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)

Version 6.0
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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 Version 16.0, March 14, 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 Objectives:**
  - 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.

2. Landmark TLF Primary Endpoint: TLF between 3 and 7 years (time from 3 year to the first TLF between 3 and 7 years), non-inferiority (NI) of Absorb BVS to XIENCE with

reflex testing to superiority. TLF is defined as composite of Cardiac Death, Myocardial Infarction (per protocol-defined MI definition, **Appendix II** of the study protocol) attributable to Target Vessel (TV-MI), or Ischemia-Driven Target Lesion Revascularization (ID-TLR).

This analysis will include approximately 4600 subjects (2000 primary analysis subjects of ABSORB III and 2600 subjects of ABSORB IV).

1.3.2 Secondary Endpoints

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.
    - For subjects who receive a planned staged procedure to treat one or more target lesions, the analysis will exclude angina or angina equivalent symptoms that occurred following the original index procedure through hospital discharge or 7 days after the final procedure, whichever occurs first.

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**
  - **Landmark analysis 3-4/3-5/3-6/3-7(/3-8/3-9/3-10) years on TLF and components**
  - **Landmark analysis 3-4/3-5/3-6/3-7(/3-8/3-9/3-10) years on MACE and TVF and their components**

- **Landmark analysis 3-4/3-5/3-6/3-7(/3-8/3-9/3-10) years on Scaffold-Thrombosis/Stent Thrombosis (per ARC definition, definite and probable)**

- **TLF through 1 year based on 4600 subjects (2000 primary analysis subjects of ABSORB III and 2600 subjects of ABSORB IV)**

- **TLF through 7 (/8/9/10) years based on 4600 subjects (2000 primary analysis subjects of ABSORB III and 2600 subjects of ABSORB IV)**

1.4 Analysis Populations

1.4.1 Intent to Treat (ITT) Population

The ITT population is defined as the subjects registered in the study at the point of randomization, regardless of the treatment actually received. Subjects will be analyzed in the treatment group to which they were randomized. Subjects enrolled but not randomized will not be included in the ITT population.

1.4.2 As-Treated (AT) Population

The As-Treated (AT) population will consist of subjects who are randomized and have received at least one study device (Absorb BVS or XIENCE) at the target lesion. Subjects who have received at least one Absorb BVS device will be included in the Absorb BVS arm; and subjects who have received at least one XIENCE device and none of Absorb BVS device will be included in the XIENCE arm.

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. The details of the testing sequence and method on handling multiplicity issue will be discussed in details in section 2.8.

The two primary endpoints will be evaluated based on both the ITT and the AT populations. The primary analysis will be based on the ITT population. The power calculation of primary endpoints can be found below:

1.5.1.1 TLF at 30 Days Primary Endpoint

The TLF at 30 days 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 30 days with a one-sided alpha of 0.025. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $TLF_{Absorb} - TLF_{XIENCE} \geq \Delta_{TLF}$

H_A: $TLF_{Absorb} - TLF_{XIENCE} < \Delta_{TLF}$.

TLF_{BVS} and TLF_{XIENCE} are the 30-Day TLF rates in the Absorb BVS and XIENCE arms, respectively. Δ_{TLF} is the non-inferiority margin for this powered primary endpoint.

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

- The true 30-Day TLF rate is assumed to be 4.9% for both the Absorb BVS arm and the XIENCE arm
- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{TLF}): 2.9%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)
- 1% loss to follow-up at 30 days

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.

Detailed justification of the true rate assumption and the non-inferiority margin can be found in a separate appendix to the SAP.

1.5.1.2 Landmark TLF Primary Endpoint

The primary endpoint of TLF between 3 and 7 years (time from 3 year to the first TLF between 3 and 7 years) will be tested for non-inferiority with reflex testing to superiority.

The hypothesis test is designed to show non-inferiority of Absorb BVS to XIENCE for the primary endpoint with a one-sided alpha of 0.025. This analysis will include approximately 4600 subjects (2000 primary analysis subjects of ABSORB III and 2600 subjects of ABSORB IV).

Details on the design of this endpoint will be included once finalized.

