# Surveillance Protocol 2015- 01, 20.07.2015

# Aortic Replacement using Individualised Regenerative Allografts: Bridging the Therapeutic Gap - ARISE

(the "Surveillance")

| prepared by | Date |
|---|---|
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| Dr. Michael Harder, corlife oHG, Sponsor | 23-7-15 |

**approved by the Local Investigator**

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| **PASS information** | |
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| Title | Aortic Replacement using Individualised Regenerative Allografts: Bridging the Therapeutic Gap - ARISE (the "Surveillance") |
| Protocol version identifier | Surveillance Protocol 2015-01, 20.07.2015 |
| Date of last version of protocol | 20.07.2015 |
| Register numbers | EU PAS:10201<br>clinicaltrials.gov: [to be applied for] |
| Active substance | Human aortic valve |
| Medicinal product | decellularized human aortic valve, Arise AV ("ARISE AV") |
| Product reference | PEI.G.11766.01.1 |
| Procedure number | OPS (Germany): 5-351.07, 5-351.08 |
| Marketing authorisation holder(s) | corlife oHG ("corlife")<br>Feodor-Lynen-Straße 23<br>D-30625 Hannover, Germany |
| Joint PASS | No |

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|---|---|
| Research question and objectives | The purpose of this investigation is to evaluate decellularized human aortic valves, Arise AV ("ARISE AV") for aortic valve replacement rates in comparison to current valve substitutes within a large prospective multicentre surveillance at 6 leading European Centres for Cardiothoracic Surgery regarding re-operation and re-intervention, hemodynamic performance, growth potential and long term durability.<br>Primary safety endpoints: All-cause mortality, major stroke, life-threatening (or disabling) bleeding, acute kidney injury—stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, major vascular complication, repeat procedure for valve-related dysfunction (surgical or interventional therapy.<br>Secondary safety data: Collection of medical data to assess the process of tissue vigilance. Collection of medical history to support the presence/absence of adverse events, e.g. infections, arrhythmia.<br>Primary efficacy endpoint: Freedom from valve dysfunction leading to re-intervention or explanation at end of the Surveillance.<br>Key secondary efficacy endpoint: Diameters of ARISE AV at end of the Surveillance in comparison to diameters at implantation, transvalvular gradients, valve competence assessed by non-invasive imaging tools such as echocardiography or cardiac magnetic resonance imaging. |
| Countries of study | Germany, The Netherlands, United Kingdom, Italy, Belgium, Spain |
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| **Marketing Authorisation holder** | |
|---|---|
| Marketing authorisation holder(s) | corlife oHG<br>Feodor-Lynen-Straße 23<br>D-30625 Hannover, Germany |
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## 1. Table of Contents

## 2. List of abbreviations

| | |
|---|---|
| AHA | American Heart Association |
| AR | Adverse Reaction |
| ARISE AV | Decellularized human aortic valve, ARISE AV |
| AVR | Aortic valve replacement |
| BE | Belgium |
| CRF | Case Report Form |
| CRP | C-reactive protein |
| CVD | Cardiovascular diseases |
| CW Doppler | Continuous-Wave Doppler |
| DAH | Decellularized aortic homograft |
| DE | Germany |
| DHV | Decellularized heart valve |
| EC | Ethics Committee |
| ECHDO | European Congenital Heart Disease Organisation |
| EGC | Ethics and Governance Council |
| ENCEPP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| ES | Spain |
| EU | European Union |
| GCP | Good Clinical Practice |
| GVP | Good Vigilance Practice |
| Hb | hemoglobin |
| IT | Italy |
| IRB | Institutional Review Board |
| LDH | Lactatdehydrogenase |
| LOCF | „last observation carried forward“ |
| MRI | Magnetic Resonance Imaging |
| NL | The Netherlands |
| NYHA | New York Heart Association |
| PEI | Paul-Ehrlich Institute |
| PW Doppler | Pulsed-Wave-Doppler |
| SAR | Serious Adverse Reaction |

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| SDC | Sodium Desoxy Cholate |
| SDS | Sodium Dodecyl Sulphate |
| SME | Small and Medium-sized Enterprises |
| STS Guidelines | Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ad hoc liaison committee for standardizing definitions of prosthetic heart valve morbidity of the American association for thoracic surgery and the society of thoracic surgeons. |
| UK | United Kingdom |

## 3. Responsible Parties

### 3.1 Market Authorisation Holder / Sponsor

corlife oHG (“corlife”)
Dr. Michael Harder, Feodor-Lynen-Straße 23, D-30625 Hannover, Germany
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### 3.2 Principle Investigator

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### 3.3 Study Director

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### 3.4 Local Investigators

The participating sites and the coordinating local investigators at the beginning of the surveillance are listed below. All participating sites, the coordinating local investigators and the local investigators are reported in the Investigators contact list (Annex 1) as amended.

| Clinical Centre | Department | Local Investigator |
|---|---|---|
| Medizinische Hochschule Hannover, MHH, Germany | Cardiac-, Thoracic-, Transplantation and Vascular Surgery | Prof. Dr. med. Axel Haverich |
| | | |

| Clinical Centre | Department | Local Investigator |
|---|---|---|
| Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum, The Netherlands, LUMC | Congenital Cardiothoracic Surgery | Prof. Mark Hazekamp |
| | | |
| Università degli studi di Padova, Azienda Ospedaliera di Padova, UNIPD/AOP, Italy | Pediatric and Congenital Cardiac Surgery | Prof. Giovanni Stellin<br>Dr. Massimo Padalino |
| | | |
| University Hospital Clinic de Barcelona, Spain | Cardiac Surgery | Prof. Dr. José Luis Pomar |
| | | |
| Royal Brompton and Harefield National Health Service Trust, United Kingdom | Cardiac Surgery | Prof. Dr. John Pepper |
| | | |
| Universitair Ziekenhuis Leuven, UZL, Belgium | Cardiac Surgery | Prof. Dr. B. Meyns |

### 3.5 Study Statistician

PD Dr. med. Dietmar Boethig

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### 3.6 ARISE Ethics and Governance Council

c/o Centre for Ethics and Law in the Life Sciences,

Leibniz Universität Hannover

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info@cells.uni-hannover.de

## 4. Abstract

| | |
|---|---|
| Title | Aortic Replacement using Individualised Regenerative Allografts: Bridging the Therapeutic Gap - ARISE (the "Surveillance")<br>Protocol No. 2015-01, version date 20.07.2015<br>main author: PD Dr. med. Samir Sarikouch, Medizinische Hochschule Hannover |
| Rationale and background | 65,000 aortic valve replacements (AVR) are performed in Europe each year to treat acquired and congenital aortic valve disease. Mortality without AVR is extremely high when symptoms occur and 50 % of affected patients die within 2 years. Current AVR options are, however, limited for young patients - especially female patients - and those unwilling to accept life-long medical anticoagulation with its inherent risks. None of the currently available prostheses for AVR is tailored toward the individual patient or allows for individual regeneration. |
| Research question and objectives | Evaluation of decellularized human heart valves for aortic heart valve replacement in comparison to current valve substitutes.<br>Safety endpoints include cardiovascular adverse events, time to re-operation, re-intervention and explantation.<br>Efficacy endpoints include freedom from valve dysfunction and hemodynamic performance. |
| Study design | This is a prospective, non-randomized, single-arm, multi-centre surveillance study to be conducted in Europe.<br>The Surveillance is designed as a study, where<br>◦ ARISE AV is prescribed in the usual manner in accordance with the terms of the approval.<br>◦ Assignment of the patient to a particular therapeutic strategy is not decided in advance by this Surveillance Protocol but falls within current practice and the prescription of ARISE AV is clearly separated from the decision to include the patient in the Surveillance. |

