Official Study Title: The SQUID Trial for the Embolization of the Middle Meningeal Artery (STEM) for Treatment of Chronic Subdural Hematoma

NCT Number: NCT04410146

Statistical Analysis Plan (SAP) Date: 16-Apr-2024

STATISTICAL ANALYSIS PLAN

Protocol Title: The **S**QUID **T**rial for the **E**mbolization of the **M**iddle Meningeal Artery (STEM) for Treatment of Chronic Subdural Hematoma

Protocol Number: CIP-201912-SQUID, version 5.0

Phase: Pivotal

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SAP Date: 16 April 2024

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CEC	Clinical Events Committee
COWAT	Controlled Oral Word Association Test
cSDH	Chronic Subdural Hematoma
CMH	Cochran-Mantel-Haenszel (statistical) test
CSF	Cerebral Spinal Fluid
CSR	Clinical Study Report
CT	Computed Tomography
CV	Coefficient of Variation
DMSO	Dimethyl Sulfoxide
EC	Ethics Committee
EQ-5D	EuroQol Group – 5 Dimensions
EQ-5D-5L	EuroQol Group - 5 Dimensions-5 Levels (measure of health)
EQ-VAS	EuroQol Group Visual Analogue Scale (measure of health)
EVOH	Ethylene Vinyl Alcohol
HVLT-R	Hopkins Verbal Learning Test, Revised
ICH	Intracerebral Hemorrhage
ICU	Intensive Care Unit
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities

MMA	Middle Meningeal Artery
MI	Myocardial Infarction
MITT	Modified Intent-To-Treat
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
NIHSS	National Institute of Health Stroke Scale
PP	Per Protocol
PT	Preferred Term
SAH	Subarachnoid Hemorrhage
SAP	Statistical Analysis Plan
SDH	Subdural Hematoma
SEPS	Subdural Evacuating Port System
SOC	System Organ Class
STEM	The SQUID Trial for the Embolization of the Middle Meningeal Artery
TEAE	Treatment Emergent Adverse Event
US	United States

3. INTRODUCTION

3.1. Preface

This document presents a statistical analysis plan (SAP) for Balt USA's Protocol CIP-201912-SQUID (*The **S**QUID **T**rial for the **E**mbolization of the **M**iddle Meningeal Artery (STEM) for Treatment of Chronic Subdural Hematoma*).

Reference materials for this statistical plan includes the protocol CIP-201912-SQUID (Version 5.0, Dated: 01-MAR-2023).

The statistical analysis plan (SAP) described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to database lock.

3.2. Purpose of Analyses

The purposes of the planned analyses described in this SAP are to demonstrate the safety and effectiveness of adjunctive middle meningeal artery embolization (MMAE) with SQUID™ for chronic subdural hematoma (cSDH) patients undergoing either surgical or medical management. Results from the analyses completed will be included in the final clinical study report for CIP-201912-SQUID, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study. These analyses will be clearly identified, where appropriate, in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report, but will be fully documented in the document containing the additional analyses.

3.3. Summary of Statistical Analysis Changes to this Plan

- Administrative updates: authorship, removing irrelevant acronyms, edits for clarity, consistency, organization, or grammar.
- Clarified analysis populations.
- Organized content and layout of subgroup analyses/other groups of interest for consistency.
- Added definition of study day.
- Clarified missing data; dates handled via data collection (not imputation), NIHSS score for subjects who die.
- Updated multiple imputation model approach, addressing potential distribution issues and missing covariates, i.e., use of fully conditional specification rather than a monotone approach.
- Removed reference to CDISC/STDM (not being used).

- Added alternative approach to be used if the Breslow data homogeneity assumption is rejected.
- Added sensitivity analyses.
- Removed overly restrictive reporting/population summary conventions.

4. STUDY OBJECTIVE

The objective of this Study is to demonstrate the safety and effectiveness of adjunctive MMA embolization with SQUID™ for cSDH patients undergoing either surgical or medical management.

5. STUDY ENDPOINTS

5.1. Primary Effectiveness Endpoint[1]

Treatment failure as defined by the occurrence of any of the following events:

1. Residual or re-accumulation of the SDH (≥10 mm)[2], on 180-day scan, from intervention
2. Re-operation (after index procedure) or surgical rescue within 180-days of intervention[3];
3. Any new, major disabling stroke, myocardial infarction (MI) or death from any (neurological) cause within 180-days of intervention.