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. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $TLF_{Absorb} - TLF_{XIENCE} \geq \Delta_{TLF}$

H_A: $TLF_{Absorb} - TLF_{XIENCE} < \Delta_{TLF.}$

TLF_{BVS} and TLF_{XIENCE} are the 1 year TLF rates in the Absorb BVS and XIENCE arms, respectively. Δ_{TLF} is the non-inferiority margin for this powered secondary endpoint.

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

- The true 1 year TLF rate is assumed to be 9.7% for both the Absorb BVS arm and the XIENCE arm
- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{TLF}): 4.8%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)
- 5% loss to follow-up at 1 year

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.

The above true rate and NI margin are different from those in ABSORB III because ABSORB IV includes more complex patients. Detailed justification of the true rate assumption and the non-inferiority margin can be found in a separate appendix to the SAP.

1.5.2.2 Powered Secondary Endpoint #2: Angina through 1 year

The testing of the powered secondary endpoint will be dependent on the outcome of the primary endpoint of TLF at 1 year and will be performed based on a pre-specified testing sequence. The details of the testing sequence and method on handling multiplicity issue will be discussed in details in section 2.8.

The percentage of patients who had angina within 1 year will be tested for non-inferiority with reflex testing to superiority. This analysis will consist of ~2600 subjects in ABSORB IV. The powered secondary endpoint will be evaluated based on both the ITT and the AT populations. The primary analysis will be based on the ITT population. The power calculation of the powered secondary endpoint can be found below:

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. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $ANGINA_{Absorb} - ANGINA_{XIENCE} \geq \Delta_{ANGINA}$

H_A: $ANGINA_{Absorb} - ANGINA_{XIENCE} < \Delta_{ANGINA}$

$ANGINA_{Absorb}$ and $ANGINA_{XIENCE}$ are the percentage of patients with angina within 1 year in the Absorb BVS and XIENCE arms, respectively. Δ_{ANGINA} is the non-inferiority margin for this powered secondary endpoint.

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

- The true percentage of patients with angina within 1 year is assumed to be 22.6% for both the Absorb BVS arm and the XIENCE arm
- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{ANGINA}): 7%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)
- 5% loss to follow-up at 1 year

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].

Detailed justification of the non-inferiority margin can be found in a separate appendix to the SAP.

If the non-inferiority of Absorb BVS to XIENCE is demonstrated and the percentage is lower in Absorb BVS compared to XIENCE, a superiority test will be performed at the two-sided alpha 0.05 level.

The null (H_0) and alternative (H_A) hypotheses are:

H_0: $ANGINA_{Absorb} - ANGINA_{XIENCE} = 0$

H_A: $ANGINA_{Absorb} - ANGINA_{XIENCE} \neq 0$

$ANGINA_{Absorb}$ and $ANGINA_{XIENCE}$ are the percentage of patients with angina within 1 year in the Absorb BVS and XIENCE arms, respectively.

With the effective sample size 2470 at 1 year, the study has approximately 86% power to demonstrate superiority with a difference of 4.9% between the Absorb BVS arm and the XIENCE arm (e.g. 17.7% in the Absorb BVS arm vs. 22.6% in the XIENCE arm) using Pearson's Chi-square test.

The sample size calculation for Pearson's Chi-square test was performed using SAS 9.3 (SAS Institute Inc., Cary, NC)[3].

1.5.3 Study Success

Study success is defined as passing the non-inferiority test of Absorb BVS to XIENCE on either the primary endpoint of percentage of patients who experienced TLF within 30 days or the primary endpoint of TLF between 3 and 7 years. Detail of the test is specified in sections 1.5.1 and 2.1.4.

1.6 Randomization and Blinding

1.6.1 Randomization

1.6.1.1 Stratified Randomization

Approximately 2600 subjects will be randomized 1:1 in the ABSORB IV trial (test device: Absorb BVS vs. control device: XIENCE). The maximum number of subjects to be registered per site is 300, which is 10% of the total number of subjects (N=2600). This cap per site will prevent the scenario where the results from a few

sites dominate the overall study result. Randomization will be stratified by diabetes mellitus (diabetic vs. non-diabetic) and ABSORB III like or not. ABSORB III like will be determined by the absence of planned staged procedure, number of target lesions ≤ 2, and no ACS or STEMI with elevated enzymes. Subjects will also be stratified by site at some pre-specified sites (expected high-enrolling sites). Other sites will be combined to ensure a sufficient number of subjects for the attainment of the desired randomization ratio. A centralized randomization service, IVRS, will be used.

