Stroke Hyperglycemia Insulin Network Effort: The SHINE Trial

STATISTICAL ANALYSIS PLAN

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1. STATISTICAL ANALYSIS PLAN AND STATISTICAL REPORTS

This document provides the details of statistical analyses planned for the SHINE Trial, including interim analyses for efficacy and futility. In addition, it discusses the statistical issues relevant to these analyses (e.g., sample data to be used, missing data).

The Statistical and Data Management Center (SDMC) generates two statistical reports – an open report to be distributed to the SHINE Trial Executive Committee and the Data and Safety Monitoring Board (DSMB), and a closed report to be distributed only to the DSMB. The timing of these reports is determined in consultation with the DSMB. Reports will be sent from the NETT SDMC to the NINDS Liaison two weeks in advance of the scheduled meeting.

Each report provides cumulative summary statistics on enrollment; subject status in the study; baseline characteristics; protocol violations; safety data, including AEs and SAEs, severity, expectedness (anticipated/unanticipated) and relatedness to the study treatment; and data management/quality information (e.g., timeliness and completeness of data entry by the Clinical Sites via the SHINE Trial Website; number of DCRs generated and resolved). The statistics are provided for the overall study as well as by clinical center when applicable in the open report. For the closed report only, the statistics are also provided by treatment group (A vs B). If a report coincides in timing with a planned interim analysis, the analysis results are appended to the report.

2. SYNOPSIS OF THE STUDY

This multicenter, randomized, controlled clinical trial of approximately 1400 patients will be conducted at approximately 56 enrolling sites. Enrollment is anticipated to occur over 3.5 years. Patients will be randomly assigned to IV insulin therapy with target glucose 80-130 mg/dL or sliding scale SQ insulin (control therapy) with target glucose less than 180 mg/dL for up to 72 hours. Therapy must be initiated within 3 hours of arrival at the enrolling center and within 12 hours of stroke onset. The primary efficacy outcome will be the dichotomized mRS score at 90 days post randomization adjusted for the baseline severity of stroke (responder analysis). The primary safety outcome will be severe hypoglycemia (<40 mg/dL). Additional safety outcomes will include overall hypoglycemia (blood glucose <55 mg/dL), symptoms and signs associated with hypoglycemia, and death. Secondary outcomes include functional outcomes at 90 days, a 6 hr vs 12 hr enrollment analysis, measures of glucose control success and adherence to the computerized glucose monitoring system.

3. OUTCOME VARIABLES

3.1 Primary Efficacy Outcome

The primary efficacy outcome is the severity adjusted 90-day mRS. Favorable outcome is defined using a responder analysis method.[1,2] This method is proposed for the SHINE trial to provide a more sensitive measure of clinical effect. The responder analysis dichotomizes mRS scores as “favorable” versus “not favorable” based on the baseline NIHSS measured at randomization. “Favorable” outcome is defined as an mRS score of 0 in patients with baseline NIHSS of 3-7, mRS of 0-1 in patients with baseline NIHSS of 8-14, and mRS of 0-2 in patients with baseline NIHSS of 15-22. These cutpoints, based on categorizing the study population by

severity of stroke, were modeled after the cutpoints used in the reanalysis of the NINDS tPA stroke trials data and the ABEST-II trial. [3,4]

3.2 Secondary Efficacy Outcomes

This study is designed to test the primary hypothesis. However, it also offers the opportunity to conduct analyses to evaluate important additional neurological and functional outcomes using the NIH Stroke Scale (NIHSS), Barthel Index (BI) and Stroke Severity Quality of Life (SSQOL).

3.3 Primary Safety Outcome

The primary safety outcome is the proportion of subjects experiencing at least one severe hypoglycemia event (<40 mg/dL) during treatment.