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| | ◦ No additional diagnostic or monitoring procedures shall be applied to the patients<br>◦ and epidemiological methods shall be used for the analysis of collected data. |
| Population | Inclusion criteria: Indication for aortic valve replacement according to current medical guidelines. Signed Informed consent of legal guardians or patients, assent of patients.<br>Exclusion criteria: The patient has not provided Surveillance informed consent. The patient shall not suffer from generalized connective tissue disorders (e.g. Marfan syndrome), or active rheumatic disorders or severe asymmetric calcification of the valve ring. The coronary arteries of the patient shall not be in abnormal position or heavily calcified. Patients shall not show hypersensitivity against Sodium Dodecyl Sulphate, Sodium Desoxycholate, human collagen (or other elastic fibers) or Benzonase®.<br>Duration of Participation: After valve implantation, patients will be followed and assessed at discharge, 3-, 6-, 12- and, if applicable, 24- months, thereafter. |
| Variables | Primary safety endpoints: Cardiovascular Adverse Reactions, e.g. all-cause mortality, major stroke, life-threatening (or disabling) bleeding, acute kidney injury, peri-procedural myocardial infarction, major vascular complication, repeat procedure for valve-related dysfunction (surgical or interventional therapy; Serious Adverse Reactions, such as infections, immunological reactions, etc.<br>Secondary safety endpoints: Blood Parameters as additional safety data to support presence/absence of Adverse Reactions; Time to reoperation, explantation and/or death.<br>Primary efficacy endpoint: Freedom from valve dysfunction leading to re-intervention or explantation at end of the study.<br>Secondary efficacy endpoint: Diameters of ARISE AV at end of the study in comparison to diameters at implantation, |

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| | transvalvular gradients, valve competence assessed by noninvasive imaging tools such as echocardiography or cardiac magnetic resonance imaging |
| Data sources | All medical data will be collected on specific case report forms (CRF). These data and or related personal data will be collected within the sole responsibility and the reasonable discretion of each Surveillance Centre. Personal data shall only be collected in a scope that is necessary for the treatment of the patient. No additional personal or health data shall be collected in connection with the Surveillance.<br>Data and safety monitoring will be performed by an independent Data Safety Monitoring Board (DSMB) |
| Study size | This Surveillance will enrol a minimum of 120 patients implanted with ARISE AV. |
| Data analysis | Actuarial analysis according to Kaplan-Meier will be used to show estimated probability of freedom from each AR. Actuarial analysis takes into account both early and late post-operative events. The time from ARISE AV implantation to endpoint ARISE AV dysfunction that requires either a catheter-based or a surgical procedure will also be calculated according Kaplan and Meier. |
| Milestones | Start of data collection: on or before 31. January 2016 |
| | End of data collection: on or before 31. December 2018 |
| | Registration in the EU PAS register: on or before 30. November 2015 |
| | Final report of study results: on or before 31. March 2019 |

## 5. Amendments and updates

Not applicable.

## 6. Milestones

| Milestone | Planned date |
|---|---|
| Registration in the EU PAS register | on or before 30. November 2015 |
| Start of data collection | on or before 31. January 2016 |
| Progress report | on or before 31. January 2017 |
| Progress report | on or before 31. January 2018 |
| End of data collection | on or before 31. December 2018 |
| Final report of study results | on or before 31. March 2019 |

## 7. Rationale and background

65,000 aortic valve replacements (AVR) are performed in Europe each year to treat acquired and congenital aortic valve disease.[1] Mortality without AVR is extremely high when symptoms occur and 50 % of affected patients die within 2 years.[2] Current AVR options are, however, limited for young patients - especially female patients - and those unwilling to accept life-long medical anticoagulation with its inherent risks. None of the currently available prostheses for AVR is tailored toward the individual patient or allows for individual regeneration.

Total artificial Tissue Engineering concepts have shown good results in technical implementation of valved polymeric conduit production and have been used successfully for in vitro and in vivo seeding of different (stem) cell lines. However, long-term animal models have given little satisfaction so far for the lack of mechanical stability of the artificial matrices, leading to early failure of valvular function.[3] Tissue-engineered biological scaffolds of porcine origin have failed dramatically in a number of pediatric patients, resulting in skepticism regarding the use of xenogenic matrices.

Allogenic matrices, established by tissue-engineering methods, have successfully been tested in large animal models and show excellent hemodynamic results and mechanical integrity. Clinical applications, with and without pre-seeding of autologous stem cells have been performed in pediatric and adult patients. In recent years, implantation of non-seeded decellularised homografts became clinical practice for pulmonary valve replacement as spontaneous recellularisation was observed by

different groups.[4]

The use of a decellularised approach for the more frequently affected aortic valve is a logical and imperative next step for this regenerative approach, but one which harbors specific physiological challenges and hurdles. Haverich et al., after successful long term testing in large animal models[5,6], have used decellularised allogenic heart valve matrices for AVR on the basis of compassionate use in 43 carefully selected patients with auspicious initial clinical results in retrospective assessment.[7]

There is a growing body of evidence suggesting sex-specific reaction of the left ventricular myocardium to pressure or volume overload.[8] However, none of the current available commercial available heart valves are targeted towards specific age groups or address sex and/or gender specific issues. Current guidelines also lack sex-specific recommendations due the lack of the “perfect” valve for a young woman, wishing to start a family.

Mechanical AVR is associated with the composite endpoint thromboembolism and bleeding of 4.0% to 4.5% per patient-year, which is a severe burden for young patients and this is aggravated by the increased risk foetal for severe congenital malformations or death.[9] Pregnancy furthermore is a widely accepted risk factor for the outcome of biological AVR leading to rapid structural valve degeneration and recurrent hospitalisations of young females/mothers resulting in various restrictions on quality of (family-)life.[10] Young patients who do not want mechanical prostheses can opt for a biological prosthesis, e.g. a pericardial xenogenic heart valve, which unfortunately does not provide satisfactory durability in young patients[9], and rapid valve degeneration can occur within months. These patients further have the option for the so-called Ross procedure which is an extensive operative procedure where the diseased aortic valve is replaced by the patient‘s pulmonary valve as an autograft. The pulmonary valve itself has to be consecutively replaced by a heart valve prosthesis leading to a “two-valve” diseased heart, as almost all autografts are impaired by progressive dilatation and the pulmonary valve prosthesis, often a conventional cryopreserved homograft, degenerates in the same way as all biological valves, thereby leading to frequent reoperations. Reoperations have a substantial higher mortality due to postoperative adhesions.[11]

As with any patient undergoing heart valve replacement, patients in this Surveillance may experience adverse reactions (AR) which may include, but are not

limited to, the following: angina, haemorrhage, arrhythmia, cardiac arrest, endocarditis, heart failure, haemolysis, myocardial infarction, prosthesis pannus, (non)-structural valve dysfunction, perivalvular leak, stenosis, stroke, regurgitation, re-operation or explantation, thromboembolism, valve thrombosis and/or death. All cardiovascular AR will be evaluated in relationship to the valve using the revised STS guidelines.[9]

No procedures in this Surveillance are experimental. Participating in this Surveillance is thought not to induce any additional risk to patient undergoing aortic valve replacement.

## 8. Research question and objectives

The purpose of this investigation is to analyse ARISE AV for aortic valve replacement rates in comparison to current valve substitutes within a large prospective multicentre surveillance at 6 leading European Centres for Cardiothoracic Surgery regarding re-operation and re-intervention, hemodynamic performance and long term durability.

This will be a non-randomized surveillance involving a minimum of 120 isolated aortic valve replacement patients receiving ARISE AV processed by corlife.

The following outcome variables will be analysed:

### 8.1 Safety endpoints, Vigilance

#### 8.1.1 Primary safety endpoints

Rate of cardiovascular AR, e.g. all-cause mortality, major stroke, life-threatening (or disabling) bleeding, acute kidney injury—stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, major vascular complication, repeat procedure for valve-related dysfunction (surgical or interventional therapy).