1.6.1.2 Timing of Randomization

Randomization will be done after successful and uncomplicated pre-dilatation of the target lesion and vessel sizing (refer to **Protocol Summary**, Treatment Strategy, for details). If there is a non-target lesion, it must be successfully treated prior to randomization. If there are two or three target lesions, after the first target lesion was successfully pre-dilated and vessel sizing criteria still met, the operator may at this point choose to randomize the patient, or pre-dilate other lesions. If other lesions are pre-dilated, all such pre-dilatations must be considered successful according to the above criteria prior to randomization. If there are two target lesions in a single epicardial coronary artery, it is strongly recommended that both be successfully pre-dilated before the patient is randomized.

Once randomization is completed and a treatment is assigned, the assigned device must be used for all lesions. An Absorb BVS scaffold may never be used in a patient randomized to XIENCE. However, if the patient is randomized to Absorb BVS and the scaffold cannot be delivered or a complication otherwise develops that requires treatment with a drug-eluting stent, a XIENCE stent must be used. If the XIENCE stent is unable to successfully treat the patient, any commercially available device approved for use in that geography may be used as necessary in the best interests of the patient. Regardless of the actual device the subject received, the subject will be included in ITT population per the original randomization assignment.

The subject is considered to be successfully registered in this study and considered in the ITT population at the point of randomization (refer to Section 6.4 of the protocol). Refer to protocol **Appendix IV (Figure 1 and 2**) for enrollment and registration timeline and flow chart.

1.6.2 Blinding

This is a single-blinded clinical trial. Subjects will be blinded to their treatment assignment and the study site personnel will be trained not to disclose the treatment assignment to the subject. In addition to standard procedural sedation, headphones playing music during the procedure will be worn by the patient to reduce the possibility of unblinding. Additionally, blinded site personnel, not present at the index procedure, will be assigned to conduct the clinical follow-up and they will be provided with a standard follow-up interview in order to reduce bias and maintain subject blinding. Subject blinding should be maintained until the 7-year follow-up visit (potentially until 8 and/or 9 and/or 10 year follow-up) for all registered subjects is completed.

The physician performing the procedure will not be blinded to the assigned treatment. Thus, if clinical follow-up with a study physician is deemed necessary at the protocol required follow-up time points, a different physician (or designee) than the one who implanted the device(s) must conduct the follow-up clinical visits in order to maintain subject blinding. Similarly, follow-up visits with research personnel must be conducted by different persons than those who were unblinded during the index hospitalization. Site personnel will be adequately trained such that the physician (or designee) conducting the clinical follow-up is adequately blinded to the treatment received by the subject. For unscheduled visits, subjects may see the physician who implanted the device(s). Treating physician should prevent unblinding of the subject when they conduct any non-protocol related visits. In addition, hospital notes, dictated notes, notes to referral physicians, billing information, and other related patient information must refer to the assigned treatment device as “study device” or other non-revealing language, to maintain the blind. The only exception to these requirements is if the hospital billing department does not allow this practice. Sites will be provided with a blinding guidance document that will instruct the sites on how to maintain blinding at the clinical sites.

The Clinical Events Committee (CEC) will be blinded to the randomization assignments. The angiographic core laboratories cannot be blinded to the device received. The Data Safety Monitoring Board (DSMB) will also be blinded to the subject’s randomization. Independent statisticians will generate blinded tables for review by the DSMB. The DSMB may request unblinded data if a safety signal is observed.

Sponsor personnel that will be unblinded will be the independent biostatisticians involved in generating and verifying the randomization code, key Clinical Science and Operations, Clinical Safety Monitors, Site Monitors, Clinical Data Management, Electronic Database Programmer, Inventory Management staff, and Clinical Information System (IS)

personnel working on the trial. Restricted access of blinded personnel to the clinical database will be maintained until unblinding of the study.

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.