4. SAMPLE SIZE DETERMINATION FOR THE PRIMARY EFFICACY OBJECTIVE

4.1 Sample Size Estimation

The primary outcome variable is the overall proportion of subjects experiencing a favorable outcome 90-days post randomization, where favorable is defined by the dichotomized mRS score as adjusted to the baseline NIHSS (stroke severity). Our preliminary data suggest a 25% rate of favorable outcome in the control group at 90 days is reasonable. A clinically relevant absolute difference in success rates between the two interventions is chosen as 7% (success $rate_{control}$=25%; success $rate_{infusion}$=32%). If the IV insulin group does not have at least a 7% or higher success rate than the control group, then IV insulin within 12 hours of symptom onset will not be considered a worthwhile therapy for hyperglycemic acute ischemic stroke patients.

Based on the above information and taking into consideration four planned interim analyses (see Section 10.1.4 for details), the study is powered to assure 80% likelihood of identifying a difference in success rates greater than or equal to 7%. Sample size estimation is based on the comparison of independent proportions adjusting for baseline NIHSS. The maximum sample size required for randomization is 1314 subjects (657/treatment group). Although every attempt will be made to avoid drop outs and losses to follow up, the required sample size is inflated for a 3% non-adherence rate. The total number of patients required for randomization is 1400.

4.2 Sample Size Re-estimation Plan

We recognize that sample size estimation is based on assumptions and if the control success rate is higher than 25% then we may begin to see a decrease in power. For example, if the control rate is as high as 30%, the power drops from approximately 80% to 77% to detect a 7% absolute difference if one truly exists. To reduce the likelihood of an underpowered study due to an incorrect overall event rate assumption, we propose to conduct a sample size re-estimation prior to the 1st interim efficacy/futility analysis (i.e., once 500 consecutively randomized subjects complete the 90-day mRS). The overall success rate of the population will be estimated using the interim data for the sole purpose of sample size re-estimation (not for interim testing of a treatment effect). Combining sample size re-estimation with the proposed group sequential design (GSD) will improve two aspects of the design – misspecification of the overall event rate (N-reestimation) and misspecification of the treatment effect (GSD) – while preserving the overall type I error rate. In addition, the

GSD will help protect from unnecessarily continuing the trial even if the re-estimation suggests a larger overall sample size.

Following the approach of Gould and Shih[5], sample size adjustment will be based on the observed overall event rate assuming a 7% absolute difference between treatment arms (the value specified under the alternative hypothesis). If the observed overall event rate is greater than the assumed, then we may require additional observations. The below table provides various hypothetical scenarios of the observed event rate and the required additional observations to maintain 80% power.

Observed Overall Event Rate	Estimated Control Rate (assuming 7% difference)	Power if No N-Adjustment	Additional Total N Required to Maintain Power at Final Analysis	N for 1st interim analysis	Delay of 1st interim look (months)*
0.265	0.23	82%	-	500	0
0.285	0.25	81%	-	500	0
0.305	0.27	79%	58	522	<1
0.325	0.29	78%	108	540	1-2
0.345	0.31	77%	154	554	1-2
0.365	0.33	76%	194	570	2-3
0.385	0.35	75%	228	582	2-3

*assuming accrual rate of 33.3 patients per month

If the sample size needs to be inflated, then we will preserve the information times for carrying out the interim analyses by deferring planned analyses until we have additional observations for each look (Strategy A of Gould and Shih). The fifth column of the above table specifies the sample size for the 1st look depending on the observed event rate detected at the sample size re-estimation. An alternative approach would be to conduct the 1st interim look as planned (at n1=500) and defer the additional observations to the future looks. If we proceed in this manner, the statistical boundaries require updating to correspond with new information times. Since the delay of the interim analysis is no more than 3 months for any of the above scenarios, we choose to maintain the current information times.

Because the trial's power is not substantially impacted if the overall observed rate is 0.26-0.30, it is suggested that the recommendation to increase the original sample size only be considered if the observed rate is 0.31 or higher. Ultimately it is the DSMB's decision to recommend an increase in the total sample size and this decision should take into account the above proposed planned as well as the safety profile. Administratively, prior to the 1st interim analysis the unblinded statistician will estimate the overall observed event rate and notify the DSMB members if the re-estimation indicates the need to increase the total sample size by 150 or more subjects. This notification will include a brief report of the estimate as well as the safety data (adverse event information by treatment arm) and data quality (protocol deviations by treatment arm). If the DSMB

recommends an increase in the sample size, then the 1st interim analysis will be delayed until the appropriate numbers of subjects are enrolled and have the primary outcome data. If the DSMB does not recommend an increase, then the unblinded statistician will proceed with the planned interim analysis.

