# PLATELET-ORIENTED INHIBITION IN NEW TIA AND MINOR ISCHEMIC STROKE (POINT) TRIAL

# STATISTICAL ANALYSIS PLAN

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# 1 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| CRF | Case Report Form |
| DCR | Data Clarification Request |
| DCU | Data Coordination Unit |
| DSMB | Data Safety and Monitoring Board |
| FASTER | Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence |
| GCP | Good Clinical Practice |
| HR | Hazard Ratio |
| ITT | Intent-to-Treat |
| MI | Myocardial Infarction |
| NETT | Neurological Emergencies Treatment Trials |
| NIHSS | National Institutes of Health Stroke Score |
| NINDS | National Institute of Neurological Disorders and Stroke |
| POINT | Platelet-Oriented Inhibition in New TIA and minor ischemic stroke |
| SAE | Serious Adverse Event |
| SDMC | Statistical and Data Management Center |
| TIA | Transient Ischemic Attack |

# 2 STATISTICAL ANALYSIS PLAN AND STATISTICAL REPORTS

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

The NETT SDMC will generate Data and Safety Monitoring (DSMB) Reports semiannually or more frequently upon request by the DSMB. Each semiannual report provides cumulative summary statistics on enrollment; subject status in the study (e.g., number completed day 7 and day 90 assessments); baseline characteristics; protocol violations; safety data, including coded SAEs, clinical outcomes data (with primary outcomes following the interim analysis schedule listed in section 12.2); and data management/quality information (e.g., timeliness and completeness of data entry by the clinical centers via the POINT Trial web-enabled clinical trials management system (WebDCU™); number of data queries generated and resolved). For all safety data, tables or figures will be stratified according to index event type: either TIA or minor stroke. The statistics for the 'Closed Session' DSMB Reports are provided by treatment group (partially blinded). The 'Open Session' DSMB report contains aggregated statistics only, i.e., not by treatment group. If a semiannual report coincides in timing with a planned interim analysis, the analysis results are appended to the report.

# 3 OBJECTIVES OF THE STUDY

## 3.1. Efficacy

The primary objective of the POINT Trial is to determine the effectiveness of clopidogrel (a loading dose of 600 mg followed by 75 mg/day) over placebo when initiated within 12 hours of time last known free of new ischemic symptoms in patients receiving aspirin therapy at 50-325 mg/day. The primary efficacy hypothesis is that event-free survival at 90 days is higher in subjects treated with clopidogrel+aspirin than in subjects treated with placebo+aspirin, when randomized within 12 hours of time last known free of new ischemic symptoms. The primary outcome measure for this hypothesis is the composite event of ischemic stroke, MI, or ischemic vascular death.

## 3.2. Safety

The safety of clopidogrel when compared to placebo is evaluated by comparing rates of all-cause death, intracranial hemorrhage, major hemorrhage, minor hemorrhage, and other treatment related complications and SAEs (see section 13.2).

**The primary safety outcome is major hemorrhage.** Major hemorrhage is one that results in symptomatic intracranial hemorrhage, intraocular bleeding causing loss of vision, need for transfusion of two or more units of red cells or equivalent amount of whole blood, need for hospitalization or prolongation of an existing hospitalization, or death. This may include bleeding events related to surgical procedures.

# 4 STUDY DESIGN

The study is of a two-arm parallel design whereby eligible subjects are randomized in a 1:1 ratio to either the clopidogrel group or to the placebo group. Each subject is followed for 90 days from randomization.

# 5 SAMPLE SIZE CONSIDERATIONS

## 5.1 Sample Size Determination for the primary efficacy Analysis

The minimum necessary sample size in the trial is established by the requirement to detect the smallest expected, clinically meaningful treatment difference comparing the treatment with placebo. A relative risk reduction of 23% is the smallest difference felt to be of clinical importance. The total sample size for the study is 4,150 subjects (rounded up from 4,142). With a sample size of 4,150 patients, with 530 events, the study will have 90% power to detect a relative risk reduction of 23% with a two-sided alpha of 0.05. The sample size was estimated based on a hazard ratio (HR) of 0.75 (equivalent to RRR of 23%) assuming an exponential survival distribution (assuming the proportion of patients with events in the placebo group is 0.1524 at 90 days), with inflation to account for two interim analysis for efficacy at equal intervals using O'Brien and Fleming stopping boundary using the Lan-Demets spending function and inflation for lost-to-follow-up and/or crossover. The intent-to-treat (ITT) principle is applied to the analysis, and therefore, we inflated the sample size to safeguard against lost-to-follow-up

and/or crossover in the actual treatment received, which may dilute the effect size. From FASTER there were 12% crossovers and 2% losses to follow-up [8]. Most events will occur early in the follow-up period and hence a smaller fraction of events will be lost and a smaller total correction in sample size is required (5.0%). Details regarding the sample size calculation are provided in Table 1.