2.1.3.2 Survival Analysis for the Landmark TLF Primary Endpoint

The primary endpoint of TLF between 3 and 7 years is based on the landmark TLF rate after 3 year (time from 3 year to the first TLF between 3 and 7 years). All TLF events within 3 year will be excluded from this endpoint. All subjects will be included in the landmark TLF primary endpoint as long as they are not lost to follow-up (or had died) by 3 year, even though they may have had TLF event within the 3-year follow-up

The analysis will be conducted when the follow-up of the pooled population (ABSORB III primary analysis group and ABSORB IV) has reached 7 years (or 6 years for the interim analysis). Log-rank test will be used for the analysis of the primary endpoint. The

assumption of proportional hazard will be checked using the following method[6]

A Cox regression will be performed for the primary endpoint with the following two covariates:

1. Treatment assignment (X_1) (e.g., for Absorb BVS, X_1=1 and for XIENCE, X_1=0)
2. The covariate defined by $X_1 \log(t)$, where t is the corresponding event/censoring time of the subjects.

The proportional hazard assumption can then be checked by testing whether the coefficient of $X_1 \log(t)$ is significantly different from 0. If the test is not significant, then the proportional hazard assumption is valid. Otherwise, the proportional hazard assumption is not satisfied.

If the assumption of proportional hazard is not satisfied, then analysis for the primary endpoint will be based on the Com-Nougue approach[7] which utilizes the difference in Kaplan-Meier failure rate estimates. Abbott Vascular noticed that the power simulated for the primary endpoint based on the Com-Nougue approach was very similar to that calculated using the asymptotic approach (difference ≤0.5%). Therefore, for the powered calculation, asymptotic test was used to approximate the power for the Com-Nougue approach using NCSS PASS 11 (Hintze, J., 2011, NCSS, LLC. Kaysville, Utah).

The primary endpoint of TLF between 3 and 7 years will be evaluated using the difference in Kaplan-Meier failure rates. The hypothesis test is designed to show non-inferiority of Absorb BVS to XIENCE for the primary endpoint with a one-sided alpha of 0.025. This analysis will include approximately 4600 subjects (2000 primary analysis subjects of ABSORB III and 2600 subjects of ABSORB IV).

The null (H_0) and alternative (H_A) hypotheses are:

H_0: $F_{Absorb} - F_{XIENCE} \geq \Delta_{PE}$

H_A: $F_{Absorb} - F_{XIENCE} < \Delta_{PE.}$

F_{BVS} and F_{XIENCE} are the Kaplan-Meier estimates of failure rate of the primary endpoint at 7 years in the Absorb BVS and XIENCE arms, respectively. Δ_{PE} is the non-inferiority margin for the primary endpoint. Details on the design of this endpoint will be included once finalized.

2.1.4 Hypothesis Testing

Formal non-inferiority test is planned for the primary endpoint and Powered Secondary Endpoints.

For the Landmark TLF primary endpoint, log rank test will be applied for non-inferiority test and superiority test. The non-inferiority test will be one-tailed. The null and alternative hypotheses will be of the following form:

H_0: HR $\geq \delta$

H_A: HR $< \delta$

where HR is the hazard ratio of treatment vs control.

The null and alternative hypotheses of the final superiority of the primary endpoint will be of the following form:

H_0: HR $= 1$

H_A: HR $\neq 1$

The null and alternative hypotheses of the interim superiority analysis of the primary endpoint will be of the following form:

H_0: HR ≥ 1

H_A: HR < 1

For the Landmark TLF primary endpoint (if proportional hazard assumption is not satisfied), the primary endpoint of TLF at 1 year, and the Angina power secondary endpoint, the non-inferiority test will be one-tailed. The null and alternative hypotheses will be of the following form:

H_0: $\text{Endpoint}_{\text{treatment}} - \text{Endpoint}_{\text{control}} \geq \Delta$

H_A: $\text{Endpoint}_{\text{treatment}} - \text{Endpoint}_{\text{control}} < \Delta$

Z-test will be used for the non-inferiority test for the Landmark TLF primary endpoint. Farrington and Manning non-inferiority test[1] will be used for the primary endpoint of TLF at 1 year and the Angina powered secondary endpoint.

