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REVISION HISTORY

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Cardioband - TR

TRI-REPAIR

Tricuspid Regurgitation Repair

with Cardioband Transcatheter System

Protocol ID TR1-1

Rev. 05 - Date: 25 May 2017

Sponsor:

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Confidentiality Statement

Protocol Signatures

Prior to participation in this study, the Principal Investigators must obtain written approval from his/her Ethics Committee, and provide a copy to the Sponsor, Valtech Cardio Ltd., or their authorized representatives, along with the Ethics Committee approved Informed Consent Form.

The Principal Investigator must also:

- Conduct the study in accordance with the study protocol, the Investigator Agreement, the Declaration of Helsinki, Good Clinical Practices, international harmonized standards for clinical investigation of medical devices (ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practices), the laws and regulations of the countries where the study will take place, indemnity / insurance requirements and any other applicable regulations.
- Agree to participate in an appropriate training program as part of the study initiation.
- Assure that informed consent is obtained from each subject prior to enrollment, using the Ethics Committee approved form.
- Assure that the study is not commenced until Ethics Committee approval has been obtained.
- Provide all required data and agree to source document verification of study data with subject's medical records.
- Allow staff of the Sponsor and its authorized representatives, as well as representatives from regulatory agencies, to review, inspect and copy any documents pertaining to this clinical investigation.
- Complete and return all case report forms, study documentation, and relevant imaging assessments promptly to Sponsor and/or the designated core laboratory for data processing.

The Principal Investigator (PI) may delegate one or more of the above functions to an associate or sub-investigator. The PI retains overall responsibility for proper conduct of the study.

Investigators' Signature

I have read and understand the contents of the clinical protocol. I agree to follow and abide by the guidelines set forth in this document.

Principal Investigator _____

Signature: _____ Date: _____

Co-Principal Investigator (If applicable) _____

Signature: _____ Date: _____

Sponsor Signature

Sponsor Representative Name (print): _____

Signature: _____ Date: _____

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1 PROTOCOL SYNOPSIS

Background	The Cardioband Transcatheter System (Cardioband) is a marketed system that was approved for treatment of secondary (functional) mitral regurgitation (FMR) (CE granted on September 2015). The Cardioband is an annuloplasty band that is similar to a surgical annuloplasty, however deployed on the beating heart through a transvenous approach. The CE mark study with 45 subjects has been completed and documented significant reduction of severity of MR and improvement in quality of life by MLHFQ, NYHA and 6-minute walk test, in subjects with moderate to severe MR. The aim of the current study is to evaluate the Cardioband annuloplasty system for repair the Tricuspid Regurgitation (TR).
Sponsor	Valtech Cardio LTD 3 Ariel Sharon Ave. Or Yehuda 60376 Israel Tel: +972-3-5335959 Fax: +972-3-5335578
Study Title	**TRI-REPAIR – Tricuspid Regurgitation Repair with Cardioband Transcatheter System**
Device	The Cardioband Adjustable implant is delivered and anchored to the tricuspid valve annulus by a transfemoral delivery system. The Cardioband will be deployed along the Anterior and posterior annulus of the Tricuspid valve and will be adjusted under trans-esophageal guidance on the beating heart.
Indication for Use	The treatment is for reconstruction and/or repair of pathological tricuspid valves.
Study justification	The current management of tricuspid regurgitation is either conservative (by medication) or by surgery, usually in concomitant with other valves repair or replacement. TR can worsen or appear late after successful mitral valve surgery which portends a poor prognosis. However, standard surgical approaches requiring cardiopulmonary bypass and especially second surgery have an excessive risk. Thus, many patients are denied surgery because of unfavorable risk-benefit balance. Therefore, there is a need for novel devices enabling interventional cardiologists and cardiothoracic surgeons to perform tricuspid annuloplasty by transcatheter methods. Cardioband replicates established surgical techniques (e.g., annuloplasty) using transfemoral approach, without sutures and with adjusted on the beating heart. Similar to the approved indication for mitral annuloplasty. The Cardioband system is

	expected to allow for treatment of patients that would otherwise not undergo Tricuspid valve repair due to the invasiveness of current techniques.
Study Design	Prospective, single-arm, multi-center study.
Objectives	To assess the safety and technical success of the Cardioband system for the treatment of symptomatic chronic functional tricuspid regurgitation.
Primary Safety Endpoint	Overall rate of Major Serious Adverse Events (MSAEs)* and serious adverse device effects (SADE) until hospital discharge and at post-operative 30 days. * Death, myocardial infarction, cardiac tamponade, device related cardiac surgery, stroke
Primary Technical Endpoint	Successful access, deployment and positioning of the Cardioband device and septolateral reduction at intraprocedure and discharge.
Secondary Endpoints	• TR grade, EROA and Regurgitant Volume (by Echocardigraphy) • Tricuspid annular plane systolic excursion (TAPSE) • Technical success • NYHA classification • 6-Minute Walk Distance (6MWD) • Kansas City Cardiomyopathy Questionnaire (KCCQ) • LVEF • LVEDVI • LVESVI • NT-pro BNP • Diuretic Therapy • GOT, GPT (ALT), and Bilirubin • BUN Creatinine clearance • Activity by wearable device Endpoints will be measured at discharge 1,6,12 and 24 months post procedure and will be compared to baseline
Number of Subjects	60 subjects
Investigational Sites	6 sites in Europe
Inclusion Criteria	1. Chronic functional tricuspid regurgitation (FTR) 2+ to 4+ on a scale of 4+ (moderate to severe) with annular diameter ≥ 40 mm with valve Systolic pulmonary pressure (sPAP) ≤ 60mmHg 2. ≥18 years old

	3. New York Heart Association (NYHA) Class II-IVa 4. Symptomatic despite Guideline Directed Medical Therapy (GDMT); at minimum patient on diuretic regimen 5. LVEF ≥ 30% 6. Patient is willing and able to comply with all specified study evaluations 7. The Local Site Heart Team concur that surgery will not be offered as a treatment option 8. Transfemoral access of the Cardioband is determined to be feasible
Exclusion Criteria	1. Aortic, mitral and/or pulmonic valve stenosis and/or regurgitation ≥ moderate 2. Severe uncontrolled hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mm Hg) 3. Previous tricuspid valve repair or replacement 4. Presence of trans-tricuspid pacemaker or defibrillator leads which cause impingement of the tricuspid valve leaflet as evaluated by echocardiography. 5. Active endocarditis 6. MI or known unstable angina within the 30 days prior to the index procedure 7. Any PCI or transcatheter valvular intervention within 30 days prior to the index procedure 8. Hemodynamic instability or on IV inotropes 9. Cerebrovascular Accident (CVA) within the past 6 months 10. Subject is on chronic dialysis 11. Anemia (Hb < 9 g/L) not corrected by transfusion 12. Bleeding disorders or hypercoaguable state 13. Active peptic ulcer or active gastrointestinal (GI) bleeding 14. Contraindication to anticoagulants 15. Known allergy to stainless steel, nickel, and/or polyester 16. Pregnant or lactating; or female of childbearing potential with a positive pregnancy test 24 hours before any study-related radiation exposure 17. In the judgment of the Investigator, co-morbid condition(s) that could limit the subject's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study 18. Life expectancy of less than 12 months 19. Impaired judgment and/or is undergoing emergency treatment 20. Currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study

	21. intra-cardiac masses, thrombi or vegetations 22. Patients with cardiac cachexia 23. Subjects in whom transesophageal echocardiography is contraindicated 24. Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically 25. Untreated clinically significant CAD requiring revascularization 26. Echocardiographic evidence of severe right ventricular dysfunction 27. Any coronary or endovascular surgery, within 3 months prior to procedure
Procedure	The system will be delivered percutaneously via the femoral vein. The procedure will be guided by fluoroscopy and trans-esophageal / intracardiac echocardiography
Follow-Up Schedule	1 month: 30 ± 14 days 6 Months: 180 ± 30 days 12 Months: 365 ± 30 days 24 Months: 730 ± 30 days Subjects in whom no devices are implanted will be followed for 6 months.
Follow Up Evaluations	Key Pre-Implantation Procedures: 1. History and Physical 2. TTE , TEE and/or CT angiography and/or MRI 3. 6 minute walk test 4. KCCQ Key Post-Procedure Procedures: 1. Serial AE assessment, history, and physical at 30 days, 6 months, 12 months, 24 months) 2. Serial TTEs (30 days, 6 months, 12 months, 24 months) 3. Cardiac MRI at 6 months (optional) 4. 6 minute walk tests (30 days, 6 months, 12 months, 24 months) 5. KCCQ
Clinical Event Committee	An independent Clinical Event Committee will adjudicate all Serious Adverse events.
First subject in Last subject in	[redacted] [redacted]

Last follow-up	[redacted]

2 LIST OF ABBREVIATIONS

ACC/AHA	American College of Cardiology/ American Heart Association	KCCQ	Kansas City Cardiomyopathy Questionnaire
CABG	Coronary artery bypass graft	LV	Left Ventricle
CAD	Coronary artery disease	LVEDV	Left Ventricle End Diastolic Volume
CEC	Clinical Events Committee	LVESV	Left Ventricle End Systolic Volume
CHF	Congestive Heart Failure	6MWT	6 minute walk test
CPB	Cardiopulmonary bypass	MI	Myocardial infarction
CRT	Cardiac Resynchronization Therapy	MLHFQ	Minnesota living with heart failure questionnaire
EC	Ethics Committee	MR	Mitral regurgitation
eCRF	Electronic Case Report Form	MRI	Magnetic Resonance Imaging
EF	Ejection fraction	MSCT	Multislice computed tomography
FDA	Food and Drug Administration	NYHA	New York Heart Association
GCP	Good Clinical Practice	TEE	Transesophageal echocardiography
GLP	Good Laboratory Practices	TTE	Transthoracic echocardiography
GMP	Good Manufacturing Practices	TR	Tricuspid Regurgitation
ICH	International Conference on Harmonization	TV	Tricuspid Valve
IFU	Instructions for use		

3 INTRODUCTION

3.1 Tricuspid regurgitation: a "forgotten" problem

Tricuspid Regurgitation (TR) is a disorder of the heart in which the Tricuspid valve, that separates the right atrium from the right ventricle, does not close properly during systole. TR is a frequent life threatening condition associated with heart failure and poor prognosis.

TR is a poor prognostic factor. Presence of significant TR is indecently associated with about two fold increase in the risk, in heart failure patients[1,2] Topilsky et al in a study involved 353 patients with isolated TR have showed that the outcome of isolated severe functional TR, independently of other cardiovascular or comorbid conditions, is characterized by excess mortality and excess cardiac events [3]

Significant TR is estimated to occur in more than 1.6 million people in the United States and less <1% of patients with moderate or severe TR undergo surgery annually [3,4] despite a 1-year mortality rate of 36.1% (Figure 1) vast majority of cases are managed conservatively due to the still evolving understanding of the disease Figure 1[5,6,7].