5.2. Primary Safety Endpoint

- Major disabling stroke or any death within 30-days, from intervention

5.3. Secondary Endpoints

- Secondary effectiveness endpoint: Modified Rankin Score (mRS) (analyzed as shift) at 180-days from intervention

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[1] Assessed at 180 days visit (180 days +/-6w)

[2] Residual or re-accumulation of cSDH on180 day scan from intervention on index side (left, right, or bilateral) as designated at the time of screening. Success on both sides is required for bilateral cSDH

[3] Re-operation or surgical rescue includes cSDH evacuation via any surgical procedure OR embolization of the MMA with any commercially available product on index side (left, right, or bilateral) as designated at the time of screening. Success on both sides is required for bilateral cSDH.

- Secondary safety endpoint: Any investigational device/procedure-related AE/SAE

5.4. Additional Endpoints

- mRS (analyzed as shift) at 30-day and 1-year from intervention
- mRS < 2 (binary) at 30-day, 180-day and 1-year from intervention
- Cognitive improvement, as measured by blinded assessment, utilizing the comprehensive neuro-cognitive battery[4] to be performed at: Baseline, 30-day, 180-day and 1-year from intervention
- EQ-5D-5L (including EQ-VAS): Baseline vs. 30-day, 180-day, and 1-year from intervention
- Hospital Days (through 180 days)
- Intensive Care Unit (ICU) Days
- NIH Stroke Scale (NIHSS): Baseline vs discharge and 90-day
- CT/MRI imaging[5]: Baseline vs 180-day

6. STUDY METHODS

6.1. General Study Design and Plan

As background for the statistical methods presented below, this section provides an overview of the STEM study design and plan of study execution. The protocol is the definitive reference for all matters discussed in what follows.

Up to 310 subjects with cSDH who present for neurological assessment will be randomized in this pivotal, international, multi-center, prospective, stratified combination randomized controlled trial.

The objective of this study is to demonstrate the safety and effectiveness of adjunctive MMA embolization with SQUID for the management of cSDH in patients undergoing either surgical or medical management. SQUID is a non-adhesive, liquid embolic agent consisting of an ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO) and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. SQUID is injected into the vascular site to be treated under fluoroscopic control. DMSO dissipates in the blood and causes precipitation of EVOH in which the tantalum powder is trapped. It then forms a consistent spongy embolus. This embolus solidifies from the outside

[4] Hopkins Verbal Learning Test, Revised (HVLT-R), Controlled Oral Word Association Test (COWAT), Animal Naming Test, Trail Making Test, Trails A and Trails B

[5] Measuring cSDH Thickness (actual measurement, ≥ 10 mm), reduction of the SDH by >50% and by >75%, cSDH Density (homogeneous vs. heterogeneous)s and densest component (hyperdense compared to cortex, isodense compared to cortex, hypodense compared to cortex, and isodense to CSF), any new intracranial hemorrhage (Subarachnoid Hemorrhage, Intracerebral Hemorrhage, SDH), new large vessel territory stroke

inwardly while moving distally in the vessel. The non-adhesive character of the embolus allows slow and controlled injections while leaving in place the microcatheter.

The duration of the enrollment period is expected to be 36 months. Due to global impact of COVID19, the enrollment period may be extended if required. The overall study duration for each subject includes a follow-up period of up to 1-year (+/- 8 weeks).

Subjects who only experience treatment failure #1 (so called radiological failure as assessed at the 180-day visit), should continue the study through 1-year follow-up according to schedule of events (Table 5 of the protocol). These subjects require an extra assessment at 1-year follow-up (CT/MRI scan).

Subjects who experience treatment failure #2 and/or #3 at any time after start of the assigned intervention, should be followed up to 1-year according to the modified schedule visit (Table 6 of the protocol) and their mRS, AE/SAE, and concomitant medication can be assessed virtually or remotely.

If subject experiences neurological death at any time after the start of the assigned intervention, a mRS of 6 will be entered into CRFs.

6.2. Randomization and Blinding

As described in Protocol Section 3, based upon the best judgment of the treating team, non-emergency cSDH Subjects will be stratified (allocated prospectively) into two main groups (strata), either Surgical or Medical Management. Within each of these strata, each subject will then be randomized (1:1) to either standard management, or MMAE with SQUID (See Figure 1).