For the Landmark TLF primary endpoint (final analysis if proportional hazard assumption is not satisfied) and the Angina powered secondary endpoint, superiority test will be two-tailed. The null and alternative hypotheses for this inequality testing will be of the following form:

H_0: $\text{Endpoint}_{\text{treatment}} = \text{Endpoint}_{\text{control}}$

H_A: $\text{Endpoint}_{\text{treatment}} \neq \text{Endpoint}_{\text{control}}$

Z-test will be used for the superiority test of the Landmark TLF primary endpoint. Pearson's Chi-square test will be used for the Angina powered secondary endpoint. If Cochran's rule[8]

is not met, i.e., if the expected frequencies for all cells are < 5, then Fisher's exact test will be used instead of Pearson's Chi-square test.

For the Landmark TLF primary endpoint (interim analysis if proportional hazard assumption is not satisfied), superiority test will be one-tailed. The null and alternative hypotheses for this inequality testing will be of the following form:

$$H_0: \text{Endpoint}_{\text{treatment}} \geq \text{Endpoint}_{\text{control}}$$

$$H_A: \text{Endpoint}_{\text{treatment}} < \text{Endpoint}_{\text{control}}$$

Z-test will be used for the superiority test of the Landmark TLF primary endpoint.

As the study was not powered to detect differences for variables other than the primary and the powered secondary endpoints, p-values presented for analyses other than these endpoints are for hypothesis generating purpose only.

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.

Furthermore, to evaluate the effects of sex on the primary endpoint, interaction effect between treatment and sex on the primary endpoint will be tested against an alpha level of 0.15.

If the interaction p-value is < 0.15, Abbott Vascular will examine subject demographics and baseline characteristics for possible correlations or confounding factors. Correlations will be examined by interaction testing. If the interaction p-value is < 0.15, Abbott Vascular will also explore the Gail and Simon test[10] using the corresponding SAS macro[11] in order to identify qualitative interaction (vs quantitative interaction) given the number of hypothesis testing performed and the likelihood of finding significance by chance.

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)

2.4 Handling of Missing Data

All analyses will be based on available data with missing data excluded. Any unused or spurious data will be noted as appropriate in the final report. Tipping-point analysis on the primary endpoint of TLF at 1 year and the powered secondary endpoint of percentage of patients who experienced angina within 1 year may be conducted as a sensitivity analysis.

2.5 Handling of Poolability Issue

2.5.1 Multiple Geography Effect

Analysis will be performed pooling data between geographies (US and OUS). OUS sites will enroll no more than 30% of the ABSORB IV population, i.e., no more than 900 subjects.

To evaluate the geography effect on the primary endpoints, interaction effect between treatment and geography on the primary endpoint will be tested against an alpha level of 0.15. For the primary endpoint of percentage of patients who experienced TLF at 30 days, the analysis will be conducted on the ABSORB IV population (N=2600). For the primary endpoint of TLF between 3 and 7 years, the analysis will be conducted on the pooled population of ABSORB III primary analysis group and ABSORB IV (N=4600).

If the interaction p-value is < 0.15, Abbott Vascular will examine subject demographics and baseline clinical and angiographic characteristics for possible correlations or confounding factors. Correlations will be examined by interaction testing. If the interaction p-value is < 0.15, Abbott Vascular will also explore the Gail and Simon test[10] using the corresponding SAS macro[11] in order to identify qualitative interaction (vs quantitative interaction).

The above poolability analysis will be done when the number of OUS subjects is adequate. Should the number of OUS subjects be small, e.g. 1% pooled population of ABSORB III primary analysis group and ABSORB IV (N=4600), the above poolability analysis may not be necessary.

2.5.2 Multiple Center Effect

Analysis will be performed pooling data across study sites.

The ABSORB IV trial will have approximately 140 sites. For the analysis of center effect, data from smaller sites may be combined for the analysis. Smaller sites are defined as sites with fewer than 20 subjects per site.

