AUTOMATED ASSESSMENT OF PULMONARY VEIN ISOLATION USING A NOVEL EP RECORDING SYSTEM (PVISION)

CLINICAL INVESTIGATION PLAN
CPVI-002

20 December 2021

SPONSOR
CathVision ApS
Titangade 11
DK-2200
Copenhagen, DENMARK

Document History Clinical Investigation Plan CPVI-002

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PROTOCOL SYNOPSIS

Title	Automated assessment of pulmonary vein isolation (PVI) using a novel EP recording system (CathVision Cube® System).
Investigational Device	CathVision Cube® System
Objectives	The primary objective is to validate the PVI Analyzer software with a novel EP recording system (CathVision Cube® System) for assisting assessment of isolation status following PVI ablation. The secondary objective is to determine the feasibility of "real-time" assessment of PVI analysis and rhythm dependent performance using the PVI Analyzer and CathVision Cube® System.
Study Design	A prospective, multi-center study with the CathVision Cube® system and the PVI Analyzer software in radiofrequency (RF), cryo balloon and pulse field ablation (PFA) procedures. Subjects with paroxysmal or persistent atrial fibrillation (AF) who are indicated to undergo first PVI procedure and meet all eligibility criteria will be enrolled in the Study. Intracardiac signals will be passively recorded using the investigational CathVision Cube® System in parallel with the commercial (CE marked) LabSystem Pro, Boston Scientific EP recording system. The investigational device will not be used for direct clinical care decisions or therapy. The validation of the automated algorithm for PVI will be performed offline.
Sample size	Up to 90 subjects shall be enrolled across participating sites to reach a sample size of 210 EGMs required for the primary endpoint of the study. [redacted] Up to 30 additional subjects may be enrolled for the PFA procedure[redacted] Thus, the total sample size will be 120 subjects.[redacted]
Investigational Sites	Four (4) investigational sites in Europe: [redacted]
Study Duration / Follow-up Period	[redacted] Subjects will have clinical follow-ups until discharged from the hospital.

Primary Performance Endpoint	Assessment of performance of automated PVI Analyzer classification of PV isolation in sinus rhythm (SR) during pulmonary vein isolation (PVI) treatment.
Secondary performance Endpoints	The secondary performance endpoints are: • Accuracy of automated PVI Analyzer classification of PV isolation in SR during PVI Cryo-balloon ablation • Accuracy of automated PVI Analyzer classification of PV isolation in SR during RF ablation • Assessment of automated PVI Analyzer classification of PV isolation in SR after PFA • Feasibility of continuous "real-time" assessment of isolation • Feasibility of assessment of isolation during AF rhythm • Feasibility of assessment of isolation at time of expert-defined isolation before the end of the ablation procedure • Comparison of device performance on same data recorded by CathVision Cube and Boston Scientific LSPro
Safety Endpoint	Evaluation of adverse events and/or device malfunctions reported with the use of the CathVision Cube® System during the procedure until discharge.
Enrollment Criteria	Inclusion Criteria Eligible subjects will meet all of the following inclusion criteria: 1. Subjects undergoing first time pulmonary vein isolation indicated by investigator for the treatment of atrial fibrillation. 2. Male or non-pregnant female aged ≥21 years. 3. Able and willing to provide written informed consent prior to any clinical investigation related procedure Exclusion Criteria Eligible subjects will not meet any of the following exclusion criteria: 1. Pregnant or nursing subjects. 2. Current participation in another investigational drug or device study that interferes with this Study. 3. Subjects who, in the opinion of the investigator, are not candidates for this Study. 4. Patients who have had a prior ablation procedure 5. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to

	participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results. 6. Life expectancy less than 12 month, in the opinion of the investigator 7. Subjects who, in the opinion of the investigator, are considered part of any vulnerable population.