- If assigned by the treating team to the Medical Management stratum, subjects will be randomized to either ‘SQUID Embolization’ (“treatment”) or to ‘Standard Medical Management’ (“control”).
- If assigned by the treating team to the Surgical Management stratum, subjects will be randomized to either ‘SQUID Embolization followed by Surgery’ (“treatment”) or to Surgery-only (“control”).

Randomization will be in a 1:1 (treatment:control) ratio and will be stratified by assignment to Medical or Surgical Management.

Each stratum will have at least 110 subjects. Comparisons will be performed between embolization (“treatment”) versus non-embolization management (“control”) in analyses that account for the stratification by assignment to Medical or Surgical Management.

The only staff who will be blinded to randomization assignment during the study includes the core lab image assessors and the neuropsychology investigator.

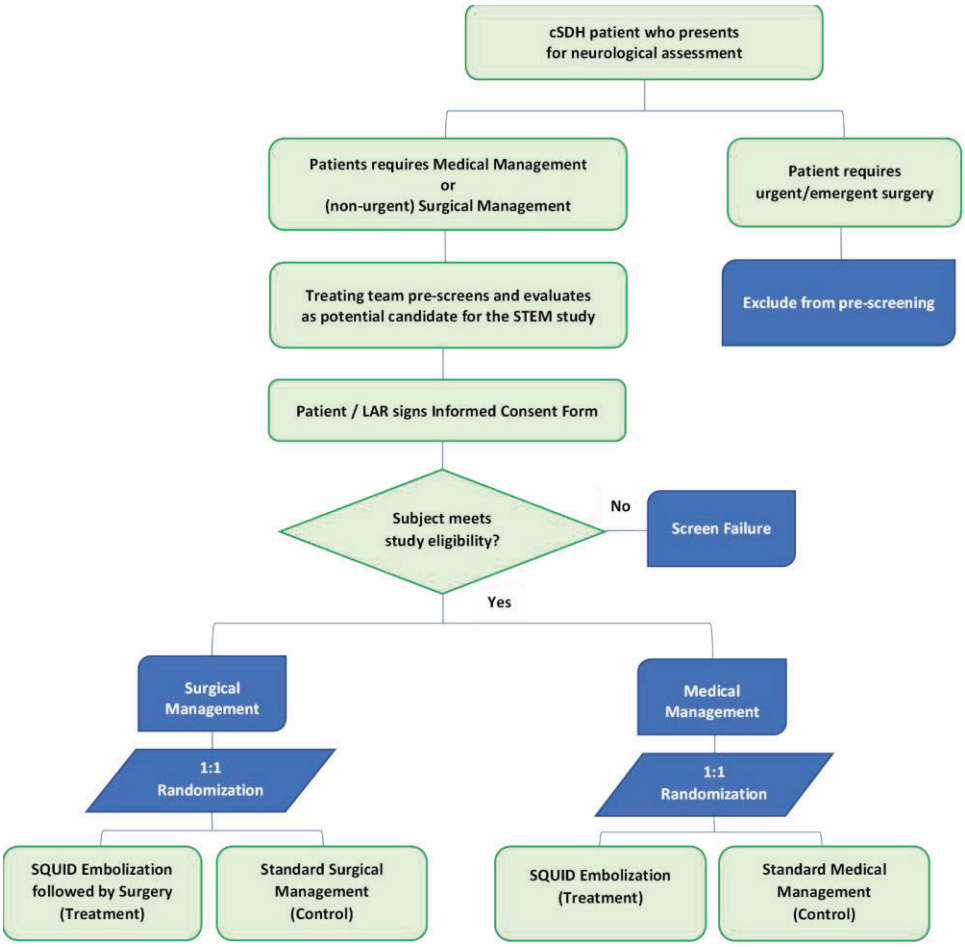

Figure 1 STEM STUDY DESIGN

7. SAMPLE SIZE

SQUID embolization vs no-embolization treatment strategies will be compared using a Cochran-Mantel-Haenszel (CMH) test, where Medical Management vs Surgical Management serves as the stratification factor. Formal hypotheses for a test of superiority are as follows:

H_0: R = 1

H_A: R ≠ 1

where R is the odds ratio of experiencing treatment failure at 180 days in the treatment (embolization) and control (no embolization) groups, respectively.