**Table 1. Assumptions and Specifications Used to Calculate Sample Size**

| | |
|---|---|
| Proportion with events at 90 days in placebo (aspirin) group | 15.24% |
| Relative risk reduction (reference: placebo+aspirin group) | 0.23 |
| Hazard Ratio | 0.75 |
| Delay between symptom onset and enrollment | 12 hour |
| Loss to follow-up at 90 days (from FASTER) | 2% |
| Crossovers at 90 days (from FASTER, non-event related) | 12% |
| Impact of crossover on events | 29% |
| Inflation factor for crossovers and losses if events at 90 days | 31% |
| Modeled inflation factor to account for crossovers/losses | 5.0% |
| Power | 0.90 |
| Total alpha (2-sided) with 2 interim analyses | 0.05 |

Given the uncertainty in the assumptions used to predict effect size and event rates, we have chosen a sample size to provide 90% power. With this sample, we will have 80% power to detect a relative risk reduction of 19%. Further, we will have 80% power if the placebo event rate is 23% lower than projected (see Figure 2) or early losses to follow-up are 4-times more frequent than anticipated. Power curves are shown below:

**Figure 1. Minimum Detectable Relative Risk Reduction for 90% Power by Placebo Event Rate by Total Sample Size**

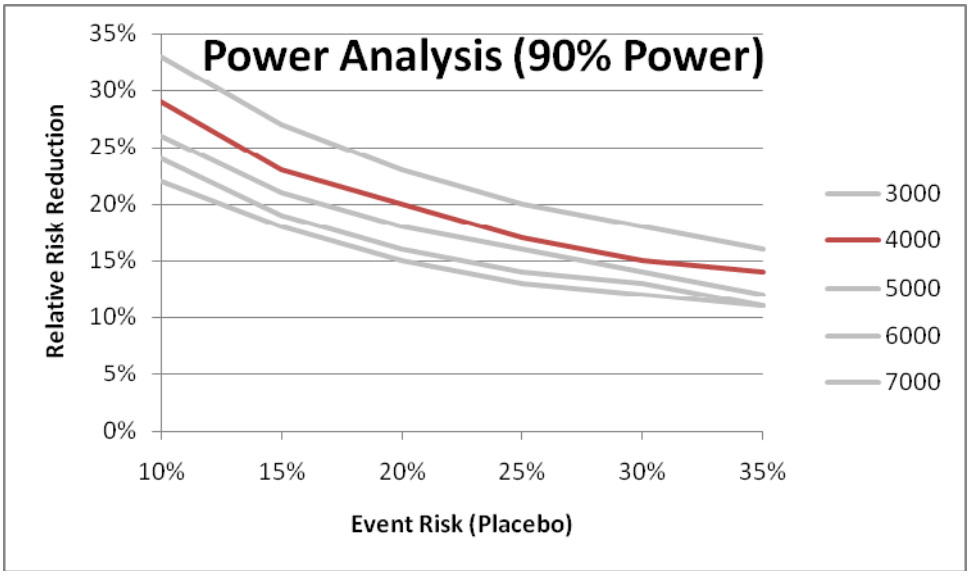
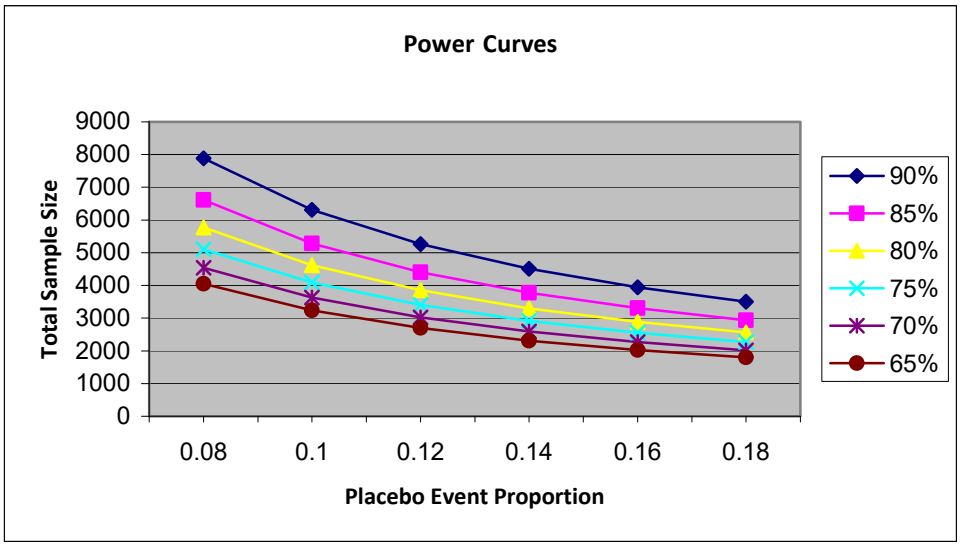


**Figure 2. Total Sample Size Needed by Placebo Event Proportion by Power**




### 5.2 Re-estimation of the Sample Size

If after 4,150 patients have been enrolled, less than 530 events have been observed, then power will be reduced. This could happen, for example, if the event rate is lower than expected in the minor stroke cohort. The power is defined by the total number of events, which depends only on the hazard ratio. For a given sample size, a decrease in event rates (overall), assuming a fixed hazard, will decrease power.

The sample size re-estimation should be based solely on the placebo event rate (not the observed difference in treatment groups). The assumed placebo rate is 15.24% with a 95% CI (13.63%, 16.85%) based on a sample of 1907 TIA patients from KPNC. At the time of the first interim analysis when approximately 1/3 of the expected number of events (177) are observed, if the one-sided upper 99% confidence limit around the observed placebo rate does not overlap with those of the assumed rate (Lower 13.63%, Upper 16.85%), then the maximum sample size will be re-estimated based on the observed placebo event rate (given a RRR of 23% as originally assumed).

Figure 2 gives the total sample size needed for a given placebo event rate at various powers. Some scenarios for stopping the trial early versus increasing the sample size are given in section 12.5 as a guide for the DSMB. The DSMB's decision to recommend an increase in the total sample size would take into account the likelihood of success of the trial using the other interim monitoring criteria (see section 12.4 for a flow chart) as well as the safety profile.

### 5.3 Re-estimation of the Sample Size Result

As stipulated in **section 5.2,** following the first interim analysis, the maximum sample size has been re-estimated to be 5,840 subjects.