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ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
ASD	Atrial Septal Defect
β-HCG	Beta Human Chorionic Gonadotropin
CA	Competent Authority
CIP	Clinical Investigatn Plan
CPK	Creatinine Phosphokinase
CS	Clinically Significant
CVA	Cerebrovascular Accident
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee
ECG	Electrocardiogram
EGM	Electrogram
EP	Electrophysiology Procedure
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
LV	Left Ventricular
NCS	Not Clinically Significant
NSR	Non-Sinus Rhythm, i.e. AF
PFA	Pulse Field Ablation
PFO	Patent Foramen Ovale
PI	Principal Investigator
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SR	Sinus Rhythm
SW	Software
TIA	Transient Ischemic Attack
TEE	Transesophageal Echocardiogram
TTM	Trans telephonic Monitoring
UADE	Unanticipated Adverse Device Effect

1 Introduction

1.1 Cardiac electrophysiology

Of the total worldwide population, 1% and 2% of rural and urban areas suffer from cardiac arrhythmia, respectively. Approximately 15% of patients do not respond to drug treatment and need a device-based interventional treatment. As a result, there is a great need of cardiac arrhythmia ablation[1,2,3]. Today, however, the exact identification of the mechanism of the arrhythmia and subsequent successful ablation treatment are challenging for physicians. The three most prevalent arrhythmias ("complex arrhythmias") for catheter ablation are atrial fibrillation, atrial tachycardia and ventricular tachycardia.

1.2 Intracardiac electrophysiology signals during cardiac electrophysiology procedures

Cardiac electrograms are generated by the potential (voltage) differences recorded at two recording electrodes during the cardiac cycle. All clinical electrogram recordings are differential recordings from one source that is connected to the anodal (positive) input of the recording amplifier and a second source that is connected to the cathodal (negative) input. Unipolar recordings are obtained by positioning the exploring electrode in the heart and the second electrode (referred to as an indifferent electrode) distant (theoretically an infinite distance) from the heart such that it has little or no cardiac signal. Bipolar recordings are obtained by connecting two electrodes that are exploring the area of interest to the recording amplifier. At each point in time, the potential generated is the sum of the potential from the positive input and the potential at the negative input. The potential at the negative input is inverted and thus subtracted from that at the positive input. Because the far-field signal is similar at each instant in time, it is largely subtracted out, leaving the local signal. In a homogeneous sheet of tissue, the initial peak of the bipolar signal coincides with depolarization beneath the recording electrode[1,2].

1.3 Rationale for this Clinical Investigation

Electrograms and their interpretation are a key tool for electrophysiologists to target ablation sites, and are acquired from electrodes on intracardiac diagnostic catheters and from surface electrocardiogram (ECG). Electrograms (EGMs) are usually sampled at 1 to 2kHz, and bandpass filtered at 30 to 500Hz for bipolar and 0.5 to 300Hz for unipolar recordings. 64 to 160 channels are the typical capacity of recording systems today.

In the operating room, other devices and technologies are present: 3D mapping (triangulation of catheter tip position with impedance- and magnetic technology, <0.2 gauss), fluoroscopy/X-ray, radiofrequency (RF) generator, cryo gas station, stimulator, saline coolant pump for ablation catheter RF-tip irrigation, hemodynamics, magnetic catheter steering (0.08T).

Frequenly the patient is defibrillated to cardiovert them from an arrhythmia. It is common that patients have implanted defibrillators (ICDs).

It is CathVision's goal to test a PVI Analyzer software intended for assiting assessment of pulmonary vein isolation, using a novel electrophysiology recording system with improved signal quality.

An early version of the PVI Analyzer software has been tested and validated previously on signals recorded by a conventional EP recording system (Lab-System Pro, Boston Scientific)"[4,5]. [redacted]

[redacted]

Pulsed Field Ablation (PFA) is a new ablation modality for the treatment of paroxysmal atrial fibrillation through the isolation of pulmonary veins. Instead of using high temperatures to destroy cells, as in the case of radio frequency ablation, or extremely low temperatures with cryo ablation, PFA uses a technique known as irreversible electroporation where short burst of high energy are applied to specific areas which destroy cells and prevent further conduction[6]. This technique has been shown to be fast, effective and safe in studies and this approach is now CE approved and commercially available.

