RESOLUTE ONYX 2.0mm Clinical Study

A Clinical Evaluation of the Medtronic Resolute Onyx Zotarolimus-Eluting 2.0 mm Stent

Statistical Analysis Plan (SAP)

Rev 2.0

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1. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the RESOLUTE ONYX 2.0 mm Clinical Study: A Clinical Evaluation of the Medtronic Resolute Onyx Zotarolimus-Eluting 2.0 mm Stent. The purpose of this plan is to provide a framework within which answers to the study objectives can be achieved in a statistically rigorous fashion, without bias or analytical deficiencies. Specifically, the plan has the following purpose: To prospectively outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the medical device industry. Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report for this study.

2. Study Objectives

The purpose of this study is to assess the safety and efficacy of the Resolute Onyx Zotarolimus-Eluting Coronary Stent System for the treatment of *de novo* lesions in native coronary arteries that allows the use of a 2.0 mm diameter stent.

3. Study Design

This study is designed as a single-arm, open-label multi-center study.

3.1. Treatment(s) and Subject Enrollment

At least 100 subjects with ischemic heart disease due to *de novo* stenotic lesions within native coronary arteries that meet the eligibility criteria and sign the informed consent form will be asked to participate in this trial. All subjects who consent will be asked to participate in the 13 month angiographic subset until at least 20 subjects have been enrolled in this subset. Subjects may receive treatment in up to two lesions, if the lesions are located in separate target vessels. Only one lesion may be treated in a single target vessel. Core size lesions should be treated with the currently approved Resolute Integrity stent. All treatment with the study stents is to be performed during a single index procedure.

In the event of one lesion to be treated with a 2.0 mm study stent and another lesion to be treated with a core size (2.25 mm - 4.0 mm) Resolute Integrity stent, the subject should be treated first with the core-sized stent. If the treatment of the first lesion fails or if the subject becomes unstable before a 2.0 mm study stent is attempted (stent introduced into guide catheter), the subject will not be enrolled, will not be followed, and will not be included in the primary analysis of this trial. Another subject should be enrolled to replace this subject for the primary analysis. If the treatment with the 2.0 mm study stent is attempted (stent introduced into guide catheter) but not implanted, the subject will be considered part of the Intention-to-Treat population (ITT) and will be followed through the 12 month endpoint and will be included in the primary analysis of this trial.

For subjects who have more than one lesion planned for treatment, FFR should be performed in the vessel expected to receive the 2.0 mm study stent to demonstrate the functional need for treating such a lesion, unless demonstrated by other means (clinical evidence and/or positive functional study).

The trial will be conducted at a maximum of 25 investigational sites within the United States (US) and Japan. Sites are allowed to enroll a maximum of 20 subjects per site or until study enrollment has been completed, whichever comes first. The expected time of participation in the trial for each subject is three years.

3.1.1. General Inclusion Criteria

Subject must meet ***all*** of the following criteria to be eligible for treatment in the trial:

1. Subject is ≥ 18 years old or ≥ 20 years old if in Japan
2. Subject is an acceptable candidate for percutaneous coronary intervention (PCI), stenting, and emergent coronary artery bypass graft (CABG) surgery
3. Subject has clinical evidence of ischemic heart disease. For single vessel disase: stable or unstable angina alone is sufficient. For multi-vessel treatment: a positive functional study or FFR to demonstrate functional need in 2.0 mm small vessel.
4. Female subjects of childbearing potential must have a negative pregnancy test within 7 days before the trial procedure
5. Subject or subject's legal representative has been informed of the nature of the trial and agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective investigational site
6. Subject agrees to comply with specified follow-up evaluations and to return to the same investigational site where the procedure was performed if participating in the angiographic subset.

3.1.2. Angiographic Inclusion Criteria

The subject and each target lesion/vessel must meet ***all*** of the following angiographic criteria for the patient to be considered for inclusion in the trial:

1. The subject requires treatment of either:

   a. A single target lesion amenable to treatment with a 2.0 mm stent

   OR

   b. Two target lesions located in separate target vessels, with at least one of the target lesions amenable to treatment with a 2.0 mm study stent
2. Target lesion(s) must be de novo lesion(s) in native coronary artery(ies)
3. Target lesion(s) treated with a 2.0 mm stent must be ≤ 27 mm in length
4. Target lesion(s) must have a stenosis of ≥ 50% and < 100%
5. At least one target vessel(s) must have a reference vessel diameter (RVD) ≥ 2.0 mm and < 2.25 mm by visual estimate
6. Target vessel(s) must have a thrombolysis in myocardial infarction (TIMI) flow ≥ 2

   Note: Measurements may be made by careful visual estimate, on-line QCA, or IVUS.