## 6 DEFINITION OF TARGET POPULATION AND STUDY SAMPLES

### 6.1. Target Population

The target population to which the clopidogrel treatment regimen may be applied are patients 18 years of age or older with high-risk TIA (defined as an $ABCD^2$ score $\geq$ 4) or minor ischemic stroke (with NIHSS $\leq$ 3) who can be randomized within 12 hours of time last known free from new ischemic symptoms.

### 6.2. Intent-to-Treat Sample

As the primary analysis, all efficacy and safety outcome measures are analyzed under the intent-to-treat (ITT) principle. Under this principle, the evaluable sample includes all randomized subjects, except for re-enrollers. Re-enrollers are patients who are determined to have been enrolled into the POINT trial more than once. For re-enrollers, only the data associated with the first enrollment will be counted in the primary analysis.

### 6.3. Safety Analysis Sample

All randomized subjects are included in the safety analysis sample, regardless of the amount of treatment administered.

## 7 RANDOMIZATION

The randomization will take place centrally via WebDCU™. Subjects will be randomized 1:1 (clopidogrel: placebo), controlling for clinical site using the blocked-urn method.

The detailed randomization scheme and source codes will be provided in the Randomization Plan document. Although a randomization scheme with any constraints would yield some bias in the inferences from using standard analytic methods, Efron (1971) shows the appropriateness of standard statistical tests under the biased coin randomization in large studies. Friedman et al (1998 p. 72) note that the variance terms under the biased coin design tend to be larger than under simple randomization. The consequence is that it would be more difficult to reject the null hypothesis, and therefore, we would be more conservative in determining the significance of the effectiveness of the treatment.

A "Real-Time" randomization procedure is implemented via the WebDCU™ system where the clinical center staff enters the eligibility information of a subject prior to enrollment. If the subject's eligibility status is confirmed, the computer program on the WebDCU™ server will evaluate the treatment arm distribution and generate a study number based on the randomization scheme. The study number will correspond to a specific medication bottle that will be already at the clinical center.

## 8 BLINDING

The study is conducted in a double-blind manner. The placebo for clopidogrel will be identical in appearance and taste. Minor side effects are unusual with the medication, so it is not anticipated that either subjects or clinicians will be able to differentiate the placebo from the active drug. Standard laboratory tests cannot detect the effects of clopidogrel.

# 9 MULTIPLICITY

The primary efficacy hypothesis is tested with the log-rank test for equality of survival curves. This hypothesis is tested with a two-sided 0.05 level of significance.

For secondary outcomes, we will not account for multiplicity. These analyses are merely supportive and exploratory and will be interpreted as such. The overall trial hinges on the primary analysis and interpretation of secondary results is already tempered by their placement. Accounting for multiple testing would also increase the risk that an interesting finding is not subsequently pursued.

# 10 MISSING DATA

Based on the FASTER (Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence) trial, it is anticipated that there would be minimal (2%) loss to follow up for the 90-day assessment of the primary outcome. All efforts should be put forth to ensure near complete follow-up, in particular with the assessment of the primary outcome (time to the composite event of ischemic stroke, myocardial infarction, or ischemic vascular death) and occurrence of death.

Nevertheless, minimal missing data may be inevitable. Since all randomized subjects are included in the primary efficacy outcome analysis, subjects missing outcome data will be censored at the last follow-up assessment time (end of study or last visit preceding loss to follow up). Missing mRS data will be imputed by carrying forward mRS from event visits or by regression imputation.

# 11 MONITORING AND EVALUATION OF CLINICAL CENTER EFFECT

On a semiannual basis, the HR of the treatment effect on outcome measures (efficacy or safety) and its 95% CI are calculated for each clinical center and for all sites combined, and they are graphed in one figure to determine whether any sites are uniquely different from the others or from the overall group. Furthermore, a plot of HRs (y-axis) by number of subjects enrolled at each site (x-axis) is generated. The expectation is that the plot should appear like a funnel where the smaller the number of subjects enrolled, the greater the variability. This graph also assists us in determining where, if any, outliers are with respect to the sites. If any outliers are detected, further investigation into the reasons is made to ensure that the trial conduct at those sites is in accordance with the protocol and GCP Guidelines. These figures and graphs are included in the closed DSMB reports.

Inclusion of clinical center effect in the efficacy analysis is discussed in Section 12.1.4 below.

# 12 EFFICACY ANALYSIS

## 12.1. Primary Outcome Variable Analysis

### 12.1.1. Primary Outcome

The primary efficacy outcome measure is the composite event of ischemic stroke, myocardial infarction, or ischemic vascular death within 90 days. These events will be adjudicated by the Adjudications Committee.

### 12.1.2. Statistical Hypothesis

The set of statistical hypotheses can be stated in terms of hazard functions as:

$H_0: h_c(t) = h_p(t)$ versus $H_A: h_c(t) \neq h_p(t)$

where $h_c(t)$ and $h_p(t)$ are the hazard rates for the clopidogrel and placebo groups, respectively. The minimum effect size of clinical interest is a relative hazard rate reduction of 25%, or relative risk reduction of 23%. The hazard rate for the placebo group is assumed to be 16.5%.

### 12.1.3. Primary Efficacy Analysis (ITT)

The primary efficacy null hypothesis of the equality of survival curves is tested with the log-rank test. The overall Type I error for the primary analysis will consider two-sided alpha=0.05 significant.

The primary analysis will be intention to treat, with inclusion and treatment group defined at the randomization assignment. Missing values will remain missing and patients will be censored at their last follow-up assessment; based on projected loss rates, it is expected that only 5 subjects will be lost at 7 days and 70 subjects lost at 90 days, so the problem is relatively minor. Kaplan-Meier estimates of the cumulative risk of an event during maximum 90-day follow-up will be reported, with HRs and 95% CI calculated using Cox proportional hazards methods (to provide an estimate of treatment effect) and the log-rank test to evaluate the treatment effect. This approach is being taken to maximize the time dependent information in the trial while still acknowledging the ease of interpretation of risks. For the Cox proportional hazards method, the Efron method will be used when there are ties since this method closely approximates the exact method, but requires less computing resources.