#### 8.1.2 Secondary safety data

Collection of medical data to assess the process of tissue vigilance. Collection of medical history to support the presence/absence of AR, e.g. infections, arrhythmia.

## 8.2 Efficacy endpoints

### 8.2.1 Primary efficacy endpoint

Freedom from valve dysfunction leading to re-intervention or explant at end of the Surveillance.

### 8.2.2 Key secondary efficacy endpoint

Diameters of ARISE AV at end of the Surveillance in comparison to diameters at implantation, transvalvular gradients, valve competence assessed by non-invasive imaging tools such as echocardiography or cardiac magnetic resonance imaging.

# 9. Research methods

## 9.1 Study design

This Surveillance is designed as a prospective, non-randomized, study (as there is no experimental procedure) involving a minimum of 120 patients receiving ARISE AV for aortic valve replacement according current medical guidelines for AVR.

A single-arm clinical Surveillance design was chosen since extensive data on conventional alternatives is available in the literature.

Long term follow-up of all patients beyond the Surveillance is recommended for complete evaluation of ARISE AV with respect to current life expectancy of patients and the potential of ARISE AV for lifelong durability.

## 9.2 Setting

### 9.2.1 The Consortium

The Sponsor and the parties listed in Table 3.4 are parties to the Consortium Agreement concluded as part of the Horizon 2020 Framework Programme for Research and Innovation (2014-2020) relating to the project “Aortic Valve Replacement using Individualised Regenerative Allografts: Bridging the Therapeutic Gap-ARISE,” (the “Consortium Agreement”) and are parties to the Grant Agreement (No: 643597) concluded pursuant to the “Rules For Participation And The European Grant Agreement” adopted on 10 April 2007 (the “Grant Agreement”), which provide for the

framework of the cooperation in the EU-funded project ARISE and which regulate the Parties' reimbursement of costs in the project ARISE.

### 9.2.2 Surveillance

The Surveillance is designed as a study, where

- ARISE AV is prescribed in the usual manner in accordance with the terms of the approval.
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by this Surveillance Protocol but falls within current practice and the prescription of ARISE AV is clearly separated from the decision to include the patient in the Surveillance.
- No additional diagnostic or monitoring procedures shall be applied to the patients
- and epidemiological methods shall be used for the analysis of collected data.

### 9.2.3 Centre selection

European centres specializing in the surgical treatment of valvular heart defects will cooperate in the ARISE Surveillance to enable recruitment of a sufficiently sized study population for robust statistical and reliable clinical evaluation of ARISE AV in comparison to conventional heart valve substitutes. An European-wide network of 6 clinical centres has thus been established to take adequate account of the heterogeneity of patients and to eliminate any bias in patient selection or bias resulting from a particular surgical technique, influence of the surgeon or treatment algorithms. Centres were chosen for their excellent results in aortic valve defect repair using conventional homografts and their high-volume surgical programs. More qualified centres may be added to supplement the Surveillance cohort. The size of the Surveillance cohort (n=120) was calculated to reliably compare ARISE AV to established aortic heart valve substitutes.

### 9.2.4 Patient Enrolment and Surveillance Timeline

The proposed recruitment of 20 patients from each of these clinical centres within 24 months is realistic given the number of aortic valve replacements (AVR) in these institutions every year. Furthermore, it is anticipated that patient demand will increase, as there already is a large waiting list at Hannover Medical School for potential ARISE AV recipients. The calculated cohort size of at least 120 patients will allow for evaluation of re-intervention rates, hemodynamic performance and durability of ARISE AV for AVR in valvular heart disease. Patient recruitment is expected to be completed within 24 months after start of the Surveillance. Data analysis will be performed 36 months after start of the Surveillance to ensure a minimal follow up of 12 months for all Surveillance patients.

### 9.2.5 Donor Selection for ARISE AV

All tissue donors comply with the requirements of the Directives 2004/23/EC and 2006/17/EC. Identical criteria are applied as for donation of conventional homografts.

### 9.2.6 Valve Description

Starting in 2002, Haverich et al. were one of the first research teams to report the clinical application of tissue engineered heart valves in pediatric patients.[12] Active seeding became unnecessary as spontaneous re-endothelialisation by circulating endothelial progenitor cells was observed by several groups. Since then non-seeded, decellularised heart valves have been used with early results published in 2011.[13]

Decellularised allogenic matrices for pulmonary valve replacement have been approved in 2013 by European member states (Germany, Italy, Switzerland) in the low pressure pulmonary circulation following an 18 month dialogue with the respective competent authorities focusing on all aspects such as bioburden, mechanical stability, hemodynamic performance and immunological reactions.

The systemic position of aortic valves, however, requires much higher mechanical stability and higher operative expertise due to associated dilated ascending aorta and to the adjacent coronary arteries, which may be diseased and thus must also be addressed. Spontaneous recellularisation of the transplanted heart valve, which is

the basis of the regenerative concept, also may take much longer as the aortic valve is much thicker than all other heart valves. As AVR is the more common procedure, in fact 50 times more frequently performed than pulmonary valve replacement, DAH are expected to be used often in so-called 'redo situations', which adds another challenge to technical feasibility, e.g. for the re-implantation of the coronary arteries, which we will analyze in this study.

### 9.2.7 Legal Aspects

ARISE AV has been approved by the Paul-Ehrlich-Institute for marketing pursuant to Section 21a of the German Drug Law (Arzneimittelgesetz) by approval no. PEI.G.11766.01.1 dated 14.07.2015. Corlife qualifies as a so-called tissue establishment pursuant to administrative decision no. 41401/H-137 by the Staatliches Gewerbeaufsichtsamt Hannover, Germany, according to Section 20c of the German Drug Law.

ARISE AV is processed in accordance with the requirements of the Tissues & Cells Directive and the corresponding provisions of the German Drug Law as well as in compliance with other applicable German laws (ie Data Protection Act).

The Sponsor is not aware of any European Directive or Regulation limiting the import and export of tissue preparations among Member States, once approval has been granted. Article 9 of the Tissues & Cells Directive only provides for specific proceedings for the import of tissues from third countries (i.e., non-EU Member States). Although, the Tissues & Cells Directive in connection with Directives 2006/17/EC and 2006/86/EC set forth specific requirements on the donation, procurement, testing, processing, conservation, storage and distribution of tissues and for the establishments and persons involved in the aforementioned activities, the Tissues & Cells Directive does not set forth specific approval requirements on specific tissues or tissue preparations.

However, since national laws of the EU Member States can be stricter than the requirements of the relevant EU-Directives, some countries impose specific, and/or additional requirements on the import of the ARISE AV.

### 9.2.8 Valve Implantation Records

As the product has been approved by the competent authorities, the Local Investigator will maintain a log of all valves implanted for the evaluation at the centre. The log shall include:

1. patient Surveillance number
2. main diagnosis
3. valve number
4. valve size
5. date of implant

Corlife will also provide an Implant Identification Card for every patient.

### 9.2.9 Valve Storage

The storage environment should be clean, cool, and dry. Store ARISE AV at 2°C to 8°C (36°F to 46°F). The ARISE AV has been qualified for a maximum storage life of 60 days from the date of tissue donation. The expiry date of the device is recorded on the outer package label.

### 9.2.10 Patient Population

Young patients with severe aortic valve disease today are facing a real dilemma. Once the indication for aortic valve replacement has been confirmed by their physician, they have to choose either a mechanical valve replacement option, which directly affects their quality of life as strict life-long blood anticoagulation is needed to avoid cerebral thromboembolism. These “blood thinners” have an inherent risk for severe bleeding episodes, which needs to be considered in both professional and leisure activities.

