Abbott	Statistical Analysis Plan Cover Page

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SPIRIT 48
A Clinical Investigation to Assess the Abbott Next Generation Drug Eluting Stent 48mm Everolimus Eluting Coronary Stent System in Treatment of de novo Native Coronary Artery Disease
Study Document No: ABT-CIP-10321
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Sponsor

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Protocol #ABT-CIP-10321
SPIRIT 48 Study

A Clinical Investigation to Assess the Abbott Next Generation Drug Eluting Stent 48mm Everolimus Eluting Coronary Stent System in Treatment of *de novo* Native Coronary Artery Disease

Statistical Analysis Plan (SAP)

Version E

September 2, 2021

[redacted]

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

The statistical analysis plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis for ABT-CIP-10321, the SPIRIT 48 study. This plan is based on the Version D, March 24, 2021 Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The objective of the study is to evaluate the safety and effectiveness of the ABT NG DES 48 in improving coronary artery luminal diameter in subjects with coronary artery disease (CAD) due to *de novo* native coronary artery long lesions.

1.3 Clinical Investigation Design

The SPIRIT 48 study is a prospective, single-arm, open-label, multi-center clinical investigation to evaluate the safety and effectiveness of the ABT NG DES 48 in the treatment of *de novo* native coronary artery long lesions. Up to 107 subjects will be registered in the study at up to 33 global sites. Subjects registered in the study must have exactly one single *de novo* native coronary target lesion (defined in **CIP Section 5.3**), which is eligible to be treated by a single ABT NG DES 48. Planned overlap is not allowed for the treatment of target lesion. If a bailout stent is necessary for the target lesion, a stent other than the ABT NG DES 48 with appropriate size must be used. A non-target lesion, if is located in a different epicardial coronary vessel than the target lesion, is allowed to be treated by stents other than the ABT NG DES 48 per site's standard of care during index procedure. All subjects must be treated with only one ABT NG DES 48.

- Lesions and Stent Usage: up to two treated lesions, must have exactly one long lesion that is treated by one ABT NG DES 48
  - Single lesion: one *de novo* native coronary artery long lesion (> 32 mm and ≤ 44 mm) as the target lesion, that must be treated with a single ABT NG DES 48
  - Two lesions: one target lesion and one non-target lesion, each in different epicardial coronary vessels:
    - Target Lesion: one *de novo* native coronary artery long lesion (> 32 mm and ≤ 44mm), that must be treated with a single ABT NG DES 48
    - Non-target lesion: one *de novo* native coronary artery lesion, that must be treated by stents other than the ABT NG DES 48 per site's standard of care

A maximum of 40% of subjects with two treated lesions can be registered in the study. At least 50% of the subjects will be registered at US sites.

Each subject will be followed for a two-year period. All Subjects will have a hospital or office follow-up visit at 30 days, 6 months, 1 year and 2 years. An office visit is required for 1-year follow-up. All follow-ups must be conducted directly with the subject.

1.4 Endpoints

1.4.1 Primary Endpoint

The primary endpoint for this study is target lesion failure (TLF)[a], defined as a composite of the following clinical endpoints at 1-year:

- Cardiac death
- Target Vessel Myocardial Infarction [TV-MI] (MI is per Society for Cardiovascular Angiography and Interventions (SCAI) definition [1])
- Clinically-indicated Target Lesion Revascularization [CI-TLR]

The primary endpoint will be compared to a pre-specified performance goal (PG) as 20%.

1.4.2 Secondary Endpoints[b]

The secondary endpoints for this study are target lesion failure (TLF) at each following clinical follow-up time point:

- In hospital
- 30 days
- 180 days
- 2 years

1.4.3 Other Endpoints[b]

- Acute Success (combined clinical and angiographic)
  - Device Success (Lesion basis)
  - Procedural Success (Subject basis)
- Clinical Endpoint in hospital and at each clinical follow-up time point (30 days, 180 days, 1 and 2 years)

  Composite:
  - All death, all MI and all revascularization (DMR)
  - Cardiac death/MI

  Individual:
  - Any death
    - Cardiac
    - Vascular
    - Non-cardiovascular

[a] The first adjudicated COVID-19 l kely related component of the primary endpoint event along with the subsequent follow-up data will be censored and will not contr bute towards the primary endpoint analysis.

[b] MI is per SCAI definition.

