Xeltis Bioabsorbable Pulmonary Valved Conduit Pivotal Study (Xplore2/*Pivotal*)

Study Title	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
Clinical Investigation Plan Version and Date:	Protocol amendment Xplore2 – to pivotal study 7.0, 26 May 2021
Study Registration:	clinicaltrials.gov nr: NCT03022708
FDA IDE number	G160278
Study Identifier:	XEL-CR-03
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Investigational Device	Bioabsorbable Pulmonary Valved Conduit

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CONFIDENTIAL

SPONSOR SIGNATURE SHEET

Study number	XEL-CR-03 clinicaltrials.gov nr: NCT03022708
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The sponsor, coordinating investigator and trial statistician have approved the protocol version 7.0 dated 26 May 2021, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ISO 14155 standard and any local legally applicable requirements.

Sponsor representative: Jochen Reinöhl, Chief Medical Officer

Digitally signed by Jochen Reinoehl, MD
Date: 2021.05.28 13:43:57 +02'00'

Place/Date | Signature

Coordinating Investigator: Dr. David Morales

CCHMC/5.28.2021

Place/Date | Signature

SIGNATURE PAGE LOCAL PRINCIPAL INVESTIGATOR AT STUDY SITE

Study number	XEL-CR-03 clinicaltrials.gov nr: NCT03022708
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I have read and understood this trial protocol version 7.0 dated 26 May 2021, and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ISO 14155 standard and any local legally applicable requirements.

The information contained in this protocol is provided to me in confidence, for review only by myself, the Independent Review Board authorized to review and approve the study at this study site, the designated research staff participating in this clinical study, and applicable regulatory agencies.

I understand that the information/technology contained in this protocol is proprietary and may not be disclosed to any other party, in any form, without prior authorization from Xeltis, except to the extent necessary to obtain informed consent from potential study participants.

Site Name: Name Principal investigator:

Place/Date Signature

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SYNOPSIS

Table 1. Synopsis

Study Title:	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
Study Type:	Non-randomized Pivotal Study
Study ID:	XEL-CR-03
Clinical Phase:	Phase of development: pivotal study
Background and Rationale:	The bioabsorbable pulmonary valved conduit is used for the reconstruction of the Right Ventricular Outflow Tract (RVOT). There is no specific device related surgical procedure necessary for the implantation. Pulmonary valve replacement is the only treatment proven to reduce right ventricular size and improve right ventricular function in the long term.
Objective(s):	**Primary Objectives:** 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** To assess the mortality rate of subjects at 6 months following implantation of the Bioabsorbable pulmonary valved conduit. * To assess 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 months follow up. **Exploratory objectives** 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.
Outcome(s):	**Primary Endpoints** Composite rate of events of device related death, re-operation or re-intervention at 12 months follow-up.

	Secondary Endpoints Overall rate of device related death due to device failure at 6 months follow up post implantation. Overall rate of mortality at 60 months follow up post implantation. Overall rate of subjects who require reoperation or reintervention due to device failure at 6 months. Overall rate of subjects with a mean pressure gradient across the area of conduit implantation (RV to PA) of less than 40 mm Hg at 6 and 12 months follow up. Overall rate of subjects with pulmonary regurgitation of equal or less than moderate at 6 and 12 months follow up. **Exploratory endpoints** Measurement of growth of the conduit in 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. Overall satisfaction of the implanting surgeon of the implantation procedure of the Bioabsorbable pulmonary valved conduit. **Long term follow-up Endpoint** The number of device related serious adverse events will be assessed over 60 months long term follow up. *This includes only device related deaths.
Study design:	A prospective, multi-center, single arm, non-randomized, pivotal clinical study. 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 be operated. Subjects where the device could not be implanted for any reason, including the subject receiving the implant but experiencing surgical problems leading to 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. Subjects will undergo a safety evaluation peri-operatively, at 7 days / discharge, at 6 weeks, at 3 and 6, 9 months and subsequently at 12, 18, 24, 36, 48 and until 60 months (end of study).

	The Xplore 2-Pivotal study will continue to assess the feasibility 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 now been amended to this pivotal study with enrollment expect to begin in the summer of 2020 with up to 50 additional patients at 16 study sites in US (United States) and OUS (Out of United States). Approximately 50% of study patients will be included in the US centers. Initially, 16 and 18 mm pulmonary valved conduits will be included., 20 and 22 mm pulmonary valved conduits will be added once available and approved.
Inclusion criteria:	Subjects requiring correction or reconstruction of the Right Ventricular Outflow Tract (RVOT) due to congenital heart malformations. This includes patients in need of replacement of a previously implanted, but dysfunctional, homograft / pulmonary valved conduit, as well as patients undergoing a Ross procedure. **Inclusion Criteria:** 1. Patient requiring RVOT reconstruction, suitable for 16 mm, 18 mm, 20mm, and 22mm valved conduit. 2. Male or Female. 3. Age > 2 years and < 22 years. 4. Right Ventricular to Pulmonary Artery peak gradient > 35mm Hg or moderate or severe Pulmonary regurgitation (≥3+), or have both (except for the patients undergoing a Ross procedure). 5. The patient, and the patient's parent / legal representative where appropriate, has been informed of the nature of the study, agrees to its provisions and has provided written informed consent by signing the approved informed consent form. 6. The patient, and the patient's parent / legal representative where appropriate, and the treating physician agree that the subject will return for all required post-procedure follow up visits and the subject will comply with clinical investigation plan required follow-up visits.
Exclusion criteria:	**Exclusion Criteria:** 1. Need for or presence of prosthetic heart valve at other position. 2. Need for concomitant surgical procedures (non-cardiac). 3. Patients with previously implanted pacemaker (including defibrillators), or mechanical valves. 4. Active infection or requiring current antibiotic therapy (if temporary illness, subject may be a candidate 4 weeks after discontinuation of antibiotics) or viral infection. 5. Active endocarditis.

	6. Leukopenia, defined as White Blood cell Count < than: • 2-12 years: 5.0 ×10^3 /µL • 12 years - Adult: • Male: 4.5×10^3 /µL • Female: 4.5 ×10^3 /µL 7. Acute or chronic anemia, defined as Hemoglobin < than: • 2-12 years 11.5 g /dl • 12-18: • Male: 13 g /dl • Female 12 g /dl • Adult: • Male: 13.5 g /dl • Female: 12 g /dl Patients can be transfused to meet eligibility criteria. 8. Thrombocytopenia, defined as Platelet count < than: • 150,000/mm3 Patients can be transfused to meet eligibility criteria. 9. Severe chest wall deformity, which would preclude placement of the PV conduit. 10. Pulmonary hypertension (≥ half of systemic systolic pressure). 11. Right ventricular outflow tract aneurysm. 12. Known hypersensitivity to anticoagulants and antiplatelet drugs and to the device materials. 13. Immunocompromised patient defined as: autoimmune disease, patients receiving immunosuppressant drugs or immune stimulant drugs. 14. Subject has chronic inflammatory, autoimmune disease, tuberous sclerosis, and / or rhabdomyoma. 15. Need for emergency cardiac or vascular surgery or intervention. 16. Major or progressive non-cardiac disease (liver failure, renal failure, cancer) that has a life expectancy of less than one year. 17. Currently participating, or participated within the last 30 days, in an investigational drug or device study. 18. Alcohol or drug abuse as defined by DSM IV-TR criteria for substance abuse – this includes the illicit use of cannabis within the last 12 months. 19. Pregnancy. 20. Females who are sexually active and are not willing to use adequate contraceptive precautions for the next 2 years. 21. Subject has medical, social or psychosocial factors that, in the opinion of the Investigator, could impact safety or compliance.

Measurements and procedures:	**Baseline measurements** • Main diagnosis and co-existing cardiovascular diseases (e.g. congestive heart failure, cardiomyopathy, arrhythmias); • New York Heart Association functional class; • Previous cardiovascular operations; • Other co-existing medical conditions (e.g. liver, kidney and lung disease, substance abuse, diabetes, and history of endocarditis); • Echocardiography, ECG; • Chest X-ray, Angiography, CT scan and MRI data will be collected if available (in case assessment done as standard care); • Blood sample testing, including coagulation profile [prothrombin time, partial thromboplastin time and International Normalized Ratio (INR), as appropriate]. **Peri-operative measurements (during hospitalization)** • Procedure(s), including any concomitant operative procedure(s); • Implant model, size and serial number and suturing technique; • RVOT – bioabsorbable pulmonary valved conduit Usability Questionnaire; • Blood sample testing, including hematology, chemistry and clotting times; • Echocardiography; • Adverse events. **Follow up measurements (6 weeks and months 3, 6, 9 and 12)** • New York Heart Association functional class; • Blood sample testing, including coagulation profile and tests for red blood count, white blood count, hematocrit and hemoglobin; • Status of anticoagulant and/or antiplatelet therapy; • Medication; • Echocardiography (to be assessed by the central Corelab); • ECG; • Adverse events; • Chest X-ray, angiography, CT scan and MRI data will be collected if available (assessment done as standard care). **Long term follow up (months 18, 24, 36, 48 and 60)** Same follow up as for month 3-12.

Study Product / Intervention:	The Pulmonary Valved (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 16, 18, 20, or 22 mm. The valve itself is formed by three leaflets, which are incorporated within the conduit wall. The PV conduit is used for correction or reconstruction of the Right Ventricular Outflow Tract (RVOT), 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 anticoagulation regimen, according to hospital standard practice. The subject will be put on endocarditis prophylaxis, according to hospital standard practice.
Control Intervention (if applicable):	Not applicable – no control intervention.
Number of Participants with Rationale:	Up to 50 additional subjects will be enrolled in up to 16 US and OUS study centers. Sites will not be allowed to enroll more than 12 patients. The pivotal study should provide sufficient clinical safety and efficacy data to warrant marketing approval in the US and OUS.
Study Duration:	The endpoints will be assessed at 6- and 12-months post implant and subjects will be followed up yearly until 60 months post implant for long term safety. After the last subject has had the last visit there will be a 4-month period to monitor and clean the data, closing of the study sites and finalization of the final study report.

Study Schedule:	First patient in: May 2018 Last patient in: October 2018 Study paused to await M12 results (25 October 2018) Pivotal study First patient in (continuation): October 2020 Last patient in (continuation): December 2021 Last patient out: December 2026
Study Centre(s):	Global multi-center study. Up to 16 US and OUS clinical trial centers will be included in this pivotal study.
Statistical Considerations:	Background and sample size calculation: the expected rate of 12 months reintervention, reoperation and device related death (composite endpoint) from the literature is 20-30% (Contegra). For sample size calculation 15% composite event rate was taken into consideration. It is assumed that the rate to be observed with the Xeltis valved conduit to be 5%. Two-sided alpha of 5% and power of 90% was used. With these assumptions additional 50 patients need to be enrolled (55 with 10% dropout rate but 6 patients already included in the EFS part). Approximately 50% of all patients will be included from the US study centers. Approximately 50% of all patients will be included from the US study centers. Detailed statistical justification will be provided in the statistical section and the statistical analysis plan (SAP).
GCP Statement:	This study will be conducted in compliance with the clinical investigation plan, the current version of the Declaration of Helsinki, the ISO 14155, 21 CFR 812 and other relevant FDA requirements (21 CFR 820, 21) as well Medical Device Regulations 2017/745.

CLINICAL INVESTIGATION PLAN

I. Purpose

Xeltis Inc and Xeltis BV are sponsoring this multi-center prospective, single-arm, non-randomized pivotal clinical study to assess the safety and efficacy of the pulmonary valved conduit in subjects requiring Right Ventricular Outflow Tract (RVOT) correction or reconstruction due to congenital heart malformations.

The purpose of this pivotal study is to evaluate the Xeltis Pulmonary Valved conduit device with respect to clinical safety and efficacy of patients such that Xeltis obtains market approval for the PV conduit in the US and OUS.

II. Background

Congenital malformations of the Right Ventricular Outflow Tract (RVOT) comprise 15-20% of all congenital heart defects and 66-80% are accompanied by cyanosis [1-3]. This group includes Tetralogy and Trilogy of Fallot (TOF), double outlet right ventricle (DORV) and pulmonary atresia (PA) with or without ventricular septal defect (VSD). The most pathophysiological significance of these malformations represents pulmonary artery blood flow reduction which causes the most common clinical manifestations, such as cyanosis, shortness of breath and fatigue.

Right ventricle to pulmonary artery valved conduits have made possible the repair of many complex congenital cardiac lesions involving atresia or hypoplasia of the right ventricular outflow tract. These lesions include Truncus Arteriosus (TA), pulmonary atresia with ventricular septal defect, severe Tetralogy of Fallot, Transposition of the Great Arteries (TGA) with ventricular septal defect and pulmonary atresia, and various forms of double outlet right ventricle. Conduits have also made possible the pulmonary autograft replacement of the aortic root with the pulmonary root (Ross procedure). Numerous valved conduits have been introduced since an aortic homograft was first used clinically in the mid-1960's. Conduit types include bioprotheses in Dacron tubes, stented bovine or porcine xenografts in pericardial tubes, glutaraldehyde fixed aortic or pulmonary roots, non-valved tissue or prosthetic conduits, glutaraldehyde fixed bovine jugular vein (Contegra), and aortic and pulmonary homografts.

