Abbott

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Absorb GT1 Japan PMS
Absorb GT1 Bioresorbable Vascular Scaffold (BVS) System Post-marketing Surveillance (PMS)
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Sponsor [redacted]

[redacted]

Abbott Vascular

Protocol 16-310

Absorb GT1 Bioresorbable Vascular Scaffold System Post-marketing Surveillance Protocol

Statistical Analysis Plan (Part I: Methodology)

[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 for Protocol 16-310, the Absorb GT1 Post-marketing surveillance study (hereinafter referred to as "Surveillance"). This plan is based on the [redacted] study protocol.

1.2 Study Objectives

The purpose of the Surveillance is to know the frequency and status of adverse device effects and adverse events in order to assure the safety of the new medical device, Absorb GT1 Bioresorbable Vascular Scaffold System ([redacted] hereinafter referred to as "Absorb GT1"), and to collect efficacy and safety information for evaluating clinical use results.

1.3 Study Design

Based on the Ministerial Ordinance on Good Post-marketing Study Practice (GPSP) for Medical Device, the Surveillance will **continuously register** approximately 2000 subjects with ischemic heart disease potentially indicated for treatment with the Absorb GT1 in two phases. **Only on-label use of the Absorb GT1 will occur** in this Surveillance until otherwise allowed by the Sponsor although this is a post-marketing surveillance.

Phase 1 will contain the first 250 registered subjects at approximately 45 sites to confirm the efficacy of physician training and to establish optimal training for increasing medical institutions participation in post-marketing evaluation. Subject will continue to register in Phase 2 at up to 200 sites until all 2000 subjects are registered in the Surveillance. The main purpose of Phase 2 is to confirm safety. Data will be collected until all subjects complete 5-year follow-up. All subjects will have a follow-up telephone contact or office visit at 3 months and 1, 2, 3, 4 and 5 years.

1.3.1 Primary Endpoints

Phase 1 (250 subjects)

All subjects will be treated by imaging-guided implantation technique using IVUS/OCT. At least first 150 subjects will be analyzed by the core lab.

- Exclusion of very small vessels (Evaluation of RVD to exclude small vessels)
- Scaffold apposition assessed by intravascular imaging (analyzed by the IVUS/OCT core lab)

Phase 1 + Phase 2 (2000 subjects)

- Device deficiency at procedure of implantation
- Scaffold thrombosis (ST)
    - If ST rate at 3 months is ≤ 0.9%, then commercial sale will be started
    - If ST rate at 2 years is ≥ 1.5%, then investigation will be implemented to identify the cause

Scaffold thrombosis events occurred during the Surveillance will be adjudicated by a scaffold thrombosis image-review committee.

1.3.2 Other Endpoints

To be evaluated per typical DES clinical studies.

1.3.2.1 Clinical Endpoints

Clinical endpoints will be evaluated in hospital and at each follow-up time point (3 months, and 1, 2, 3, 4, and 5 years).

- Component endpoints
    - Death (Cardiac/Vascular/Non-Cardiovascular)
    - Myocardial Infarction (TV-MI/NTV-MI)
    - Target Lesion Revascularization (ID-TLR/NID-TLR)
    - Target Vessel Revascularization (ID-TVR/NID-TVR)
    - All coronary revascularization
- Composite endpoints
    - DMR (All death/All MI/All revascularization)
    - TVF (Cardiac death/All MI/ID-TVR)
    - MACE (Cardiac death/All MI/ID-TLR)
    - TLF (Cardiac death/TV-MI/ID-TLR)
    - Cardiac death/All MI

Clinical events committee (CEC) will evaluate all deaths and suspected of MIs for 3 years maximally. Surveillance sites will cooperate in providing materials needed to adjudication (e.g., death report, discharged summary) to the Sponsor, if a patient is dead or is suspected to have MI.

1.3.2.2 Angiographic Endpoints (core lab analysis)

Pre-procedure

- Morphology
- TIMI blood flow
- Lesion length
- RVD
- MLD
- %DS

Post-procedure

- TIMI blood flow
- RVD (Proximal, Distal, Segment)
- MLD (Proximal, Distal, In-stent, In-segment)
- %DS (Proximal, Distal, In-stent, In-segment)
- Acute gain (In-stent, In-segment)

1.3.2.3 IVUS/OCT Endpoints (core lab analysis)

The IVUS/OCT endpoints will be updated according to the finalized definitions from the core labs.

