed the treatment/study will be summarized by region and country. Number of subjects who completed the treatment/study will be presented only by treatment group.
The categorization of region is based not only on consideration of geography but also on type of health care system and access to health care in each country. The categories for regions will be:

- Region 1: United States (US);
- Region 2: Western European countries (including Belgium, Denmark, Finland, France, Germany, Italy, Portugal, Spain, Switzerland, and United Kingdom), plus Australia, Canada, and Israel;

- Region 3: Eastern European countries (including Czech Rep, Hungary, Russia, Croatia and Lithuania), plus Brazil, and Asian countries (including Japan, South Korea and Taiwan, China).

6.1.2 Demographics and Baseline Characteristics

The summaries in this subsection will be based on the ITT population, unless otherwise specified.
Unless otherwise specified, baseline data is defined as the most recent non-missing measurement collected prior to and/or on the date/time of the first infusion.

The demographic data include age, gender, ethnicity, race, height, weight, and body mass index (BMI). Baseline characteristics include baseline disease characteristics, eligibility imaging parameters, and time to procedures. Demographic and baseline characteristics will be presented for the modified intent-to-treat (mITT, defined in Section 4), intent-to-treat (ITT, defined in Section 4), and per-protocol (PP, defined in Section 4) populations. Demographic variables and baseline characteristics of the two study arms will be tabulated as well as for all subjects combined. For continuous endpoints, the summary statistics will generally include number of subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, and minimum and maximum. For categorical endpoints, the summary statistics will generally include number of subjects in corresponding analysis population, and number and percentage of subjects in each category.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of subjects with history (including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term, and by preferred term only. A listing of medical history will be generated.

TOAST classification for the stroke will be summarized. The number (%) of subjects receiving IV thrombolytic/tPA will be summarized.

The number (%) of subjects who received thrombectomy and time of the thrombectomy will be summarized. For subjects who received thrombectomy, the pre-procedure rating of modified treatment in cerebral infarction (mTICI) score and final rating of vessel patency and perfusion will be summarized.

The number and percentage of subjects with intracerebral hemorrhage at baseline (intraventricular hemorrhage, subarachnoid hemorrhage, remote intraparenchymal hemorrhage, subdural hematoma, epidural hematoma, HI-1 small petechia, HI-2 confluent petechiae, and PH-1, PH-2) will be summarized by treatment.

6.1.3 Concomitant Medications and Non-drug Therapies

The summaries in this subsection will be based on the ITT population. All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary. All concomitant non-drug therapies will be coded using the MedDRA dictionary. A concomitant medication/therapy will be defined as any therapy that was taken on or after the day of the first

infusion of study drug. This includes therapies that start prior to the initiation of the first infusion if their use continues on or after the date of first infusion. To define concomitant use for therapies with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a therapy are missing, that therapy will be considered concomitant.
- if the start date of a therapy is missing and the stop date of that therapy falls on or after the date of the first infusion, that therapy will be considered concomitant.
- if the start date of a therapy is prior to the date of the first infusion and the stop date of that therapy is missing and the therapy is listed as continuing, that therapy will be considered concomitant, or
- if the start date of a therapy is prior to the date of the first infusion and the stop date of that therapy is missing and the therapy is not listed as continuing, that therapy will be considered non-concomitant.

For a therapy with a partial start date, the year/month of the therapy date will be compared to that of the first infusion date to determine whether the therapy is concomitant.
The number (%) of subjects taking concomitant medication and non-drug therapies will be summarized. Non-drug therapies will be presented only by treatment group. Listings of concomitant medications and non-drug therapies will be presented.
The number (%) of subjects receiving maintenance fluid will be summarized. The number (%) of subjects received DC, time and the reasons of DC will be summarized.
Number (%) of subjects with decision of comfort measures only (CMO), time and reasons of CMO will be summarized.

6.1.4 Protocol Deviations

The summaries in this subsection will be based on the ITT population. Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as major or minor deviations. The major protocol deviations will be summarized and listed. The minor protocol deviations will also be listed. All summaries for protocol deviations will be presented by treatment group.

6.1.5 Study Drug Exposure

The summaries in this subsection will be based on dosed subjects in the ITT, mITT and PP populations. The total amount of BIIB093 received in mg via infusion will be calculated based on the infusion rate, infusion time period, and concentration, and will be summarized as a continuous variable. The number of hours on study drug (BIIB093 or placebo), calculated as hours between the end date and time of the last infusion and the start date and time of the first infusion subtracting the interruption period time, will be summarized as a continuous variable. This table will be presented by treatment group.

6.2 Efficacy

6.2.1 General Methods of Analysis

The efficacy assessments will be primarily based on the mITT population. Primary and secondary efficacy endpoints will also be analyzed based on the per-protocol population. The analysis method for each endpoint in the mITT population will also be used for the Per-Protocol analysis and any pre-defined subgroup analyses. Subjects will be analyzed in the group to which they are randomized for the mITT analysis and based on actual treatment received in the Per-Protocol analysis.

The primary and secondary endpoints and main analyses on them are listed in the protocol, and details are presented in the following sections.

Summary statistics will be presented. For continuous endpoints, the summary statistics may include number of subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, and minimum and maximum. For categorical endpoints, the summary statistics may include number of subjects in corresponding analysis population, number, and percentage of subjects in each category. Statistical testing for efficacy endpoints will be performed between the BIIB093 treatment group and placebo. All tests will be 2-sided with significance level equals to 0.05 (unless otherwise specified).

Table 1. Main Analyses for Efficacy Endpoints in Part 1

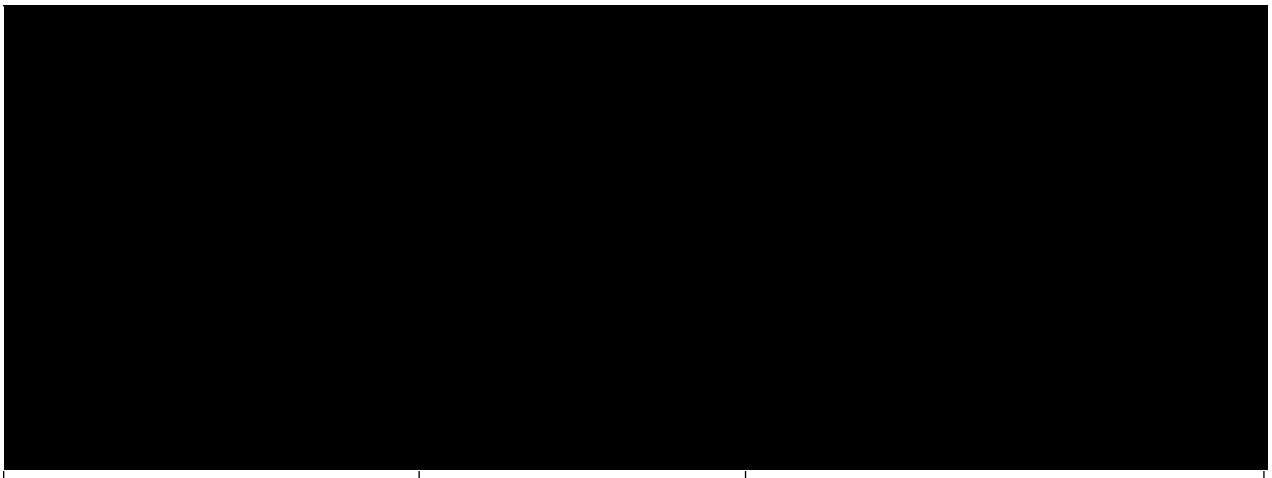
Endpoints	Analysis method	Analysis Population	SAP Section
Primary endpoint			
mRS as 5-category ordinal scale (0/1, 2, 3, 4, 5/6) at Day 90	Ordinal logistic regression with multiple imputation	mITT per-protocol	6.2.2
Secondary endpoints			
Time to all-cause death over the 90-day period	Cox proportional hazards regression model	mITT per-protocol	6.2.3 1
Proportion of subjects who achieved mRS 0-4 at Day 90	Logistic regression	mITT per-protocol	6.2.3 2
Midline shift at 72 hours (or at time of DC or CMO, if earlier)	Analysis of Variance (ANOVA) with multiple imputation	mITT per-protocol	6.2.3 3
Supportive efficacy analyses			