Pulmonary cryopreserved homografts (human cadaver valves) have been the "gold standard" since the mid-1980s; however, are limited in availability especially in sizes required for the pediatric population [4]. In addition, the homograft may develop stenosis secondary to low grade immune reactions. Limitations of the homograft size that can be implanted in neonates, infants, and small children will predictably result in the need for conduit replacement as the child grows and in addition it has been shown that shrinkage occurs with allografts [4].

The transcatheter application of a xenograft valve like Melody is usually not an option in pediatrics as this is perceived as too risky a procedure in young children. The only other alternative for the pediatric population is a xenograft- bovine tissue (Contegra). The Contegra matches the pulmonary cryopreserved homograft in its suppleness and ease of handling, however, the commissural height of the jugular vein valve is higher than the homograft aortic or pulmonary valve, making it more prone to distortion and regurgitation. The wall of the Contegra tends to be thicker – more so in the larger sizes, often creating an anastomotic mismatch when the native pulmonary artery is thin walled. This may contribute to the higher incidence of distal anastomotic obstruction reported on midterm follow-up as the main problem for failure. It is known from the literature that young children implanted with Contegra face higher risk of early conduit failure and reoperation [5-6].

Currently available homografts and synthetic/ animal derived biomaterials for surgical reconstruction of the RVOT are typically associated with rejection, stenosis, aneurysm formation, and calcification especially in younger children [5-6]. There is a need for an alternative product that can effectively be applied in RVOT reconstruction and that can reduce the frequency of reinterventions as the children grow and offer a viable solution to the limited availability of homografts.

Although significant progress has been made in recent years in the field of congenital heart disease treatment, a substantial unmet clinical need remains for implantable materials/devices such as vascular grafts and heart valves with improved long-term performance and reduced device-related complications.

To address these limitations, a new generation of bioabsorbable polymers using recent advances in supramolecular chemistry has been developed by Xeltis. These polymers create a highly porous vascular scaffold in the geometry of a pulmonary valved conduit. Based on animal tests it is expected that cells will infiltrate the polymer device, followed by gradual replacement of the polymer material with the patient's tissue resulting in functional restoration. This functional restoration with the patient's own tissue could lead to a decrease in failure rates associated with the currently available devices.

The intent to first study the device in a pediatric population instead of an adult population is supported by the fact that children are expected to have better risk-benefit profile with the study device. The currently available devices have limited success in repair of RVOT in children as compared to adults where the age is a dominant risk factor for conduit failure, especially in younger age groups [7-10]. At the same time these children grow and face the realistic situation of the need to undergo several reoperations due to a mismatch in the somatic growth of the patient and the prosthesis size. [13-14]. The fact that the patient's own tissue takes over the function as the device is being absorbed might also accommodate to the growth which could reduce the frequency of re-interventions, which are associated with substantial morbidity and mortality, as the child grows.

Limitations of the homograft size that can be implanted in neonates, infants, and small children will predictably result in the need for conduit replacement as the child grows and in addition it has been shown that shrinkage occurs with homografts [4]. This is also one of the reasons why currently available options, Contegra (porcine tissue PV conduit) / Melody device (bovine jugular vein (BJV) valve sutured within a platinum iridium frame) (both FDA approved) have focused their clinical trials either primarily on pediatrics or first in pediatrics and then moving to an adult population.

Finally, specifically to the Xeltis pulmonary valved conduit, the pediatric population have the best repair and cell remodeling capabilities. As such tissue repair by cell infiltration in the scaffold can be expected to be faster as in general wound healing occurs faster in younger patients than in older patients [13-14]. The literature shows that to date there is no conduit available that is able to grow with the patient or to resist degeneration of a homograft or xenograft over time [15]. Growth of the conduit will be assessed in the pediatric population under 18 years and is a specific objective of this study which can only be measured in this subpopulation.

Previous clinical experience

Xplore 1

A first-in-human study (XEL-CR-01, Xplore 1) with the PV conduit was conducted in 2016 in Europe and Malaysia and implanted 12 patients in Budapest (Hungary N=4), Krakow (Poland N=3) and Kuala Lumpur (Malaysia N=5). The study is a prospective, multi-center, non-randomized, single arm, clinical study. Subjects have undergone a safety evaluation peri-operatively, at 7 days / discharge, at 6 weeks, at 3 and 6 months and subsequently at 12, 18, 24, 36, and are planned to undergo follow-ups at 48 and until 60 months (end of study).
Enrollment started in July 2016 and completed in December 2016, reaching the goal of twelve (12) pediatric patients (between 2 and 12 years old) implanted with the Xeltis pulmonary valve conduit. Pediatric patients included were requiring RVOT reconstruction, suitable for 16 mm or 18 mm pulmonary valve conduit. Seven patients were implanted with an 18 mm device and five patients with a 16 mm device.
To date all 12 subjects have reached their 36 months follow-up. No deaths or conduit failures requiring reoperation or re-intervention were reported. The data is currently being monitored.
Echocardiographic Core Lab assessment of the M24 data showed severe regurgitation in four subjects and a leaflet prolapse was confirmed in 3 patients.

Xplore 2

Based on the first-in-human clinical study (Xplore 1), a root-cause analysis has been performed to better understand the severity of regurgitation and leaflet prolapse reported in this clinical study. This has shown that the leaflet prolapses in these subjects are similar to the failure mode observed in a specific in vitro durability test. This learning led to an enhancement of the design providing leaflets with a more homogenous thickness distribution.

These enhanced devices have been implanted in the ongoing early feasibility study (EFS; Xplore 2, this study) with the pulmonary valved conduit. A total of 6 subjects requiring RVOT reconstruction, suitable for 16 mm or 18 mm conduits, were screened for the study and successfully implanted with an 18 mm device between March 2018 and October 2018 at four (4) US sites. These subjects have been followed for 12 months (pausing enrolment of subjects from October 2018) to determine whether the hypothesized improvements in leaflet thickness distribution were resulting in improved echocardiographic and/or clinical outcomes.

A total of 6 subjects, aged from 2 to 9 years, requiring RVOT reconstruction, were successfully implanted with the PV-001 device. All patients had good procedural outcomes, no bleeding, no thrombosis, no embolization, no endocarditis and a normal hospital stay after surgery with regard to complications and duration.
There were no implant failures or deaths in the first twelve months of the study. One patient required a re-operation after 9 months due to a proximal obstruction. This was most likely due to the underlying disease of the patient: tuberous sclerosis and/or rhabdomyoma. This condition was therefore specified in the exclusion criteria for this pivotal study.
One patient showed either thrombosis or vegetation at 15 months post implant. It is of note that there is no general consensus amongst the investigator, and/or independent reviewers about the underlying cause. The Clinical Events Committee (CEC) has adjudicated the event as thrombosis. However, it cannot be confirmed, nor excluded from the available data, that the filamentous material within the distal conduit towards the Left AP is a primary or secondary thrombus or vegetation due to endocarditis.
Overall, no protruding (flails) leaflets or severe regurgitation has been observed up to 12 months, in contrast to the first-in-human clinical trial, where at 12 months 5 patients were reported with severe regurgitation and 4 patients with a protruding leaflet. However, at the 18 months echocardiographic follow-up one patient had progressed from moderate to severe regurgitation and a protruding leaflet was assessed.
As mentioned above, it was hypothesized that more homogenous thickness of the leaflets, careful screening of the patients (including Ross patients) in the US would provide a similar conduit (tube itself) safety profile as what has been observed in the first-in-human study (Xplore 1) but would show improved leaflet (valve) performance results. This hypothesis is now confirmed by the 12 months data of the EFS study.

III. Study Size and Duration

The Xplore 2-Pivotal study will continue to assess the feasibility 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 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 endpoints will be assessed at 6 and 12 months post implant and subjects will be followed up yearly until 60 months post implant for long term safety.

The study will be conducted in accordance with CFR Parts 11, 50, 54, 56 and 812, ISO 14155, Medical Device Regulations 2017/745, Declaration of Helsinki and ICH Guidelines for Good Clinical Practices.

IV. Device Name, System Description and Intended Use

Device Name and System Description

The Xeltis bioabsorbable Pulmonary Valved conduit (PV conduit) is designed to enable Endogenous Tissue Restoration (ETR), a new therapeutic approach in cardiovascular treatment. This bioabsorbable device is designed to work like a normal valve once implanted. After implantation, it allows ETR as the body's natural healing process occurs and develops functional tissue, including collagen, endothelial lining and capillary blood vessels.

The Xeltis pulmonary conduit is made of bioabsorbable polymers that are structured as porous matrices through electrospinning. The matrices are structured to be absorbed overtime, to leave patients with new, healthy, functioning valves. The Xeltis technology is based on Nobel prize-winning science of supramolecular chemistry.
The bioabsorbable Pulmonary Valved conduit which specifically will be studied under this clinical investigation plan is a gamma sterilized, bioabsorbable, polymer-based medical device. The device has a total overall length of 8 cm with inner diameters of 16, 18, 20, or 22 mm. The valve itself is formed by three leaflets, which are incorporated within the conduit wall.

The PV conduit is used in patients for correction or reconstruction of the Right Ventricular Outflow Tract (RVOT), 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
- 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.

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

Intended Use

The bioabsorbable pulmonary valved conduit is intended to be used for correction or reconstruction of the Right Ventricular Outflow Tract (RVOT) in patients of age > 2 years and <22. The PV conduit is also indicated for the replacement of previously implanted but dysfunctional pulmonary homografts or valved conduits and as a replacement for the native pulmonary valve for the Ross procedure.

V. Study Design

This is a multi-center prospective, single-arm, non-randomized, pivotal study that will continue to access the feasibility of the Xeltis Bioabsorbable Pulmonary Valved Conduit in subjects requiring right ventricular outflow tract correction or reconstruction due to congenital heart malformations.
Initially, 6 patients were enrolled into the study and demonstrated improved device valvular functionality and outcomes when compared to Xplore 1 results. Therefore, it was agreed to amend the EFS to a pivotal study and enroll 50 additional patients. A maximum of 16 sites will participate in the study. Approximately 50% of the study patients will be implanted at US centers. Competitive enrolment will be applied to the two regions and only if one of the regions has a seriously delay in enrolment (>3-6 months) this 50% balance might shift. A site will not be allowed to implant more than 12 patients.

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

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 at the time of surgery, 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 and 6, 9, 12 and 18 months and then subsequently at 24, 36, 48 and 60 months.

Subjects where the device could not be implanted for any reason, including the patient receiving the implant but experiencing surgical problems leading to removal of the study device during the initial implantation, will be considered treatment failures and treated with an alternative device of the surgeon's choice. If no implant attempt is made the patient is not considered a treatment failure.

VI. Study Objectives and Endpoints

Device Safety

The safety of the PV conduit will be evaluated by summarizing the survival rate of subjects at 6 and 12 months following implantation of the PV conduit.

Primary Objectives

To assess the rate of 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

- To assess the mortality rate of subjects at 6 months following implantation of the bioabsorbable pulmonary valved conduit. *
- To assess the rate of conduit failure at 6 months, requiring re-intervention or re-operation.
- To assess the pressure gradient across the pulmonary valve, and regurgitation at 6 and 12 months follow up.

Exploratory objectives

- 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 PV conduit during the surgical procedure, using exploratory parameters.

Long Term Objective

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

Primary Endpoints

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

Secondary Endpoints

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

Exploratory endpoints

- Measurement of growth of the conduit in 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.
- Overall satisfaction of the implanting surgeon of the implantation procedure of the bioabsorbable pulmonary valved conduit.

Long term Follow-up Endpoint

- The number of device related serious adverse events will be assessed over 60 months long term follow up.

**This includes only device related deaths.*

Refer to the section XVIII on Statistical Methods and Data Analysis for a detailed discussion of the definitions and methodology.

Subgroup analysis

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.

VII. Study Eligibility

Subjects of both genders who satisfy all inclusion and exclusion criteria are eligible for this clinical study. Subjects must meet the following criteria:

Inclusion Criteria

1. Patient requiring RVOT reconstruction, suitable for 16 mm, 18 mm, 20 mm, or 22 mm valved conduit.
2. Male or Female.
3. Age > 2 years and < 22 years.
4. Right Ventricular to Pulmonary Artery peak gradient > 35mm Hg or moderate or severe Pulmonary Valve regurgitation (≥3+), or both (except for the patients undergoing a Ross procedure).
5. The patient, and the patient's parent / legal representative where appropriate, has been informed of the nature of the study, agrees to its provisions and has provided written informed consent by signing the approved informed consent form.
6. The patient, and the patient's parent/legal representative where appropriate, and the treating physician agree that the subject will return for all required post-procedure follow up visits and the subject will comply with clinical investigation plan required follow up visits.