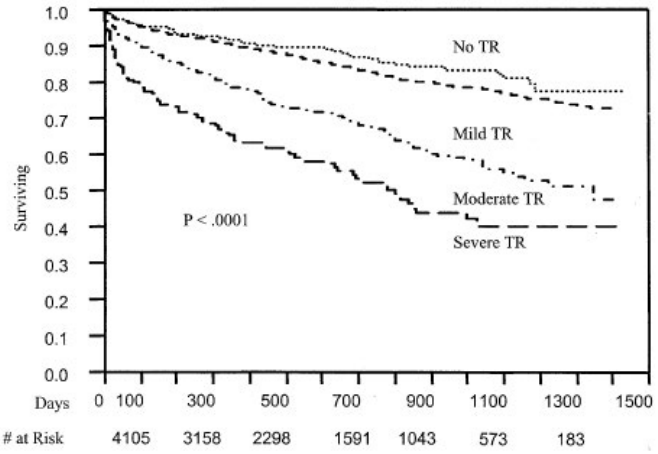

Figure 1. Kaplan-Meier survival curves for all patients with tricuspid

Figure 1: Kaplan-Meier survival curve for patients with Tricuspid regurgitation (TR). Survival is significantly worth in patients with moderate and severe TR.

It is not surprising then, that the both the ESC and AHA have changed their guidelines in recent years and urge physicians to treat TR at an earlier stage in patients with concomitant left side valve pathology requiring surgery (Figure 2) [8,9] Recent reports also show a decrease in mortality in patients treated for isolated TR at an early stage, before they suffer NYHA IV cardiac failure [3,11] Appropriate patient selection and proper timing for repair or replacement are crucial for optimal outcome, but objective criteria for clinical decision-making remain poorly defined.

	ESC/EACTS	AHA/ACC
Primary TR		
Symptomatic isolated severe TR without severe RV dysfunction	I	IIa
Severe TR undergoing left- side surgery	I	I
Moderate TR undergoing left- side surgery	IIa	Not mentioned
Asymptomatic isolated mild or moderate TR and progressive RV dilatation or RV function deterioration	IIa	IIb (only in severe TR)
Secondary TR		
Severe TR undergoing left- side surgery	I	I
Mild – moderate TR with dilated annulus (≥40 mm or >21 mm/m^2) undergoing left- side surgery	IIa	IIa (only with progressive RV dilatation or prior right heart failure)
Moderate TR and PH undergoing left- side surgery	Not mentioned	IIb
Persistent or recurrent severe TR after left – side valve surgery		
Severe TR symptomatic, progressive RV dilatation, or RV function deterioration, but without severe RV or LV dysfunction, left- sided valve dysfunction and severe PH	IIa	
Severe TR symptomatic without PH or severe RV dysfunction		IIb

Figure 2: Comparison of European and American Guidelines for treatment of tricuspid regurgitation (8, 9)

Tricuspid regurgitation etiology has been categorized to primary (Organic) and secondary or functional (FTR) (**Table 1**). The main etiologies of primary TR that accounts for only 8–10% of all severe TRs, include rheumatic disease, congenital abnormalities, endocarditis and trauma [8, 9]. There are also a variety of metabolic, enzymatic, or pharmacologic abnormalities associated with TR [12]. Functional TR (FTR) is defined as regurgitation without any identifiable structural damage to the Tricuspid valve, leaflets, or chords. FTR usually occurs in the presence of pulmonary artery hypertension from any cause (most commonly from elevated left sided pressures), RV enlargement, and tricuspid annular dilatation [13, 14]. With the decreasing prevalence of rheumatic disease, FTR is proportionally more common and accounts for most of observed cases of severe TR [14, 15].

Primary tricuspid valve disease	
Congenital	Ebstein's anomaly
	Congenital cleft valve
	Congenital tricuspid stenosis
	Tricuspid atresia
Acquired	
	Rheumatic
	Infective endocarditis
	Degenerative. Tricuspid valve prolapse
	Carcinoid heart disease
	Toxic (eg, Phen-Fen or methysergide valvulopathy)
	Tumors (eg, fibroelastoma, myxoma)
	Trauma
	Latrogenic (eg, pacemaker lead trauma, radiation injury, biopsy instrument)
Secondary or functional tricuspid valve disease	
	Right ventricular dilatation (eg, atrial septal defect, Pulmonary regurgitation)
	Right ventricular hypertension (eg, pulmonary hypertension, pulmonary stenosis)
	Right ventricular dysfunction (eg, cardiomyopathy, myocarditis)
	Segmental right ventricular dysfunction (eg, ischemia or infarction, endomyocardial fibrosis, arrhythmogenic right ventricular dysplasia)
	Chronic atrial fibrillation (asymmetric tethering leads to eccentric jet)

Table 1: Ethology of tricuspid regurgitation

Dilation of the TA occurs mainly in its anterior and posterior sides (Figure 3) corresponding to the free wall of the right ventricle, while the dilation of the septal segment is limited because of its close anatomical relationship with the fibrous skeleton of the heart [15].

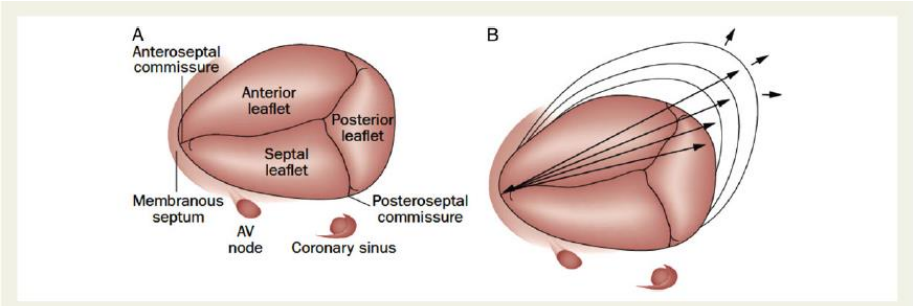

Figure 3: anatomy of the tricuspid valve
A) Normal tricuspid valve. (B) Asymmetric dilation and deformation of the tricuspid annulus leading to tricuspid regurgitation. Adapted from Shinn and Schaff [16].

3.2 Limitations of available treatment

The current treatment is either conservative or surgical. The conservative, mostly medical therapy is usually intended to treat the underlying etiology of TR, such as right heart failure, pulmonary hypertension, and underlying lung disease and include diuretics, pulmonary vasculature vasodilates, or treatment used to improve lung function, respectively. Surgical treatment is performed in some cases however, even after the guidelines have expanded the indications for TR treatment, they are poorly defined and these patients seem to be under-treated [17], most probably due to high morbidity and mortality related to TV surgery, especially in those patients who already underwent cardiac surgery. Most of the surgeons prefer to repair the TV rather than replacing it [9] especially in the FTR.

As for TV repair, there are 4 main surgical techniques; Kay repair, De Vega, Clover (degenerative) and annuloplasty (Figure 4). The Kay repair is a simple and validated solution [11] in which a bi-cuspidation of the TV accomplished by placating the annulus along the posterior leaflet. The sutures are tied, obliterating the posterior leaflet and thus, creating a bicuspid valve. The De-Vega technique used to be one of the most common procedures for TV repair, where a single "purse-ring" suture is placed around the tricuspid annulus, avoiding the area of the atrioventricular node. The suture is tied, completing the annuloplasty. The 'Clover' repair is a technique in which the central part of the free edges of the tricuspid leaflets are stitching together, producing a 'clover'-shaped valve. This technique which is reserved mainly for degenerative TR with valve prolapse.

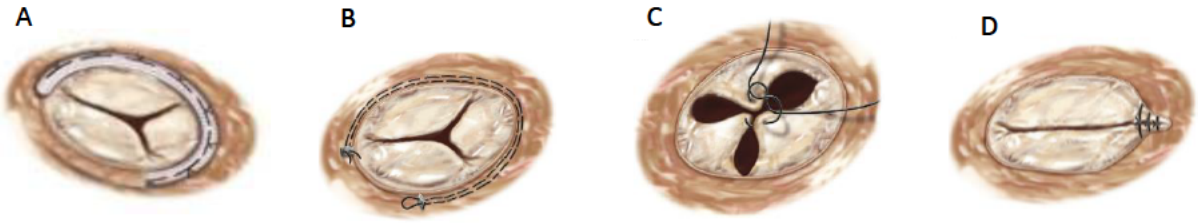

Figure 4: Tricuspid surgical repair technics .A Annuloplasty. B De-Vega technique C. Clover repair D. Kay repair

3.3 Tricuspid repair with ring annuloplasty

The standard **repair treatment** for Tricuspid regurgitation (TR) in either degenerative or functional disease is performed during an open-heart surgical operation and usually consists of placement of an annuloplasty ring. Remodelling the annulus by ring annuloplasty after Tricuspid valve repair is essential to a complete and long-lasting repair. Traditionally the same annuloplasty rings could be used both for mitral and for Tricuspid annuloplasty. However in order to avoid the risk of injury to the conduction system and aortic root a specific rings were specifically designed for Tricuspid regurgitation repair as "C" shape instead of a full "D" shape ring.
Annuloplasty repair results were found to be superior over De Vega and modified De Vega technics [18, 19, 20], and therefore annuloplasty is the method of choice for surgical Tricuspid repair. Variety of commercial annuloplasty rings/bans are available for commercial use (**Table 2**) full rings such as Duran were adjusted to open ring in order to avoid suturing at the coronaries and Aortic area.

Ring/band	Approved for use	reference
Contour 3D (Medtronic)	CE, FDA	21
MC3 (Edwards)	CE, FDA	22
Duran (Medtronic)	CE, FDA	23
Carpentier-Edwards Physio Tricuspid Annuloplasty Ring (Edwards)	CE, FDA	24
Koehler band (Koehler Medical LTD)	N/A	25

Table 2: Commercially available surgical Tricuspid annuloplasty rings

3.4 Tricuspid regurgitation in the context of mitral valve disease

Tricuspid regurgitation in the context of mitral valve disease is frequent and is associated with substantial reduction in survival and quality of life. In many patients, the correction of left-sided cardiac lesions does not lead to resolution of tricuspid regurgitation. Significant tricuspid regurgitation after mitral valve surgery portends a poor prognosis, a course that is often not altered by subsequent surgical therapy [26]. Moreover TR can worsen and even appear late after successful mitral valve surgery, which portends a poor prognosis [27].