2 Device Description

2.1 Name of the Device(s) Under Investigation

The CathVision Cube® system is under investigation in this Study. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

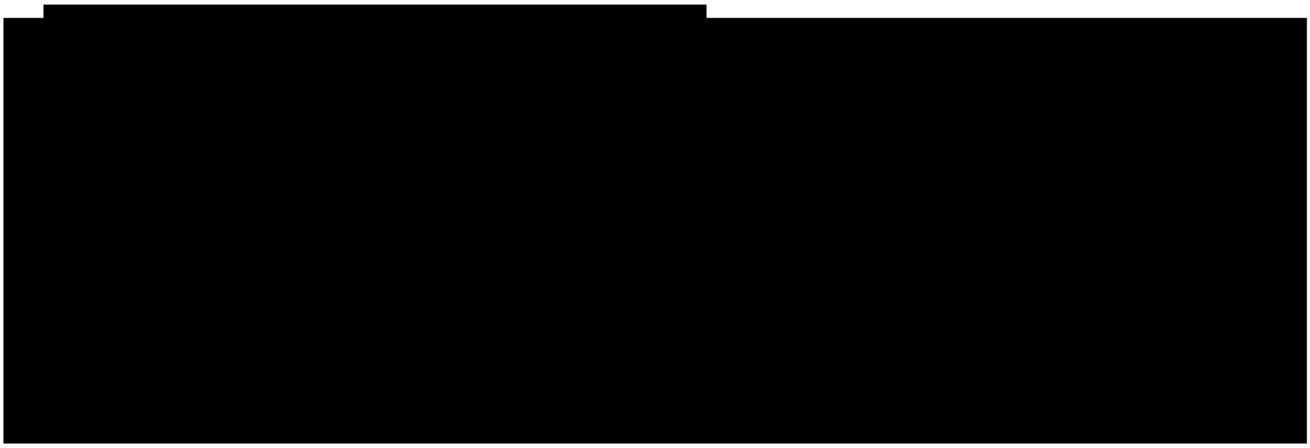
2.2 Intended Purpose

[redacted]

[redacted]

2.3 Description of the Device(s) Under Investigation (Signal Processing Overview)

[redacted]



[redacted]

[redacted]

2.4 Device Labelling and Handling

[redacted]

Each manufactured device is assigned a unique serial or lot number that is printed on the device labeling, providing a means of traceability. [redacted]

3 Risk-Benefit Analysis

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. [redacted]

Potential subject risks include adverse events and potential product failures similar to commercially available EP recording systems, with a similar likelihood of occurrence.

[redacted]

4 Clinical Investigation Plan (CIP)

4.1 Study Objectives

The primary objective is to validate the PVI Analyzer software with a novel EP recording system (CathVision Cube® System) for assessment of isolation status following PVI ablation.

The secondary objective is to determine the feasibility of "real-time" assessment of PVI analysis and rhythm dependent performance using the Investigational Device and CathVision Cube® System.

4.2 Study Design

A prospective, multi-center study to evaluate the performance of automated PVI Analyzer software with the CathVision Cube® system in RF and Cryo-balloon procedures

Subjects with paroxysmal or persistent atrial fibrillation (AF) who are indicated to undergo first PVIEP procedure and meet all eligibility criteria will be enrolled in the Study and undergo the EP procedure. Intracardiac signals will be passively recorded using the investigational CathVision Cube® System in parallel with the commercial (CE marked) Lab-System Pro, Boston Scientific EP recording system. [redacted] The EP procedure will be guided by the study site standards of care (CLOSE protocol for RF, and routine cryoballoon or PFA procedures according to operators preference).

[redacted]

4.3 Study Duration

[redacted]

Subjects will have clinical follow-up until discharged from hospital, regardless of the duration of hospitalization. After the EP procedure, the estimated number of days of hospitalization is 1-2.

4.4 Site Selection

The Study will be conducted in 4 centers [redacted] All sites are high-volume centers experienced in RF ablation procedures [redacted]

[redacted]

4.5 Subject Population and Eligibility Criteria

Up to 90 subjects shall be enrolled in the Study, distributed in two different procedures (RF and cryo-balloon) according to medical decision and standard of care at the study sites. The subjects are distributed among the participating sites with a maximum of 50 subjects per site, and a maximum of 25 subjects per procedure type per site. Once enrollment of 90 patients is completed, a further 30 subjects with a maximum of 15 per site may be enrolled for treatment with PFA, to a maximum of 120 subjects in total.