Sample size was computed based on the primary effectiveness endpoint (treatment failures by the 180-day visit) in PASS 2013 for two independent proportions in a stratified design, assuming the following:

- 19% failure rate in each of the embolization arms (SQUID embolization followed by surgery or SQUID embolization alone)

- 36% failure rate in each of the control (non-embolization) arms (Standard Surgical or Standard Medical Management)
- (This is equivalent to an odds ratio of 0.4170.)
- 1:1 randomization
- 90% desired power
- Two-sided superiority test at alpha of 0.05

Although H_A is two-sided, endpoint success will only be concluded if statistical significance is achieved at the 0.05 level and the point estimate for the odds ratio is < 1.

Under these assumptions, the required sample size is 286 evaluable subjects (143 in each arm). To account for attrition, a total sample size of up to 310 subjects will be randomized.

8. GENERAL CONSIDERATIONS

8.1. Analysis Populations

There will be five (5) analysis populations defined for this study.

Population	Definition
Enrolled Population	Includes all subjects who sign informed consent.
Safety Population	Includes all subjects who sign informed consent and are randomized. Subjects included in the safety population will be analyzed according to the treatment actually received regardless of randomization assignment.
ITT Population	Includes all subjects who sign informed consent and are randomized. Subjects included in the ITT population will be analyzed as randomized.
MITT Population	Includes all subjects who sign informed consent, are randomized, and the assigned intervention has started. This is the primary analysis population. Subjects included in the MITT population will be analyzed as randomized.
Per Protocol (PP) Population	Includes all subjects who complete the study without major protocol deviation. Major protocol deviations are deviations that affect the scientific integrity of the study and will be identified prior to database lock for final analysis.

8.2. Subgroups / Site Poolability

Summaries of the primary endpoint and secondary endpoints will be presented according to the following subgroups. Unless otherwise indicated, these will use the asymptotic or exact CMH test for the following subgroups (MITT population):

a. Strata (Surgical or Medical Management)
b. Region (US or Outside US)
c. cSDH type (Unilateral cSDH or Bilateral cSDH)
d. cSDH size (<20 mm vs. ≥20 mm) per corelab
e. Subdural Evacuating Port System (SEPS) device use (yes or no)
f. Antiplatelet and anticoagulant medication usage
g. Age (years): (≤85 and >85; ≤65 and >65)
h. Sex (male versus female)
i. Race
j. Baseline mRS
k. BMI

Note that while results will be reported for each subgroup level, the study is not powered for any of these comparisons.

Additional analyses of groups are of interest, though since these are defined by variables collected after randomization, they are separate and distinct from subgroup analyses:

a. Unilateral cSDH vs. Bilateral cSDH index treatment
b. Number of burr holes placed during the index procedure

Poolability of results across sites will be assessed as follows. Every combination of site and randomization stratum (Surgical Management vs Medical Management) will be considered as a separate stratum for this analysis. Evidence of heterogeneity of treatment effect for the primary effectiveness endpoint across these combinations will be evaluated using the Breslow-Day test. A p-value less than 0.15 will result in an investigation of the potential causes of heterogeneity, including the potential for incorporation of appropriate covariates into the relevant analyses. (Potential covariates include the subgroups in Section **Error! Reference source not found.**.) Separate analyses by site may also be considered.

Small combinations of site and randomization strata, defined as less than 5 subjects at a site within the Surgical Management or Medical Management strata, will not be included in the inferential heterogeneity test, but treatment failures will be summarized descriptively for all combinations of sites and strata.

An evaluation of poolability by region will also be conducted using the same test (i.e., Breslow-Day test) and interpretation as the test for poolability across sites.

8.3. Management of Analysis Data

8.3.1. Study Day

Analysis for all populations day zero will be the date of randomization.

8.3.2. Missing Data

8.3.2.1. Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis. Refer to CRF completion guidelines.