Patients who have severe TR at the time of MV surgery should have their TV repaired at the time of the initial MV surgery [8, 9]. In patients with less than severe TR, however, TR might progress after surgery if the TV is left untreated. Matsuyama et al. reported significant TR (at least grade 3) on echocardiography performed late after MVR in 37% of the patients with grade 2 TR before surgery [28]. In addition, Tricuspid regurgitation is frequently and exist in one-third of the patients with mitral stenosis [29, 30], and after MVR for rheumatic disease [3132, 32]. In 14%, TR occurred in the absence of significant left heart disease, pulmonary hypertension, or obvious organic TV disease[31]. TR is diagnosed late after MVR, 10 years on average after the initial surgery [31, 32]. Although late TR has most often been reported in patients with rheumatic heart disease, it is not confined to rheumatic patients [33, 34, 35]. Moderate or severe TR was reported in as many as 74% of patients 3 years after surgical repair of ischemic MR [35]. De Bonis et al. reported 14% grade 3 or more TR in patients who had surgery for functional MR secondary to dilated cardiomyopathy (70% ischemic and 30% nonischemic), and those patients had concomitant TV repair [34]. Grade 3 or more TR was still present in 22% of the patients 3.5 years after surgery. Dreyfus et al. reported 34% late TR (grade 3 or 4) in a group of 163 patients with a mixed etiology for MR who were followed for 5 years after MV repair [35[35]. Tricuspid regurgitation after MVR predicts poor outcome [28, 36] reported the risk factors for heart failure and death in 708 patients after MVR. Moderate-to-severe TR on echocardiography during follow-up was an independent predictor of New York Heart Association functional class III or IV heart failure, heart failure-related death, and even all-cause mortality during the 5 years of follow-up.

Tricuspid regurgitation is also a predictor of poor outcome in patients undergoing balloon mitral valvotomy for mitral stenosis. Patients with pre-procedural severe TR have more severe MV disease, higher pulmonary vascular resistance, a smaller increase in MV area after valvotomy, as well as poorer outcome: lower overall survival, more heart failure, and need for repeat valvotomy or MVR (Figure 5).

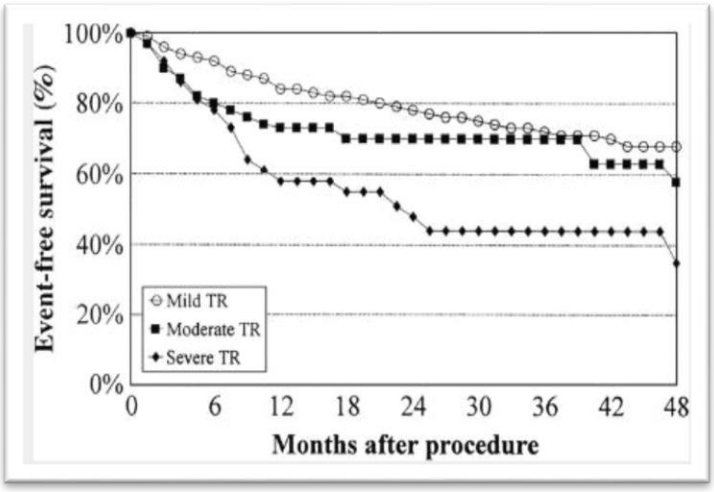

Figure 5: Event free survival after balloon mitral valvotomy by TR severity Events were defined as death, New York Heart Association functional class III or IV, MV surgery, or repeat mitral valve balloon valvotomy (n = 318). Patients with severe tricuspid regurgitation (TR) had significantly worse event-free survival compared with patients with mild TR. Reprinted, with permission, from Sagie et al [37].

patients with severe TR after MVR undergoing isolated TR surgery usually have a poor outcome with high perioperative mortality that might reach 50%, but it was usually reported between 11% and 20% [38, 39, 40, 41, 16] The great risk with TV surgery, especially in prior cardiotomy patients, leaves these patients under-treated. Percutaneous intervention that entails low procedural risks together with the possibility of fixing or replacing the vale could indeed have an important role in the treatment of this large group of patients.

3.5 Similarities between Mitral and Tricuspid

The mitral and Tricuspid valves or the atrioventricular valves are similar both in structure and in function; both controls the flow of blood from the atria into the ventricles. During systole, the valvar leaflets, which bulge toward the atrium, stay pressed together throughout the contraction, and therefore do not prolapse. During diastole, when the ventricles are relaxing, the atrioventricular valves open to allow the flow of blood to fill the ventricles. The atrioventricular valvar complex has four main components, namely the annulus, leaflets, tendinous cords, and papillary muscles [142]. Carpentier described the mitral valve as consisting of two opposing leaflets while the tricuspid valve normally possesses three distinct leaflets, which traditionally are described as being anterior, posterior, and septal (Figure 6). It is natural then, that they will also share the pathogenesis of regurgitation or insufficiency. For example, in patients with pulmonary hypertension (functional TR), the right ventricle becomes globular, leading to tethering of tricuspid leaflets, similar to functional mitral regurgitation. Regurgitation of flow across the atrioventricular valves can further be sub-

classified into functional and degenerative. Degenerative (primary) incompetence is considered to be a disease of the valve itself while functional regurgitation is usually considered to be a disease of the ventricles. The gold standard treatment for atrioventricular valves incompetence is by surgical repair or replacement. Surgical treatment for pathologies of the atrioventricular valves has been shown to improve overall survival when compared to medical therapy alone, particularly in the case of degenerative mitral regurgitation [43]. In case of repair, the surgeon will usually place an annuloplasty ring to reduce and maintain the overall circumference of the valve.

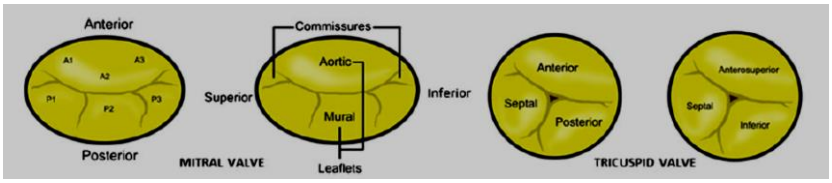

Figure 6: The atreoventricular valves leaflet. The mitral valve on the left and the tricuspid valve on the right. (Adopted from Carpentier 1976)

Due to the invasive nature of surgery, and the common co-morbidities associated with this population, there are significantly number of patients that often biases against surgical intervention, particularly for those who are in excessive high risk for surgery and therefore transcatheter therapies are required to meet the broad clinical needs.

3.6 Transcatheter valve repair

In the past decade, transcatheter aortic valve replacement (TAVR) has widely adopted intervention that replaced surgical AVR [4445]. The success of TAVR has stimulated attempts at transcatheter mitral valve replacement (TMVR) for percutaneous treatment of mitral regurgitation (MR). This has proven to be far more complex than TAVR, however there are several devices that are approved for Mitral valve repair; The Mitraclip device (Mitraclip, Abbott Vascular, Santa Rosa, California) is available for use in the EU and lately received U.S. Food and Drug Administration approval. The Cardioband device (Valtech cardio LTD, Or Yehuda, Israel) was also recently approved in the EU [46, 47]. First-in-human testing has begun also for transcatheter Mitral valve replacement [48]. The next attention therefore is the "forgotten valve", the tricuspid valve.
Today, there is no designated system for transcutaneous repair of TR approved for clinical use. Few have reported their experience with Valve in Valve repair, using devices designed for TAVR inserted into a prosthetic tricuspid valve via a the SVC an49d IVC [49].

Lauren Et al. reported the successful implantation of a self-expandable tubular stent tailored to the dimensions of the inferior vena cava at the landing zone with significant reduction in IVC pressures [50]. Similar attempt was done with the Sapien XT valve. It is important to notice that such and intervention leads to ventricularisation of the RV and cause severe deterioration for patients with severe RV heart failure. A first in human report of the use of the Mitralign system (Mitralign Tewksbury, Massachusetts) in a trans jugular approach to treat TR was recently published using a technique that eventually causes bi-cuspidalisation of TV valve and reduction of annulus dimension [51].As Cardioband is the only commercially available direct annuloplasty device that mimic the surgical approach with transcatheter techniques, it is natural to test the use of Cardioband for Tricuspid annuloplasty.

The Cardioband Transcatheter System (Valtech cardio LTD) is currently indicated for the treatment of secondary (functional) mitral regurgitation (FMR). The Cardioband is direct annuloplasty transcatheter system, deployed on the beating heart through a transvenous approach. The implant is deployed along the posterior annulus of the mitral valve and is adjusted under trans-esophageal guidance on the beating heart. A CE mark study has been completed and documented reduction of severity of MR and improvement in functional tests in subjects with moderate to severe MR [4646]. As the Cardioband delivery system enables catheter movement in few dimensions the same delivery system can be used to implant the same annuloplasty band in the right side for repair of Tricuspid regurgitation. Catheter used directions are demonstrated in Figure 7.

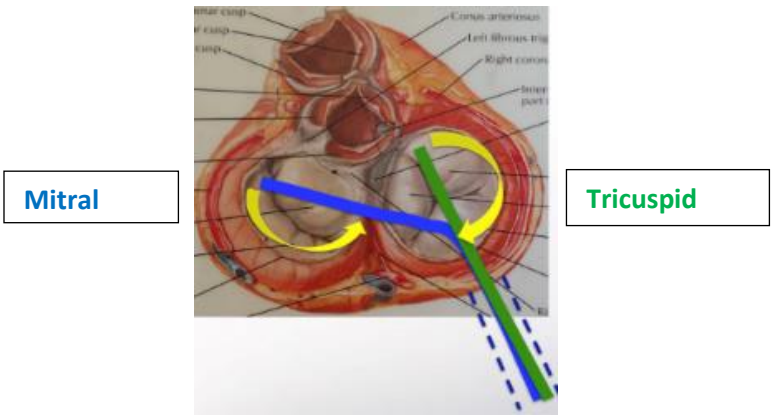

Figure 7: Cardioband system can be used for Mitral and Tricuspid annuloplasty

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4 CARDIOBAND TR ADJUSTABLE ANNULOPLASTY SYSTEM

4.1 Intended Use

Cardioband TR reconstruction System is indicated for the reconstruction and/or repair of pathological Tricuspid valves.

4.2 General Description

The Cardioband Transfemoral (TF) Delivery system is designed to introduce and deploy the Cardioband implant in the appropriate location along the tricuspid annulus and then adjust the Cardioband implant in order to narrow the annulus.

4.2.1 Cardioband Implant

Cardioband implant is an adjustable annuloplasty band designed for valve repair by transfemoral procedure.

The Cardioband implant is deployed and fixated along the anterior - posterior annulus and is then adjusted to remodel the tricuspid valve.

The Cardioband implant consists of a contraction wire and polyester fabric covering that are attached to an Adjustment mechanism. The polyester covering is marked with radio-opaque (RO) markers at

set distances along the implant. The Implant guidewire is connected to the adjustment mechanism of each implant in order to enable over-the-wire adjustment after implantation.

4.2.2 The Cardioband Adjustable System

The Cardioband System consists of the following main parts:

1. ***Cardioband implant*** (Figure 8, Figure 9)

2. ***Cardioband Delivery System*** (Figure 10) is a transfemoral delivery system, designed to introduce and deploy the Cardioband implant in the appropriate location along the annulus and then adjust the Cardioband implant. The Delivery system consists of the following main parts:
   a. Transfemoral Steerable Sheath (TSS)
   b. Dilator, used for introduction of the TSS to the femoral vein and left atrium.
   c. Implant Delivery System (IDS), which includes a Guide Catheter (GC) and an Implant Catheter.
   d. Size Adjustment Tool.