Subgroup analyses for the primary endpoint • receiving rtPA at baseline (yes or no), • receiving endovascular thrombectomy at baseline (yes or no), • regions as defined in section 6.1.1, • baseline NIHSS (≤20 vs. >20), • use of ASPECTS (yes or no).	Ordinal logistic regression with multiple imputation	mITT	6.2.4.2
Sensitivity/Supplementary analyses for the primary endpoint • mRS as 5-category at Day 90 • mRS as 7-category at Day 90	Ordinal logistic regression with multiple imputation	mITT ITT Age ≤70 years old ITT	6.2.4.3

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 2. If there are 2 or more assessments available in the same analysis window for a subject, unless otherwise specified, the assessment that is closest to the target visit day/time will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

Table 2. Visit Windows for Efficacy Endpoints in Part 1

mRS, [redacted]		
Analysis visit	**Target visit day**	**Analysis visit window**
[redacted]	[redacted]	[redacted]
Day 90	90	>60 up to last day in Part 1
Midline shift		
Analysis visit	Target timepoint in hour	**Analysis visit window**
Hr 72	72	[24, 102]
NIHSS		
Analysis visit	Target timepoint in hour	Analysis visit window
Baseline	0	Most recent non-missing pre-dose value



Subject's current location		
Analysis visit	**Target visit day**	**Analysis visit window**
Day 7	7	[1 (post infusion only), 18]
Day 30	30	(18, 60]
Day 90	90	>60 up to last day in Part 1

6.2.2 Primary Efficacy Endpoint

The primary estimand [ICH E9 (R1) Addendum 2014, 2017] employs the treatment-policy strategy to evaluate the treatment effect of BIIB093 compared to placebo regardless of DC or other co-therapy as determined by the following 4 attributes:

- Population: Intended post-approval population for BIIB093 defined through the study inclusion/exclusion criteria. All subjects in the mITT population (in Section 4.2) will be used in analyzing this estimand.
- Variable: Day 90 mRS as a 5-category ordinal scale
- Handling intercurrent events: regardless of whether use of any SOC therapy or procedure had occurred. The intercurrent events for the primary endpoint are use of standard of care therapies or procedures after the starting of infusion and before Day 90 assessment including DC, rtPA, and thrombectomy.
- Population-level summary: odds of achieving a lower disability

All observed data, including data collected after intercurrent events, i.e., standard of care including decompressive craniectomy and other concomitant SOC therapy, will be included. Missing data will be imputed using multiple imputation. Death is scored as 6 in mRS and thus there will be no missing mRS values due to death.

The primary estimand is then the shift in Day 90 mRS as a 5-category ordinal scale [ICH E9 (R1) Addendum 2014, 2017] regardless of whether use of any SOC therapy or procedure had occurred.

The primary endpoint of mRS as 5-category ordinal scale (0/1, 2, 3, 4, 5/6) at Day 90 will be analyzed using ordinal logistic regression (proportional odds model), adjusting for baseline covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20). Odds ratio, the 95% confidence interval as well as the p-value will be reported. If the interim sample size re-estimation is conducted and the sample size is increased, the final hypothesis testing for the primary endpoint will be conducted using the Cui-Hung-Wang (CHW) method (Cui et al 1999; Mehta and Pocock 2011; see Section 6.6.2).

The proportional odds ratio assumption will be tested using likelihood ratio test based on observed data. In the case the assumption does not hold (p-value < 0.05) or non-convergence, the Mann-Whitney test will be used as the primary inference and the source of non-proportionality or non-convergence will be investigated (see Section 9 for the sample SAS code). Following the Mann-Whitney test, dichotomized analysis will be conducted to assess the treatment effects. If sample size is increased but proportional odds assumption does not hold, the CHW method with combination of Mann-Whitney test statistics will be used.

Multiple imputation will be used to account for missing values for the 90-day mRS. Assessment of mRS is made on Day 30 and Day 90 or early termination visit. Death is scored as 6 in mRS and thus there will be no missing mRS values due to death. Missing mRS values due to reasons other than death will be imputed based on a linear model performed on the 7-category mRS scores leveraging the information of the patient at other time points in part 1. The model will also include treatment as a classification variable and the covariates described above. Multiple imputations will be performed using PROC MI in SAS. Fully conditional specification method will be used in this SAS procedure. Imputed values based on the original 7-category will be rounded to the closest valid mRS score and then combined as 5-category. A total of 100 imputations will be conducted with random seed pre-specified: each result in a complete dataset for all subjects. The point and interval estimate of the odds ratio as well as p-value from the primary analysis models will be obtained using PROC MIANALYZE.

The missing data pattern will be evaluated including reasons for missingness, missing data by treatment arms and visit, and potential covariates associated with missingness. Supplementary analyses will be planned to evaluate the robustness of the primary analysis results (Section 6.2.4.3).

6.2.3 Secondary Efficacy Endpoints

If the null hypothesis for the primary endpoint is rejected, the secondary efficacy endpoints will be tested in the following order in a hierarchical manner at the significance level of 0.05. To control the type 1 error rate among the secondary endpoints, a sequential closed testing procedure will be used such that if statistical significance is not achieved from an endpoint for a comparison, all endpoint(s) of a lower rank for that comparison will not be considered as statistically significant.

1. Time to all-cause death over the 90-day period
2. Proportion of subjects who achieved mRS 0-4 at Day 90
3. Midline shift at 72 hours (or at time of DC or CMO, if earlier)

6.2.3.1 Time to All-cause Death Over the 90-day Period

Time to all-cause death is defined as the time period from randomization to the time of death. For a subject who does not die in Part 1 of the study, time to all-cause death is censored at the time when the subject is last known to be alive while in Part 1 of the study. A Cox proportional hazards regression model will be used to assess the treatment effect on overall survival at Day 90 after adjusting for baseline covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20) as covariates. Hazard ratio and its 95% confidence interval as well as the p-value will be reported. Kaplan-Meier curves and estimates will be presented for both treatment groups. Greenwood's formula will be used to calculate the standard error on the Kaplan-Meier estimates (see Section 9 for the sample SAS code).

6.2.3.2 Proportion of Subjects Who Achieved mRS 0-4 at Day 90

A logistic regression model will be used to estimate an odds ratio (and 95% CI) of improvement on the mRS dichotomized as 0-4 vs. 5-6 at Day 90. The model will include region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20) as baseline covariates. Odds ratio, the 95% confidence interval as well as the p-value will be reported (see Section 9 for the sample SAS code). Subjects with missing values will be assigned with the worst-case value, that is 5-6.

6.2.3.3 Midline Shift at 72 Hours (or at Time of DC or CMO, if Earlier)

Analysis of Variance (ANOVA) will be used to compare the two study arms to assess the treatment effects on midline shift. The ANOVA will adjust for baseline covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no) and baseline NIHSS (≤20 vs. >20) (see Section 9 for the sample SAS code). Multiple Imputation method will be used for missing data imputation, where the imputation model for the missing observations in the treatment group and the control group is constructed from the observed data in the corresponding group. Only data collected in the [24, 102] hours will be considered for the primary analysis. Sensitivity analysis without the time interval constraint will be conducted.

The relationship between midline shift at 72 hours (or DC/CMO if earlier) and mRS at Day 90 may be explored.

6.2.4 Supportive Efficacy Analyses

6.2.4.1 Per-protocol Analysis

Primary and secondary efficacy endpoints will be analyzed for the per-protocol population with the same model for the mITT population. Subjects will be analyzed based on actual treatment received in the Per-Protocol analysis. Multiple imputation including only subjects in PP population similar as in Section 6.2.2 will be used to account for missing values for the Day 90 mRS. Multiple imputation including only subjects in PP population similar as in Section 6.2.3.3 will be used to account for the missing values for the midline shift data.