The primary outcome is composite of ischemic stroke, MI, or ischemic vascular death occurring up to 90 days. However, the 90 day visit may occur within +-14 days of the target visit. For patients with an event, the time to event will be the days from randomization to the first adjudicated primary outcome event (if it occurred before 90 days). Events occurring after 90 days (e.g. day 91) will not be counted in the primary analysis. Patients for whom there was no event and whose follow-up visit occurred after day 90 will be censored at exactly 90 days. For patients without a 90 day visit, the censoring date will be determined by the last collected QVSFS (censoring time will be the actual days from randomization). The Kaplan Meier curves will use the actual days up to day 90. For this figure, the “# at risk” will be reported at baseline, 7 days, and 90 days.

Likewise, the ITT analysis will be repeated for the primary and secondary efficacy and safety outcomes.

### 12.1.4. Additional Efficacy Analyses of the Primary Outcome: Adjusting for Clinical Centers (Tertiary Analysis)

Ideally, all prognostic variables used in the randomization scheme should be accounted for in the analysis of the primary efficacy outcome measure. For the POINT Trial, clinical center is included in the randomization scheme; as a result, clinical center should be accounted for in the analysis. However, due to the large number of participating centers (150), a statistical analysis model with center as a fixed effect would yield unstable estimates of the treatment effect, especially if some centers contribute a small number of subjects. Therefore, the center effect is omitted in the primary analysis of the composite event. However, as a secondary analysis, at the end of the study, we plan to analyze the primary efficacy outcome variable adjusted for clustering within center using a robust sandwich covariance matrix estimate to account for the intracluster dependence (proc phreg data=DATA covs(aggregate); id SiteID;). Sites with only 1 enrollment may be collapsed into a single category.

### 12.1.5. Additional Efficacy Analyses of the Primary Outcome: Adjusting for Geographic Region (Tertiary Analysis)

The geographic region of clinical site (classified as US vs Outside US) will be assessed.

### 12.1.6. Additional Efficacy Analyses of the Primary Outcome: Adjusting for Covariates (Tertiary Analysis)

For other exploratory analyses of the primary outcome variable, the composite event is assessed for treatment differences adjusting for a variety of covariates deemed clinically or prognostically important, such as age and time between symptom onset and randomization, whether a brain infarction is demonstrated on an initial scan. These adjustments are made in the form of a Cox proportional hazards model. Each covariate is evaluated individually first with a model that includes an interaction effect with the treatment (clopidogrel or placebo). If a significant interaction ($p<0.10$) is observed, subgroup analyses may be considered (see Section 12.1.7). Quantitative and qualitative interaction between the treatment and each covariate also are visually assessed by graphical methods. A multivariable model that includes covariates that contributed significantly ($p<0.05$) as treatment modifiers individually may then be constructed.

### 12.1.7. Additional Efficacy Analyses of the Primary Outcome: On-Treatment Analyses (Secondary Analysis)

To account for study treatment discontinuations prior to 90 days, the primary efficacy outcome variable will be analyzed while on-treatment only, i.e., those who are known to have permanently discontinued the study drug will be censored one day after the date known to have permanently discontinued the study drug. Furthermore, this survival

analysis of the composite events outcome will analyze all randomized subjects according to the treatment that they actually received (i.e., if they were assigned to receive study drug bottle containing drug A, but due to administrative/enrollment error, received a study drug bottle containing drug B, they would be analyzed with the group they actually received). For the interim analyses, to be included the subject must have been randomized at least 90 days prior to the data freeze.
The treatment effect in this analysis is tested at the two-sided alpha level of 0.05.

Likwise, the As-Treated analysis will be repeated for the primary and secondary efficacy and safety outcomes.

#### 12.1.8. Additional Efficacy Analyses of the Primary Outcome: Subgroup Analyses (Tertiary Analysis)

The primary efficacy outcome variable is analyzed by the following subgroups, assuming sufficient numbers of subjects are enrolled in the subgroups (~10%):

- Index event type: either TIA or minor stroke
- Age (<65 or≥65)
- Gender
- Race/ethnicity
- Hypertension
- Aspirin use prior to randomization
- Statin use prior to randomization
- Imaging evidence of infarction on initial assessment
- Geographic region of clinical site (US versus all other countries)
- Current Smoker (at time of Index Event) versus former/non-smoker
- Severity of index ischemic stroke among those with index ischemic stroke (baseline NIHSS 0,1 vs. 2,3)
- Risk of index TIA among those with TIA (ABCD2 score >5 vs. <=5)
- Time from index event to randomization (<6 hours, >=6 hours)
- 
- Prevailing aspirin dose (This subgroup analysis will be performed for the primary efficacy and primary safety outcome.)

The treatment effect in each of the subgroups is tested at the two-sided alpha level of 0.05.

### 12.2. Interim Efficacy Analysis

For the interim analyses of the composite event for the primary efficacy analysis, O'Brien and Fleming (1979) stopping boundaries are adopted. Assuming that the two interim analyses occur after approximately 177 (1/3 of 530 total events) and 353 (2/3) events have been observed and adjudicated, the nominal alpha levels to reject the null hypotheses for overwhelming efficacy are as follows:

**Table 2. Nominal Critical values and Alpha Levels for Three Interim Analysis for Overwhelming Efficacy (O'Brien-Fleming, $\alpha$=0.05 two-sided)**

| Analysis Order | Number of Events | Nominal critical point (Z-value scale) | Alpha level |
|---|---|---|---|
| 1 | 177 | ±3.710 | 0.0002 |
| 2 | 353 | ±2.511 | 0.012 |
| Final | 530 | ±1.993 | 0.0463 |

Depending upon the DSMB request, additional interim analyses may be conducted. The spending function approach gives flexibility in the timing and frequency of interim analyses. The most current version of the EAST® software (Cytel Corporation) is used as the interim monitoring tool.