3. ***Anchor Drives***

[redacted]

For additional details, please refer to Instructions for Use [redacted].

[redacted]

4.4 Justification of the clinical investigation

Currently the best option for Tricuspid regurgitation is repairing the valve with an "annuloplasty ring" in an open heart surgery, usually in concomitant with mitral or other valve repair. Occasionally however the patients are in too high risk for operation, the risk of reoperation is extremely high and has been reported to reach up to 20% mortality [32, 33, 3435]. Cardioband proposes a non-invasive, fully adjustable, direct annuloplasty repair. The evidence presented above indicates that Cardioband

1) lower surgical risks of operation and re-operation by using established transfemoral techniques
2) Enable a significant reduction of the mitral septo-lateral annulus, and therefore MR reduction
3) Enable fine-tuning of the repair by adjusting the device size on a beating heart per the patient anatomy

Cardioband for treatment of Tricuspid repair targets an unmet clinical need, in that the device is based on established surgical devices, and is expected to allow for treatment of patients that would otherwise not undergo Tricuspid valve repair due to the invasiveness of current techniques. Given these potential benefits, and the favourable safety profile of the Cardioband device for MR repair there is ample justification for a prospective investigation focusing on the clinical performance and safety of the Cardioband system for tricuspid regurgitation valve repair.

5 INVESTIGATION DESIGN & ENDPOINTS

5.1 Clinical Study Overview

This clinical investigation is a single arm, multi-center, prospective study with intra-patient comparisons.
Candidates for Cardioband TR treatment are symptomatic patients with functional tricuspid valve repair. Patients are selected upon clinical conditions and severity of TR. Anatomical feasibility is assessed by Echocardiography and/or other exams (such as CT and angiography) according to the site common practice. Patients will be screened and enrolled according to the study inclusion and exclusion criteria.

Patients will undergo tricuspid valve repair with Cardioband implanted via transcatheter procedure under Transoesophageal / Intracardiac echocardiography (TEE/ICE) and fluoroscopy guidance. Post-procedure clinical care will be performed according to standard management of valve repair; Clinical follow-up including standard post-procedural management of surgical valve repair and Transthoracic Echo (TTE) assessment of the degree of Tricuspid regurgitation will be obtained at hospital discharge, 30 days, 6, 12 and 24 months post-index procedure.

As the follow up at 30 days is of most importance in terms of the patient's safety: The first 3 patients will have to complete 30 days follow up before the recruitment of additional patients. In related to the first 3 patients, recruitment will continue in case of elongated hospitalization or complications that are unrelated to the study device as will be judge by the study clinical event committee.

5.2 Study objectives

The objective of this study is to assess the safety and technical success of the Cardioband system for the treatment of symptomatic chronic functional tricuspid regurgitation.

5.3 Study Endpoints

5.3.1 Primary endpoints

Safety:
Overall rate of Major Serious Adverse Events (MSAEs)* and serious adverse device effects (SADE) until hospital discharge and at post-operative 30 days.
* Death, myocardial infarction, cardiac tamponade, device related cardiac surgery, stroke.

Technical Success:
Successful access, deployment and positioning of the Cardioband device and septolateral reduction at intra-procedure and discharge

5.3.2 Secondary endpoints

- TR grade, EROA and Regurgitant Volume (by Echocardigraphy)
- Tricuspid annular plane systolic excursion (TAPSE)
- Technical success
- NYHA classification
- 6-Minute Walk Distance (6MWD)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- LVEF
- LVEDVI
- LVESVI
- NT-pro BNP
- Diuretic Therapy
- GOT, GPT (ALT), and Bilirubin
- BUN Creatinine clearance
- Activity by wearable device

Endpoints will be measured at discharge, 1, 6, 12 and 24 months post procedure and will be compared to baseline

5.4 Study Stopping Criteria

The study will be stopped if in the first 5 patients up to 2 patients will experience one of the following serious adverse device effects:

- Death
- Need for operation/band replacement

The same stopping criteria will be applied to the total study population as it follows:

Device-related SADE and study stopping criteria

SADE	5 pts	10 pts	20	30
Death or need for emergency operation	2	2	3	3

Events will be assessed by an independent clinical event committee (CEC).

In case of early termination of the investigation all the relevant parties will be promptly informed by the sponsor with a report of the reasons of this early termination.

5.5 Statistical Considerations

5.5.1 Sample size

A sample size of up to 60 patients, enrolled in this proposed multi-center study, is considered adequate to further confirm the safety and performance of the Cardioband System in TR patients. Considerable clinical data on the safety of clinically equivalent devices exists, this will enable a comparison of the clinical data obtained in this study of the safety and performance of the Cardioband System, with literature data from prior studies.

5.5.2 Sample size Justification

Reference values for calculations are based on a literature review of predicate devices [redacted] and clinical experience in previous studies of Valtech adjustable mitral annuloplasty devices [redacted].
Therefore, this sample size allows accurate estimates of risk associated with the device even for rare events.

The sample size for the study was selected through the width of the two-sided exact 95% confidence interval of the potential adverse event rates. [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Rates for anticipated complications (adverse events) will be compared with historical data on morbidity and mortality in similar populations and for analogous devices.

5.5.3 Analysis of performance and safety endpoints

The performance and safety endpoints of the Cardioband System will be assessed by recording the echocardiographic parameters and by monitoring the patient clinical status. Safety assessments will consist of recording of all adverse events, and regular monitoring of haematology and blood chemistry parameters, and vital signs. These parameters are evaluated during the patients' follow-up visits.
Study results will be presented in tabular format. Two sided 95% exact confidence intervals will be presented where required. Continuous variables will be summarized by a mean, standard

deviation, minimum, median and maximum. Categorical variables will be summarized by a count and percentage. If statistical tests will be done the significance level will be equal to or lower than 5%. Nominal p-values will be presented. Where confidence limits are appropriate, the confidence level will be 95%.
Baseline demographic and other baseline characteristics, together with safety analyses will be performed on all subjects.

The numbers of subjects who entered and completed each visit of the study will be provided, as well as the reasons for all discontinuations, grouped by major reason (e.g., lost to follow-up, adverse event, etc.). A list of discontinued subjects, protocol deviations, and subjects excluded from the efficacy analysis will be provided.

Descriptive statistics will be provided for the efficacy and safety outcome results.

The analysis of all adverse events will include incidence tables and incidence tables by severity, relationship to treatment and baseline parameters. Serious adverse events will be listed and discussed individually.

6 SUBJECT ENROLMENT

The inclusion and exclusion criteria listed below must be used for the purpose of enrolling patients into this clinical investigation.

6.1 Inclusion criteria

Patients who participate in this study must meet all of the following inclusion criteria:

1. chronic functional tricuspid regurgitation (FTR) 2+ to 4+ on a scale of 4+ (moderate to severe) with annular diameter ≥ 40 mm with valve Systolic pulmonary pressure (sPAP) ≤ 60mmHg
2. ≥18 years old
3. New York Heart Association (NYHA) Class II-IVa
4. Symptomatic despite Guideline Directed Medical Therapy (GDMT); at minimum patient on diuretic regimen
5. LVEF ≥ 30%
6. Patient is willing and able to comply with all specified study evaluations
7. The Local Site Heart Team concur that surgery will not be offered as a treatment option
8. Transfemoral access of the Cardioband is determined to be feasible

6.2 Exclusion criteria

Patients who fulfill any of the following criteria may not participate in this study.

1. Aortic, mitral and/or pulmonic valve stenosis and/or regurgitation ≥ moderate
2. Severe uncontrolled hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mm Hg)
3. Previous tricuspid valve repair or replacement
4. Presence of trans-tricuspid pacemaker or defibrillator leads which which cause impingement of the tricuspid valve leaflet as evaluated by echocardiography.

5. Active endocarditis
6. MI or known unstable angina within the 30 days prior to the index procedure
7. Any PCI or transcatheter valvular intervention within 30 days prior to the index procedure
8. Hemodynamic instability or on IV inotropes
9. Cerebrovascular Accident (CVA) within the past 6 months
10. Subject is on chronic dialysis
11. Anemia (Hb < 9 g/L) not corrected by transfusion
12. Bleeding disorders or hypercoaguable state
13. Active peptic ulcer or active gastrointestinal (GI) bleeding
14. Contraindication to anticoagulants
15. Known allergy to stainless steel, nickel, and/or polyester
16. Pregnant or lactating; or female of childbearing potential with a positive pregnancy test 24 hours before any study-related radiation exposure
17. In the judgment of the Investigator, co-morbid condition(s) that could limit the subject's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study
18. Life expectancy of less than 12 months
19. Impaired judgment and/or is undergoing emergency treatment
20. Currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study
21. intra-cardiac masses, thrombi or vegetations
22. Patients with cardiac cachexia
23. Subjects in whom transesophageal echocardiography is contraindicated
24. Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically
25. Untreated clinically significant CAD requiring revascularization
26. Echocardiographic evidence of severe right ventricular dysfunction
27. Any coronary or endovascular surgery, within 3 months prior to procedure

[redacted]

6.4 Echocardiographic imaging

Echocardiographic data will be collected from the TEE and TTE images for the corelab interpretation of the degree of TR reduction and adverse events, if any. A physician or sonographer familiar with valvular heart disease and experienced in performing echocardiograms should perform each assessment. [redacted]

[redacted]

6.5 Subject withdrawal

6.5.1 Withdrawal

Subjects may withdraw from the study at any time for any reason, according to the terms of the Informed Consent document, which includes continuation of clinical study follow-up whenever possible, and ongoing medical care as appropriate. Subjects may also be withdrawn from the study at any time at the discretion of the investigator.

It should be understood that an excessive rate of withdrawals could render the study difficult to interpret. Hence, unnecessary withdrawal of subjects should be avoided. Should a subject withdraw or is withdrawn, every effort must be made to complete and report the observations as thoroughly as possible. If possible, in case of withdrawal, permission for yearly study telephone follow up to assess long-term outcomes and safety will be obtained from the subject.

6.5.2 Procedures for handling withdrawal

Subjects who withdraw or are withdrawn from the study should:

- Have the reason(s) for their withdrawal recorded (if possible).
- May be seen by an investigator and all final assessments should be performed and recorded.
- Be asked about the presence of any AEs. If an ongoing AE if present, the patient should be followed up until satisfactory clinical resolution of the event is achieved.

If a subject is withdrawn, Valtech monitor should be informed as soon as possible by the site. One additional subject will be enrolled for each subject withdrawn (or died) for any reason before the primary endpoint period completed.

For each patient with missing significant data for the primary endpoint, such as data regarding performance (access, deployment and positioning) of the Cardioband device, and/ or missing an Echocardiography, an additional patient will be recruited.