6.2.4.2 Subgroup Analyses for the Primary Endpoint

Shift in Day 90 mRS will be assessed within different subgroups in the mITT population using the ordinal logistic regression. Multiple imputation as in Section 6.2.2 will be used to account for

missing values for the Day 90 mRS. Forest plots will be used to present results across subgroups. Specifically, the following pre-defined subgroups will be considered:

- receiving rtPA at baseline (yes or no),
- receiving endovascular thrombectomy at baseline (yes or no),
- regions as defined in section 6.1.1,
- baseline NIHSS (≤20 vs. >20),
- use of ASPECTS (yes or no).

Odds ratio and the 95% confidence interval will be reported. If there are model fitting problems due to not enough data for certain subgroups such as receiving endovascular thrombectomy, only descriptive statistics will be presented.

6.2.4.3 Sensitivity/Supplementary Analyses for the Primary Endpoint

- A supplementary analysis on the primary endpoint will be performed in the ITT population ≤70 years old. Multiple imputation including subjects in the ITT population ≤70 years old similar as in Section 6.2.2 will be used to account for missing values for the 90-day mRS.
- A sensitivity analysis on missing value handling will be performed for the primary endpoint by assigning median placebo value to missing values in the mITT population.
- A shift analysis of mRS as a 7-category ordinal scale (0, 1, 2, 3, 4, 5, 6) at Day 90 will be analyzed using ordinal logistic regression (proportional odds model), adjusting for baseline covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20) in the mITT population. -Multiple imputation on 7-category mRS same as in Section 6.2.2 will be used to account for missing values for the 90-day mRS.
- A shift analysis of the primary endpoint (mRS as 5-category) and that of mRS as a 7-category scale at Day 90 will be conducted on the ITT population with at least one post-baseline mRS before or at Day 90 visit (with the patients of age greater than 70 years included). Similar as in Section 6.2.2, multiple imputation including subjects in the ITT population with at least one post-baseline mRS before or at Day 90 visit will be used to account for missing values for the 90-day mRS.

[redacted]

[redacted]

[redacted]

6.2.6 Efficacy Analysis for the Age Over 70 Population

If applicable, the same analytical models may be used for the primary and secondary endpoint in the Age Over 70 Population as in the mITT Population. If the models cannot be applied, descriptive statistics and interval estimates will be provided (Specifically, Kaplan-Meier method will be used to assess the treatment effect on overall survival at Day 90. Confidence intervals for the proportion of mRS categories, confidence intervals for the means of the midline shift, and confidence intervals for the proportion of survival at Day 90 based on the Kaplan-Meier method will be provided if estimable.). Missing values will be handled similarly as in Sections 6.2.2 and 6.2.3 for the mITT population.

Descriptive summaries will be provided for the additional endpoints in the Age over 70 Population.

[redacted]

6.5 Safety Analyses

All AEs, laboratory data, ECG and vital signs will be evaluated for safety on the safety population and on the safety population age ≤70, respectively. Additionally, selected analyses will be provided for the safety population age>70. The safety analyses will be conducted based on the actual treatment received, i.e., BIIB093 (including both clinical and commercial formulation) vs. placebo.

6.5.1 Adverse Events

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be analyzed based on the principle of treatment emergence. A treatment-emergent event is defined as follows:

- had onset any time after the start of study treatment administration, and/or
- had worsened after the start of study treatment administration since the event was previously reported (this included worsening of signs, symptoms, laboratory values, or diagnoses that were present prior to the first infusion of study drug but then worsened any time after the start of study drug treatment).

The incidence of treatment-emergent AEs will be summarized for each treatment group overall, by severity, and by relationship to study drug. Serious AEs will be presented by treatment group and by relationship to study drug. The summary tables will include incidence estimates for overall system organ classes, as well as for individual events within each system organ class. If a subject experiences an event more than once with varying severity during the study, he/she will be counted only once with the maximum severity within each system organ class/preferred term. For incidence of relationship to study drug, a subject will be counted only once and only in the category of the strongest relationship to study drug within each system organ class/preferred term.

The following AE incidence tables will be provided for the safety population, the safety population age ≤70, and safety population age>70 respectively:

1. AEs by system organ class and preferred term sorted by decreasing frequency*
2. AEs by system organ class and preferred term sorted by alphabetical order
3. AEs by system organ class, high level group term and preferred term
4. AEs by system organ class
5. AEs with at least 2% higher in incidence for BIIB093 compared to placebo by system organ class and preferred term*
6. AEs by preferred term
7. AEs with an incidence of 5% or more in any treatment group by preferred term*
8. Severe AEs by system organ class and preferred term*
9. Severe AEs by preferred term
10. AEs by maximum severity by system organ class and preferred term (System organ class will be presented alphabetically. Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, very severe, unknown and total. A subject will be counted only once at the maximum severity within each system organ class and preferred term.)
11. AEs by maximum severity by preferred term (Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, very severe, unknown and total. A subject will be counted only once at the maximum severity within each preferred term.)
12. Related AEs by system organ class and preferred term*
13. SAEs by system organ class and preferred term*
14. SAEs by preferred term
15. Related SAEs by system organ class and preferred term*
16. AEs that led to discontinuation of study treatment by system organ class and preferred term*
17. AEs that led to withdrawal from study by system organ class and preferred term*
18. SAEs with fatal outcome by system organ class and preferred term*

*Additional descriptive safety summaries will be provided for the BIIB093-dosed subjects by BIIB093 formulation respectively.

The following listings will be provided.

1. Listing of AEs

2. Listing of SAEs (including pre-dosing SAEs)
3. Listing of AEs that led to discontinuation of study treatment
4. Listing of AEs that led to withdrawal from study
5. Listing of deaths

The incidence of treatment-emergent AEs will be summarized by system organ class and preferred term for each treatment group by time interval defined as [Day 1, Day 7] and [Day 8, end of Part 1].

The number (%) of subjects with recurrent stroke checked by investigators will be summarized by treatment group.

6.5.2 Adverse Events of Special Interest

The incidence of adverse events of special interest will also be presented for the safety population, the safety population age ≤70, and safety population age>70 respectively. These adverse event of special interest categories are defined mainly based on Standardized MedDRA Queries (SMQs), SOCs, and/or PTs. The AEs of special interest categories may include but are not limited to hypoglycaemia events. Hypoglycaemia events are defined as follows:

- SMQ of hypoglycaemia (narrow search terms).

Hypoglycaemia events will also be separately summarized by formulation for subjects dosed with BIIB093. Hypoglycaemia events will be listed by actual treatment received and BIIB093 formulation.

6.5.3 Clinical Laboratory Results

Clinical laboratory evaluations include hematology and blood chemistry, which are performed at a local laboratory.

- Hematology:
  - White blood cells (leukocytes), absolute neutrophil count
  - Red blood cells
  - Hemoglobin
  - Hematocrit
  - Platelet count
- Blood chemistry:
  - Liver: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin

- Renal: blood urea nitrogen (BUN), creatinine
- Electrolytes: sodium, potassium, bicarbonate
- Other: glucose, calcium, phosphorus, albumin

Shift analyses

Laboratory abnormalities will be summarized with shift tables. Tables will present changes relative to each parameter's normal ranges. Each subject's hematology and blood chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the local laboratory or as "unknown" if no result is available.

Shifts from baseline to high/low status for hematology and blood chemistry parameters will be presented. In each summary, the denominator for the percentage is the number of patients at risk for the shift. The number at risk for shift to low is the number of subjects whose baseline value was not low and who had at least one post-baseline value. The number at risk for shift to high is the number of subjects whose baseline value was not high and who had at least one post-baseline value. Subjects will be counted only once for each parameter and each type of shift regardless of how many post-dosing assessments had that type of shift. Subjects with shift to low or high will be listed by laboratory parameter and shift type.