Exclusion Criteria

1. Need for or presence of prosthetic heart valve at other position.
2. Need for concomitant surgical procedures (non-cardiac).
3. Patients with previously implanted pacemaker (including defibrillators), or mechanical valves.
4. Active infection or requiring current antibiotic therapy (if temporary illness, subject may be a candidate 4 weeks after discontinuation of antibiotics) or viral infection.
5. Active endocarditis.
6. Leukopenia, defined as White Blood cell Count < than:
    - 2-12 years: 5.0 $\times 10^3$ /µL
    - 12 years - Adult:
        - Male: 4.5$\times 10^3$ /µL
        - Female: 4.5 $\times 10^3$ /µL
7. Acute or chronic anemia, defined as Hemoglobin < than:
    - 2-12 years 11.5 g /dl
    - 12-18:
        - Male: 13 g /dl
        - Female 12 g /dl
    - Adult:
        - Male: 13.5 g /dl
        - Female: 12 g /dl

    Patients can be transfused to meet eligibility criteria.
8. Thrombocytopenia, defined as Platelet count < than:
    - 150,000/mm3

    Patients can be transfused to meet eligibility criteria.
9. Severe chest wall deformity, which would preclude placement of the PV conduit.
10. Pulmonary hypertension (≥ half of systemic systolic pressure).
11. Right ventricular outflow tract aneurysm.
12. Known hypersensitivity to anticoagulants and antiplatelet drugs and to the device materials.
13. Immunocompromised patient defined as: autoimmune disease, patients receiving immunosuppressant drugs or immune stimulant drugs.
14. Subject has chronic inflammatory, autoimmune disease, tuberous sclerosis, and / or rhabdomyoma.
15. Need for emergency cardiac or vascular surgery or intervention.
16. Major or progressive non-cardiac disease (liver failure, renal failure, cancer) that has a life expectancy of less than one year.
17. Currently participating, or participated within the last 30 days, in an investigational drug or device study.
18. Alcohol or drug abuse as defined by DSM IV-TR criteria for substance abuse – this includes the illicit use of cannabis within the last 12 months.
19. Pregnancy.
20. Females who are sexually active and are not willing to use adequate contraceptive precautions for the next 2 years
21. Subject has medical, social or psychosocial factors that, in the opinion of the Investigator, could impact safety or compliance.

VIII. Investigational Center Information

It is intended that up to 16 investigational centers will participate in this pivotal tudy.

Clinical Study Agreement

A Clinical Study Agreement must be signed by the participating institutions, acknowledged by the site investigator and returned to Xeltis prior to making available the study device or enrolling a patient.
A current curriculum vitae reflecting the Investigator's current position and title will also be required from each investigator and sub-investigator(s) participating in this study.

Investigational Review Board / Ethics Committee (IRB/EC)

Investigational Review Board (IRB; US) or Ethics Committee (EC; OUS) approval of the study (clinical investigation plan, informed consent, etc.) must be received and the contents of the IRB/EC approval letter approved by Xeltis before commencement of the study at a clinical center. The IRB/EC letter provided to Xeltis must include:

- Name of study
- Name/Address of IRB/EC
- Date of IRB/EC Approval and Expiration Date of Approval
- Sufficient identification of version/date of the clinical investigation plan, amendments, Informed Consent and Assent

An IRB/EC member list or ID certification number must also be provided to Xeltis.

Access to Center and Study Materials

The investigator(s) or his/her delegate(s) and the study coordinator(s) must be accessible to the Xeltis monitoring staff, or designee, and the Study Manager. This accessibility is of particular importance for completing and/or correcting the data provided and for communication during the monitoring visit. For the study monitors, access to the subject records for source data verification will need to be granted during each monitoring visit.

Required Equipment

There is no additional equipment necessary other than the equipment that would normally be available for surgery to reconstruct the RVOT. Other assessment like ECG and laboratory assessments are all done according to hospital guidelines. Core Lab is only used for Echocardiography. Echocardiography is performed with the hospital standard equipment, according to the acquisition protocol provided by the Core Lab. Echocardiography data will be captured using the predefined Echo acquisition protocol (see appendix C). The Transthoracic Echo data will be transferred electronically to the Core Lab for further analyses. Transfer occurs using a protected environment provided by the sponsor to the site.

Supply of Study Materials and Device Accountability

All Investigators will receive the Clinical Investigation Plan, e-CRF worksheets to assist with electronic data entry and study agreement documents.
Xeltis or its or designee, will control the supply of investigational devices, and administrative forms necessary to conduct and administer the study. A limited amount of investigational product will be distributed to approved clinical sites. Approval to receive devices will require the center to have made provisions for strict control of the investigational devices and documentation of IRB/EC approval forwarded to the sponsor.

A record of device accountability shall be maintained at each center to track investigational product information including, but not limited to the lot number of each investigational product and the date received, used and/or disposal. Completed e-CRFs and the device accountability records will be reviewed as part of the device tracking and ongoing center monitoring. Based upon return and review of these forms, additional investigational product will be supplied to the respective investigators as per need, in time for planned implants.
All expired / unused devices will be returned to Xeltis. Any PV conduits that are explanted will also be returned. The site will contact Xeltis, who will organize transportation in accordance with established procedures. The return of devices (unused or explanted) will be recorded on the applicable device accountability records. At the end of the study all remaining devices shall be sent back to Xeltis, and a final reconciliation will be performed by Xeltis.

Criteria for Study Site Termination or Suspension

Reasons for possible suspension of a clinical investigator or a clinical center may at the sponsor's discretion include but are not limited to the following:

- Failure to obtain informed consent
- Non-compliance to the inclusion/exclusion criteria
- Failure to follow through with Investigational Review Board (IRB/EC) for approval or continuation of the clinical study
- Inadequate device tracking or off-label investigator device use
- Failure to follow-up subjects per scheduled follow-ups
- Failure to submit data in a timely manner
- Failure to follow-up with findings on a monitoring report

Differences in Methods between Centers

There will be no differences in the methods used to collect data between the investigational centers. All centers will be using the same clinical investigation plan and methods to evaluate subjects.
The surgical techniques used at the participating centers will not differ a lot, since the implantation is done according to the same international guidelines with the same conduits/devices. In addition, the same proctoring support has been (will be) applied for all implanting centers. New and existing centers will need to adhere to the same process of patient selection, screening and implantation techniques. All sites will be following the same follow-up timetables and the echocardiographic acquisition guidelines will be the same. The CEC will also adjudicate all event of all sites.

IX. Data Collection Overview

All data collection will be completed via the electronic Web-based Data Entry System. Each activated center will have access to the Data Entry System.

A review of medical record is required to determine preliminary eligibility according to inclusion and exclusion criteria. Baseline data will be collected within 30 days prior to the implant date for inclusion to 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.

Echocardiographic assessments will be performed during pre-implant and follow-up time points per ECHO Acquisition Protocol. All echocardiographic data will be reviewed by a Core Lab.

Data will be collected via the patients' medical record, echocardiogram tapes, and digital storage media.

The study follow-up visits with the appropriate time windows are described in Table 2. The data collection requirements are described in Table 3.

Table 2. Follow up windows

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 3. Data Collection

STUDY ITEM														
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
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]	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 12 and 24 months.

Procedures at each visit

Note: Chest X-ray / Angiography / CT / MRI – these assessments are often performed per standard of care before surgery and post-operatively. Data from any of these assessments will be collected in the e-CRF if they are available. Collection of these assessments applies for the duration of the study, if they are available.

Screening Committee (SC)

A Screening Committee (SC) will review the medical records on anatomic appropriateness and clinical risk factors to ensure proposed patients are eligible for treatment with the Xeltis pulmonary valved conduit. SC members are medical experts in clinical specialties relevant to the device being studied in this clinical trial. Prior to the onset of the trial, a SC charter will be established that outlines the roles and responsibilities and describes the SC process.
The following information, but not limited to - should be submitted to the SC:

- Completed Patient Screening Worksheet including standard medical information to screen patients for a complex cardiac surgery procedure:
- Medical History, Co-Morbidities, Bloodwork, Medication etc.
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE should be sufficient to evaluate details of the heart/Pulmonary valve to allow appropriate screening of the patients.
- Any other available medical imaging like CT and/or MRI.

Visit 1: Baseline (within - 30 days)

Informed consent must be obtained before screening assessments (baseline visit) are performed. All consented subjects will undergo baseline assessments, which must be done by a qualified member of the clinical team. The Screening Visit will take place within 30 days before surgery, and the following screening assessments and procedures will be done:

- Baseline demographic information will be collected during screening, and include age, sex and race/ethnicity.
- Medical history (MH) includes all ongoing medical or surgical issues. Remote medical and surgical history > 5 years from the time of screening should only be included if considered relevant to the current surgery (e.g. previous similar surgery and outcomes).
  The MH should also include all prescription medications that the subject is currently taking or has taken in the previous 30 days and those that are related to the implantation of the PV conduit. Vitamins and other nutritional supplements need not be recorded since they are not expected to affect the subject's safety during the trial.
- New York Heart Association functional class.
- Echocardiography. Echocardiography will be performed as per Core Lab echo acquisition protocol.
- Electrocardiogram – ECG. The ECG will be done as per hospital standard of care.
- Blood sample testing; hematology and chemistry as well as coagulation profile [including prothrombin time, partial thromboplastin time and International Normalized Ratio (INR). Blood sample testing will be done as per hospital standard of care.

- Physical exam / vital signs. The physical examination should include a focused examination relating to the patient's medical history and current surgical plans including general, respiratory, cardiovascular, abdominal, extremities and brief neurologic evaluations, and recording of height and weight. Any signs of erythema, edema and lesions should be recorded. Includes resting blood pressure, respiratory rate, pulse and oral temperature that will be measured at each visit.

The following will also take place at the Baseline visit:

- Allocation of Subject Number which will consist of a combination of the 3-digit site number followed by a sequential 3-digit subject number.
- Adding subject's data into the Screening and Recruitment Log.
- Review of inclusion/exclusion criteria to confirm subject eligibility.

If subjects are ineligible for the clinical trial, they will be deemed a Screen Failure and their demographic data and specific reason for ineligibility will be captured on applicable CRF pages.

Historical data (prior to consent form) is allowed for the ECG and transthoracic echo but may not be older than 3 months prior to the treatment date and only if the ECHO was executed according to the predefined echo acquisition protocol.
For any female subjects of child bearing ability, a pregnancy test will be performed.

Anticoagulation Medication

Anticoagulation and/or antiplatelet treatment therapy may be given as per physician order / standard of care.

Endocarditis prophylaxis

Endocarditis prophylaxis may be given as per physician order / standard of care.

Visit 2: Day 0, Implantation PV conduit

Before the implantation the following will be assessed:

- Continued eligibility (including pregnancy, which can be evaluated with urine test)
- Concomitant medication
- Any changes to health status (including adverse events) since baseline visit

During the surgery, the size of the PV conduit will be approximated and cut to length. The PV conduit will be implanted using standard surgical techniques and the methods described in Section XII Implant procedure.

The explanted anatomical structures which are being replaced by the PV conduit will be handled according to individual hospital procedures. No study specific testing will be done on these structures and there is no requirement for this study to store the native tissue.

Subjects where the device could not be implanted for any reason, including the patient receiving the implant but experiencing surgical problems leading to 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.

The following data will be collected during the RVOT reconstruction:

- Subject eligibility: there are no significant intra-operative complications other than RVOT obstruction and bleeding which, in the opinion of the Investigator, may interfere with assessment of safety.
- Procedure(s), including any concomitant operative procedure(s).
- Date of operation.
- Implant size, reference and lot number.
- Suturing technique.
- Adverse events.
- Concomitant medication usage, including blood products. Medications to induce and maintain anesthesia need not be recorded in the CRF, however, all medications given for treatment emergent AEs during surgery should be recorded.
- Record details of cutting distal / proximal parts of the device.
- Record time to anastomosis distal/ proximal, time to hemostasis (achieved in minutes, time between final anastomosis is achieved and chest closure is started before or after protamine).
- A questionnaire will be given to the surgeon to complete, to collect data on handling of the device. This should be performed for each implant.
- In the case of death: date and cause of death.
- In the case of death: autopsy report, if performed.

The patient, and the patient's parent/legal representative where appropriate, will receive an Implant/Patient card after the implantation of the PV conduit. They will be asked to carry this Implant/Patient card with them at all times.

Visit 3: Day 1

- Physical exam/Vital signs. The physical examination should include a focused examination including general, respiratory, cardiovascular, abdominal, extremities and brief neurologic evaluations, and recording of height and weight. Any signs of erythema, edema and lesions should be recorded. Includes resting blood pressure, respiratory rate, pulse and oral temperature that will be measured at each visit.
- Blood sample testing; hematology and chemistry as well as coagulation profile [including prothrombin time, partial thromboplastin time and International Normalized Ratio (INR). Blood sample testing will be done as per hospital standard of care.
- Medication.
- Adverse events.
- In the case of death: date and cause of death.
- In the case of death: autopsy report, if performed.