5. DEFINITION OF TARGET POPULATION AND STUDY SAMPLES

5.1 Target Population

The target population for the SHINE trial is patients 18 years of age and older who have a clinical diagnosis of ischemic stroke and a known history of type 2 diabetes mellitus and glucose >110 mg/dL or admission blood glucose ≥150 mg/dL in those without known diabetes mellitus.

5.2 Intent-to-Treat Sample

As the primary analysis, all efficacy and safety outcome measures will be analyzed under the intent-to-treat principle (ITT). Under this principle, the evaluable sample includes all subjects who are randomized. Each subject will be analyzed according to the treatment group to which they were randomly assigned at the time of randomization.

5.3 Safety Analysis Sample

All randomized subjects are included in the safety analysis sample.

5.4 Per Protocol Sample

In addition to the defined ITT analysis sample, a per protocol sample is defined as a subset of the ITT sample. This sample will be used for secondary sensitivity analyses of the primary and secondary outcomes. The per protocol will include all randomized subjects that do not have the following protocol deviations:

- Eligibility violation
- Treatment never started
- Missing 90-day primary outcome (not including missing due to death prior to the 90 days)
- Stroke mimics defined as any diagnosis other than ischemic stroke or TIA

6. RANDOMIZATION

A web-based central randomization system will be developed by the SDMC and installed on the WebDCU™ SHINE study website using a combination of covariate balance and response-adaptive randomization (RAR) method.[6] The randomization design is aimed to preserve the randomness of treatment assignment, prevent serious imbalance in important baseline prognostic variables and promote subject recruitment while preserving the statistical test power. In summary, the probability of treatment assignment under the

proposed scheme will be based on the prevention of serious imbalance in the pre-specified prognostic variables and the favorable outcome rate of each treatment arm. The specific prognostic variables at the time of randomization are: baseline NIHSS strata (3-7; 8-14; 15-22); use of IV thrombolysis (Y/N); and, site. Favorable outcome will be based on the baseline severity adjusted dichotomized mRS as previously described.

The SHINE Randomization algorithm will be fully detailed and documented in the SHINE Randomization Plan and Validation Documents. These documents will be developed prior to the enrollment initiation and stored in a secure location at the SDMC. The documents will be archived with the study database at the end of the trial. In summary, the trial will start with a 1:1 allocation scheme focusing on covariate balance. The RAR will be implemented once an adequate amount of primary outcome information is collected. With RAR, each enrolling subject will have a higher probability (greater than 50% chance) of being assigned to the treatment arm with the higher success rate based on previous subjects' responses. The SDMC's computer system will run both the 1:1 allocation and the RAR. Participating sites and members of the study team will not notice any difference between the randomization schemes and sites will only need to press one randomization button on the computer screen to obtain the assigned treatment during the course of the study. To ensure proper randomization, the unblinded statistical programmer will have access to the randomization information in order to oversee the quality control of the computer program.

7. BLINDING

The study is conducted in a single blind manner with double blind outcome assessment. The site treatment team will be unblind to treatment assignment however the study subject and 90-day outcome assessor are both blind to the treatment assignment. Treatment allocation is concealed and subjects will not be told of their actual treatment until the trial completion unless emergency unblinding is required.

The SDMCs unblinded staff will produce two identical sealed envelopes that contain identification of treatment codes. Prior to initiation of the Trial, one envelope of (2) is given to the NINDS Liaison to the DSMB. Another is maintained in a locked file cabinet at the SDMC in its limited access central file room.

The DSMB is partially unblinded for the closed reports (data reported by A and B only). However, if it so wishes, it may be completely unblinded at any time during the Trial. If the DSMB wishes to be unblinded on a particular subject only, the NINDS Liaison to the DSMB should email the request to the unblinded SDMC biostatistician.