6.5.3 Lost to follow up

If a subject does not appear for a follow-up visit and cannot be contacted for collecting follow-up information the primary physician will be contacted and will be asked about the subject's health condition. At least 3 attempts should be made to contact the subject through all available routes attempt to contact the patient should be recorded. If there is no contact with the patients and/or primary physician - he/she will be considered 'lost to follow up'. One additional subject may be enrolled for each lost to follow up before the primary endpoint period completed.

6.6 Screening failure

A screening failure will be defined as patient who fulfilled the theoretical eligibility criteria, and was intended to treat, however Cardioband was not be implanted due to new information detected at the time of procedure, preventing the implantation. A screening failure will be followed until discharge from hospital.

7 STUDY VISITS AND PROCEDURES

The study will commence following institutional medical ethics committee and regional competent authority approval. Study evaluation continues until 24 months of follow up post implantation has been obtained on all available participating subjects.

Screening of patients will be performed according to the hospital standard screening for tricuspid valve repair and replacement. In addition, patients will be screened for their suitability for Cardioband therapy. A central eligibility committee will be established to determine final enrolment of patients across all investigational sites. The eligibility committee will include at least a Heart Failure specialist, and an Echocardiography specialist. Patients will give a written consent for health information release prior to screening process. The treatment procedure will be performed according to the instructions outlined in the current approved IFU.

Data will be collected at the following time points (as expected in the course of a surgical treatment): baseline, procedure, discharge and clinical follow-up at 30 days, 6 months, 12 months and 24 months from index procedure. Data from any other additional time points may be collected and analyzed if available.

The procedures associated with each study visit are outlined and summarized in **Table 4**.

Procedure	Screening	Baseline	Implantation	Discharge	30 days	6, 12, 24 months
Visit Number	**-1**	**0**	**1**	**2**	**3**	**4**
Range	**- 1 month**	**- 1 month**	**0**	**NA**	**-1 wk/+ 2 wks**	**+/- 1 month**
Data release Consent	X					
Study informed consent		X				
Demographics		X				
Wearable data watch		X	X	X	X	X
Medical History		X				
Routine Blood tests		X		X	X	X
Pregnancy test (if applicable)		X				
General Clinical State		X		X	X	X
Adverse Events		X	X	X	X	X
Medica ion Profile		X		X	X	X
Tricuspid Regurgitation Assessment by TTE	X	X		X	X	X
Tricuspid Regurgitation Assessment by TEE		X	X			
Tricuspid valve anatomy (by Echo and/or CT)	X					
Coronary Angiography (within the past 12 months, optional)	X					
Cardiac MRI (optional)	X					X
6-minute walk test		X			X	X
QoL questionnaire (KCCQ)		X			X	X
NYHA Functional Class		X			X	X
Cardioband Implantation			X			

Table 4: Schedule of Visits and Procedures

7.1 Unscheduled Visits

An unscheduled visit will be any visit to the clinical site other than the specific visits requested in the protocol. The Investigator or trained and qualified investigational staff will perform all procedures necessary to evaluate the study participant at these visits, and record the visit in the subject's chart. At the very least, safety information such as occurrence of adverse events will be recorded during the unscheduled visit. The Principal Investigator must be notified by the subject immediately of any unscheduled visits to any medical facilities during the study period. (Subjects will be instructed to report).

8 CARDIOBAND IMPLANT PROCEDURE

Cardioband is implanted by transfemoral procedure. [redacted]

8.1 Cardioband system procedure

Prior to the procedure, subjects must be evaluated to determine eligibility for transfemoral venous access. Absolute or relative contraindications to transfemoral procedures will be evaluated by the principal investigator and or interventional cardiologist.

The Cardioband system procedure is performed under echocardiography and fluoroscopy guidance. The procedure summarized in the following steps:

1. The subject is prepared as per standard practice for transvenous catheterization.
2. Cardioband implant size is selected according to the tricuspid annulus size measured preoperatively and the implant is mounted as specified in the IFU.
3. The transfemoral steerable sheath (TSS) with the Dilator are inserted through the femoral vein, the tip of the TSS is steered into the RA under echo guidance.
4. After removing the dilator and guidewire, the implant delivery system is inserted.
5. The system is navigated to the anterior part of the annulus, proximal to the aortic root. The first anchor is placed.
6. The system is navigated to the next anchoring site while deploying the implant fabric along the anterior and posterior annulus.
7. Implant deployment and anchoring is continued until the Cardioband implant reaches the coronary sinus opening.
8. The implant is then disconnected from the implant catheter. The Implant Delivery system is removed.
9. The Size adjustment tool (SAT) is then inserted over the implant guidewire and engaged with the implant.
10. Adjustment is performed using the SAT, under echocardiography guidance.
11. After achieving the desired result, the SAT is detached.
12. The System is removed upon completion.

Additional details on procedures, contraindications, and risks are provided in the device *Instructions for Use*.

9 CLINICAL RISK BENEFIT EVALUATION

9.1 Expected benefits

Tricuspid regurgitation is a significant disease with one year mortality 36.1 %[3, 4], but less <1% of patients with moderate or severe TR undergo surgery. The vast majority of cases are managed conservatively due to the excessive risk of open heart surgery [56, 7].
Thus, there is an unmet clinical need for devices enabling to perform a valve repair in a non-invasive fashion and without cardiopulmonary bypass.

Cardioband was proved to llower the surgical risks by using established transfemoral techniques; Based on established annuloplasty surgical devices. Cardioband was showed to reduce the Mitral septo-lateral annular dimension and therefore reduce the MR. MR Reduction accompanied with improvement of the NYHA stage, 6 minute walk test and MLHFQ questionnaire.

Although there are no guaranteed benefits from participation in this study the Cardioband System is expected to allow for treatment of patients that would otherwise not undergo Tricuspid valve repair due to the invasiveness of current techniques. In addition Cardioband enable fine-tuning of the repair by adjusting the device size on a beating heart.
Given these benefits showed for mitral valve repair, there is ample justification for a prospective investigation focusing on the clinical performance and safety of the Cardioband system for treatment of the Tricuspid valve as well.

9.2 Anticipated risks

The potential risks associated with Cardioband can be divided into three categories: First, there are the risks associated with transcatheter repair procedures the patient population (high risk for surgery) and anaesthesia. These risks are expected to be similar to risks that were reported for mitral valve repair by transcatheter devices in similar populations (e.g. Carillion, mitraclip, etc.). Second, there are the risks uniquely associated with annuloplasty procedures using ring/band which similarly are not expected to significantly differ between marketed systems and the Cardioband System. Third, there are risks specifically associated with the Cardioband procedure. The latter are also expected to be similar to those reported for those reported for the use of Cardioband for mitral repair.

A risk analysis according to ISO 14971 Application of Risk Management to Medical Devices has been conducted.

9.3 Potential Risks and Adverse Events

The following ANTICIPATED EVENTS have been identified as possible complications of the Cardioband TF procedure:

1. **Risks associated with the procedure and administration of anaesthesia including but not limited to the following:** Death; Stroke/ transient ischemic attack; Haemolysis; Heart block; Perforation or damage of vessels, myocardium or valvular structures; Pericardial

effusion/cardiac tamponade; Haematoma; Blood loss requiring transfusion; Infection including endocarditis and septicaemia; Arrhythmia; Air embolus; Thromboembolism; Fever; Hypertension/hypotension; Allergic dye reaction; Allergic Anaesthesia reactions; Aneurysm; Atrial Septal defect requiring intervention; Arterio-venous fistula; Cardiac Arrest; Coagulopathy; Deep Venous thrombus (DVT); Dyspnoea; Edema; Esophagus irritation; Esophagus perforation or stricture; Gastrointestinal bleeding or infarct; Hematoma; Haemolysis; Haemorrhage requiring transfusion; Infection and pain in insertion or incision site; Lymphatic complication; Mesenteric ischemia; Multi-system failure; Myocardial infarction; Nausea/vomiting; Peripheral ischemia; Prolonged angina; Prolonged ventilation; Pulmonary Congestion; Pulmonary thrombo-embolism; Renal insufficiency; Respiratory failure/atelectasis/pneumonia; septicaemia; Urinary tract infection; Vascular trauma, dissection or occlusion; Vessel spasm; vessel perforation or laceration; worsening heart failure .

2. **Potential risks specifically associated with the use of annuloplasty rings/bands include, but may not be limited to the following:** reoperation and explants; residual or recurrent or worsening regurgitation requiring intervention; haemolysis; conduction system disturbances including atrioventricular block; endocarditis; low cardiac output; right heart failure; failure or degeneration of the natural valvular apparatus due to progression of disease; inadequate repair of the valvular and subvalvular structure; detachment/dislodgment (partial or full) of the annuloplasy ring/band from its site of attachment; migration or malposition; malfunction of the ring/band due to distortion or fracture at the implant or physical or chemical deterioration of band components; bleeding complications related to use of anticoagulant therapy; prosthesis thrombosis; infection.

3. **Risks specifically associated with the Cardioband, in addition to the general risks of annuloplasty, include, but may not be limited to the following :**Conversion to standard valve surgery; Failure to deliver the band to the intended site; tissue damage or vascular injury due to anchor insertion; Unsuccessful adjustment of the band; Tissue damage from insertion and removal of system components; Cardioband components embolism; Partial device dehiscence (anchor detachment) and disturbances to the conduction system.

The potential for the occurrence of device dehiscence, device mal-position, and residual or recurrent regurgitation requiring intervention is expected to be similar to that seen for Mitral valve repair with the Cardioband device. Clinical study for MR repair have demonstrated that Cardioband procedure is relatively safe and can reliably result in a significant reduction of the annular septo-lateral dimension and MR, and functional improvement in patients with FMR [46].

As with any device undergoing clinical investigation, there may be unforeseeable risks, which are not known at this time. Medical and/or surgical intervention may be required to correct clinical complications associated with the device procedure.

9.4 Risk/benefit ratio

Cardioband proposes a less invasive, fully adjustable, direct annuloplasty for tricuspid regurgitation repair, and as presented above targets an unmet clinical need for Tricuspid repair in a patients that are at high risk for surgery.

Cardioband had shown to enable a “surgical annuloplasty” for mitral regurgitation repair through a percutaneous approach. [redacted] The benefit–risk profile is expected to be similar for the tricuspid regurgitation annuloplasty repair and will be rigorously addressed in the clinical trial.

10 ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

10.1 Reporting requirements

Timely and complete reporting of Adverse Events (AE) and safety assessments allows:

- Protection of safety and study subjects.
- Greater understanding of the overall safety profile of the study treatment.
- Appropriate modification of study protocols and improvement in study design and procedures.
- Adherence to regulatory requirements.

The definitions and reporting requirements adopted in this study are derived from the current International standard on clinical investigations: EN ISO 14155:2011 Clinical Investigations of medical devices for human subjects – Good Clinical Practices.

10.2 Definitions

Based on ISO 14155:2011

Adverse event

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. This includes events related to the procedures involved.

