Statistical Analysis Plan

STUDY: XEL-CR-03

Prospective, non-randomized, pivotal clinical study to assess the safety and efficacy of the bioabsorbable pulmonary valved conduit in subjects undergoing Right Ventricular Outflow Tract (RVOT) reconstruction

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STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURE PAGE

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The undersigned have reviewed this statistical analysis plan and approve of it in its entirety.

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0 AMENDMENTS FROM PREVIOUS VERSIONS

Changes to the Statistical Analysis Plan will be documented in the table below. Previous versions of the Statistical Analysis Plan can be found on NERI Connect. The version numbers below should match the version numbers in the document's revision history on NERI Connect.

Version	Change
1.0	Initial draft
2.0	Change number of participating sites. Update version of Clinical Investigation Plan referenced.
3.0	Adapt endpoints and statistical methods to match updates made for the pivotal trial.
4.0	Updated based on BfArM comments

1. LIST OF ABBREVIATIONS

Abbreviation	Explanation
AATS	American Association for Thoracic Surgery
ADE	Adverse Device Effect
AE	Adverse Events
CHD	Congenital Heart Disease
CI	Confidence Interval
CSR	Clinical Study Report
CT	Computed Tomography
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration
IDE	Investigational Device Exemption
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IRB	Investigational Review Board
ITT	Intent-to-Treat
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PA	Pulmonary Artery
PV	Pulmonary Valve
RV	Right Ventricle
RVOT	Right Ventricular Outflow Tract Obstruction
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
UADE	Unanticipated Adverse Device Effect
VSD	Ventricular Septal Defect

WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document outlines the detailed statistical analysis methods to be implemented to provide the appropriate clinical information to demonstrate initial clinical safety and device functionality of the bioabsorbable pulmonary valved (PV) conduit.

1.1 Study Objectives

Primary Objective

The primary objectives of the study are:

- To assess the rate of combined events of death and/or conduit failure requiring re-intervention** or reoperation, at 12 months following implantation of the bioabsorbable pulmonary valved conduit*.

Secondary Objectives

The secondary objectives of this study are:

- To assess the mortality rate of subjects at 6 months following implantation of the Bioabsorbable pulmonary valved conduit. *
- To assess the overall mortality rate at 60 months.
- To assess the rate of conduit failure at 6 months, requiring reintervention** or reoperation.
- To assess the pressure gradient across the pulmonary valve, and regurgitation at 6 and 12-month follow-up.

Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate the growth of the conduit as measured at 6, 36, 48, and 60 months in pediatric population of age of below 18 years old.
- To evaluate the usability of the Bioabsorbable pulmonary valved conduit during the surgical procedure, using exploratory parameters.

Long term follow-up Objective

- Long-term safety will be assessed up to 60 months' post-implantation by summarizing the survival rate.

* *This includes only device-related deaths.*
** *Re-interventions are defined as catheter-based interventions: Stent or valve implantation in the Xeltis Pulmonary Valved Conduit*

1.2 Study Synopsis / Design

This study is a prospective, 5 year, multi-center, non-randomized, single-arm, open-label, pivotal clinical study to assess the safety and efficacy of the bioabsorbable pulmonary valved (PV) conduit in subjects requiring right ventricular outflow tract (RVOT) correction or reconstruction due to congenital heart malformations. PV replacement is the only treatment proven to reduce the right ventricular size and improve right ventricular function in the long term.

The Xplore 2-Pivotal study will continue to assess the safety and efficacy of this novel medical device. Initially, the EFS enrolled 6 subjects between March and October 2018. The study was paused (October 2018) to await the 12 months results of the first 6 subjects. Based on the positive results, the EFS study has been amended to the Pivotal study with the enrollment beginning in the summer of 2020 with up to 50 additional patients at 16 (O)US centers. Approximately 50% of study patients will be included at US centers. The amendment to a pivotal study should provide sufficient clinical safety and efficacy data to warrant marketing approval in the US as well as outside the US.