Potentially Clinically Significant laboratory abnormalities analyses

For hematology and blood chemistry, the number of subjects with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 3. Subjects need to have at least one post-baseline evaluation and a baseline value not potentially clinically significant (including missing) to be included in the analysis.

Table 3. Criteria to Determine Potentially Clinically Significant (PCS) Laboratory Abnormalities

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
HEMATOLOGY		
White blood cells	<3.0 x 10^9/L	>16 x 10^9/L
Neutrophils	<1.5 x 10^9/L	>13.5 x 10^9/L
Red blood cells	≤3.5 x 10^{12}/L	≥6.4 x 10^{12}/L
Hemoglobin - Females	≤95 g/L	≥175 g/L
Hemoglobin - Males	≤115 g/L	≥190 g/L
Hematocrit - Females	≤32%	≥54%
Hematocrit - Males	≤37%	≥60%
Platelet count	≤75 x 10^9/L	≥700 x 10^9/L
BLOOD CHEMISTRY		
Alanine aminotransferase (ALT)	N/A	>3 x ULN
Aspartate aminotransferase (AST)	N/A	>3 x ULN
Alkaline phosphatase (ALP)	N/A	>3 x ULN

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
Total bilirubin	N/A	>1.5 x ULN
Blood urea nitrogen (BUN)	N/A	≥10.7 mmol/L
Creatinine	N/A	≥176.8 umol/L
Sodium	≤126 mmol/L	≥156 mmol/L
Potassium	≤3 mmol/L	≥6 mmol/L
Bicarbonate	≤16 mmol/L	≥35 mmol/L
Glucose	≤2.2 mmol/L	≥9.7 mmol/L
Calcium	≤2 mmol/L	≥3 mmol/L
Phosphorus	≤0.6 mmol/L	≥1.7 mmol/L
Albumin	≤25 g/L	≥625 g/L
ULN = upper limit of normal		

By visit summaries

For numeric laboratory parameters, actual values, change from baseline and percent change from baseline will be summarized by visit. Number of evaluable subjects, mean, standard deviation, 25% and 75% quartiles, min and max values will be presented at each visit.

Plots of mean values (with standard error) for numeric laboratory parameters at each visit will be provided.

Listings of individual laboratory measurements by patients for all the parameters will be provided.

For laboratory by visit summaries, the analysis visit should be defined using visit windows (see Table 4 below). If there is more than 1 value in the same analysis visit window (>1 value for the same analysis visit) for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 4. Visit Windows for Local Lab by Timepoint Summaries

Analysis visit	Target timepoint in hour	Analysis visit window
Baseline	0	Most recent non-missing pre-dose value
Hr 24	24	(0, 36]
Hr 48	48	(36, 60]
Hr 72	72	(60, 96]

Day 7	168	>96
Analysis visit for blood glucose	Target timepoint in hour	Analysis visit window
Baseline	0	Most recent non-missing pre-dose value
Hr 1	1	(0, 1.5]
Hr 2	2	(1.5, 2.5]
…		
Hr 23	23	(22.5, 23.5]
Hr 24	23	(23.5, 25]
Hr 26	26	(25, 27]
Hr 28	28	(27, 29]
…		
Hr 46	46	(45,47]
Hr 48	48	(47, 50]
Hr 52	52	(50, 54]
Hr 56	56	(54, 58]
Hr 60	60	(58, 62]
Hr 64	64	(62, 66]
Hr 68	68	(66, 70]
Hr 72	72	(70, 96]
Day 7	168	>96

Analysis of blood glucose

The blood glucose from local laboratory is collected at screening, day 1, day 2, day 3 and day 7 with the normal ranges. Additionally, the Point-of-Care (POC) blood glucose is collected pre-dose, hourly for the first 24 hours, every 2 hours for Hour 25-48, and every 4 hours for Hour 49 to 72 without normal ranges. The normal ranges for POC blood glucose data are assigned with 70 mg/dl and 139 mg/dl, which are the reference range recommended by the American Diabetes Association for random blood glucose measurements. For all the analyses, the two sources of data (local laboratory and POC) will be combined and analyzed together.

Summary of lowest post-baseline value of blood glucose will be provided for the safety population, the safety population age ≤70, and safety population age>70 respectively. The

number (%) of subjects with post-baseline blood glucose abnormalities (<55 mg/dL, <80 mg/dL) will be summarized by treatment group for the safety population, the safety population age ≤70, and safety population age>70 respectively. Blood glucose values for subjects with post-baseline blood glucose <55 mg/d and <70 mg/dL will be listed respectively by actual treatment received and BIIB093 formulation.

Analysis of Liver Function Tests

Potential serious hepatotoxicity is defined as ALT or AST > 3× ULN and total bilirubin > 2× ULN at any time post-baseline, not necessarily concurrent. A scatterplot of the maximum post-baseline ALT or AST value relative to ULN and maximum post-baseline total bilirubin value relative to ULN (not necessarily concurrent) for each subject will be provided. A line plot of ALT, AST, ALP and total bilirubin values over time for subjects with potential serious hepatotoxicity will be provided. In addition, a summary of the number and percentages of subjects meeting the laboratory abnormality criteria listed below will be provided:

- ALT > 3×ULN
- ALT > 5×ULN
- AST > 3×ULN
- AST > 5×ULN
- AST or ALT > 3×ULN
- AST or ALT > 5×ULN
- Total Bilirubin > 2×ULN
- ALP >1.5×ULN
- AST or ALT ≥3× ULN and Total Bilirubin > 2× ULN

Concurrent is defined as on the same day. A listing of subjects with potential serious hepatotoxicity will be provided.

6.5.4 ECG

The number and percentage of subjects with shifts from unknown or normal baseline to categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment group for the safety population, the safety population age ≤70, and safety population age>70 respectively. ECG parameters include Heart Rate, PR Interval, RR Interval, QRS Duration, QT Interval, QTcF, and QTcB, where QTcB is calculated as $QT/(RR/1000)^{1/2}$. The actual values and change from baseline for each of the ECG parameters will be summarized by treatment group and by visit summary. If there are multiple records fall into the same visit windows, the worst record will be presented in the summary.

Table 5. Visit Windows for ECG by Timepoint Summaries

Analysis visit	Target timepoint in hour	Analysis visit window
Baseline	0	Most recent non-missing pre-dose value
Hr 4-6	5	(0, 14.5]
Hr 24	24	(14.5, 36]
Hr 48	48	(36, 60]
Hr 72	72	(60, 96]
Day 7	168	>96

6.5.5 Vital Signs

Vital signs measures include oxygen saturation, heart rate (pulse), respiratory rate, temperature, and systolic and diastolic blood pressure. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities will be presented by treatment group. Summary statistics for actual values and change from baseline will also be presented. The definitions of these abnormalities for temperature, pulse, and blood pressure values are provided in Table 6.

Table 6. Criteria to Determine Clinically Relevant Vital Signs Abnormalities

Vital Sign	**Criteria for Abnormalities**
Temperature	>38°C and an increase from pre-dosing of at least 1°C
Pulse	>120 beats per minute and an increase from pre-dosing of more than 20 beats per minute, or <50 beats per minute and a decrease from pre-dosing of more than 20 beats per minute
Systolic Blood Pressure	>180 mmHg and an increase from pre-dosing of more than 40 mmHg, or <90 mmHg and a decrease from pre-dosing of more than 30 mmHg
Diastolic Blood Pressure	>105 mmHg and an increase from pre-dosing of more than 30 mmHg, or <50 mmHg and a decrease from pre-dosing of more than 20 mmHg

6.6 Interim Analysis

An interim futility analysis may be performed based on the primary endpoint when approximately 30% of planned mITT subjects complete Day 90. At the same interim analysis an unblinded sample size re-estimation may be performed. The decision whether or not to conduct the sample size re-estimation at the interim analysis will be documented by an official communication from the study Sponsor to the Independent Data Monitoring Committee (IDMC) that will occur within 30 days after randomization of 30% of the planned enrollment has been

achieved. The sample size re-estimation employs an approach in which the sample size will be increased when the interim results are in the promising zone (Mehta & Pocock 2011). To control Type I error after the sample size adaptation, if it occurs, the final hypothesis testing for the primary endpoint will be conducted using the CHW method (Cui et al 1999; Mehta and Pocock 2011) at the significance level of α=0.05 (two-sided).