This definition does not imply that there is a relationship between the adverse event and the device under investigation. An AE can therefore be any unfavorable and unintended sign, symptom,

laboratory observations or disease temporally associated with the use of the investigational product, whether or not related to the investigational product.

The following should be reported as AE:

- Untoward medical conditions or signs or symptoms that were absent before starting study treatment.
- Untoward medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory values or tests which are clinically significant.
- Clinical signs or symptoms that require therapy.

Adverse device effect (ADE)
Adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

Therefore, some adverse device effects may be related to device deficiencies, defined as follows:

Device deficiency
Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, misuse or use errors and inadequate labeling.

- *Device Malfunction*: failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation protocol.
- *Use Error*: act or omission of an act by the user that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses, and mistakes. An unexpected physiological response of the patient is not by itself considered use error.

A device deficiency shall be reported as AE or SAE according to the AE and SAE definitions.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence if:

- A suitable action had not been taken,
- intervention had not been made
- circumstances had been less fortunate,
- Shall be reported as well as an adverse event.

Serious adverse event (SAE)
Adverse event that
a) Led to a death,
b) Led to a serious deterioration in the health of the subject that either

1) Resulted in a life-threatening illness or injury, or
2) Resulted in a permanent impairment of a body structure or a body function, or
3) Required in-patient hospitalization or prolongation of existing hospitalization, or
4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) Led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be a serious adverse event.

Unanticipated serious adverse device effect (USADE)
Serious adverse device effect which by its nature, incidence, severity or outcome has not been Identified in the current version of the risk analysis report.
NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

10.3 Reporting procedures

Adverse event and adverse device effect information will be collected throughout the study. The investigator or research coordinator will record these events on the CRF's. The event, date of onset, severity, duration, and relationship to the device will be recorded. Any adverse event will be monitored until it is adequately resolved or stabilized.

The investigator has the responsibility to report adverse events as they occur:

- The Ethics Committee must be informed of any serious adverse device effect.
- Valtech and the monitor must be informed of any adverse event without undue delay.
- All serious adverse events must be reported by completing a serious adverse event eCRF form as soon as of knowledge of the event. An automatic notification will be generated to Valtech and to the monitor upon the issue of such eCRF. Investigator should not wait to receive additional information to fully document the SAE, and should start the completion of the electronic form as soon as possible. The report of SAE should be followed by a full written report detailing relevant aspects of the SAE in question. Where applicable, information from relevant medical records and autopsy reports should be obtained.
- Other adverse events must be reported as soon as possible.

10.3.1 Adverse Events Reporting Requirements in Germany

In Germany, events will be reported in accordance with the “Medizinprodukte-Sicherheitsplanverordnung” (MPSV).

According to MPSV § 3 Nr.5 and 6, serious adverse events occurring during clinical investigations must be notified by the Sponsor and Investigator.

The investigator will report to the sponsor within 24 hours of having information of an event occurred.

The sponsor's reporting to BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte, the Federal Institute for Drugs and Medical Devices) as per regulation, will be performed immediately of the sponsor becoming knowledge of the occurrence of the SAE.

1. For SAEs occurring in Germany, where a causal relationship between the SAE and the investigational medical device, the study or the study procedure cannot be excluded reporting will be made using the current SAE Report Form provided by BfArM.

2. For SAEs occurring in other countries, where the clinical trial is performed and where a causal relationship between the SAE and the investigational medical device, the study or the study procedure cannot be excluded reporting will be made using the MEDDEV Form / Summary table.

3. For all SAEs occurred where a causal relationship between the SAE and the investigational medical device can be excluded reporting to BfArM will be made on a quarterly basis by sending the MEDDEV Form.

10.4 Adverse event treatment and follow-up

Treatment of any AE is at the discretion of the investigator. Investigators must follow-up subjects with AE until the event has resolved (subject recovered) or until the condition has stabilized. Otherwise, appropriate medical care must be arranged for the subject. Abnormal test results should be repeated until return to baseline or acceptable levels.

10.5 Monitoring of adverse event documentation

During the monitoring visit, the monitor must perform the following verification activities:

- Confirmation of the accuracy of subject information supplied by the investigator concerning the seriousness of the event and causal relationship to the device;
- Ensuring that the appropriate adverse event CRFs have been completed by the site personnel;
- Verification of whether or not the investigator has followed established reporting procedures and, if required, has reported the event to Valtech and/or the EC, as appropriate.
- Confirmation that copies of EC reports and correspondence are maintained in the Site Regulatory Binder.

For any negative change in subject test results, clinical status, or treatment (e.g., increased dose of diuretic, reduction in ejection fraction), the monitor must ensure that the corresponding AE has been documented. If a reportable AE is discovered that has not been reported, the Monitor must immediately initiate the proper reporting procedures in collaboration with the investigator, as defined by applicable regulatory requirements. If the change is not associated with an AE, the reason for the change must be appropriately explained on the appropriate CRF or narrative form.
Any problems identified during these activities should be documented in writing and notified to Valtech.

10.6 Sponsor assessment of events and safety update

Sponsor representatives for vigilance notifications are identified in the Table below:

Valtech representative responsible for vigilance notifications	[redacted]
Valtech European Authorized Representative EC REP	[redacted]

Upon notification of adverse events, Valtech will initiate and complete a review and evaluation of the event within time frames that will maintain reporting compliance with applicable regulatory agencies.

If insufficient information is available to reach a definitive diagnosis, Valtech will instruct the monitor responsible for the site to contact the site to request additional confirmatory information. The hospital discharge letter is usually the most informative document, which should contain a complete summary of the event, the results of diagnostic tests, whether surgery was performed and its outcome, the subject's post-operative course, discharge, post-discharge treatment and follow-up, if any. If the outcome is death, an autopsy report must be requested.
Upon review of AE data (including seriousness, frequency of occurrence and statistical significance) within Valtech if study termination is required due to an unreasonable risk or significant occurrence of risk to human subjects, the study will be terminated.

10.7 Clinical Events Committee

All Serious adverse events will be reviewed by an independent Clinical event Committee (CEC) for adjudication of the event relation to the study device or procedure. Major SAEs and SAEs that are related or possibly related to device or procedure will be reviewed by all CEC members, other SAEs will be reviewed by the CEC chairperson.

11 ETHICAL ASPECTS AND REGULATORY REQUIREMENTS

This study will be conducted in conformity with the ethical principles set forth by the Declaration of Helsinki, Good Clinical Practice (GCP) principles, international harmonized standards for clinical investigation of medical devices (ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practices), the laws and regulations of the countries where the study will take place, and indemnity / insurance requirements.

In addition, for this study Valtech has chosen to voluntarily comply with United States requirements, including those related to sponsor responsibilities (21 CFR 812.40), selection of investigators (21

CFR 812.43), monitoring (21 CFR 812.46), and any other applicable requirement for the purpose of facilitating acceptance of data in support of US regulatory submissions.

11.1 Ethics Committee review and approval

This investigational plan and the informed consent must be reviewed and approved by the appropriate Ethics Committee where the trial will be conducted before enrolment of subjects. Changes to the investigational plan that may increase the risk or present new risks to the subject, or that may adversely affect the validity of the trial, must be approved in writing by Valtech and the Ethics Committee.

Prior to the subject enrolment, a signed copy of the Ethics Committee approval form or a signed copy of the Ethics Committee approval letter addressed to the investigator must be submitted to Valtech certifying this approval. Investigators are responsible for submitting and obtaining initial and continuing review of the trial by their Ethics Committee with the recurrence of at least once a year.

All correspondence with the Ethics Committee should be filed in the Investigator's Study File and a copy forwarded to Valtech and the site monitor.

11.2 Clinical investigation regulatory notifications

All necessary arrangements for the registration and approval of this study with the appropriate regulatory authorities will be undertaken by Valtech. As appropriate, the assigned submit amendments in the Investigational Plan to the appropriate Competent Authority and investigators to obtain Ethics Committee re-approval. Depending upon applicable national regulations and requirements, Valtech will submit the required Competent Authority reports, including: unanticipated adverse device effects, withdrawal of Ethics Committee approval, current investigator list, annual progress reports, recall information, final reports, and investigational plan deviations, where appropriate.
Valtech Cardio Ltd. will report all reportable Serious Adverse Events to the Competent Authorities in accordance with European Medical Devices directives, the MEDDEV 2.7/3 and all applicable national regulations.

Valtech will be represented in Europe by:

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11.3 Training Requirements

Prior to investigation site activation, Valtech will provide study training relevant and pertinent to the involvement of personnel conducting study activities, investigator responsibilities, as well as device training.

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11.4 Investigator responsibilities

The selected investigators will provide written agreement to the following sponsor requests:

- To adapt the clinical routine if required by the protocol and local procedures to comply with the standardization required for the study;
- To comply with Good Clinical Practice, FDA Regulations and/ or ISO 14155:2011 for the conduct of clinical investigations of medical devices;
- To collect clinical data as outlined in this protocol and complete all relevant documentation (such as the case report form) in a legible and timely condition;
- To permit authorized sponsor representatives, monitors and auditors to inspect all records pertaining to the trial.

The principal investigator will be required to submit curriculum vitae for participating medical team. Participating medical team will attend an education session to familiarize themselves with the protocol and GCP before the initiation of the study.

11.5 Patient information and informed consent

Informed consent is mandatory and must be obtained from all subjects and/or their legal representatives as per local regulations, prior to their participation in the study. The investigator must inform every subject in details about the nature of the study, its purpose, the treatments, those aspects of the study that are experimental, the procedures involved including all invasive procedures and the discomfort it may entail, the possible risks including to an embryo, foetus or nursing infant when applicable, the reasonably expected benefits, the expected duration and the approximate number of subjects involved and the subject's responsibilities.

The patient will also give his written consent for health information release, i.e. screening informed consent, in order to determine if the patient is a potential candidate for the device.

Study subjects must additionally be informed that:

- Participation in this study is voluntary and that he/she may withdraw from this study at any time for any reason and that that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physicians.
- Notification will be provided in a timely manner and in a written form if information becomes available that can significantly affect their future health and medical care.
- Alternative procedures or treatment that may be available and the important potential benefits and risks of these available procedures or treatments.

- Any compensation for additional costs and/or injury caused to a subject attributable to participation in the study.
- Financial expenses, if any, to the subject for participating in the study as well as prorated payments, if any, to the subject for participating in the study.
- Any foreseeable circumstances and/or reasons under which the subject's participation in the study may be determined.
- The person(s) to contact for further information regarding the study and whom to contact in the event of study related injury.

Written consent will be obtained from each subject to be involved in the study. According to the Declaration of Helsinki, including legally incompetent patients is not recommended and as such is not allowed in the study. Potential study subject and/or his/her guardian should be given the opportunity to ask questions and time for consideration.

A blank copy of the informed consent form approved by the Ethics Committee must be maintained in the Investigator's study file. The original of each subject's signed consent form must be filed by the investigator in the Subject CRF Binder, and a signed copy of the patient information and informed consent form must be given to each subject.