The majority of patients nowadays try to avoid anticoagulation for these reasons. Young patients who do not want mechanical prostheses can opt for a biological prosthesis, e.g. a pericardial xenogenic heart valve, which unfortunately does not provide satisfactory durability in young patients[11], and rapid valve degeneration can occur within months. These patients further have the option for the so-called Ross

procedure which is an extensive operative procedure where the diseased aortic valve is replaced by the patient‘s pulmonary valve as an autograft. The pulmonary valve itself has to be consecutively replaced by a heart valve prosthesis leading to a “two-valve” diseased heart, as almost all autografts are impaired by progressive dilatation and the pulmonary valve prosthesis, often a conventional cryopreserved homograft, degenerates in the same way as all biological valves, thereby leading to frequent reoperations. Reoperations have a substantial higher mortality due to postoperative adhesions.[11]

The routine practice of cardiovascular surgery employed by the Local Investigator will determine the indications for replacement of a patient’s natural aortic valve or previously implanted prosthesis. Due to the complexity and variations in surgical procedures for valvular heart disease, and the individual anatomy and other patient related factors, the choice of surgical technique and approach is left to the discretion of the individual surgeon.

*The decision to treat the patient with ARISE AV is independent from participation in this Surveillance.*

### 9.2.11 Inclusion Criteria

The following inclusion criteria will be used in this Surveillance:

1. Indication for aortic valve replacement according to current medical guidelines in valvular heart disease
2. Informed consent of legal guardians or patients, assent of patients

### 9.2.12 Exclusion Criteria

1. The patient has not provided Surveillance informed consent.
2. The patient shall not suffer from
    a. generalized connective tissue disorders (e.g. Marfan syndrome), or
    b. active rheumatic disorders, or
    c. severe asymmetric calcification of the valve ring.

3. The coronary arteries of the patient shall not be in abnormal position or heavily calcified.
4. Patients shall not show hypersensitivity against sodium dodecyl sulphate (SDS), sodium desoxycholate (SDC), human collagen (or other elastic fibers) or Benzonase®.

### 9.2.13 Surveillance Procedures

Corlife will provide the Surveillance-sites with the Surveillance Protocol and Case Report Forms (CRFs), and, on request, with all other related documentation. Corlife will conduct all aspects of data quality assurance (data review and, if needed, monitoring of Surveillance sites, to eliminate ambiguities). Each Surveillance site should adhere to all the requirements specified in this protocol and the CRFs. Assessments of patients should be obtained by the Local Investigator for the preoperative, operative, and discharge period and postoperatively at 3, 6 and 12 months and 24 months, as applicable. An assessment beyond the Surveillance will be subject of a separate Surveillance/agreement.

The Local Investigator should make every attempt to follow the patients and should document the information gathered during the follow-up visits on the CRFs. The patients should be encouraged by the Local Investigator to report any address or telephone number changes to the Local Investigator. They should also be informed of the importance of returning for scheduled follow-up visits even if they are not having any problems. If a patient is lost to follow-up the efforts undertaken to locate the patient should be documented.

*All patient's personal and health data shall be collected within the sole reasonable discretion of the Local Investigator and only in a type and scope required for the specific medical treatment of a patient. No additional personal or health data shall be collected by the investigators and this Surveillance does not require the collection or use of any personal or health data in addition to such data that is required for the specific medical treatment of a patient.*

### 9.2.14 Preoperative Procedures

The Local Investigator should screen all isolated biological aortic valve replacement cases for participation in the Surveillance.

*The indication for aortic valve replacement with ARISE AV will be solely based upon the current clinical guidelines in the Local Investigators institution.*

The Local Investigator should determine and document whether each patient meets the selection criteria previously outlined before enrolment into the Surveillance. The Local Investigator will also obtain informed consent for Surveillance participation from each patient or parents, and informed assent from children, prior to implantation of ARISE AV. A patient identification number (Sec. 9.4) shall be assigned to each patient who signs a consent form. If a patient is enrolled in the Surveillance, however the Surveillance valve is not implanted, an explanation should be indicated on the patient selection form of the CRF. No further Case Report Forms should be completed for these patients.

The Local Investigator should determine and record each patient's demographics (date of birth, sex), height, weight, New York Heart Association (NYHA) functional class, cardiac rhythm, past and present cardiovascular and non-cardiovascular conditions and previous cardiovascular operations. An echo shall be performed. The investigator should seek to provide preoperative information on left ventricular function based on magnetic resonance imaging (MRI) imaging in all cases and provide copies to the MRI Core Laboratory in Hannover; however, MRI is not mandatory in children needing anaesthesia for the MRI scan. Copies of the MRI should be provided to:

Medizinische Hochschule Hannover
HTTG (OE6210)
ARISE Surveillance Office
Carl-Neuberg-Straße 1
D-30625 Hannover
Telefon: +49 (0)511 532 7849
Fax: +49 (0)511 532 18507
mail: sarikouch.samir@mh-hannover.de

### 9.2.15 Operative Procedures

The surgical technique employed will be that developed and perfected by the Local Investigator in his/her normal practice of cardiac surgery. Special attention should be given to proper sizing, orientation and irrigation of the valve during surgery.

The Local Investigator should record the implant date, implanting surgeon, aetiology, diagnosis for current replacement, information regarding the particular valve implanted (including size, number, suture technique) and other details concerning the surgery such as condition of the annulus/valve being replaced, debridement procedures, concomitant procedures and intra-operative AR.

### 9.2.16 Discharge

At discharge, the Local Investigator should record the date of the patient's discharge from the hospital, patient status, cardiac rhythm and AR. Echo/Doppler evaluation is required at discharge.

### 9.2.17 Postoperative Follow-up Visits (3, 6, 12 months, and 24 months, as applicable)

The postoperative follow-up will be that developed and perfected by the Local Investigator in his/her normal practice. The following is recommended:

Postoperative follow-up visits are recommended at 3 months, 6 months, one year, and, if applicable, two years. If studies are performed at other times in response to symptoms, the Local Investigator should document these studies as an interim visit.

Doppler/echocardiography is recommended for all patients at all visits. Cardiac magnetic resonance imaging is routinely performed in all patients within one year after the implantation of the Surveillance valve. However MRI is not mandatory in children needing anaesthesia for the MRI scan. Copies of the MRI scans shall be provided to the MRI Core Laboratory in Hannover (Sec. 9.2.14).

It is recommended, that at each postoperative assessment, the Local Investigator should determine the patient's availability for future follow-up. If any patient needs to be seen at other than a regularly scheduled follow-up visit, obtained information should be documented by the Local Investigator on the follow-up Case Report Form and indicated as an interim visit.

### 9.2.18 Patient Withdrawal

The Local Investigator should make reasonable attempt to follow the patient at each of the required assessment periods. Patients may withdraw from the Surveillance

without penalty or loss of benefits to which they are otherwise entitled. A Surveillance patient that has been withdrawn from the Surveillance will not be replaced.

If a participant, who has given informed consent, withdraws or loses capacity to consent during the Surveillance, the participant would be withdrawn from the Surveillance. Identifiable data already collected with consent would be retained and used in the Surveillance.

#### 9.2.19 Missed Visit / Lost to Follow-Up

If a patient cannot be reached for a follow-up visit, the Local Investigator should document on the respective CRF the effort(s) he/she made to contact that patient or the patient's primary health care provider. If the patient cannot be reached in any way the assessment will be considered as missed visit for that time interval. At subsequent scheduled follow-up visits, new efforts should be undertaken to locate the patients.