At any interim analysis, if we cross the stopping boundary, the DSMB may recommend stopping the study for overwhelming efficacy of one treatment over the other, although the better treatment may not necessarily be clopidogrel. If and only if the stopping boundary is crossed, prior to making the final decision for recommendation to stop the study, it is expected that the DSMB would request thorough analyses of secondary outcomes and subgroup analyses to confirm the findings of the primary outcome results.

### 12.3. Interim Futility Analysis

Futility analyses are planned to be conducted to coincide in timing with the tentatively scheduled interim analyses for efficacy (at three equal intervals of information). However, if the recruitment is much slower than anticipated or if new information from sources external to the study about the clopidogrel treatment becomes available, the futility of the therapy may be assessed earlier or in between planned intervals of interim analyses.

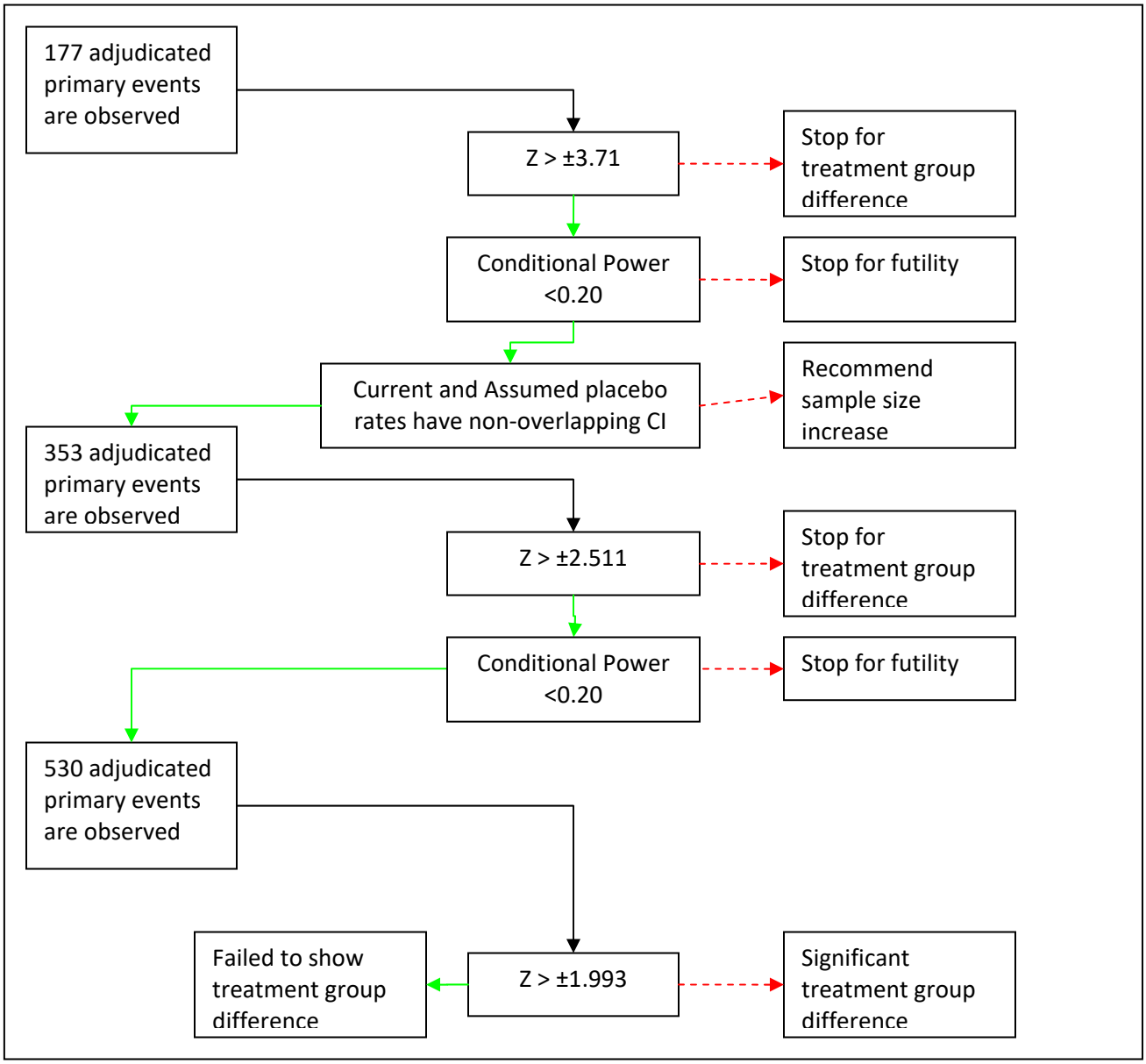
The stochastic curtailment method is adopted based on conditional power (Lan KKG et al, 1982). The informal criterion for determination of futility is that at each interim look, if the conditional power (defined as the probability of rejecting the null hypothesis at the final analysis given the data accumulated so far and under the assumption that the alternative hypothesis under the original design is true) falls below 20%, then the DSMB evaluates all study information (such as overall recruitment rate and secondary outcome assessment data) to consider stopping the study for futility. The evaluation is conducted in a blinded manner.