8.3.2.2. Imputation Methods

The primary analysis for the primary effectiveness endpoint and secondary effectiveness endpoints will use multiple imputation for missing data. A logistic regression multiple imputation method (fully conditional specification in SAS PROC MI, based on 50 imputed data sets) will be used to impute missing primary effectiveness and secondary effectiveness responses. Separate imputations will be performed by randomized arm and strata. Baseline values of the following variables will be utilized in the imputation model:

a. Region (US or Outside US)
b. cSDH type (Unilateral cSDH or Bilateral cSDH
c. cSDH size (<20 mm vs. ≥20 mm) per corelab
d. Subdural Evacuating Port System (SEPS) device use (yes or no)
e. Antiplatelet and anticoagulant medication usage
f. Age (years)
g. Sex (male versus female)
h. Race
i. Baseline mRS
j. BMI

The primary effectiveness endpoint will also be analyzed using a tipping-point analysis described in Yan, Lee, and Li (2009). Campbell, Pennello, and Yue (2011) and Liublinska and Rubin (2014) provide additional details on the method. For this analysis, multiple CMH tests will be performed on datasets that have missing data across both arms and will set all

combinations of missing data as treatment failures. Combinations that do and do not result in rejecting the null hypotheses at the 5% level will be summarized.

Observed cases, without imputation, will be used for all other analyses unless otherwise specified.

If the relationship of an AE is missing, it will be considered treatment-related. Missing AE severity will be coded as severe.

8.3.3. Pooling of Study Centers

The justification for pooling results across clinical sites is primarily clinical, since all sites follow the same protocol. A statistical assessment for poolability of the primary results across clinical sites will be conducted. In addition, an evaluation of poolability by region (defined as US versus Outside US) will be conducted.

Further details on the assessment of poolability are provided in Section 8.2.

8.3.4. Coding Conventions for Events

All adverse events and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 26.0) system for reporting (preferred term and body system).

8.3.5. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) or R (Version 3.6.1 or later). If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

8.4. Planned Study Analyses

8.4.1. Statistical Summaries: Descriptive and Inferential

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, 25^{th} and 75^{th} percentiles (interquartile range), minimum, and maximum will be tabulated. For categorical variables, the counts and percentages of each value will be tabulated. Expansion of descriptive table categories may occur if such elaborations are thought to be useful. Confidence intervals will also be provided as appropriate.

P-values will be two-sided, with values less than 0.05 indicating statistical significance.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. The standard deviation / standard error will be displayed to two levels of precision greater than the data collected.

Change from baseline scores will be calculated as the post-baseline measurement minus the baseline value.

Collected data will be presented in listings.

8.4.2. Interim Analyses

No formal interim analyses will be conducted unless requested by the Data Safety Monitoring Board.

8.5. Multiple Testing Procedures

In order to maintain family-wise Type I error at an overall level of 0.05, statistical testing of the secondary effectiveness endpoint (mRS [analyzed as shift] at 180-days from intervention) will only be performed if the primary effectiveness endpoint has rejected its null hypothesis. Both the primary effectiveness and secondary effectiveness endpoints will be tested at the 0.05 level in this sequential testing approach. None of the additional effectiveness endpoints listed in Section 10.3 will be formally tested.

9. SUMMARY OF STUDY DATA

9.1. Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects in each stratum and treatment arm (where applicable) for the following categories: subjects enrolled, subjects randomized, subjects in the safety population, subjects in the ITT population, subjects in the MITT population, and subjects in the PP population.

End of trial information will also be summarized, including the number of subjects completing the study and the number of subjects with incomplete follow-up, with reasons.

A by-subject data listing of study completion information including the reason for incomplete follow-up, if applicable, will be presented.

9.2. Protocol Deviations

All protocol violations will be presented in a data listing, with a flag to indicate if a violation was considered major and resulted in the exclusion of the participant from the PP population. A summary table will be generated based on the classification of protocol deviations.

9.3. Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively by treatment arm, by treatment arm and stratum, and overall. The demographic data and baseline characteristics will be summarized for the Safety, ITT, MITT, and PP populations. Individual participant demographics and baseline characteristics will be provided in the listings.

9.4. Medical and Surgical History

Medical (including surgical) history will be coded using the MedDRA Version 26.0 and will be summarized descriptively by treatment arm, by stratum, and overall, for the Safety, ITT, MITT, and PP populations.

Subject medical history data including specific details will be presented in a listing.