Visit 4: Day 7 / Discharge visit - whichever comes first (± 2 days)

The subject will be assessed at day 7 or at the discharge from the hospital. The following assessments will be done:

- Physical exam/Vital signs. The physical examination should include a focused examination including general, respiratory, cardiovascular, abdominal, extremities and brief neurologic evaluations, and recording of height and weight. Any signs of erythema, edema and lesions should be recorded. Includes resting blood pressure, respiratory rate, pulse and oral temperature that will be measured at each visit.
- Blood sample testing; hematology and chemistry as well as coagulation profile [including prothrombin time, partial thromboplastin time and International Normalized Ratio (INR). Blood sample testing will be done as per hospital standard of care.
- Adverse Events.
- Medication.
- Echocardiography. Echocardiography will be performed as per Core Lab guidance document.
- Electrocardiogram – ECG.
- In the case of death: date and cause of death.
- In the case of death: autopsy report, if performed.

Visit 5 and 6: Follow-up Week 6 (± 7 days) and Month 3 (± 14 days)

- Date of follow up.
- Physical exam / Vital signs. The physical examination should include a focused examination including general, respiratory, cardiovascular, abdominal, extremities and brief neurologic evaluations, and recording of height and weight. Any signs of erythema, edema and lesions should be recorded. Includes resting blood pressure, respiratory rate, pulse and oral temperature that will be measured at each visit.
- Blood sample testing; hematology and chemistry as well as coagulation profile [including prothrombin time, partial thromboplastin time and International Normalized Ratio (INR). Blood sample testing will be done as per hospital standard of care.
- Status of anticoagulant and/or antiplatelet therapy at each follow up visit.
- Echocardiography. The echocardiography will be performed as per Core Lab guidance document.
- Electrocardiogram – ECG. The ECG will be done as per hospital standard of care.
- Medication.
- Adverse events.
- In the case of death: date and cause of death.
- In the case of death: autopsy report, if performed.

Visit 7: Follow-up Month 6 (± 14 days)

- Date of follow up.
- Physical exam/Vital signs. The physical examination should include a focused examination including general, respiratory, cardiovascular, abdominal, extremities and brief neurologic evaluations, and recording of height and weight. Any signs of erythema, edema and lesions should be recorded. Includes resting blood pressure, respiratory rate, pulse and oral temperature that will be measured at each visit.
- New York Heart Association functional class.
- Blood sample testing; hematology and chemistry as well as coagulation profile [including prothrombin time, partial thromboplastin time and International Normalized Ratio (INR). Blood sample testing will be done as per hospital standard of care.
- Status of anticoagulant and/or antiplatelet therapy at each follow up visit.
- Echocardiography. The echocardiography will be performed as per Core Lab guidance document.
- Electrocardiogram – ECG. The ECG will be done as per hospital standard of care.
- Medication.
- Adverse events.
- In the case of death: date and cause of death.
- In the case of death: autopsy report, if performed.

Visit 8-14: Long-term follow up at 9, 12, 18, 24, 36, 48, 60 months (± 30 days)

- Date of follow up.
- Physical exam/Vital signs. The physical examination should include a focused examination including general, respiratory, cardiovascular, abdominal, extremities and brief neurologic evaluations, and recording of height and weight. Any signs of erythema, edema and lesions should be recorded. Includes resting blood pressure, respiratory rate, pulse and oral temperature that will be measured at each visit.
- New York Heart Association functional class.
- Blood sample testing; hematology and chemistry as well as coagulation profile [including prothrombin time, partial thromboplastin time and International Normalized Ratio (INR). Blood sample testing will be done as per hospital standard of care.
- Status of anticoagulant and/or antiplatelet therapy at each follow-up visit.
- Echocardiography. Echocardiography will be performed as per Core Lab echo acquisition protocol.
- Electrocardiogram – ECG. The ECG will be done as per hospital standard of care.
- Medication.
- Adverse events.
- At 9, 12, 18, and 24 months: pregnancy tests for patients of childbearing potential.
- In the case of death: date and cause of death.
- In the case of death: autopsy report, if performed.

Regarding laboratory assessments, the following applies for all post implant visits:
In case anemia is detected, further laboratory assessments shall be performed in order to detect hemolysis. Plasma free hemoglobin (PFH) will be the primary lab result used to diagnose hemolysis; however, if PFH results are inconclusive or not available, serum lactate dehydrogenase and haptoglobin (part of standard study assessments) and reticulocyte count may be used together to diagnose hemolysis, and may be done without reporting a clinical investigation plan deviation. If neither PFH nor the combination of serum lactate dehydrogenase, haptoglobin and reticulocyte count are completed in the presence of anemia, the site must report a clinical investigation plan deviation.

X. Screening and Informed Consent

Prior to enrolling subjects, the local IRB/EC must approve the Clinical Investigation Plan that has been approved by the FDA and/or the local competent authorities (CA). Each investigational study center's IRB/EC will be required to also approve the Subject Informed Consent for the study. In addition, the subject or the subject's legal representative will be required to provide written informed consent via the IRB/EC approved Subject Informed Consent for enrollment. In accordance with the ethical principles that have their origin in the Declaration of Helsinki, each subject must be informed about the study and the subject or the subject's legal representative must sign and date the Subject Informed Consent acknowledging that participation in the study is voluntary.

Subject will undergo a pre-implant baseline assessment to ensure they meet the inclusion and exclusion criteria within 30 days prior to the implant date. Subject Informed Consent must be signed prior to conducting any procedure performed for study purposes.

XI. Study Enrollment (Pre-implant Baseline)

When a subject signs an informed consent to participate in the study, he/she is considered enrolled in the study and will be assigned a study identification number by the center.

Table 2 outlines the pre-implant baseline testing and data collection that will be obtained within 30 days prior to and continuing until implantation. This data will be used by the investigational center to confirm inclusion and exclusion criteria are met prior to implantation.

Surgical delay > than 30 days from original screening will require verification that the inclusion and exclusion criteria continue to be met by the patient.

XII. Implant Procedure

The surgeon can choose the appropriate size diameter (16 mm,18 mm, 20 mm, or 22mm,) of the PV conduit and implant it during open heart surgery.

The implantation of the PV conduit will be performed only in centers specialized in pediatric cardiac surgery. All implanting surgeons have already implanted or will receive training on how to implant the device before the actual implantation takes place.

The implantation will be conducted using standard surgical techniques through a standard median sternotomy. The use of cardiopulmonary bypass, aortic cross-clamping and cardioplegia for myocardial protection are at the surgeon's discretion. The implantation is a standard procedure for reconstruction of the right ventricular outflow tract. In case of interventions limited to the reconstruction of the RV outflow tract, including enlargement of the pulmonary arteries, this can be performed on a beating, continuously perfused heart. If a concomitant procedure is necessary, a more complete dissection of the heart and intracardiac repairs might be needed.

The PV conduit is a seamless conduit (without sutures in the structure). It is sutured again using standard surgical techniques to the pulmonary bifurcation area (distal anastomosis) with a running monofilament nonabsorbable suture, such as Prolene (size 6.0). The diameter of the PV conduit will be determined according to the diameter of the pulmonary artery bifurcation, aiming at the biggest size that can be placed safely without being compressed by the sternum.
In order to know which part of the conduit is the distal end and which is the proximal end, the surgeon makes a decision based on visual inspection of the lumen where the leaflet position of the valve determines blood flow direction.

Proximally, the PV conduit is inserted either to the native pulmonary artery annulus or to the anterior part of the RV, using a running monofilament nonabsorbable suture, such as Prolene (size 5.0). For patients who previously received a transannular patch, a reduction plasty of the dilated RV infundibulum can be performed if necessary and consisting in complete resection of the old infundibular patch using standard surgical techniques.

The only modification which is allowed is cutting the device to the desired length, either at distal or proximal side. The surgeon may not decrease the size of the valve diameter by adapting the diameter.

XIII. Scheduled Follow-up Testing and Data Collection

See Section IX for a detailed listing of the follow up time points, follow-up testing, and data collection requirements.

XIV. Unscheduled Follow-up Visits

If detailed data collection is required between clinical investigation plan-scheduled visits because of clinical symptoms, adverse events, or any other reason, a follow-up form must be completed with all appropriate sections and noted as an "unscheduled" follow up. In addition, if applicable, all adverse events must be documented on the respective AE form.

XV. Adverse Event Reporting, Definitions and Classification

According to ISO 14155, adverse events are defined as follows:

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device and whether or not anticipated or unanticipated .
Note 1: this includes events related to the investigational medical device or the comparator
Note 2: this includes events related to the procedure involved.
Note 3: for users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.
Note 1: this definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device.
Note 2: this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Note 3: this includes “comparator” if the comparator is a medical device.

Device deficiency (DD)

Inadequacy of medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.
Note 1: device deficiencies include malfunctions, use error, or inadequacy in the information supplied by the manufacturer including labeling.
Note 2: this also includes device deficiencies related to the investigational medical device or the comparator.

Serious Adverse Event (SAE)

An adverse event that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
   - a life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function including chronic diseases, or
   - in-patient or prolonged hospitalization, or
   - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event; an SAE attributed to the study device.

For unanticipated events the study will apply the wording used by FDA (21 CFR 812.3):

Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the safety, or welfare of subjects.

Device malfunction (21 CFR 801.4)

The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labelling for the device. The intended performance of a device refers to the intended use for which the device will be labelled or marketed. In this clinical study the malfunction are not adverse events but are device deficiencies which are important to capture to assess performance. Examples are mild regurgitation, leaflet immobility.

Data on device malfunction will be collected during the investigation to assess performance and will be reported to FDA/IRB/EC's in the annual progress reports. Or to local regulatory agencies/CA's as required by local laws and regulations.

Adverse event information will be collected throughout the investigation. Upon identification, the investigator must complete the adverse event from in the database. Xeltis clinical personnel or their designee may request further information from the investigator if necessary, for review of the event by the Clinical Events Committee (CEC).
All AEs/SAEs that occur after any patient/subject has been enrolled in the study in the study whether or not they are related to the study procedure / device or study assessments, must be recorded on the e-CRF.
The following information will be collected within the database: subject identification, description of the event or event code, the date of event onset, the relationship of the event to the implant procedure, device, concomitant medications or subject management. Additional information may be collected in preparation for event adjudication by the CEC.

The investigator must report any unanticipated adverse device effects (UADE), all related SAEs and device deficiencies that could have led to an SAE to the Sponsor within 24 hours after the investigator first learns of the event. The Sponsor must report any UADE to the regulatory agencies, IRB/ECs, and all investigators within 10 days of receipt of notice of the event.
Reporting of Adverse Events occurring during the trial will follow applicable regulation. The CEC will adjudicate the Adverse Events defined below

Adverse Event Definitions

Definitions are listed below for anticipated serious adverse events (SAE). These events could be device or procedure related. These adverse events are derived from INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) definitions and the AATS Definitions [16]. For adverse events that have similar risk but no category, an "other" category is included. More detailed adverse event definitions are included in the following sections.

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis is any infection involving a valve on which an operation has been performed. The diagnosis of prosthetic valvular endocarditis is based on one of the following criteria:

(1) reoperation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histologic or bacteriologic studies;

(2) autopsy findings of abscess, pus, or vegetation involving a repaired or replaced valve; or

(3) in the absence of reoperation or autopsy, meeting of the Duke Criteria for endocarditis [16]. Positive blood cultures are not required for the diagnosis of prosthetic valve endocarditis. Culture-negative endocarditis should refer only to negative blood culture results and not just the absence of any proof of infection. Morbidities associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event are included under this category, but not counted in other categories of morbidity.

Structural Valve Deterioration

Structural valve deterioration includes dysfunction or deterioration involving the prosthetic valve (exclusive of infection or thrombosis), as determined by reoperation, autopsy, or clinical investigation. Clinical investigation should include periodic echocardiographic surveillance. Substantially increased regurgitation or stenosis of the prosthetic valve over time should be reported with quantitative or semi quantitative methods. The term structural valve deterioration refers to changes intrinsic to the valve, such as wear, fracture, calcification and leaflet tear.

Non-structural Dysfunction

Non-structural dysfunction is any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the prosthetic valve or hemolysis. The term non-structural dysfunction refers to problems (exclusive of thrombosis and infection) that do not directly involve valve components yet result in dysfunction of a prosthetic valve, as diagnosed by reoperation, autopsy, or clinical investigation. Examples of non-structural dysfunction include the following:

- inappropriate sizing or positioning;
- residual leak or obstruction after valve implantation or repair;
- clinically important intravascular hemolytic anemia.

In addition, non-structural dysfunction includes development of pulmonic regurgitation as a result of technical errors, dilatation of the sinotubular junction, or dilatation of the valve annulus after implantation of the pulmonary valve or after pulmonary valve-sparing operations if the cusps are seen to be normal at reoperation, autopsy, or clinical investigation.

Sudden or progressive dysfunction or deterioration of the prosthetic valve may be structural, non-structural, or both, as determined by reoperation, autopsy, or clinical investigation.