[redacted]

- All MI
  - Q-wave MI (QMI)
  - Non-Q-wave MI (NQMI)
- TV- MI
  - Type
    - QMI
    - NQMI
- Any Revascularization
  - All TVR (including TLR)
    - ID–TVR
  - All TLR
    - ID–TLR
  - All Non-TVR
- Stent thrombosis (per ARC definition)
  - Type
    - Definite
    - Probable
    - Possible
  - Time
    - Acute (≤1 day)
    - Subacute (>1 day ≤30 days)
    - Late (>30 days ≤365 days)
    - Very late (>365 days)

A secondary analysis with MI per ARC 2 definition [2] and 4th universal definition [3] will be performed for all the endpoints containing MI.

1.5 Randomization

This is an open-label clinical investigation, no randomization will be required.

1.6 Blinding

This is an open-label clinical investigation, no blinding will be required.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

The primary analysis of the primary endpoint will be based on the Full Analysis Set (FAS). The analysis of acute success will be conducted on all registered subjects with the attempt of ABT NG DES 48 implantation. All other descriptive analyses on the baseline characteristics and clinical endpoints will be performed on both the FAS population and the per-protocol (PP) population.

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, percent diameter stenosis, and lesion length), results will be summarized with the number of observations, means, standard deviations, minimums, maximums, and 95% confidence intervals for the means.
If warranted, comparison between subgroups intended for subgroup analysis will be conducted. Results within each comparison group will be summarized using the same statistics described as above for single group. Furthermore, difference between two comparison groups will be summarized with the difference of the two means along with its 95% confidence interval. These calculations will be done under the assumption that the data for the comparison groups are independent and approximately normal in distribution. If otherwise specified, the confidence interval for the difference of two means is calculated assuming unequal variance between the two groups. If asymptotic assumptions fail, then nonparametric summary statistics (medians, 25th and 75th percentiles) may be displayed as an alternative. In addition, more appropriate non-parametric tests will be considered if the assumptions for the parametric tests are violated. For the comparison of two independent samples, if the data are not normally distributed, Wilcoxon rank sum test will be performed instead of the parametric t-test.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables such as cardiac death/Target-Vessel MI/CI-TLR or procedure and device success, results will be summarized with subject counts, percentages, and exact 95% Clopper-Pearson confidence intervals.

If warranted, comparison between subgroups intended for subgroup analysis will be conducted. Results within each comparison group will be summarized using the same statistics described as above for single group. Furthermore, differences between two comparison groups will be summarized with the difference in percentages and the asymptotic 95% confidence interval for the difference of two percentages.

[redacted]

[redacted]

[redacted]

[redacted]

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables [5]. Survival curves will be constructed using Kaplan-Meier estimates for analyzing the survival distributions through 30 days, 180 days, 1 and 2 years for clinical endpoints. Subjects without events will be censored at their last known event-free time point.

2.2.4 [redacted]

[redacted]

[redacted]

[redacted]

2.3 Endpoint Analysis

Statistical testing of the primary endpoint will be one-tailed and performed at the 0.05 significance level against a pre-specified performance goal. Analyses of other trial endpoints will be descriptive in nature. The clinical endpoints will be determined per protocol.

2.3.1 Primary Endpoint

The primary endpoint for this study is target lesion failure (TLF), defined as a composite of cardiac death, target vessel myocardial infarction [TV-MI] (MI is per Society for Cardiovascular Angiography and Interventions (SCAI) definition [1]), and clinically indicated target lesion revascularization [CI-TLR] at 1 year. The 1-year TLF will be compared to a pre-specified performance goal of 20%.

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

H_0: $P_D \geq 20\%$

H_A: $P_D < 20\%$

Where P_D represents the target lesion failure (TLF) rate at 1 year. The primary endpoint will be performed on the FAS population [redacted] The primary endpoint will be considered met if the null hypothesis is rejected at the one-sided 5% significance level.

Descriptive summary of TLF at different follow-ups may be displayed for the FAS and PP population.

[redacted]

2.3.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

Target lesion failure (TLF) at each clinical follow-up time point:

- In hospital
- 30 days
- 180 days
- 2 years

The secondary clinical endpoints will be analyzed descriptively based on the FAS and PP population. Descriptive statistics including confidence interval will be provided to gain better understanding of the data. The derivation of confidence intervals is described above within the statistical method section.

2.3.3 Other Endpoints

Like the primary and secondary endpoints, other clinical endpoints will also be summarized descriptively using FAS and PP population, except for that the acute success endpoint will be analyzed based on all registered population with the attempt of ABT NG DES 48 implantation. Descriptive statistics including confidence intervals will be provided to gain better understanding of the data. The derivation of confidence intervals is described above within the statistical method section.