### 9.3 Variables

#### 9.3.1 Outcome Variables (Safety and Efficacy)

Four outcome variables based on CRF information will be analyzed by the Sponsor together with the Study Director and the Study Statistician:

1. Primary safety endpoints:
    a. Cardiovascular AR, such as all-cause mortality, major stroke, life-threatening (or disabling) bleeding, acute kidney injury—stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, major vascular complication, repeat procedure for valve-related dysfunction (surgical or interventional therapy
    b. SAR, such as infections, immunological reactions, etc.
2. Secondary safety endpoints:
    a. Blood Parameters as additional safety data to support presence/absence of AR
    b. Time to reoperation, explantation and/or death

3. Primary efficacy endpoint: Freedom from valve dysfunction leading to re-intervention or explantation at end of the study.
4. Secondary efficacy endpoint: Diameters of ARISE AV at end of the study in comparison to diameters at implantation, transvalvular gradients, valve competence assessed by non-invasive imaging tools such as echocardiography or cardiac magnetic resonance imaging.

### 9.3.2 Primary Safety Endpoint: Cardiovascular AR

The "Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations" (STS guidelines) were approved by the Council of the Society of Thoracic Surgery (STS), published in September 1988 and revised in 1996. This Surveillance of cardiovascular AR should be conducted in accordance with the revised STS guidelines. In reporting AR, all cardiovascular related symptoms, including abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anaemia, fever, arrhythmia, haemorrhage, transient ischemic attack, stroke, paralysis, congestive heart failure, cardiac failure, and myocardial infarction should be assessed as to their relation to the valve.

The Local Investigator should record all new AR (i.e. not previously reported adverse reactions). All pertinent details related to the AR and evaluation of the valve relatedness should be completed in accordance with the revised STS guidelines. If an adverse reaction results in reoperation/valve explantation or death, the Local Investigator will complete the respective CRF. Copies of an autopsy report and/or death summary should be included with the CRF’s. The Local Investigator should make reasonable effort to return the explanted valve(s) (at autopsy or reoperation) to corlife. Return kits for explanted valves will be provided upon request by corlife.

The primary safety objective is to assess the rate of all cardiovascular AR /complication rates for ARISE AV and the process of tissue vigilance.

### 9.3.3 Secondary Safety Data

The following data should be collected: Hb, LDH, Haptoglobin, CRP, Leukocytes. Blood studies should be performed within 7 days preoperatively and at discharge.

Blood data will support the absence/presence of related AR. For example, haemolysis should be reported as an adverse event if anaemia is present; however, in the absence of anaemia, haemolysis will be considered to be compensated and does not require reporting. Time to events, such as death, reoperation including explantation will be evaluated for those outcomes, calculated from the date of operation.

#### 9.3.4 Primary Efficacy Endpoint: Freedom from valve dysfunction

Echocardiographic studies should be obtained and analyzed at discharge and at 3, 6 Months and at annual follow-ups. The requested variables include peak and mean systolic gradient, using pw and cw doppler, in the left ventricular outflow tract, respective the aortic valve. The echo evaluation (videotape or CD) should remain at the Surveillance site, but be available to corlife Surveillance personnel upon request. The MRIs will be analyzed by the MRI Core Laboratory at Medical School in Hannover (Sec. 9.2.14) for potential valvular stenosis, via phase contrast flow measurements in the aorta and for valvular competence, via phase contrast flow measurements and by ventricular volumetry. MRI cine images will be used to visualize the Surveillance valve in patients with poor echocardiographic windows.

#### 9.3.5 Secondary Efficacy Endpoint: ARISE AV diameters and left ventricular function

Diameters of ARISE AV at end of the Surveillance will be analyzed in comparison to diameters at implantation and to age matched reference values. Preoperative non-invasive data on left ventricular size and function, such as left ventricular end diastolic, end systolic volume, ejection fraction and ventricular mass will be derived from MRI and compared to postoperative status.

### 9.4 Data sources

#### 9.4.1 Management of Personal Data

All medical data will be collected on specific case report forms (CRF) provided by Sponsor. Any medical data and or related personal data will be collected within the sole responsibility and the reasonable discretion of each Surveillance Centre. Personal data shall only be collected in a scope that is necessary for the treatment of the patient. No

additional personal or health data shall be collected in connection with the Surveillance.

Each patient/participant in the Surveillance shall provide his or her consent to the collection and use of his/her personal data by the health personnel of the treating Surveillance Centre. No personal health data must be disclosed to Sponsor, the Principle Investigator, the Study Director or any other person participating in the Surveillance without the prior written consent of the patient.

Medical data shall only be reported to Sponsor on the CRFs provided by Sponsor in anonymized fashion. For ensuring appropriate anonymization, each Surveillance Centre shall assign a three-digit patient number for each patient participating in the Surveillance. Such patient number shall be randomly created by each Surveillance Centre by using a combination of capital letters and numbers. None of the letters and numbers used when creating a patient number must be related to the specific patient (e.g., the use of name initials or numbers from a patient's birth date are not permitted). It is important that each patient number is randomly created without application of any system or coding mechanism. Each CRF shall only contain such patient number and no other data that would allow the Sponsor or any other person participating in the Surveillance to identify a reported patient. Each Surveillance Centre is prohibited from disclosing personal data of a patient/participant in the Surveillance to the Sponsor or any other person participating in the Surveillance. In order to avoid any potential detriments to a patient for the lack of disclosure of his or her personal data to the Sponsor, investigator, or any other person participating in the Surveillance, each Surveillance Centre is obligated to immediately direct any notifications made to a Surveillance Centre under a patient number to the specific patient such notification relates to.

### 9.4.2 Data and Safety Monitoring

Data and safety monitoring is a requirement for conducting a Surveillance in a clinical context and is usually undertaken by a body consisting of a statistician, an expert in ethics and a medical expert. Data and safety monitoring will be performed by the independent DSMB

The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated Surveillance data for participant safety,

Surveillance conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to the Sponsor concerning the continuation, modification, or termination of the study. The DSMB considers Surveillance-specific data as well as relevant background knowledge about the disease, test agent, or patient population under Surveillance. For this purpose, the DSMB will only have access to anonymized medical data as recorded on CRFs (Sec. 9.4.1, 9.6.1).

Corlife shall report any SAR pursuant to Section 11 and any statistical analysis pursuant to Section 9.7 to the DSMB and, if required, to the competent authorities and the tissue banks providing the homografts. The DSMB is responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

### 9.5 Study size

Efficacy, primary end point: The combined endpoint will be assessed by a sequential two-sided single-arm binomial test as shown below.

Two aspects will be evaluated for the safety of AVR using DAH, operative mortality and adverse clinical events during follow up:

1. According recent guidelines the mortality rate for AVR should certainly be less than 5%, the overall operative mortality risk for isolated biological AVR is 3.2% [9]
2. Operative mortality will be analyzed under the control of the data safety monitoring board (DSMB).

An average of 5.4 % adverse clinical events per patient-year has been described for mechanical valves as well as for biological valves during follow up including sustained structural valve deterioration, nonstructural valve dysfunction, thromboembolism and bleeding and endocarditis (STS 2013). This has been the basis for the sample size calculation using a sequential test for a two-sided single arm binomial study to show at any point whether the expected rate of 5.4 events per 100 patient years is significantly exceeded (Figure 1). With a power of 80% this can be shown for a real event rate lower than 10.6 events per 100 patient years (Figure 2).