Valve Thrombosis

Valve thrombosis is any thrombus not caused by infection attached to or near a prosthetic valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Valve thrombus found at autopsy in a patient whose cause of death was not valve related or found at operation for an unrelated indication should also be counted as valve thrombosis.

Major Bleeding

An episode of suspected internal or external bleeding that results in death, the need for re-operation or hospitalization; or necessitates transfusion of red blood cells as follows:

Within any 24-hour period:
For subjects > 50 kg:

1. ≥ 4U packed red blood cells (PRBC) within any 24-hour period during the first 7 days post-implant.
2. Any transfusion of packed red blood cells (PRBC) after 7 days following implant with the Investigator recording the number of units given within a 24 hour period.

For subjects < 50 kg:

1. ≥ 20cc/kg packed red blood cells (PRBC) within any 24-hour period during the first 7 days post-implant.
2. Any transfusion of packed red blood cells (PRBC) after 7 days following implant with the Investigator recording the number of units given within a 24 hour period.

***NOTE**: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.*

Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g. Oliguria, pre-syncope or syncope) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types:

1. Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
2. Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac) and those without signs of tamponade.
***NOTE:** For those without signs of tamponade, please record the reason for percutaneous drainage.*

Minor Hemolysis

A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half time (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant in the absence of clinical symptoms or findings of hemolysis.

Major Hemolysis

A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant and associated with clinical symptoms or findings of hemolysis.

Major Hemolysis requires the presence of one or more of the following conditions:

- Hemoglobinuria (“tea-colored urine”)
- Anemia (decrease in hematocrit or hemoglobin level that is out of proportion to levels explainable by chronic illness or usual post-implant state)
- Hyperbilirubinemia (total bilirubin above 2 mg/dl, with predominately indirect component)

Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

- total bilirubin
- aspartate aminotransferase/AST
- alanine aminotransferase/ALT)

Major Infection

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Myocardial Infarction

Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction

The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following implant together with ECG findings consistent with acute myocardial infarction.

Non-Perioperative Myocardial Infarction

The presence at > 7 days post-implant of two of the following three criteria:

a) Chest pain which is characteristic of myocardial ischemia,
b) ECG with a pattern or changes consistent with a myocardial infarction, and
c) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

Renal Dysfunction

Two categories of renal dysfunction will be identified:

Acute Renal Dysfunction

Abnormal kidney function requiring dialysis (including hemofiltration) in subjects who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL (in children, creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours.

Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy or (for subjects older than age 5 years) the inability to discontinue ventilatory support within six days (144 hours) implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Right Heart Failure

Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.0 L/min/m^2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring either RVAD implantation or inotropic therapy; or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after implantation.

Arterial Non-CNS Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) Standard clinical and laboratory testing
2) Operative findings
3) Autopsy findings

This definition excludes neurological events.

Venous Thromboembolism Event

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Sensitization response

Allergic type hypersensitivity reactions may occur after repeat exposure to similar materials as the device. Signs of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

Other

An event that causes clinically relevant changes in the subject's health (e.g. abnormal immunological reaction).

Adverse Event Classification

All reported adverse events will be classified, based on the following categories:

- Relatedness (i.e. device, procedure, concomitant medication, or patient management);
- Timing (i.e. implant or post-implant);
- Status (i.e. ongoing or resolved)

Device Related

An adverse event will be considered device related if it is a direct result of, or is affected by the presence, or operation (intended or otherwise) of the investigational device.

Causal Relationship of Adverse Events

The relationship of an adverse event to the device should be assessed using the guidelines presented in below. An adverse event for which there has been no causal relationship reported initially will require follow-up to determine causality. Of the definitions “possibly”, “probably” and “related” to an investigational medical product are considered adverse reactions. “Unlikely” and “not related” do not qualify as a causal relationship.

1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error.

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;
- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

The Investigator will determine a classification of the relationship to device/procedure and enter it on the Case Report Form. Where there is uncertainty about classifying the serious event, it should not exclude the relatedness and the event should be classified as “possible”. The CEC however, will in their review make the final determination of the adverse event relationships to the device or procedure.

Procedure Related

An adverse event will be considered procedure related if it is a direct result of the implantation procedure, which cannot be directly attributed to any particular device or implant tool.

Concomitant Medication Related

An adverse event will be considered related to concomitant medication (e.g. Heparin Induced Thrombocytopenia) when it is reasonable to believe that the event is directly associated with medications used in conjunction with the investigational device and it is not otherwise specific to the device, procedure or patient management.

Clinical Events Committee (CEC)

A CEC will be established by the sponsor or their designee to assess, review, and classify all adverse events as defined in the clinical investigation plan and deaths during the clinical study.
The CEC will consist of a minimum of three physicians including a chairperson appointed by the sponsor or the CEC committee. The CEC will consist of at least one pediatric cardiac surgeon and one cardiologist, independent from the study sponsor and investigators. The CEC will regularly review and adjudicate reported adverse events including deaths.

Prior to the onset of the study, the CEC, along with support from the sponsor or their designee will establish a charter and guidelines outlining the minimum data required and the algorithm followed in order to classify an event. This charter along with the guidelines will be approved by the committee during the first round of meetings. Members will be provided data summaries from the clinical study.

Data Safety Monitoring Committee (DSMB)

An independent data safety monitoring board (DSMB) will be established. The committee will independent of the sponsor and be composed of at least 3 members (at least one pediatric cardiac surgeon and one cardiologist), who are not directly involved in the conduct of the trial. The DSMB will review the study after the first three subjects have been implanted and followed for 3 months, then 6 months after all subjects have been implanted, 12 months after all subjects have been implanted and at the end of the study. Enrollment and implanting of further subjects may occur as the DSMB reviews the serious adverse events (both anticipated and unanticipated).

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 or to evaluate the impact of clinical investigational plan deviations on the scientific validity and data integrity of the study. 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. The DSMB will be provided with all data at the time of review, including all serious device related events during the study.

Deaths

All subject deaths must be documented and entered into the database as soon as possible upon knowledge by the center, according to guidelines for other serious events (within 24 hours). If the subject dies during the study, the center must notify the Xeltis support team as soon as possible upon first learning of the death. Follow any IRB/EC requirements for reporting of deaths or adverse events.
In the event of a subject death, efforts should be made to perform an autopsy and obtain an autopsy report in order to assess the state of the heart, major vessel and remove the Xeltis PV Conduit, if still present. For subjects that do not undergo autopsy, written documentation from the investigator will be required regarding circumstances as to why an autopsy was not performed. A death summary and an autopsy report, if available, are required. Reports should be sent upon completion to Xeltis or their designee to provide to the CEC.

Explant Handling and Final Device Disposition

The explanted PV Conduit should be analyzed by local staff. Explanted products should be returned to Xeltis for analysis according to the instructions provided by the sponsor, and using the dedicated explant kit provided by the sponsor (see also Physician manual, appendix D). Prior to returning to Xeltis, please contact the sponsor. Final disposition of the PV conduit must be provided on the device accountability record.
Complete the appropriate data collection form. All associated adverse events should be reported and entered into the database.

XVI. Withdrawal and Study Exit

In the event a subject is unable to continue participation or the subject/their legal representative chooses to withdraw the subject from the clinical study, the investigational center should attempt to ensure that any adverse events are resolved and documented as such. As part of the Informed Consent, the patient shall agree to the site being able to obtain at least a minimum of information from the subject's primary care physician(s) on how he/she is doing. Every effort should be made to obtain the follow-up information at the time of withdrawal. A Study Exit Form must be completed and the subject will no longer be followed in the clinical study. Notify the Xeltis clinical support team as soon as possible upon learning of a subject withdrawal/ study exit.

If the subject fails to comply with follow-up visits, the study center must make repeated attempts to contact the subject's legal representative or primary care physician. Each attempt to contact the subject's legal representative must be documented in the subject's records and on the Study Exit Form.

If the subject is officially withdrawn from the study, the investigator will document the reason for withdrawal and indicate any relationship of the withdrawal to the study or the device on the Study Exit Form. If a subject is withdrawn from the study at any time, there will be no penalty or loss of future medical care.

XVII. Database

All data collection will be completed in a Web-based Data Entry format. Each activated center will have training and access to the database. A copy of the e-CRF worksheets created by Xeltis to facilitate data entry into the database are included in the Appendices for reference (Appendix B).

STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

XVIII. Planned Analysis

Reference is made to the study objectives and endpoints as listed in section VI.

An analysis will be performed on subject who are enrolled and implanted. A report will be generated after the final patient has completed the secondary endpoint at 6-month visit. A report will be generated after the 12-month endpoint visit for the last patient, after the 24-month endpoint of the last patient, as well as after the final patient / final visit at 60 months. Reports will be submitted to FDA and other required regulatory authorities.

The DSMB will review safety and outcome, and will 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, enrolment summary
After 6 months follow up for all implanted patients (N=6)	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 5 Timelines safety evaluation continuation

Timeline	Type of Data
6 months after enrolment start	Adverse events, clinical investigation plan violations, enrolment summary, echocardiographic results
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 all implanted patients have been followed-up for 6 months and all additional available follow-up.	Adverse events, clinical investigation plan violations, enrolment summary, echocardiographic results
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

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. The DSMB will be provided with all data at the time of the safety review, including all serious device related events during 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.

Safety Analysis

For the planned analyses, safety variables including adverse events, adverse device effects, laboratory parameters and vital signs will be summarized.

The number and percentage of patients with at least one adverse event, as defined in the clinical investigation plan, will be summarized overall, by SAE and AE s and by relationship to study device. The number and percentage of patients with at least one adverse device effect will be summarized, while laboratory parameters and vital signs will be summarized using descriptive statistics.
No formal statistical hypothesis testing will be performed. No data imputation will be performed for missing data.

Additional Analysis

12-Month Primary Endpoint

The primary endpoint is a combined endpoint of death and/or conduit failure requiring re-intervention or reoperation, at 12 months. The rate of event will be compared against the expected rate of 15% with a one sample Wald test.

To define the survival 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 have a non-device related death at or prior to the scheduled 12 month follow up visit are censored at their date of death. Subjects who withdraw prior to the scheduled 12 month visit are followed up to confirm their survival status at 12 months and are censored at 365 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 365 days.

The overall mortality will include all deaths, related and non-related.

The re-operation or re-intervention rate at 12 months follow-up due to device failure includes in the calculation all re-operations and reinterventions to remove or replace the implant with an alternative device. The rate will be summarized by number and percentage of subjects.

Kaplan-Meier (KM) estimates of cumulative event probabilities will be plotted by treatment versus time. The number and percentage of subjects with a device related death at or prior to the scheduled 12-month visit will be displayed with the Kaplan-Meier (KM) 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 KM estimates and the 95% CI's will also be presented.

6-Month Endpoint

To define the survival rate at 6 month endpoint, the deaths included in the calculation of the 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 months 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.

The re-operation or re-intervention rate at 6 months follow-up due to device failure includes in the calculation all re-operations and reinterventions to remove or replace the implant with an alternative device. The rate will be summarized by number and percentage of subjects.

Kaplan-Meier (KM) estimates of cumulative event probabilities will be plotted by treatment versus time. The number and percentage of subjects with a device related death at or prior to the scheduled 6 month visit will be displayed with the Kaplan-Meier (KM) estimate and 95% confidence interval at 180 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 KM estimates and the 95% CI's will also be presented.

Further endpoints (the number of subjects with reoperation or re-intervention due to conduit failure at 12 months follow up, the number of subjects with a mean pressure gradient across the area of conduit implantation (RV to PA) of less than 40 mm Hg at 12 months follow up, the number of subjects with pulmonary regurgitation of equal or less than moderate at 12 months follow up and the number of subjects with growth of the conduit at different timepoints will be summarized by number and percentage of subjects for the Safety Analysis Set.

Descriptive statistics will be performed on the main safety and exploratory parameters. Analyses will be performed using all subjects who received study intervention, and had a device implanted.
No formal statistical hypothesis testing will be performed.

Outcomes and adverse event information will be summarized for the DSMB at 6 months and 12 months. The DSMB will perform an outcomes and safety review on all subjects receiving the study intervention. A final analysis will be performed at 60 months. Safety analyses can also be performed at the DSMB request. The DSMB will be provided with all data on all subjects at the time of the review.

Handling of Missing Data and Drop-outs

In device related death analyses, missing values will not be accepted as death must be followed regardless of the patient's completion status. However, for the combined primary endpoint of death and device failure, multiple imputation will be used in a sensitivity analysis of the primary endpoint.

Sample Size

Background and sample size calculation: the expected rate of 12 months reintervention, reoperation and device related death (composite endpoint) from the literature is 20-30% (Contegra). For sample size calculation 15% composite event rate was taken into consideration. It is assumed that the rate to be observed with the Xeltis valved conduit to be 5%. Two-sided alpha of 5% and power of 90% was used.

The formal hypothesis to be tested is:

H0: Rate of combined event at 12 months =15%

H1: Rate of combined event at 12 months = 5%

With these assumptions additional 50 patients need to be enrolled (55 with 10% dropout rate but 6 patients already included in the EFS part).