11.5.1 Confidentiality and subject data protection

All information and data concerning subjects or their participation in this trial will be considered confidential.
Only those working on Valtech's behalf, the independent Ethics Committee and regulatory authorities will have access to subject medical records and other study documents for verification of study procedures and data without violating the confidentiality of the subject. All data used in the analysis and reporting of this evaluation will not bear identifiable reference to the subjects.

The investigator must assure that the subject's anonymity will be maintained and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements.

- Subjects must be identified only by their assigned study number in the CRFs and other records and documents submitted to Valtech, the monitor, and other authorized parties.
- The investigator will keep a Subject Identification List with complete identification information (full name, hospital ID if applicable and study ID) on each subject. This list will be kept at the investigational site solely.
- Documents not for submission to Valtech, such as subject's written informed consent, should be maintained by the investigator in strict confidence.

The subject should also be informed about the use of his/her health information collected during the study (study data). This information will be provided to the patient in the patient informed consent.

11.6 Insurance

For any injuries which can be traced to the study, subjects participating in the study are covered by insurance policies, as required by regulation for clinical studies. An product liability insurance policy

taken out by Valtech will cover liability for possible injury to the subject, provided the investigator and his/her staff have followed the instruction of sponsor in accordance with this protocol and any amendments thereto, that the investigational product administered to the subject in this study have been supplied by sponsor and that the investigator and his/her staff have in general performed this study in accordance with scientific practice and currently acceptable techniques and know how.

11.7 Protocol deviations

A deviation is defined in the ISO14155 standard as an instance of failure to follow, intentionally or unintentionally, the requirements of the CIP. The principle investigator shall document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation. The investigator should not deviate from the investigational plan without the prior written approval of Valtech, except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the investigation.
Prior approval from the EC shall be obtained if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation;
Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.
All deviations will be documented and explained, regardless the reason for the deviation. All deviations, regardless of their reason, will be reported to Valtech via a Study Deviation CRF (one CRF for each deviation). Valtech will assess the significance of all deviations and evaluate the need to take subsequent action (e.g. amending the Clinical Investigation Plan or terminating the investigation). When relevant, this shall be reported to the appropriate regulatory bodies.
Deviations will be monitored on routine visits and will be summarized in monitoring reports as well as at the final study report.
The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

11.8 Study documentation and record keeping

The investigators must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. These documents include those required by applicable regulations, and the subjects' source documents, as described below.

11.9 Regulatory documents

Regulatory documents are those documents that individually and collectively permit evaluation of the study compliance with applicable regulations and the quality of the data produced. These documents include:

1. Signed protocol and amendments
2. Sample CRFs
3. EC Approval letter
4. Informed consent form
5. CV of participating study team
6. Correspondences with EC and sponsor

7. Interim reports to EC
8. Investigational product accountability and shipping records
9. Site signature (delegation) log
10. Monitor visit log
11. Other appropriate documents in accordance with GCP guidelines

These documents will be filed in an Investigator File provided by Valtech. This file shall be used to facilitate and ensure filing of all relevant regulatory documents during and after the study. The investigator will be responsible for keeping the Investigator's Study File updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

11.10 Source documents

Source documents are original hospital records, clinical charts, screening log, subject identification list/enrolment log, original laboratory report, memoranda, pharmacy dispensing records, recorded data from automated instruments, transcriptions certified after verification as being accurate, microfiches, photographic negatives, microfilm, magnetic or electronic media, x-rays, subject's files, and records kept at pharmacy, at the laboratories and medico-technical departments involved in the study. The investigator must maintain source documents for each subject in the study. All information recorded on the CRFs must be traceable to these source documents.

11.11 Retention of study documents

The investigator shall arrange for the retention of all study documents and records, including subject records, CRFs, drug inventory/accountability log, signed informed consent forms and the subject identification list for at least the number of years required by the local regulations after completion or discontinuation of the study.

If the investigator moves or retires, he/she must nominate someone in writing to be responsible for archiving. Archived data may be held in electronic records, provided that a back-up exists and a hard copy can be obtained from it if required.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made with sponsor or Research Center to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator in case of regulatory audit.

Study records are to be discarded only upon notification by Valtech. If audits are required, the Principal Investigator shall allow access to the original medical records and provide all requested information.

The study physicians should contact Valtech before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, Valtech should be notified if the study physician plans to leave the institution.

11.12 Case report forms (CRF)

The site will record all information in an Electronic Data Capture (EDC) system, i.e. eCRF. The EDC system used is validated software, and complies with CRF filling requirements, including audit trail and signature validation. Further information may be found in this document, section 12.5 – Data capture.

11.12.1 Completion of CRFs

It is the responsibility of the investigator to ensure that CRFs are legible and completely filled in to the EDC system, in a timely manner.

An investigator or any personnel signature authorized by the investigator is required to personally sign each CRF on the appropriate pages to verify that the investigator has reviewed and concurs with the recorded data. No other person is permitted to sign for the investigator. The signature must be made at the time that the CRF is reviewed by the investigator signing the CRF.

11.12.2 CRF transmittal and retention

The EDC system is protected by user and password. Data collected via eCRF will be retained by Valtech for at least the number of years required by the local regulations after completion or discontinuation of the study.

11.12.3 CRF review and data clarification

The monitor (responsible CRA) will review the CRFs for completeness and accuracy at site or in-house. In addition to the monitor's queries, the EDC system shall generate automatic queries according to predefined edit checks. Errors detected or suspected will require clarification and/or correction. Any data correction must be approved by the investigator. Wherever possible the investigator should assist in clarification or correction of errors detected within a timely manner.

11.13 Investigational device accountability

The Valtech devices to be used during this study will be supplied by Valtech. Investigational products should be maintained under adequate security by the investigator. Until the Valtech system is implanted, the system and its accessories should be stored at room temperature and protected from freezing, moisture and excessive heat. Required conditions for storing investigational product will also be printed on the label. The investigator or designee must maintain current and accurate record of the receipt, inventory and dispensing, including shipping invoices (if applicable) of all study supplies. Investigational product Accountability Log will be made available to facilitate inventory control. Accountability logs are subject to inspection by authorized parties at any time. Upon completion or termination of the study, unused investigational product must be returned to the sponsor.

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12 STUDY MONITORING

12.1 General requirements

Valtech or its designees will conduct investigational site monitoring to ensure that all investigators are in compliance with the investigational plan and the Investigator's Agreement. The monitors will verify source documentation against completed eCRF's and resolve any discrepancies. Monitors and Valtech will evaluate circumstances where an investigator deviates from the investigational plan.

Valtech retains the right to remove either the investigator or the investigational site from the study. Valtech will fulfill its responsibilities in collecting and tracking data forms and instituting quality control measures for the data entry verification and trial compliance. Valtech will review significant new information including unanticipated adverse events and ensure that such information is provided to the Competent Authorities, investigators and to all reviewing Ethics Committees.

12.2 Study oversight

Primary data collection based on source-documented hospital chart reviews will be performed by the Valtech personnel or its designee monitor at each clinical site. Electronic case report forms will be completed in an expedited fashion.

Each site will be visited regularly to ensure that the study is conducted in full compliance with all applicable regulations and the investigational plan. A pre-study meeting will be held with each potential investigational site in order to inform the prospective investigator and staff concerning features of the investigational device, investigation plan, applicable regulations and requirements, and expectations of the study, including the number and time frame for subject enrolment, subject selection, informed consent, required clinical data and record keeping.

The prospective investigational site will be evaluated to ensure that it has an adequate subject base and can provide sufficient staff and documentation support to conduct the study properly.

The Valtech study monitor will maintain personal contacts with the investigator and staff throughout the study by telephone, mail, e-mail, and on-site visits. The monitor will compile and file an observation report at each visit. Monitoring is intended to ensure continued protocol compliance, adequate subject enrolment, accurate data reporting, and adequate accounting of the investigational device.

Upon closure of the study at an investigational site, the study monitor will make a final onsite visit. The purpose of this visit is to collect all outstanding study documents, ensure that the investigator's files are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study 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 as a final report for investigators and Valtech's acceptance.

12.3 Data management

The sponsor agrees to be responsible of the verification that the trial is conducted implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable federal, state and local laws, rules and regulations and guidelines relating to the conduct of the clinical trial.

12.4 Data collection and review

The investigator, or an individual designated by the investigator, is responsible for recording all data from the trial on the eCRF's supplied by Valtech.

Valtech personnel or its designee will review completed eCRF's at the investigational site at regular intervals throughout the investigation. To this end, the investigator must permit inspection of the investigation files and subject CRF's by such representatives and/or responsible governmental agencies.
All eCRF's will be tracked at Valtech and missing or unclear data will be requested as necessary throughout the investigation. Valtech or the monitor will request additional documentation, such as physician and/or laboratory procedure notes, in the event that complications or malfunctions are observed and reported.

12.5 Data capture

An Electronic Data Capture (EDC) system will be used for this study (EDC2go by Genae, a CRO and Data company based in Belgium and in the US). EDC2go is a software based CRF, designed to be FDA 21 CFR Part 11 compliant to collect data electronically. The system allows validation of data in terms of completeness accuracy. Each deviation from required fields, such as missing data, out of range data, or inappropriate data, will generate an automatic query, for the site to address.

The system is compliant with FDA 21 CFR Part 11; meaning it is secured, and users are obliged to have their own password-protected username. Each data entry is registered and a complete audit trail is available at all times.

A query will be generated when:

1. A validation rule is not followed – generated automatically by the EDC system, or

2. During a monitoring visit, when there is inconsistency with the source documents - Manually by the monitor.

The queries will remain open in the EDC system, until the designated site staff answer the question. The monitor will then be alerted of a new available answer, and only following re-monitoring, if the answer is sufficient, the query will be closed.

Upon study completion, all data will be collected, and all queries will be answered, the data will be extracted and forwarded to an expert statistician for analysis. The data collected will be incorporated into the final report of this clinical study.

13 SPONSOR DUTIES AND RESPONSIBILITIES

13.1 Role of the Sponsor

As the sponsor of this clinical study, Valtech has the overall responsibility for the conduct of the investigation. Valtech will have certain direct responsibilities and will delegate other responsibilities.

The general duties of Valtech consist in submitting the clinical investigation notification to National Competent Authorities, obtaining Ethics Committee approvals prior to patient's enrollment, selecting qualified investigators, ensuring proper investigational site monitoring, and ensuring that informed consent is obtained. Valtech will prepare written progress reports and a final report, as required.

Valtech will select qualified investigators; ship devices only to qualified participating investigators, obtain a signed Investigator's Agreement, and provide the investigators with the information necessary to conduct the study.

Valtech or its designees will conduct investigational site monitoring to ensure that all investigators are in compliance with the investigational plan and the Investigator's Agreement. The monitors will verify source documentation against completed eCRF's and resolve any discrepancies. Monitors and Valtech will evaluate circumstances where an investigator deviates from the investigational plan. Valtech retains the right to remove either the investigator or the investigational site from the study.

