STUDY CODE: APR002 STUDY NAME: BELIEVE

STUDY TITLE:

BEhavior of valve Leaflets and the Incidence of rEduced mobility post-surgical aortic valVE implant

Statistical Analysis PLAN

Clintrial.gov NCT03200574

STUDY CODE: APR002 **STUDY NAME: BELIEVE**

STUDY TITLE:

BEhavior of valve Leaflets and the Incidence of rEduced mobility post-surgical aortic valVE implant

STATISTICAL ANALYSIS PLAN

Version N° 2.00 **Date: 14-May-2019**

Confidentiality Statement

Part or all of the information in this statistical analysis plan may be unpublished material. Accordingly, this document is to be treated as confidential and restricted to its intended use. This material is the property of LivaNova PLC and must not be disclosed or used except as authorized in writing by LivaNova PLC.

	Name	Signature	Date
Prepared by	**Teresa GRECO** Study Biostatistician		14MAY2019
Approved by	**Nelly RIVERA** Clinical Project Manager	Nelly V. Rivera Nelly V. Rivera (May 14, 2019)	14May2019
Approved by	**Giacomo Mordenti** Director Global Biometrics	Giacomo Mordenti (May 14, 2019)	

TABLE OF CONTENT

1 INTRODUCTION

This Statistical Analysis Plan (SAP) includes all definitions and analysis details for the analysis of the study BELIEVE APR002 in accordance with the version B of the Clinical Investigational Plan (hereafter defined "CIP" or "protocol") dated 05 Dec 2018, and the e-CRF version 2 dated 09 May 2019. The analysis will be performed by the Department of Global Biometrics at LivaNova in accordance with this SAP.

2 STUDY DESIGN

2.1 STUDY OBJECTIVES

2.1.1 Primary objective

The purpose of this study is to report the overall incidence of reduced leaflet motion identified by four-dimensional (4D), volume-rendered, computed tomography (CT) imaging in LivaNova Perceval bioprosthetic aortic heart valve up to 1 year post-implant on subjects that are off anticoagulation for at least 30 days.

2.1.2 Secondary objectives

The secondary objective is to assess all relevant device and subject demographic characteristics, procedural events through hospital discharge and short-term outcomes, up to 1 year post-implant.

2.2 OVERALL STUDY PLAN

Study main characteristics are described below. Please refer to the CIP for additional details.

- Prospective, interventional, multi-center study.
- Single-arm: subject implanted with Perceval aortic heart valve.
- Minimum of 75 asymptomatic and symptomatic subjects with evaluable 4D CT scans.
- Approximately 11 investigational sites where the devices are commercially available.
- Study duration: approximately 3 years (24 months for the enrollment phase and 1 year for the follow up phase).
- Blinding of CT scan imaging: (i) asymptomatic subjects and principal investigators (PIs) blinded from the CT imaging and Core Laboratory (Lab) findings; (ii) symptomatic subjects and the PI can be unblinded to CT imaging results; (iii) Core Lab blinded to subject status.
- Main assessments: (i) subject inclusion and implant data; (ii) hospital discharge (or 30-days after implant); (iii) anticoagulation (ACT) or dual antiplatelet therapy (DAPT) discontinuation (or Planning) visit (iv) first CT scan at minimum of 1 month after the discontinuation of ACT/DAPT; (v) second CT scan within 1 year post-implant for subjects in which reduced leaflet motion was previously detected; (vi) 1 year post-implant.

The visits are planned as reported in Figure 1

Figure 1: Schedule of Study Procedure

Procedure	Pre-Implant / Implant Data	Hospital Discharge	ACT / DAPT Discontinuation (or Planning) Visit	1st CT-Scan Follow-up Visit	Reduced Leaflet Follow-Up (2nd CT-Scan)	1 Year Follow-Up	Unscheduled Visits
Applicable Subjects	All Subjects	All Subjects	Subjects on ACT / DAPT	All Subjects	Subjects with Reduced Leaflet Motion on 1st CT Scan	All Subjects	Subjects with reduced leaflet function symptoms or other condition needing study related Follow-up
Timing	After Successful Implant	≤ 30 days of Implant (before the subject is discharged)	1 – 6 mo. Post-Implant (3 mo. preferred)	Non-ACT/DAPT Pts. 30 days after Hospital Discharge (+ 60 day window) ACT/DAPT Pts. 30 days after ACT/DAPT Therapy discontinuation (+ 60 day window)	6 – 10 mo. Post-Implant	1 year after the day of surgery (± 30 day window)	At Discretion of Investigator

2.3 SAMPLE SIZE CALCULATION

A sufficient number of subjects will be enrolled in this study to allow a minimum of 75 evaluable CT scans for the primary endpoint. Evaluable scans are those where a determination of normal or abnormal leaflet motion is possible. Considering an attrition rate of 15% of subjects, the sample size targeted for enrollment is approximately 88 subjects.

A sample size of 75 evaluable CT scans produces an Exact two-sided 90% CI with a width lower than 13% when the sample proportion is lower than 10% (evaluation calculated using PASS software, version 13).

2.4 RANDOMIZATION

Not applicable.

3 DOCUMENT AND CHANGE HISTORY

3.1 CHANGES IN ANALYSIS COMPARED TO CLINICAL INVESTIGATIONAL PLAN

No changes in the analysis have been applied compared to protocol.

Although not specified in the CIP, “Per-Protocol” population has been included in this SAP as population analysis set.

3.2 SAP AMENDMENT RATIONALE AND CHANGE HISTORY

Version	Date	Section(s)	Description of modifications
1.00	14MAR2018	All	Initial Release.
2.00	13MAY2019	All	SAP has been amended following the: • Protocol Amendment Version No. B dated on 05 Dec 2018: The study was initially designed with three cohorts of valve types to be analyzed: Perceval, SOLO Smart, and CROWN PRT. In an effort to focus the research to the Perceval device, the other cohorts (SOLO/CROWN) are being removed from the research study. The subjects that have received one of the two devices prior to removal from the study will be followed and presented as a sub-category in safety tables but will not be included in the endpoint analysis. Additionally, with this change the total number of subjects required for the study is approximately 88 which should yield 75 evaluable CT Scans. • CRF specification Amendment Version 2 dated on 09 May 2019.
2.00	13MAY2019	All	Removal of Crown PRT and Solo Smart references. Minor editorial changes applied to increase SAP clarity.
2.00	13MAY2019	2.3, 5.2, 10, 11	Study sample size reconsidered based on the following changes: • Study cohort changed from three to one. • The study is descriptive in nature, aiming at describing the risk of reduced leaflet motion as such it is considered non-confirmative and no multiplicity adjustment will be applied to the inferential statistical methods that will be presented. • Confidence levels updated to 90% rather than 95%. • Expected acceptable confidence interval width updated to be 13% rather than 8.3%. • Statistical two-sided confidence interval calculation to compute the sample proportion (Reduced Leaflet Mobility) updated to be based directly on the Exact Binomial distribution rather than Normal approximation (Wald).
2.00	13MAY2019	5.3, 18.13	Subgroups analysis updated to remove the classification by valve.
2.00	13MAY2019	6.4, 7.3, 18.13	Section updated to include the reference at the primary endpoint-related deviations as reported in the Risk Based Study Management Plan.
2.00	13MAY2019	13.1	Sections updated to specify where a SAE relationship will be further judged by Sponsor or Clinical Events Committee (CEC), only the final assessment will be analyzed by means of the following judgment order: 1. Site/CoreLab, 2. Sponsor, 3. CEC.
2.00	13MAY2019	10.4	Primary Analysis updated to calculate the Exact 2-sided 90% confidence limits, for the reduced leaflet motion proportion, based on the Binomial distribution.
2.00	13MAY2019	10.5	Section updated to clarify the procedures for the multiple imputation of missing data at first CT scan visit.
2.00	13MAY2019	13	Safety analyses updated to: • Include the enrollment occurrence (subjects enrolled at implant/after implant) stratification. • Remove the reference to treatment emergent adverse events since these are not of main interest in device studies. • Replace reference to “System Organ Class (SOC)” and “Preferred Term (PT)” with “SAE general category” and “SAE term”, respectively.
2.00	13MAY2019	18.6	Visit windows clarified as per Protocol Version B.

4 OVERVIEW OF PLANNED STATISTICAL ANALYSIS

4.1 MAIN STATISTICAL ANALYSIS

Main statistical analysis will be performed after all evaluable subjects have completed the first CT scan at expected 1-6 months post-implant.

4.2 FINAL STATISTICAL ANALYSIS

Final analysis will be performed after all enrolled subjects have completed the study (1 year visit), and the data has been hard locked. The results of the final analysis will be the basis for the integrated Clinical Study Report (CSR).