9.5. Prior and Concomitant Medications

The number and percentages of subjects taking any anti-platelet, anti-coagulation, or steroid medications will be summarized. The number and percentages of subjects with at least one anti-platelet, anti-coagulation, or steroid medication will be summarized. All summaries will be performed for the Safety, ITT, MITT, and PP populations.

10. EFFECTIVENESS ANALYSES

10.1. Primary Effectiveness

10.1.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint is treatment failure.

Treatment failure as defined by:

- Residual or re-accumulation of the SDH (≥10 mm)[6], on 180-day scan from intervention; or
- Re-operation (after index procedure) or surgical rescue within 180-days of intervention[7]; or
- Any new, major disabling stroke, myocardial infarction (MI) or death from any (neurological) cause within 180-days of intervention.

10.1.2. Primary Effectiveness Analysis

The primary effectiveness endpoint assessed at the 180-day visit is the percentage of subjects who are considered treatment failures. The number and percentage of participants who are considered treatment failures will be provided separately by all combinations of embolization (treatment arm) vs. non-embolization (control arm) and by stratum. The primary analysis will be based on the MITT Population.

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[6] Residual or re-accumulation of cSDH on180 day scan from intervention on index side (left, right, or bilateral) as designated at the time of screening. Success on both sides is required for bilateral cSDHs.

[7] Re-operation or surgical rescue includes cSDH evacuation via any surgical procedure OR embolization of the MMA with any commercially available product. Success on both sides is required for bilateral cSDH.

The treatment arm and the control arm will be compared using a Cochran-Mantel-Haenszel (CMH) test, where Medical Management vs Surgical Management serves as the stratification factor. Formal hypotheses for a test of superiority are as follows:

H_0: $R = 1$

H_A: $R \neq 1$

where R is the odds ratio of experiencing treatment failure at 180 days in the treatment and control groups, respectively. Rejection of the null hypothesis at the 5% level, with a lower observed incidence for SQUID embolization than control ($\hat{R} < 1$), therefore constitutes a finding of superiority of treatment (embolization) to control (non-embolization). A 95% CI for the common odds ratio will be presented.

The Breslow-Day test for homogeneity of odds ratios across strata will also be conducted, to assess the assumption of a common odds ratio. If the Breslow-Day test indicates the homogeneity assumption is not appropriate (based on $p<0.05$), analysis will be based on a generalized estimating equation logistic regression approach to account for random effects by treating the strata as clusters.

Multiple imputation will be used to impute missing data. See Section 8.3.2.2 for further details.

10.1.3. Primary Effectiveness Sensitivity and Supportive Analyses

The following sensitivity analyses will be performed for the primary effectiveness endpoint using the MITT population:

1. Observed Cases (without imputation): Subjects with missing primary outcomes will be omitted from the analysis.
2. Unstratified analysis: An analysis that pools subjects across strata will also be conducted, using Pearson's chi-square test and computing 95% confidence intervals for the difference in rates of treatment failure. This analysis will use multiple imputation.
3. Tipping Point analysis: See Section 8.3.2.2 for further details.
4. A missing data sensitivity analysis will be performed that includes any primary effectiveness event as a failure (including events past 180 days) to capture results for subjects missing earlier assessments.
5. An additional sensitivity analysis to examine intended vs. applied treatments will include non-target failures as failures. This analysis will use multiple imputation.

The following supportive analyses will be performed for the primary effectiveness endpoint.

1. The primary analysis will be repeated for the Safety, ITT, and PP populations. For the ITT analysis, multiple imputation will be used.

10.2. Secondary Effectiveness

10.2.1. Secondary Effectiveness Endpoint

The secondary effectiveness endpoint is mRS score (analyzed as shift) at 180-days from intervention. This endpoint will be tested sequentially following the primary effectiveness endpoint analysis. See Section 8.5 for more details on the sequential testing procedure.

The 'shift' analysis evaluates the entire range of the mRS at a visit (all 7 levels: 0 = no symptoms at all, 1 = no significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death) unlike the binary mRS analysis which classifies the 7 levels into two groups (<2 and ≥2).

10.2.2. Secondary Effectiveness Analyses

The number and percentage of participants who exhibit each level of the mRS score at 180-day, by stratum, will be provided by treatment arm. The analysis will be based on the MITT Population, with multiple imputation for missing data.