The pooling of the smaller sites will be based on the following rules:

- Sort all smaller sites based on the number of subjects per site in an ascending order; if there are ties, sort further by site number
- Starting from the smallest site in this list, combine sites by going up the list until the combined group size first reaches 20 or larger. At this point, a super site is identified
- Repeat the above grouping process from the next smallest site above the newly formed super site.
- The grouping process ends when all smaller sites have been accounted for

This way, the sizes of the super sites (which are a result of grouping smaller sites) will range between 20 and up to 38 (19+19). Abbott Vascular believes this represents a reasonable range of sample sizes which will provide meaningful estimates of within-sites variations and in the meantime will not alter between-sites variation.

To evaluate the center effect on the primary endpoints, interaction effect between treatment and center on the primary endpoint will be tested against an alpha level of 0.15. For the primary endpoint of TLF at 30 days, the analysis will be conducted on the ABSORB IV population (N=2600). For the primary endpoint of TLF between 3 and 7 years, the analysis will be conducted on the pooled population of ABSORB III primary analysis group and ABSORB IV (N=4600).

If the interaction p-value is < 0.15, sensitivity analysis on the primary endpoint using random effect model (center as a random effect) will be explored. In addition, Abbott Vascular will examine subject demographics and baseline clinical and angiographic characteristics for possible correlations or confounding factors. Correlations will be examined by interaction testing. If the interaction p-value is < 0.15, Abbott Vascular will also explore the Gail and Simon test[10] using the corresponding SAS macro[11] in order to identify qualitative interaction

(vs quantitative interaction) given the number of hypothesis testing performed and the likelihood of finding significance by chance.

2.5.3 Multiple Study Stent Effect

Analyses will be performed pooling data across study stents (XIENCE V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro (OUS only), and XIENCE Pro^X (OUS only) for the XIENCE arm. Once Absorb GT1™ BVS System is commercially available, it can also be used in the ABSORB IV trial. Analyses will be performed pooling data across Absorb™ BVS and Absorb GT1™ BVS for the Absorb BVS arm.

The study stents used for the XIENCE arm are considered to be interchangeable in the study. To provide evidence for poolability between study stents, analysis showing that XIENCE V and XIENCE PRIME are bioequivalent has been submitted to the FDA in the XIENCE PRIME PMA submission (P110019). XIENCE PRIME, XIENCE Xpedition, and XIENCE Alpine are the same stent mounted on different delivery systems. XIENCE Pro is a rebranded version of XIENCE V (workhorse) and XIENCE Prime (long lengths) in OUS, and XIENCE Pro^X is a rebranded version of XIENCE Xpedition in OUS. Descriptive analysis using summary statistics described in Sections 2.1.1, 2.1.2 and 2.1.3 will be performed to assess the consistency of results between the study stents, including sensitivity analysis performed on clinical outcomes stratified by study stents. For the primary endpoint of TLF at 30 days, the analysis will be conducted on the ABSORB IV population (N=2600). For the primary endpoint of TLF between 3 and 7 years, the analysis will be conducted on the pooled population of ABSORB III primary analysis group and ABSORB IV (N=4600).

In addition, a data poolability test regarding primary endpoints between Absorb™ BVS and Absorb GT1™ BVS will be conducted at an alpha level of 0.05. For the primary endpoint of TLF at 1 year, the analysis will be conducted on the Absorb BVS arm in the ABSORB IV population. For the primary endpoint of TLF between 1 and 5 years, the analysis will be conducted on the Absorb BVS arm in the pooled population of ABSORB III primary analysis group and ABSORB IV.

The above analysis will be done when the number of subjects for a specific stent is adequate. Should the number of subjects be small, e.g. 1% ABSORB IV primary analysis population for the primary endpoint of TLF at 30 days (N=2600), or 1 % pooled population of ABSORB III primary analysis group and ABSORB IV (N=4600) for the landmark TLF primary endpoint, the analysis may not be necessary for that stent.

2.5.4 Pooling with Other Studies

In general, Abbott Vascular will examine consistency among ABSORB studies via homogeneity test such as Chi-square test for the key endpoint TLF. If there is evidence of inconsistency, subject demographics and baseline clinical and angiographic characteristics will be examined. In addition, sensitivity analysis will be performed to evaluate the impact of influential studies to the clinical outcomes.

Subjects in the ABSORB III and the ABSORB IV trials are directly poolable due to the almost identical protocol and the seamless enrollment between the two trials.