4.3 OTHER STATISTICAL ANALYSES

Progress annual report may be prepared for eventual sending to the study team for internal evaluations of the study progress.

Specific statistical analysis may be provided to regulatory agencies upon request. In addition, internal evaluation could be requested during the study after assessing a reasonable number of subjects with results on the first CT scan at 1-6 months post-implant (i.e. every 50 subjects with the first CT-scan evaluation).

The Sponsor may also perform comparisons with previous studies in the same indication by means of meta-analytic approaches also using network meta-analyses, when required. More details will be presented in an ancillary SAP detailing this and any other exploratory analyses.

Additional statistical analyses may be run after the completion of the final analysis. In that case, an addendum of this SAP will be created describing the analyses to be performed.

5 ANALYSIS CONVENTION

5.1 GENERAL PRINCIPLES

The statistical analysis will be performed on the analysis study database with SAS version 9.4 or above (SAS Institute, Cary, N.C.).

If two or more of the analysis sets as defined in Section 6 coincide or the difference is less than 5%, presentations will only be prepared for the population less restrictive.

The default significant level will be 10%. Confidence Intervals (CIs) will be calculated at 90% confidence level and all tests will be two-sided, unless otherwise specified in the description of the analyses.

All the data collected and derived in the study will be presented in subject data listings.

5.2 DESCRIPTIVE STATISTICS

Descriptive statistics will be calculated using as reference the number of subjects in the relevant analysis population (any exception will be specified) according to the nature of the data as follows:

- Continuous variables: number of non-missing observations, arithmetic mean, standard deviation, minimum and maximum values, median and quartiles.

  If there are less than 5 observations, only the number of non-missing observations, arithmetic mean, median, minimum and maximum will be presented.
- Categorical variables: number of non-missing observations (n), the number of missing and the relevant percentage on the analysis population, number and relative frequencies. If not defined otherwise, the percentage denominator will be the number of subjects with non-missing information.

  In case of subcategories, the relative frequencies will be calculated based on the subjects in the subcategory, in this case a footnote will be added explaining the different denominators.
- Time-to-event variables: number of non-missing observations (n), minimum, first quartile, median including 90% CI, third quartile, and maximum. For calculating the survival estimate 90% CI bounds the log-log transformed estimate of CI bounds will be used. Greenwood formula will be used to estimate the variance of the log-log transformation of the Kaplan-Maier estimator.

  In addition, Kaplan-Meier estimates and plots will be provided with:
  - the respective number at risk and the Kaplan-Meier estimates at time points 1 month, 3 months, 6 months, 9 months and 1 year.
  - the median and its 90% CI.
  - the Hazard Ratio (HR), its 90% CI and the relevant p-value, when applicable.

  Subjects ongoing and who are free from event at the analysis cut-off date will be censored at the analysis cut-off date. Subjects who have discontinued without an event will be censored at the date of discontinuation.

5.3 SUBGROUPS DEFINITIONS

The following subgroups will be defined:

- Concomitant Procedures (at implant):
  - Subject implanted with a concomitant procedure performed.
  - Subject implanted without a concomitant procedure performed.
- Subject symptoms (at first/second CT scan, as appropriate):
  - Asymptomatic
  - Symptomatic
- ACT/DATP (at hospital discharge):

  - Subject on ACT/DAPT at hospital discharge (or 30-days after implant)
  - Subject off ACT/DAPT at hospital discharge (or 30-days after implant)
- Core Lab evaluation (at first/second CT scan, as appropriate) by:
  - CT scan
  - Transesophageal Echocardiogram (TEE)

5.4 DEFINITIONS

Investigational Device (ID)	PERCEVAL (PMA P150011)
Baseline	Last non-missing observation (scheduled or unscheduled) before implant. Measurements collected the day of implant, in absence of other time information, are considered baseline data. If a subject is missing the planned baseline collection, the previous non-missing evaluation will become the baseline value. If any observation will be available before or on the day of implant, an unscheduled assessment done before the discharged visit can be used as baseline.
Study Day Count	The day of implant is defined as study Day 1. Calculate the study day according to the following rules: If date < study Day 1 then study day = Date – study Day 1 If date $\geq$ study Day 1 then study day = Date – study Day 1 +1

Study phases	
Pre-implant (Screening)	Screening and pre-implant assessments, where informed consent is signed and eligible criteria are met, before subjects will be considered enrolled in the study.
Implant (Enrollment)	During the implant until the establishment of a successful procedure.
Hospital Discharge	Before the subject is discharged or within 30 days of implant.
ACT/DAPT discontinuation visit	Visit required only for subjects on ACT/DAPT at hospital discharge: from 1 to 6 months (3 months preferred) post-implant.
Follow-up evaluations:	
First CT scan	Minimum of 30 days (+ 60 days) after discharge or discontinuation of ACT/DAPT (expected from 1 to 6 months post-implant).
Second CT scan	For subject with reduced leaflet motion previously detected by Core Lab; after the 1st CT scan, but prior to 1 year follow-up visit (expected from 6 to 10 months post-implant).
1 year	Clinic visit at 1 year ± 1 month after the day of the implant.
Pre-implant period	Period from signing of the informed consent until the day before the implant.
Post-implant period	Period from successful implantation of Perceval bioprosthetic heart valve to 30-days after hospital discharge visit (for subjects discharged off ACT/DAPT) or ACT/DAPT discontinuation visit (for subjects discharged on ACT/DAPT).
Post-ACT/DAPT period	Period from 31st day after the hospital discharge (for subjects discharged off ACT/DAPT) or 1st day after the ACT/DAPT discontinuation (for subjects discharged on ACT/DAPT) to 1 year visit.
Pooling of sites and countries	Unless otherwise specified, data from all of the study sites and countries will be pooled and the analysis performed on the complete database including subjects from all sites and countries.
Screening Failure	Subjects who are screened, informed consent was obtained, and not included in the study due to eligible criteria not met.
Implant procedure completers	Subjects successfully implanted who complete the post-implant period, namely who discontinued the ACT/DAPT at minimum 30 days.

Study completers	Subjects who complete the 1 year visit.

6 ANALYSIS POPULATION

6.1 SCREENING POPULATION

The “Screening population” (SCR) is defined as all subjects will sign the informed consent.

6.2 ENROLLED ANALYSIS POPULATION

The “Enrolled population” (ENR) is defined as all subject who will be enrolled in the study. Subjects who signed the informed consent but do not satisfy the eligible criteria should be withdrawn from the study prior to implant and will be considered as screening failure.

Screening failures will be reordered into logs that are supplied to the sites. These logs can be collected by monitors for internal sponsor records and screen failures will be not entered into e-CRF.

All enrolled subjects will be analyzed under the Intention-To-Treat (ITT) principle, such that subjects will be analyzed according to the final implant attempt to place an aortic Perceval valve. The ENR will be used mainly for subject disposition summaries.

6.3 SAFETY ANALYSIS POPULATION

The “Safety” population (SAF) is defined as all enrolled subjects successfully implanted with one of the study aortic heart valves. The SAF population will coincide with the ENR population and will be used for efficacy, performance and safety summaries.

6.4 PER-PROTOCOL POPULATON

Per-Protocol” population (PP) is defined as all subject in the SAF without the major

primary endpoint-related protocol deviations as defined and reported in the latest version of the study Risk Based Study Management Plan.

The PP population will be used for the sensitivity analysis on primary endpoint.

6.5 USAGE OF ANALYSIS POPULATIONS

Table 1: Use of analysis sets

	ENR	*SAF*	*PP*
Subject disposition	X	X	X
Discontinuations		X	
Protocol deviations		X	
Subject demographics		X	
Implant characteristics		X	
Other baseline characteristics		X	
Medical history		X	
Prior cardiovascular procedures		X	
Concomitant procedures		X	
Prior and concomitant medication		X	
Compliance		X	
Primary analyses		X	X
Secondary efficacy analyses		X	
Secondary performance analyses		X	
Safety		X	

7 DISPOSITION

7.1 SUBJECT DISPOSITION

For describing the subject disposition, the following populations will be summarized overall and for the subgroups defined in Section 5.3.

- Subject signed the informed consent and enrolled (only overall)
- Subjects in the SAF
- Subjects in the PP
    - Reasons for PP exclusion
- Implant procedure completers
- Study completers

For subject in the SAF the percentage denominator will be the number of subject signed the informed consent and enrolled (ENR). For all other calculations, the percentage denominator will be the number of subject in the SAF.