Both the futility criteria and the decision rules for the potential sample size re-estimation will be based on the calculation of conditional power using the primary endpoint (5-category mRS at Day 90). The conditional power based on the treatment effect observed from the interim data is calculated using:

$$CP = 1 - \Phi\left(\frac{z_{\frac{\alpha}{2}}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\tilde{n_2}}} - \frac{z_1\sqrt{\tilde{n_2}}}{\sqrt{n_1}}\right), \quad (1)$$

where n_1 is the sample size at interim (number of subjects in the mITT population included in the interim analysis), n_2=654 is the total initially planned sample size for the study, $\tilde{n_2} = n_2 - n_1$ is the sample size after interim and z_1 is the test statistic observed at interim.

6.6.1 Interim Analysis for Non-Binding Futility

The study may be stopped for futility if the conditional power is too low , $CP < 0.05$ based on the primary endpoint (5-category mRS at Day 90). This conditional power cut-off is chosen such that the chance to stop for futility and the power loss are low under the presumed treatment effect, and the chance to stop study early for futility is reasonably high if there is truly no treatment effect. The proposed rule for futility is non-binding. In addition to the primary efficacy result, the totality of data will be considered, including but not limited to secondary efficacy endpoints and consistency of efficacy data over time and across key subgroups.

6.6.2 Interim Analysis for Sample Size Re-Estimation

The promising zone definition and decision rules for the unblinded sample size re-estimation are pre-specified as follows for this study:

- If the study does not stop for futility (i.e., if CP ≥ 0.05) and CP < 0.43, there will be no sample size change, i.e., the trial continues to recruit the original planned sample size 768.
- If 0.43 <= CP < 0.90, there will be a one-step sample size increase to approximately 1044 subjects (Age ≤70 population increases to 964 from 688; >70-85 population remains approximately 80).
- If CP ≥ 0.90, there will be no sample size change, i.e., the trial continues to recruit the original planned sample size 768.

The upper bound of the promising zone is defined as CP<0.90 to align with the targeted power (90%) of the initial sample size n_2. The lower bound of the promising zone CP_{min} is derived using the method described in Mehta & Pocock 2011.

To adjust for the sample size adaptation if that occurs, the primary analysis of 5-category mRS at Day 90 will use the CHW method (Cui et al 1999; Mehta & Pocock 2011) to preserve the type I error. The final CHW test statistic is defined as follows:

$$Z^*_{2,chw} = \sqrt{\frac{n_1}{n_2}}Z_1 + \sqrt{\frac{\tilde{n}_2}{n_2}}\tilde{Z}^*_2$$

where n_1, n_2, $\tilde{n}_2$, and Z_1 are defined as for equation (1), and $\tilde{Z}^*_2$ is the incremental Wald test statistic based on the independent subjects' data either observed after or not being used at the interim analysis. If sample size is increased but proportional odds assumption does not hold, the CHW method with combination of Mann-Whitney test statistics will be used.

An interim analysis will be conducted by a completely independent team and be reviewed by the IDMC. IDMC may recommend stopping for futility based on the pre-specified criteria. If the interim sample size re-estimation is performed, then the IDMC may recommend a one-step sample size increase to approximately 1044 subjects only when the interim results are within the promising zone. The hypothesis testing for the primary endpoint will be two-sided at the significance level of 0.05 whether the sample size is increased or not. A clear process will be specified and implemented to ensure that the blind will be strictly maintained for investigators, patients, and sponsor's study personnel until database lock. Additional details on the interim analysis are listed in the Appendix 9.3.

7 STATISTICAL ANALYSES FOR LONG-TERM DATA

7.1 Study Subjects

7.1.1 Accounting of Subjects

Disposition of subjects will be summarized for the ITT population and the summary data will include number (%) of subjects randomized and dosed, number (%) of subjects who completed the study Part 2, and number (%) of subjects who withdrew from study Part 2.

7.1.2 Protocol Deviations

The major protocol deviations during Part 2 will be summarized and listed for the ITT population. The minor protocol deviations will also be listed. All summaries for protocol deviations will be presented only by treatment group.

7.2 Efficacy Analyses

7.2.1 General Methods of Analysis

Table 7. Analysis for Efficacy Endpoints in Part 2

Endpoints	Analysis Method	Analysis Population	SAP Section
mRS at Months 6 and 12	(Ordinal) logistic regression/Descriptive summary	mITT/ Age Over 70 Population	7.2.2
Time to all-cause death over the 1-year period	Cox proportional hazards regression model/Descriptive summary	mITT/ Age Over 70 Population	7.2.3
Barthel index at Months 6 and 12	Descriptive summary	mITT Age Over 70 Population	7.2.4
EQ-5D-5L at Months 6 and 12	Descriptive summary	mITT Age Over 70 Population	7.2.5
SIS-16 at Months 6 and 12	Descriptive summary	mITT Age Over 70 Population	7.2.6
HCRUQ at Month 12	Descriptive summary	mITT Age Over 70 Population	7.2.7
Zarit Burden Interview at Month 12	Descriptive summary	mITT Age Over 70 Population	7.2.8

7.2.2 Modified Rankin Scale

The mRS at Months 6 and 12 will be analyzed in the mITT population in the same way as Day 90 mRS using the ordinal logistic regression combining mRS 0/1 and 5/6. The proportional odds ratio assumption will be tested using likelihood ratio test. In the case the assumption does not hold, the Mann-Whitney test will be used. The mRS 0-4 versus 5- 6 dichotomizations will also be examined using logistic regression. All regression analyses will control for region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no) and baseline NIHSS (≤20 vs. >20) as baseline covariates. Odds ratio and the 95% confidence interval will be reported.

The same model in the mITT population will be used in the Age over 70 population. If the model is not applicable, descriptive statistics of observed mRS at Months 6 and 12 in the Age over 70 population will be provided by time points and by treatment group.

7.2.3 Time to All-cause Death Over the 1-year Period

Time to all-cause death is defined as the time period from randomization to the time of death. For a subject who discontinues and does not die in Part 1 of the study, time to all-cause death is censored at the time when the subject is last known to be alive while in Part 1 of the study. For a subject who continues and does not die in Part 2 of the study, time to all-cause death is censored at the time when the subject is last known to be alive while in Part 2 of the study. A Cox proportional hazards regression model will be used to assess the treatment effect on overall survival at 1-year in the mITT population after adjusting for region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20) as baseline covariates. Hazard ratio, 95% confidence interval as well as the p-value will be reported. Kaplan-Meier curves and estimates will be presented for both treatment groups. Greenwood's formula will be used to calculate the standard error on the Kaplan-Meier estimates (see Section 9 for the sample SAS code).

Kaplan-Meier estimates will be provided for the Age over 70 population.

7.2.4 Barthel Index

Descriptive statistics (mean, median, SD, 25% percentile, 75% percentile, minimum and maximum) of observed BI at Months 6 and 12 in the mITT population and in the Age over 70 population will be provided by time point and by treatment group, respectively.

7.2.5 Health-related Quality of Life

Summary statistics for the EQ-5D and EQ VAS at Months 6 and 12 will be presented for observed data in the mITT population and in the Age over 70 population.

7.2.6 SIS-16

Descriptive statistics (mean, median, SD, 25% percentile, 75% percentile, minimum and maximum) of observed SIS-16 subdomain scores at Months 6 and 12 in the mITT population and in the Age over 70 population will be provided by time point and by treatment group, respectively.