Treatments will be compared using a van Elteren test. Conceptually, the van Elteren test is a stratified version of a Wilcoxon Rank Sum test, testing whether there is a shift in two distributions in a stratified experiment [Stokes 2000, Mehrotra 2010]. Formal hypotheses for a test of superiority are as follows [Puri 1969]:

H_0: $F_{T,i} = F_{C,i}$ for i =1 and 2

H_A: $F_{T,i} \neq F_{C,i}$ for i =1 or 2

where $F_{T,i}$ and $F_{C,i}$ are the cumulative distribution functions of the mRS scores for the treatment and control arms, respectively, and i indexes the two strata (Surgical Management and Medical Management). The Wilcoxon rank sum test has been studied and used to conduct shift analyses of mRS scores in the unstratified case [e.g., Bath 2008, OAST Collaborators 2007], and as its stratified extension, the van Elteren test has been widely used to analyze both continuous and ordered categorical response data in many fields [Savitz 2007, Mehrotra 2010].

A statistically significant result indicates that there is a 'shift' in the mRS responses between the treatment arms in at least one of the strata. To aid in understanding, the distributions of mRS scores will be presented graphically and with descriptive statistics, separately for each combination of treatment arm and stratum.

Multiple imputation will be used to impute missing data for this endpoint. See Section 8.3.2.2 for further details.

10.2.3. Secondary Effectiveness Sensitivity and Supportive Analyses

The following sensitivity analyses will be performed for the secondary effectiveness endpoint using the MITT population:

1. Observed Cases (without imputation): Subjects with missing primary outcomes will be omitted from the analysis.

2. Unstratified analysis: An analysis that pools subjects across strata will also be conducted, using a Wilcoxon rank-sum test and to assess the significance of the 'shift'. This analysis will use multiple imputation.
3. Tipping Point analysis: See Section 8.3.2.2 for further details.

The following supportive analyses will be performed for the secondary effectiveness endpoint.

1. The primary analysis will be repeated for the Safety, ITT, and PP populations. For the ITT analysis, multiple imputation will be used.

10.3. Additional Endpoints

The following additional effectiveness endpoints are supportive or exploratory in nature.

- mRS (analyzed as shift) at 30-day and 1-year from intervention
- mRS ≤ 2 (binary) at 30-day, 180-day, and 1-year from intervention
- Comprehensive neuro-cognitive battery to be performed at: Baseline, 30-day, 180-day and 1-year from intervention
    - Hopkins Verbal Learning Test, Revised (HVLT-R)
    - Controlled Oral Word Association Test (COWAT)
    - Animal Naming Test
    - Trail Making Test, Trails A and Trails B
- Hospital Days
- ICU Days
- EQ-5D-5L (including EQ-VAS): Baseline vs. 30-day, 180-day, and 1-year from intervention
- NIHSS: Baseline vs discharge and 90-day
- CT imaging: Baseline vs 180-day
    - cSDH Thickness
        - Actual measurement
        - ≥ 10 mm (Y/N)
    - cSDH Density
        - Homogeneous vs. heterogeneous
        - Densest component (hyperdense compared to cortex, isodense compared to cortex, hypodense compared to cortex, isodense to CSF)
    - Reduction of the SDH thickness by > 50% (Y/ N)
    - Reduction of the SDH thickness by > 75% (Y/ N)

- New intracranial hemorrhage of any kind (Subarachnoid Hemorrhage (SAH), Intracerebral Hemorrhage (ICH), SDH)
- New large vessel territory stroke

All additional endpoint analyses will be performed on the MITT and ITT populations without any imputation for missing data. These are considered supportive or exploratory in nature and will be summarized by treatment arm with descriptive statistics and 95% confidence intervals (where appropriate), without formal hypothesis testing. Unless otherwise stated, results will be pooled across the Surgical Management and Medical Management strata.

10.3.1. mRS

The number and percentage of participants who exhibit each level of the mRS score (analyzed as shift) at 30-day and 1-year will be provided by treatment arm.

The number and percentage of participants who exhibit mRS ≤ 2 (binary) at 30-day, 180-day, and 1-year will also be provided by treatment arm. 95% confidence intervals for the percentage will be provided. These analyses will be conducted both with and without pooling across strata.

10.3.2. Comprehensive Neurocognitive Battery

The following neurocognitive function tests results will be provided in listings. Analyses are described in a separate STEM Study Neurocognitive Battery Charter.