The study plans to enroll 56 patients between the ages of 2 and 22 years old from 16 study centers in the US and OUS. Subjects will provide written informed consent prior to undergoing any study related assessments or procedures, which may occur up to 30 days prior to surgery. After establishing eligibility during screening and confirming continued eligibility on the day of surgery (Day 0), subjects will undergo surgical implantation of the PV conduit. Subjects will undergo a safety evaluation peri-operatively, at 7 days / discharge, at 6 weeks, at 3, 6, and 9 months and subsequently at 12, 18, 24, 36, 48, and until 60 months (end of study). Study endpoints will be assessed at 6 and 12 months post implant and subjects will be followed up until 60 months post implant for long term safety. Subjects where the device could not be implanted for any reason, including the subject receiving the implant but experiencing surgical problems leading to the removal of the study device during the initial implantation, will be considered treatment failures and treated with an alternative device of the surgeon's choosing. If no implant attempt is made the patient is not considered a treatment failure.

1.3 Study Product / Intervention

The bioabsorbable PV conduit is a gamma sterilized, bio-absorbable, polymer-based medical device. The device has a total overall length of 8 cm with inner diameters of initially 16 or 18 mm, devices with 20 and 22 mm added once available and approved. The valve itself is formed by three leaflets, which are incorporated within the conduit wall.

The PV conduit is used for RVOT correction or reconstruction, in patients less than 22 years with any of the following congenital heart malformations:

- Tetralogy of Fallot
- Truncus Arteriosus
- Pulmonary Atresia
- Transposition of Great Arteries with Ventricular Septal Defect (VSD)
- Pulmonary Stenosis in combination with other defects in congenital heart defect (CHD) syndromes

In addition, the PV conduit can be used for the following indications:

- Replacement of previously implanted, but dysfunctional, pulmonary homografts or valved conduits (except for mechanical valves, see exclusion criterion 3).
- Patients undergoing a Ross procedure, where the PV conduit would replace the patient's own pulmonary valve which is used to replace a diseased aortic valve.

The PV conduit is surgically implanted using the same surgical technique as would be used for any standard homograft or off the shelf PV conduit. No special medication is required other than standard practice. The subject will be put on an anticoagulation regimen and an endocarditis prophylaxis, according to hospital standard practice.

1.4 Study Data Collection

Baseline data will be collected within 30 days prior to the implant date for inclusion in the study. Clinical data will be collected at the time of pre-implant baseline, implant, and planned follow-ups at Day 1, Day 7 / Discharge (whatever comes first), 6 weeks, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 36 months, 48 months and 60 months post implant.

The study follow-up visits with the appropriate time windows are described in Table 1. The data collection requirements are described in Table 2.

Table 1. Follow-up windows

Study Visit	Follow-up Window
Baseline - Pre-Implant Evaluation	Within 30 day prior to implant
Implant	During surgery – Day 0
Day 1	Day 1 Post-Implant
Discharge if before day 7	Discharge
Day 7	Days 5-9 Post-Implant
6-week follow-up	Days 35-49 Post-Implant
3-month follow-up	Days 84-98 Post-Implant
6-month follow-up	Days 168-196 Post-Implant
9-month follow-up	Days 244-304 Post-Implant
12-month follow-up	Days 335-395 Post-Implant
18-month follow-up	Days 517-577 Post-Implant
24-month follow-up	Days 700–760 Post-Implant
36-month follow-up	Days 1065-1125 Post-Implant
48-month follow-up	Days 1430-1490 Post-Implant
60-month follow-up	Days 1795-1855 Post-Implant

Table 2. Data Collection

Study Item	Baseline	Implant	Day 1	* Day 7 or Discharge	6-wk	3-mo	6-mo	9-mo	12-mo	18-mo	24-mo	36-mo	48-mo	60-mo
Informed Consent	X													
General Patient information and Demographics	X													
Medical History	X													
Inclusion/Exclusion Verified	X	X												
Physical Examination Including signs of erythema, edema and lesions	X		X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight	X			X	X	X	X	X	X	X	X	X	X	X

Study Item	Baseline	Implant	Day 1	* Day 7 or Discharge	6-wk	3-mo	6-mo	9-mo	12-mo	18-mo	24-mo	36-mo	48-mo	60-mo
Vital Signs[1]	X		X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Profile[2]	X		X	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile[3]	X		X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Profile[4]	X		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[5,6]	X	X						X	X	X	X			
Echocardiography	X			X	X	X	X	X	X	X	X	X	X	X
ECG	X			X	X	X	X	X	X	X	X	X	X	X
Chest X-ray, Angiography, CT, MRI will be data will be collected if available	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medications Documented	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA Score	X						X	X	X	X	X	X	X	X
Implantation Evaluation		X												
All Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X

*Day 7 or discharge – whichever comes first
1 Vital Signs: Heart Rate, Respiratory Rate, Temperature, and Blood Pressure
2 Coagulation Profile: PT, PTT, INR
3 Hematology Profile: HGB, HCT, WBC, RBC, Platelet Count, Haptoglobin
4 Chemistry Profile: NA+, K+, BUN/Urea, Creatinine, ALT/ALAT, AST/ASA, Total Bilirubin, Albumin, LDH, CRP
5 For patients with childbearing potential. Can be done by urine test. Stable healing occurs between 1-2 years; therefore, contraceptives should be used up to 2 years after implantation.
6 Pregnancy test in follow-up period: at 9, 12, 18 and 24 months.

