Abbott	Statistical Analysis Plan Cover Page

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TRILUMINATE
Trial to Evaluate Treatment with Abbott Transcatheter Clip Repair System in Patients with Moderate or Greater Tricuspid Regurgitation (TRILUMINATE)
Study Document No: Protocol 16-517
Version 1.3
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Sponsor

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Protocol 16-517

TRILUMINATE Trial

Trial to Evaluate Treatment with Abbott Transcatheter Clip Repair System in Patients with Moderate or Greater Tricuspid Regurgitation (TRILUMINATE)

Statistical Analysis Plan (Part I: Methodology)

Version 1.3
August 16th 2018

[redacted]

[redacted]

[redacted]

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[redacted]

1. SYNOPSIS OF TRIAL 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 16-517, the TRILUMINATE Trial. [redacted]

1.2 Trial Objectives

To evaluate safety and effectiveness of the Tricuspid Valve Repair System (TVRS) in patients with symptomatic moderate or greater tricuspid regurgitation (TR) who are deemed appropriate for percutaneous transcatheter intervention by the site heart team.

1.3 Trial Design

The TRILUMINATE Trial is a prospective, single arm, multi-center study of the TVRS for treating symptomatic moderate or greater TR in patients currently on medical management and who are deemed high-risk for tricuspid valve surgery and appropriate for percutaneous transcatheter intervention.

A minimum of 85 subjects will be prospectively enrolled and undergo the TVRS procedure in up to 25 sites, in Europe, Canada and the United States:

- A clinical report will be included as part of the submission for CE Mark and other regulatory submissions, as appropriate.

[redacted]

All subjects will have scheduled office visit evaluations at baseline, discharge, 30 days, 6 months, 1 year, 2 years, and 3 years.

The US subjects enrolled into the TRILUMINATE Protocol (#16-517) will receive additional follow-up assessments at 4 years (±28-days) and 5 years (±28-days) post-procedure. The subject may perform the follow-up with a phone interview with the investigational site, or with visits as deemed clinically warranted by the site investigator.

[redacted]

1.3.1 Primary Endpoints

The primary effectiveness endpoint is echocardiographic TR reduction at least 1 grade at 30 days post-procedure, to be tested against a pre-specified performance goal.

The primary safety endpoint is a composite endpoint of Major Adverse Event (MAE) at 6-months to be evaluated against a pre-specified performance goal.

MAE is defined as a composite of:

- Cardiovascular Mortality,
- MI,
- Stroke,
- New onset renal failure,
- Endocarditis requiring surgery, and
- Non-elective Cardio-Vascular (CV) surgery for TVRS device-related AE post-procedure.

1.3.2 Secondary Endpoints

1.3.2.1 Acute Secondary Endpoints

- Acute Procedural Success (APS): Successful implantation of the Clip resulting at least 1 grade reduction in TR severity as determined by the Echocardiography Core Laboratory (ECL) assessment of a discharge echocardiogram (30-day echocardiogram will be used if discharge echocardiogram is unavailable or uninterpretable). Subjects who die or undergo tricuspid valve surgery before discharge are an APS failure.
- Acute Device Success: Successful access, delivery of the Clip and removal of device delivery system. Successful delivery of the Clip is the deployment of the device as planned, with no additional unplanned surgery or re-intervention related to the device or access procedure.
- Implant Success Rate: Successful delivery and deployment of the Clip(s) with achievement of leaflet approximation(s) and retrieval of the delivery catheter.
- Total Procedure Time: Total Procedure Time is defined as the time elapsed from the first of any of the following: intravascular catheter placement or trans-esophageal echocardiogram (TEE), to the removal of the last catheter and TEE.
- Device Time: Device time is defined as the time the Steerable Guide Catheter is placed in the right atrium until the time the TVRS Delivery System is retracted into the Steerable Guide Catheter.

[redacted]

- Fluoroscopy Duration: Fluoroscopy duration is defined as the duration of exposure to fluoroscopy during the TVRS procedure.
- Length of hospital stay for the index TVRS procedure
- Location to which subject was discharged (home, home health or another facility)
    - If subject discharged to another facility, length of stay at facility to which subject was discharged