8. MISSING DATA

Under the ITT principle, all subjects who are randomized are included in the analysis. Although every attempt will be made to prevent incomplete data, a certain amount of missing data is inevitable due to losses to follow up or withdrawn consents. The investigators also need to consider primary outcome data that is collected late (i.e., past the pre-specified data entry timelines of +/-14 days). Based on discussions with the SHINE Executive Committee and clinical expertise, primary outcome data (i.e., 90-day mRS) collected past the data entry timelines will only be used for the primary analysis if the collection falls within -14 days/+30 days from the scheduled date. Data collected

outside the 30-day window (only allowed up to 180 days to collect data) will be considered missing for the primary outcome.

A thorough analysis of variables, reasons and patterns of missing data will be conducted. Based on other large acute stroke trials that capture 90-day mRS, we anticipate no more than a 3% lost to follow up rate. At the time of each planned analysis (interim and final), the unblinded statistician will report the amount of missing primary outcome data. Multiple imputation using SAS PROC MI and MIANALYZE will be used to impute the missing 90-day mRS outcome data. In summary, 5 imputed data sets will be generated using PROC MI. The imputation model will include the primary analysis variables (90-day mRS, treatment, baseline NIHSS, thrombolysis use) plus age, gender and 6-week mRS. Each imputed data set will be analyzed according to the specified primary analysis (Section 10.1.2) and MIANALYZE will be used to combine the results from the multiple imputed data sets to obtain a single set of parameter estimates. The multiple imputation method assumes missing at random (MAR) which means that the probability of missing outcome data can depend on the observed values of the individual but not on the missing values of the individual. Although we anticipate minimal missing data, sensitivity analyses will be conducted to assess the impact of any bias due to missing data. The primary analysis will be re-run using the following methods:

- Complete case analysis (only those with 90-day outcome)
- Worst case analysis (assume any subject with missing 90 day outcome to be considered a 'failure')
- Inclusion of primary outcome data collected outside the defined window

If the treatment effect is robust, we expect these sensitivity analyses to yield similar inferences, particularly if the missing data are minimal (~3%). Any discrepancies between the sensitivity analyses and the primary analysis results will be investigated to understand the reason for the discrepancy.

9. CLINICAL SITE EFFECTS

Several procedures have been incorporated into the study design (i.e., procedure manual, training and certification programs, protocol violation monitoring, blinding) to reduce center effects; however, these effects should not be ignored for this trial. The distribution of center demographics will be examined. Means, standard deviations, proportions and 95% confidence intervals will be presented. Center and center*treatment interaction terms will be included in a secondary analysis of the primary outcome as a random effect.

10. EFFICACY ANALYSIS

10.1 Primary Outcome Variable Analysis

10.1.1 Statistical Hypothesis

The set of statistical hypotheses is:

$$H_0: \text{b coefficient}_{\text{treatment}} = 0 \quad \text{versus} \quad H_A: \text{b coefficient}_{\text{treatment}} \neq 0$$

where b coefficient$_{treatment}$ is the regression coefficient for the variable 'treatment' .

10.1.2 Primary Efficacy Analysis at the End of the Trial

The primary outcome analysis of the 90-day mRS will use a stratified dichotomy methodology for assessing improvement as defined in the Primary Outcome section above. Outcome differences will be analyzed under the intention-to-treat principle, therefore all randomized subjects will be included in the primary analysis sample. To assess efficacy, the treatment groups will be compared with respect to the proportion with favorable outcome 90 days post randomization after controlling for the variables included in the randomization scheme. The primary statistical analysis will develop a generalized linear model using the PROC GENMOD procedure in SAS® v9 with treatment group as the factor of interest and baseline NIHSS strata (3-7, 8-14, 15-22) and thrombolysis use (Yes/No; includes both IV and IA therapies) as covariates. A Wald chi-square test will be performed to compare the treatment group proportions using a two-tailed significance level of 0.05. Adjusted relative risks will be reported with two-sided 95% confidence intervals. Additional analyses will identify potential confounding (prognostic) variables to be used as covariates in subsequent secondary analyses of the primary outcome. Specific covariates include age, gender, race, ethnicity, admission blood glucose, previous stroke, lacunar subtype, and time between stroke onset and treatment. If statistically significant differences are evident, then post-hoc analyses will be conducted to determine if differences had an effect on the conclusions from the pre-specified primary analysis.