2 REPORTING

2.1 General Considerations

All statistical programming for reporting purposes will be performed using IBM SPSS Statistics® version 23 or above. The analyses performed for all regulatory reporting will be programmed using SDTM compliant datasets.

2.2 Interim and Final

Descriptive reports are expected after 6-months, 24-months, and 60-months follow-up for all patients. These reports will present the results of all analyses set forth in this document, as applicable for the time point. Full clinical study reports (CSR) will be written after all 12-month and 5-year follow-up visits are completed.The 12-month report will include the results of the confirmatory hypothesis test.

2.3 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will review the safety outcome and provide a report following their evaluation. The DSMB has evaluated the safety at three time points in the initial EFS:

Table 4. Timelines safety evaluation

Timeline	Type of Data
After 3 patients followed for 3 months	Adverse events, clinical investigation plan violations, enrollment summary
After 6 months follow-up for all implanted patients	Same as above
After 12 months follow-up for all implanted patients	Same as above

For the pivotal study, the DSMB will evaluate safety at the following additional time points:

Table 1 Timelines safety evaluation continuation

Timeline	Type of Data
After 50% of the additional subjects have been implanted and followed-up for 6 months	Adverse events, clinical investigation plan violations, enrolment summary, echocardiographic results
After three patients implanted with the size 16 device and three patients implanted with the size 22 device have reached the 6 weeks follow-up. (If enrollment for one subgroup goes faster, two separate meetings can be performed)	Same as above
After all implanted patients have been followed-up for 6 months and all additional available follow-up.	Same as above
After 12 months follow-up for all implanted subjects	Same as above
After 24 months follow-up for all implanted subjects	Same as above
Upon completion or termination of the study.	Same as above

At the time of the safety review, the DSMB will be provided a summary of enrollment, violations of the clinical investigation plan, and all adverse events including all serious device-related events during the study.

An ad hoc meeting of the DSMB may be called at any time by the DSMB Chair, investigator or sponsor if immanent participant safety issues arise. If a significant safety concern arises during the study, the DSMB Chair may convene a meeting to review safety and any other aspect of the study.

Based on the safety review of the data, the DSMB may recommend that Xeltis modify or stop the trial. No formal statistical rule will be defined.

2.4 Regulatory Authorities (incl. Food & Drug Administration)

NERI will provide support for the annual submissions to the Food & Drug Administration (FDA) per the reporting requirements.

On-going discussion and required reporting to the FDA and other required regulatory authorities will continue throughout the study as needed.

After the first 25 patients have been treated and have reached their six weeks follow-up, an additional interim analysis will be performed and submitted to German authorities (baseline characteristics and safety data, no hopothesis testing). In the case of a good outcome, the next set of patients will be treated to reach the expected number of 50 subjects.

Note Germany: This clinical study will commence at the sites with 16 and 18 mm devices. Later on, additional device sizes will be added as enrollment continues.

3 STUDY ENDPOINTS

The primary safety study endpoint:

1. Composite rate of events of device-related death, re-operation or re-intervention at 12 months follow-up.

Secondary safety endpoints include the following:

1. Overall rate of device-related death due to device failure at 6 months follow-up post implantation.
2. Overall rate of mortality at 60 months follow-up post implantation
3. Overall rate of subjects who require reoperation or re-intervention due to device failure at 12 months
4. Overall rate of subjects with a mean pressure gradient across the area of conduit implantation [right ventricle (RV) to pulmonary artery (PA)] of less than 40 mm Hg at 6 and 12 months follow-up
5. Overall rate of subjects with pulmonary regurgitation of equal or less than moderate at 6 and 12 months follow-up

Additional exploratory endpoints include the following:

1. Measurement of growth of the conduit in the pediatric population measured at 6, 36, 48 and 60 months. A competent valve (regurgitation levels equal of less than moderate) with increased valve diameter in age groups < 18 years in correlation with the increased body surface area
2. Overall satisfaction of the implanting surgeon of the implantation procedure of the Bioabsorbable pulmonary valved conduit.