3.1.3. General Exclusion Criteria

Subjects will be excluded from the trial if ***any*** of the following criteria are met:

1. Known hypersensitivity or contraindication to aspirin, heparin and bivalirudin, thienopyridines, cobalt, nickel, platinum, iridium, chromium, molybdenum, polymer coatings (e.g. BioLinx) or a sensitivity to contrast media, which cannot be adequately pre-medicated
2. History of anallergic reaction or significant sensitivity to drugs such as zotarolimus, rapamycin, tacrolimus, everolimus, or any other analogue or derivative
3. Platelet count < 100,000 cells/mm³ or > 700,000 cells/mm³, or a white blood cell (WBC) count < 3,000 cells/mm³ within 7 days prior to index procedure
4. Serum creatinine level > 2.5 mg/dl within 7 days prior to index procedure

5. Evidence of an acute MI within 72 hours of the trial procedure:

   a) Q wave myocardial infarction (QWMI)

   OR

   b) Elevated cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the upper reference limit (URL) and with at least one of the following:

   - o Symptoms of ischemia
   - o New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
   - o Development of pathological Q waves in the ECG
   - o Imaging evidence of new loss of viable myocardium or new regional wall

   Note: Subjects with evidence or suspicion of an acute MI (per Investigator or Sub-Investigator determination) must have cardiac enzyme results reviewed prior to enrollment.
6. Previous percutaneous coronary intervention (PCI) of the target vessel(s) within 9 months prior to the procedure

   Note: Refer to Table 1 in Section 3.1.5 for criteria of previous PCI to the target and other (non-target) vessel(s).
7. Planned PCI of any vessel within 30 days post-index procedure and/or planned PCI of the target vessel(s) within 12 months post-procedure. (no staged procedures)

   Note: Refer to Table 1 Section 3.1.5 for additional procedure criteria for planned PCI of the target and other (non-target) vessel(s)
8. During the index procedure, the target lesion(s) requires treatment with a device other than percutaneous transluminal coronary angiography (PTCA) prior to stent placement (including, but not limited to, cutting/scoring balloon, atherectomy, laser, thrombectomy, etc.)
9. History of a stroke or transient ischemic attack (TIA) within the prior 6 months
10. Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months
11. History of bleeding diathesis or coagulopathy or will refuse blood transfusions
12. Concurrent medical condition with a life expectancy of less than 12 months
13. Any previous treatment of the target vessel(s) for restenosis, including brachytherapy
14. Currently participating in an investigational drug or another device trial that has not completed the primary endpoint or that clinically interferes with the current trial endpoints; or requires coronary angiography, IVUS or other coronary artery imaging procedures

    Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
15. Documented left ventricular ejection fraction (LVEF) < 30% at the most recent evaluation
16. Inability to comply with the required trial antiplatelet regimen (see protocol Section 5.3)

3.1.4. Angiographic Exclusion Criteria

Subjects will be excluded from the trial if ***any*** of the following criteria are met (for subjects with two target lesions, both target lesions/vessels must not meet any of the criteria below):

1. Target lesion(s) are located in native vessel(s) distal to anastomosis with a bypass graft (including but not limited to saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA)) with more than 40% diameter stenosis anywhere within the graft

   Note: A target lesion distal to a graft may be accessed through the graft.
2. Previous stenting in the target vessel(s) :

   a) within 9 months prior to procedure

b) ≤ 15 mm from the target lesion(s)

3. Target vessel(s) has/have other lesions with greater than 40% diameter stenosis based on visual estimate or on-line QCA
4. The target vessel(s) has/have evidence of thrombus
5. The target vessel(s) is/are excessively tortuous (two bends > 90º to reach the target lesion)
6. The target lesion(s) has/have any of the following characteristics:

   a) Lesion location is aorto-ostial, or within 5 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX)

   b) Involves a side branch > 2.0 mm in diameter

   c) Is at or distal to a > 45º bend in the vessel

   d) Is severely calcified
7. Unprotected left main coronary artery disease (an obstruction greater than 50% in the left main coronary artery)

3.1.5. Criteria for Additional Procedures

Only one target lesion per target vessel for a maximum of two target vessels may be treated during the trial index procedure. Any other lesion in the target vessel(s) can only be treated after 12 months post-procedure. Any lesion in other (non-target) vessels can be treated after 30 days post-procedure with a Resolute Integrity Stent (preferred) or any approved stent. The criteria for pre and planned post-procedure interventions in the target vessel(s) and other (non-target) vessels are provided in Table 1.