7.2.7 HCRUQ and Subject's Current Location

Descriptive summary statistics for observed HCRUQ at Month 12 in the mITT population and in the Age over 70 population will be presented by treatment group, respectively.

Subject's current location (e.g., hospice, nursing home, rehabilitation facility, home) will be summarized at each visit (month 6 and month 12).

7.2.8 Zarit Burden Interview

Descriptive summary statistics for observed Zarit Burden Interview total score at Month 12 in the mITT population and in the Age over 70 population will be presented by treatment group, respectively.

7.3 Safety Analyses

7.3.1 Serious Adverse Events

All treatment-emergent SAEs during part 1 and part 2 will be evaluated for safety on the safety population and on the safety population age ≤70, respectively. The incidence of treatment-emergent SAEs will be summarized for each treatment group overall, by severity, and by relationship to study drug. The summary tables will include incidence estimates for overall system organ classes, as well as for individual events within each system organ class. Additionally, selected analyses will be provided for the safety population age >70.

Listing of SAEs and deaths during part 2 will be provided.

8 Changes from the Protocol Defined Analyses

The company decided to terminate the study. The analysis populations will now include data from China (Protocol V3.5) along with ROW (Protocol V3.0). Data from China will be included in Region 3.

9 References

Cui L, Hung HM, Wang SJ. 1999. Modification of sample size in group sequential clinical trials. Biometrics; 55:853--857.

Mehta CR, Pocock SJ. 2011. Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statistics in Medicine. 30: 3267-3284.

10 Appendix

10.1 Schedule of Activities

Table 8. Schedule of Activities – Part 1 (Screening through Day 90)

	Screening / Enroll-ment	Hrs >0-12	Hr 24 (±12h)	Hr 48 (±12h)	Hr 72 (±12h)	Day 7 (±24h)/ Hospital Discharge	Day 30 (±7 d) Telephone/ Telemedicine Visit	Day 90 (±14 d)[1] In-person Visit Preferred	Craniectomy /Comfort Care (if Applicable)	Early Term. Visit[2]
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-
Informed consent	X	-	-	-	-	-	-	-	-	-
Demographics, medical history, physical examination (including height and weight), rtPA/thrombectomy status[3]	X	-	-	-	-	-	-	-	-	-
Time of symptoms onset or if unknown, last known normal	X	-	-	-	-	-	-	-	-	-
Imaging (MRI/CTP/NCCT) for lesion size or ASPECTS estimation[4]	X	-	-	-	-	-	-	-	-	-
Pregnancy test	X	-	-	-	-	-	-	-	-	-
NIHSS[5]	X	[redacted]								
Clinical laboratory samples (hematology, blood chemistry)[6,7]	X	-	X	X	X	X	-	-	-	X[8]
Vital signs[9]	X	-	X	X	X	X	-	-	-	X[8]
12-lead ECG[7,10]	X	Hr 4-6	X	X	X	X	-	-	-	X[8]
Enrollment/ Randomization[11]	X	-	-	-	-	-	-	-	-	-
Craniectomy/comfort care/cranioplasty assessment form(s)	-	-	-	-	-	-	-	-	X	-
Pharmacogenetic sample (optional)	-	←after infusion start but before hosp. discharge→					-	-	-	-
Study Treatment Administration	-	←……72-hr infusion……→				-	-	-	-	-
Blood glucose measurement[12]	X	X	X	X	X	X	-	-	-	-

	Screening / Enroll-ment	Hrs >0-12	Hr 24 (±12h)	Hr 48 (±12h)	Hr 72 (±12h)	Day 7 (±24h)/ Hospital Discharge	Day 30 (±7 d) Telephone/ Telemedicine Visit	Day 90 (±14 d)[1] In-person Visit Preferred	Craniectomy /Comfort Care (if Applicable)	Early Term. Visit[2]
Imaging (NCCT or MRI) for midline shift[13]	-	-	-	-	X Hr 72-96	-	-	-	X	X[14]
mRS	-	-	-	-	-	-	X	X	-	X
Subject disposition[15]	-	-	-	-	-	X	X	X	-	X
TOAST classification[16]	-	-	-	-	-	X	-	-	-	
Concomitant Medications/procedures	← ……Monitor and record throughout Part 1 of the study……→									
[redacted]										
AEs and SAEs[17]	← ……Monitor and record throughout Part 1 of the study……→									

AE = adverse event; ASPECTS = Alberta Stroke Program Early CT Score;; [redacted]; CMO = comfort measures only; CTP = computed tomography perfusion; DC = decompressive craniectomy; ECG = electrocardiogram; [redacted]; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; NCCT = non-contrast computed tomography; NIHSS = National Institutes of Health Stroke Scale; rtPA=recombinant tissue plasminogen activator; SAE = serious adverse event; [redacted]; SOC = standard of care; Term = termination; TOAST = Trial of Org 10172 in Acute Stroke Treatment; [redacted]

[1] The Day 90 visit should be conducted in person whenever possible followed by telemedicine or phone in order of preference. All other visits after hospital discharge can be conducted by telephone/telemedicine or in person at the study subject's/representative's request.

[2] Early termination is defined as withdrawal from the study (see Section 10.3). Subjects who discontinue study treatment for any reason or who move to comfort care/palliative care should not be withdrawn from the study (see Section 10.1). Rather, they should either continue protocol-required tests and assessments or continue in the study with a limited study assessment schedule (see Section 10.1).

[3] Pre-morbid mRS will be collected based on all available information including medical records, patient, family, and/or LAR report.

[4] MRI(DWI)/CTP/NCCT as SOC at screening (prior to enrollment). If not available as SOC, a study-specific MRI(DWI), CTP, or NCCT, in order of preference, will be obtained. If thrombectomy is performed prior to randomization, imaging inclusion must use MRI(DWI) after thrombectomy.

[5] For subjects who undergo thrombectomy, the pre-procedure NIHSS should be used to determine eligibility. For subjects who are designated for DC or CMO/palliative care NIHSS should be obtained within 12 hours prior to that designation or as close as possible to this decision.

[6] Assessments performed at local laboratory.

[redacted]

[8] Only performed if subject has not yet been discharged.

[9] Supine blood pressure, heart rate, oxygen saturation, respiratory rate, and temperature prior to dosing.

[10] Subject must be supine.

[11] Subjects will be randomized/enrolled after all screening assessments have been completed and after the Investigator has verified that the subject is eligible to participate.

[12] Hourly (±30 min) for Hour 1 to 24, every 2 hours (±30 min) for Hour 24 to 48, and every 4 hours (±60 min) for Hour 48 to 72. If treatment for low blood glucose (<70 mg/dL or ~ 3.9 mmol/L) is initiated, then blood glucose monitoring is required every 15 min (±10 min) until blood glucose is ≥80 mg/dL (~4.4 mmol/L) for 3 consecutive readings without exogenous bolus glucose supplementation. Blood glucose monitoring may be more often at the discretion of the Investigator.

[13] Imaging by NCCT or MRI for midline shift (method should be consistent with baseline imaging method whenever possible) should be performed between 72 to 96 hours and as close to 72 hours as possible, or within 12 hours prior to DC, or the initiation of CMO/palliative care in subjects designated for DC or CMO/palliative care, respectively.

[14] This only applies if termination visit is prior to 72-96 hours.

[15] Subject disposition: location (e.g., hospice, nursing home, rehabilitation facility, home), level of rehabilitation, and if death occurred, the primary cause of death, and date and time of death will be recorded. Brain death and death associated with withdrawal of care must be documented.

[16] TOAST classification may be performed up to Day 7.

[17] All AEs and SAEs from the beginning of the Study Drug administration and all SAEs from the time of consent. AEs of special interest (i.e., hypoglycemia defined as confirmed glucose <55 mg/dL) will be upgraded as an SAE.

