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ABSORB IV RCT
A Clinical Evaluation of Absorb™ BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions
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Abbott Vascular

Protocol 10-392

ABSORB IV
RANDOMIZED CONTROLLED TRIAL

A Clinical Evaluation of ABSORB™ BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects with de novo Native Coronary Artery Lesions

Statistical Analysis Plan
(Part I: Methodology)

[redacted]

March 16, 2017

[redacted]

[redacted]

[redacted]

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1. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used in the ABSORB IV RANDOMIZED CONTROLLED TRIAL, the second part of Protocol 10-392. This plan is based on the [redacted], March 16 , 2017 of the study protocol.

1.2 Study Objectives

- **ABSORB IV Primary Objectives:**
  - To evaluate 30-day clinical outcomes of the Absorb BVS[&] compared to XIENCE[*] in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel..
  - To evaluate long-term clinical outcomes of Absorb BVS compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel.
- **ABSORB IV Secondary Objective:**
  - To evaluate 1-year clinical outcomes of the Absorb BVS[&] compared to XIENCE[*] in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel..
  - To evaluate the incidence of angina occurring within 1-year, with treatment of Absorb BVS compared to XIENCE.

1.3 Study Design

ABSORB IV is a prospective, randomized (1:1, Absorb BVS to XIENCE), single-blind, multi-center study, registering approximately 2600 subjects at approximately 140 sites.

The enrollment of the 2600 subjects in ABSORB IV will start after the enrollment completion of the 2000 primary analysis subjects in ABSORB III.

Table 1 provides the device sizes, the reference vessel diameter (RVD) and lesion length for ABSORB IV.

[&] The term "Absorb BVS" will be used to represent both Absorb™ BVS and Absorb GT1™ BVS.
[*] Commercially approved XIENCE family stent system, inclusive of XIENCE V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro (OUS only), and XIENCE Pro^{X} (OUS only).

Table 1. Absorb BVS and XIENCE Sizes

Device	Lesion and Device Sizes	
	RVD [1]	Lesion Length[1]
Absorb BVS[4] (Target lesion)	RVD ≥ 2.50 mm - ≤ 3.75 mm Scaffold diameter: 2.5, 3.0 and 3.5 mm	Lesion length ≤ 24 mm Scaffold Length[2]: 8, 12, 18and 28 mm [3]
XIENCE[5] (Target lesion)	RVD ≥ 2.50 mm - ≤ 3.75 mm Stent diameter: 2.5, 2.75, 3.0, 3.25, 3.5, 4.0 mm	Lesion length ≤ 24 mm Stent Length: 8, 12, 15, 18, 23 and 28 mm [3]

[1] Reference vessel diameter (RVD) and lesion length are based on visual estimation.

[2] Both the 8 mm and 12 mm lengths will be available for the 2.5/3.0 diameter Absorb BVS. Only the 12 mm length will be available for the 3.5 mm diameter. The commercially approved CE marked 23mm Absorb BVS device will not be used in this study.

[3] For target lesion, planned overlapping is not allowed (i.e. the lesion must be eligible for treatment with a single stent). However, bailout overlapping is allowed if required.

[4] Once Absorb GT1™ BVS System is commercially available, it can also be used in the ABSORB IV trial.

[5] XIENCE V, XIENCE Prime, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro, and XIENCE Pro^X will be used in this study.

All registered subjects in ABSORB IV will receive the following clinical follow-up:

- 30 ± 7 days follow-up telephone contact/office visit
- 90 ± 14 days follow-up telephone contact/office visit
- 180 ± 28 days follow-up telephone contact/office visit
- 270 ± 28 days follow-up telephone contact/office visit
- Annual visits: 1-7 years ± 28 days follow-up telephone contact/office visit

All registered subjects in ABSORB IV will potentially be followed up at 8 (± 28 days) and/or 9 and/or 10 years (± 28 days) via telephone contact/office visit if it is necessary as determined by the Sponsor. Patients will be consented for these additional follow-up visits at the time of written informed consent.

1.3.1 Primary Endpoints

The primary endpoints of the ABSORB IV trial are:

1. TLF through 30 days: the percentage of patients who experienced TLF within 30 days, tested for non-inferiority of Absorb BVS to XIENCE.

   This analysis will consist of ~2600 subjects in ABSORB IV.