The sample size is computed using Stata 16 (StataCorp, College Station, TX, USA) as follows:

```
power oneproportion 0.15 0.05, test(wald)alpha(0.05) power(.90)
Performing iteration ...
Estimated sample size for a one-sample proportion test
 Wald z test
 Ho: p = p0  versus  Ha: p != p0
 Study parameters:
         alpha =    0.0500
         power =    0.9000
         delta =   -0.1000
            p0 =    0.1500
            pa =    0.0500
 Estimated sample size:
             N =        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. For detailed sample size justification refer to the combined

Statistical Analysis Plan

A detailed analysis plan will be produced at the start of the study. The Stata software will be used for all computations. Significance will be set at 5% (2 sided). 95% confidence intervals (CI) will be produced.

Subgroup analysis of the primary endpoint, such as but not limited to, will be performed based on the included patients populations medical history (prior surgery), age, sex, device size, region/country etcetera. More details will be provided in the Statistical Analysis Plan (SAP).

Analysis Populations

Adverse Events and outcomes will be summarized using an intent-to-treat analysis group. All primary and secondary endpoints will be analyzed using an as-treated analysis group.
The intent-to-treat analysis group will consist of all subjects that sign the IRB/EC -approved written Informed Consent form and undergo anesthesia for an implant.
The as-treated analysis group will consist of only subjects who received the intended treatment at the implant procedure.
The per-clinical investigation plan analysis group will consist of only subjects who received the intended treatment at the implant procedure excluding those that were found not to have met eligibility requirements after implant.

In the section difference of methods between centers (Paragraph VIII) it is described why it is believed that the potential difference in patient populations between US and OUS centers is minimal and therefore the groups are poolable. In addition, centers will not be allowed to include more then 12 patients. However, estimates of the cumulative event-free survival will be computed while stratifying on region (US & OUS) and separate estimate 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.

RISK ANALYSIS

The safety and performance of pulmonary conduits similar to the Xeltis PV Conduit have been demonstrated through previous preclinical testing and studies. Therefore, it is not anticipated that subjects enrolled in this study will be exposed to any procedure risks beyond those normally associated with the surgical implantation of other PV conduits. Device specific risks are listed below following risks known associated with valved conduits. The adverse event definitions detailed in the previous sections highlight and expose a standard level of expected risks. Unanticipated risks and associated events will be captured through the adverse event reporting.

XIX. Potential Known Risks Associated with Surgical Implantation of Valved Conduits

General complications reported with the surgical implantation of available valved conduits include general risks that are related to the surgical procedure/RVOT reconstruction. These general risks could also apply to the surgical implantation of the Xeltis PV conduit:

- thrombosis
- endocarditis
- infection
- bleeding / hemorrhage
- intra-pericardial hematoma
- heart tamponade
- impaired leaflet functionality structural deterioration (perforation, thickening)
- pulmonary insufficiency- regurgitation
- thromboembolism
- conduit rupture
- calcification
- stenosis
- conduit dilatation
- pulmonary hypertension due to heart failure
- abnormal immunological reaction
- hemolysis

There may be other unforeseen risks at this time.

Risk Related to the Investigational Device

Risk assessment were conducted relating to the specific design and use of the PV conduit. Risks were classified according to recommended method (failure mode and effect analyses) in accordance with the most recent version of ISO 14971 Medical devices- Risk management.
The risk identified have been classified to the possible occurrence rate and are listed below.

Probable risks:

- Pulmonary insufficiency (due to small tears in the leaflet(s), leaflet prolapse or kinking of the tip of the leaflet(s)structural deterioration of the leaflets, including related emboli
- Abnormal inflammatory response
- Dilatation of conduit
- Right ventricular failure, including those caused by calcification (*) and stenosis

Possible risks:

- Prolonged surgery
- Thrombosis
- Hemolysis
- Bleeding / hemorrhage
- Conduit rupture
- Heart failure

Improbable risks:

- Major infection, i.e. endocarditis, sepsis/infection
- Allergic type hypersensitivity reactions may occur after repeat exposure to similar materials as the device

(*) preclinical studies showed less calcification of the PV conduit wall and survival rates compared to other commercially available animal derived PV conduits.

In addition, conduit rupture, embolism, thrombosis, impaired functionality was not observed in the preclinical studies. There may be other unforeseen risks at this time.

Risks Related to the Study Conduct

The methods for data collection involve only standard, well-established methods and do not differ from clinical, medical, or device related findings, additional imaging (e.g. chest X-ray, angiography, Computed Tomography scan, Magnetic Resonance Imaging) modalities may be requested by the investigator and send for analyses to relevant Core Lab.
Additionally, Xeltis has attempted to minimize the risk of the PV conduit through careful design and pre-clinical testing. Pre-clinical testing includes bench testing to verify performance, biocompatibility tests, destructive analysis, and packaging qualifications.
Risks normally associated with pulmonary conduits and their implantation will be minimized by selecting investigators who are experienced in the diagnosis and treatment of patients with congenital heart dis-ease. In addition, investigators will be trained on the device implantation and clinical investigational plan prior to participating in the study. Product labelling is also provided which further addresses risk mitigation.
Prior to implant, patients should go through a complete medical evaluation. After implantation, patients will be followed at regular intervals. Frequent follow-up will promote faster identification and resolution of adverse events.
Therefore, the clinical study data collection requirements (such as ECHO, blood tests etc.) of Xeltis PV conduit pose no additional risk to the subject.

XX. Risk Minimization / mitigation

As an outcome of the risk assessment the following warnings/contra-indications and precautions statements were defined:

Contraindications
None known.

Warnings

- For single use only.
- Do not re-sterilize by any method.
- Do not attempt to repair a damaged PV conduit.
- Do not use cutting needles, as they may cause structural damage to the PV conduit.
- Do not clamp the PV conduit this could perforate or damage the PV conduit.
- Do not pass a catheter through the conduit (up to 12 months postoperative), as this may damage the PV conduit.
- Do not use a hemostatic sealant/hemostat as this may close the pores of the PV conduit.
- Do not use electrosurgical cautery in close proximity to the device.
- Do not use if:
  - The PV conduit has been dropped, damaged, or mishandled in any way, or if there is any sign of deterioration.
  - The expiration date has elapsed.
  - The container seal is damaged, broken or missing.
  - Any layer of the packaging shows humidity signs.

Precautions

- Avoid severe angulation of the device.
- Avoid permanent deformation of the valved region of the conduit by contact with other anatomical structures.
- Ensure that the sterile barrier has not been broken prior to use.
- Ensure PV conduit is implanted in the right orientation, considering the direction of the flow.
- Ensure the use of synthetic non-absorbable monofilament sutures.
- Always have a qualified surgical team and an alternative conduit replacement material available during implantation or re-intervention procedures in the event that explantation is necessary.
- Use atraumatic instruments.
- Collect and discard all trimmed of portions of the device, do not use for any other purpose.

Risks normally associated with pulmonary conduits and their implantation will be minimized by selecting investigators who are experienced in the diagnosis and treatment of subjects with congenital heart disease. In addition, investigators will be trained on the device implantation and clinical investigational plan prior to participating in the study.

Product labeling is also provided which further addresses risk mitigation.
Prior to implant subjects should go through a complete medical evaluation. After implantation, subjects will be followed at regular intervals. Frequent follow-up will promote faster identification and resolution of adverse events.
The severity of system related events will be minimized by restricting use of the Xeltis PV conduit to hospitals with trained personnel who are experienced in treating patients for whom the device is intended.

Finally, a Data Safety and Monitoring Board (DSMB) will review the study after enrollment and implantation of the first three subjects. Implantation of further subjects will occur as the DSMB reviews the summarized survival and adverse events. The DSMB will provide a report following the review. The DSMB may recommend that Xeltis modify or stop the trial based on their findings.

XXI. Potential Benefits

A variety of porcine or bovine pericardial valves within heterologous or synthetic graft tubes, monocusp patches or non-valved conduits are available. These are prone to mid to long term complications such as structural degeneration, calcification, stenosis, thrombosis and embolism. Pulmonary homografts have been reported as being close to ideal in terms of compatibility and longevity, but are not widely available.
The potential benefits of the PV conduit, as a surgical valved conduit to treat congenital cardiovascular malformations, comprise:

1) As the polymer is absorbed, functional tissue is generated, which is expected to reduce the frequency of re-operation due to reduction of complications associated with existing devices, especially in younger population like pediatrics this is of benefit
    a. Preclinical data showed less calcification compared to commercially available xenograft heart valve
2) As tissue if formed and polymer is absorbed the device and replaced by natural tissue it might reduce the frequency of reoperation as children grow up.
3) The synthetic polymer in the Xeltis device does not carry risks related to potential diseases of xenografts and its subsequent fixation in glutaraldehyde, as seen in other available devices.

The above listed benefits can potentially lead to decreased morbidity and improved quality of life for the patients.

XXII. Risk Benefit Summary

There are few options for the successful long-term treatment of children with congenital heart malformations. Right Ventricular Outflow Tract (RVOT) reconstruction is commonly used to address the different malformations that occur and the use of a patch or valve or valved conduit is current practice. Techniques for surgical correction of RVOT anomalies include repair and/or replacement of the pulmonary valve often combined with sub or supra-valvular reconstruction. This repair has been greatly improved by the availability of extra-cardiac valved conduits (homografts, stented or stentless xenografts).

A variety of porcine or bovine pericardial valves within heterologous or synthetic graft tubes, mono-cusp patches or non-valved conduits are available. These are prone to mid to long term complications such as structural degeneration, calcification, stenosis, thrombosis and embolism. Pulmonary homografts have been reported as being close to ideal in terms of compatibility and longevity, but are not widely available in all sizes. For this reason, there is a need for a substitute that can effectively be applied in RVOT reconstruction and can reduce the frequency of reoperation as the children grow.

The investigational device, the Xeltis PV conduit, provides a bioabsorbable scaffold that enables natural repair of tissue inside and around the implant. It is expected to reduce the risk of complications that are seen with current conduits that are available to date such as distal stenosis and calcification. This occurrence in existing devices often leads to the need for re-operation or re-intervention which may be a recurrent problem. Natural restoration of functional tissue around and through the PV conduit can potentially lead to longer life span of the implant.

The principle of the polymer composition is to implant a bioabsorbable prosthesis, where the prosthesis is immediately mechanically functional, while its physiochemical characteristics enables cell infiltration and tissue formation. Tissue is restored and will be functional by the time the polymer is absorbed. As the polymer is absorbed, functional tissue is generated, which is expected to reduce the frequency of re-operation due to reduction of complications associated with existing devices.

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. There is also no special medication required other than standard practice, therefore the risks related to the implantation of the PV conduit are expected to be comparable to those related to the implantation of currently available devices, except for possible risks as listed in the section XIX.

Preclinical animal studies of the Xeltis PV conduit have identified cases of mild to moderate regurgitation as well as elevated pressure gradients, and minor structural deterioration of the leaflets. Conduit rupture, long term inflammatory response, inflammation, embolism, calcification, and thrombosis have only been observed at low levels. Importantly, wall calcification has been significantly less compared to currently available devices and survival rates are significantly higher compared to currently available devices as demonstrated in the animal studies.

The pulmonary valved conduit has already been implanted in eighteen (18) subjects that required Right Ventricular Outflow Tract (RVOT) correction or reconstruction or Ross procedure in 2 different studies (Xplore 1 and Xplore 2).

In summary, the Xplore 1 study shows good procedural success, and after three years follow-up absence of deaths, bleeding, stroke, endocarditis and thrombosis. After these three years follow-up the conduit part of the valve performed really well without any signs of dilatation (as indication for aneurysms) and absence of stenosis. Also, no device-related serious adverse events were reported. No intervention nor operation has occurred in Xplore-1 after 3 years follow-up. Severe regurgitation and prolapsing leaflets have been observed in this study.

Improvements on the leaflets were implemented for the devices used in the Xplore 2 clinical study to overcome these risks for regurgitation and leaflet prolapse.

A thorough analysis of relevant data has shown that the regurgitation was caused by leaflet prolapse. As observed in the Xplore 1 subjects, the failure mode observed was very similar to the failure mode in a specific in vitro durability test. This learning led to a risk mitigation by improving the design of the leaflets with a more homogenous thickness distribution resulting in a more fatigue resistant design while maintaining mobility. Devices with these optimized leaflets have been implanted in six (6) subjects that required RVOT correction or reconstruction or Ross procedure (Xplore 2 trial).