7.2 SUBJECT DISCONTINUATION

Number and percentage of discontinuations will be presented for subjects in the SAF. Reasons for study termination (e-CRF section "Study Termination") will be presented and percentage denominator will be the number of subjects discontinuing. The details for "other reasons" will be presented in a listing, if applicable.

The distribution of the time to study termination will be summarized using time-to-event methods. The starting date of the time to study termination will be from the implant (study day 1). Time will be months until termination. The time to study termination will be censored at the date of study termination or analysis cut-off date, if applicable.

If more than 20% of enrolled subjects terminate the study due to Serious Adverse Events (SAEs) other than leading to death, time to withdrawal due to SAEs will be calculated and evaluated as described above only for subjects who discontinued due to SAEs.

All data will be presented in a subject data listing sorted by subject ID.

7.3 PROTOCOL DEVIATIONS

Major primary endpoint-related (PER) and major other protocol deviations will be summarized overall based on the SAF population.

Protocol deviations will be classified as collected in the "Protocol Deviation" e-CRF or in Section 6.4. Major protocol deviations will be presented in a subject data listing sorted by site, type (PER and other) and subject ID. Minor protocol deviations will be presented in a separate listing also sorted by site and subject ID.

8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Subject demographics and baseline characteristics will be summarized descriptively overall.

8.1 SUBJECT DEMOGRAPHICS

The demographics characteristics will be analyzed by means of summary statistics, as appropriate, for the SAF.

Subject demographics are age [year], age group [<18 years (if applicable), ≥18 years and <65 years, ≥65 years and <85 years, and ≥85 years], gender, race, and ethnicity.

8.2 IMPLANT CHARACTERISTICS

The following implant characteristics will be analyzed by means of summary statistics in the SAF: successful implant, labeled valve size, surgical approach, abnormality of ascending aorta (and specifications), availability of condition of aortic leaflets (and specifications), abnormality of aortic root (and specifications), post-operative cardiac rhythm.

8.3 OTHER BASELINE CHARACTERISTICS

For parameters collected on more than one occasion during the study including baseline, the assessment at baseline will be presented with assessments collected later on in the study and not in a separate table. These parameters are:

- Subject clinical assessment: NYHA classification, infections, cardiac rhythm, ACT/DAPT status and medication change/discontinuation, aortic valve dysfunction symptoms.
- Vital signs: height [m] (only at prior to implant/implant visit), weight [kg], body mass index (BMI) [kg/m^2], body surface area (BSA) [m^2], systolic blood pressure (SBP) [mmHg], diastolic blood pressure (DBP) [mmHg], and presence of congestive heart failure.
- Hemodynamic performance thought transthoracic echocardiogram (TTE).

The other remaining characteristics at implant will be summarized descriptively, as appropriate: concomitant procedures, intraoperative TEE, cardiac rhythm at implant. Details on complications of concomitant procedures will be listed by subject ID, if applicable.

8.4 MEDICAL HISTORY AND PREVIOUS CARDIOVASCULAR PROCEDURES

Medical history will be analyzed by means of summary statistics. It includes but it is not limited to history of systemic hypertension, coronary artery disease, angina, myocardial infarction, heart failure, carotid artery disease previous carotid artery intervention or percutaneous transluminal carotid angioplasty (PTCA), transient ischemic attack (TIA), stroke, endocarditis, peripheral vascular disease, pulmonary hypertension, chronic lung disease, diabetes, dyslipidemia, neoplasia, tobacco user.

Previous cardiovascular procedures will be summarized descriptively, as appropriate: coronary artery bypass surgery (CABG) and specifications, percutaneous coronary intervention, arrhythmia procedure and specifications, pulse generator implant and specifications, revision of the Aortic Valve Replacement Surgery and specification, STS predicted risk of mortality [%], where applicable. Details for “other arrhythmia procedure” and year of intervention/implants will be presented in a listing, if applicable.

8.5 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be collected in the “Medication” e-CRF as per enrollment. For the analysis, the following algorithm will be used to define prior and concomitant medication:

- Prior will be any medication stopped prior to study day 1, regardless of its start date.
- Concomitant will be any medication not stopped before study day 1, regardless of its start date or medication started after study day 1.

These will be summarized by number and percentage of subject receiving them and sorted alphabetically separately for prior and concomitant medications by a predefined list of medication type in “Medications” e-CRF.

Bar plot of the medication type will be created showing the percentage distributions.

9 COMPLIANCE

Compliance will be calculated, for subjects in the SAF, at each follow-up study visit by using the following approach:

- Compliance at V_i [%] = [1-(number of assessments not done or out of window at Vi / expected number of assessments performed at V_i)] x 100,

where V_i represent the current visit for i=1,…,K and K=3 is the maximum number of follow-up visit could be performed by a subject (Section 5.4).

The number of expected assessments performed at V_i will be calculated as the sum of number of assessments performed and number of assessments not done or out of window, for subject still active in the study at V_i.

An assessment at V_i will be considered as "performed" if a complete visit date is available in the corresponding e-CRF and at least one information is entered.

An assessment at V_i will be considered as "not done or out of window" if a visit-specific protocol deviation will be marked as "Visit/Follow-up Not Done" or "Visit/Follow-up Out of Window" in the corresponding "Protocol Deviation" e-CRF.

10 PRIMARY ANALYSIS

10.1 PRIMARY ENDPOINT

The primary endpoint for the study is the incidence of reduced leaflet motion at a minimum of 30 days after the date of hospital discharge or ACT/DAPT discontinuation recorded on "Visit" e-CRF (expected within 1 to 6 months post-implant, preferably 3 months), as assessed by an independent Core Lab.

The valve leaflets will be assessed using 4D volume-rendered CT imaging or TEE for subjects unable to undergo CT scan (e.g. inappropriate renal function). Leaflet motion in all leaflets will be defined as normal, mildly reduced (<50% reduction in leaflet opening), moderately reduced (50-70% reduction in leaflet motion), severely reduced (>70% reduction in leaflet motion) and immobile (no or negligible leaflet motion).

10.2 TESTING STRATEGY AND MULTIPLICITY ADJUSTMENT

The primary statistical analysis will be focused on estimation rather than formal hypothesis testing confirmatory in nature, that is, two-side 90% CI will be provided instead of p-value.

No adjustment for multiplicity will be made.

10.3 PRIMARY ENDPOINT DERIVATION

Reduced leaflet motion will be evaluated by means of the following parameters judged by Core Lab through the CT/TEE images:

- NL Orientation Left Motion
- NL Orientation Right motion
- NL Orientation Non Motion
- Rotated Left Non Motion
- Rotated Right Non Motion
- Rotated Right Left Motion

Parameters will be judged by Core Lab as normal, mildly reduced (<50% reduction), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion in at least one valve leaflet).

No Reduction (success) of leaflet motion will be assigned if all of the above parameters will be recorded as normal or mildly reduced.

Reduction (failure) of leaflet motion will be assigned if at least one of the above parameters will be recorded as moderately reduced, severely reduced, or immobile.

Primary analysis will be based on results of the first CT scan as specified in the Table 2, using all subject in the SAF and done by overall.

Table 2: Use of CT scan results to define incidence in the primary analysis

Scenario #	*Reduced leaflet motion at first CT scan*	*Primary Analysis*
1	No	Not Reduction
2	Yes	Reduction

10.4 PRIMARY ANALYSIS

Incidence of reduced leaflet motion will be estimate as the proportion ($\hat{p}$) of subjects with reduced leaflet motion divided by the size of the population at risk in the SAF.

The 2-sided 90% CI will be calculated by means of Exact confidence limits based on the Binomial distribution.

10.5 SENSITIVITY ANALYSES

The analysis of the primary endpoints, which will provide incidence of reduced leaflet motion and its 90% CI, will be assessed in sensitivity analyses using different assumptions and populations (in each case, the same estimate and 90% CI calculation as specified in previous Section 10.4 will be applied):

- Sensitivity Analysis 1: using the rationale to define the presence/absence of reduced leaflet motion as described in Table 3.

Table 3: Use of CT scan results to define incidence in the primary sensitivity analysis

Scenario #	*Reduced leaflet motion at first CT scan*	*Reduced leaflet motion at second CT scan*	*Sensitivity Analysis 1*
1	No	No	No Reduction
2	No	Yes	Reduction
3	Yes	No	No Reduction
4	Yes	Yes	Reduction

If the first CT scan showed no signs of reduced leaflet motion (scenario 1 and 2), a repeat exam is not mandated and will only be done if it becomes clinically indicated.

If no second CT scan will be performed, reduction/not reduction will be assigned as in Table 2.