Evaluation of futility using conditional power allows flexibility in that it can be calculated and assessed at anytime during the study without inflation of the Type I error probability and that the threshold does not necessarily have to be pre-specified. The drawback is that the overall Type II error probability may not be preserved, whereas a formal but less flexible hypothesis testing approach using the beta-spending function for futility boundaries (Pampallona S et al, 2001) does preserve power. However, for the POINT Trial, the flexibility

of this informal approach to assessing futility holds more appeal because it allows other information to be taken into consideration, such as recruitment and safety data and conditional power at other alternative effect sizes (Freidlin B and Korn EL, 2002).

An interim monitoring tool, the most current version of the EAST® software is used to estimate the conditional power.

### 12.4. Interim Monitoring Schematic



## 12.5. Secondary and Tertiary Clinical Efficacy Outcomes Analyses

### 12.5.1. Secondary Analyses

Several secondary analyses will be performed to evaluate of the impact of therapy. Prior to these analyses, univariate analyses of covariates, identified from previous studies as having confounding effect on the outcome measurements, are conducted to determine their inclusion in the multivariable models. In addition, stepwise regression methods may be applied to assess the best set of covariates to include in a particular model. Some of the suspected significant confounders are: age, time from symptom onset to randomization, African Americans, those previously taking aspirin, those with index TIA vs. minor ischemic stroke.

The usual verification of variable and model assumptions and goodness of fit assessments accompany each analysis. Time to event outcomes will be assessed via log rank test (unadjusted) and via cox proportional hazard model adjusting for covariates. A Wilcoxon log-rank test will be used for ordinal outcomes (mRS). A logistic regression will be used for binary outcomes (90 day mRS). The significance of each test is set at a two-sided alpha of 0.05.

ITT analyses and As-treated analyses will be performed for the following secondary outcomes for efficacy/net-benefit:

- Composite event of ischemic stroke, MI, ischemic vascular death, or major hemorrhage
- Ischemic stroke
- Ischemic vascular death
- MI
- Composite event of ischemic stroke and hemorrhagic stroke

ITT analyses and As-treated analyses for efficacy/net-benefit will be performed for the following secondary outcomes for safety/tolerability:

- Primary efficacy outcome from day 0 to 7 and day 8 to 90, and from day 0 to 30 and day 31 to 90 (HR and 95% CI will be calcuated via cox model for each time point stratified)
- Primary safety outcome from day 0 to 7 and day 8 to 90, and from day 0 to 30 and day 31 to 90 (HR and 95% CI will be calcuated via cox model for each time point stratified)
- All-cause Death
- Hemorrhagic stroke
- Symptomatic intracerebral hemorrhage
- Other symptomatic intracranial hemorrhage (SAH, SDH or IVH)
- Major Hemorrhage other than Intracranial Hemorrhage
- All minor hemorrhage (including asymptomatic intracranial hemorrhage)

### 12.5.2. Tertiary Analyses (given sufficient number of events, ≥15 events in total for both treatment arms, are available for analyses to be meaningful)

- Composite of ischemic stroke, MI, all-cause death, or major hemorrhage
- Composite ischemic stroke, TIA, MI, or ischemic vascular death
- TIA (as outcome)

- Coronary Revascularization
- Vascular death
- SAEs together and by major class (MedDRA Body System)
- New handicap/disability defined as 90 day mRS (>=2)
- 90 day mRS (ordinal)
- Asymptomatic intracranial hemorrhage (ICH, SAH, SDH or IVH)

These analyses are used to confirm or support the findings based on the primary outcome analysis. If most of the secondary outcomes show a change in the opposite direction from the primary or no change, we might have less confidence in the primary outcome.

# 13 SAFETY ANALYSES

## 13.1 13.1. Safety Monitoring

The detailed guidelines for monitoring for safety by the Medical Monitor and the DSMB are provided in the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials (http://www.ninds.nih.gov/research/clinical_research/policies/data_safety_monitoring.htm).

To expedite review, safety data will be analyzed by the DSMB as reported by the site investigator, prior to adjudication. The unblinded statistician at the NETT SDMC will produce the reports on a regular basis and at the request of the DSMB.

The DSMB may request an additional interim analysis of efficacy if safety concerns must be balanced against efficacy and may recommend stopping the study prior to the planned interim analysis if, in their judgment, the risk to patients outweighs the benefit of treatment. The final decision to terminate the study will be made by the NINDS, based on the DSMB recommendation.

## 13.2 Summary of Adverse Events

All SAEs are summarized by “preferred term” and associated system-organ class according to the MedDRA adverse reaction dictionary and by treatment group in terms of frequency of the event, number of subjects having the event, timing relative to randomization, severity, and relatedness to the study drug.

For the following specific events, the proportions and their 95% confidence intervals by treatment group are provided:

- Death from any cause within 90 (± 14) days of randomization (expected rate 3%)
- Intracranial hemorrhage within 90 days (expected rate 0.5%)
- Major hemorrhage within 90 days (expected rate 2%)
- Minor hemorrhage within 90 days (expected rate 2%)

Expected rates of these events are based on historical data from the clopidogrel treated patients from pilot cohort studies (Johnston, et al., 2000; 2007), and these expected rates will be presented alongside the actual rates.

Other serious adverse events will be reported by treatment group. At the end of the study, the cumulative incidences of these events are compared between the two treatment groups using Fisher's exact test at the two-sided alpha level of 0.01.

## 14 BIOMARKER ANCILLARY STUDY

As an ancillary study to the POINT Trial, participants will be asked to donate a one-time blood sample collected at time of enrollment in trial; no follow up is conducted. The objective is to determine whether clopidogrel-resistant genotypes modify the stroke prevention response in high-risk TIA and minor ischemic stroke patients.