Table 9. Schedule of Activities – Part 2 (Day 91 through Month 12)

	Month 6 (± 30 days) Telephone/Telemedicine Visit[1]	**Month 12 (± 30 days) Telephone/Telemedicine Visit**[1]
mRS	X	X
Subject disposition[2]	X	X
EQ-5D-5L, BI, SIS-16	X	X
HCRUQ, Zarit	-	X
SAEs	X	X

BI = Barthel Index; EQ-5D-5L = EuroQol 5-level assessment of health outcome; HCRUQ = HealthCare Resource Utilization Questionnaire; mRS = modified Rankin Scale; SIS-16 = Stroke Impact Scale 16 Questions, Zarit = Zarit Burden Interview.

[1] In-person clinic visits may be conducted at the study subject's/representative's request.

[2] Subject disposition: location (e.g., hospice, nursing home, rehabilitation facility, home), level of rehabilitation, and if death occurred, the primary cause of death and date and time of death will be recorded. Brain death and death associated with withdrawal of care must be documented.

10.2 Sample SAS Code

The following SAS code (sas version 13.2 and later) illustrated the key SAS procedures to be used for the primary and secondary analyses. This section is not meant to provide the comprehensive list all SAS codes to be used under the definition of this SAP. The data set and variable names are examples for illustration purposes and do not represent the actual submission-ready data formats.

Note: TRT01P = "Placebo" or "BIIB093"; Region, rtPA, thrombectomy, ASPECTS, NIHSS are categorical variables defined per SAP.

10.2.1 Primary Endpoint – 5-Category mRS at Day 90:

The primary endpoint of mRS as 5-category ordinal scale (0/1, 2, 3, 4, 5/6) at Day 90 will be analyzed using the following ordinal logistic regression (proportional odds model), adjusting for baseline covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20). Odds ratio, the 95% confidence interval as well as the p-value will be reported.

```
proc logistic data=ADMRS; *Ordinal Logistic Regression
class TRT01P (ref="Placebo") region rtPA thrombectomy ASPECTS NIHSS/
param=ref order=data; * data that is ordered as the last/highest mRS
class value will be the reference level. The odds ratio is then the
odds for being lower (than reference) mRS compared to placebo.;
model aval=TRT01P region rtPA thrombectomy ASPECTS NIHSS/ clodds=wald;
where avisit="Day 90" and mITT="Y";
run;
```

The proportional odds ratio assumption will be tested using the following likelihood ratio test between the proportional odds model and the logistic regression model with nonproportional odds for treatment group effect.

```
 %macro LRTest(data=dsname,model1=,model2=,class=,freq=,print=1);
/*-----------------------------------------------------------------
  Computes the likelihood ratio test between the two models.  Small p-
values mean the extra parameters in the larger model significantly
describe some variation in the data.  Called by the %LRTestCycle
macro.

  data=   name of the input data set.
  model1= the MODEL statement for the first model without the word
'MODEL'.
  model2= the MODEL statement for the 2nd model.
  class=  the CLASS statement without the word 'CLASS'.
  freq=   name of the FREQ variable, if there is one
  print=  1=print the test results
  -----------------------------------------------------------------*/
proc logistic data=&data; *Will use proportional odds model;
   %if (%length(&class)>0) %then class &class;;
   model &model1;
```

```
    %if (%length(&freq)>0) %then freq &freq;;
   ods select globaltests;
   ods output globaltests=temp1;
proc logistic data=&data; *Will use nonproportional odds for treatment
group;
   %if (%length(&class)>0) %then class &class;;
   model &model2;
    %if (%length(&freq)>0) %then freq &freq;;
   ods select globaltests;
   ods output globaltests=temp2;
data temp2;
   set temp2;
   ChiSq2=ChiSq;
   DF2=DF;
data temp;
   merge temp2 temp1;
   where Test='Likelihood Ratio';
   keep Chisq DF P;
   ChiSq=abs(ChiSq2-ChiSq);
   DF= abs(DF2-DF);
   if (DF^=0) then P=1-probchi(ChiSq,DF);
   else P=.;
run;
%if %eval(&print eq 1) %then %do;
proc print data=temp noobs;
   var DF ChiSq P;
run;
%end;
%mend;

%LRTest(data=ADMRS,model1=aval=TRT01P region rtPA thrombectomy ASPECTS
NIHSS/ clodds=wald,model2=aval=TRT01P region rtPA thrombectomy ASPECTS
NIHSS/ clodds=wald unequalslopes=TRT01P,class=TRT01P (ref="Placebo")
region rtPA thrombectomy ASPECTS NIHSS/ param=ref order=data,print=1);
```

Mann-Whitney test

```
proc NPAR1WAY data=ADMRS wilcoxon;
class TRT01P;
var AVAL;
exact wilcoxon;
where avisit="Day 90" and mITTFL="Y";

run;
```

10.2.2 Secondary Endpoint – Time to all-cause death over the 90-day period

Cox proportional hazards regression model will be used to assess the treatment effect on overall survival at Day 90 after adjusting for region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20) as baseline covariates. Hazard ratio, 95% confidence interval as well as the p-value will be reported.

```
proc phreg data=Death90;
class TRT01P (ref = 'Placebo') region rtPA thrombectomy ASPECTS NIHSS;
model aval*ddfl(0)=TRT01P region rtPA thrombectomy ASPECTS
NIHSS/alpha=0.05 rl=both;
where mITTFL="Y";
title "Cox model on mortality by Day 90";
run;
```

Note: aval represents time at death; ddfl = 0 indicates censoring;

10.2.3 Secondary Endpoint – Proportion of subjects who achieved mRS 0-4 at Day 90

A logistic regression model will be used to estimate an odds ratio (and 95% CI) of improvement on the mRS dichotomized as 0-4 vs. 5-6 at Day 90. The model will include region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20) as baseline covariates. Odds ratio, the 95% confidence interval as well as the p-value will be reported.

```
proc logistic data=ADMRS04; *Logistic Regression
class TRT01P (ref="Placebo") region rtPA thrombectomy ASPECTS NIHSS/
param=ref order=data; * data that is ordered as the last/highest mRS
class value will be the reference level. The odds ratio is then the
odds for being lower (than reference) mRS compared to placebo.;
model aval=TRT01P region rtPA thrombectomy ASPECTS NIHSS/ clodds=wald;
            where avisit="Day 90" and mITT="Y";
run;
```

10.2.4 Secondary Endpoint – Midline Shift at 72 hours (or at time of DC or CMO, if earlier)

Analysis of Variance (ANOVA) will be used to compare the two study arms to assess the treatment effects on midline shift. The ANOVA will adjust for baseline covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no) and baseline NIHSS (≤20 vs. >20)

```
proc glm data=ADMLS outstat=contrasts (where=(_type_='CONTRAST'))
;*noprint;
     class TRT01P region rtPA thrombectomy ASPECTS NIHSS;
     model AVAL = TRT01P region rtPA thrombectomy ASPECTS NIHSS;
run;
```