- Sensitivity Analysis 2: using the PP population by excluding subject with major primary endpoint-related protocol deviations as described in Section 6.4.
- Sensitivity Analysis 3: Multiple Imputation (MI) analysis to adjust the primary analysis for the uncertainty introduced by the missing observations at first CT scan visit.

The objective of the MI (sensitivity analysis 3) is to impute reduction or no reduction for all subjects with missing values at first CT scan visit, and to perform this multiple time, so that the uncertainty or the imputation can be correctly accounted for in the analysis. Subject with missing data at first CT scan visit will have their missing value imputed according to *Missing At Random* assumptions and taking into consideration specific baseline characteristics.

The following steps will be carried out for the MI of missing data at first CT scan visit for the SAF set:

- The monotone missing data will be imputed using sequential regression multiple imputation, where a logistic regression model is estimated for imputation of the reduced leaflet motion (binary variable). The regression model will include as explanatory variables the age class [year], gender, ethnicity, presence of subject risk factor at baseline, NYHA at baseline, abnormality of ascending aorta or aortic root at implant, presence of aortic regurgitation measured by intraoperative TEE. These can be restricted to be age class [year], gender, ethnicity, presence of subject risk factor at baseline if convergence problem will occur.

  Imputed data will consist of M=200 imputed datasets. This number may be reduced at Quality Control (QC) dry run if the amount of missing data is very low and incidence estimates are stable.

  The random seed number for the sequential regression multiple imputation will be 2019.
- Each of the M imputed datasets will be analyzed using the following analysis method:

- Proportion of subjects with reduced leaflet motion will be analyzed based on observed and imputed data in the SAF. A logistic regression model will be performed using the observed/imputed binary data as the dependent variable and only the intercept as regression coefficient as $logit(\hat{p}) = log\left(\frac{\hat{p}}{1-\hat{p}}\right) = \beta_0 + \varepsilon$.
- Results from analysis of each imputed dataset will be combined using Little's and Rubin's imputation rules (Little and Rubin 1987) to produce a pooled predictive estimate of model intercept and its 90% confidence interval.
- Proportion $\hat{p}$, and its 90% CI, will be derived from the pooled estimates as $\hat{p} = \frac{e^{\widehat{\beta_0}}}{1+e^{\widehat{\beta_0}}}$.

11 SECONDARY EFFICACY ANALYSES

11.1 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints for the study will be evaluated in the SAF and are:

- Incidence of reduced leaflet motion (thrombus) with subanalysis in symptomatic and asymptomatic subjects based on CT outcomes and ACT/DAPT modalities up to 1 year post-implant.
- Incidence of reduced leaflet motion on second 4D CT scan with contrast up to 1 year post-implant, in subjects in which reduced leaflet motion was previously detected.
- Incidence and relationship of reduced leaflet motion to the devices, procedure, or other causes up to 1 year post-implant.
- Freedom from valve safety events (all-cause mortality, valve re-intervention, myocardial infarction, structural valve deterioration, moderate or severe valve regurgitation, valve endocarditis, valve thrombosis, thromboembolic events, hemolysis and major bleeding) up to 1 year post-implant.
- NYHA classification at 1 year post-implant.

11.2 INCIDENCE OF REDUCED LEAFLET MOTION IN SYMPTOMATIC AND ASYMPTOMATIC SUBJECTS

Incidence of reduced leaflet motion up to 1 year post-implant will be evaluated separately in symptomatic and asymptomatic subject using the same method described for the evaluation of the primary analysis.

Symptomatic are those subjects with clinical symptoms, such as, but not limited to shortness of breath, fatigue, or signs of thromboembolic events, as assessed by the treating physician.

A subject will be identified as symptomatic as will be recorded in “Subject Clinical Assessment” e-CRF at the first CT scan visit. List of symptomatic subjects will be reviewed and validated by study team reviewers and confirmed by Steering Committee before data lock.

Within each symptomatic/asymptomatic subgroup, subjects will be categorized on the basis of medication used and discontinued at least 30 days before the first CT scan: any, anticoagulant only, dual antiplatelet medications only, anticoagulant and dual antiplatelet medications.

A forest plot will be used to graphically represent the estimate point of the proportion together with its 90% CI in each category (medication used within symptomatic/asymptomatic subjects); number of subject with reduced leaflet motion and number of total subject in each category will be also displayed.

In addition, all CT or TEE parameters, results and units received from Core Lab (see Sections 10.3 and 12), will be summarized descriptively, as appropriate in the correspondent visit, by overall and subgroup defined in Section 5.3. Details on reference range lower and upper limits will be listed by marking any abnormality with a flag. Leaflet categories (normal, mildly reduced, moderately reduced, severely reduced and immobile) will be also summarized including actual number and percentages.

11.3 INCIDENCE OF REDUCED LEAFLET MOTION IN SUBJECTS IN WHICH IT WAS PREVIOUSLY DETECTED

Incidence of reduced leaflet motion up to 1 year post-implant will be evaluated, as described for the sensitivity analysis 1 of the primary endpoint (Table 3), selecting only subjects in which reduced leaflet motion was detected during the first CT scan (Table 3, scenarios n. 3 and 4).

A shift table will be displayed, for each Core Lab parameter defined in Section 10.3, to evaluate the changes in the imaging evaluation by Core Lab, between the first and second CT scans.

This analysis will be repeated by subgroup defined in Section 5.3.

11.4 INCIDENCE AND RELATIONSHIP OF REDUCED LEAFLET MOTION TO THE DEVICES, PROCEDURE, OR OTHER CAUSES

Incidence and its 90% CI, of reduced leaflet motion up to 1 year post-implant will be calculated (by overall and in subgroup defined in Section 5.3) in the following categories (reference category is underlined):

- Labeled valve size implanted [S/M/L/XL]

- Surgical procedure:
  - Approach [minimal invasive (mini-thoracotomy or mini-sternotomy)/full sternotomy]
    - Minimal invasive approach (mini-thoracotomy/mini-sternotomy)
  - Abnormality of ascending aorta or aortic root [Yes/No]
- Previous cardiovascular procedures [Yes/No]
- Subject risk factors:
  - Cardiac risk factor [Yes/No]

    Yes if at least one of the following is marked: systemic hypertension; coronary artery disease; angina; myocardial infarction; heart failure; carotid artery disease; PTCA; stroke; TIA; endocarditis.
  - Vascular or pulmonary risk factors [Yes/No]

    Yes if at least one of the following is marked: peripheral vascular disease; pulmonary hypertension; chronic lung disease.
  - Diabetes [Yes (mellitus type I or II/No]
  - Dyslipidemia [Yes/No]
  - Neoplasia [Yes (Life expectancy more or less than 1 year) /No]
  - Tobacco user [Yes (current or former)/No]

A forest plot will be used to graphically represent the estimate point of the incidence together with its 90% CI in each category; number of subject with reduced leaflet motion and number of total subject in each category will be also displayed.

Logistic models (Walker and Duncan 1967, Cox 1958) will be run to evaluate the univariate (one by one) association between reduced leaflet motion and each category listed above including the subgroup defined in Section 5.3: concomitant procedures [refers to “without”], subject symptoms [refers to “asymptomatic”], ACT/DATP [refers to “off”], Core Lab evaluation [refers to “TEE”]. Coefficient regression estimates, by referring to the underlined sub-categories, will be provided together with its 90% CI.

11.5 FREEDOM FROM VALVE SAFETY

The following mortality and morbidity outcomes will be analyzed by means of time to event methods:

- all-cause mortality

- valve re-intervention
- myocardial infarction
- structural valve deterioration
- moderate or severe valve regurgitation
- valve endocarditis
- valve thrombosis
- thromboembolic events
- hemolysis
- major bleeding
- pacemaker implantation

Cox's proportional hazards regression models (Cox 1972, Breslow 1975) will be performed including, one by one, the following covariates: age class [refers to "≥18 and <65" years], gender [refers to "male"], ethnicity [refers to "not Hispanic or Latino"], presence of subject risk factor at baseline [refers to "No"], , NYHA at baseline [refers to "Class I"], abnormality of ascending aorta or of aortic root at implant [refers to "No"], presence of aortic regurgitation measured by post-implant intraoperative TEE [refers to "No"], reduced leaflet motion at first CT scan [refers to "No"], including the subgroup defined in Section 5.3: concomitant procedures [refers to "without"], subject symptoms [refers to "asymptomatic"], ACT/DATP [refers to "off"], Core Lab evaluation [refers to "TEE"].

Hazard rate, and its 90% CI, will be reported for each covariate.

Proportional hazard assumption will be investigated for each time-dependent outcome. In case of non-proportional hazards, a Weibull model will be assumed as parametric form of the distribution of survival times.