1.3.2.2 Clinical Composite Endpoints

- MAE at discharge, 30 days,1 year, 2 years and 3 years

1.3.2.3 Clinical Components Endpoints

- Clinical Endpoints will be assessed at 30 days, 6 months, 1 year, 2 years and 3 years:
    - Components of MAE
    - All-cause mortality
    - NYHA Functional Class
    - Tricuspid valve surgery (including type of surgery),
    - New use of any cardiac rhythm management devices (Pacemakers, ICDs, and CRT), including reason for intervention
    - Additional TVRS intervention and reason for intervention
- Additional Clinical Endpoints:
    - Mode of Clip anchoring of coapted leaflets (anterior, posterior and/or septal) at procedure
    - Major bleeding at 30 days
    - Pulmonary Thromboembolism at 30 days
    - New Onset Renal Failure at 30 days and 6 months
    - New Onset Liver Failure at 30 days and 6 months
    - New onset atrial fibrillation at 30 days, 6 months and 1 year.
    - Change in diuretic(s) used at 30 days, 6 months, and 1 year (as compared to

baseline)

1.3.2.4 Patient Reported Endpoints

Patient-reported Quality of Life (QoL) and Health Economics and Outcomes Research (HEOR) Endpoints: at baseline, 30 days, 6 months, 1 year, 2 years and 3 years*:

- Distance walked in the 6-Minute Walk Test (6MWT distance or 6MWD, excluding 30 day)
- Kansas City Cardiomyopathy Questionnaire (KCCQ) QoL scores
- Short Form Health Survey (SF-36) QoL scores
- Number and duration of re-hospitalizations and reason for re-hospitalization (i.e., heart failure, cardiovascular, non-cardiovascular)

*Actual rates/scores and the relative change from baseline to each follow-up time point.

Note: As applicable to patients in the US trial sites, it is anticipated that the patients enrolled in the TRILUMINATE trial will be U.S. Medicare beneficiaries age 65 and over.

1.3.2.5 Device or Procedure-Related Adverse Events

Prevalence of Device or Procedure-Related Adverse Events

Device or procedure-related adverse events will be broken down into those that occur within 30 days of the procedure and those that occur after 30 days of the procedure. Examples of device-related adverse events are:

- Myocardial perforation
- Damage to tricuspid valve apparatus
- Access Site bleeding requiring surgery
- Non-vascular bleeding

1.3.2.6 Echocardiographic Endpoints

Echocardiographic endpoints will be assessed by the Echocardiography Core Laboratory (ECL) and reported at baseline, discharge, 30 days, 6 months, 1 year, 2 years, and 3 years post-implantation (unless indicated).

[redacted]

- TR Severity Grade
- Effective Regurgitant Orifice Area (EROA)
- Regurgitant Volume
- Regurgitation Jet Area
- Vena Contracta Width
- Proximal Isovelocity Surface Area (PISA) Radius
- Inferior Caval Vein Diameter
- Tricuspid Annular Diameters (Antero-P and S-L)
- Tricuspid Annular area
- Tricuspid Valve Area
- Tenting Area (At baseline only)
- Tenting Distance (At baseline only)
- Tricuspid Leaflet Tethering Distance (At baseline only)
- Right Ventricular End Diastolic Dimension (RVEDD)
- Right Ventricular End Systolic Dimension (RVESD)
- Right Ventricular Fractional Area Change
- Right Ventricular Systolic Pressure (RVSP)
- Right Atrial Volume
- Tricuspid Annular Plane Systolic Excursion (TAPSE)
- Right Ventricular Free Wall Strain
- Mean Tricuspid Valve Gradient
- Cardiac Output
- Forward Stroke Volume (Left Ventricle)
- Left Ventricular Ejection Fraction (LVEF)
- Single Leaflet Device Attachment
- Embolization of the TVRS Clip or TVRS System components

[redacted]

- Tricuspid Valve Stenosis

1.3.3 Exploratory Endpoints

Right Heart Catheterization: Right heart catheter measurements at:

- Immediately before TVRS procedure: Measurements to include: right atrial a-wave/v-wave, right atrial and ventricular pressures, pulmonary resistance, PA pressures and cardiac output),
- Post-procedure Right Atrial Catheterization, immediately after TVRS procedure (right-atrial a-wave/v-wave, right atrial pressure)

[redacted]

1.4 Analysis Populations

[redacted]

The primary analysis population (PAP) [redacted]

In addition, analysis will be performed on the Per-Treatment Evaluable (PTE) population [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

2. ANALYSIS CONSIDERATIONS

2.1 Statistical Methods

Descriptive analysis will be performed to summarize baseline, echocardiographic, clinical and safety event data. Depending on the type of data (e.g., continuous or categorical), statistical methods described in the following sections will be used.

[redacted]

2.1.1 Descriptive Statistics for Continuous Variables

For continuous variables such as age, results will be summarized with the numbers of observations, means, and standard deviations, and, if specified in the table mockups, with quartiles, minimums, maximums, and 95% confidence intervals for the means. Differences between two groups, where specified, will be summarized with 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 arms 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.