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained. Patients must meet ALL of the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

Inclusion Criteria

Eligible subjects will meet all of the following inclusion criteria:

1. Subjects undergoing first-time pulmonary vein isolation indicated by investigator for the treatment of atrial fibrillation
2. Male or non-pregnant female aged ≥21 years.
3. Able and willing to provide written informed consent prior to any clinical investigation related procedure

Exclusion Criteria

Eligible subjects will not meet any of the following exclusion criteria:

1. Pregnant or nursing subjects.
2. Current participation in another investigational drug or device study that interferes with this Study.
3. Subjects who, in the opinion of the investigator, are not candidates for this Study.
4. Patients who have had a prior ablation procedure
5. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.
6. Life expectancy less than 12 month
7. Subjects who, in the opinion of the investigator, are considered part of any vulnerable population.

Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent, has been confirmed to meet all inclusion criteria and none of the exclusion criteria, and has undergone initiation of the treatment procedure.

[redacted]

Subjects are enrolled until the maximum of 90 subjects across sites has been reached, [redacted]. Once RF and cryoballoon enrolment is complete, 30 additional PFA subjects will be enrolled at three sites. This additional data will be analyzed separately, as specified in the Stastistical Analysis Plan (SAP).

5 Study Endpoints

5.1 Primary Performance Endpoint

The primary performance endpoint is to validate the PVI Analyzer analysis software with a novel EP recording system (CathVision Cube® System) for assessment of isolation status following PVI ablation. The overall performance of PV isolation classification shall be superior to a specified level of performance.

1. Automated PVI Analyzer classification of PV isolation in SR during PVI ablation treatment with a specificity and sensitivity both superior to 80%.

Safety Endpoint

The safety endpoint of the Study will evaluate the adverse events and/or device malfunctions reported with the use of the CathVision Cube® System. [redacted] it is expected that AEs related to the device and device malfunctions will be minimal or absent.

5.2 Secondary Performance Endpoints

The secondary performance endpoints shall determine the feasibility of "real-time" assessment of PVI analysis and rhythm dependent performance using the PVI Analyzer software with the CathVision Cube® System:

1. Accuracy of automated PVI Analyzer classification of PV isolation in SR during PVI Cryo-balloon ablation with a specificity and sensitivity superior to 80%.
2. Accuracy of automated PVI Analyzer classification of PV isolation in SR during RF ablation with a specificity and sensitivity superior to 80%.
3. Assessment of automated PVI Analyzer classification of PV isolation in SR after PFA

4. Feasibility of PVI Analyzer analysis of PV isolation in NSR during PVI ablation treatment.

5. Feasibility of continuous “real-time” PVI Analyzer analysis during PVI ablation treatment.
6. Performance assessment of PVI Analyzer classification accuracy at the time of expert-defined isolation before the end of the PVI ablation procedure.
7. Comparison of algorithm performance on same data recorded by CathVision Cube and Boston Scientific LSPro systems

5.3 Study Procedures

Informed Consent

The Patient Informed Consent form must receive approval from the Sponsor and Ethics Committee (EC) prior to beginning clinical investigation enrollment.

The Investigator or authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the EC. [redacted] Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

The subject shall be provided with the Informed Consent form written in a language that is understandable to the subject and has been approved by the EC. The subject shall have adequate time to review, ask questions, and consider participation. [redacted] If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and thereafter by the Investigator (or designee) obtaining the consent prior to performing any clinical investigation-specific tests of procedures. [redacted]

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or authorized designee (if applicable) will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

Subject Identification

To maintain confidentiality, the subject's name will not be recorded on any study document other than the informed consent form. Each enrolled subject will be pseudonymized [redacted]

[redacted]

5.4 Visits

[redacted]

Schedule of assessments and Visits

	Visit 1 Screening (max. 30 days before index EP procedure)	Visit 2 Index EP procedure	Visit 3 Discharge
Informed Consent	✓		
Demographics	✓		
Cardiac Medical History	✓		
Arrythmia History	✓		
Cardiac Medications	✓	✓	✓
Inclusion/Exclusion	✓		
12 lead ECG	✓		✓
Urine Pregnancy Test*	✓		
EP procedure		✓	
Adverse Events		✓	✓
Device Malfunctions		✓	
Protocol Deviations	✓	✓	✓

* Women of child-bearing potential only. Max 7 days before Index EP Procedure (Visit 2)

Visit 1: screening visit

[redacted]

Test results from routinely performed standard assessments may be used to determine eligibility. [redacted]

If pre-screening criteria are met, informed consent will be obtained, and screening will proceed. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Screen Failures

Subjects not meeting all study eligibility criteria will be designated as screen failures. [redacted]

Visit 2: index procedure

During the index EP procedure, only procedures or steps from institutional standard of care / best practice will be used to treat the subjects.