Pre-procedure (or after pre-dilatation)

- Lumen diameter
- Lumen area

Post-procedure

- Lumen diameter
- Lumen area
- MLA
- Incomplete apposition of the Absorb GT1 strut (per lesion, per strut)
- Fracture of the Absorb GT1 strut

1.4 Analysis Populations

[redacted]

- **Intent-to-Treat (ITT)**

  [redacted]

- **Full Analysis Set (FAS)**

  [redacted]

- **Absorb Only Population (AOP)**

  [redacted]

1.5 Sample Size Calculations

[redacted]

[redacted] the sample size of the Surveillance was established as 2000 patients.

[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

2. ANALYSIS CONSIDERATIONS

2.1 Statistical Methods

Baseline demographic, clinical, angiographic, IVUS/OCT, procedural, and device data, and treatment results will be summarized using descriptive summary statistics.

2.1.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, percent diameter stenosis and lesion length), results will be summarized with the numbers of observations, means, and standard deviations and where specified in the table mockups, with quartiles, minimums, maximums, and 95% confidence intervals for the means as per the table mockups. Differences between two comparison groups of interest, where specified, will be summarized with relative risks, the differences of the two means, and 95% confidence intervals for the difference between the means. These calculations will be done under the assumption that the data for the two groups of interest are independent and approximately normal in distribution. The confidence interval for the difference of two means will be calculated under the assumption of unequal variances. If the asymptotic assumptions fail, then nonparametric summary statistics (medians, 25th and 75th percentiles) may be displayed as an alternative.

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[3] 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 Descriptive Statistics for Categorical Variables

For categorical variables such as gender, MACE and TVF, results 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 comparison groups of interest, when specified, will be summarized with the difference in percentages 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[5], 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, 3 months and 1, 2, 3, 4 and 5 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 (ST)

  Subjects will be included in the analysis if they either had the ST by that time or they did not have ST 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 ST 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]

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

[redacted]

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

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[6]

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

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

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]

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

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

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 Analyses

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.

Summary tables for safety and efficacy endpoints will include number of subjects at risk, number of censored subjects, number of events, failure rates (Kaplan-Meier estimates) and standard error of the survival rate for each time interval. For the primary analysis report, all available data will be used.

2.2 Subgroups for Analysis

Subgroups, including but not limited to the following, will be evaluated for the FAS and AOP. Baseline demographics, baseline subject characteristics, procedure information, morphology, quantitative coronary angiography, IVUS/OCT, and hierarchical/non-hierarchical adverse event data will be summarized with descriptive statistics. Comparisons will be made within the subgroup when appropriate.

Sex:

- Male
- Female

Diabetes:

- All Diabetes Mellitus
- Non-Diabetes Mellitus

Stent diameter:

- 2.5 mm
- 3.0 mm
- 3.5 mm

2.3 Analysis Window

- Baseline (pre-procedure)
- Procedure
- Post-procedure to discharge
- 3 months (by visit preferred; by telephone is allowed) (Day 90 ± 14 days)
- 1 year (by visit preferred; by telephone is allowed) (Day 365 ± 28 days)

- 2 years (by visit or telephone) (Day 730 ± 28 days)
- 3 years (by visit or telephone) (Day 1095 ± 28 days)
- 4 years (by visit or telephone) (Day 1460 ± 28 days)
- 5 years (by visit or telephone) (Day 1825 ± 28 days)

Scheduled imaging follow-up is not required for this surveillance. If any imaging is performed as site standard practice or is performed for diagnosis, the imaging modality and results should be recorded in case report forms.

2.4 Handling of Missing Data

[redacted]

2.5 Adjustments for Covariates

[redacted]

2.6 Multiplicity Issues

[redacted]

2.7 Documentation and Other Considerations

All analyses will be performed using SAS® for Windows, version 9.3 or higher.

3. ACRONYMS AND ABBREVIATIONS

Acronym/	Description
%DS	Percent Diameter Stenosis
AOP	Absorb Only Population
BVS	Bioresorbable Vascular Scaffold
CEC	Clinical Event Committee
DMR	All Death/All MI/All Revascularization
FAS	Full Analysis Set
ITT	Intent-To-Treat
IVUS	Intravascular Ultrasound
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MLA	Minimal Lumen Area
MLD	Minimum Luminal Diameter
OCT	Optical Coherence Tomography
PMS	Post-marketing surveillance
QCA	Quantitative Coronary Angiography
RVD	Reference Vessel Diameter
SAP	Statistical Analysis Plan
ST	Scaffold/Stent Thrombosis
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization

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