The long term follow-up endpoint is the number of device-related serious adverse events over 60 months long term follow-up.

4 ANALYSIS GROUPS, SAMPLE SIZE DETERMINATION & POWER

4.1 Subject Populations for Analysis

Intent-to-Treat: The intent-to-treat (ITT) analysis group will consist of all subjects that sign the IRB/EC - approved written Informed Consent form and undergo anesthesia for an implant, regardless of whether or not the subject receives the intended treatment at the implant procedure. This group is identical to the safety population, on which the safety-related tabulations and analyses are based.

As-Treated: The as-treated analysis group will consist of only subjects who received the intended treatment at the implant procedure.

Per-Clinical Investigation Plan: The per-clinical investigation plan analysis group will consist of subjects from the as-treated analysis group, with the exclusion of those subjects that were found not to have met eligibility requirements after implantation.

Adverse Events and outcomes will be summarized using the intent-to-treat analysis group. All primary and secondary safety endpoints and the additional exploratory endpoints will be analyzed using the as-treated analysis group. Analysis of the primary endpoints will also be repeated on the per-clinical investigation plan analysis group.

4.2 Treatment Misallocations

As this is a single-arm, non-randomized, open label clinical study, there are no accommodations for treatment misallocations.

Subjects for who the PV conduit could not be implanted for any reason, including patients receiving the implant but experiencing surgical problems leading to the removal of the study device during the initial implantation, will be considered treatment failures and treated with an alternative device of the surgeon’s choosing. These subjects will be included in the Intent-to-Treat analysis group, but excluded from the As-Treated and Per-Clinical Investigation Plan analysis groups.

4.3 Clinical Investigation Plan Deviations

Deviations from the clinical investigation plan will be identified as far as possible by programmable checks. These will be detailed in a separate deviation document, along with other checks made by monitor and clinical review. All checks will be made prior to database lock/release.

4.4 Sample Size Determination and Power Assessment

Historical data from the literature for an established competitive device (Contegra Pulmonary Valved Conduit) suggest event rates of 20-30% for the composite of 12-months reintervention, reoperation and device-related death. In a conservative approach, a reference rate of 15% was derived as performance goal. The observed rate of primary endpoint events will be compared against the expected rate of 15% with a

one sample Wald test. Based on prior experience, it is assumed that the rate to be observed with the Xeltis valved conduit to be 5%,
Denoting the probability of occurrence of the primary endpoint within 12 months as π, the formal null hypothesis to be tested is:
H_0: π =15%
The planned alternative hypothesis for sample size calculation is:
H_1: π = 5%

Two-sided alpha of 5% and power of 90% was assumed.

With these assumptions, a sample size of 50 patients is necessary for the statistical test. Allowing for a 10% dropout rate, 55 patients need to be treated in the study. Therefore, additional 50 patients need to be enrolled (6 patients already included in the EFS part).

The sample size was computed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) as follows:

```
proc power;
onesamplefreq
test=Z method=normal
varest=sample
proportion=0.05
nullproportion=0.15
sides=2
power=0.9
alpha=0.05
ntotal = .
;
run;
Actual power: 0.901
N Total: 50
```

Approximately 50% of all patients will be included from the US study centers.

It is believed that 50 additional subjects will provide sufficient clinical safety and device functionality data, to submit for market approval.

Some further details and arguments are given in the Clinical Investigation Plan chapter XIX 1.1 – 1.4.

4.5 Subgroups

4.5.1 Study Centers

In the CIP (Paragraph VIII) it is described why the potential difference in patient populations between US and OUS centers are believed to be minimal and therefore the groups are poolable. In addition, centers will not be allowed to include more than 12 patients. However, estimates of the cumulative event-free survival will be computed while stratifying on the region (US & OUS) and separate estimates by region will be shown as part of the planned subgroup analyses. Moreover, demographic and clinical characteristics of patients from the two regions will be described and compared to exclude non-poolability.

4.5.2 PV Conduit Size

To assess possible differences in the safety profile of different sizes of the PV conduit safety analysis will be repeated for subgroups by device diameter (16, 18, 20, 22 mm).