[redacted]

[redacted]

1.3.2 Secondary Endpoint

1.3.2.1 Powered Secondary Endpoint #1: TLF through 1 year

TLF through 1 year: the percentage of patients who experienced TLF within 1 year, tested for non-inferiority of Absorb BVS to XIENCE.

This analysis will consist of ~2600 subjects in ABSORB IV.

1.3.2.2 Powered Secondary Endpoint #2: Angina through 1 year

Angina through 1 year will be tested first for non-inferiority of Absorb BVS to XIENCE with reflex testing to superiority.

This analysis will consist of ~2600 subjects in ABSORB IV.

- Angina is defined as any angina or angina equivalent symptoms determined by the physician and/or research coordinator after interview of the patient, and as adjudicated by a clinical events committee (CEC).
- This analysis will exclude angina or angina equivalent symptoms that occurred following the index procedure through hospital discharge or 7 days, whichever occurs first.

[redacted]

1.3.2.3 Additional Secondary Endpoints

In ABSORB IV the following clinical secondary endpoints will be analyzed.

- **Acute Success**: (Combined Clinical/Angiographic Endpoint)

- Device success (Lesion level analysis)
- Procedural success (Subject level analysis)

- **Clinical Endpoint** in hospital and at each follow-up point (30, 90, 180, 270 days; 1, 2, 3, 4, 5, 6, 7 years, and potentially 8 and/or 9 and/or 10 years)
  - **Component**
    - Death (Cardiac, Vascular, Non-cardiovascular)
    - Myocardial Infarction
      - Attributable to target vessel (TV-MI)
      - Not attributable to target vessel (NTV-MI)
    - Target Lesion Revascularization (TLR)
      - Ischemia driven TLR (ID-TLR)
      - Non ID TLR (NID-TLR)
    - Target Vessel Revascularization (TVR)
      - ID TVR
      - NID TVR
    - All coronary revascularization

  - **Composite Endpoints**
    - Death/All MI
    - Cardiac Death/All MI
    - Cardiac Death/TV-MI/ID-TLR (TLF)
    - Cardiac Death/All MI/ID-TLR (MACE)
    - Cardiac Death/All MI/ID-TLR/ID-TVR, non TL (Target Vessel Failure, TVF)
    - Death/All MI/All revascularization

  - **Composite Endpoints Scaffold-Thrombosis / Stent Thrombosis (per ARC definition)**
    - Timing (acute, sub-acute, late and very late)
    - Evidence (Definite, Probable)

  - **Rehospitalization**
    - Coronary artery disease related
    - Cardiovascular, non-CAD related
    - Non-cardiovascular related

  - **Repeat coronary arteriography**

[redacted]

[redacted]

[redacted]

1.4 Analysis Populations

1.4.1 Intent to Treat (ITT) Population

[redacted]

1.4.2 As-Treated (AT) Population

[redacted]

1.5 Sample Size Calculations

All sample size calculations were performed using NCSS PASS 11 (Hintze, J., 2011, NCSS, LLC. Kaysville, Utah), unless otherwise specified.

1.5.1 Primary Endpoints

The two primary endpoints will be independently tested. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The power calculation for the primary endpoint of TLF at 30 days is based on the following assumptions:

[redacted]

- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{TLF}): 2.9%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)

[redacted]

With the effective sample size 2574 (Absorb: 1287, XIENCE: 1287) at 30 days, the study has approximately 92% power to demonstrate non-inferiority of Absorb BVS to XIENCE using Farrington and Manning test.

[redacted]

1.5.2 Powered Secondary Endpoints

1.5.2.1 Powered Secondary Endpoint #1: TLF through 1 year

The TLF at 1 year will be tested for non-inferiority. This analysis will include ~2600 subjects in ABSORB IV.

The hypothesis test is designed to show non-inferiority of Absorb BVS to XIENCE for the TLF at 1 year with a one-sided alpha of 0.025. [redacted]

[redacted]

[redacted]

[redacted]

The power calculation for the primary endpoint of TLF at 1 year is based on the following assumptions:

[redacted]

- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{TLF}): 4.8%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)

[redacted]

With the effective sample size 2470 (Absorb: 1235, XIENCE: 1235) at 1 year, the study has approximately 98% power to demonstrate non-inferiority of Absorb BVS to XIENCE using Farrington and Manning test.