An additional analysis will be performed in order to evaluate the time free from ACT/DAPT to primary endpoint (reduced leaflet motion) up 1 year post-implant. Kaplan-Meier estimates and plots of time to event after implant will be produced as in Section 5.2. Subjects will be included in the analysis starting from their stop date of ACT/DAPT until the first evaluation of leaflet motion.

11.6 NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

Subject improvement after valve implant will be determined by the McNemar-Bowker (extension of McNemar test to more than two categories) to test, at 90% two-side significance level, the marginal homogeneity between pre-operative and post-operative NYHA proportions.

Besides, the NYHA classification will be summarized in a shift table by overall and, for the appropriate visits, by subgroup defined in Section 5.3.

Evaluation performed in corresponding of first and second CT scan visits will be displayed also categorizing by subject with/without reduction leaflet motion and within each leaflet motion category (normal, mildly reduced, moderately reduced, severely reduced and immobile). Number of non-missing observations (n) and percentage on the SAF population will be displayed.

A bar plot will be provided to graphically display the overall NYHA marginal percentages, by visit.

12 SECONDARY PERFORMANCE ANALYSIS

12.1 SECONDARY PERFORMANCE ENDPOINT

The secondary performance endpoint for the study will be evaluated in the SAF and is:

- Hemodynamic performance up to 1 year post-implant through TTE assessed by Echocardiographic Core Lab.

12.2 HEMODYNAMIC PERFORMANCE

Hemodynamic performance of Perceval prosthetic heart valve will be assessed by flow velocities, pressure gradients, effective orifice area and degree of regurgitation. Descriptive statistics will be displayed by visit (overall and, for the appropriate visits, by subgroup defined in Section 5.3) as reported in the following sections. Evaluation performed in corresponding of first and second CT scan visits will be displayed also categorizing by subject with/without reduction leaflet motion and within each leaflet motion category (normal, mildly reduced, moderately reduced, severely reduced and immobile).

12.2.1 Flow velocities, Pressure gradients and effective orifice area

Hemodynamic performance will be presented as per Core Lab results. Actual values will be analyzed appropriately at each assessment visit.

The following parameters will be analyzed appropriately:

- Left ventricular internal dimension-diastole (LVIDd) [cm]
- Left ventricular internal dimension-systole (LVIDs) [cm]
- Interventricular septal thicknesses-diastole (IVSd) [cm]
- Left ventricular posterior wall diameter (PWd) [cm]
- Left ventricular mass [g]
- Left atrium diameter [cm]
- Left atrium volume [mL]
- Left ventricular end-diastolic volume (LVEDV) [mL]
- Left ventricular end-systolic volume (LVESV) [mL]
- Ejection fraction (EF) [%]
- Mitral E [cm/sec] (early diastolic velocity from mitral inflow Doppler)
- Mitral A [cm/sec] (late diastolic velocity from mitral inflow Doppler)

- Mitral valve deceleration time [L/min]
- Septal E [cm/sec] (early diastolic velocity recorded from tissue Doppler at the septal mitral annulus)
- Septal A [cm/sec] (late diastolic velocity recorded from tissue Doppler at the septal mitral annulus)
- Tricuspid regurgitation velocity [m/sec]
- Right atrium pressure IVC diameter [mmHg]
- Right ventricular systolic pressure (RVSP) [mmHg]
- Left ventricular outflow tract (LVOT) diameter [cm]
- LVOT CSA [cm^2]
- LVOT velocity [m/sec]
- LVOT TVI [cm]
- LVOT peak gradient [mmHg]
- LVOT mean gradient [mmHg]
- Aortic peak velocity [m/sec]
- Aortic TVI [cm]
- Aortic peak gradient [mmHg]
- Aortic mean gradient [mmHg]
- Effective orifice area (EOA) TVI [cm2]
- EOA velocity [cm2] (orifice area by velocity method)
- Heart rate [bpm]
- Stroke volume [mL]
- Cardiac output [L/min]
- Stent perimeter [mm]
- Stent major axis [mm]
- Stent minor axis [mm]
- Stent area [mm^2]

Median and quartiles will be displayed graphically by visit for the following parameters: EF [%], aortic peak gradient [mmHg], aortic mean gradient [mmHg], EOA TVI [cm2].

Additional specific analyses may be performed to evaluate the geometrical data. Details of any such analyses will be documented in an ancillary SAP.

12.2.2 Degree of regurgitation

Presence of aortic regurgitation (and specifications of location and degree) will be summarized appropriately. Shift tables will be also displayed to evaluate the severity changes over time.

The following Core Lab variable will be displayed:

- Aortic regurgitation

- Total aortic regurgitation severity
- Paravalvular severity
- Transvalvular severity

12.2.3 Valve re-intervention

Overview tables on valve re-intervention will be generated by overall using the SAF:

1) Summary of the number and percentage of subjects with at least one:

- valve re-intervention
- valve re-intervention with valve explants
- re-intervention without valve explants
- valve in valve procedure

The percentage denominator will be the number of subjects in the SAF.

2) For subject with at least one re-intervention with valve explants or valve in valve procedure, summary of the number and percentage of subjects:

- with at least one another valve implanted
- survived
- died

The percentage denominator will be the number of subjects with at least one re-intervention with valve explants or valve in valve procedure.

3) If >5% of subjects with more than one re-intervention, summary of the number and percentage of re-intervention for:

- valve re-intervention
- valve re-intervention with valve explants
- re-intervention without valve explants
- valve in valve procedure

The percentage denominator will be the total number re-interventions.

4) If >5% of subjects with more than one re-intervention with valve explants or valve in valve procedure, summary of the number and percentage of re-intervention with at least one another valve implanted. The percentage denominator will be the number of re-interventions with valve explants or valve in valve procedure.

All re-intervention details will be listed in subject listing sorted by and subject ID.

13 SECONDARY SAFETY ANALYSIS

All safety data will be presented for the SAF and will be summarized descriptively by overall and, where specified, by occurrence of enrollment (subjects enrolled at implant/after implant) and/or study period (post-implant and post-ACT/DAPT).

13.1 ANALYSIS OF SERIOUS ADVERSE EVENTS

Only SAEs are to be recorded in this study.

The causal relationship of SAEs to procedure or device is categorized as follows:

Category	Assessment by investigator/sponsor/CEC:
Related	Definitely related Probably related
Not related	Not related
Unknown	Unknown

To be in line with the CIP, “Probably related” assessment will be reworded in order to read “Likely related” in the Statistical Outputs.

A device related SAE is considered to be expected if specifically marked as “Expected” in the “Expectedness” field of e-CRF; otherwise it will be considered “Unexpected”.

Where a SAE relationship will be further judged by Sponsor or CEC, only the final assessment will be analyzed by means of the following judgment order: 1. Site, 2. Sponsor, 3. CEC.

13.1.1 Adverse Events overviews

The following overview tables will be generated by overall and study period (post-implant and post-ACT/DAPT at 3, 6, 9 and 12 months post-implant as defined in Section 5.4) further stratified by enrollment occurrence (before or at implant/after implant).

- Summary of the number and percentage of subjects with at least one
  - SAE
    - SAE by procedure relatedness
    - SAE by device relatedness
    - Device related SAE by expectedness
  - SAE leading to study termination
    - SAE leading to study termination by procedure relatedness
    - SAE leading to study termination by device relatedness
    - Device related SAE leading to study termination by expectedness
  - SAE leading to death
    - SAE leading to death by procedure relatedness
    - SAE leading to death by device relatedness
    - Device related SAE leading to death by expectedness

The percentage denominator will be the number of subjects.

- Summary of the number and percentage of SAEs for:
  - SAE
    - SAE by procedure relatedness
    - SAE by device relatedness
    - Device related SAE by expectedness
  - SAE leading to study termination
    - SAE leading to study termination by procedure relatedness
    - SAE leading to study termination by device relatedness
    - Device related SAE leading to study termination by expectedness
  - SAEs leading to death
    - SAE leading to death by procedure relatedness
    - SAE leading to death by device relatedness
    - Device related SAE leading to death by expectedness

The percentage denominator will be the total number of SAEs.

13.1.2 Adverse Events Incidences

The incidence of SAE is defined as the number of subjects with occurrence of this SAE during the period of interest: post-implant and post-ACT/DAPT (at 3, 6, 9 and 12 months post-implant) as defined in Section 5.4.

The incidence rate of an SAE is defined as the number of subjects with occurrence of this SAE during the period of interest divided by the total number of subjects in the SAF during the period of interest.

The incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by SAE general category and term, sorted alphabetically by overall and enrollment occurrence (further stratified by study period) for each of the following SAE categories and SAE subcategories:

- SAE
  - SAE by procedure relatedness
  - SAE by device relatedness
  - Device related SAE by Expectedness
- SAE leading to study termination
  - SAE leading to study termination by procedure relatedness
  - SAE leading to study termination by device relatedness
  - Device related SAE leading to study termination by expectedness
- SAE leading to death
  - SAE leading to death by procedure relatedness
  - SAE leading to death by device relatedness
  - Device related SAE leading to death by expectedness

Bar plots will be generated to show the incidence rates of overall SAE, SAE leading to study termination, SAE leading to death.

Incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by SAE general category and term (sorted alphabetically) for SAEs only (overall and enrollment occurrence further stratified by study period) by the following SAE descriptors:

- SAE Criteria: in-patient hospitalization, prolonged hospitalization, permanent disability/incapacity, intervention to prevent life-threatening injury or permanent damage, life-threatening illness or injury.
- Action taken: treatment provided, aortic valve prosthesis re-intervention, pulse generator implanted, surgical intervention, non-surgical intervention, changes in medication regimen.

Linearized rate will be calculated, by overall and enrollment occurrence, as number of late (> 30 days) events, *e*, divided by late subject-years, *SY*, defined as the subject years accumulated in the period starting from the 31st day after implant. Linearized rate 90% CI will be calculated by means of the exact Poisson confidence limits as following:

$$90\%\ CI\ lower\ limit = \frac{\chi^2_{2e,0.05}}{2SY}$$

$$90\%\ CI\ upper\ limit = \frac{\chi^2_{2(e+1),0.95}}{2SY}$$

where $\chi^2_{v,a}$ is the chi-square quantile for upper tail *a* probability on *v* degrees of freedom (Garwood 1936, Ulm 1990).

Plots will be generated to show the linearized rates, together with its 90% CI, of overall SAE, SAE leading to study termination, SAE leading to death.

Linearized rate, its 90% CI, will be summarized by SAE general category and term, sorted alphabetically by overall and enrollment occurrence, for each of the following SAE categories and subcategories:

- SAE
  - SAE by procedure relatedness
  - SAE by device relatedness
  - Device related SAE by expectedness
- SAE leading to study termination
  - SAE leading to study termination by procedure relatedness
  - SAE leading to study termination by device relatedness
  - Device related SAE leading to study termination by expectedness
- SAE leading to death
  - SAE leading to death by procedure relatedness
  - SAE leading to death by device relatedness
  - Device related SAE leading to death by expectedness

The following listings will be produced for all enrolled subjects:

- Deaths (the listing will present flags indicating the relevant study period);
- SAEs leading to study termination other than death;
- Unexpected device related SAEs.

13.2 ANALYSIS OF LABORATORY PARAMETERS

Not applicable for this study.

13.3 ELECTROCARDIOGRAM

Cardiac rhythm will be evaluated as described in Sections 8.2 and 8.3. Abnormal ECG findings will be recorded as SAE.

13.4 PHYSICAL EXAMINATION PARAMETERS

Subject Clinical Assessment will be evaluated as described in Section 8.3.

14 SUBGROUP ANALYSIS

Subject disposition will be described within each subgroup population as detailed in the corresponding paragraph in Section 7.1.

Primary analyses will be summarized by specific subgroups (subject symptoms, ACT/DATP, Core Lab evaluation) as described in Section 5.3. A forest plot will be used to graphically represent

the estimate point of the proportion together with its 90% CI in each subgroup; number of subjects with reduced leaflet motion and number of total subject in each subgroup will be also displayed.

Tabular presentations for all secondary endpoints will be done by group defined in Section 5.3 as described in the corresponding paragraph:

- "Secondary Efficacy Analysis" (Section 11)
- "Secondary Performance Analysis" (Section 12)

Specific analysis will be performed within symptomatic/asymptomatic grouping as described in Section 11.2 "Incidence of reduced leaflet motion in symptomatic and asymptomatic subjects".

15 INTERIM ANALYSIS

Not applicable for this study.

16 ABBREVIATIONS

Acronym	Verbatim
4D	Four Dimensional
ACT	Anticoagulant (therapy)
AdaM	Analysis Data Model
ANOVA	Analysis of Variance
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CIP	Clinical Investigational Plan
CSR	Clinical Study Report
CT	Computed Tomography (scan)
DAPT	Dual Antiplatelet Therapy
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EF	Ejection Fraction
EOA	Effective Orifice Area
FDA	Food and Drug Administration
HR	Hazard Ratio
IVSd	Interventricular Septal Thicknesses-Diastole
IFU	Instruction For Use

ITT	Intention-To-Treat population
LVEDV	Left Ventricular End-Diastolic Volume
LVESV	Left Ventricular End-Systolic Volume
LVIDd	Left Ventricular Internal Dimension-Diastole
LVIDs	Left Ventricular Internal Dimension-Systole
LVOT	Left Ventricular Outflow Tract
LVEF	Left Ventricular Ejection Fraction
MI	Multiple Imputation
MPG	Mean Pressure Gradient
NYHA	New York Heart Association
PER	Primary Endpoint-Related (major protocol deviation)
PI	Principal Investigator
PP	Per-Protocol population
PPG	Peak Pressure Gradient
PTCA	Previous Carotid Artery Intervention or Percutaneous Transluminal Carotid Angioplasty
PWd	Posterior Wall Diameter
QC	Quality Control
RVSP	Right ventricular systolic pressure
SAE	Serious Adverse Event
SAF	Safety population
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCR	Screening population
TESAE	Treatment Emergent Serious Adverse Event
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram

17 REFERENCES

The following articles were referenced in this SAP:

- BEhavior of valve Leaflets and the Incidence of rEduced mobility post-surgical aortic valVE implant (BELIEVE). Clinical Investigation Plan (CIP) Version A, March 2017
- Breslow NE. Analysis of Survival Data under the Proportional Hazards Model. International Statistical Review / Revue Internationale de Statistique. 43(1):45-57, 1975.
- Cox DR. The regression analysis of binary sequences (with discussion). Journal of the Royal Statistical Society: Series B. 20:215-242, 1958.
- Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society: Series B. 34(2): 187-220, 1972.
- Garwood F. Fiducial limits for the Poisson distribution. Biometrika. 28(3/4):437-442; 1936.
- International Standard ISO 14155:2011(E). Clinical investigation of medical devices for human subjects — Good clinical practice. Boutique AFNOR pour: SORIN CRM SAS. Second edition February 2011.
- Patient CaseBook e-CRF, dated 31st January 2018.
- Little RJA, Rubin DB. Statistical Analysis with Missing Data. John Wiley & Sons, New York. 1987.
- Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology. 131(2):373-375, 1990.
- Walker SH, Duncan DB. Estimation of the probability of an event as a function of several independent variables. Biometrika. 54:167-178, 1967.

18 APPENDIX 1: ANALYSIS SPECIFICATIONS

The purpose of this section is to give technical details for the implementation of the SAP.

18.1 PERCENTAGES AND DECIMAL PLACES

If not otherwise specified, the following rules are applied:

- Percentages are presented to 1 decimal point.
- Percentages equal to 0 or 100 are presented as such without a decimal point.
- For descriptive summary statistics, the same number of decimal places as in the raw data are presented when reporting minimum and maximum values, 1 more decimal place when reporting mean, median, quartiles and confidence interval (CI) and standard deviation (SD).
- P-values are presented to 3 decimal points. P-values < 0.001 will be reported as such.
- Ratios are presented to 3 decimal points.

The above described displaying rules must not be changed (e.g., rounding) for the CSR text and are used 1:1 in the body report as well.

18.2 PRESENTATION OF DIFFERENCES AND CHANGES

For changes from baseline, the later value will constitute the minuend and the baseline value the subtrahend. Changes will be calculated only for subjects with values at both considered visits.

18.3 PRESENTATION OF UNITS

If applicable, parameters will be displayed together with the used unit of measurement. The unit of measurement is enclosed in square brackets ([ ]). This applies to both tables and listings.

18.4 PRESENTATION OF DATES

Where applicable (e.g., in listings), dates will be displayed in ISO8601 format (example: 2014-09-29T12:16, see CDISC 2013). In case of incomplete dates, both the original value and the imputed value are displayed.

18.5 HANDLING OF MISSING VALUES

At each time point/visit, all subjects still in the study are reported. Missing values will be taken into account as missing in the analysis. The number of observed values and the number of missing values must sum up to the number of subjects in the study at the respective time point/visit.

Missing measurements/missing values are identified by the SDTM variable **STAT=ND. If this variable is not recorded (it's a permissible variable) the missing values of **ORRES should be used.