5 RANDOMIZATION

5.1 Procedure

As this is a single arm, non-randomized, open label clinical study, randomization procedures are not applicable.

Sufficient literature is available on Contegra to base the comparison between the Xeltis pulmonary valved conduit and Contegra on historical Contegra data. Moreover, there are only a limited number of subjects in the world (5,505 cases in the US from 2011-2014 (1,373 per year on average) – STS Congential Heart Surgery Database) requiring pulmonary valve surgery. Therefore, it is justified to conduct a single arm clinical trial.

5.2 Treatment Labels

Due to the design of the study, treatment labels are not applicable.

6 STATISTICAL METHODS OF ANALYSIS

6.1 Statistical Inference

The primary objective is to assess the rate of combined events of death and/or conduit failure requiring re-intervention or reoperation, at 12 months following implantation of the bioabsorbable pulmonary valved conduit. The analysis will test the hypothesis that the composite event rate is less than 15, the reference value for the event rate derived in a conservative manner from the results of the Contegra valve. The rate of events will be compared against the expected rate of 15% with a one sample Wald test with a two-sided alpha of 5% and power of 90%.

Descriptive statistics will be performed on the safety, performance and exploratory parameters.

Two-sided 95%-confidence intervals (CI) will be produced for estimates.

6.2 Handling of Missing Values and Drop-outs

In device-related death analyses, missing values will generally not be accepted as death must be followed regardless of the patient's completion status. However, for the combined event of death and device failure, the relationship to the study procedure and study device and the relevance for the primary endpoint will ultimately be classified by the clinical events committee (CEC). If the patient is confirmed at 12 months FU to have experienced a primary endpoint event but the exact date is not known, the endpoint is counted for the confirmatory test. Drop-outs will be excluded from the primary analysis.

No data imputation will be performed for any other missing data. When data are not available, or partially available, data summaries will be based on available data.

6.3 Statistical Analysis

Descriptive statistics will be performed on the main safety and exploratory parameters. For metric data, these summaries will include – in order: N, Mean, 95% Confidence Interval (95% CI) of Mean, Standard Deviation, Median, Range (here and elsewhere 'range' should be presented as (minimum value, maximum value) in a single row). Where frequencies are presented, they will be accompanied by percentages. Missingness will be accounted for by including the frequency of missings and discontinued subjects in each table.

Unless otherwise noted, analyses will be performed using all subjects who received study intervention, and had a device implanted (the as-treated analysis group).

6.3.1 Analysis of Primary Safety Endpoint

The primary endpoint is a combined endpoint of death and/or conduit failure requiring re-intervention or reoperation, at 12 months.

To define the event rate at 12 month endpoint, the deaths included in the calculation of the rate is defined as a device-related death at or prior to the scheduled 12-month visit. Subjects who withdraw prior to the scheduled 12 month visit are followed up to confirm their survival status at 12 months. If they are confirmed dead due to a device related death, the composite event is assumed to have occurred at their date of death. In case of non-device related death, they are censored at their date of death. If the subjects are still alive, they are considered to be drop-outs and are excluded from the primary analysis. All subjects are censored at 365 days post implantation at the latest.

The event rate at 12 months follow-up includes in the calculation all re-operations and reinterventions as defined in chapter IV of the clinical investigation plan. If a subject required re-operations or reinterventions and later died or if a subject required multiple re-operations or reinterventions then the earliest such date is included in the calculation.

The rate will be summarized by the number and percentage of subjects. The rate of events will be compared against the expected rate of 15% with a one sample Wald test with a two-sided alpha of 5% and power of 90%.

Analysis of the primary endpoint will also be repeated on the per-clinical investigation plan analysis group.

As an estimator of the probability π, the proportion of patients who reached the primary endpoint is calculated, together with the two-sided Wald 95%-confidence interval.

Sensitivity analyses

Cumulative incidence function (CIF) estimates of cumulative event probabilities will be calculated by the Aalen-Johansen estimator using the exact censoring times,

considering non-device related death as competing risk. The curves will be plotted over time. The number and percentage of subjects with an device-related event at or prior to the scheduled 12 month visit will be displayed with the CIF estimate and 95% confidence interval at 365 days. While the number of patients 'at risk', the number of patients having had an event and the number of patients censored at each day alongside the CIF estimates and the 95% CI's will also be presented.

In an alternative version of this analysis, all withdrawn subjects will be censored at the time of withdrawal, without considering information about their later survival.