[redacted]

1.5.2.2 Powered Secondary Endpoint #2: Angina through 1 year

[redacted]

The hypothesis test is designed to show non-inferiority of Absorb BVS to XIENCE for angina within 1 year with a one-sided alpha of 0.025. [redacted]

The power calculation for the powered secondary endpoint of angina within 1 year is based on the following assumptions:

[redacted]

- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{ANGINA}): 7%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)

[redacted]

With the effective sample size 2470 (Absorb: 1235, XIENCE: 1235) at 1 year, the study has approximately 99% power to demonstrate non-inferiority of Absorb BVS to XIENCE using Farrington and Manning test[1].

[redacted]

1.6 Randomization and Blinding

1.6.1 Randomization

[redacted]

[redacted]

1.6.2 Blinding

[redacted]

[redacted]

2. ANALYSIS CONSIDERATIONS

2.1 Statistical Methods

Baseline demographic, clinical, angiographic, procedural, and device data, and treatment results will be summarized using descriptive summary statistics. All data collected will be summarized overall and by treatment arms for ABSORB IV (N=2600) and the pooled population of ABSORB III primary analysis group and ABSORB IV (N=4600).

2.1.1 Statistics for Continuous Variables

For continuous variables (e.g., age, percent diameter stenosis, and lesion length), results within treatment arm will be summarized with the numbers of observations, means, and standard deviations, and in addition, with medians, quartiles, minimums, maximums, and 95% confidence intervals for the means, when specified. Differences between the treatment arms, when specified, will be summarized with the differences of the two means and 95% confidence intervals for the difference between the means, and p-values from t-test may also be presented for hypothesis generating purposes.

Formulas for calculation of the confidence intervals for the continuous variables are given below:

1. 100(1- α)% Confidence Interval For A Single Mean[2]

$$\bar{x} \pm t_{\frac{\alpha}{2}} \frac{s}{\sqrt{n}}$$

where:

$\bar{x}$ = sample mean

s = sample standard deviation

n = sample size

$t_{\frac{\alpha}{2}}$ = the alpha/2 t - statistic for $n-1$ degrees of freedom

2. 100(1-α)% Confidence Interval For The Difference of Two Means Under The Assumption Of Equal Variances Between The Two Groups[2]

$$\left(\bar{x}_1 - \bar{x}_2\right) \pm t_{\frac{\alpha}{2}} \sqrt{s_p{}^2 \left(\frac{1}{n_1} + \frac{1}{n_2}\right)}$$

where:

$\bar{x}_1$ = sample mean for group 1 $\bar{x}_2$ = sample mean for group 2

$s_p^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}$

s_1 = sample standard deviation for group 1 s_2 = sample standard deviation for group 2

n_1 = sample size for group 1 n_2 = sample size for group 2

$t_{\frac{\alpha}{2}}$ = the alpha/2 t - statistic for $n_1 + n_2 - 2$ degrees of freedom

3. 100(1-α) % Confidence Interval for the Difference of Two Means under the Assumption of Unequal Variances between the Two Groups[2]

$$(\bar{x}_1 - \bar{x}_2) \pm t_{\frac{\alpha}{2}} SED$$

With the degrees of freedom for the approximate t statistic is determined by Satterthwaite's formula[2] as follows:

$$df = \frac{(w_1 + w_2)^2}{\frac{w_1^2}{n_1 - 1} + \frac{w_2^2}{n_2 - 1}}$$

where:

$\bar{x}_1$ = sample mean for group 1

$\bar{x}_2$ = sample mean for group 2

s_1 = sample standard deviation for group 1

s_2 = sample standard deviation for group 2

n_1 = sample size for group 1

n_2 = sample size for group 2

$$SED = \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}$$

$$w_1 = \frac{s_1^2}{n_1}$$

$$w_2 = \frac{{s_2}^2}{n_2}$$

2.1.2 Statistics for Categorical Variables

For categorical variables such as gender, MACE, and TVF, results within treatment arm will be summarized with subject counts and percentages/rates, and where specified in the table mockups, with exact 95% Clopper-Pearson[3] confidence intervals. Differences between the two treatment arms, when specified, will be summarized with the difference in percents and the Newcombe[4] score 95% confidence interval for the difference of two percentages.