[redacted]

Visit 3: discharge

[redacted]

5.5 Study Completion

Upon Study termination, if applicable, the Competent Authorities and ECs will be notified.

Completed Cases

Individual cases from subjects will be considered completed when all assessments [redacted] have been performed in accordance with the CIP.

Withdrawn Subjects

Any subject may voluntarily withdraw from the Study at any time without prejudice. The investigator may withdraw a subject from the Study at any time if (s)he considers that

remaining in the Study compromises the subject's health or the subject is not sufficiently cooperative. In either event, reason(s) for withdrawal should be recorded when provided or available.

[redacted]

Premature Study Termination

The Sponsor, Ethics Committee, or Competent Authority have the right to suspend or terminate the Study prematurely for any safety, ethical or administrative reason at any time. In addition, Investigators can terminate the Study at their sites if considered necessary.

[redacted]

[redacted]

5.6 Investigational Device Accountability

[redacted] Investigational devices are to be used only in accordance with this CIP and under supervision of the PI or a duly designated person. It is the PI's responsibility to ensure that all study devices are kept in a secure location, with access limited to individuals authorized by the investigator. [redacted]

6 Examinations and Evaluations

6.1 Demographics

[redacted]

6.2 Cardiac and Arrythmia Medical History

[redacted]

6.3 Cardiac Medications

[redacted]

[redacted]

6.4 12-Lead ECG

[redacted]

6.5 Pregnancy Test (women of childbearing potential only)

[redacted]

8. Safety Reporting and Device Deficiencies

[redacted]

7.1 Adverse Events Definitions

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the medical device under investigation. Note:

a. This definition includes events that are anticipated as well as unanticipated events
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

An untoward medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or clinically significant abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

Conditions or diseases that are chronic but stable should not be recorded as an AE. Changes in a chronic condition or disease that are consistent with natural disease progression are NOT considered AEs and should not be recorded. These medical conditions should be adequately documented in the subject's medical history. However, medical conditions present at enrollment that worsen in intensity or frequency in a manner inconsistent with the natural course of the disease during the treatment or post-treatment periods should be reported and recorded as AEs.

[redacted]

[redacted]

Note: Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

7.2 Serious Adverse Event Definition

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,
b) Led to a serious deterioration in health of the subject, that either resulted in
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient hospitalization or prolongation of existing hospitalization, or
    4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
    5. chronic disease
c) Led to fetal distress, fetal 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 an SAE.

Additionally, important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when they jeopardize the subject or require medical or surgical intervention to prevent one of the serious outcomes listed above.

Adverse device effect (ADE) is an AE related to the use of an investigational medical device. Note, this definition includes AEs resulting from insufficient or inadequate instructions for use, operation, or any malfunction of the investigational medical device. In addition, this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious adverse device effect (SADE) is an ADE that that has resulted in any of the consequences characteristic of a SAE.

An **unanticipated adverse device effect** (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in predicate devices, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.3Assessment of Adverse Events

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition). All AEs, regardless of severity, occurring at the index EP through study exit visit must be recorded. Events occurring prior to the endovascular procedure must be listed in the medical history.

Any Adverse Event(s) that may occur in this Study needs to be reported directly to the Sponsor within 5 working days and to the EC according to the local legislation. Participants experiencing Adverse Events must be treated by the investigator per clinical standard practice at the hospital.

[redacted]

7.4 Reporting/Recording of AEs

Throughout the course of the Study, all efforts will be made by the investigator to remain alert to possible AEs. The first concern will be the safety of the subject, and for providing appropriate medical intervention. [redacted] Any AE should be recorded on the appropriate study CRF.