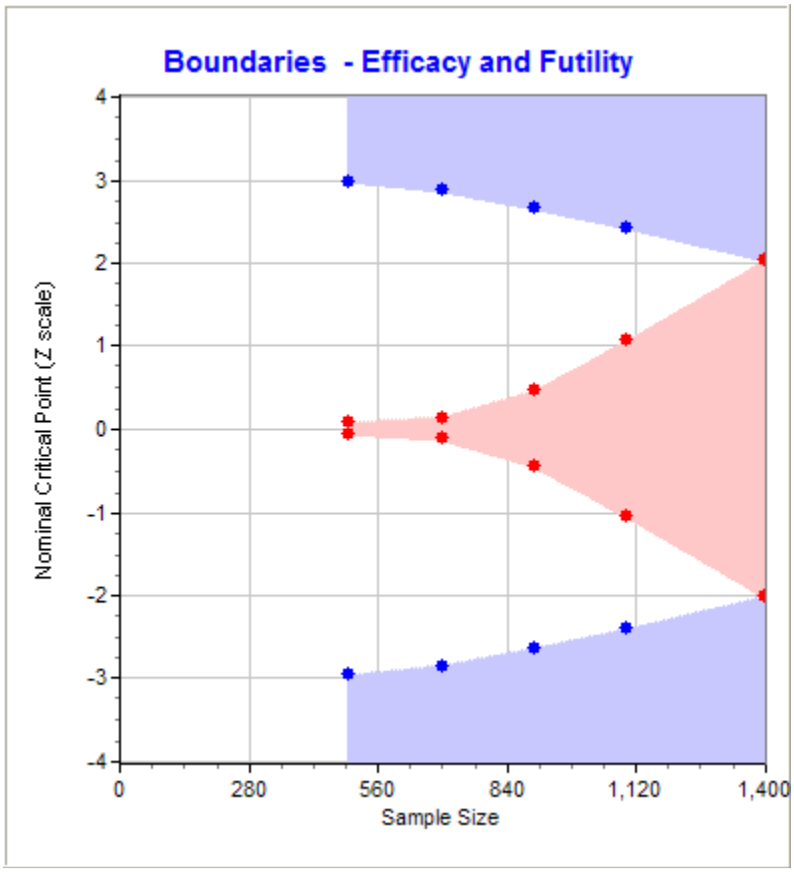
10.1.3 Interim Analysis Plan

The study is designed using four interim looks for both efficacy and futility of the primary outcome and one final look for a total of 5 planned analyses of the primary outcome. The interim analysis plan uses the error spending function method with O'Brien and Fleming (OBF) type stopping guidelines[7-9]. The error spending function distributes the type I and II error rates across the interim monitoring points giving the flexibility of changing the intervals of monitoring while still preserving the overall type I and II error rates. The OBF-type boundary is considered conservative as its boundaries make it difficult to terminate a study early on by requiring extreme early evidence of efficacy or futility. It spends smaller amounts of alpha at the first look and gradually increases the spending as more information is acquired. The trial may be stopped for overwhelming efficacy of one treatment group over the other or for futility at the planned interim analyses if the test statistic crosses the respective boundaries.

The current plan is to conduct the first interim analysis after approximately 500 randomized subjects complete the primary outcome assessment (90-day mRS). Assuming an accrual rate of 33.3 patients per month, it is anticipated that the 1st look will occur roughly 2.5yrs from the start of enrollment. Subsequent analyses will occur after every additional 200 subjects complete the 90-day mRS (i.e., 700, 900, and 1100). The interval may be altered if requested by the DSMB. The stopping boundaries are defined using the gamma family spending functions with a gamma value of -4 (closely resembles OBF boundaries)[10]. Specific to the futility boundaries, they are derived as non-binding meaning that if a futility boundary is

crossed there is the ability for it to be overruled without inflation of the type 1 error rate. If the crossing of an efficacy boundary is overruled, then this decision can impact the type II error rate but not the type I error rate. EAST® 5 software (Cytel Corporation) was used for the boundary calculations.