For efficacy and safety endpoint(s), relative risks (i.e., the ratio of rates), confidence interval for the relative risks, the difference in rates and the confidence interval for difference in rates (using previously-described formulas), and p-values may also be presented for hypothesis generating purposes. The p-values will be based on either Pearson's Chi-square test or Fisher's exact test by checking the expected frequency for each cell in the 2x2 contingency table against Cochran's rule[6], i.e., if the expected frequencies for all cells are ≥ 5, then Pearson's Chi-square test will be used, otherwise Fisher's exact test will be used.

For the determination of event rates at all time points (in-hospital, 30 days, 180 days and 1 to 7 (/8/9/10) years), the denominators are defined as below based on the type of events.

- Death/MI/Revascularization (DMR) event

  Subjects will be included in the analysis if they either had the DMR event by that time or they did not have the DMR event but had follow-up through that time point. In other words, subjects will be included in a given analysis if it can be determined whether or not the subject would have had the DMR event by the time point.

- Stent/Scaffold Thrombosis, Vascular/Bleeding, CVA, and Angina

  Subjects will be included in the analysis if they either had the specific event (for example, for analysis on ST, only ST is considered) by that time or they did not have the event but had follow-up through that time point. In other words, subjects will be included in a given analysis if it can be determined whether or not the subject would have had the event by the time point.

Formulas for calculating confidence intervals for the categorical variables are given below.

1. 100(1-α) % Exact Clopper-Pearson Confidence Interval for A Single Proportion[3]

$$\text{Lower Confidence Limit} = \frac{x}{x + (n - x + 1)F_{1-\frac{\alpha}{2}}(2(n-x+1), 2x)}$$

$$\text{Upper Confidence Limit} = \frac{(x+1)F_{1-\frac{\alpha}{2}}(2(x+1), 2(n-x))}{n - x + (x+1)F_{1-\frac{\alpha}{2}}(2(x+1), 2(n-x))}$$

where:

n = sample size

x = number of "events"

$F_{1-\frac{\alpha}{2}}(df_1, df_2)$ = the (1 - alpha/2) F - statistic for degrees of freedom df_1 and df_2

2. 100(1-α) % Newcombe Score Confidence Interval for the Difference of Two Proportions [4]

   a. 100(1-α) % Wilson Score Confidence Interval for A Single Proportion[5]

$$\text{Lower Confidence Limit} = \left(\hat{p} + Z^2_{\alpha/2}/2n - Z_{\alpha/2}\sqrt{\left(\hat{p}(1-\hat{p}) + Z^2_{\alpha/2}/4n\right)/n}\right)/\left(1 + Z^2_{\alpha/2}/n\right)$$

$$\text{Upper Confidence Limit} = \left(\hat{p} + Z^2_{\alpha/2}/2n + Z_{\alpha/2}\sqrt{\left(\hat{p}(1-\hat{p}) + Z^2_{\alpha/2}/4n\right)/n}\right)/\left(1 + Z^2_{\alpha/2}/n\right)$$

   where:

   $\hat{p} = x/n$

   n = sample size

   x = number of "events"

   $Z_{\alpha/2}$ = 100(1-α/2)th percentile of the standard normal distribution

   b. 100(1-α) % Newcombe Score Confidence Interval for the Difference of Two Proportions[4]

$$\text{Lower Confidence Limit} = (\hat{p}_1 - \hat{p}_2) - Z_{\alpha/2}\sqrt{L_1(1-L_1)/n_1 + U_2(1-U_2)/n_2}$$

$$\text{Upper Confidence Limit} = (\hat{p}_1 - \hat{p}_2) + Z_{\alpha/2}\sqrt{U_1(1-U_1)/n_1 + L_2(1-L_2)/n_2}$$

where:

$\hat{p}_1$ = sample proportion for group 1
$\hat{p}_2$ = sample proportion for group 2
L_1 and U_1 are the lower and upper Wilson Score confidence limits for p_1
L_2 and U_2 are the lower and upper Wilson Score confidence limits for p_2
$Z_{\alpha/2}$ = 100(1-α/2)th percentile of the standard normal distribution

2.1.3 Survival Analysis

2.1.3.1 General Survival Analysis

Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point. Survival curves will be constructed using Kaplan-Meier estimates. Unadjusted log-rank test results will be displayed for comparison of survival distributions at 30 days, 180 days and 1, 2, 3, 4, 5, 6, 7 (/8/9/10) years. Similar analyses will be performed for the 3-4/3-5/3-6/3-7(/3-8/3-9/3-10) year landmark endpoints.