Data from the ABSORB IV trial may be pooled with other trials in order to provide:

- Powered analysis on the long term benefits of Absorb BVS compared to XIENCE (e.g., landmark analysis).
- Powered analysis for key clinical endpoints (e.g., TLF).
- Powered subgroup analysis.
- Analysis of complete PSP vs incomplete PSP

2.5.5 Pooling Subjects under Different Protocol Versions

To evaluate the effect of the changes implemented in the protocol version 14.0 (e.g. angiographic inclusion/exclusion criteria, treatment strategy, and antiplatelet therapy strategy, etc.) on the primary endpoints, interaction effect between treatment and protocol version (prior to version 14.0 vs. version 14.0 and any subsequent versions) on the primary endpoints will be tested against an alpha level of 0.15. For the primary endpoint of TLF at 30 days, the analysis will be conducted on the ABSORB IV population (N=2600). For the primary endpoint of TLF between 3 and 7 years, the analysis will be conducted on the pooled population of ABSORB III primary analysis group and ABSORB IV (N=4600).

If the interaction p-value is < 0.15, Abbott Vascular will also explore the Gail and Simon test[10] using the corresponding SAS macro[11] in order to identify qualitative interaction (vs quantitative interaction).

2.6 Adjustments for Covariates

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

2.7 Interim Analysis

Interim study reports with descriptive analysis may be produced for regulatory or reimbursement purposes.

2.8 Handling of Multiplicity Issue

In ABSORB IV, the primary endpoint of TLF within 30 days and the primary endpoint of TLF between 3 and 7 years (hence excluding any treatment effect within 1 year) are mechanistically, functionally and temporally separated from each other. Therefore the primary endpoints will be tested independently. The alpha for each of the two primary endpoints will be controlled at 0.025. Because of the independent testing, the study-wise Type-I error rate will be controlled at an alpha level of 0.05 (Figure 1).

The powered secondary endpoints of TLF within 1 year and the percentage of patients who experienced angina within 1 year will be tested according to a pre-specified sequence when all subjects in ABSORB IV finish 1 year follow-up (Figure 2).

Figure 1 Overall Study-wise Type-I Error Control (Alpha=0.05)

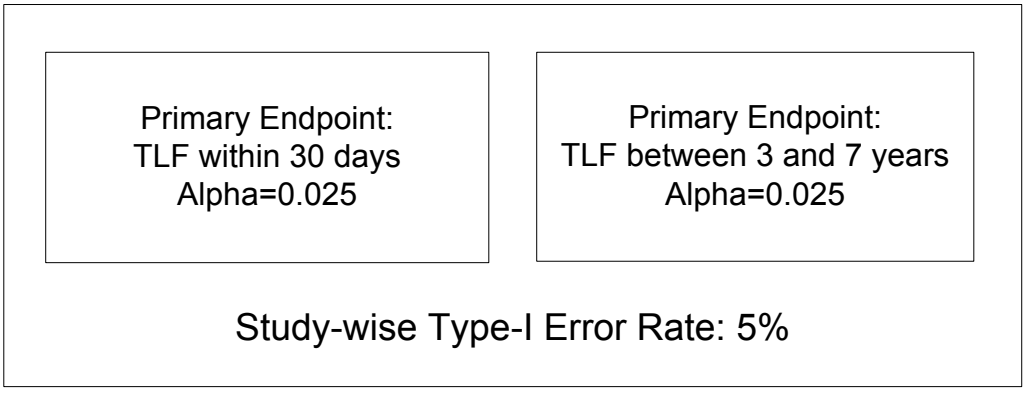
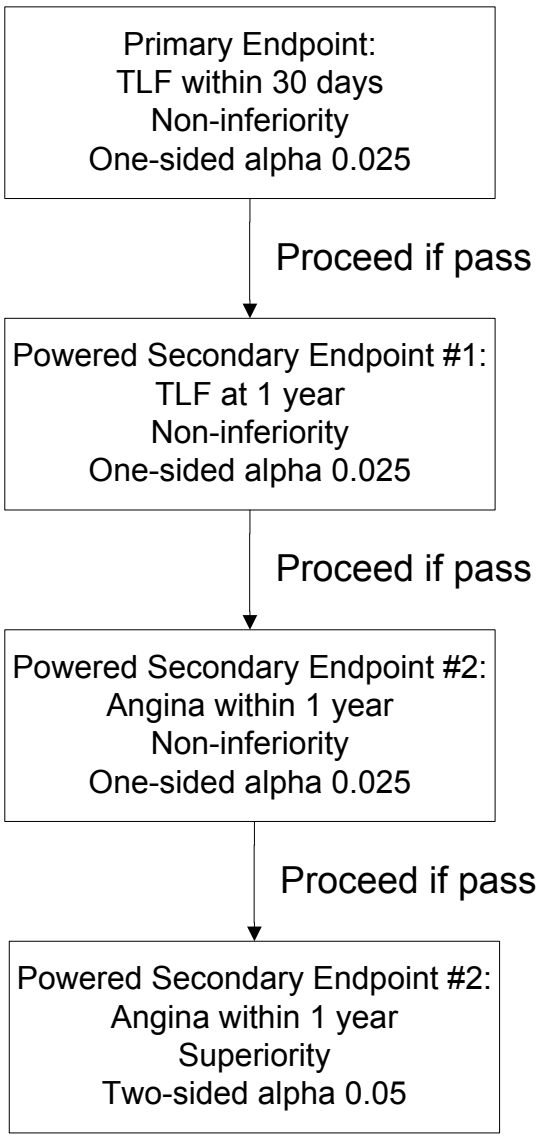