Consistent to Xplore 1, Xplore 2 also showed good results (e.g. absence of deaths, bleeding, stroke, thrombosis) and in addition confirmed the hypotheses to have reduced the risks of regurgitation (no severe regurgitation was observed at 12 months follow-up in all six patients).
In summary, the Xplore 2 study shows consistent with Xplore 1 long-term performance and safety of the conduit with absence of stenosis and dilatation. The Xplore 2 study also shows good hemodynamic results and provides the first indication that the risk of regurgitation has been reduced.

The potential lack of the long-term complications and observed lack of device related re-operations and re-interventions in the Xplore 1 and Xplore 2 clinical studies provide the first positive indication that risks are reduced compared to other available valves, like Contegra (comparison made based on literature [18]. Therefore, PV conduits can provide a significant benefit that outweighs the known risks of the device.

There may also be other benefits that are unforeseen at this time.

STUDY OVERSIGHT AND INTEGRITY

The Xeltis study will be monitored by Clinical Research Organizations (see details on page 1), according to the guideline summarized below. Safety overview will be monitored by a Data Safety Monitoring Board and a Clinical Events Committee, refer to XV. Adverse Event Reporting, Definitions and Classification

XXIII. Summary of Monitoring Procedures and Responsibilities

The Xeltis Pulmonary Valved Conduit Study will be monitored according to the guideline summarized below. The Sponsor personnel or designee will perform site monitoring visits during the clinical study, to ensure compliance with the Clinical Investigation Plan and applicable regulations. Adequately trained monitors appointed by the study sponsor will perform study monitoring in order to ensure that the investigation is conducted, recorded and reported in accordance with:

- The signed Investigator Agreement
- The Investigational Plan
- Applicable laws and regulations.

The monitoring will also ensure that data is collected in a timely and accurate complete manner and that the Investigator continues to have appropriate staff and facilities to conduct the clinical study safely and effectively. Monitoring will be performed in accordance with a pre-specified monitoring plan.

Monitoring Visits

The sponsor is responsible for making sure that the safety of the study participants is closely monitored during the study, especially during the first year. At least 3 monitoring visits/site shall be planned during the first year, however the first monitoring visit will be scheduled only after the first subject has been enrolled and implanted at each clinical site. In case it is necessary more visits will be planned. This first year post-operatively is viewed as the most important, as the conduit will have been mostly resorbed and replaced by new tissue. After the first year, less frequent visits are expected as all measurements will be standardized and the same as for the earlier time-points. Device related events that are missed are less likely to occur at that stage.

The monitoring visits will be made to assess the Investigator's adherence to the Investigational Plan, IRB/EC review of the progress (if appropriate), maintenance of the records and reports and review of source documents for accuracy, completeness, legibility and omissions. The following factors will be taken into account when determining the timing of the monitoring visits: subject accrual at each center, total number of subjects enrolled at each center, and clinical investigation plan compliance at each center.

For the following 4 years, at least one yearly monitoring visit shall take place. In case of safety related issues more visits shall be planned, as per need. In between the visits, the study monitors will keep regular contact with the site, in order to detect any safety related issues quickly. The study investigators and other study personnel will be requested to immediately report to the Sponsor and/or Study monitor whenever they suspect any safety related issues with the patients. Source Data Verification will be performed at 100 % for all patients.

A monitoring plan will be written, defining the roles and responsibilities of the Sponsor and the sponsor's contracted Clinical Research Organizations (including study monitor), Principal Investigator and/or designee (i.e. co-investigator(s) and site study coordinator.
All monitoring activities will be conducted according to all applicable regulations.
The Investigator will ensure adherence to the Clinical Investigation Plan, oversee recruitment rates and adherence to follow-up schedules, as well as ensure timely data collection, review and quality.
The study monitor will ensure accurate data recording on the e-CRF and will perform monitoring visits on a regular basis and as required. The study monitor shall inform the Sponsor of any issues related to facilities, technical equipment or medical staff at the study centers.
The Principal Investigator and/or designee shall permit and assist the study monitor in the verification of completed e-CRF against data in the source documents.

During the study the study monitor will review all Patient Informed Consent Forms and the process for obtaining it.
The study monitor shall also be responsible for notifying any deficiencies, in writing, to the related site's Principal Investigator and convene with the study center personnel for appropriate re-training and timely corrective actions.
In order for monitoring to take place, the source data/documents shall be accessible to monitors and questions shall be answered during monitoring. The study monitor shall submit written reports to the Sponsor after each monitoring visit or contact with the Investigator or site.

Study Closure

Upon closure of the study at an investigational site, the sponsor or the study monitor will make a final onsite visit (Close-Out Visit). The purpose of this visit is to collect all outstanding study documents, ensure that the investigator's files and case report forms are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study investigational devices and supplies shipped to the investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements for the study are met. The observations and actions made at this visit will be documented in a final report for the sponsor.

CLINICAL INVESTIGATION PLAN DEVIATIONS

A clinical investigation plan deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the clinical Investigational Plan or the investigator agreement or where a study subject did not comply with the study schedule as planned.

Prior notification to the Sponsor is expected in those situations in which the investigator anticipates, contemplates, or makes a conscious decision to depart from the procedure specified in the Investigational Plan, except when necessary to protect the life or the physical wellbeing of a subject in an emergency. Notification is required in situations where the unforeseen circumstances are beyond the control of the Investigator (e.g. inadvertent mistakes, equipment failure, subject ill and unable to perform testing, etc.)
Clinical Investigation plan deviations must be recorded on the Deviation data form. Include a description of the deviation, justification for the deviation, corrective action and whether the clinical manager, or designee, was notified prior to the deviation.
Deviations will be reported to the Sponsor, or designee, regardless of whether medically justifiable, pre-approved by the Sponsor or taken to protect the subject in an emergency. Clinical investigation plan deviations should be reported as soon as possible upon notification of the deviation. Study deviations may be discovered through a variety of sources, such as during the data review, telephone conversations, and center monitoring. Report clinical investigation plan deviations to your IRB/EC in accordance with IRB/EC policies and/or local laws.

FDA regulations (812.150) require the investigators to notify the sponsor and reviewing IRB/EC as soon as possible but in 5 working days for the following deviations:

- any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. 812.150(a)(4) 56.108(a)(3) and (4)
- If an investigator uses a device without obtaining informed consent, (21 CFR 812.150(a)(5)

For OUS regions local applicable regulations will be applied with regard to reporting of deviations and timelines to be adhered to.

A Deviation data form is to be completed for each clinical investigation plan deviation, including but not limited to:

- Failure to obtain informed consent
- Incorrect version of informed consent document used
- Subject did not meet inclusion/exclusion criteria
- Non-adherence to PV conduit Implant Instructions
- Missed follow-up visit
- Follow-up visit out of window
- Failure to adhere to clinical investigation plan required testing
- Implant occurring during IRB/EC lapse of approval
- Data entry in eCRF delayed for more than 30 days after the visit date
- Unacceptable echo quality and/or not following echo acquisition guidelines.

RECORDS AND REPORTS

XXIV. Investigational Records

The investigator is responsible for the preparation (review and signature) and retention of all records cited below. All of the below records, with the exception of case history records, should be kept in the Investigator Center File, i.e., the study binder provided to the investigator. The following records are subject to inspection and must be retained for a period of two years after marketing approval of the device:

- All correspondence that pertains to the investigation.
- Subject's case history records, including the signed subject informed consent form; all relevant observations; observations of adverse events; medical history; implant and follow-up data; documentation of the dates and reasons for any deviations from the clinical investigation plan.
- Device Accountability Logs, containing Center delivery dates of devices, implant dates and returned to Sponsor dates, quantities and serial numbers of devices delivered at the center, quantities and serial numbers of devices returned to Sponsor, expiration dates and subject IDs of the subjects implanted.
- Signed Clinical Trial Agreement and current curriculum vitae.
- IRB/EC documentation and correspondence (Approved clinical investigation plan, informed consents and all amendments).
- Center personnel training documentation forms.
- Evidence of sponsor monitoring logs.
- Financial Disclosure.

XXV. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all data, all death and adverse events and any deviations from the investigational plan, other reports are listed in the table below.

All reports are subject to inspection and to the retention requirements described above for the investigator records. If an IRB/EC takes any action as a result of this study, copies of all pertinent documentation must be forwarded to the sponsor.

For OUS reporting will be adapted based on country specific requirements.

Table 4 Investigator Reports

REPORT	SUBMIT TO:	DESCRIPTION
Unanticipated Adverse Device Effect	Sponsor and IRB/EC	The investigator must report an UADE to Sponsor within 24 hours of investigators knowledge. Within 10 working days the UADE must be reported to the IRB/EC and the FDA/CA.
Withdrawal of IRB/EC Approval	Sponsor	The investigator must report a withdrawal of the reviewing IRB/EC approval as soon as possible but in 5 working days.
Progress Report	Sponsor and IRB/EC	The investigator must submit annual updates to the IRB/EC per local IRB/EC requirements.
Deviation from the Investigational Plan	Sponsor and IRB/EC	The IRB/EC and sponsor must be notified within 5 working days of the event of an emergency deviation from the clinical investigation plan to protect the life or physical well -being of a subject. Except for the deviations under emergencies, prior notification must be submitted to sponsor or designee.
Failure to Obtain Informed Consent	Sponsor and IRB/EC	The investigator must notify the sponsor and IRB/EC within 5 working days after device use.

XXVI. Sponsor Records

Xeltis or their designee will retain records, including but not limited to:

- All correspondence which pertains to the investigation.
- Device disposition records containing center delivery date of device, implant device serial numbers, expiration dates, and quantities of devices shipped and returned.
- Signed Clinical Study Agreements, financial disclosure forms, and recent CV of investigators.
- All adverse events deaths and complaints.
- All data formats that are submitted, samples of the informed consents, investigational plans (including amendments), and report of prior investigations.

XXVII. Sponsor Reports

Table 6. Sponsor Reports

REPORT	SUBMIT TO:	DESCRIPTION
Unanticipated Adverse Device Effect	FDA, all IRB/ECs and all Investigators. CA where applicable	Xeltis will report any and all unanticipated device effects within 10 working days of receipt of notice.
Withdrawal of IRB/EC Approval	FDA, all IRB/ECs and all Investigators CA where applicable	Notification will be made within 5 days.
Withdrawal of FDA Approval	All IRB/ECs and Investigators	Notification will be made within 5 working days.
Current Investigator List	FDA	Xeltis will submit a list of names and addresses of all participating investigators at 6-month intervals (starting at 6-month after FDA approval).
Progress Report	FDA, all IRB/ECs and all Investigators CA where applicable	An annual report will be prepared and submitted by the sponsor to the FDA. The report will be delivered to the sites for use with IRB/EC reporting requirements.
Recall and Disposition	FDA, all IRB/ECs and all Investigators CA where applicable	Notification will be made within 30 working days and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices.
Final Report	FDA, all IRB/ECs and all Investigators CA where applicable	Xeltis will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months after completion or termination.
Failure to Obtain Informed Consent or Assent	FDA, CA where applicable	A copy of the investigator's report will be submitted within 5 working days of the notification.

PUBLICATION STRATEGY

XXVIII. Publication Committee

At the conclusion of the trial, a publication may be prepared for release in one or more reputable scientific journals. The publication of the results requires prior approval from Xeltis. The data and results from the Clinical Trial are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation.

An Investigator may only publish data generated by this clinical investigation in accordance with the terms of the Clinical Trial Research Agreement. In addition, the Data Safety Monitoring Board having full access to the data, will advise the Sponsor regarding the suitability and scientific validity of all proposed publications and presentations. All manuscripts for publication shall be reviewed by Xeltis.

A final report will be sent to the IRB/EC and Regulatory Authorities, as per applicable regulations.

APPENDIX A. ABBREVIATIONS AND ACRONYMS

ADE	Adverse Device Effect
AE	Adverse Events
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority (i.e. Ministry of Health representative)