7.5 Adverse Events Requiring Expedited Reporting

7.5.1 Investigator Responsibilities

The Investigator is responsible for reporting all SAEs, SADEs, device deficiencies that could have led to a SADE, and any new finding in relation to any event previously mentioned. The Invertigator should report them to the EC according to national regulations and EC requirements. [redacted]

The Investigator will document all SAEs and SADEs, including device deficiencies in the study subject's file and report it to the Sponsor and to the Sponsor's (Designee) within 24 hours of knowledge of event. [redacted]

In the event of a subject's death, the Investigator will make reasonable effort to obtain a copy of the autopsy report and/or death summary. The Investigator will determine the cause of death and its relationship to the investigational device; [redacted]

7.5.2 Sponsor Responsibilities

Upon notification of SAEs, the Sponsor will initiate and complete a review and evaluation of the event within time frames that will maintain reporting compliance with applicable regulatory

agencies. [redacted]

[redacted]

7.6 Anticipated Adverse Events Related to the CathVision Cube® System

[redacted]

7.7 Anticipated EP-Procedure Adverse Events

Anticipated complications/AEs are defined as complications/events that can be reasonably associated with the EP catheter ablation procedures. The mitigations and treatments for these AEs will follow published guidance for the same AEs occurring with other commercially available devices [1].

[redacted]

[redacted]

7.8 Device Deficiencies

Device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate information supplied by the manufacturer. This includes the failure of the device to meet its performance specifications or otherwise perform as intended.

[redacted]

Device malfunction is the failure of an device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

User error: is the act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

The Device Deficiency CRF is specific for reporting all device deficiencies, or malfunctions that occur during the course of the Study, whether or not they were associated with an adverse event. Device Deficiency CRFs should be submitted to the Sponsor within 24 hours of the occurrence defining the device deficiency. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

8 Statistical Methods

A detailed description of the protocol for the statistical analysis of each specified endpoint is given in the Statistical Analysis Plan (SAP). This includes the plan for interim and final analyses.

8.1 Study Population

8.2 Sample Size Calculation

This Study is intended to demonstrate that the performance of the PVI Analyzer software is superior to clinically relevant performance level, as established by prior publications.

[redacted]

[redacted] a clinically relevant lower limit of performance has been established and defined as 80% specificity and 80% sensitivity.

[redacted]

[redacted]

[redacted]

[redacted]. In total, 90 subjects are expected to be required to reach the sample size requirement for both specificity and sensitivity.

In conclusion, a maximum of 90 subjects will be required.

[redacted]

[A] Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series.

each site shall enroll a maximum 25 subjects for RF and Cryo, respectively (50 subjects maximum per site).

A cohort of 30 subjects undergoing PFA will be added to the study, [redacted]

8.3 Descriptive Analyses

Continuous variables will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations, if any, will also be summarized.

Categorical variables will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Number and percent of missing data, if any, will also be summarized.

[redacted]

9 COMPLIANCE

9.1Ethics Committee (EC)

Prior to the initiation of the Study, the CIP, and the informed consent form will be submitted to the EC for approval. By signing the Clinical Study Agreement, the investigator is assuring that an EC will be responsible for the initial and continuing review of the proposed Study. A copy of the EC approval letter for the CIP, the informed consent, and the CIP signature page must be submitted to the Sponsor or its Designee prior to release of investigational supplies to the study site. The approval letter must refer to the specific CIP and the informed consent form. Any Investigator who is also a member of the EC is not to participate in the study approval decision. This non-participation must be noted in the approval letter. [redacted]

[redacted]

9.2 Competent Authority (CA)

The Study will be reviewed by the relevant Competent Authority as well. The Sponsor or its Designee is responsible for obtaining regulatory approval for the Study from the relevant Competent Authority. No subjects may be enrolled in the Study until written notification of such approval has been given by the Sponsor. The Sponsor or its Designee is responsible for reporting SAE and Device Deficiencies that might have led to a SADE as appropriate to the

relevant Competent Authority. [redacted]

The Study will not start without the written approval of the EC and the Competent Authority. Upon Study termination, if applicable, the Competent Authorities and ECs will be notified.

9.3 Good Clinical Practice Statement

This Study will be conducted in compliance with the CIP, the signed Clinical Study Agreement and with the ethical principles stated in the latest version of the Declaration of Helsinki (2013), the applicable guidelines for good clinical practices, EU MDR 2017/745, EN ISO 14155:2020 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), and the applicable local and international regulations, in order to provide the greatest protection of the individual. Any deviations from the CIP that may affect the safety and welfare of study participants will be immediately reported to the Sponsor and to the Ethics Committee (EC) [redacted]

9.4 Investigator responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the Study is conducted in accordance with the Clinical Study Agreements, the CIP, ISO 14155:2020, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject. [redacted]

- [redacted]

[redacted]

[redacted]

9.5 Sponsor Responsibilities

All information and data sent to the Sponsor concerning subjects or their participation in this Study will be considered confidential. Only authorized Sponsor or Sponsor's Designee will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this Study. [redacted] All data used in the analysis and reporting of this Study will be without identifiable reference to specific subject name and will be pseudonymized. [redacted]

[redacted]

9.6 Clinical Investigation Plan Amendments

[redacted] All CIP modifications must be approved by the CA/EC before implementation.