The below graph depicts the stopping boundaries based on the test statistic at each planned look. The inner wedge represents rejection of the alternative (futility) and the outer boundaries represent rejection of the null (overwhelming efficacy). The boundaries have the property that under the null hypothesis of no difference the overall probability of crossing either outer boundary does not exceed the overall type I error rate and under the alternative hypothesis the overall probability of crossing the inner boundary does not exceed the type II error rate.



The following table lists the test statistics (shown in the above graph) and the corresponding p value as well as the probability of crossing either of the boundaries (futility or efficacy) at a particular look. Using the 5th column as an example, under the null hypothesis of no difference, the probability of crossing the specified boundary for either efficacy or futility is 0.05 at the 1st look, 0.10 for

the 2nd look and so forth. Overall the probability of stopping the study (for futility) by the 4th look is 0.75 under the null and 0.66 under the alternative (stopping for efficacy).

Analysis	Approximate Sample Size	Minimum Test Statistic Z value (p value) to reject H_o	Minimum Test Statistic Z value (p value) to reject H_a	Boundary Crossing Probabilities Under H0	Boundary Crossing Probabilities Under H1
1	500	2.97 (0.003)	0.06 (0.949)	0.05	0.12
2	700	2.86 (0.004)	0.13 (0.896)	0.10	0.13
3	900	2.65 (0.008)	0.45 (0.652)	0.27	0.19
4	1100	2.42 (0.016)	1.05 (0.293)	0.33	0.22
Final	1400	2.02 (0.043)	2.02 (0.043)	0.25	0.34

The SDMC will be responsible for conducting these analyses and compiling the reports for the DSMB. Since several factors need to be taken into consideration before stopping a study, safety and study progress also will be taken into consideration by the DSMB and Executive Committee in the decision to stop the study if an efficacy or futility boundary is crossed.

10.2 Secondary Outcome Variable Analysis

This study is designed to test the primary hypothesis. However, it also offers the opportunity to conduct analyses to evaluate important additional neurological and functional outcomes using the NIHSS, BI and SSQOL. All secondary analyses will be conducted using the intention to treat study population. Favorable outcomes for the NIHSS and BI are defined as: a score of 0 or 1 on the NIHSS and a score of 95-100 on the BI at 90 days post randomization. Because there are only three secondary efficacy outcomes, adjustment for multiplicity will not be made. Each of these dichotomous outcomes will be analyzed using a chi-square test at a significance level of 0.05. With a study sample size of 1400, we have 80% power to detect absolute differences in favorable outcome for the: NIHSS of 7% (assuming control group is 25%) and BI of 8% (assuming control group is 40%). The SSQOL 90-day score will be analyzed as a continuous outcome. Mean scores overall and for each domain will be compared between the two treatment arms, adjusting the alpha level for multiple testing. Secondary analyses of all secondary outcomes will adjust for the specific covariates that are listed above in the primary analysis section as well as additional covariates identified at the time of analysis.

In addition to the above clinical outcomes, we also will examine/compare blood glucose measurements over time as well as protocol conduct metrics between

treatment arms: time to target, time in target, early/late time to treatment and adherence to the computerized glucose monitoring system.

Secondary Outcome	Definition	Descriptive Statistics
Time to Target	(Randomization Time – Time Target is met (hrs)); target met defined as BG of 70-180 in the control arm and BG of 70-130 in the treatment arm.	Two-sided 95% confidential intervals; means, Comparison of means between treatment arms.
Time in Target	Blood Glucose Measurements During Treatment	Proportion of measurements out of target; area under the curve; box plots over time (every 4hrs) by treatment arm and by primary outcome.
Time to Treatment	Randomization Time - Stroke Onset Time (hrs)	Comparison of means between treatment arms.
Time on Treatment	Randomization Time – Infusion stop time (Form 15)	Comparison of means between treatment arms.