Figure 2 Type-I Error Control for the Primary Endpoint of TLF at 1 Year and the Powered Secondary Endpoint of Angina at 1 Year (Alpha=0.025)


Primary Endpoint:
TLF within 30 days
Non-inferiority
One-sided alpha 0.025
Proceed if pass
Powered Secondary Endpoint #1:
TLF at 1 year
Non-inferiority
One-sided alpha 0.025
Proceed if pass
Powered Secondary Endpoint #2:
Angina within 1 year
Non-inferiority
One-sided alpha 0.025
Proceed if pass
Powered Secondary Endpoint #2:
Angina within 1 year
Superiority
Two-sided alpha 0.05

The objectives of the ABSORB-RESOLVE imaging sub-study are separate from the ABSORB IV objectives and therefore it will not be included in multiplicity control of the ABSORB IV trial.

2.9 Sensitivity Analysis

The primary endpoint of TLF at 30 days and the powered secondary endpoints of TLF at 1 year and Angina at 1 year will be analyzed separately for

1. ABSORB IV subjects that are ABSORB III-like
2. ABSORB IV subjects that are not ABSORB III-like

The landmark TLF primary endpoint will be analyzed separately for

1. The pooled population of ABSORB III primary analysis group and ABSORB IV subjects that are ABSORB III-like
2. ABSORB IV subjects that are not ABSORB III-like.

2.10 Exploratory Analysis on Patient Perception

Patients' perception on which treatment they have received will be collected in ABSORB IV in order to evaluate any potential perception bias on the powered secondary endpoint of angina within 1 year.

ABSORB IV subjects are grouped according to actual treatment received: a) Absorb BVS and b) XIENCE. Additional subgroups will be created based on the subjects perceptions on which treatment they received: a) Absorb BVS (definite or probable belief that they received Absorb BVS), b) XIENCE (definite or probably belief that they received XIENCE), and c) Don't Know. The following exploratory analyses are planned:

- Within each treatment arm, angina rate within 1 year among perception groups using event rates and 95% confidence intervals, and Chi-square tests for trend.
- Treatment effect of Absorb BVS compared to XIENCE may be examined among perception groups using event rates and 95% confidence intervals, and Chi-square tests.
- The interaction between treatment and perception and its impact on angina within 1 year will be examined using logistic regression.

Because the number of subjects that falls into each group is unpredictable, not all analyses may be appropriate, especially if the sample size is small in certain groups. On the other hand, if the sample size is sufficiently large in each group, further exploratory or subgroup analyses may be

performed. For example, the combined group of subjects' perception of definitely or probably receiving each device may be analyzed as 2 separate groups.

2.11 Documentation and Other Considerations

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

3. REFERENCES

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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