10 Study Conduct

10.1 Informed Consent Process

It is the responsibility of the Investigator to inform each subject prior to the screening evaluation, of the purpose of this Study, including possible risks and benefits and document the informed consent process in the subject's chart. Any changes made to the informed consent must be approved by the Sponsor or its Designee, prior to submission to an EC. After approval by the Sponsor or its Designee, the informed consent must be submitted to and approved by the applicable EC.
The process of obtaining informed consent at a minimum shall include the following steps:

- Ensure that the principal investigator or its authorized Designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate

- Not waive or appear to waive the subject's legal rights
- Use native non-technical language that is understandable to the subject
- Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
- Include personally dated signatures of the subject and the principal investigator or an authorized Designee responsible for conducting the informed consent process
- Provide the subject with a copy of the signed and dated informed consent form and any other written information
  Ensure important new information is provided to new and existing subjects throughout the clinical investigation

One original informed consent form is to be retained by the study site and a copy is to be given to the subject. [redacted]

The informed consent must be written in a language in which the subject is fluent. If a foreign language translation is required, a statement of certification of the translation must be issued. Regulations require that foreign language informed consent forms be submitted to the EC for approval. The investigator must forward a copy of the consent form, the certified foreign language translation and an EC approval letter to the Sponsor or its Designee.

10.2 Study Training

[redacted]

Documentation of training will be maintained up to date and periodically reviewed by the CRO [redacted]

10.3 Study Monitoring and Source Document Verification

[redacted]

During the Study, the CRA will visit the study facilities regularly and utilize telephone and written communications on an ongoing basis to ensure adherence to the Protocol, ICH-GCP, SOPs and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy, and verifiability of CRF entries compared to source data..

Subject safety will be ensured by noting that the consent was properly documented, the CIP was followed, and that AEs were reported and followed-up as appropriate.

10.4 Study Close-out

10.5 Protocol Deviations

A protocol deviation is any noncompliance with the CIP, GCP, or IFU requirements. The noncompliance may be either on the part of the subject, the investigator, or the trial staff.

Protocol Deviations must be documented on the appropriate Protocol Deviation CRF within 30 days of awareness of the deviation.

[redacted]

[redacted]

10.6 Insurance

In order to cover possible damage to health, in relation to participation in this Study, the Sponsor, has, as required by law, obtained appropriate insurance coverage.

10.7 Data Handling

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.8 Confidentiality

In accordance with GCP and with the national data protection laws, all information concerning the subjects in the Study must be treated as strictly confidential by all persons involved in the Study. Health data will be recorded and forwarded to the Sponsor or its Designee, participating EC and Competent Authorities, for evaluation as required. Data processing will be performed in compliance with the EU General Data Protection Regulation (GDPR) 2016/679, and all applicable national laws.

Any information that is obtained in connection with this Study that can be identified with the subjects will remain confidential. [redacted]

[redacted]

[redacted]

At the end of the trial, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing EC, Institutional policies, or sponsor requirements.

10.9 Record Keeping and Retention

Data generated for the Study should be stored in a limited-access file area and be accessible only to Designees of the study site, the Sponsor and its Designees and relevant health authorities/regulatory agencies. All reports and communications relating to study subjects will identify subjects only by subject identification number and will be pseudonymized. Complete subject identification will be kept by the investigator. This information will be treated with strict adherence to professional standards of confidentiality. The Investigator is ultimately responsible for maintaining all essential trial documentation and source documentation.

[redacted]

[redacted] The Investigator will not discard any records without notifying the Sponsor. [redacted]

10.10 Final Report

[redacted]

10.11 Publication Policy

The data and results from the clinical investigation are the sole property of the Sponsor. [redacted]

[redacted]

11. REFERENCES

[redacted]