6.3.2 Analysis of Secondary Safety Endpoints

Analysis of the secondary safety endpoints will be as follows:

1. Overall mortality at 60 months follow-up post implantation will be calculated using the Kaplan-Meier estimator. In this analysis all deaths will be included in the calculation, regardless of whether they were device-related or not. Subjects who were withdrawn from the study prior to the 60-month follow-up visit are followed up to confirm their survival status at the time of the 60-month visit. If no further information is available the subject is censored at the time of the last study contact. Subjects alive at the time of study completion are censored at that time.
2. For the analysis of freedom from device-related death due to device failure at 6-month follow-up post implantation, the deaths included in the calculation of the survival rate is defined as a device-related death at or prior to the scheduled 6-month visit. Subjects who have a non-device-related death at or prior to the scheduled 6 month follow-up visit are censored at their date of death. Subjects who withdraw prior to the scheduled 6-month visit are followed up to confirm their survival status at 6 months and are censored at 180 days, confirmed dead due to a device-related death at their date of death, or censored at their non-device-related date of death. All other subjects are censored at 180 days.
3. For the analysis of freedom from re-operation or re-intervention at 12-month follow-up due to device failure, the re-operation or re-intervention rate at 12-month follow-up due to device failure includes in the calculation all re-operations and re-interventions as defined in chapter IV of the Clinical Investigation Plan. Subjects who have a re-operation or re-intervention at or prior to the scheduled 12-month follow-up visit that is not due to device failure are censored at their date of event. Subjects who withdraw prior to the scheduled 12-month visit are followed up to confirm their status at 12 months and are censored at 365 days, confirmed to have had a re-operation or re-intervention at their date of event, or censored at their date of death (device or non-device-related). All other subjects are censored at 365 days.
4. For the secondary safety endpoint, the "Mean pressure gradient across the area of conduit implantation (RV to PA) of less than 40 mmHg" will be derived based on the 'PV V2 Mean Gradient Results (mmHg)' value collected in the "Hemodynamic Evaluation" section on the 'Echocardiography Form' of the 6 and 12 month follow-up eCRF page, as:

- "Yes" if 'PV V2 Mean Gradient Results' < 40 mmHg
- "No" if 'PV V2 Mean Gradient Results' ≥ 40 mmHg.

The overall rate of subjects with a mean pressure gradient across the area of conduit implantation of less than 40 mm Hg at 6 and 12 month follow-up will be summarized by number and percentage of subjects.

5. The degree of pulmonary regurgitation (the percentage of blood that regurgitates back through the pulmonary valve due to valve insufficiency) is defined as follows:
   - None
   - Trace
   - Mild (regurgitation <20%)
   - Moderate (regurgitation between 20%–40%)
   - Severe (regurgitation >40%)

   For the secondary safety endpoint, the "Pulmonary Regurgitation" will be derived based on the 'PI Severity Result' score collected on the 'Echocardiography Form' of the 6 and 12 month follow-up eCRF page as:

   - "Yes" if 'PI Severity' = None, Trace, Mild or Moderate
   - "No" if 'PI Severity' = Severe

   The overall rate of subjects with pulmonary regurgitation of equal or less than moderate at 6 and 12 months follow-up will be summarized by number and percentage of subjects.

6.3.3 Analysis of Additional Exploratory Endpoints

Analysis of the additional exploratory endpoints will be as follows:

1. Growth of the conduit in the pediatric population, as measured at 6, 36, 48 and 60 months, will be summarized and presented by study visit as metric data. Conduit growth will be assessed from the 'Neo Annulus Diameter (cm)' collected on the 'Echocardiography Form' of the follow-up eCRF page. Change in growth over time will be derived by subtracting the value collected at discharge or Day 7, (whichever occurs first) from the value obtained at the follow-up visit, and will be summarized and presented as metric data. The number of subjects with any growth of the conduit at the different time points will be summarized by the number and percentage of subjects.

   In addition, the correlation between valve diameter and body surface area in patients <18 years of age with a competent valve (pulmonary regurgitation levels equal to or less than moderate) will be reported as the Pearson correlation coefficient and p-value. Valve diameter and pulmonary regurgitation will be derived from the 'Neo Annulus Diameter' and 'PI Severity Result' values respectively, collected on the 'Echocardiography Form' of the corresponding follow-up eCRF page.