Table 1: Previous and Additional Procedure Criteria

Time Point	Target Vessel(s)	Non-target Vessel(s)
Prior to Index		
> 9 months pre-procedure	Any approved treatment, provided: • Target lesion must be at least 15 mm away from a previously placed stent or treatment • No more than 40% stenosis anywhere in the vessel other than the target lesion	Any approved treatment
9 months to > 30 days pre-procedure	No PCI	Any approved treatment
30 days to > 24 hours prior to index procedure	No PCI	Any bare metal stent provided: • No MACE events resulted if ≤ 30 days from the index procedure • Two post-procedural serial CK-MB measures below the upper limits of normal if ≤ 72 hours

≤ 24 hours prior to index procedure	No PCI	No PCI
Post Index		
≤ 30 days post-procedure	No PCI*	No PCI**
> 30 days to 12 months post-procedure	No PCI**	Resolute Integrity (preferred) or any approved treatment
> 12 months post-procedure	Resolute Integrity (preferred) or any approved treatment for the intended indication	Resolute Integrity (preferred) or any approved treatment for the intended indication

* In case of acute/subacute closure (within 30 days post procedure) the target lesion(s)/segment(s) should be treated with the study device.

** If deemed medically necessary by the Investigator, the subject should receive any necessary treatment

3.2. Endpoints

3.2.1. Primary Endpoint

Target lesion failure (TLF) at 12-months post-procedure, defined as cardiac death, target vessel myocardial infarction (TMVI) (Q wave or non-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.

3.2.2. Key Secondary Endpoints

Secondary endpoints of this trial include the following:

Clinical Endpoints:

- Acute Success (Device, Lesion, Procedure)
- The following secondary endpoints will be assessed at hospital discharge, 30 days, 6 months, and 12 months post-procedure, and annually thereafter through year 3:
    - Cardiac Death
    - Target Vessel Myocardial Infarction (TVMI)
    - Cardiac Death and TVMI
    - Target Lesion Revascularization (TLR)
    - Major Adverse Cardiac Event (MACE)
      Defined as death, myocardial infarction (Q wave and non-Q wave), emergent coronary bypass surgery, or clinically-driven repeat target lesion revascularization by percutaneous or surgical methods
    - Target Lesion Failure (TLF)
    - Target Vessel Failure (TVF)
    - Stent Thrombosis (ST)

Imaging Endpoint:

- The following secondary endpoint will be assessed at 6 months for subjects who received Myocardial Perfusion Imaging (MPI) per standard care at baseline:
    - Percentage of Myocardium with Reversible Ischemia per Myocardial Perfusion Imaging

Other clinical parameters of stress testing will be collected at baseline and at follow-up testing to assess change following the stenting procedure. These parameters include stress induced angina symptoms, incidence of ST-depression, and exercise capacity.

Angiographic Endpoints:

- The following Angiographic Endpoints will be assessed at 13 months post-procedure (for at least 20 patients):
    - Late Lumen Loss (LL)
    - Binary Angiographic Restenosis (BAR) rate (defined as >50% diameter stenosis (DS))
    - Percent Diameter Stenosis

3.3. Sample Size Justification

If the 12-month TLF rate of the Resolute Onyx 2.0 mm stent is shown to be significantly less than 19%, then the trial will be considered to have met its primary objective. In other words, the assessment of TLF is a testing with the following null and alternative hypotheses:

H_0: $\pi \geq 19\%$ vs. H_1: $\pi < 19\%$,

where π is the true Resolute Onyx 2.0 mm stent 12-month TLF rate.

The assessment of the null hypothesis will be carried out at the one-sided 0.05 level of significance. Rejection of the null hypothesis indicates the Resolute Onyx 2.0 mm stent 12-month TLF rate is significantly below 19%.

