Abbott	Statistical Analysis Plan Cover Page

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FlexNav EU CE Mark Study
Assessment of the Abbott FlexNav™ Delivery System for Portico Transcatheter Aortic Valve Implantation in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis
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Statistical Analysis Plan

Protocol [redacted]

FlexNav EU CE Mark Study

Assessment of the Abbott FlexNav™ Delivery System for Portico Transcatheter Aortic Valve Implantation in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis

Statistical Analysis Plan (SAP)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Statistical Analysis Plan

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[redacted]

[redacted]

Statistical Analysis Plan

1.0 SYNOPSIS OF STUDY DESIGN

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 the protocol [redacted] FlexNav EU CE Mark clinical study. [redacted]

1.2 Clinical Investigation Objectives

The primary objective of the FlexNav EU study is to characterize the safety of the second-generation Portico FlexNav Delivery System.

1.3 Clinical Investigation Design

The FlexNav EU study is a prospective, multi-center, single-arm investigational study and will include up to 200 high or extreme risk patients with symptomatic, severe native aortic stenosis who meet eligibility criteria for Portico™ Transcatheter Aortic Heart Valve implantation via a transfemoral access approach. Clinical investigation visits will occur at baseline, implant procedure, discharge, 30 days, 6 months and 12 months post-implantation for enrolled subjects. Thirty-day safety outcomes data for the first 73 subjects to undergo an attempted Portico™ valve implant using the FlexNav™ Delivery System will be summarized to support commercialization of the FlexNav™ Delivery System and Loading System in Europe.

1.4 Endpoints

1.4.1 Primary Endpoint

The primary safety endpoint for this study is VARC-2 defined major vascular complications at 30 days post index procedure.

1.4.2 Descriptive Endpoints

The following descriptive endpoints at 30 days will be reported in the CE Mark submission:

- Non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days from the index procedure.
- All-cause mortality at 30 days from the index procedure.
- Disabling stroke at 30 days from the index procedure.
- Non-disabling stroke at 30 days from the index procedure.
- Life threatening bleeding requiring blood transfusion at 30 days from the index procedure.
- Major bleeding at 30 days from the index procedure.
- Acute kidney injury at 30 days from the index procedure.
- Minor vascular complication rates at 30 days from the index procedure.

[redacted]

- Permanent pacemaker insertion at 30 days from the index procedure.
- Paravalvular Leak (PVL) at 30 days from the index procedure.
- NYHA functional classification at 30 days from the index procedure.
- KCCQ Quality of Life (QOL) score from baseline to 30 days from the index procedure.
- Technical device success defined as successful vascular access, delivery and deployment of the Portico Valve; retrieval with the delivery system and correct positioning of a single valve in the proper anatomical location.

Additional descriptive endpoints at one year include:

- Composite of all-cause mortality or disabling stroke at one year from the index procedure.
- All-cause mortality at one year from the index procedure.
- Disabling stroke at one year from the index procedure.
- Non-disabling stroke at one year from the index procedure.
- Paravalvular Leak (PVL) at one year from the index procedure.
- KCCQ Quality of Life (QOL) score from baseline and one year from the index procedure.
- NYHA functional classification at one year from the index procedure.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Population

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, etc.), results may be summarized with the numbers of observations, means, and standard deviations, with quartiles, minimums, maximums, and 95% confidence intervals for the means.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. gender, etc.), results may be summarized with subject counts and percentages/rates, and where specified in the table mockups, with exact 95% Clopper-Pearson confidence intervals.

2.2.3 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.

[redacted]

2.2.4 Analyses in Response to COVID-19 Impact

As the Coronavirus Disease 2019 (COVID-19) pandemic has spread around the globe, the following analysis mechanism will be implemented to minimize the potential confounding effect from this emerging infectious disease for the study endpoints set forth in final report. In alignment with the guidance document "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" updated on 03-June-2020, additional consideration was given to the impact of the COVID-19 pandemic on the descriptive endpoint analyses for this study. As such, prespecified methods are included in the sections that follow to indicate the handling of any outcomes impacted by COVID-19 as well as efforts to minimize missing endpoint data during the COVID-19 pandemic. Specific analyses to address COVID-19 impacts are included in relevant subsections in Section 2.0 and Section 3.0.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint

The primary safety endpoint for this study is VARC-2 defined major vascular complications at 30 days post index procedure. [redacted]

[redacted]

2.4 Sample Size Calculations

The minimum sample size of 73 subjects is based [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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2.5 Interim Analysis

No formal interim analyses are planned for this study. [redacted]

2.6 Timing of Analysis

[redacted]

2.7 Study Success

[redacted]

2.8 Subgroups for Analysis

Subgroup analysis will be performed to examine the consistency of the primary endpoint across baseline risk categories, [redacted]

2.9 Handling of Missing Data

[redacted]

2.10 Poolability Analysis

Poolability analysis may be performed [redacted]

2.11 Multiplicity

[redacted]

[redacted]

3.0 DESCRIPTIVE ENDPOINT AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables, including but not limited to: gender, age, medical history, procedural characteristics etc. will be summarized using descriptive statistics for the enrolled subjects.

3.2 Adverse Events

All the adverse events, serious adverse events will be summarized for all subjects who enrolled in this study in terms the number of events, the percentage of subjects with events. All Clinical Events Committee (CEC) adjudicated adverse events will also be summarized for all subjects who enrolled in the study in terms of the number of events, the percentage of subjects with events. In addition, [redacted]

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, valve explant etc. will be summarized at all scheduled visits.

3.4 Protocol Deviation

Protocol deviations will be summarized for subjects in whom a protocol deviation was reported [redacted]

3.5 Descriptive Endpoints

The analyses for the descriptive endpoints listed in Section 1.4.2 will be performed using the methods described in Section 2.2 for the analysis population described in Section 2.1.

[redacted]

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.4 or higher.

[redacted]

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5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse Event
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

6.0 REFERENCE

[redacted]