2. For the analysis of the overall satisfaction of the implanting surgeon with the implantation procedure of the Bioabsorbable PV conduit, results of the Surgeon

Questionnaire will be summarized and presented as frequency data. The Surgeon Questionnaire is comprised of 7 questions that collected general feedback from the surgeons regarding the preparation, condition, and implantation of the Bioabsorbable PV conduit. Six of the 7 questions elicit responses on an ordered 5-point scale (strongly agree, disagree, agree, strongly agree, not applicable). The last question collects data on any unexpected events that occurred while operating the conduit.

6.3.4 Analysis of Long Term Follow-Up Endpoint

For the analysis of the long term follow-up endpoint, the number and percentage of patients in the ITT analysis group with at least one device-related serious adverse event over the course of the 60-month follow-up period will be summarized.

6.4 Adverse Events

Adverse Events will be summarized for all subjects that sign the IRB-approved written Informed Consent form and undergo anesthesia for an implant (the ITT analysis group).

Serious and non-serious adverse events (AE), as defined in Section XV of the clinical investigation plan, will be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA Coding will be performed using the 5 levels: Lowest Level Term, Preferred Term, Higher Level Term, Higher Level Group Term, and System Organ Class.

The number and percentage of patients with at least one adverse event will be summarized overall, by SAE and AE, and by relationship to study procedure and device. The number and percentage of patients with at least one adverse device effect (ADE) and the number and percentage of patients with at least one unanticipated adverse device effect (UADE) will be summarized. Additional information will be provided via narratives for any UADEs.

Missing and partial dates will be construed in a ‘worst case’ sense. For subjects with multiple reports of the same AE, the maximum intensity and maximum relationship to the study procedure and study device will be calculated. The relationship of the endpoints to the study procedure and study device will ultimately be classified by the clinical events committee (CEC).

Additionally, numbers of subjects with events will be summarized giving frequencies and percentages by body system (by descending overall frequency of events within the body system). A further table will summarize events by preferred term (frequencies and percentages by descending overall frequency) overall and by maximum severity.

Adverse events will also be grouped into the following categories derived from Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions and the American Association for Thoracic Surgery (AATS) Definitions and summarized.

- Prosthetic Valve Endocarditis
- Structural Valve Deterioration
- Non-structural Dysfunction

- Valve Thrombosis
- Major Bleeding
- Cardiac Arrhythmias
- Pericardial Fluid Collection
- Minor Hemolysis
- Major Hemolysis
- Hepatic Dysfunction
- Major Infection
    - Localized Non-Device Infection
    - Sepsis
- Myocardial Infarction
    - Peri-Operative Myocardial Infarction
    - Non-Perioperative Myocardial Infarction
- Acute Renal Dysfunction
- Chronic Renal Dysfunction
- Respiratory Failure
- Right Heart Failure
- Arterial Non-CNS Thromboembolism
- Venous Thromboembolism Event
- Wound Dehiscence
- Sensitization Response
- Other

Serious AEs will be listed. In addition, procedure- and device-related serious AEs will be summarized (frequencies and percentages) by MedDRA preferred term and by AE category.

6.5 Other Safety Data

Other safety data will be summarized for all subjects that sign the IRB/EC-approved written Informed Consent form and undergo anesthesia for an implant (the ITT analysis group).

6.5.1 Vital Signs

Descriptive by-visit summaries of vital signs data will be presented as for metric data. Vital signs will include heart rate, respiration rate, temperature, and blood pressure.

6.5.2 Device Administration

Device implantation details will be reported for each subject. In the case of device malfunction during the procedure or thereafter, additional information will be provided regarding the type of malfunction and other related details collected via narratives.

Note: If an adverse event / adverse device effect (serious or not) was associated with the device malfunction, or if the device malfunction led to an adverse event / adverse device effect (serious or not) then this will be reported as such and therefore also included in the reporting of those data.

6.5.3 Laboratory Tests

Hematology and Clinical Chemistry and Coagulation laboratory safety data will be summarized by the visit as for metric data. A listing of all lab data for each subject at each visit will also be provided.

Note: Any clinically significant abnormal laboratory readings that occur in a subject after implantation will be reported as an adverse event and therefore also included in the reporting of those data.