2.4 Sample Size Calculations

To test the hypothesis specified for the primary endpoint of TLF at 1-year follow-up, with the following assumptions:

- One-sided alpha: 0.05
- True event rate for the primary endpoint: 10%
- Performance goal: 20%
- Attrition rate: 5%

[redacted]

A total sample size of 107 will provide approximately 93% power to test the primary endpoint [redacted] To avoid undue influence from a single study site, each site may register at most 20% of the total subjects.

2.5 Interim Analysis

[redacted]

2.6 Timing of Analysis

The primary endpoint analysis will be analyzed after database lock per FAS population when all subjects in FAS population have completed their 1-year follow-up visit.

[redacted]

2.7 Study/Trial Success

[redacted]

2.8 Subgroup for Analysis

Subgroup analyses will be performed to examine the consistency of the primary endpoint across subgroups. Subgroups to be examined include, but are not limited to, those defined by age (< 65 years vs ≥ 65 years), gender (female vs male), and race.

2.9 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.

2.10 Poolability

Analysis will be performed by pooling data across study sites. [redacted]

[redacted]

2.11 Multiplicity

A formal statistical test will only be performed on the primary endpoint for the FAS population [redacted]

2.12 Adjustments for Covariates

[redacted]

2.13 Sensitivity Analysis

The following sensitivity analyses of the primary endpoint will be carried out:

- The primary endpoint will be performed for the per-protocol (PP) population as a sensitivity analysis.
- Tipping point analysis will be conducted as a sensitivity analysis to evaluate the impact of the missing data for the primary endpoint. [redacted]

[redacted]

- COVID-19 Related Events: [redacted]
- The exact test based on the binomial distribution will be conducted to test the primary endpoint [redacted]

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized to describe FAS population at baseline and index procedure: age, gender at birth, ethnicity, race, height, weight, BMI, Left Ventricular Ejection Fraction (LVEF), hypertension, diabetes mellitus, previous MI, creatinine kinase (CK), Troponin-I, Troponin-T, Serum Creatinine, etc.

3.2 Adverse Events and Other Treatment Results

All adverse device effects, serious adverse device effects, UADEs, and USADEs will be summarized for all subjects who registered in this trial in terms of the number of events and the percentage of subjects with events per MedDRA coding. Procedure related AEs may also be summarized.
All CEC adjudicated adverse events will also be summarized for all subjects who registered in the trial in terms of the number of events and the percentage of subjects with events.

[redacted]

3.3 Subject Early Termination

Subjects early termination reasons including death, withdrawal, lost-to-follow-up, etc. will be summarized at all scheduled visits.

[redacted]

3.4 Protocol Deviation

Protocol deviations will be summarized for subjects in whom protocol deviations are reported.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

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

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
ABT	Abbott
AE	adverse event
ARC	Academic Research Consortium
CAD	coronary artery disease
CEC	Clinical Events Committee
CI	clinically-indicated
CI-TLR	clinically-indicated target lesion revascularization
CIP	clinical investigation plan
CK	creatine kinase
CK-MB	creatine kinase myocardial-band isoenzyme
COVID-19	coronavirus disease 2019
CRF	case report form
DES	Drug-eluting stent
ECG	Electrocardiogram
EECS	everolimus eluting coronary stent
EECSS	everolimus eluting coronary stent system
eCRF	electronic case report form
FDA	Food and Drug Administration
LVEF	Left Ventricular Ejection Fraction
MI	myocardial infarction
mm	millimeter
NG	next generation
NQMI	non-Q wave myocardial infarction
PG	performance goal
QMI	Q-wave myocardial infarction
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SAE	serious adverse event
SCAI	Society for Cardiovascular Angiography and Interventions
TLF	target lesion failure
TLR	

[redacted]

Acronym or Abbreviation	Complete Phrase or Definition
TVF	target lesion revascularization
TVR	target vessel failure
UADE	target vessel revascularization
USADE	unanticipated adverse device effect unanticipated serious adverse device effect

6.0 REFERENCES

[1] Moussa, I. D. *et al.* Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *Journal of the American College of Cardiology* **62**, 1563-1570, doi:10.1016/j.jacc.2013.08.720 (2013).

[2] Garcia-Garcia, H. M. *et al.* Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Circulation* **137**, 2635-2650, doi:10.1161/CIRCULATIONAHA.117.029289 (2018).

[3] Thygesen, K. *et al.* Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* **138**, e618-e651, doi:10.1161/CIR.0000000000000617 (2018).

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[6] Clopper C. J. & Pearson E. S. The use of the confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26, 404-413 (1934).

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[8] Higgins, Julian PT, et al. "Measuring inconsistency in meta-analyses." *Bmj* 327.7414, 557-560 (2003).

[redacted]

[redacted]

[redacted]

[redacted]