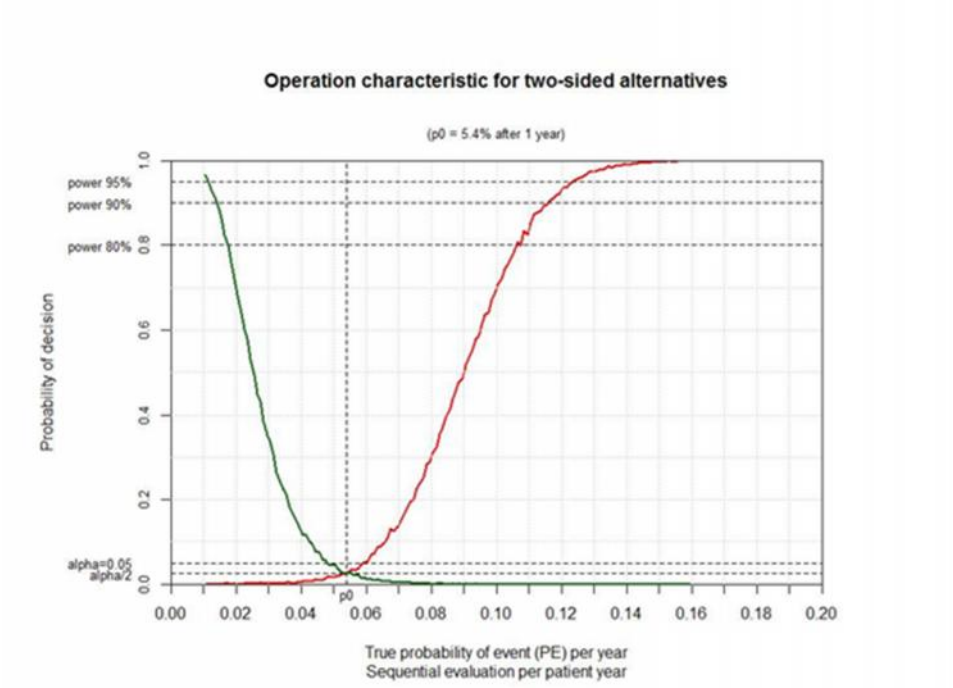


Figure 1

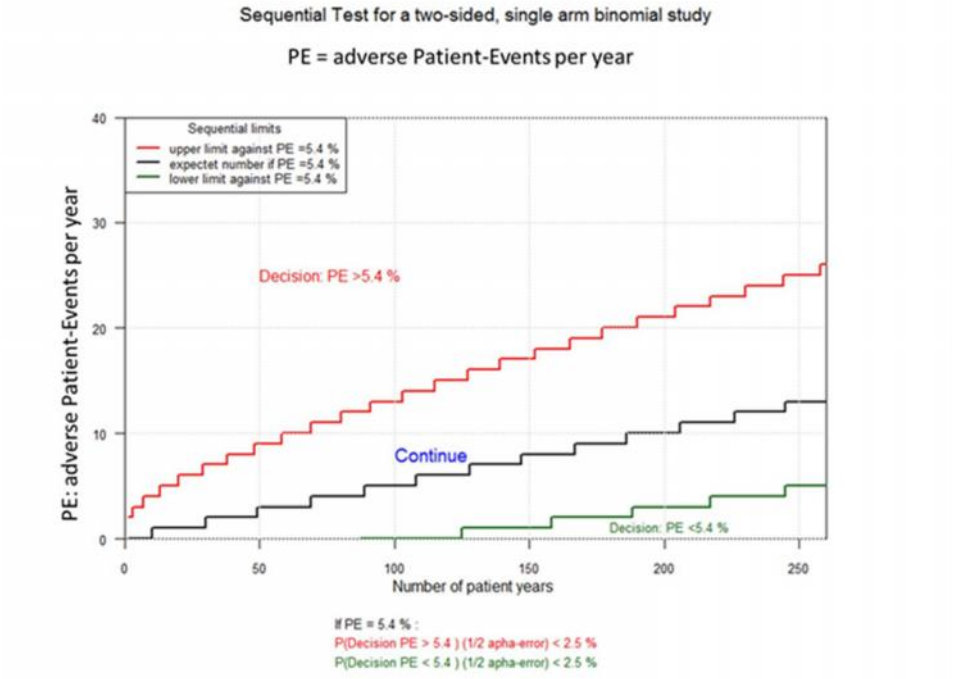


Figure 2

## 9.6 Data management

### 9.6.1 Case Report Forms (CRFs)

Paper-based Case Report Forms (CRFs) for individual patients will be provided by corlife. All CRFs must contain a specific three-digit patient number created in each

Surveillance Centre. The centers shall assign a three-digit patient number for each patient participating in the Surveillance. Such patient number shall be randomly created by each Surveillance Centre by using a combination of capital letters and numbers. None of the letters and numbers used when creating a patient number must be related to the specific patient (e.g., the use of name initials or numbers from a patient's birth date are not permitted). It is important that each patient number is randomly created without application of any system or coding mechanism.

Personal patient data shall not be contained on any CRF. The Local Investigator or its designee (Surveillance Centre) should keep a separate log of patient names and current addresses to facilitate record keeping and the ability to contact patients for future follow-up. The separate log of patient names, or any personal data contained in the log, shall not be made available to the Sponsor or other participants in the Surveillance. Completed CRFs shall be forwarded exclusively to Sponsor. Neither Sponsor nor Local Investigator or Principal Investigator or Study Director or Medical Statistician shall disclose completed CRFs to the other participants in the Surveillance.

CRFs shall support the Local Investigator when collecting data. CRFs shall not influence the physician in collecting data beyond the established policy at the respective site. The Local Investigator shall only collect data that is relevant for the individual patient's medical treatment with an ARISE AV. The Sponsor does not provide the Local Investigator with instructions for data collection.

CRFs are collected by the Sponsor for scientific analysis only. Sponsor will not intervene or discuss with the Local Investigator (Surveillance Centre) details on the investigator's medical treatment of individual patients on the basis of information contained in a CRF or otherwise.

CRFs will be used as an integral part of the Surveillance and subsequent reports. Therefore, the forms should be legible and complete. Not missing data (for whatsoever reason) should be lined out. Errors should be lined out, but not obliterated and the correction inserted, signed and dated by the investigator. Copies of changed CRFs must be provided to the Sponsor and retained in the patient Surveillance file.

A CRF should be completed and signed by the Local Investigator or designee listed in the Clinical Studies Agreement for each subject receiving a Surveillance valve, including subjects withdrawn from the Surveillance for any reasoning a timely manner. The reason for withdrawal should be noted on the CRF by the Local Investigator for

each subject. Since there is a potential for errors, inaccuracies, and illegibility in transcribing data onto CRF's, originals or photocopies of all relevant operative records and reports, postoperative examinations, laboratory and other test results should be kept on file.

CRF's and copies of test results should be available to the Sponsor for evaluation. CRF's should be kept current to reflect subject status at each phase during the course of the Surveillance. Completed CRF's should be sent to the address below in a timely manner after the patient's discharge or follow-up:

corlife oHG
ARISE / CRF
Feodor-Lynen-Straße 23
D-30625 Hannover

#### 9.6.2 Statistical software

The software SPSS, Vers. 21 (or higher), will be used.

### 9.7 Data analysis

Sections 9.7.1 - 9.7.4 detail the analysis approach for each of the Surveillance outcomes. Sections 9.7.5, 9.7.6 address the issues of data poolability and missing data. Unless otherwise noted, all statistical tests will be performed at the $\alpha = 0.05$ level.

#### 9.7.1 Primary Safety Endpoint

For reporting purposes, all cardiovascular AR within the early post-operative period (within 30 days of implant) will be summarized by the percent of patients who experience an AR. Linearized rates will be used to summarize AR for the late (>30 days) post-operative period. The linearized rates will be reported as the number of events occurring after the early post-operative period per year of patient exposure. Actuarial analysis according to Kaplan-Meier will be used to show estimated probability of freedom from each AR. Actuarial analysis takes into account both early and late post-operative events.

### 9.7.2 Secondary Safety Endpoints

Blood data (Hb, LDH, Haptoglobin, CRP, Leukocytes) will be collected preoperatively and at discharge. This blood data will support the absence/presence of related AR; in particular haemolysis and leucocytosis. Data will be reported as the percent of patients with results within the normal ranges at each time interval. The percent of patients with haemolysis at each point will also be reported. Summaries will be presented for the entire Surveillance cohort and will also be stratified by valve size.