[redacted]

[redacted]

2.1.2 Descriptive Statistics for Categorical Variables

For categorical variables such as gender, MAE, results will be summarized with subject counts and percentages/rates, and where specified in the table mockups, with exact 95% Clopper-Pearson[8] confidence intervals. [redacted]

For effectiveness 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. [redacted]

[redacted]

For the determination of event rates at time points (e.g. 30 days), the counting starts from the time of enrollment.

[redacted]

[redacted]

[redacted]

[redacted]

2.1.4 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables, e.g. all-cause mortality. For analyses of clinical events (e.g. MAE) beyond 30-day follow-up, Kaplan-Meier[11] estimate will be utilized.

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 endpoints will include failure rates (Kaplan-Meier estimates), and confidence interval for the failure rates.

2.1.5 Recurrent Event Analyses

For recurrent event data such as recurrent heart failure hospitalizations at pre- and post-procedure, data may be analyzed using a generalized estimating equation model (GEE), such as Poisson regression model, with a p-value to measure the strength of evidence.

To fit the GEE model, the input dataset will be prepared to include total hospital count and total follow-up time (in days) pre- and post- index procedure for each subject along with the indicator for

[redacted]

this time cutoff.

2.2 Endpoint Analysis

2.2.1 Primary Endpoint Analyses

2.2.1.1 Primary Effectiveness Endpoint Analyses

The primary analysis population for the primary effectiveness endpoint will be based on the PAP as defined on Section 1.4. Success rate at 30 days together with a one-sided 97.5% lower confidence limit by Exact Clopper-Pearson method will be estimated and tested against a pre-specified PG of 35%. [redacted]

The same analysis as above may be performed for the PTE population.

2.2.1.2 Primary Safety Endpoint Analyses

The primary analysis population for the primary safety endpoint is the PAP population. The MAE rate [redacted] at 6 months will be calculated and tested against a pre-specified PG of 39%. The Kaplan-Meier analysis will be used to compute the MAE rate at 6 months; the standard error and confidence limits will be computed using Greenwood's method. [redacted]

The same analysis as above may be performed for the PTE population.

2.2.2 Secondary [redacted] Endpoint Analyses

Analyses of secondary [redacted] endpoints will be descriptive in nature and will be performed using the methods described in Section 2.1 for both the PAP and PTE populations.

[redacted]

2.3 Subgroups for Analysis

2.3.1 US Patients

Subgroup analyses on subjects from US sites will be performed on the PAP population for all endpoints with methodology as described in section 2.1. Further subgroup analysis may be performed for exploratory purpose.

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. Sensitivity analysis for the primary safety and effectiveness endpoints will be performed to assess the impact of missing data on the results.

Tipping point analysis [redacted] on the primary effectiveness endpoint at 30 days and primary safety endpoint at 6 months will be conducted as a sensitivity analysis by including all subjects in the PAP population.

[redacted]

[redacted]

By progressively accounting for missing data one at a time, the sensitivity analysis explores the number of missing data to be accounted for at which conclusion from the primary analyses results will be altered.

[redacted]

[redacted]

[redacted]

2.6 Multiplicity Issues

[redacted] the overall Type I error rate of the study is conservatively controlled at 2.5% and there is no need to adjust the level of significance for multiplicity.

[redacted]

2.8 Documentation and Other Considerations

All analyses will be performed using SAS®[13] for Windows, version 9.2 or higher.

[redacted]

3. ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse event
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AST	Aspartate aminotransferase
APS	Acute procedural success
CE	Conformité Européene (EU)
CV	Cardiovascular
CIP	Clinical Investigation Plan (EU)
EROA	Effective Regurgitant Orifice Area
6MWT	6 minutes walking test
6MWD	6 minutes walking distance
KCCQ	Kansas City Cardiomyopathy Questionnaire
SF-36	Short Form 36
CRT	Cardiac Resynchronization Therapy Device
DMSRES	Death/MI/Stroke/Renal failure/Endocarditis/non-elective cardiovascular
ECL	Echocardiographic Core Laboratory
FDA	Food and Drug Administration
HEOR	Health Economics and Outcomes Research
HRR	High risk registry
ICD	Implantable cardioverter-defibrillators
LVEF	Left ventricular ejection fraction
MAE	Major adverse event
MR	Mitral regurgitation
MI	Myocardial infarction
N	Sample size; also *N*
PA	Pulmonary Artery
PAP	Primary analysis population
PG	Performance goal
PTE	Per-Treated-Evaluable
QoL	Quality of life
RVEDD	Right Ventricular End Diastolic Dimension