Unless otherwise specified in the SAP, missing values will not be imputed. If missing values are imputed, the result of all imputation strategies and newly derived information must be stored

in the ADaM data set. The shifts required for the shift tables should already be included in the ADaM data set.

Imputed values will be listed in the subject data listing and be marked as imputed.

18.6 VISIT WINDOWS

Measurements will be assigned to visits according to the windows allowed in the Protocol and reported in Figure 2. These are defined in Section 5.4 and resumed below:

- Pre-implant/implant: during and after successful implant.
- Hospital Discharge: ≤30 days post-implant.
- ACT/DAPT discontinuation visit: 1-6 months post-implant.
- First CT scan visit: ≥30 days (+ 60 days) after discharge (for subjects discharged off ACT/DAPT) or after ACT/DAPT discontinuation (for subjects discharged on ACT/DAPT).
- Second CT scan visit: after the first CT Scan and 6-10 months post-implant.
- 1 year visit: 1 year ± 1 month post-implant.

Figure 2: Visit Window Guide

Visit Name	Calculate from:	Window Start Day	Window Stop Day
Pre-Implant / Implant Data	Enrollment date	- 90	0
Hospital Discharge (completed prior to actual discharge)	Implant date	0	30
ACT / DAPT Discontinuation or Planning Visit	Implant date *90 days after Implant date preferred*	30	180
1st CT-scan Follow-up Visit (no ACT/DAPT)	Hospital Discharge date *30 days after Hospital Discharge preferred*	30	90
1st CT-scan Follow-up Visit (DC on ACT/DAPT)	ACT / DAPT Discontinuation date	60	240
2nd CT-scan (if needed) *A minimum of 6 weeks after 1st CT-scan*	Implant date	180	300
1 year follow-up	Implant date	335	395

18.7 CONVERSION OF TIME INTERVALS

If a time interval was calculated in minutes, hours or days and needs to be converted into months or years the following conversion factors will be used:

- 1 month = 30.4375 days
- 1 year = 365.25 days

18.8 MANDATORY TABLES WITHOUT DATA

Recommended tables must be created. If no subject qualifies for the table, the header will be created and the table itself will be replaced by “No subject in this category”.

18.9 STORING OF IMPUTATION DATA

The result of all imputation strategies (e.g., incomplete start dates of SAE), combination of observations (e.g., combination of consecutive SAEs) and new derived information (e.g., treatment-emergent flag) must be stored in ADaM data set.

18.10 OUTLIERS

Not applicable for this study.

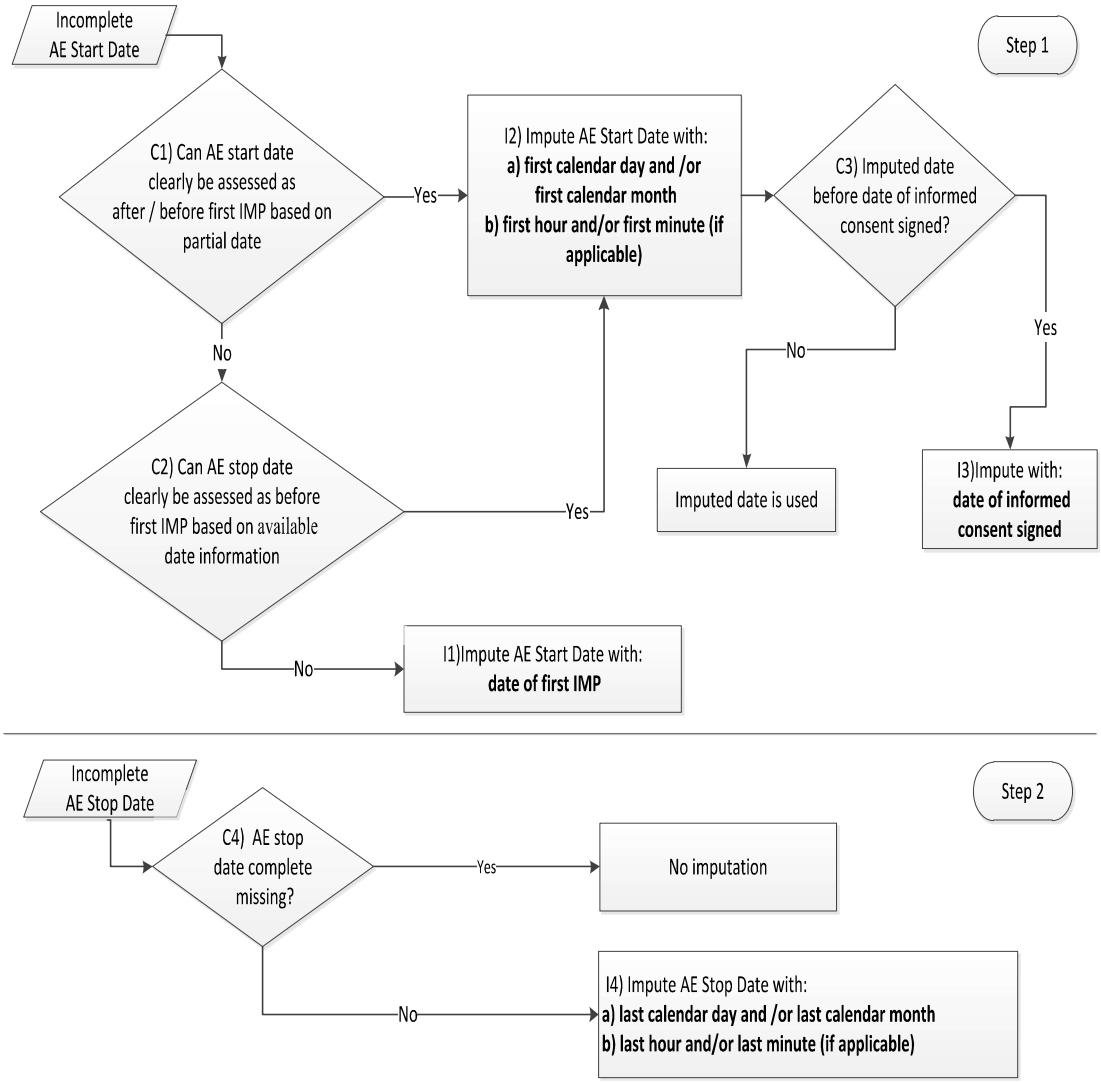
18.11 HANDLING OF MISSING DATES FOR ADVERSE EVENTS

The term missing date refers to a completely missing date or to an incomplete date where parts are not available e.g., missing day.

Missing start and end date will be imputed conservatively, i.e., missing values will be imputed in such a way that the duration of the SAE is considered with the longest possible duration.

In case the SAE requires hospitalization, the hospitalization information could be added to the algorithm.

Figure 3: Graphical overview about the imputation strategy



I1-I4: imputation steps
C1-C4: checkpoints

Further explanations on the flow chart:

The different steps of the displayed imputation strategy must be completed from the first to the last step. All procedures in each step must be completed in the order given.

Imputation:

- I1: Impute with date of first IMP - investigational medicinal product - (namely device implant).
- I2: Impute with first calendar day and / or first calendar month.

  Imputation will be done based on the available partial information starting with month and then day. The respective first month and day will be chosen for imputation:

▪ Missing date	Imputed date
▪ 2014-Mar	2014-Mar-*01*
▪ 2014	2014-*Jan-01*

- I3: Impute with date of informed consent signed.
- I4: Impute with last calendar day and / or calendar last month.

  Imputation will be done based on the available partial information starting with month and then day. The respective last month and day will be chosen for imputation:

▪ Missing date	Imputed data
▪ 2014-Mar	2014-Mar-*31*
▪ 2014	2014-*Dec-31*

Checkpoints:

- C1: The decision must be taken based on the available information (date) before imputation.
- C2: SAE stop date before first IMP

  1) The decision must be taken based on the available information (date) before imputation.

  2) If the end date is completely missing (with or without the information that the DAE was continuing) this will be considered as after first IMP.

  3) If no IMP was given this will be treated as SAE stop date before first IMP.
- C3: The decision must to be taken based on the available information (date) before imputation.
- C4: The decision must to be taken based on the available information (date) before imputation.A replacement of missing year for SAE start information is not foreseen. If needed, this will be considered on a case-by-case decision which must be documented together with the documentation of ADaM data sets.

Assignment SAEs to study periods

Assignment of SAE to study periods will be done after replacement of missing date information.

List of deaths

Death will be identified by outcome of SAE equals “fatal” (AETERM in “Sudden cardiac death”, “Death unknown cause”, “Death non cardiovascular”) or SAE Criteria Met equals “death” or Reason for Termination equals “death”.