Time to death from the date of operation will be analyzed by the method of Kaplan and Meier. Time to reoperation from the date of operation as well as time to explant from the date of reoperation will be similarly analyzed. For time to explantation and time to reoperation, the time to first explantation or reoperation will be calculated for those patients requiring explantation or reoperation. These analyses will also be reported stratified by valve size. Analyses for time to explantation and time to reoperation will also be stratified by fatal versus non-fatal reactions.

### 9.7.3 Efficacy Analysis: Freedom from valve dysfunction

The time from ARISE AV implantation to endpoint ARISE AV dysfunction that requires either a catheter-based or a surgical procedure will be calculated according Kaplan and Meier. Matched comparison to conventional cryopreserved homografts and bovine jugular vein grafts will be performed to compensate for known effects of patients age, number of previous operations and complexity of the valvular heart defect.

### 9.7.4 Efficacy Analysis: ARISE AV diameters and left ventricular function

For secondary endpoints it is also planned to undertake matched comparisons to conventional biological aortic valve prostheses. In addition, appropriate growth of ARISE AV will be assessed in comparison to age matched reference groups using valve diameter z-scores and/or standard deviation scores.

### 9.7.5 Poolability

Patient baseline risk will be statistically compared between all participating centres. Statistics will be provided by the Surveillance Statistician (Sec. 3.5). Chi-

square tests will be used to compare categorical risk factors while analysis of variance will be used to compare continuous risk factors. Comparisons will be based on the following demographic and pre-operative variables: age, sex, underlying valvluar heart defect, previous (heart valve replacement) surgery, valvular lesion, pre-operative NYHA, concomitant cardiac procedures, and coexisting cardiovascular conditions. Also included in the analysis will be the size of implanted valve. Additional analyses, such as propensity score matching, may be performed if the need arises.

#### 9.7.6 Missing Data

All statistical tests on the efficacy endpoints will be performed two ways: (1) using only those patients with no missing data at baseline and one year (complete case) and (2) by the method of last observation carried forward (LOCF). The complete case and LOCF analyses will be compared. However, the method of last observation carried forward will be used in addition to the complete case analyses (i.e. analyses based on only those patients with baseline and one year data) for the comparison of NYHA classification and hemodynamic performance to baseline at one year to investigate the effect of loss-to-follow-up. NYHA classification and hemodynamic performance will still be summarized at each of the time points described in the previous version of the protocol. However, these data will only be statistically compared to baseline at one year.

### 9.8 Quality control

#### 9.8.1 Local Investigator Responsibilities

The Local Investigator is responsible for obtaining IRB/EC approval for the Surveillance at his/her Institution and by competent authorities, as applicable. The study will not start before this approval has been sent to corlife and to the Study Director.

Surveillance records including CRF's, signed Local Investigator's Agreement, originals of all blood and hemodynamic studies, signed informed consents, IRB/EC approval letters, documentation of IRB/EC submissions, and other documents pertaining to the conduct of the Surveillance should be kept on file by the Local Investigator.

The responsibilities of the Local Investigator(s) comply with the requirements set forth in Declaration of Helsinki, the local laws of the country – including regulations of the European Union and the regulations given by Good Clinical Practice (GCP) and Good Vigilance Practice (GVP). The Local Investigator(s) should adhere to the regulations that provide the greatest protection to the patient. Any protocol deviations should be fully documented and explained on the CRF and reported to the local IRB/EC if applicable. Any unusual or unanticipated adverse reaction should be reported immediately to the Sponsor (Sec. 11) and if applicable, to the IRB/EC as outlined in the Local Investigator's Statement and Agreement. If deemed necessary by the Principal Investigator, the IRB/EC, or the Sponsor, the investigation may be suspended pending a thorough Surveillance of the incident.

If the Local Investigator wishes to assign the files to someone else or move them to another location, he should inform the Sponsor and the concerned patients in writing. If there is a change or addition of Local Investigators, an amended Local Investigator's Agreement should be completed promptly. Any other personnel changes should be reported immediately to the Study Director to schedule a training program. Evaluation visits will be scheduled throughout the course of the Surveillance. It is essential that the Local Investigator set aside a sufficient amount of time for these visits to permit an adequate review of the Surveillance's progress, completed CRFs and original records.

### 9.8.2 Sponsor / Surveillance Monitor Responsibilities

A Surveillance monitor assigned to the Surveillance by the Sponsor may monitor the progress of the Surveillance. The Surveillance monitor must be acquainted with the Local Investigator and other key people involved in the Surveillance. The Surveillance monitor will remain in close contact with the site throughout the duration of the Surveillance to answer any questions concerning CRFs. The Surveillance monitor will be responsible for reviewing CRFs on their legibility and suitability for scientific analysis, will inquire with the Local Investigator on potentially missing data, and will be visiting the site periodically to monitor Surveillance progress and compliance with the Surveillance protocol. The local data protection laws will be followed. The Surveillance monitor shall not have access to the original patient file but shall only have access to anonymized patient data. Monitoring visits will be scheduled throughout the duration of

the Surveillance at a mutually convenient time for the monitor and principal investigator or designee. Monitoring will be conducted along Good Clinical Practice (GCP), as applicable.

Contact data of Surveillance monitors:

Ms Nicolin Heister: nicolin.heister@corlife.eu

Ms Dr. Carmen Puschmann: carmen.puschmann@corlife.eu

Tel. +49 511 563539 57, Fax: +49 511 563539 55

### 9.8.3 The independent Data Safety Monitoring Board (DSMB)

An independent external Data Safety Monitoring Board has been established to continuously monitor and protect patient safety throughout the clinical study with an emphasis on progress, safety data and critical efficacy endpoints of the clinical study. The Clinical Study Director will closely collaborate with the DSMB throughout the study period and the DSMB will be integrated in the set-up up of the clinical trial including the implementation of the study database. DSMB meetings may be requested by the sponsor, the Coordinator, the EU Project Officer, EGC members or institutional review boards at any time to discuss any safety concerns. The Board will conduct remote reviews throughout the project lifetime and will be invited to participate in SC meetings. All life-threatening severe adverse events (SAE) will be reported immediately to the DSMB in addition to regulatory requirements. In the case of accumulation of severe unexpected adverse events (SUSAR), the DSMB will convene in an extraordinary meeting to advise the sponsor on the continuation, modification, or termination of the study.
The following experts have agreed to join the ARISE DSMB:

Prof. Siegfried Kropf, University of Magdeburg (DE), is head of the Institute for Biometry and Medical Informatics and avails of extensive experience in multi-centre trials in congenital and acquired heart disease with special interest in parametrical and non-parametrical statistical analysis of clinical studies. He also has been involved in Data Safety Monitoring Boards for numerous clinical studies funded by the German Science Foundation and for the German Competence Network for Congenital Heart Defects.

Prof. John Dark, Newcastle University (UK), is Professor of Cardiothoracic Surgery and Consultant Cardiothoracic Surgeon at Newcastle University and Freeman Hospital. He is a specialist for transplantation and member of numerous international working groups dealing with donation, transplantation and ethics. He is a past-President of the European Society for Organ Transplantation and of the International Society for Heart and Lung Transplantation, and serves on the Council of the British Transplantation Society.

Prof. Rune Haaverstad, Haukeland University of Bergen, Norway is head of the Department of Cardiothoracic Surgery and specialist for aortic surgery. He has been involved in numerous heart valve studies dealing with aortic valve replacement and repair and published extensively on aortic valve replacement.

#### 9.8.4 Audits and Inspections

In the event that audits are initiated by competent authorities, the Local Investigator shall allow access to the original medical records to such and provide all requested information.

### 9.9 Limitations of the research methods

The results may be biased due to the open, non-randomized, non-controlled design. The analytical methods (physical examination, echocardiography) are known, established, harmonized by guidelines but not standardized. MRI data are analyzed by the Study Director to avoid subjective factor in the analysis.

However, the limitations can indeed affect but not distort the result. Primary safety endpoints are AR and re-interventions. These endpoints are clearly definable and are not subject to individual interpretation.