Accounting for a 10% clinical loss to follow-up and one-sided 0.05 level of significance, a sample size of 100 subjects yields more than 80% power to reject the above null hypothesis in favor of the alternative, assuming the true Resolute Onyx 2.0 mm stent 12-month TLF rate is 9.4%.

3.4. Analysis Strategy

Descriptive statistics will be presented for this study. Hypothesis testing with performance goal will be evaluated for primary endpoint.

4. Analysis Populations

Intent-to-Treat (ITT): For this trial, all subjects who sign the written informed consent and also have the study stent (Resolute Onyx 2.0 mm stent) introduced into the guide catheter will be counted in the ITT set, which will be the primary analysis set.

Per-Protocol (PP): The ITT population excluding subjects who do not meet certain key entry criteria (for exclusion criteria below, if any answer is "yes", the subjects are excluded from PP population):

1. Did not receive any study device
2. Received study device, and another type of DES
3. Did not meet the following inclusion criteria:
    a. General Inclusion 3: Subject has clinical evidence of ischemic heart disease, For single vessel disease: stable or unstable angina alone is sufficient. For multi-vessel treatment: a positive functional study or FFR to demonstrate functional need in 2.0 mm small vessel.
    b. Angiographic Inclusion 1: The subject requires treatment of either:
        i. A single target lesion amenable to treatment with a 2.0 mm stent

        OR

        ii. Two target lesions located in separate target vessels, with at least one of the target lesions amenable to treatment with a 2.0 mm study stent

c. Angiographic inclusion 2: Target lesion(s) must be de novo lesion(s) in native coronary artery(ies)

4. Did not meet the following exclusion criteria:
   a. General exclusion 5: Evidence of an acute MI within 72 hours of the trial procedure:

      a) Q wave myocardial infarction (QWMI)

      OR

      b) Elevated cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the upper reference limit (URL) and with at least one of the following:

      - Symptoms of ischemia
      - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
      - Development of pathological Q waves in the ECG
      - Imaging evidence of new loss of viable myocardium or new regional wall

      Note: Subjects with evidence or suspicion of an acute MI (per Investigator or Sub-Investigator determination) must have cardiac enzyme results reviewed prior to enrollment.

   b. General exclusion 7: Planned PCI of any vessel within 30 days post-index procedure and/or planned PCI of the target vessel(s) within 12 months post-procedure. (no staged procedures)

      Note: Refer to Table 1 Section 3.1.5 for additional procedure criteria for planned PCI of the target and other (non-target) vessel(s)

   c. General Exclusion 8: During the index procedure, the target lesion(s) requires treatment with a device other than percutaneous transluminal coronary angiography (PTCA) prior to stent placement (including, but not limited to, cutting/scoring balloon, atherectomy, laser, thrombectomy, etc.)
   d. General Exclusion 14: Currently participating in an investigational drug or another device trial that has not completed the primary endpoint or that clinically interferes with the current trial endpoints; or requires coronary angiography, IVUS or other coronary artery imaging procedures

      Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.

   e. Angiographic Exclusion 2: Previous stenting in the target vessel(s):

      a) within 9 months prior to procedure

      b) ≤ 15 mm from the target lesion(s)

The primary endpoint will also be analyzed in PP population.

5. Interim Analysis

There is no planned interim analysis for this trial.

6. Statistical Methods of Analyses

6.1. General Considerations

All statistical analyses will be performed using Statistical Analysis Software (SAS) for Windows (version 9.1 or higher) or other widely accepted statistical or graphical software. Subject data listings and tabular and graphical presentations of results will be provided.

All analyses will be based on "intent to treat" (ITT) principle, unless otherwise specified. For clinical events, the numerator of the event rate will be the number of "ITT" subjects having an event before the time of interest. The denominator will be the number of subjects who either have an event by the time of interest, or have follow-up information beyond the lower window of the follow-up.

The Clinical Study Report will be available for the primary endpoint (12 months) and for secondary endpoints annually through study close-out at 3 years.

6.2. Analysis of the Primary Endpoint

The number and percentage of subjects with 12-month TLF will be presented. A one-sided upper 95% confidence interval of the Resolute Onyx 2.0 mm stent 12-month TLF rate will be calculated through binomial (exact) method. If this upper limit is below 19%, the clinical objective will be considered to have been met.

With regard to clinical outcomes analysis, in subjects receiving treatment of two lesions with a Resolute Onyx 2.0 mm stent, the lesion to be included in the primary analysis, the "analysis lesion", will be randomly selected at the time of analysis. For subjects receiving treatment of a Resolute Onyx 2.0 mm stent and another size stent, the primary analysis will include the lesion treated with the 2.0 mm stent, regardless of the other stent size. A secondary analysis will be conducted for all target lesions.

The algorithm to randomly select the "analysis lesion" is specified below:

The seed of the ranuni function will be specified in the statistical analysis plan prior to the database lock and will not be changed. Therefore, bias cannot be introduced in the random selection of the lesion in the primary analysis.

A random lesion will be chosen for the primary analysis as follows:

1. Sort the lesions according to patient number and CASS site (with one observation per patient/CASS).
2. Assign a random number to each observation using the SAS ranuni function (the seed will be pre-specified in the statistical analysis plan).
3. Resort the lesions according to patient number and newly created random number.
4. Choose the first patient/CASS observation according to the sort in step 3.

As a supplementary analysis, to account for missing data, subjects who drop out prior to 330 days post-procedure and do not experience TLF will have their 12-month TLF-free status (yes/no) imputed using the multiple imputation, tipping point analysis and worst case analysis.

The multiple imputation approach will use SAS V9 PROC MI. The covariates to be used in the imputation model are lesion-length, baseline RVD, age, sex, diabetes, history of MI, Canadian Cardiovascular Society Angina Class, and TLF status at visits prior to dropout. One hundred imputed data sets will be generated. An overall TLF rate and its one-sided upper 95% confidence intervals will be generated across the one hundred imputed data sets. For the subjects have 2 or more target lesions, the longest lesion length and the smallest baseline RVD will be used in the imputation model.

The tipping point analysis will impute the most 12-month TLF-missing status as yes so that the one-side upper 95% confidence interval of 12-month TLF rate will be less than or equal to the performance goal of 19%.

The worst case analysis will impute all the 12-month TLF-missing status as yes then calculate the one-side upper 95% confidence interval of 12-month TLF rate to compare the performance goal of 19%.

Statistical non-significance in the primary endpoint for gender comparisons will confirm the homogeneity by gender in this trial (see analysis of homogeneity below).

6.3. Analysis of Secondary Endpoints

Descriptive statistics for the secondary endpoints will be provided. Categorical variables will be reported using counts and percentages, and continuous variables will be reported by giving the number of known values, the mean, standard deviation, minimum and maximum values. The time-sensitive nature of any response variable may be displayed by using a Kaplan-Meier plot. For the myocardial infarctions (MI) component of the endpoints, the extended historical MI definitions will be used.

6.4. Analysis of Baseline Characteristics

All clinically relevant baseline variables will be tabulated and reported. Categorical variables will be reported using counts and percentages, and continuous variables will be reported by giving the number of known values, the mean, standard deviation, minimum and maximum values.

6.5. Handling of Missing Data

Every effort will be undertaken to minimize missing data. In time-to-event outcomes drop-outs will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach. Unless otherwise specified, no statistical techniques will be used to impute missing data for continuous or categorical characteristics and outcomes. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

For the primary endpoint, a sensitivity analysis will be conducted to assess the impact of censored data and will include a worst-case analysis.

6.6. Analysis of Poolability and Homogeneity

Given this is a multi-center trial, to account for the pooling of results across sites the following analysis will be performed:

1. **Pooling data of the small sites:**
   The sites with enrollment of 5 subjects or more are reported individually. The sites with enrollment of 4 or less are pooled into super-sites according to their geographical closeness so that the combined super-sites would have five or more enrolled subjects. If a super-site is with 5 or more subjects, the pooling of this supersite will stop and the pooling of the next super-site will start.
2. **Assessment of baseline characteristics across sites:**
   Important baseline demographic and lesion characteristics (lesion-length, baseline RVD, age, sex, diabetes, history of MI and worst Canadian Cardiovascular Society Angina Class (CCSC)) will be tabulated for each site. Assessment of differences in baseline characteristics across sites

will be performed using one-way analysis of variance for continuous parameters and logistic regression for categorical parameters.

3. **Analysis on the primary endpoint (TLF at 12 months) across sites:**
   Rates of the primary endpoint for each patient group will be presented by site and comparison across sites will be carried out using logistic regression to assess site homogeneity, with the primary endpoint as the dependent variable, and the sites as independent variable. If there is significant difference in baseline characteristics observed in step 1, then this comparison will be adjusted by adding the entire baseline variables listed above into the logistic regression model as additional independent variables.

To account for the pooling of results across regions (US vs. OUS), the following analysis will be performed:

1. **Assessment of homogeneity of baseline characteristics between US and OUS cohorts:**
   The two-sample t-test, Fisher's exact test or CMH (Modified Ridit scores) will be used depending on the distributions of the baseline covariates. The covariates that will be considered include: lesion-length, baseline RVD, age, sex, diabetes, history of MI and worst Canadian Cardiovascular Society angina class. Statistical non-significance (significance level set at 0.15) for any of the covariates is supportive evidence of the comparability of Resolute arms without adjusting for that covariate. However, any covariate for which the group difference is deemed to be clinically and statistically significant could be adjusted by using propensity scores as discussed below to account for any covariate imbalances.
2. **Assessment of Outcome Comparability:**
   If any of the above baseline covariates is significantly different, then the outcome of 12 months TLF rate between the two cohorts will be compared as the following: For each individual a propensity score will be calculated using logistic regression, with indicator for cohort (US, non-US) membership as the dependent variable and the above mentioned covariates as the independent variables (covariates will be included regardless of whether or not they are deemed homogenous). Patients will then be categorized into quintiles based on this propensity score. The 85% confidence interval of propensity score quintile adjusted odds ratio of region will be calculated. If the 85% confidence interval contains one (1), then the two cohorts will be considered poolable.

To account for the poolability by gender, the following analysis will be performed:

1. **Assessment of homogeneity of baseline characteristics by gender:**
   The two-sample t-test , Fisher's exact test or CMH (Modified Ridit scores) will be used depending on the distributions of the baseline covariates. The covariates that will be considered include: lesion-length, baseline RVD, age, diabetes, history of MI and worst Canadian Cardiovascular Society angina class. Statistical non-significance (significance level set at 0.15) for any of the covariates is supportive evidence of the comparability without adjusting for that covariate. However, any covariate for which the group difference is deemed to be clinically and statistically significant could be adjusted by using propensity scores as discussed below to account for any covariate imbalances.
2. **Assessment of Outcome Comparability:**
   If any of the above baseline covariates is significantly different, then the outcome of 12 months TLF rate between the two cohorts (male vs. female) will be compared as the following: For each individual a propensity score will be calculated using logistic regression, with indicator for cohort membership as the dependent variable and the above mentioned covariates as the independent variables (covariates will be included regardless of whether or not they are deemed homogenous). Patients will then be categorized into quintiles based on this propensity score. The

85% confidence interval of propensity score quintile adjusted odds ratio of gender will be calculated. If the 85% confidence interval contains one (1), then the two cohorts will be considered poolable.

Statistical non-significance in the primary endpoint for site, region and gender comparisons will confirm that the sites, regions and gender are homogeneous in this trial. Otherwise, the cause of the significant difference will be investigated and further analyses plan will be discussed with FDA.

7. Data Screening and Acceptance

Screening and acceptance testing of these data will be carried out in accordance with Data Management Plan. To this end, all data involved in the determination of endpoints will be screened for missing and unusual values. Any missing data that affect the ability to determine or analyze any endpoint will be queried by Data Management for confirmation of irretrievability. Unusual values, such as outliers, will also be queried, and if confirmed, will be used as recorded.

8. APPENDICES

Appendix I: Incomplete Date of AE Onset

The table below is guiding on how to input missing dates for AE onset

Valid Portion	Missing Portion	Imputed Value for missing Portion
Month, Year	Day	Set Day = first day of that month and year, then set the day = later of (New onset date, procedure date).
Year	Day, Month	Set date = later of (January 1st of that year, procedure date).
None	Day, Month, Year	Date of Procedure

Appendix II: Follow-up Visit Windows for Endpoint Analyses

Follow-up interval	Study Time Window Post Procedure
30 days	30±5 days
6 months	180 ±14 days
12 months*	360 ±30 days
13 months (2.0mm Angio subset)	390 ±14 days
24 months	720 ±30 days
36 months	1080 ±30 days

*12 month Clinical Follow up must occur at least 1 day prior to the 13 month Angiographic Follow up