Time to onset of SAE

Time to onset of SAE will be calculated based on implant date and based on the imputed value for SAE start date.

Duration of SAE

Duration of SAE will be calculated based on the imputed values for SAE start date and stop date.

If duration of SAE could not be calculated due to unknown date information the following assessment to categories will be used:

- If the SAE is marked as “continuing” in the e-CRF the duration will be categorized as “continuing”
- Otherwise the duration category will be set to “missing”.

18.12 TITLES AND FOOTNOTES

- Header: Company name, Study name and deliverable (e.g. LivaNova, Study APR002 BELIEVE – Deliverables: Main Analysis)
- Footer: Cutoff date (if applicable), Snapshot date, Draft / Final
- Footnotes:
  - All the footnotes will begin with a dash followed by Trailing space, with indentation for second line when needed
  - Footnotes referring to a particular element of the Table, Listing or Figure, will have a standard order based on symbols as per American Medical Association (AMA) Manual of Style 10th Edition
  - Name and Version of the Coding System used, when coded events are reported
  - Final footnote will contain full program path and program name, Run/Execution date
- Title:
  - Title1: Table xx.x.x.x
  - Title 2: Table Title
  - Title 3: Analysis Population

Subgroup to be displayed as subtitle (preferably left aligned).

18.13 DATA DERIVATIONS

Derived variable	Derivation algorithm based on e-CRF version 8 dated 18th July 2017
Concomitant Procedures	"Implant Surgical Details" e-CRF: • Group "Implanted with a concomitant procedure" if CPYN= "Yes" • Group "Implanted without a concomitant procedure" if CPYN= "No"
Subject symptoms	"Subject Clinical Assessment" e-CRF at "at 1 Month After ACT Dx (1st CT-Scan)" or "Reduced Leaflet Visit (2nd CT-Scan)" Visits: • Group "Asymptomatic" if SCSYMPYN = "No" • Group "Symptomatic" if SCSYMPYN = "Yes"
ACT/DATP	"Subject Clinical Assessment" and e-CRF: • Group "Subject **on** ACT/DAPT at hospital discharged (or 30-days after implant)" if SCDISCYN= "Yes" • Group "Subject **off** ACT/DAPT at hospital discharged (or 30-days after implant" if SCDISCYN= "No"
Core Lab evaluation by	"Vist (at 1 Month After ACT Dx or at Reduced Leaflet)" e-CRF: • Group "CT scan" if IMGTYPE= "4D CT Acquisition" • Group "TEE" if IMGTYPE = "Transesophageal Echo"

Pre-implant period	If *Enrolled Date*= DXSTDAT2 ("Implant Surgical Details" e-CRF) then
	• *Start date*: ICFDAT ("Inclusion/Exclusion Criteria" e-CRF)
	• *End date*: DXSTDAT2 -1
	If *Enrolled Date*= ICFDAT then
	Start date=*End date*= "None".

Post-implant period	If DXPER= "Yes" ("Implant Surgical Details" e-CRF) *Start date*: DXSTDAT2, *End date*: • if SCDISCYN= "No" ("Subject Clinical Assessment" e-CRF) then *End date*= VISDAT (at Hospital Discharge visit) + 30 • if SCDISCYN= "Yes" ("Subject Clinical Assessment" e-CRF) then *End date*= VISDAT (at ACT Discontinuation visit) + 30
Post-ACT/DAPT period	*Start date*: • if SCDISCYN= "No" ("Subject Clinical Assessment" e-CRF) then *Start date*= VISDAT (at Hospital Discharge visit) + 31 • if SCDISCYN= "Yes" ("Subject Clinical Assessment" e-CRF) then *Start date*= VISDAT (at ACT Discontinuation visit) + 31 *End date*: VISDAT (at Year 1 visit)
Implant procedure completer	• DXPERF= "Yes" ("Implant Surgical Details" e-CRF) and • DSSTDAT ≥ ACTDIDAT ("Study Termination" e-CRF) + 31 ○ if DSSTDAT missing, last available VISDAT ≥ ACTDIDAT + 31
Study completer	• DSDECOD= "Completed" ("Study Termination" e-CRF)
SCR population	ICFDAT not missing ("Inclusion/Exclusion Criteria" e-CRF)
Enrolled Date	Derived from maximum between Consent Date and Implant Date. "Inclusion/Exclusion Criteria" e-CRF and "Implant Surgical Details" e-CRF Max(ICFDAT; DXSTDAT2)
ENR population	• SCR flag= "Yes" and • DXSTDAT2 not missing ("Implant Surgical Details" e-CRF) and • existing *Enrolled Date*
SAF population	• ENR flag= "Yes", and • DXPERF= "Yes" ("Implant Surgical Details" e-CRF)
PP population	• As reported in the Believe Risk Based Study Management Plan.
Time to study termination (months)	"Implant Surgical Details" e-CRF and "Study Termination" e-CRF [DSSTDAT – DXSTDAT2 + 1] / 30.4375

Time to event (months)	"Implant Surgical Details" e-CRF *[Even date* – DXSTDAT2 + 1] / 30.4375 Subjects ongoing and who are free from event at the analysis cut-off date will be censored at the analysis cut-off date. Subjects who have discontinued without an event will be censored at the date of discontinuation.
Age at Enrollment (years)	"Demographics" e-CRF and "Inclusion/Exclusion Criteria" e-CRF Age= [ICFDAT - BRTHDAT + 1]/365.25 As only month and year of birth are reported in the CRF, 1st day of the month will be used for birth date.
Change from baseline	Test Value at Visit X - Baseline Value

Where

ACTDIDAT = "Date Subject Discontinued ACT/DAPT Therapy"

BRTHDAT= "Date of Birth"

CPAETERM= "Complications/Please specify if any of the following intraoperative complications occurred. /AE Term"

CPYN= "Was concomitant procedure performed?"

DIMODEL= "Valve Model"

DSDECOD= "Reason for Termination"

DSSTDAT= "Date of Study Termination"

DVDECOD= "Deviation Description"

DVICSPEC= "If Informed Consent, specify reason"

DXPERF= "Was the implant successful?"

DXSTDAT2 = "Date of Implant"

ICFDAT = "Informed Consent Date"

IEYN= "Met All Eligibility Criteria?"

IMGTYPE= “Specify the imaging modality currently being used for the subject”

MHCVDAT = “If Myocardial Infarction, date”

MHSTDAT3= “If Stroke, date”

NY= “No/Yes”

SCDISCYN= “Was the subject discharged on anticoagulant and/or dual platelet therapy? “

VISDAT = “Visit Date”

VITYPE= “Type of Reintervention”

BELIEVE_SAP_V2_2019-05-14_Final

Final Audit Report 2019-05-14

Created:	2019-05-14
By:	Teresa Greco (Teresa.Greco@livanova.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAAxuqLJjg6xsc3K2xzaMkTb6ptQkXZ2cWy

"BELIEVE_SAP_V2_2019-05-14_Final" History

Document created by Teresa Greco (Teresa.Greco@livanova.com)
2019-05-14 - 6:00:41 AM GMT- IP address: 2.36.200.254

Document e-signed by Teresa Greco (Teresa.Greco@livanova.com)
Signature Date: 2019-05-14 - 6:03:03 AM GMT - Time Source: server- IP address: 2.36.200.254

Document emailed to Giacomo Mordenti (giacomo.mordenti@livanova.com) for signature
2019-05-14 - 6:03:03 AM GMT

Document viewed by Giacomo Mordenti (giacomo.mordenti@livanova.com)
2019-05-14 - 6:41:21 AM GMT- IP address: 93.244.9.149

Document e-signed by Giacomo Mordenti (giacomo.mordenti@livanova.com)
Signature Date: 2019-05-14 - 6:41:41 AM GMT - Time Source: server- IP address: 93.244.9.149

Document emailed to Nelly V. Rivera (nelly.rivera@livanova.com) for signature
2019-05-14 - 6:41:42 AM GMT

Document viewed by Nelly V. Rivera (nelly.rivera@livanova.com)
2019-05-14 - 2:04:59 PM GMT- IP address: 196.17.100.76

Document e-signed by Nelly V. Rivera (nelly.rivera@livanova.com)
Signature Date: 2019-05-14 - 2:09:43 PM GMT - Time Source: server- IP address: 50.201.200.170

Signed document emailed to Teresa Greco (Teresa.Greco@livanova.com), Nelly V. Rivera (nelly.rivera@livanova.com) and Giacomo Mordenti (giacomo.mordenti@livanova.com)
2019-05-14 - 2:09:43 PM GMT