### 9.10 Other aspects

None.

## 10. Protection of human subjects

The Surveillance will, as far as applicable, adhere to the regulations that provide the greatest protection to the patient including the requirements set forth in the:

- Declaration of Helsinki;
- Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, as amended; and

- Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, as amended; and
- Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, as amended;
- Laws of the respective country – including regulations of the European Union; and
- Grant Agreement 643597, Deliverable 3.2 Submission package, this includes notice of final study valve approval (PEI), final version of study protocol, study registration number (Clinicaltrials.gov and ENCePP) and ethical approvals required for study start.
- Grant Agreement 643597, Deliverable 3.3 All approvals package, this includes notice of signed study contracts of all participating clinical centres including all ethical approvals and national competent authorities.

## 10.1 Informed Consent and Institutional Review Board (IRB) / Ethics Committee (EC)

For purposes of this Surveillance, and to comply with European Data Protection Laws, written informed consent will be obtained from all patients and/or legal guardians as well as informed assent by participating children. The patient must be adequately informed of his/her participation in the clinical Surveillance and what will be required of him/her in order to comply with the protocol. The patient will be informed that confidentiality and anonymity will be maintained at all times. In addition, informed consent is required to allow appropriate data monitoring including access to medical records by the Sponsor and regulatory agencies. Minors who are capable of discernment, should also sign the informed consent form.

Non-binding examples for the information and informed consent form are given in Annex 1. The centres are encouraged to use the documents that are valid in the relevant country.

The IRB/EC should approve the informed consent and protocol for use at its institution prior to enrolment of the first patient. A written statement by the IRB/EC indicating approval of the informed consent and protocol must be submitted to the Sponsor prior to enrolment. These approvals will be forwarded to the European Commission as they are part of the Grant Agreement.

### 10.2 Insurance for Clinical Subjects

The product ARISE AV, used in this Surveillance, is covered by product liability insurance. Corlife will not provide insurance in addition to such coverage.

## 11. Management and reporting of adverse events/adverse reactions

### 11.1 Adverse Reaction (AR)

An AR is any untoward medical occurrence in a subject which does not necessarily have to have a causal relationship with Surveillance treatment. An AR can therefore be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease, temporary or permanent, whether or not related to the ARISE AV implantation. AR information will be collected throughout the Surveillance. AR (event, date of onset, severity, duration, and relationship to device) should be recorded (Adverse Reaction data) by the Local Investigator.

### 11.2 Serious Adverse Reaction (SAR)

'Serious Adverse Reaction' means an unintended response, including a communicable disease, in the recipient associated with the application of ARISE AV that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity (Article 3 (n), Directive 2004/23/EC).

SAR includes, but is not limited to:

1. death

2. serious deterioration in the health of the subject that
    a. resulted in a life-threatening illness or injury;
    b. resulted in permanent impairment of a body structure or a body function;
    c. required in patient hospitalization or prolongation of existing hospitalization;
    d. resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
    e. led to fetal distress, fetal death or congenital abnormality or birth defect.

### 11.3 Reporting AR

AR are reported in the CRF.

### 11.4 Reporting SAR

The Local Investigator(s) should report any SAR during the investigation to the Sponsor within 24 hours after the Local Investigator(s) first learns of the event. Notification should be done

1. to corlife via Fax. +49 511 563 539 55 or email. SAR notifications to corlife should not include any personal patient data;
2. to the local tissue bank having imported ARISE AV, if applicable;
3. to the local competent authority;
4. to Ethics Committee EC/IRB in accordance with the EC/IRB requirements.

A template for SAR reporting is delivered with each and any ARISE AV. The Sponsor will forward all valve-related SAR to the DSMB.

### 11.5 Autopsy/Death

The Local Investigator shall make reasonable efforts to obtain a copy of the autopsy report and/ or death summary. Information on the cause of death and its

relationship to the Surveillance device should be determined by the Local Investigator and recorded as an SAR. Anonymized copies of an autopsy report, if available, and/or a death summary should be included with the CRF.

### 11.6 Explanted Valves

Patients who have the Surveillance valve explanted are exempt from further follow-up 30 days post-explant. Every effort should be made to return the explanted valve(s) (at autopsy or reoperation) to corlife. Return kits for explanted valves are provided upon request by corlife.

## 12. Plans for disseminating and communicating study results

Corlife will submit the required regulatory reports, such as SAR reports, withdrawal of IRB/E, approvals of the competent authorities, recall information, as applicable.

Corlife will report progress reports to the Local Coordinating Investigators, the DSMB and the EGC.

The final report will be submitted to the Local Coordinating Investigators, the DSMB, the EGC, the competent authorities, the EC/IRB, the ENCEPP and the European Commission.

The Consortium will publish all major results of this Surveillance within 12 months after discharge of the last patient.

Any and all publication of the principal results from any single center experience within the study shall be subject to prior written approval from the coordinator and the publication committee as outline in the Consortium Agreement.

## 13. References

1 Head SJ et al. The European Association for Cardio-Thoracic Surgery (EACTS) database: an introduction. Eur J Cardiothorac Surg. 2013 Sep;44(3):e175-80.

2 Otto CM. Aortic stenosis-listen to the patient, look at the valve. N Engl J Med. 2000 Aug 31;343(9):652-4

3 Emmert MY et al. Transcatheter aortic valve implantation using anatomically oriented, marrow stromal cell-based, stented, tissue-engineered heart valves: technical considerations and implications for translational cell-based heart valve concepts. Eur J Cardiothorac Surg. 2014 Jan;45(1):61-8.

4 Neumann A et al. Heart valve engineering: decellularised allograft matrices in clinical practice. Biomed Tech (Berl). 2013 Oct 1;58(5):453-6.

5 Tudorache I et al.. Orthotopic replacement of aortic heart valves with tissue engineered grafts. Tissue Eng Part A. 2013 Aug;19(15-16):1686-94.

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8 Foryst-Ludwig A et al. Sex differences in physiological cardiac hypertrophy are associated with exercise-mediated changes in energy substrate availability. Am J Physiol Heart Circ Physiol. 2011 Jul;301(1):H115-22.

9 Svensson LG et al. STS guidelines: Aortic valve and ascending aorta guidelines for management and quality measures. Ann Thorac Surg. 2013 Jun;95(6 Suppl):S1-66

10 Heuvelman HJ et al. Pregnancy outcomes in women with aortic valve substitutes. Am J Cardiol. 2013 Feb 1;111(3):382-7.

11 Onorati F et al. Mid-term results of aortic valve surgery in redo scenarios in the current practice: results from the multicentre European RECORD (REdo Cardiac Operation Research Database) initiative. Eur J Cardiothorac Surg. 2014 Mar 30.

12 Cebotari S et al. Clinical application of tissue engineered human heart valves using autologous progenitor cells. Circulation.2006;114:I132-137.

13 Cebotari S et al. Use of fresh decellularised allografts for pulmonary valve replacement may reduce the reoperation rate in children and young adults: Early report. Circulation. 2011;124:S115-123.

## Annex 1. List of stand-alone documents

| # | Document Reference Number | Date | Title |
|---|---|---|---|
| 1 | Appendix 01 | 20.07.2015 | Example for a Patient Information Sheet |
| 2 | Appendix 02 | 20.07.2015 | Example for an Executive Patient Information Sheet |
| 3 | Appendix 03 | 20.07.2015 | Example for a Short Patient Information Sheet |
| 4 | Appendix 04 | 20.07.2015 | Example for an Informed Consent Form to the processing of personal data |
| 6 | Appendix 05 | 20.07.2015 | Case Report Form |
| 7 | Appendix 06 | as amended | Product Liability Insurance |
| 8 | Appendix 07 | as amended | Investigators contact list |

## Annex 2. ENCePP checklist for study protocols

## Annex 3. Additional Information

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