13.2 Study suspension or termination procedures

Valtech reserves the right to terminate this study and remove all study materials from the study site at any time. The study may be suspended or terminated for any of the following reasons:

- It becomes apparent that subject enrolment is unsatisfactory with respect to quality or quantity
- Data recording is inaccurate and/or incomplete
- Violation or deviations from the signed protocol
- The incidence and/or severity of adverse events in this or in other studies indicate a potential health hazard caused by the treatment under study.

Should a determination be made that the study should be suspended or terminated at one or all sites, then:

1. Enrolment shall be suspended or terminated at one or all the sites
2. Currently enrolled subjects will be followed according to the protocol, which may be amended to accommodate study suspension or termination
3. Valtech shall promptly inform the investigators and Ethics Committees of the suspension or termination and the reasons for it.

Should Valtech decide to terminate the study, the investigator will complete the eCRFs as far as possible. The completed eCRFs and any study materials will then be collected by Valtech.

13.3 Sponsor study files

Valtech will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the investigational plan. Valtech will maintain records related to the signed Investigator's Agreements.

14 REFERENCES

1. Neuhold S et al. 2013. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. J., Eur Heart J, Vol. 34, pp. 844-52.

2. Agricola E et al. 2012. Impact of functional tricuspid regurgitation on heart failure and death in patients with functional mitral regurgitation and left ventricular dysfunction. Eur J Heart Fail, Vol. 14, pp. 902-8.

3. Topilsky Y et al. 2014. Clinical outcome of isolated tricuspid regurgitation JACC Cardiovasc Imaging, Vol. 7, pp. 1185–1194.

4. Stuge O and Liddicoat J. 2006. Emerging opportunities for cardiac surgeons within structural heart. J Thorac Cardiovasc Surg, Vol. 132, pp. 1258–61.

5. Nath J et al. 2004. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol, Vol. 43, pp. 405–9.

6. Agarwal S. et al. 2009. Interventional cardiology perspective of functional tricuspid regurgitation. Circ Cardiovasc Interv, Vol. 2, pp. 565-73.

7. Supino PG et al. 2006. The epidemiology of valvular heart disease: a growing public health problem. Heart Fail Clin, Vol. 2, pp. 379-93.

8. Nishimura RA et al. 2014. AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. Jul;148(1):2014

9. Vahanian A. 2012. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)., Eur J Cardiothorac Surg. 2012 Oct;42(4):S1-4

10. Arsalan M. et al. 2015. Tricuspid regurgitation diagnosis and treatment .2015, Eur Heart J. Eur Heart J. 2015 Sep 10.

11. Navia JL et al. 2010. Surgical management of secondary tricuspid valve regurgitation: annulus, commissure, or leaflet procedure? J Thorac Cardiovasc Surg. Vol. 139, pp. 1473-1482.

12. Cheng R et al. 2015.Tricuspid Regurgitation, the Forgotten Valvular Lesion. Rev Cardiovasc Med, Vol. 16, pp. 171-81.

13. Mutlak D. et al. 2009. Functional tricuspid regurgitation in patients with. J. 2009, Chest, Vol. 135.

14. Mutlak D. et al. 2007. Echocardiographybased spectrum of severe tricuspid regurgitation: the frequency of apparently idiopathic tricuspid regurgitation. J Am Soc Echocardiogr, Vol. 20, pp. 405-8.

15. Taramasso M. et al. 2012. The Growing Clinical Importance of Secondary Tricuspid Regurgitation. Journal of the American College of Cardiology, Vol. 59, pp. 703-710.

16. King RM et al. 1984. Surgery for tricuspid regurgitation late after mitral valve replacement. Circulation, Vol. 70, pp. 193-7.

17. O'Neill WW and O'Neill BP. 2015. Transcatheter tricuspid valve intervention: the next frontier. J Am Coll Cardiol, Vol. 31, pp. 1196-8.

18. Huang X. et al.2014. Repair of functional tricuspid regurgitation: comparison between suture annuloplasty and rings annuloplasty. Ann Thorac Surg., Vol. 97, pp. 1286-92.

19. Guenther T. et al. 2013. Tricuspid valve repair: is ring annuloplasty superior? Eur J Cardiothorac Surg, Vol. 43, pp. 58-65.

20. Ghoreishi M. et al.2011. Undersized tricuspid annuloplasty rings optimally treat functional tricuspid regurgitation. Ann Thorac Surg., Vol. 92, pp. 89-95.

21. Ratschiller T. et al. 2014. Early experiences with a new three-dimensional annuloplasty ring for the treatment of functional tricuspid regurgitation. Ann Thorac Surg, Vol. 98, pp. 2039-44.

22. Yoda M. et al. 2011. Mid-term results of tricuspid annuloplasty using the MC3 ring for secondary tricuspid valve regurgitation. Interact Cardiovasc Thorac Surg., Vol. 13, pp. 7-10.

23. Jung SH. et al. 2010. Outcomes following use of a modified Duran ring tricuspid valve reconstruction procedure for secondary tricuspid regurgitation Circ J., Vol. 74, pp. 925-30.

24. Onoda K. et al. 2000. Long-term follow-up after Carpentier-Edwards ring annuloplasty for tricuspid regurgitation. Ann Thorac Surg, Vol. 70, pp. 796-9.

25. Gatti G. et al. 2007. Tricuspid valve annuloplasty with a flexible prosthetic band. Interact Cardiovasc Thorac Surg., Vol. 6, pp. 731-5.

26. Anyanwu AC and Adams DH.2010. Functional tricuspid regurgitation in mitral valve disease: epidemiology and prognostic implications. Semin Thorac Cardiovasc Surg., Vol. 22, pp. 69-75.

27. Rogers JH and Bolling SF. 2010. Valve repair for functional tricuspid valve regurgitation: anatomical and surgical considerations. Semin Thorac Cardiovasc Surg., Vol. 22, pp. 84-9.

28. Matsuyama K. et al.2003. Predictors of residual tricuspid regurgitation after mitral valve surgery. Ann Thorac Surg. Vol. 75, pp. 1826-8.

29. Sagie A. et al. 1997. Echocardiographic assessment of mitral stenosis and its associated valvular lesions in 205 patients and lack of association with mitral valve prolapse. J Am Soc Echocardiogr, Vol. 10, pp. 141-8.

30. Boyaci, V. et al. 2007. Outcome of significant functional tricuspid regurgitation late after mitral valve replacement for predominant rheumatic mitral stenosis. Angiology, Vol. 58, pp. 336-42.

31. Izumi, K. et al. 2002. Progression of isolated tricuspid regurgitation late after mitral valve surgery for rheumatic mitral valve disease. J Heart Valve Dis, Vol. 11, pp. 353–356.

32. Porter, Y. et al. 1999. Tricuspid regurgitation late after mitral valve replacement: clinical and echocardiographic evaluation. J Heart Valve Dis, Vol. 8, pp. 57–62.

33. Matsunaga A and Duran CM. 2005, Progression of tricuspid regurgitation after repaired functional ischemic mitral regurgitation. Circulation, Vol. 112, pp. 453-7.

34. De Bonis M. et al. 2008. Evolution of tricuspid regurgitation after mitral valve repair for functional mitral regurgitation in dilated cardiomyopathy. Eur J Cardiothorac Surg, Vol. 33, pp. 600-6.

35. Dreyfus GD. Et al. 2005. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg., Vol. 79, pp. 127–132.

36. Ruel M. et al. 2004. Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves. J Thorac Cardiovasc Surg. Vol 128, pp. 278-83.

37. Shiran A and Sagie A.2009. Tricuspid regurgitation in mitral valve disease incidence, prognostic implications, mechanism, and management. J Am Coll Cardiol, Vol. 53, pp. 401-8.

38. Mangoni AA. Et al. 2001. Outcome following isolated tricuspid valve replacement. Eur J Cardiothorac Surg., Vol. 19, pp. 68–73.

39. Hornick P. et al. 1996. Tricuspid valve replacement subsequent to previous open heart surgery. J Heart Valve Dis, Vol. 5, pp. 20-5.

40. Kwon DA. Et al. 2006. Prediction of outcome in patients undergoing surgery for severe tricuspid regurgitation following mitral valve surgery and role of tricuspid annular systolic velocity. Am J Cardiol, Vol. 98, pp. 659-61.

41. Sanfelippo PM. Et al. 1976. Tricuspid valve prosthetic replacement. Early and late results with the Starr-Edwards prosthesis. J Thorac Cardiovasc Surg., Vol. 71, pp. 441-5.

42. Bateman MG. et al. 2013. The clinical anatomy and pathology of the human atrioventricular valves: implications for repair or replacement. J Cardiovasc Transl Res, Vol. 6, pp. 155-65.

43. Montant P. et al. 2009. Long-term survival in asymptomatic patients with severe degenerative mitral regurgitation: a propensity score-based comparison between an early surgical strategy and a conservative treatment approach. J Thorac Cardiovasc Surg, Vol. 133, pp. 1339-48.

44. Smith CR et al. 2011.Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med, Vol. 364, pp. 2187-98.

45. Leon MB et al. 2010. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med, Vol. 363, pp. 1597–607.

46. Maisano F. et al. 2015. Cardioband, a transcatheter surgical-like direct mitral valve annuloplasty system: early results of the feasibility trial. Taramasso M, Nickenig G. 2015, Eur Heart J.

47. Maisano F. et al. 2014. First-in-man transseptal implantation of a "surgical-like" mitral valve annuloplasty device for functional mitral regurgitation. JACC Cardiovasc Interv. Vol 7, pp. 1326-8.

48. Cheung A. et al. 2014. Short-term results of transapical transcatheter mitral valve implantation for mitral regurgitation. J Am Coll Cardiol, Vol. 64, pp. 1814-9.

49. Kefer J. et al. 2014. Transcatheter Sapien valve implantation in a native tricuspid valve after failed surgical repair. Catheter Cardiovasc Interv, Vol. 83, pp. 841-5.

50. Lauten A. et al. 2011. Heterotopic transcatheter tricuspid valve implantation: first-in-man application of a novel approach to tricuspid regurgitation. Eur Heart J, Vol. 32, pp. 1207-13.

51. Schofer J. 2015. First-in-human transcatheter tricuspid valve repair in a patient with severely regurgitant tricuspid valve. J Am Coll Cardiol, Vol. 65, pp. 1190-5.

52. PMA 100009: Abbott Vascular MitraClip Clip Delivery System. FDA Executive Summary for the March 20, 2013 Meeting of the Circulatory System Devices Panel

53. Braun J. et al. 2008. Restrictive mitral annuloplasty cures ischemic mitral regurgitation and heart failure. Ann Thorac Surg 85(2):430-6;

54. Gummert JF et al. 2003. . Mitral valve repair in patients with end stage cardiomyopathy: who benefits? Eur J Cardiothorac Surg 2003; 23(6): 1017-22; Discussion 1022

55. 1340CLD Rev 2_Cardioband Tricuspid Literature Search Report

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