10.2.5 Multiple Imputation for Primary Endpoint – 5-Category mRS at Day 90:

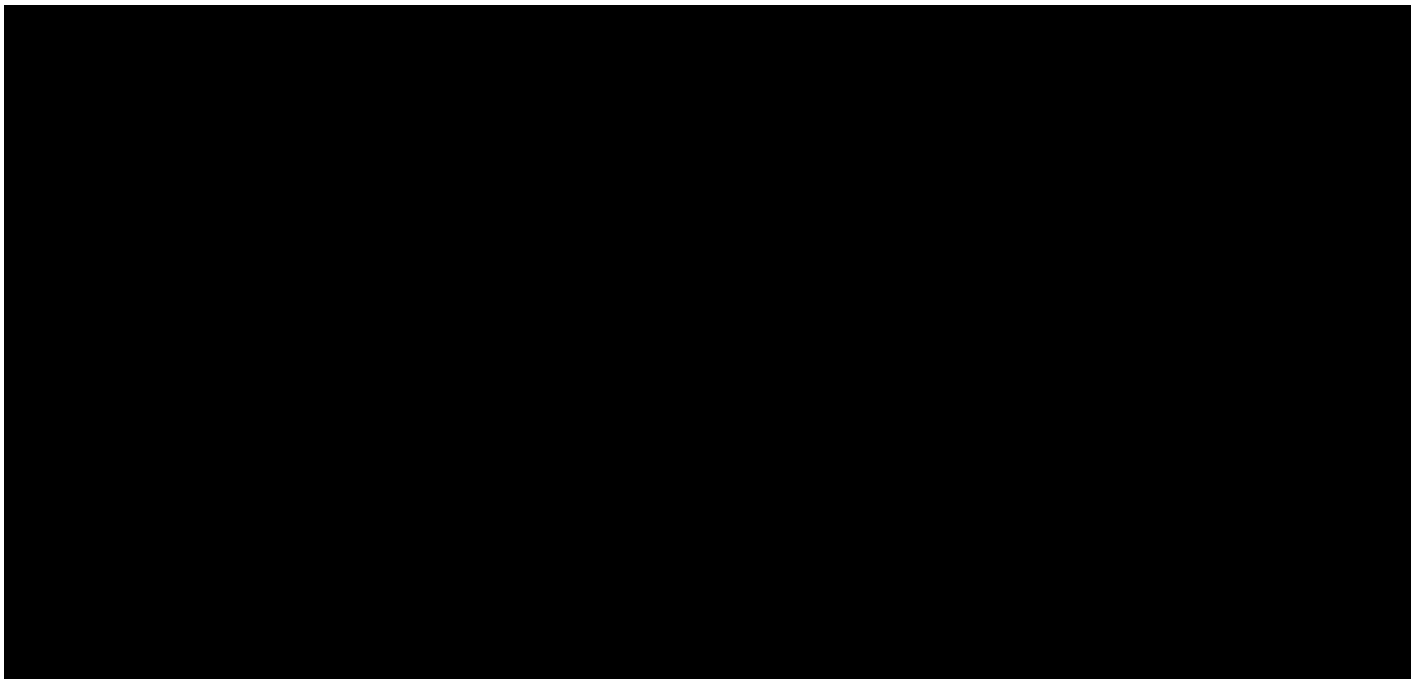
The primary endpoint of mRS as 5-category ordinal scale (0/1, 2, 3, 4, 5/6) at Day 90 will be analyzed using ordinal logistic regression (proportional odds model), adjusting for covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20).

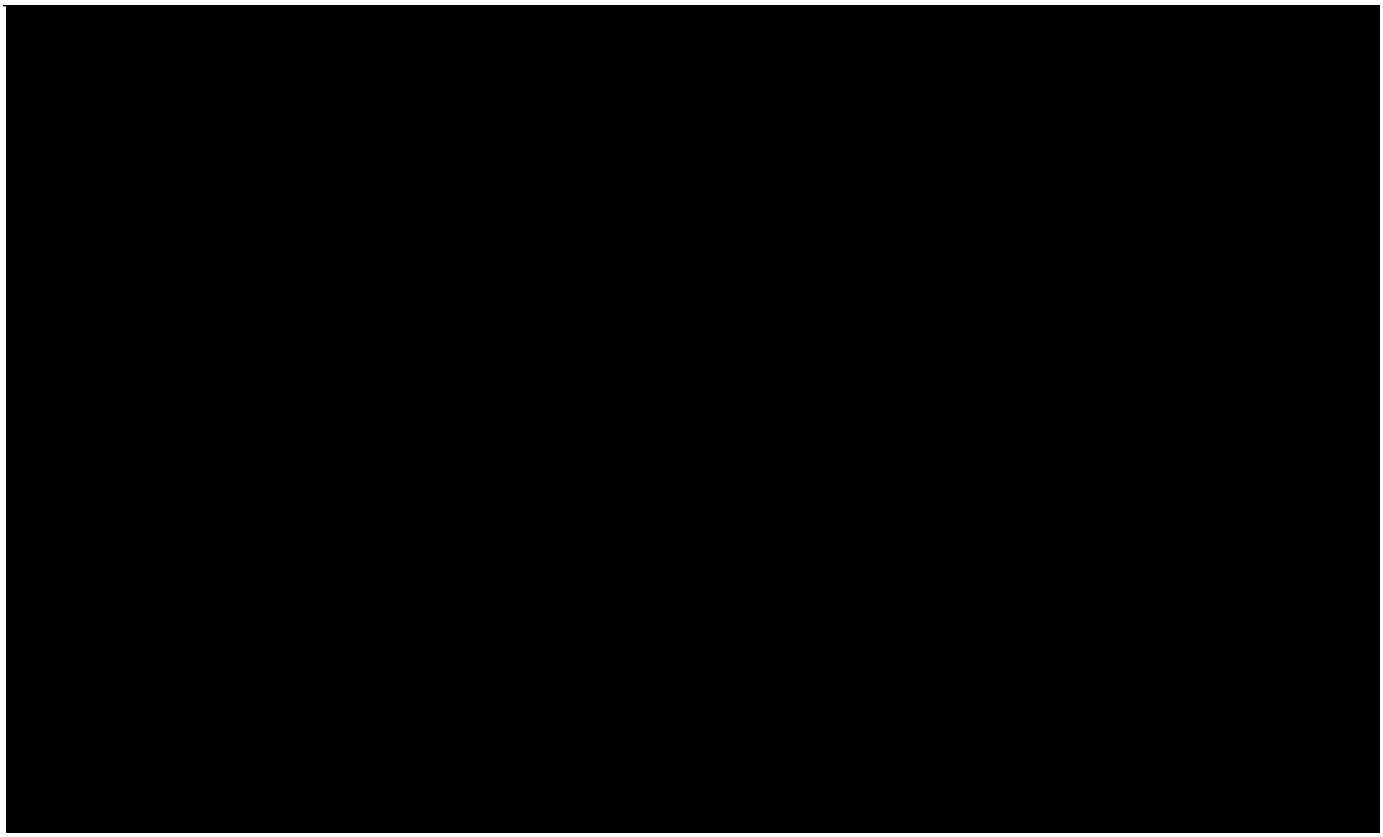
Multiple imputation will be used to handle missing data. The missing mRS values will be imputed by a regression model with independent variables including Day 30 mRS, region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS

(≤20 vs. >20). The predicted values will be rounded to the closest valid mRS score. 100 completed datasets will be created and saved in a dataset named outmi. The proportional odds model (described above) will be run for each dataset. The parameter estimates and standard errors from 100 datasets will be combined (PROC MIANALYZE).

```
proc mi data=ADMRS noprint out=outmi nimpute=100 seed=201912;
class TRT01P region rtPA thrombectomy ASPECTS NIHSS;
fcs reg (mRS90=mRS30 TRT01P region rtPA thrombectomy ASPECTS NIHSS );
var mRS30 mRS90 TRT01P region rtPA thrombectomy ASPECTS NIHSS; /*mRS30
and mRS90 are the mRS scores at Day30 and Day90*/
run;
data outmit;
set outmit;
mRS90=round(mRS90,1);
run;
proc sort data=outmi; by impnum;run;

proc logistic data=outmi;
class TRT01P (ref="Placebo") region rtPA thrombectomy ASPECTS NIHSS/
param=ref order=data;
model aval=TRT01P region rtPA thrombectomy ASPECTS NIHSS/ clodds=wald;
ods output ParameterEstimates=est;
where avisit="Day 90" and mITT="Y";
by impnum;
run;
proc mianalyze data=est;
ods output PARAMETERESTIMATES=stat;
modeleffects Estimate;
stderr  stderr;
run;
```





Signature Page

Document Name: 252LH301 Statistical Analysis Plan v3.0

Document Title:

Signed by	Role	Date / Time (UTC)
[redacted]	Signing as Author	11-Jul-2023 07:44:35
[redacted]	Signing as Approver	11-Jul-2023 11:54:31
[redacted]	Signing as Reviewer	11-Jul-2023 12:57:49