10.3 Exploratory Analyses

A sensitivity analysis of the primary outcome will be conducted using the per protocol population (as defined in Section 5.4). In addition, a sensitivity analysis of including TIAs in the stroke mimic definition will be conducted for the per protocol analysis. If discrepancies between the results exist, reasons for the differences will be explored. At the end of the study, study investigators may wish to explore other relationships between the treatment and outcomes and/or covariates. Because the number of subgroup analyses could be large, all subgroup analyses will be conducted using a two-tailed significance level of 0.01. The Publication Committee of the SHINE Trial will review proof of concept papers with analysis plan submitted by any investigators wishing to do so before any further analyses are conducted by the study statisticians.

11. SAFETY ANALYSES

11.1 Safety Monitoring

The safety monitor and DSMB will receive periodic safety reports of all adverse events and serious adverse events. Statistical monitoring for safety will be limited to subjects experiencing a severe hypoglycemia event (<40 mg/dL) during the treatment period and death rate within 90 days post randomization. It is anticipated that the respective event rates in the control arm will be 0% for severe hypoglycemia and 14% for death. For severe hypoglycemia, the absolute difference in event rates between the two treatment arms will be monitored using two-sided 95% confidence intervals. Stopping the trial due to harm will be considered if at any time the lower limit of the severe hypoglycemia interval exceeds 4%. For death rate, an unadjusted

relative risk will be estimated. Stopping the trial due to harm will be considered if at any time the 95% confidence interval excludes 1. These point estimates will be provided in each DSMB Closed Report. The table below provides different scenarios of when the boundary for safety may be crossed.

Severe Hypoglycemia Events				
N per group	Total Subjects with Event in Control Arm (%)	Total Subjects with Event in Exp Arm (%)	Risk Difference (Δ)	Lower Limit of 95% CI for Δ
50	0 (0)	7 (14)	14	4.4
50	1 (2)	9 (18)	16	4.7
100	0 (0)	10 (10)	10	4.1
100	2 (2)	14 (14)	12	4.7
200	0 (0)	16 (8)	8	4.2
200	4 (2)	22 (11)	9	4.2
500	0 (0)	31 (6.2)	6.2	4.1
500	10 (2)	45 (9)	7	4.2
700	0 (0)	41 (6)	6	4.1
700	14 (2)	59 (8.4)	6.4	4.1

Death Events				
N per group	Total Subjects with Event in Control Arm (%)	Total Subjects with Event in Exp Arm (%)	Unadjusted Relative Risk	Lower Limit of 95% CI for RR
50	5 (10)	14 (28)	2.8	1.09
50	7 (14)	17 (34)	2.4	1.10
100	10 (10)	22 (22)	2.2	1.10
100	14 (14)	27 (27)	1.9	1.08
200	20 (10)	35 (17.5)	1.8	1.05
200	28 (14)	45 (22.5)	1.6	1.05
500	50 (10)	74 (15)	1.5	1.06
500	70 (14)	98 (20)	1.4	1.06
700	70 (10)	99 (14)	1.4	1.06
700	98 (14)	132 (19)	1.4	1.06

11.2 Analysis of Safety Outcomes

All adverse events and serious adverse events will be summarized by AE code in terms of frequency of the event, number of subjects having the event, severity, expectedness (anticipated/unanticipated) and relatedness to the study treatment. Clinically important adverse events including neurological worsening lasting greater than 24hours and associated with glucose concentration of < 55mg/dL and severe hypoglycemia (glucose <40 mg/dL) will be summarized. The proportion of subjects experiencing each of these events will be provided by treatment arm with two-sided 95% confidence intervals and unadjusted relative risks will be provided.

In addition to the continual monitoring of adverse events by the safety monitor and DSMB and the planned statistical monitoring for safety (described above), final analyses of specified safety outcomes will be conducted. The proportion of subjects experiencing severe hypoglycemia during the treatment period will be compared between the two treatment arms using Fisher's exact test. For the 90-day death outcome, the log-rank test will be used to compare survival curves between the two treatment arms. Providing the assumption of proportional hazards is valid, a Cox proportional hazards model will be used to analyze time to death within 90 days from randomization adjusting for use of thrombolysis treatment, baseline NIHSS score and age. All tests for safety will use a two-tailed significance level of 0.05.

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