(1) **PRIMARY OUTCOME**: Relative risk of vascular outcome events for carriers of specific ABCB1 and CYP2C19 genotypes vs. non-carriers among subjects receiving clopidogrel.
(2) **SECONDARY OUTCOME**: Subgroup analysis by enrolling/index event type, performed separately for TIA and minor ischemic stroke cohorts.

Approximately one-quarter to one-third of subjects are expected to be carriers of the CYP2C19 poor metabolizer allele, which has been associated with an increased risk of vascular events with hazard ratios (HR) ranging from 1.5 to 3.6 across studies. Of primary interest is the relative risk of vascular outcome events for carriers versus non-carriers amongst those receiving clopidogrel. Assuming approximately 80% of the remaining POINT patients consent to participate in this proposal, then the total sample contributing to the repository is approximately 2,534 (anticipating that this substudy will start enrolling August 2012). Cox proportional hazard regression will be used to model the time to composite event of ischemic stroke, MI, or ischemic vascular death. The model will be fit using all available data from both treatment groups and will adjust for treatment group (clopidogrel or placebo), allele type (carrier vs non-carrier), and the interaction of carrier and treatment group. From this model, the relative risk (hazard ratio) for carriers receiving clopidogrel relative to the noncarriers receiving clopidogrel (reference group) will be estimated. This model will also adjust for other covariates as specified in section **12.1.5**. The following suspected significant confounders are: age, time from symptom onset to randomization, African Americans, those previously taking aspirin, those with index TIA vs. minor ischemic stroke. A model building approach will be used, considering first the univariate association of each potential confounder. The allele type should have no affect on outcome rates for the placebo group, but the model will be fit with all available data to improve the variance estimates and thus improve statistical power.

Of secondary interest is a subgroup analysis by the enrolling/index event type (either TIA or minor ischemic stroke cohort). The same analysis will be performed separately for the TIA cohort and the minor ischemic stroke cohort.

Given a sample size of approximately 2,534 total, there will be 1,267 patients (1/2) randomized to clopidogrel. Given the expected event rate of 12% in the clopidogrel group, a total of 149 ischemic outcome events are anticipated in the clopidogrel group. Assuming 30% of subjects are carriers of the CYP2C19 poor metabolizer allele, a 0.05 alpha level two-sided log-rank test for equality of survival curves will have at least 80% power to detect a difference between the relative risk for carriers receiving

clopidogrel relative to the noncarriers receiving clopidogrel (reference group) when the true hazard ratio is 1.64. **Table 3** below gives the minimum detectable hazard ratio under various assumptions about the total number of samples available and the proportion of carriers.

| Table 3. Minimum Detectable Hazard Ratios with 80% Power | | | | |
|---|---|---|---|---|
| **Total number of samples in biomarker study** | **Expected N in clopidogrel group** | **Proportion of Carriers** | **Expected number of vascular outcome events** | **Hazard Ratio (HR)** |
| 2534 | 1267 | 0.2 | 152 | 1.76 |
| 2534 | 1267 | 0.3 | 152 | 1.64 |
| 2534 | 1267 | 0.4 | 152 | 1.59 |
| 2534 | 1267 | 0.5 | 152 | 1.58 |

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## 16 APPENDIX: SAMPLE SCENARIOS FOR INTERIM STOPPING VERSUS SAMPLE SIZE INCREASE

**Table A.1 Sample Scenarios for Interim Stopping versus Sample Size Increase at the First Interim Analysis**

| SCENARIO | Observed Placebo Rate (Hypothetical Values) | Upper 99% CL (for observed placebo rate) | Observed Trt Rate (Hypothetical Values) | N at first interim analysis Number at risk | Z-value at 1st Interim Analysis (Stop if \|Z\| > 3.71) | Conditional Power (1/3) under the original design | Re-estimated N at final analysis (530 events) for 90% Power (HR=0.75) | DSMB Recommendations at 1st Interim Analysis | Conditional Power (2/3) under the original design | DSMB Recommendations at 2nd Interim Analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 15.24% | 18.4% | 11.73% | 1383 | 1.89 | 0.94 | N/A | Continue as planned | 0.99 | Continue as planned |
| 2 | 14.0% | 17.1% | 14.0% | 1332 | 0.00 | 0.59 | N/A | Continue as planned | 0.06 | Stop for futility |
| 3 | 14.0% | 17.0% | 12.0% | 1435 | 1.10 | 0.84 | N/A | Continue as planned | 0.74 | Continue as planned |
| 4 | 12.0% | 14.6% | 10.0% | 1696 | 1.32 | 0.88 | N/A | Continue as planned | 0.86 | Continue as planned |
| 5 | 10.0% | 12.4% | 12.5% | 1658 | -1.63 | 0.18 | 6,311 | Stop for futility | N/A | N/A |
| 6 | 10.0% | 12.2% | 8.5% | 2017 | 1.15 | 0.85 | 6,311 | Consider safety profile, Perform another interim analysis sooner than planned, discuss increasing N | 0.77 | Continue as planned (with increased sample size) |

The assumed placebo rate of the original design was 15.24% with a 95% CI (13.63%, 16.85%).

Scenario 1 assumes the observed placebo and treatment groups are as hypothesized under the original design.

Scenario 2

177 primary events are observed and the first interim analysis is performed. The observed placebo rate is 14%. Although 14% is less than the expected placebo event rate of 15.24%, the 99% upper confidence limit overlaps with those of the assumed rate (13.63%, 16.85%). A sample size increase is not warranted. The log rank test is performed and the corresponding Z value is 0. Since 0 is less than 3.71 (the critical value for the O'brien-Flemming stopping boundary at look 1), the trial is not stopped for overwhelming efficacy. The conditional power under the original design is 0.59 at the time of the 1st interim analysis which does not meet the criteria to stop for futility (>0.20). The DSMB recommends the trial be continued. After 353 events are observed, second interim analysis is performed. At this time the conditional power is 0.06 (which is < 0.20). The trial is stopped for futility.