[redacted]

Acronym or Abbreviation	Complete Phrase or Definition
RVESD	Right Ventricular End Systolic Dimension
RVEF	Right Ventricular Ejection Fraction
RVSP	Right Ventricular Systolic Pressure
SAE	Serious adverse event
SAP	Statically analysis plan
SLDA	Single Leaflet Device Attachment
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEE	Trans-esophageal echocardiogram
TR	Tricuspid Regurgitation
TVRS	Tricuspid Valve Repair System
US	United States

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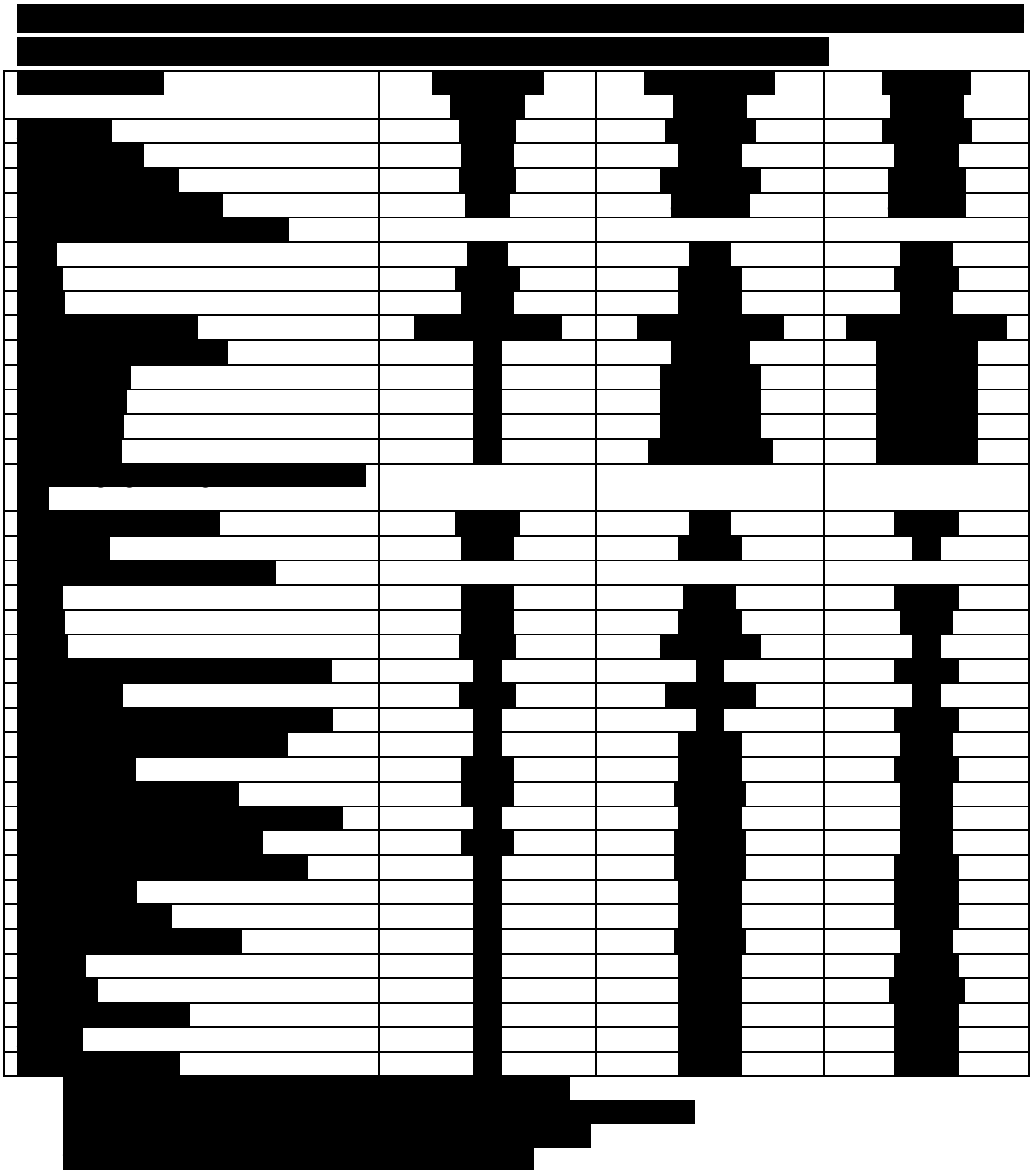

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