6.5.4 Echocardiography

Descriptive summaries of echocardiographic results will be presented by study visit, as metric or categorical summaries (as appropriate). Summarized results will include all 2D measurements, RV systolic function, hemodynamic evaluation, and overall qualitative assessments collected on the 'Echocardiography Form' of the follow-up eCRF page. Graphical depictions of echocardiographic results (eg: box and whisker plots or equivalent) will be provided for select measurements [ie: pulmonary insufficiency (PI Severity Result), mean pressure gradient (PV V2 Mean Gradient Results), and conduit growth (change in Neo Annulus Diameter)]. In addition, listings of all echocardiography results will be presented for each patient and study visit.

6.5.5 Electrocardiogram

Descriptive summaries of electrocardiography (ECG) results will be presented by study visit. Summaries of change in overall assessment of ECG data from baseline to end of the trial will be presented by shift table (Normal, Abnormal {Not Clinically Significant}, Abnormal {Clinically Significant}).

Note: Any clinically significant abnormal readings that occur in a subject after implantation will be reported as an adverse event and therefore also be included in the reporting of those data.

6.5.6 Additional Imaging (Chest X-ray / Angiography / CT / MRI)

Data from all additional imaging performed over the course of the study, including chest X-rays, angiographies, CT scans, and/or MRI scans, will be summarized and presented by study visit, as metric or categorical data (as appropriate). Additional information will be provided via narratives for any abnormal findings.

6.6 Other Data

6.6.1 Subject Disposition

Subject accountability analyses will be performed on the ITT analysis group. Duration of clinical follow-up will be summarized by visit window. Follow-up proportions will be based on the presence of any follow-up at a follow-up visit. Subjects eligible for a follow-up visit are those who have reached the beginning of the time window of the visit. If subjects return for a visit outside of the visit window, this will be counted as compliant but with a violation of the clinical investigation plan.

In addition, the number and percentage of patients: successfully implanted and completed study, successfully implanted and discontinued study early, and not successfully implanted will be tabulated. Main reasons for discontinuation will be summarized. A flow diagram (eg: Consort flow diagram) of patient disposition will also be created.

Reasons for exclusion from the Per Clinical Investigation Plan analysis group will be summarized. Deviations from the clinical investigation plan will be listed.

6.6.2 Study Sites

The number of all subjects participating in the study will be tabulated by site.

6.6.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized for the ITT analysis group, as descriptive or categorical summaries (as appropriate). Key demographic and baseline characteristic data include: age, race/ethnicity, weight, height, NYHA classification, and congenital heart malformation identified as the indication for Right Ventricular Outflow Tract (RVOT) correction/reconstruction.

6.6.4 Medical History

Medical history details recorded at baseline will be summarized, as descriptive or categorical summaries (as appropriate), for the ITT analysis group. Key medical history findings (yes/no) include: renal failure, liver condition, any coagulation disorder, aneurysm, peripheral vascular disease, gastrointestinal disease, myocardial infarction, cerebrovascular accident, previous cardiovascular interventions, previous RVOT correction or replacement.

6.6.5 Previous and Concomitant Medications

Previous and concomitant medications will be summarized according to the World Health Organization Drug Dictionary (WHO-DD) for the ITT analysis group. The number and percentage of patients will be presented for previous and concomitant medications separately. Previous medications will include any medication started prior to study treatment irrespective of whether it continues after the commencement of study treatment (in which case such a medication would be both ‘previous’ and ‘concomitant’).

6.6.6 Other Data

All other data from the case report form, whether or not explicitly mentioned in this document, will be listed.

7 INTERIM ANALYSIS

Safety will be monitored by the DSMB on an ongoing basis throughout the study, as described in Section 2.3.

After the first 25 patients have been treated and have reached their six weeks follow-up, an additional interim analysis will be performed.

In addition, interim reports are expected after 6-months, 12-months, 24-months, 36-months, 48-months, and 60-months follow-up for all patients. These reports will present the results of all analyses set forth in this document, as applicable for the time point.

8 SUBGROUP ANALYSES

The primary endpoint will be further explored in subgroups identified according to, but not limited to, the medical history (prior surgery), the median age, sex, device size, region/country.

9 SHELLS FOR TABLES, FIGURES AND LISTINGS

A separate document with table, figure and listing shells will be provided to the sponsor prior to beginning any analyses.

10 QUALITY CONTROL OF STATISTICAL ANALYSES

To ensure the accuracy and validity of the statistical analysis, all statistical reports and programming will undergo independent review. This level of review will consist of a visual inspection of all statistical reports and associated programming code and an examination of selected output with the aim of identifying possible errors or problems.

11 REFERENCES

Clinical Investigation Plan