Scenario 4

177 adjudicated primary events are observed and the first interim analysis is performed. The log rank test is performed and the corresponding Z value is 1.32. Since 1.32 is less than 3.71 (the critical value for the O'brien-Flemming stopping boundary at look 1), the trial is not stopped for overwhelming efficacy. The conditional power is computed to be 0.88 under the design alternative which is greater than the criteria to stop for futility (>0.20). The observed placebo rate is 12%. Although 12% is less than the expected placebo event rate of 15.24%, the 99% upper confidence limit (14.6%) overlaps with those of the assumed rate (13.63%, 16.85%). The trial is continued and the next interim look is planned after 2/3 of events have been observed.

Scenario 6

177 primary events are observed and the first interim analysis is performed. The log rank test is performed and the corresponding Z value is 1.15. Since 1.15 is less than 3.71 (the critical value for the O'brien-Flemming stopping boundary at look 1), the trial is not stopped for overwhelming efficacy. The conditional power is computed to be 0.85 which is greater than the criteria to stop for futility (0.85>0.20). Thus, no formal stopping criteria have been met.

However, the observed placebo rate is 10%. The 99% upper confidence limit around the current placebo estimate (12.2%) does not overlap with those of the assumed rate (13.63%, 16.85%). This suggests a sample size increase is needed. The sample sizes under various placebo event rates are given in Figure 2. To achieve at least 90% power, more than 6,300 patients would be needed to observe 530 events given the current estimate of the placebo event rate (10%). However, given the substantial increase in sample size required to attain 90% power, the DSMB decides to look again sooner than planned after 50% of events (or 265 events) have been observed.

**Table A.2 Conditional Power given RRR of 23% and 10% for various placebo proportions**

| RRR | Hazard Ratio | Placebo Rate | Trt rate | Expected N at first interim analysis Number at risk | Z Log-Rank Test | p-value | t (177 events) | Conditional Power under the null | Conditional Power under the original design | Conditional Power under current trend |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.23 | 0.75 | 15.24% | 11.73% | 1383 | 1.89 | 0.0586 | 0.33 | 0.13 | 0.94 | 0.94 |
| 0.23 | 0.75 | 14% | 10.78% | 1506 | 1.88 | 0.0602 | 0.33 | 0.13 | 0.94 | 0.94 |
| 0.23 | 0.75 | 12% | 9.24% | 1756 | 1.86 | 0.0628 | 0.33 | 0.13 | 0.94 | 0.93 |
| 0.23 | 0.75 | 10% | 7.70% | 2108 | 1.84 | 0.0654 | 0.33 | 0.13 | 0.94 | 0.93 |
| 0.10 | 0.9 | 15.24% | 13.72% | 1288 | 0.79 | 0.4281 | 0.33 | 0.03 | 0.79 | 0.22 |
| 0.10 | 0.9 | 14% | 12.60% | 1403 | 0.79 | 0.4313 | 0.33 | 0.03 | 0.78 | 0.22 |
| 0.10 | 0.9 | 12% | 10.80% | 1636 | 0.78 | 0.4362 | 0.33 | 0.03 | 0.78 | 0.21 |
| 0.10 | 0.9 | 10% | 9.00% | 1964 | 0.77 | 0.4410 | 0.33 | 0.03 | 0.79 | 0.21 |

The table A.2 shows the conditional power when the difference in treatment groups is equivalent to a RRR of 23% (HR=0.75) for various placebo rates. The Conditional power is constant given a constant RRR (rows 1-4). Decreasing the RRR to 10% results in a decrease in conditional power, but again the conditional power is constant for a fixed RRR (rows 5-8).

## Table A.3 Coding of Composite Outcomes

| webDCU Code Group 556 | Major Hemorrhage | Hemorrhagic stroke | Major Hemorrhage other than Intracranial Hemorrhage (a.k.a. Major systemic hemorrhage) | Coronary Revascularization | Ischemic stroke | Asymptomatic intracranial hemorrhage (ICH, SAH, SDH or IVH) | All minor hemorrhage (including asymptomatic intracranial hemorrhage) |
|---|---|---|---|---|---|---|---|
| 1 | | | | | Ischemic stroke | | |
| 2 | Symptomatic hemorrhagic transformation of an ischemic stroke | Symptomatic hemorrhagic transformation of an ischemic stroke (OF INDEX EVENT OR FOLLOW-UP EVENT) | | | Symptomatic hemorrhagic transformation of an ischemic stroke (NOT OF INDEX EVENT) | | |
| 3 | | | | | Asymptomatic hemorrhagic transformation of an ischemic stroke (NOT OF INDEX EVENT) | | |
| 4 | Symptomatic intracerebral hemorrhage | Symptomatic intracerebral hemorrhage | | | | | |
| 5 | | | | | | Asymptomatic intracerebral hemorrhage | Asymptomatic intracerebral hemorrhage |
| 6 | Other Symptomatic intracranial hemorrhage | Other Symptomatic intracranial hemorrhage If | | | | | |
| 7 | | | | | | Other Asymptomatic intracranial hemorrhage | Other Asymptomatic intracranial hemorrhage |
| 9 | | | | Myocardial infarction with Coronary Revascularization | | | |
| 10 | | | | | | | |
| 11 | | | | Coronary Revascularization without Myocardial Infarction | | | |
| 12 | Major Hemorrhage other than Intracranial Hemorrhage | | Major Hemorrhage other than Intracranial Hemorrhage | | | | |
| 13 | | | | | | | Minor hemorrhage other than intracranial hemorrhage |