CEC	Clinical Events Committee
CHD	Congenital Heart Disease
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
DORV	Double Outlet Right Ventricle
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiography
EDC	Electronic Data Capture
ETR	Endogenous Tissue Restoration
FDA	Food and Drug Administration
GCP	Good Clinical Practice
INR	International Normalized Ratio
IRB/EC	Investigational Review Board/Ethics Committee
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
RVOT	Right Ventricular Outflow Tract Obstruction
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
TA	Truncus Arteriosus
TF	Tetralogy of Fallot
TTH	Time to Hemostasis
UADE	Unanticipated Adverse Device Effect
VSD	Ventricular Septal Defect

APPENDIX B ECHOCARDIOGRAPHY ACQUISITION PROTOCOL

XEL-CR-03 Echocardiography Acquisition Protocol

The purpose of this 2D echo-Doppler study is to demonstrate the safety of the bioabsorbable Pulmonary Valve conduit used for reconstruction of the right ventricular outflow tract. Echocardiography will be used to make sequential assessments of transvalvular gradients and regurgitation. In order to assess changes in either of these parameters over time, it is critical that echocardiograms will be conducted in a standardized fashion at all sites participating in this protocol and at each subject visit at that site. This Echocardiographic Acquisition Protocol will address the issues of transthoracic echocardiographic acquisition with the goal of standardization of images. Standardized interpretation will be performed by centrally reading all images by the Core Lab, without any clinical knowledge of study subjects.
It is important to note that the echo performed at baseline will be compared to the follow up echocardiograms to determine if there is a change in hemodynamics and regurgitation; therefore it is critical that the baseline echoes be of good quality to allow all assessments.

Ensure the following information is entered correctly into the Echo Machine:

- Subject Study Number (not the name or medical record number of the subject)*
- Simultaneous ECG on Echo image. Provide 3-5 beats for all images.
- Ensure Date and Time on system is correct
- Only one echo per web transmission

* If the institution is required to enter the subject's name, the image copies should be de-identified before submission to the Core Lab.

Equipment

Contemporary echocardiographic equipment must be used in this protocol. Echocardiographic machines should be (ideally) no more than five years old and must accommodate current transthoracic ultrasound probes. Transthoracic echocardiography probes must have and use second harmonic imaging. Echocardiographic images should be obtained with simultaneous ECG on the echo screen.

All images must be recorded digitally in DICOM format. All echoes must have appropriate labeling to include Patient ID, date of Echo and Echo Interval.

A sample of digital images must be sent to the central Core Lab prior to enrollment of the first subject, to ensure that digital images can be centrally viewed. In setting up the digital acquisition, three consecutive beats must be obtained for all views.

Whenever possible, the site should use the same ultrasound machine throughout this study for both baseline and follow-up echocardiograms and the examinations should be performed by the same sonographer/echocardiographer.
Throughout the echocardiographic imaging, subject ID should be used on the echocardiographic machine and not the subject name. In addition, the date of the study should be displayed on the screen.

Physicians/ Sonographer

A physician or sonographer familiar with valvular heart disease and experienced in performing echocardiograms should perform each study. Prior to enrolling the first subject, the echocardiographer must take part in the training material supplied for this study to insure they are familiar with the echo imaging protocol. After completion of training, the echocardiographer will be required to submit a qualifying study that should be performed following this acquisition protocol (Test echocardiogram). The echocardiographer investigator will need to sign and complete the case report form (Site Echocardiography Checklist) that accompanies the images to the core laboratory.

If it is impossible or impractical to have a single person perform all the study echocardiograms, we strongly suggest limiting participation to two sonographers/physicians. Both will be required to undergo training and submit a qualifying study.

Transthoracic Echo (TTE) Imaging Protocol

The primary purpose of this acquisition protocol is to standardize the image acquisition. Echocardiograms should be performed at the intervals required by the protocol. Listed below are the views required for the Corelab assessment. It is understood that a complete clinical assessment using an echocardiogram may require information additional to that required by the protocol. This list contains the minimum information that is required to be sent to the Corelab.

While performing the echocardiogram, it is vital to remember that the primary purpose is to assess the pulmonic valve/conduit gradients and regurgitation.

The minimum required TTE views include:

a. Parasternal Long Axis (PLAX) View

- Standard parasternal long axis 2D view

b. Parasternal Long Axis of Right Ventricular Inflow

- RV inflow 2D view
- RV inflow color Doppler of TR jet
- Obtain TR jet velocity with CW

c. Parasternal Long Axis of RV Outflow and Pulmonary Valve/PAView

- RV outflow 2D view
- RV outflow color Doppler
- PW Doppler of RVOT
- CW Doppler of pulmonary valve/valve conduit

d. Parasternal Short Axis, Aortic Valve Level

- Color Doppler of pulmonary valve
- PW Doppler of RVOT
- CW Doppler of pulmonary valve/valve conduit
- Color Doppler of tricuspid valve
- Obtain TR jet velocity with CW

e. Apical Four Chamber View (standard and RV-focused)

- Standard apical four chamber 2D view
- RV focused apical 4 chamber view (optimized for right ventricle)
- Ensure the entire right ventricle and right atrium are visualized
- Color Doppler of tricuspid valve
- Obtain TR jet with CW Doppler
- Obtain PW tissue Doppler of RV lateral annulus
- Obtain Mmode of the Tricuspid annulus

f. Subcostal View

- Standard 2D subcostal 4 chamber view
- Ensure the right ventricle and atrium are visualized
- Obtain 2D of RVOT from the subcostal short axis view
- Color Doppler of pulmonary valve conduit
- PW Doppler of RVOT
- CW Doppler of pulmonary valve/valve conduit
- Standard 2D view of inferior vena cava

The Site Echocardiographic Checklist

The Site Echocardiographic Checklist is used as a guide to ensure the required images outlined above are taken. The Checklist also provides the Core Lab with important identification information such as subject ID, date of echo and echo interval.
It is important to complete all fields on the Site Checklist and to submit this form with the images. If an assessment listed on the form was not performed, please provide an explanation. The Checklist must indicate the name of the sonographer responsible for the echocardiogram. The Site Checklist should be sent to the Core Lab together with the images.

APPENDIX C BIBLIOGRAPHY

1. Kirklin J.W., Barrat-Boyes B. Cardiac surgery, 3rd editon – Churchill Livingstone, 2005.
2. Miyague N.I. Epidemiological study of congenital heart defects in children and adolescents. Analysis of 4,538 cases / N.I. Miyague, S.M. Cardoso, F. Meyer, et al. // Arq. Bras.Cardiol. – 2003. – vol. 80, № 3. – p. 269 – 278.
3. Walters H.L. Congenital Heart Surgery Nomenclature and Database Project: double outlet right ventricle / H.L. Walters, C. Mavroudis, C.I. Tchervenkov, et al. // Ann. Thorac. Surg. – 2000. – vol. 69. – p. 249 – 263.
4. Therrien J, Siu SC, Harris L, et al. Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation 2001; 103:2489–2494
5. Uva M.S. Surgery for tetralogy of Fallot at less than six months of age / M.S. Uva, F. Lacour – Gayet T. Komiya, et al. // J. Thorac. Cardiovasc. Surg. – 1994 – vol. 107 – p. 1291 – 1300.
6. Yong MS, Yim D, d'Udekem Y, et al.Medium-term outcomes of bovine jugular vein graft and homograft conduits in children. ANZ J Surg. 2015 May;85(5):381-5.
7. Kido T, Hoashi T, Kagisaki K, et al. Early clinical outcomes of right ventricular outflow tract reconstruction with small caliber bovine jugular vein conduit (Contegra) in small children. J Artif Organs. 2016 May 28.
8. Batlivala SP, Emani S, Mayer JE, McElhinney DB. Pulmonary valve replacement function in adolescents: a comparison of bioprosthetic valves and homograft conduits. Ann Thorac Surg. 2012 Jun;93(6):2007-16.
9. Brown JW, Ruzmetov M, Rodefeld MD, Vijay P, Turrentine MW. Right ventricular outflow tract reconstruction with an allograft conduit in non-ross patients: risk factors for allograft dysfunction and failure. Ann Thorac Surg. 2005 Aug;80(2):655-63;
10. Mokhles MM, van de Woestijne PC, de Jong PL, Witsenburg M, Roos-Hesselink JW, Takkenberg JJ, et al. Clinical outcome and health-related quality of life after right ventricular outflow tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg. 2011 Sep;40(3):571-8.
11. Ong K, Boone R, Gao M, Carere R, Webb J, Kiess M, et al. Right ventricle to pulmonary artery conduit reoperations in patients with tetralogy of fallot or pulmonary atresia associated with ventricular septal defect. Am J Cardiol.2013 Jun 1;111(11):1638-43.
12. Nordmeyer J, Tsang V, Gaudin R, Lurz P, Frigiola A, Jones A, et al. Quantitative assessment of homograft function 1 year after insertion into the pulmonary position: impact of in situ homograft geometry on valve competence. Eur Heart J. 2009 Sep;30(17):2147-54.
13. Maximina H. Yun Changes in Regenerative Capacity through Lifespan Institute of Structural and Molecular Biology, Division of Biosciences, University College London, Gower Street, London
14. Joyce Pittman Effect of Aging on Wound Healing, Current Concepts, *Wound Ostomy Continence Nurs.* 2007;34(4):412-415.,Published by Lippincott Williams & Wilkins
15. Antonio F. Corno (2012). Valved Conduits Right Ventricle to Pulmonary Artery for Complex

Congenital Heart Defects, Current Concepts in General Thoracic Surgery, Dr. Lucio Cagini (Ed.), ISBN978-953-51-0870-2,InTech,DOI:10.5772/51081. Available from: http://www.intechopen.com/books/current-concepts-in-general-thoracic-surgery/valved-conduits-right-ventricle-to-pulmonary-artery-for-complex-congenital-heart-defects

16. Laura Mercer-Rosa, MD, MSCE; Wei Yang, PhD; Shelby Kutty, MD; Jack Rychik, MD; Mark Fogel, MD; Elizabeth Goldmuntz, MD Quantifying Pulmonary Regurgitation and Right Ventricular Function in Surgically Repaired Tetralogy of Fallot, A Comparative Analysis of Echocardiography and Magnetic Resonance Imaging
17. Guidelines for reporting mortality and morbidity after cardiac valve interventions Akins, Cary W. et al. The Journal of Thoracic and Cardiovascular Surgery, Volume 135, Issue 4 , 732 – 738
18. FDA Humanitarian Device Exemption (HDE) Approval 21Nov2003. Contegra Pulmonary Valved Conduit: HDE Number: 020003. Docket 03M-0536. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H020003.

APPENDIX D CLINICAL INVESTIGATIONAL PLAN REVISIONS

The clinical investigation plan amendments are listed below along with the justifications for change and the associated dates of the clinical investigation plan revisions.

Version 1	**Change**	**Justification for Change**	**Page(s)**
Submitted to FDA November 2016			
Version 1.1	**Change**	**Justification for Change**	**Page(s)**
	Adding clinicaltrials.gov number	Number received	Front page
	Secondary objectives – removed rate of conduit failure at 6 months, is stated in primary objectives	Mistake in previous version	5
	Adding text to exclusion criteria 12 (synopsis) – extended hypersensitivity for device material to exclusion criteria	Updated together with other requests FDA	8, 18
	Adapting text – Laboratory assessment to take place at all Follow Up visits after Implantation	Updated according to request FDA	9, 25-27
	Referring to tables 1 and 2 has been corrected to 2 and 3.	Mistake in previous version	21
	Data collection table – added assessments at all postoperative FU visits: – Recording signs of sensitization: erythema, edema and lesions – Adding laboratory assessments to all Follow Up visits – Adding Haptoglobin assessment at all Follow up visits	Updated according to request FDA	22
	Added assessments at all postoperative FU visits: – Recording signs of sensitization: erythema, edema and lesions – Adding laboratory assessments to all Follow Up visits	Updated according to request FDA	23, 25-27
	Adding review of medication at all Follow Up visits	Previously missing	26-27
	Removing reference to appendix for Patient Informed Consent – separate document	Mistake in previous version	27
	Adapting text on assessment if anemia is detected	Adapted as Haptoglobin was added as standard assessment at all FU visits	27
	Added Sensitization to Adverse Event Definitions	Added as Sensitization was added as assessment, on request FDA	35
	Adding Sensitization to risks Changed wording regarding animal studies.	Updated according to request FDA	44
	Adding reference number 1	Mistakenly deleted in previous version of CIP.	97

Version 1.2	Change	Justification for Change	Page(s)
	Adding text before inclusion criteria	Addition of Ross procedure as indication for PV Conduit	7
	Changing inclusion criteria number 4	Addition of Ross procedure as indication for PV Conduit	7, 17
	Changing text on indications / intended use	Addition of Ross procedure as indication for PV Conduit	10, 15
	Changing text on implant procedure	Addition of Ross procedure as indication for PV Conduit	28
	Updating draft worksheets accordingly to protocol changes	Addition of Ross procedure as indication for PV Conduit	58, 60
	Correcting units for Echocardiography measurements on worksheet	Incorrect unit in last version	78

Version 1.3	Change	Justification for Change	Page(s)
	Update maximum number of sites to 8	Addition of maximum 3 extra sites	10, 11, 14, 15, 19, 42
	Correct sentence on survival rates in animal studies	Incorrect sentence	47

Version 2.0	Change	Justification for Change	Page(s)
	Major changes due to good M12 data and planned re-start of enrollment: • Changed primary endpoint from 6 month to 12 months • Adding of additional up to 24 subjects and re-start enrollment • Adding Time to Hemostasis • Change in Coordinating Investigator • Additional device sizes available (20 and 22mm) • Screening committee added • Additional DSMB meetings added	Good initial M12 data, enlarging sample size, and restart of study.	Minor wordings throughout the document
Version 3.0	**Change**	**Justification for Change**	**Page(s)**
	Major changes due to good M12 data and planned re-start of enrollment: • Adding of additional up to 50 subjects and re-start enrollment • Additional DSMB meetings added • Investigational sites in US and OUS	Changed to Pivotal study enlarging sample size to an additional 50 cases as well as sites US and OUS	Minor wordings throughout the document

Version 4.0	Change	Justification for Change	Page(s)
	Clarifications on primary endpoint and statistical analysis as recommended by FDA, minor corrections for consistency	FDA and other regulatory authority comments	Throughout the document
Version 5.0	German country specific version		
Version 6.0	German country specific version		
Version 7.0	Update to new CRO for sites in Europe and Asia Update ISO 14155:2020 adverse event definitions Update inconsistencies	Change of CRO	Throughout the document