- Hopkins Verbal Learning Test, Revised (HVLT-R)
- Controlled Oral Word Association Test (COWAT)
- Animal Naming Test
- Trail Making Test, Trails A and Trails B

10.3.3. Hospital Days

The total number of in-patient hospital days from baseline until 180-day will be summarized descriptively for each treatment arm and stratum.

10.3.4. ICU Days

The total number of ICU days from baseline until 180-day will be summarized descriptively for each treatment arm and stratum.

10.3.5. EQ-5D-5L (including EQ-VAS)

The EQ-5D questionnaire is made up of two components: health state description and evaluation.

In the description part, health status is measured in terms of five dimensions (5D); mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. The respondent's self-rate their level of severity for each dimension using a five-level (EQ-5D-5L) scale, where level 1 means normal, and 5 means the worst state of health. For each domain, the number and percentage of subjects in each level will be summarized by treatment and visit.

In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS). The VAS score will be summarized descriptively for each treatment arm by visit for the observed value as well as for the change from baseline value.

All results will be listed.

10.3.6. NIHSS

NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patent's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal.

The total score is the sum of all items. The total score will be summarized descriptively for each treatment arm by visit for the observed value as well as for the change from baseline value. Subjects who die before having an NIHSS score assessed will be counted as having the maximum score of 42.

All results will be listed.

10.3.7. CT Imaging

- cSDH Thickness
  - Actual measurement
  - ≥ 10 mm (Y/N)
- cSDH Density
  - Homogeneous vs. heterogeneous
  - Densest component (hyperdense compared to cortex, isodense compared to cortex, hypodense compared to cortex, isodense to CSF)
- Reduction of the SDH by 50% (Yes/No) and by 75% (Yes/No)
- New intracranial hemorrhage of any kind (Subarachnoid Hemorrhage (SAH), Intracerebral Hemorrhage (ICH), SDH)
- New large vessel territory stroke

These analyses will be based on each target cSDH. The cSDH thickness measurement will be summarized descriptively for each treatment arm by visit for the observed value as well as for

the change from baseline value. For other variables, the number and percentage of subjects in each level will be summarized by treatment and visit.

All results will be listed.

11. SAFETY ANALYSES

All safety analyses will be conducted using the Safety population.

11.1. Primary Safety Endpoint

The primary safety endpoint is the occurrence of major disabling stroke or any death within 30 days from intervention.

There is no hypothesis test associated with this endpoint. The incidence of major disabling stroke or any death within 30 days from intervention will be presented by treatment arm (aggregated across and also within each of the surgical management and medical management strata). 95% confidence intervals will be presented for the incidence in each arm and for the difference between treatment arms (aggregated across and within strata).

11.2. Secondary Safety Endpoint

The secondary safety endpoint is the occurrence of any investigational device/procedure-related (Embolization) AE/SAE.

11.3. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary (v26.0) will be used for coding AEs.

Summaries of AEs will be presented for Treatment Emergent AEs (TEAEs). TEAEs are AEs that occur or worsen after initiation of randomization.

The following summary tables will be presented, summarizing counts of events and the number and percentage of subjects experiencing the events.

- Overall Summary of AEs
- AEs by system organ class (SOC) and preferred term (PT)
- AEs by PT
- AEs by SOC, PT, and Severity
- AEs by SOC, PT, and Relationship to Study Device
- AEs by SOC, PT, and Relationship to Study Procedure
- Serious AEs (SAEs) by SOC and PT
- SAEs by PT
- AEs with a Fatal Outcome by SOC and PT

- Adverse Device Effects (ADEs) by SOC and PT
- Serious Adverse Device Effects (SADEs) by SOC and PT
- Unanticipated Adverse Device Effects (UADEs) by SOC and PT
- Unanticipated Serious Adverse Device Effects (USADEs) by SOC and PT
- Device deficiency AEs by SOC and PT (Treatment arm only)

If more than one event occurred with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study device, respectively. The potential endpoints of major disabling stroke, myocardial infarction, death of any cause, and re-operation/surgical rescue will be site reported.

The following listings will be created, separately for AEs that occur before versus on or after (day of intervention and day of randomization for medical management only arm):

- All AEs
- All SAEs
- All UADEs
- All USADEs
- All AEs leading to death

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