Summary tables for safety and efficacy endpoints will include failure rates (Kaplan-Meier estimates), hazard ratios, confidence interval for the hazard ratio, and a p-value. For the primary analysis report, all available data will be used.

[redacted]

[redacted]

2.1.4 Hypothesis Testing

[redacted]

[redacted]

2.2 Subgroups for Analysis

All of the following subgroup analyses are intended for the final product IFU. All data collected will be summarized for ABSORB IV (N=2600) and the pooled population of ABSORB III primary analysis group and ABSORB IV (N=4600).

2.2.1 Sex

Sex-specific subgroup analyses[9] will be performed on the ITT population. Baseline demographics, baseline subject characteristics, procedure information, morphology, quantitative coronary angiography, and hierarchical/non-hierarchical adverse event data will be summarized and compared between females and males.

[redacted]

2.2.2 Diabetes

Diabetic subgroup analysis will be performed on the ITT population. Baseline demographics, baseline subject characteristics, procedure information, morphology, quantitative coronary angiography, and hierarchical/non-hierarchical adverse event data will be summarized with descriptive statistics. Comparisons will be made between treatment arms within the following subgroups:

- Medication treated diabetes mellitus, defined as subjects treated with oral hypoglycemic agents or insulin,
- Non-medically treated diabetes mellitus
- Insulin-treated diabetes mellitus, defined as subjects treated with insulin,
- Non-insulin treated diabetes mellitus, defined as subjects not dependent on insulin,
- All diabetes mellitus, defined as any diabetics with or without medical treatment
- Non diabetes mellitus.

2.2.3 Other Subgroups

The following subgroups will be evaluated for the ITT population. The treatment comparisons in these analyses are not powered for hypothesis testing and are not meant for confirmatory inference. Baseline demographics, baseline subject characteristics, procedure information, morphology, quantitative coronary angiography, and hierarchical/non-hierarchical adverse event data will be summarized with descriptive statistics. Comparisons will be made between treatment arms within each of these subgroups.

Ethnicity:

- Non-white
- White

Age:

- Age ≥ Median, Age < Median
- Age <45, ≥ 45 and <55, ≥55 and <65, ≥65 and <80, and ≥80

Number of Target Lesion/Vessel Treated:

- Single target lesion/vessel treated, which includes subjects who had only one target lesion/vessel treated
- Dual target lesion/vessel treated, which includes subjects who had two target lesion/vessel treated
- Three target lesion/vessel treated, which includes subjects who had three target lesion/vessel treated.

Angina Status

- Acute coronary syndrome (unstable angina, NSTEMI, recent STEMI)

- Stable angina or silent ischemia
- Recent STEMI
- NSTEMI
- Unstable Angina
- Stable Angina
- Silent ischemia

Antiplatelet Therapy

- P2Y12 Receptor Inhibitor (Yes/No)
- Clopidogrel or Ticlopidine (Yes/No)
- Prasugrel or Ticagrelor (Yes/No)
- Clopidogrel (Yes/No)
- Ticlopidine (Yes/No)
- Prasugrel (Yes/No)Ticagrelor (Yes/No)

RVD by QCA

- RVD ≥ Median, RVD < Median
- Small Vessel (RVD ≥ 2.25 mm, RVD < 2.25 mm)

Implanted Device Diameter

- Device Diameter 2.5 mm vs. 3.0 mm vs. 3.5 mm

Population

- ABSORB III-like (Yes/No)
- ACS (Yes/No)

Implantation technique

- Compete PSP vs Incomplete PSP
  - The implantation technique used during the index procedure must satisfy all of the following criteria to be considered as complete PSP, otherwise it will be incomplete PSP
    1. Pre-dilatation performed
    2. QCA RVD ≥ 2.25 mm
    3. Post-dilatation performed with pressure > 16 atm and nominal scaffold diameter < diameter of post-dilatation balloon ≤ nominal scaffold diameter + 0.5 mm
- Each of the three individual component of complete PSP listed above (Yes/No)

2.3 Analysis Window

- Pre-procedure
- Post-procedure
- 30 days

- 90 days
- 180 days
- 270 days
- 1 year (365 days)
- 2 years (730 days)
- 3 years (1095 days)
- 4 years (1460 days)
- 5 years (1825 days)
- 6 years (2190 days)
- 7 years (2555 days)
- 8 years (optional, 2920 days)
- 9 years (optional, 3285 days)
- 10 years (optional, 3650 days)

[redacted]

[redacted]

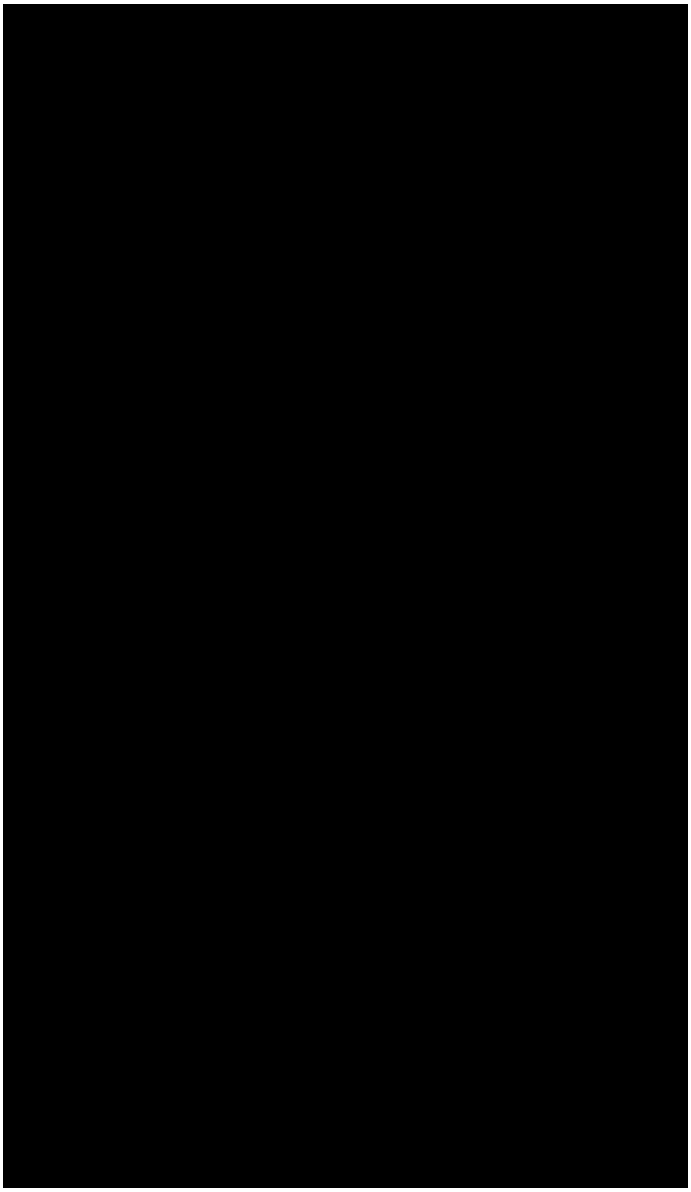
[redacted]

[redacted]

2.6 Adjustments for Covariates

Unless otherwise specified, no adjustments for covariates will be made for any of the variables in the analyses.

[redacted]



[redacted]

[redacted]

2.11 Documentation and Other Considerations

All analyses will be performed using SAS® for Windows, version 9.1 or higher.

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4. ACRONYMS AND ABBREVIATIONS

Acronym/ Abbreviation	Term
ARC	Academic Research Consortium
AT	As-Treated
CEC	Clinical Events Committee
CK-MB	Creatine Kinase Myocardial-Band Isoenzyme
CVA	Cerebrovascular Accident or Stroke
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ITT	Intent To Treat
IVRS	Interactive Voice Response Service
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
mm	Millimeter
NCSS/PASS	Number Cruncher Statistical System/Power Analysis and Sample Size software
NI	Non-inferiority
NSTEMI	Non-ST-segment elevation MI
PCI	Percutaneous Coronary Intervention
PMA	Pre-Marketing Approval
RVD	Reference Vessel Diameter
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
STEMI	ST-segment elevation MI
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization