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STUDY CODE: 2017/170/HP **STUDY NAME:** AXONE-Acute

STUDY TITLE:

AXONE-Acute: Acute assessment of a micro multipolar lead for enhanced cardiac resynchronisation therapy

FINAL CLINICAL STUDY REPORT

Version N° 1.0 **Date: 06 MAR 2019**

Investigational Device: AXONE System

The present clinical investigation was performed in accordance with ISO14155, Declaration of Helsinki and other applicable regulations.

HISTORY

Rev.	Change	Reason for Change
A	Initial release	NA

SIGNATURE PAGE

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1. SUMMARY OF THE CLINICAL STUDY REPORT

Optimal left ventricular (LV) lead positioning is a key parameter in the success of cardiac resynchronization therapy (CRT). LV lead implantation can be complex and time consuming, mainly due to anatomical reasons. To overcome some of these difficulties, a downsized quadripolar LV lead was developed by MicroPort CRM. The AXONE is a very thin lead, aimed at 1) improving the chance of positioning the lead, particularly in areas where a standard LV lead cannot be placed, and 2) improving hemodynamic response of cardiac resynchronization therapy by enlarging electrical stimulation zone.

The AXONE-Acute study (Acute assessment of a micro multipolar lead for enhanced cardiac resynchronisation therapy) was designed to evaluate safety and performance of the AXONE system in acute setting. In patients candidate for CRT implantation, the AXONE lead electrical performances were tested acutely, before removal and implantation of commercially available LV lead. The two co-primary endpoints were success rates of LV pacing and LV multizone pacing – success being defined as a pacing threshold ≤ 3.5V/0.5ms. Secondary endpoints included testing procedure-related or AXONE lead-related adverse events at 1 month post testing procedure, implant efficiency (including procedure/fluoroscopic time, radiation dose, handling assessment), assessment of electrical parameters (pacing threshold, impedance) and LV multipoint pacing success rate.

The study was conducted in 4 investigational sites in France. Twenty four patients were enrolled and AXONE testing procedure was attempted in 20 patients. First patient was enrolled on August 8th, 2018. Last patient last visit occurred on December 13th, 2018.

The co primary endpoints of the study were not met. An LV multizone pacing success rate ≥ 70% had been pre-defined as acceptable; this rate was 55% in the study. An LV pacing success rate ≥ 85% had been pre-defined as acceptable; this rate was 80% in the study.

However, the concept of cross vein lead placement using the AXONE system appears promising, as it could be performed in the vast majority of the patients (18/20).The cross-vein placement reached in 55 % of patients allowed pacing sites clearly different from what can be achieved with a conventional IS-4 lead.The handling assessment scores were good.

The median protocol-related procedure time was slightly above the predefined value (21 vs 20 min). This and the feedback of the investigators suggest that the time allowed to the AXONE procedure could benefit from an extended duration.

Mean LV pacing threshold was 1.79 ± 1.1 V in unipolar pacing and 1.63 ± 0.93 V in bipolar pacing. Mean impedance was 1683 ± 345 Ohms in unipolar pacing and 3532 ± 288 Ohms in bipolar pacing.

Acute safety profile of the lead was good: no adverse events were classified as clearly related to the AXONE system or the testing procedure. However, it was noticed that pericardial reactions or effusions were more frequently observed than expected. Although these phenomena were benign, without clinical consequences, it should be closely monitored during future evaluation.
No device deficiency was reported.

From these results, it seems that the Axone concept and global system is a valid approach to treat patient candidates to cardiac resynchronization. However, efforts should be made on improving pacing capabilities of the AXONE lead.

2. INTRODUCTION

Cardiac resynchronisation therapy (CRT) is a widely accepted treatment for drug refractory heart failure patients in NYHA Class II, III or IV, with reduced left ventricular ejection fraction and QRS width over 150 ms [(1)]. These recommendations are based on the results of the controlled randomized trials that included patients with dyssynchrony on the basis of QRS width, the latest (Care-HF [(2,3)], REVERSE [(4)], MADIT-CRT [(5)] and RAFT[(6)]) showing a significant reduction in morbidity-mortality.

Nevertheless, using these criteria 30 to 35 % [7] of the patients do not demonstrate any significant benefit or can even be aggravated by the treatment.

This non-responder rate may be explained by:

- a sub-optimal patient selection.
- a sub-optimal therapy delivery including a sub-optimal leads implantation.

Further to this assessment and the fact that clinical practice and many studies demonstrate that success of cardiac resynchronization therapy is associated with the site of left ventricular stimulation [8,9,10,11], we have decided to focus on how optimizing the Left Ventricular (LV) lead placement and improving resynchronization therapy.

The implantation of the LV lead can be complex and time consuming [12,13,14]. Common problems met during the implantation that mostly prevent successful LV lead placement, include variations in the position of the coronary sinus, difficulties to access small and tortuous veins, high stimulation thresholds and phrenic nerve stimulation.

To overcome some of these difficulties, quadripolar LV leads have been recently developed by several companies. The ability to electronically reposition the pole of stimulation has been shown to efficiently suppress phrenic nerve capture during resynchronization therapy delivery[15]. Quadripolar leads also allow pacing at more basal LV site which seems to be associated with a better hemodynamic response, although long term data are not available yet[16,17,18].

Thus, it appears obvious that the design of the lead is one of the most important items defining the success of its implantation: thin aspect, curvature of the end should allow its easiest insertion into narrow veins or stable position in the large vein.

Then to overcome the limitation of lead placement with actual LV leads, a lead below 2 French with specific distal shape is currently developed by MicroPort CRM. The objectives of this very thin lead, are 1) to improve the chance of positioning the lead, particularly in areas where a standard LV lead cannot be placed, and 2) to improve hemodynamic response of cardiac resynchronization therapy by enlarging electrical stimulation zone.

3. INVESTIGATIONAL DEVICE DESCRIPTION

3.1. GENERAL DEVICE DESCRIPTION

AXONE system is a novel lead for Left Ventricle pacing, aiming to deliver CRT to heart failure patients.

AXONE lead has two main characteristics:

- A downsized lead body(diameter around 1 French: 0.4mm) (Figure 1)

  Thanks to its small size, AXONE lead can reach small veins that cannot be accessed with the available marketed leads. It gives multiple options for the lead placement in the coronary venous system. This results in more effective implant procedures and higher chances of reaching the target vein.

  Unlike marketed LV leads, AXONE is designed without any internal lumen, and has a wire structure to allow downsized diameter. Therefore the implantation technique differs from marketed leads, and involves a catheter described below.

- A multi-zone pacing lead with a 4 selectively programmable electrodes (Figure 1)

  Since AXONE allows wider access to the coronary veins, the left ventricle can be paced from distant locations (“multi-zone” pacing) whereas a conventional LV lead has a smaller pacing zone. This multi-zone pacing may subsequently result in better cardiac resynchronization due to the enlarged pacing area.

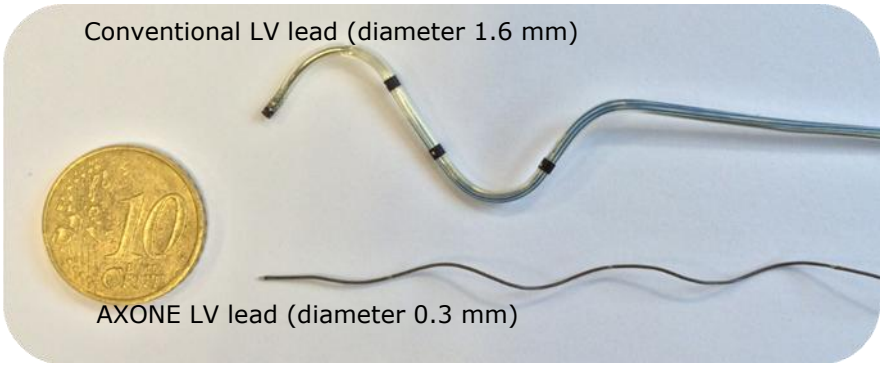

Figure 1 – AXONE lead diameter

AXONE lead is intended to be used in conjunction with a specific catheter designated as AXONE Fastrack (Figure 2).

The purposes of this catheter are:

- to navigate into the coronary veins (AXONE lead is not designed to be pushed in the veins),
- to select the adequate AXONE lead model using the X-ray markers,
- to allow AXONE lead delivery at the target vein,
- to provide extra stability and insulation to the AXONE lead.

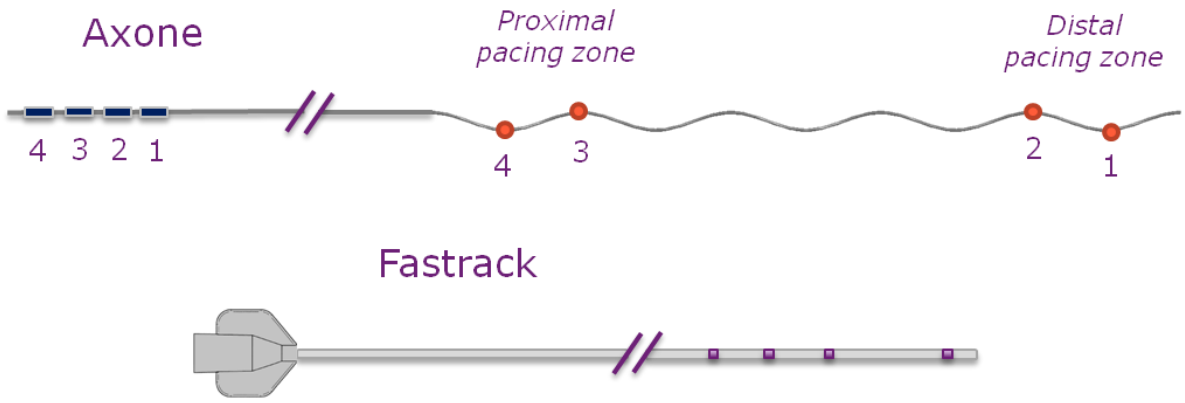

Figure 2 – AXONE lead and FASTRACK catheter

The design of the AXONE system relies on advanced technology, allowing the following innovative features:

- AXONE pacing zone is pre-shaped into a three dimension spiral, to improve mechanical contact into the vein and lead stability,
- Electrodes placement into the spiral shape is optimized to enhance electrical contact with tissues,
- AXONE pacing electrodes have a reduced surface (0,6mm² versus ~5 mm² in conventional LV leads), to limit energy consumption,
- AXONE conducting wire is exclusively made of Platinium-Iridium, to ensure X-ray visibility despite downsized diameter,
- FASTRACK catheter has an hydrophilic coating to ensure smooth navigation into the coronary veins network.

3.2. MODELS & DEVICE SUPPLY

Several models of AXONE lead are proposed to suit the patient's coronary vein anatomies:

1. AXONE lead Model L
2. AXONE lead Model M
3. AXONE lead Model S
4. AXONE lead Model XS

The Fastrack catheter is compatible with all AXONE models.

Models	Full Length (mm)	Electrode distance 1-4 (mm)	Electrode distance 1-2 and 3-4 (mm)
AXONE lead Model L	1235	170	20
AXONE lead Model M	1195	130	20
AXONE lead Model S	1150	90	20
AXONE lead Model XS	1120	60	20
AXONE Fastrack	870	NA	NA

Table 1 – AXONE system characteristics

The AXONE investigational device has been developed exclusively for clinical research purpose as a temporary single-use lead. The AXONE lead and Fastrack catheter are manufactured by Sorin CRM SAS/ MicroPort CRM (Legal Manufacturer: Sorin Group Italia S.r.l - Via Crescentino s.n. - 13040 Saluggia (VC) – ITALIE).

3.3. PURPOSE OF THE DEVICE

In the present study the AXONE system was tested acutely but not implanted chronically. It is intended to be tested for research purpose in patients scheduled for a CRT intervention.

In its final implantable version the AXONE system will be expected to provide improved “implantability” (e.g. better success rate of the procedure, more viable pacing locations) for better CRT implantation efficiency, as well as multi-zone LV pacing for improved quality of cardiac resynchronization. These features may improve the outcome of patients who are currently not responding or poorly responding to CRT, and to patients who were formerly untreatable due to their narrow and tortuous coronary veins.

3.4. DEVICE USE

The AXONE lead is placed with a specific catheter approach as shown in the figure below.

1. Insertion of the catheter AXONE Fastrack with a conventional 0.014” guidewire, until target position is reached
2. Removal of the guidewire, and selection of the AXONE model according to the anatomy
3. Insertion of the AXONE lead within the catheter, then pullback of the AXONE Fastrack

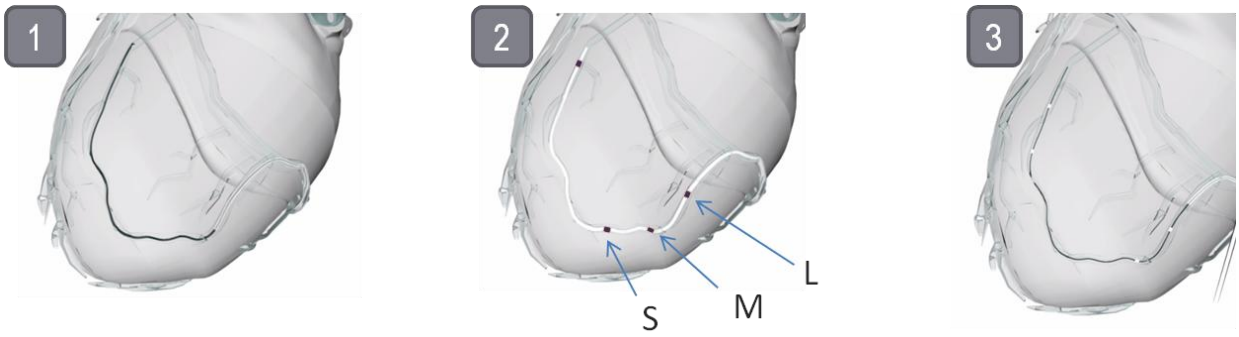

Figure 3 – AXONE implantation with Fastrack catheter

3.5. DEVICE SAFETY EVALUATION

A list of anticipated intra-operative Adverse Events related to Device/Implant testing procedure was prepared prior to initiation of the clinical investigation and included in the study protocol. The list is given in below table. These events are not different from the usual adverse effect related a CRT system or implantation procedure.

Events	Possible adverse effects
Cardiac tissue perforation	Coronary sinus dissection, pericardial effusion, hypotension, cardiac tamponade, cardiogenic shock
Myocardial trauma	Iatrogenic atrio-ventricular block, formation of clot at injury site possible embolism of clots, bleeding
Local vein perforation (ex: sub-clavian vein)	Hematoma, air embolism, pneumothorax
Arrhythmia	Extrasystoles, tachycardia, ventricular/atrial fibrillation
Contamination	infection, septicemia

Table 2 – Anticipated Adverse Events related to device or implant testing procedure

4. CLINICAL INVESTIGATION PLAN SUMMARY

4.1. STUDY OBJECTIVES

In order to assess the feasibility of LV pacing using the AXONE lead family, the objectives of this pilot study are:
- to evaluate the performance of AXONE during an implant testing procedure including the ability to reach target veins and to deliver efficient LV pacing (primary objective),
- to evaluate the acute safety of AXONE and testing procedure,
- to confirm the design of AXONE lead models.

4.2. STUDY DESIGN

AXONE study is a pre-market, prospective, single-arm multicenter data collection clinical research study designed to characterize the acute performance of AXONE lead models.

Study design and related study procedures are described below.

4.2.1. Patient Screening & enrolment

Screened subjects were patients planned for primary implantation of a CRT device. Written informed consent of each subject was obtained prior to performance of any protocol specific procedures, and inclusion/exclusion criteria were checked. Medical history information was collected.

4.2.2. Implant testing Procedure

The AXONE implant testing procedure was achieved during planned implantation of the CRT device. The following procedures were conducted, in preparation for the conventional LV implantation:

- Perform a venogram of the whole venous network using an occlusive balloon catheter and collect image of the venogram,
- Implant the Right ventricular lead (used as electrical ground for AXONE testing).

AXONE implant testing procedure was limited to 20 minutes. The timer started at insertion of the Fastrack catheter in patient body. At this stage the patient was considered evaluable. The AXONE lead (and catheter) had to be removed 20 minutes after start of implant testing procedure.

Steps of the testing procedure are summarized below:

1. Insert a fastrack catheter to select the target vein
2. Select one of the AXONE model based on the observed venous anatomy

3. Placement of the AXONE system is performed according to the following principles, with respect of Figure 4 in order to best manage priorities against time:
    a. Target cross-vein placement (bifurcation of a collateral vein)
    b. If cross vein-placement is unsuccessful (or if cross-vein placement was completed in less than 10 min), select AXONE XS model and test a single-vein position: ideally in a collateral vein parallel to mitral annulus.
4. Perform and collect the following electrical measurements with the PSA with respect of Figure 4 in order to best manage priorities against time:
    a. Pacing Thresholds at 0.5ms pulse width
    b. Phrenic capture testing at 10 volts If time allows: Stability defined as 20 consecutive paced beats at Pacing Threshold + 1Volt
    c. Collect documentation for the tests
5. Remove AXONE lead and Fastrack

Implantation of standard LV lead and CRT system was then completed. All serious and non serious (related or not) adverse events were collected.

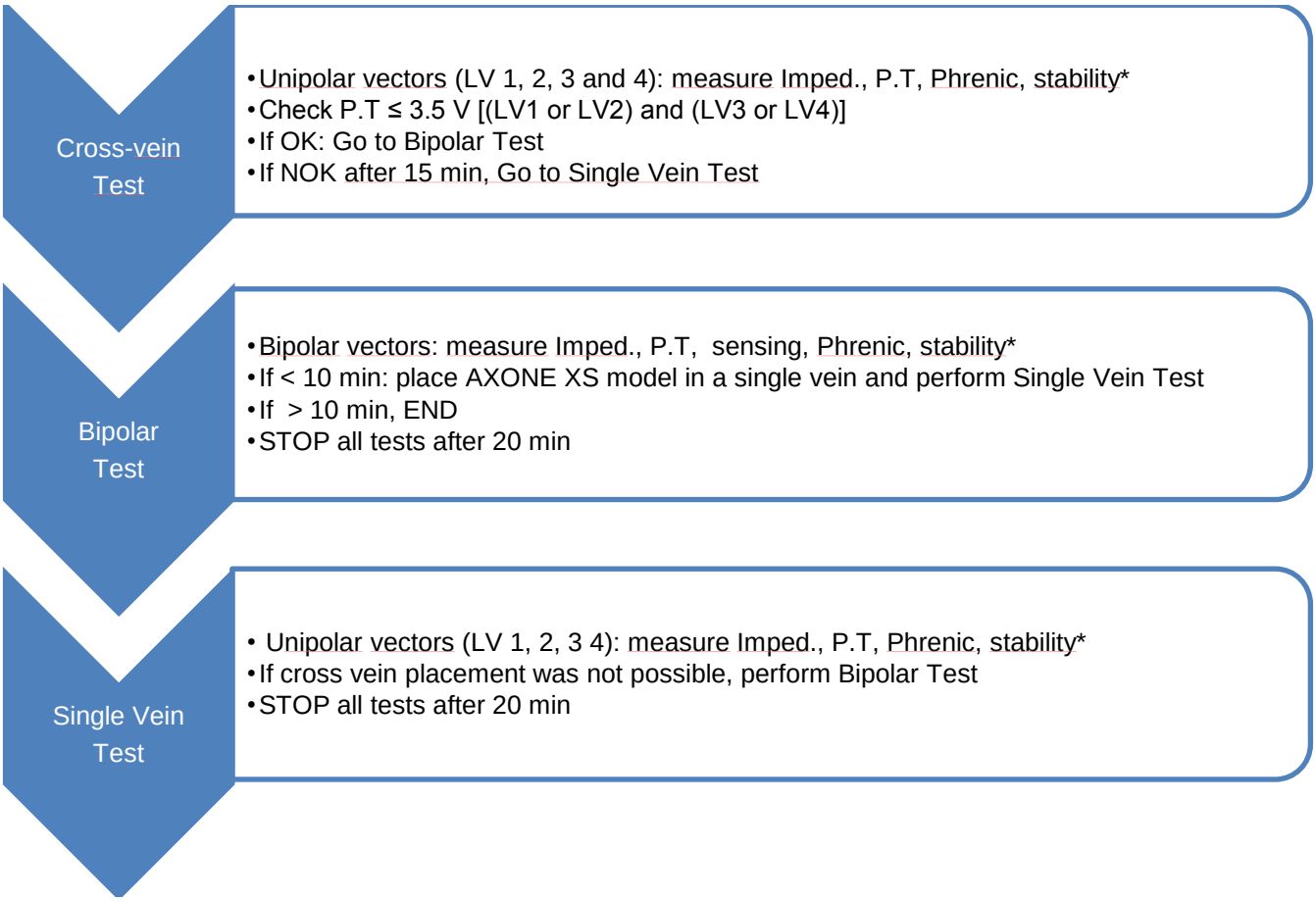

Figure 4 – Implant testing Procedure flowchart for time management

**20 consecutive beats without extra systoles, if time allows*

4.2.3. **Post-intervention follow-up**

The safety was evaluated remotely at 1 month ± 7 days after the implant testing procedure, collecting all adverse events.

Study completion for a subject occurs after 1 month following the implant testing procedure, or after documentation and resolution of any safety event. Next subject follow-up is scheduled by the physician according to his/her standard clinical practice.

4.3. STUDY ENDPOINTS

4.3.1. Primary endpoints

The study has 2 co-primary endpoints assessed independently.

- **LV Multizone pacing success rate:** Percent of patients where the placement of the AXONE lead provides two distant LV pacing vectors matching:
  - Pacing Threshold ≤ 3.5V/0.5ms.

  Two pacing vectors are considered distant if they involve one vector from the distal electrode zone (electrode 1 or 2) and one vector from the proximal electrode zone (electrode 3 or 4) (see Figure 2).
- **LV pacing success rate:** Percent of patients where the placement of the AXONE lead allows at least one LV pacing vector matching:
  - Pacing Threshold ≤ 3.5V/0.5ms.

4.3.2. Secondary endpoints

- Implant testing Procedure-related or AXONE lead-related Adverse Events at 1 month post testing procedure.
- Electrical performance focusing on LV pacing threshold (Volts) and LV pacing impedance (Ohm).
- AXONE Implant Efficiency: procedure time for successful placement, fluoroscopic time, radiation dose, handling assessment.
- LV multipoint pacing success rate: the placement of the AXONE provides two pacing vectors matching:
  - Pacing Threshold ≤ 3.5V/0.5ms.

4.4. THE ETHICAL CONSIDERATIONS

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice described in ISO 14155, and the applicable regulatory requirement(s). The CIP and informed consent forms were submitted to the Ethics Committee (EC) for written approval. Any additional requirements imposed by the EC or regulatory authority (or Competent Authorities (CA)) was followed.

4.5. THE DATA QUALITY ASSURANCE

Monitoring of the clinical study was overseen by the Sponsor monitoring team. The aim of the data quality assurance was to ensure that high-quality data was obtained and that the study was conducted in compliance with the CIP, investigator agreement, applicable laws, regulations, and good clinical practice as established in the sponsor's monitoring plan.

4.6. SUBJECT POPULATION

A maximum of 25 patients were planned to be enrolled, for a maximum of 20 evaluable patients. Four investigational sites were planned, located in France. The sites involved in the study were chosen according to their enrollment capacity, research infrastructure and quality pre-requisites, and expertise in the field of CRT.

The inclusion criteria were the following:

- Male or female patient aged ≥18 years old.
- Patient presenting a CRT-P or CRT-D indication according to the latest ESC guidelines.
- Primary implant of a CRT device (including upgrade from a single or dual-chamber pacemaker or ICD).
- Signed and dated informed consent.

- Patient affiliated with, or beneficiary of a social security category.

The exclusion criteria were the following:

- Class IV of NYHA (ambulatory or not).
- Allergy to contrast media used for imaging during cardiac catheterization.
- Severe Renal Failure (clearance of creatinine < 30ml/mn/m²).
- Previous failure catheterization of the coronary sinus, or previous failure of left ventricular lead implantation.
- Already included in another clinical study involving intra-cardiac active implantable device, or participation to any other clinical trial in the last 2 weeks.
- Person deprived of liberty by administrative or judicial decision or placed under judicial protection (guardianship or supervision).
- Known pregnancy, breastfeeding women or in childbearing age without an adequate contraceptive method (failure rate < 1%).

4.7. THE TREATMENT AND TREATMENT ALLOCATION SCHEDULE

Not applicable.

4.8. CONCOMITANT MEDICATIONS/TREATMENTS

Not applicable.

4.9. DURATION OF FOLLOW-UP

Duration of follow-up is 1 month post implant testing procedure.

4.10. STATISTICAL ANALYSIS

4.10.1. General statistical considerations

This study is assessing the feasibility of LV pacing by the AXONE lead, therefore it is exploratory by nature. No statistical design or statistical hypothesis testing is performed. In particular, this study is not powered to demonstrate the safety and performance against a performance goal. However indicative levels of clinical acceptability have been pre-defined for each of the co-primary endpoints, as follows:

- LV Multizone pacing success rate ≥ 70%
- LV pacing success rate ≥ 85%

4.10.2. Sample size calculation

The sample size requirement for the study has been determined by assessing the minimal number of patients that will provide reliable results. Based on expertise and given the variability in human anatomy, 20 evaluable patients (meaning fulfilling all selection criteria and initiating AXONE implant testing procedure) is considered to be needed.

In case AXONE lead testing was scheduled but finally not attempted (patient becoming unstable clinically at the beginning of the procedure, failure to catheterize coronary sinus etc), the patient would not be considered as evaluable in the study. The number of such patients was recorded and the reason for not attempting the test. As soon as AXONE lead testing was initiated the patient was considered as evaluable in the study, even if AXONE testing was interrupted for any reason.

It was expected that AXONE implant testing procedure may not be initiated in around 20% of patients, meaning a maximum of 25 patients may be enrolled.

4.10.3. Analysis population

The following analysis population sets were defined:

- Intention-to-Treat (ITT): all patients evaluable.
- Full Analysis set (FAS): all ITT patients with evaluable data for the primary endpoints.

- Per Protocol (PP): all ITT patients without major protocol deviations, providing evaluable data for primary endpoints.

The principal planned analysis population for the primary endpoint is the Full analysis set population. The principal planned analysis population for safety is the Intention-to-Treat population.

4.10.4. Primary endpoint analysis

The study has 2 co-primary endpoints assessed independently. For the 2 co-primary endpoints, missing data will be considered conservatively as not fulfilling the condition. In particular, in multi-zone LV pacing success rate endpoint, patients with missing electrical data because the AXONE lead could not be positioned in a suitable vein, will be considered as not fulfilling the success criteria.

4.11. CIP AMENDMENTS

Not applicable.

5. STUDY RESULTS

5.1. STUDY POPULATION

5.1.1. Disposition of subjects

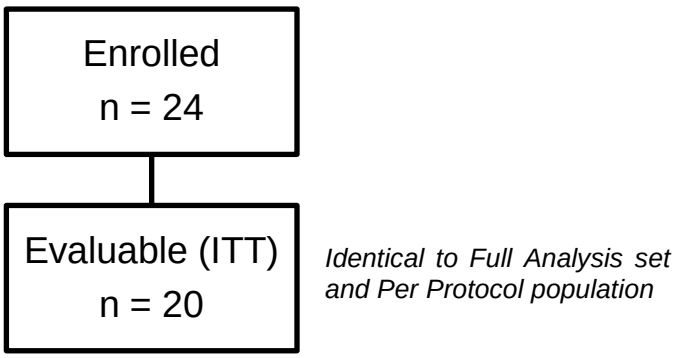

Figure 5 - Patient disposition

Twenty four subjects were enrolled in the study. Testing procedure of the AXONE system was attempted in 20 subjects, which corresponds to the ITT population (evaluable patients).

Reasons for not attempting testing procedure (n=4) are detailed below:

- One AXONE implant procedure not started because of a venous occlusion and standard implantation long and complex (*subject 203*),
- One AXONE implant procedure not started because "patient with several stenosis and valves within his coronary system. Too difficult to find an adapted vein for left ventricular leads; the physician prefers to not perform an AXONE attempt" (*subject 204*),
- One AXONE implant procedure not started because of a coronary sinus dissection (*subject 302*),
- One AXONE implant procedure not started because of patient's anatomy (*subject 405*).

The same 20 patients had the fastrack successfully placed (14 cross-vein, 2 single-vein, 4 cross-vein and single-vein); corresponding to Full analysis set.

Two fastracks failed to be placed cross-vein (*subjects 303 and 304*), with following comment (identical for both patients): "Impossible to advance the fastrack further and suddenly to have a cross-vein site".
Fourteen fastracks were not placed single-vein (optional in the protocol if cross vein placement successful). In most cases, lack of time was invoked as the reason for not placing fastrack in single vein.

None of the 20 patients had any major protocol deviation (Per Protocol population).

Therefore, the three populations (Intention to treat, Full Analysis set and Per Protocol) are identical.

All evaluable subjects (n=20) were followed-up until the 1-month follow-up visit, for a mean follow-up duration for 32.4 ± 2.48 days.

5.1.2. **Study period and enrollment summary**

Study dates	
First patient enrolled	**08 AUG 2018**
Last subject enrolled	**12 NOV 2018**
First intervention	**09 AUG 2018**
Last intervention	**13 NOV 2018**
Last visit last patient	**13 DEC 2018**

Table 3 – Description of study period

5.1.3. **Number of subjects per site**

Center	Principal Investigator	Enrolled subjects	Evaluable subjects (ITT)
CHU de Rouen, France	Pr Frédéric ANSELME	6 (25%)	6 (30%)
CHU de Rennes, France	Pr Christophe LECLERCQ	5 (21%)	3 (15%)
CHU de Bordeaux, France	Pr Philippe RITTER	6 (25%)	5 (25%)
CHU de Lille, France	Pr Didier KLUG	7 (29%)	6 (30%)
	Total	**24 (100%)**	**20 (100%)**

Table 4 – Participating sites and enrolment

5.1.4. **Medical history**

5.1.4.1. Subject demographics

Subject demographics	**Enrolled (n=24)** n (%) or mean ± SD	**ITT (n=20)** n (%) or mean ± SD
Total	**24 (100%)**	**20 (100%)**
Male gender	15 (62.5%)	12 (60%)
Age at enrolment (years)	66.8 ± 10.2	66.2 ± 10.5
Height (cm)	170 ± 8.2	170 ± 8.5
Weight (kg)	83.3 ± 18.5	84 ± 19.7
BMI (kg/m²)	28.7 ± 5.5	28.9 ± 5.8
QRS duration (ms)	162.9 ± 32.6	163.4 ± 28.2
Device implantation		
CRT-D	16 (66.7%)	15 (75%)
CRT-P	3 (12.5%)	2 (10%)
Upgrade	5 (20.8%)	3 (15%)
NYHA Class		
I	2 (8.3%)	1 (5%)
II	15 (62.5%)	12 (60%)
III	7 (29.2%)	7 (35%)
LVEF (%)	32.7 ± 10.4	32.5 ± 9.9

Table 5 - Subject demographics

5.1.4.2. Concomitant diseases and medication

Concomitant diseases and medication	**Enrolled (n=24)** n (%) or mean ± SD	**ITT (n=20)** n (%) or mean ± SD
Conduction disorder		
Left CBB	12 (50%)	12 (60%)
Paroxysmal 1st AVB + Left CBB	1 (4.2%)	0
Paroxysmal 2nd AVB + Right CBB	1 (4.2%)	1 (5%)
Paroxysmal 3rd AVB + Left CBB	1 (4.2%)	0
Permanent 1st AVB + Left CBB	4 (16.7%)	4 (20%)
Permanent 2nd AVB	1 (4.2%)	1 (5%)
Permanent 3rd AVB	2 (8.3%)	0
None	2 (8.3%)	2 (10%)
Cardiomyopathy		
Idiopathic	6 (25%)	6 (30%)
Ischemic	9 (37.5%)	7 (35%)
Secondary (non-ischemic)	7 (29.2%)	5 (25%)
dilated	5 (20.8%)	3 (15%)
hypertrophic	1 (4.2%)	1 (5%)
post-chemotherapy (antracyclines)	1 (4.2%)	1 (5%)
Idiopathic + Dilated	1 (4.2%)	1 (5%)
None	1 (4.2%)	1 (5%)
Valvular heart disease		
Mitral	8 (33.3%)	7 (35%)
Mitral + Aortic	3 (12.5%)	2 (10%)
Mitral + Aortic + Tricuspid	2 (8.3%)	2 (10%)
None	1 (4.2%)	9 (45%)
Associated conditions		
Diabetes	8 (33.3%)	5 (25%)
Dyslipidemia	17 (70.8%)	14 (70%)
Acute Smoking	1 (4.2%)	1 (5%)
Adiposity	3 (12.5%)	3 (15%)
Cancer	2 (8.3%)	2 (10%)
Sleep Apnea	5 (20.8%)	4 (20%)
Systemic Hypertension	14 (58.3%)	12 (60%)
Renal Failure	2 (8.3%)	2 (10%)
Hyperthyroidism	0	0
Pulmonary Artery Hypertension	0	0
Chronic Pulmonary Failure	0	0
Previous surgery or interventional procedure	9 (37.5%)	6 (30%)
Pacemaker/Defibrillator Implant	5 (20.8%)	3 (15%)
Coronary Artery Bypass Graft	3 (12.5%)	3 (15%)
Coronary Angioplasty	7 (29.2%)	5 (25%)
Valves Replaced/Repaired	1 (4.2%)	1 (5%)
Baseline medication		
Beta Blockers	21 (87.5%)	18 (90%)
Sacubitril - Valsartan	13 (54.2%)	11 (55%)
Antiarrhythmic Class	3 (12.5%)	3 (15%)
Spironolactone	8 (33.3%)	6 (30%)
Diuretic	15 (62.5%)	12 (60%)
Anticoagulation	10 (41.7%)	10 (50%)
ACE Inhibitor (or substitute)	11 (45.8%)	8 (40%)

Table 6 – Concomitant diseases and medication

5.2. IMPLANTED DEVICES

In single vein placement, all AXONE leads were model XS (n=5).
In cross vein placement, 10 AXONE leads were model S, 1 was model M, 7 were model L and none were model XS.
This distribution of the model XS was expected, since this model was designed to be used in a single-vein situation.
Note: one patient had fastrack placed single-vein but no AXONE lead placement due to lack of time (subject 403): 20 minutes elapsed during single vein fastrack placement.

5.3. CIP COMPLIANCE

Eleven minor protocol deviations were reported and no major protocol deviation.
All protocol deviations (11 / 11) correspond to AXONE testing procedure duration above the 20 minute limit (subjects 105, 106, 201, 301, 303, 304, 306, 401, 402, 403, 404).

The explanation for the Axone testing procedure slightly exceeding the 20 minutes is the following. After the 20 minutes, the conventional LV lead must be positioned. The implanter has 2 options:

a) remove completely the Fastrack and insert the guidewire to catheterize the target vein

b) Keep Fastrack in place to allow quick insertion of the guidewire through the fastrack until target vein

The implanter‘s decision to take option a) or b) depends on the patient anatomy, and on the target vein. The option b) actually adds a few minutes to the Axone testing procesure (as the Fastrack is not yet removed), however it saves time on the conventional LV lead placement. Therefore it had no impact on the overall procedure time.

All patients were kept in for the analysis (no exclusion).

5.4. PRIMARY OBJECTIVE RESULTS

5.4.1. First co-primary endpoint: LV multi-zone pacing success rate

The first co-primary endpoint was the percent of patients, in the Full Analysis set, where the placement of the AXONE lead allows at least two distant LV pacing vectors with a pacing threshold ≤ 3.5/0.5 ms, missing data being considered conservatively as not fulfilling the condition. A rate above or equal to 70% had been pre-defined as acceptable. Two pacing vectors will be considered distant if one of them involves LV1 or LV2 and the other involves LV3 or LV4.
This rate is **11/20 = 55%** (95% CI: 32% to 77%) according to Clopper-Pearson confidence interval.

Conclusion: The observed rate is unsatisfactory (too low), although the actual rate might be equal or above 70% (upper boundary of the confidence interval ≥ 70%).

5.4.2. Second co-primary endpoint: LV pacing success rate

The second co-primary endpoint was the percent of patients, in the Full Analysis set, where the placement of the AXONE lead allows at least one LV pacing vectors with a pacing threshold ≤ 3.5/0.5 ms, missing data being considered conservatively as not fulfilling the condition. A rate above or equal to 85% had been pre-defined as acceptable.
This rate is **16/20 = 80%** (95% CI: 56% to 94%) according to Clopper-Pearson confidence interval.

Conclusion: the observed rate is unsatisfactory (too low), although the actual rate might be equal or above 85% (upper boundary of the confidence interval ≥ 85%).

5.5. SECONDARY OBJECTIVES RESULTS

5.5.1. Testing procedure or AXONE-related Adverse Events at 1 month post-procedure

Ten adverse events were reported, of which 5 serious adverse events. Detail on the ten adverse events is given in Appendix.

No unanticipated adverse event occurred. No event was classified as clearly related to the AXONE device or the testing procedure. One event was classified as « Unknown » relationship to the AXONE device or the testing procedure (*subject 106*: Pericardial effusion and atrial fibrillation).
The overall safety is assessed in section 5.6.

5.5.2. **Electrical performance focusing on LV pacing threshold and impedance**

5.5.2.1. Unipolar testing : pacing thresholds

Unipolar LV pacing thresholds was censored for 16 measurements in 6 patients, i.e. the pacing threshold was searched up to 3.5 or 5V, was not found, and was not searched above, probably because the procedure was lasting too long. This censorship is most probably non-informative, i.e. the pacing threshold is above the highest tested voltage but otherwise follows the same distribution as any other measurement. Testing equipment was limited at 10V this threshold being too high to be practically usable, and infinite/unreachable values were set at 9.99V.
In order to provide consistent interpretation of quantitative statistics (means, standard deviations, medians, quartiles), unaffected by values above 9.99 V or censorship at 3.5 V and 5 V, these statistics were computed for patients with thresholds equal or below 3.5 V.
These statistics must be interpreted together with the proportion of measurements equal or below 3.5 V.
In order to keep maximal information, histograms were computed with a simply-imputed data set. Measurements censored above 3.5 V or 5 V (i.e. tested up to this thresholds and found to be above this threshold) were randomly assigned to a value above this threshold. Measurements above 9.99 V were set to 9.99 V for histograms.

Cross-vein tests	LV1	LV2	LV3	LV4
non-miss / total	14 / 20	15 / 20	15 / 20	14 / 20
Prop ≤ 3.5 V	10 / 14	12 / 15	10 / 15	9 / 14
mean ± SD	1.54 ± 1.11	1.91 ± 1.19	1.77 ± 1.04	2.14 ± 1.06
med [Q1, Q3]	1.2 [0.5, 2.27]	1.35 [1, 3.12]	1.45 [0.8, 2.72]	2.6 [1.13, 3.03]
[min, max]	[0.3, 3.5]	[0.5, 3.5]	[0.5, 3.4]	[0.6, 3.4]

Table 7 – Distribution of tested unipolar pacing thresholds for cross-vein tests (expressed in Volts/0.5 ms)

Single-vein tests	LV1	LV2	LV3	LV4
non-miss / total	4 / 20	4 / 20	3 / 20	3 / 20
Prop ≤ 3.5 V	4 / 4	4 / 4	2 / 3	2 / 3
mean ± SD	0.78 ± 0.26	1.15 ± 0.93	2.85 ± 0.92	3.1 ± 0.28
med [Q1, Q3]	0.85 [0.57, 0.96]	0.8 [0.54, 1.88]	2.85 [2.2, 3.5]	3.1 [2.9, 3.3]
[min, max]	[0.4, 1]	[0.5, 2.5]	[2.2, 3.5]	[2.9, 3.3]

Table 8 – Distribution of tested unipolar pacing thresholds for single-vein tests (expressed in Volts/0.5 ms)

All tests	LV1	LV2	LV3	LV4
non-miss / total	18 / 40	19 / 40	18 / 40	17 / 40
Prop ≤ 3.5 V	14 / 18	16 / 19	12 / 18	11 / 17
mean ± SD	1.32 ± 1	1.72 ± 1.15	1.95 ± 1.07	2.32 ± 1.02
med [Q1, Q3]	0.95 [0.5, 2.11]	1.15 [0.77, 3]	1.85 [0.92, 2.88]	2.6 [1.38, 3.23]
[min, max]	[0.3, 3.5]	[0.5, 3.5]	[0.5, 3.5]	[0.6, 3.4]

Table 9 – Distribution of tested unipolar pacing thresholds for single-vein and cross-vein tests (assumed to be equivalent) (expressed in Volts/0.5 ms)

All tests	Total
non-miss / total	72 / 160
Prop ≤ 3.5 V	53 / 72
mean ± SD	1.79 ± 1.1
med [Q1, Q3]	1.4 [0.8, 2.93]
[min, max]	[0.3, 3.5]

Table 10 – Distribution of all tested unipolar pacing thresholds pooled for single-vein and cross-vein tests (expressed in Volts/0.5 ms)

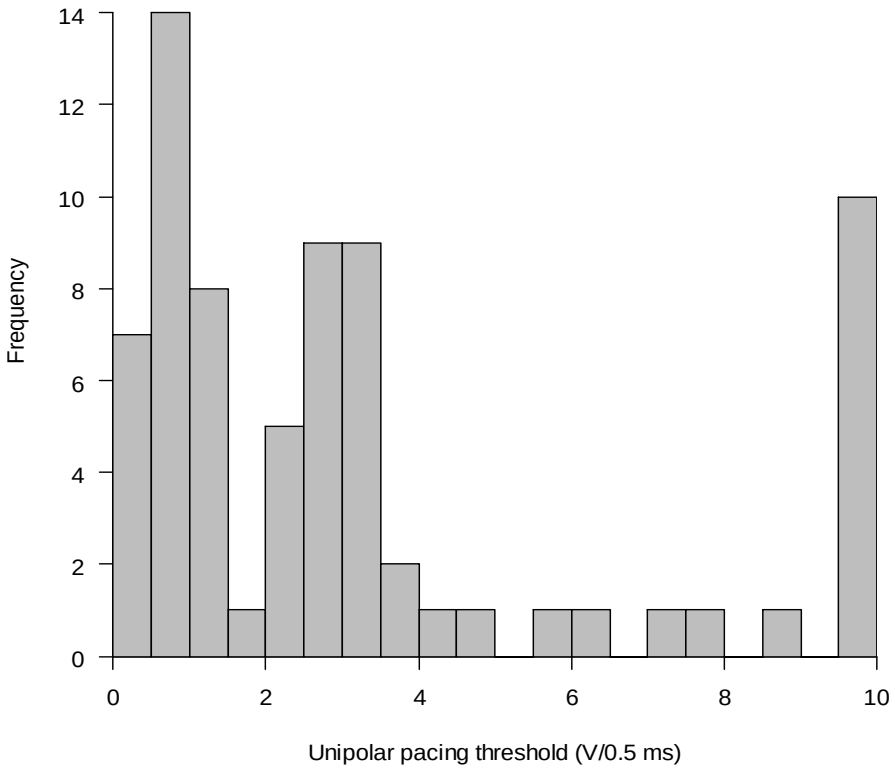

Figure 6 – Distribution of all tested unipolar pacing thresholds pooled for single-vein and cross-vein tests. Infinite/unreachable values are set at 9.99 V. Censored values are simply imputed.

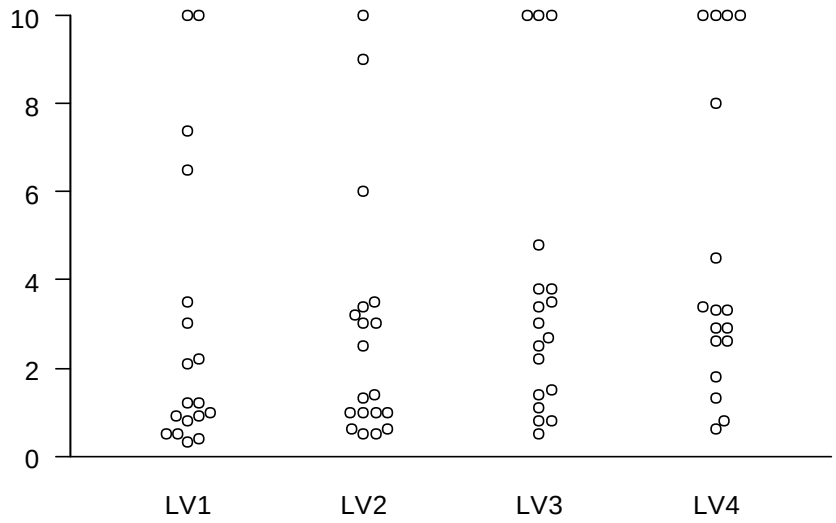

Figure 7 – Distribution of all tested unipolar pacing thresholds (single-vein + cross-vein tests). Infinite/unreachable values are set at 9.99 V. Censored values are simply imputed.

5.5.2.2. Bipolar testing : pacing thresholds

Cross-vein bipolar testing was performed for 12 patients and single-vein bipolar testing was performed for 1 patient only. Single-vein and cross-vein results are pooled.

	LV1-2	LV1-4	LV3-4	LV3-2	total
non-miss / total	10 / 40	4 / 40	8 / 40	6 / 40	28 / 160
Prop ≤ 3.5 V	9 / 10	3 / 4	5 / 8	5 / 6	22 / 28
mean ± SD	1.73 ± 1.05	2.07 ± 0.29	1.18 ± 0.81	1.64 ± 1.08	1.63 ± 0.93
med [Q1, Q3]	1.6 [0.77, 2.67]	1.9 [1.9, 2.32]	0.9 [0.73, 1.53]	1.4 [0.93, 2.17]	1.45 [0.8, 2.41]
[min, max]	[0.5, 3.3]	[1.9, 2.4]	[0.6, 2.6]	[0.8, 3.5]	[0.5, 3.5]

Table 11 – Distribution of bipolar pacing thresholds (cross-vein and single-vein testing pooled) (expressed in Volts/0.5 ms)

Figure 8 – Distribution of all tested bipolar pacing thresholds (single-vein + cross-vein tests)

5.5.2.3. Impedance (Ohms)

Impedances above 4000 Ohms have been excluded from quantitative analyses.

	LV1	LV2	LV3	LV4	total
non-miss / total	18 / 40	20 / 40	21 / 40	19 / 40	78 / 160
Prop ≤ 4000 Ω	18 / 18	20 / 20	19 / 21	15 / 19	72 / 78
mean ± SD	1872 ± 375	1650 ± 308	1629 ± 324	1569 ± 322	1683 ± 345
med [Q1, Q3]	1944 [1453, 2102]	1652 [1442, 1813]	1580 [1448, 1748]	1457 [1317, 1809]	1656 [1414, 1908]
[min, max]	[1295, 2674]	[1064, 2391]	[1180, 2467]	[1150, 2284]	[1064, 2674]

Table 12 – Distribution of unipolar impedance (cross-vein and single-vein testing pooled) (expressed in Ohms)

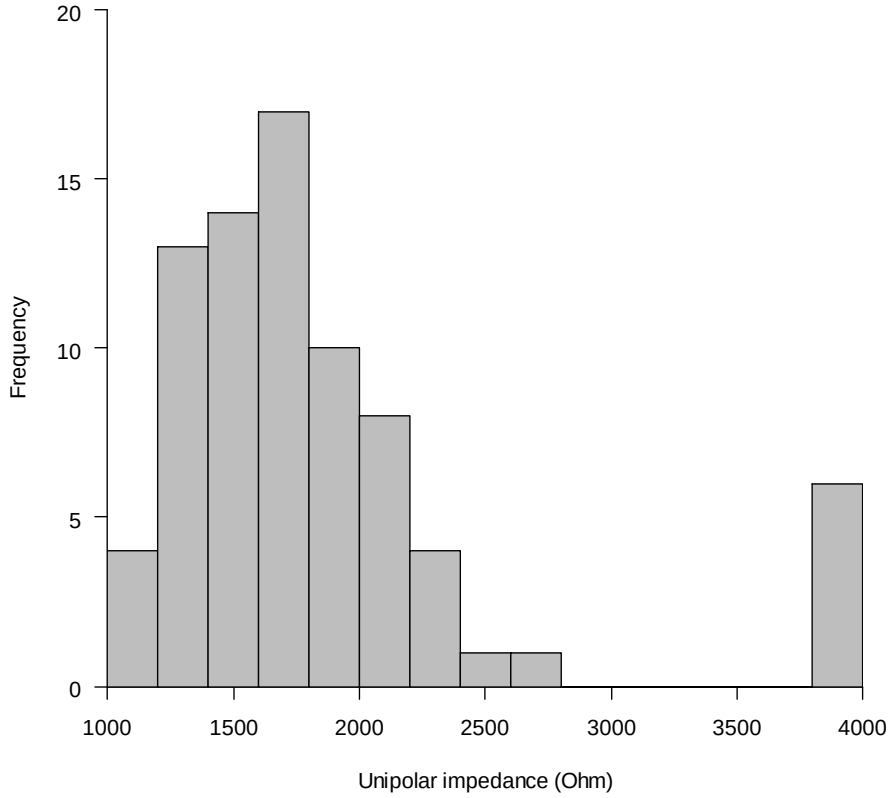

Figure 9 – Distribution of all tested unipolar impedances (single-vein + cross-vein tests)

	LV1-2	LV1-4	LV3-4	LV3-2	total
non-miss / total	10 / 40	4 / 40	7 / 40	6 / 40	27 / 160
Prop ≤ 4000 Ω	4 / 10	3 / 4	5 / 7	3 / 6	15 / 27
mean ± SD	3447 ± 188	3711 ± 324	3486 ± 288	3543 ± 433	3532 ± 288
med [Q1, Q3]	3372 [3330, 3589]	3809 [3426, 3947]	3583 [3311, 3678]	3563 [3177, 3899]	3563 [3346, 3724]
[min, max]	[3319, 3724]	[3350, 3975]	[3000, 3724]	[3100, 3966]	[3000, 3975]

Table 13 – Distribution of bipolar impedance (cross-vein and single-vein testing pooled) (expressed in Ohms)

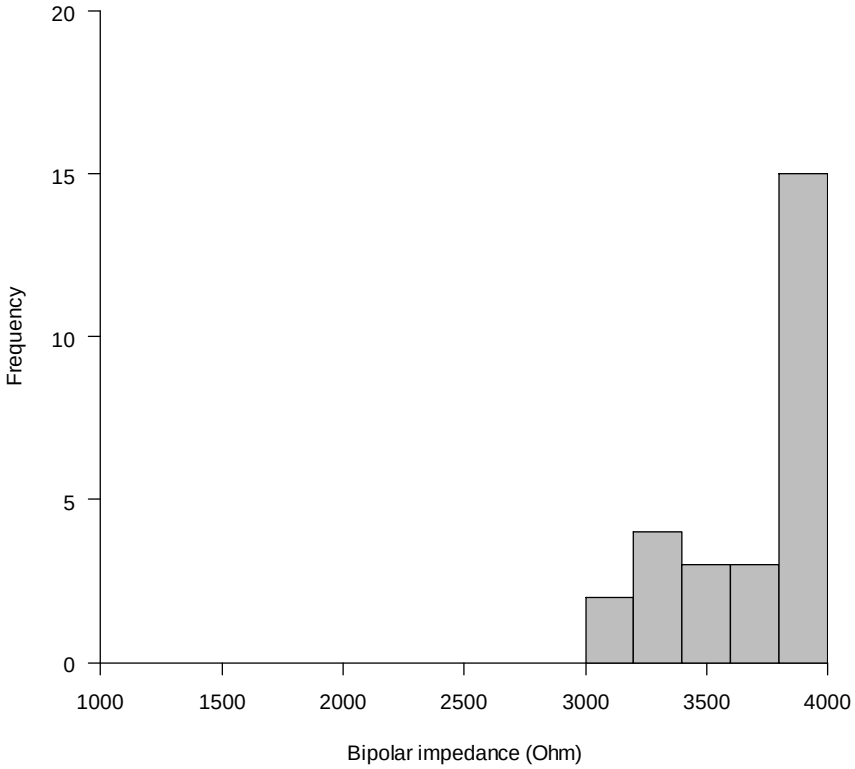

Figure 10 – Distribution of all tested bipolar impedances (single-vein + cross-vein tests)

5.5.2.4. Phrenic nerve stimulation at 10 V/0.5 ms

	LV1	LV2	LV3	LV4	total
non-miss / total	14 / 40	16 / 40	15 / 40	12 / 40	57 / 160
n (%)	1 (7.1%)	3 (18.8%)	1 (6.7%)	0 (0.0%)	5 (8.8%)

Table 14 – Number of phrenic nerve stimulations at 10 V/0.5 ms for unipolar testing (cross-vein and single-vein testing pooled)

	LV1-2	LV1-4	LV3-4	LV3-2	total
non-miss / total	7 / 40	2 / 40	6 / 40	4 / 40	19 / 160
n (%)	1 (14.3%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	2 (10.5%)

Table 15 – Number of phrenic nerve stimulations at 10 V/0.5 ms for bipolar testing (cross-vein and single-vein testing pooled)

When pooling all tests (unipolar and bipolar), 76 tests were performed out of 320 possible tests with actually 7 (9.21%) phrenic nerve stimulations at 10 V/0.5 ms.

5.5.2.5. Twenty beats capture test

When a pacing threshold was found (unipolar or bipolar, single-vein or cross-vein) and enough time was available, an optional 20- beats test could be performed at the pacing threshold + 1 V/0.5 ms.
Out of 90 pacing thresholds that were found (min = 0.3 V/0.5 ms, max = 9.0 V/0.5 ms), 12 had the optional 20-beats test. Of these 12 tests, 11 (91.7%) were successful. The failed test was a bipolar LV3-4 cross-vein 20-beats test after a 6 V/0.5 ms pacing threshold was detected (*subject 406*). Twenty beats tests were mostly performed when a pacing threshold was low.

	Pacing threshold
mean ± SD	1.73 ± 1.56
med [Q1, Q3]	1 [0.84, 2.04]
[min, max]	[0.7, 6.0]

Table 16 – Distribution of pacing thresholds that conducted to the 20-seconds beat testing (at pacing threshold + 1 V/0.5 ms). All but one were equal or below 3.5 V/0.5 ms

If the 20-beats test had to be performed only when finding a pacing threshold ≤ 3.5 V/0.5 ms, the actual test rate would be 11 / 75 and the actual success rate would be 100% (11 / 11).

5.5.3. **AXONE Implant Efficiency**

AXONE implant efficiency was assessed through the following parameters:
- procedure time for successful placement
- fluoroscopic time
- radiation dose
- handling assessment

Procedure time, fluoroscopy time and radiation dose are described in the below table:

Procedure characteristics	N / total	Mean ± SD	Median	[Min, max]
Time to beginning of AXONE test procedure (min)	20 / 20	56.1 ± 20.0	49.5	[26, 106]
Protocol-related total procedure time (min)	20 / 20	21.55 ± 3.61	21	[17, 35]
Cross-vein				
Fastrack placement time (min)	18 / 18	5.17 ± 6.1	3	[1, 26]
AXONE lead placement time (min)	18 / 18	2.39 ± 2.5	2	[1, 11]
Time to find a threshold ≤ 3.5 V (min)	14 / 14	3.36 ± 3.05	2.5	[1, 11]
Total Time to placement with threshold ≤ 3.5 V (min)*	14 / 14	11.57 ± 6.26	11.5	[3, 28]
Single-vein				
AXONE lead placement time (min)	5 / 5	4.6 ± 6.99	1	[1, 17]
Time to find a threshold ≤ 3.5 V (min)	4 / 4	3 ± 2.16	2.5	[1, 6]
Total protocol-related fluoroscopic time (min)	20 / 20	5.2 ± 2.89	5	[1, 12]
Total protocol-related radiation dose (dose-area prod, Gray.cm²)	20 / 20	6.3 ± 6.34	6	[0, 24]

Table 17 – Procedure characteristics (durations, fluoroscopy time and radiation dose)
** Time between fastrack insertion and pacing threshold ≤ 3.5 V in the cross-vein test*

Protocol-related total procedure time was ≥ 21 minutes for 11 (55.0%) patients (reported as a protocol deviation, *see section 5.3.*). It was equal or less than 24 minutes for 19 (95.0%) patients. It was equal or below 19 minutes for 2 (10.0%) patients.
For one patient (*subject 201*) protocol-related total procedure time was 35 minutes (maximum value). The fastrack cross-vein placement time was very long for this patient (26 minutes). Moreover, for this patient the physician noted *"Myocardium muscle very hard to stimulate with AXONE and standard LV lead"*.

Procedure characteristics	XS model	S model	M model	L model
Cross-vein				
Fastrack placement time (min)	NA	10 / 10 6.8 ± 7.64	1 / 1 1	7 / 7 3.43 ± 2.64
AXONE lead placement time (min)	NA	10 / 10 3 ± 3.27	1 / 1 1	7 / 7 1.71 ± 0.49

Time to find a threshold ≤ 3.5 V (min)	NA	8 / 8 2.88 ± 2.59	1 / 1 1	5 / 5 4.6 ± 3.85
Total Time to placement with threshold ≤ 3.5 V (min)*	NA	8 / 8 13.38 ± 7.23	1 / 1 3	5 / 5 10.4 ± 3.05
Single-vein				
AXONE lead placement time (min)	5 / 5 4.6 ± 6.99	NA	NA	NA
Time to find a threshold ≤ 3.5 V (min)	4 / 4 3 ± 2.16	NA	NA	NA

Table 18 – Procedure time per AXONE lead size

** Time between fastrack insertion and pacing threshold ≤ 3.5 V in the cross-vein test*

Handling assessment is detailed in the below table:

AXONE system handling assessment	N / total	Mean ± SD*	Very poor N (%)	Poor N (%)	≥ Acceptable N (%)	≥ Good N (%)
AXONE Fastrack handling						
Fastrack diameter	20 / 20	3.15 ± 0.88	1 (5%)	3 (15%)	16 (80%)	8 (40%)
Ease of use of guide-wire insertion in Fastrack	20 / 20	3.15 ± 1.14	3 (15%)	2 (10%)	15 (75%)	11 (55%)
Fastrack sliding in veins	20 / 20	3.1 ± 1.21	0 (0%)	1 (5%)	17 (85%)	9 (45%)
Ability to pass tortuosity	20 / 20	2.85 ± 1.39	0 (0%)	2 (10%)	15 (75%)	8 (40%)
Ability to make progress into anastomosis veins	20 / 20	2.7 ± 1.38	1 (5%)	1 (5%)	15 (75%)	6 (30%)
X-ray visibility of Fastrack markers	20 / 20	1.95 ± 0.89	8 (40%)	5 (25%)	7 (35%)	0 (0%)
Guide-wire maneuverability inside the Fastrack	20 / 20	3.3 ± 0.86	1 (5%)	2 (10%)	17 (85%)	10 (50%)
Guide-wire removal from Fastrack	20 / 20	3.3 ± 0.66	0 (0%)	2 (10%)	18 (90%)	8 (40%)
AXONE Lead Handling						
Lead model selection using Fastrack markers	20 / 20	3.1 ± 1.02	2 (10%)	3 (15%)	15 (75%)	9 (45%)
Lead body diameter	20 / 20	3.3 ± 0.92	1 (5%)	3 (15%)	16 (80%)	11 (55%)
Usability of the straw for the lead insertion	20 / 20	2.4 ± 1.47	3 (15%)	3 (15%)	11 (55%)	6 (30%)
Lead sliding in the Fastrack	20 / 20	3.35 ± 0.81	1 (5%)	1 (5%)	18 (90%)	10 (50%)
X ray visibility of the lead body	20 / 20	2.9 ± 1.07	3 (15%)	3 (15%)	14 (70%)	7 (35%)
X ray visibility of the lead electrodes	20 / 20	1.95 ± 0.76	6 (30%)	9 (45%)	5 (25%)	0 (0%)
Withdrawal of Fastrack over Axone	20 / 20	2.85 ± 1.04	2 (10%)	6 (30%)	12 (60%)	7 (35%)
General questions						
Ease of implantation	20 / 20	2.9 ± 0.91	1 (5%)	6 (30%)	13 (65%)	6 (30%)
Electrical performance†	19 / 20	2.37 ± 1.46	1 (5.3%)	2 (10.5%)	12 (63.2%)	4 (21.0%)
General impression	20 / 20	2.65 ± 0.93	3 (15%)	4 (20%)	13 (65%)	3 (15%)

Table 19 – Results of handling assessment secondary endpoint

**very poor=0, poor=1, acceptable=2, good=3, very good=4*

† One datum not applicable for subject 201.Even if he had a successful implantation of one lead and a successful unipolar testing with a pacing threshold ≤ 3.5 V / 0.5 ms, the physician noted that "myocardium muscle very hard to stimulate with AXONE and standard LV lead" and so the electrical performance question was not applicable.

The Fastrack handling is rated acceptable ≥75% in all aspects, except for the X-ray visibility of markers.

The Axone handling is mainly rated is rated acceptable ≥75% in 4 aspects, however less for “Usability of straw / Xray visibility of lead body / Withdrawal of Fastrack”

Ease of implantation, electrical performances and general impression is broadly acceptable but below 75%.

5.5.4. **LV multipoint pacing success rate**

The LV multipoint pacing success rate is the percent of patients where the placement of the AXONE provides at least two pacing vectors (distant or proximal, including bipolar vectors) matching with pacing threshold ≤ 3.5V/0.5ms. This rate is **15/20 = 75%** (95% CI: 51% to 91%).

5.6. PERFORMANCE, SAFETY AND EFFICACY EVALUATIONS

The co primary endpoints of the study, related to acute electrical performance, and defined LV multizone pacing success rate and LV pacing success rate, were not met. An LV multizone pacing success rate ≥ 70% had been pre-defined as acceptable; this rate was 55% (95% CI: 32% to 77%) in the study. An LV pacing success rate ≥ 85% had been pre-defined as acceptable; this rate was 80% (95% CI: 56% to 94%) in the study.
The AXONE lead demonstrated a good safety profile in acute setting: no unanticipated adverse event occurred, and no event was classified as clearly related to the AXONE device or the testing procedure

Of note,two cases of pericardial effusion were reported (*subjects 401 and 106*) and were classified as serious due to prolonged hospitalization.

- *Subject 401* (Female, 70 years old, BMI 20): hospitalization prolonged by 1 day without treatment. The pericardial effusion has « no hemodynamic impact and no evolution ». According to the site, this event was definitely related to the CRT procedure.
- *Subject 106* (Female, 50 years old, BMI 32): hospitalization of 2 days and treated by medication adjustement (bisoprolol dosage increased). The pericardial effusion has « millimetric size and no evolution ». It induced a paroxysmal episode of atrial fibrillation associated with palpitations that lasted for 2 days and spontaneously stopped. According to the site, relationship to CRT procedure or AXONE device or testing procedure was unknown.

In these two cases, the events were of minor severity and were resolved without treatment. The rate of pericardial effusion in the study represents an incidence of 10%.
The expected incidence of pericardial effusion from literature is nowadays around 1% in ICD population [19]. This rate is majored in CRT-D procedures due to the number of leads, and majored by female gender, older age and low BMI – all due to thinner chamber wall thickness.
Although the observed rate of pericardial effusion in the study is higher than expected, no conclusion can be drawn at this stage. Indeed the relationship cannot be formally imputed to AXONE, actually pericardial effusion could occur with any of the leads implanted during the procedure. However this observation calls for specific attention in the next clinical phases.
Another SAE was reported for « Pericarditis » (*subject 203*), causing 10-day hospitalization and treated by percutaneous drainage. In this patient, the implantation of the right ventricular lead was unusually difficult due to occluded access of vena cava, and only one position in the right ventricle could be achieved. On the contrary, the placement of the LV lead was straightforward. During the procedure drainage was performed to remove 250ml of blood. This case of pericarditis was classified « not related » to the AXONE device or testing procedure, and should be distinguished from the two previous cases of pericardial effusion as this one is most likely related to the right ventricular lead.
Last reported SAE is a failure to implant a LV lead during the procedure, leading to a second procedure for the implantation of an epicardial LV lead. This is an anticipated type of event, not related to the AXONE lead or its testing procedure.
Overall, the AXONE device presents with a reassuring safety profile in acute setting. Potential cases of pericardial effusions and its resulting incidence rate should be closely monitored in future studies.

No device deficiency was reported during the study.

6. DISCUSSION AND OVERALL CONCLUSIONS

From this initial acute study, it can be concluded that the performances of the lead were unsatisfactory. The rates of patients with at least two distant LV pacing vectors with a pacing threshold ≤ 3.5/0.5 ms, and the rate of patients with at least one LV pacing vectors with a pacing threshold ≤ 3.5/0.5 ms, were below our predefined acceptable values (55 vs 70% and 80 vs 85% respectively).

On the other hand, the concept of cross vein lead placement using the AXONE system seems to be validated as it could be performed in the vast majority of the patients (18/20), within a time constraint of 20 minutes.
Although the electrical performances were not adequate for all patients (pacing thresholds sometimes over 3.5V), acceptable performances could be found in a majority of patients where suitable veins could be reached.

Finally, the cross-vein placement reached in 55 % of patients allowed pacing sites clearly different from what can be achieved with a conventional IS-4 lead.

The handling assessment scores were acceptable or good for almost all items. As expected due to the small size of Axone, the X–ray visibility of the Fastrack markers and the Axone lead electrodes has to be enhanced (only scores below 2). The general impression of the physicians regarding the Axone system is also pretty good (2.65) with a very poor score in only three cases (15%).

As no events were classified as clearly related to the Axone devices, the procedure appeared rather safe. However, it has to be noticed that pericardial reactions or effusions were more frequently observed than expected. Although these phenomena were benign, without clinical consequences, it should be closely monitored during future evaluation.

From these results, it seems that the AXONE concept and global system is a valid approach to treat patients candidates to cardiac resynchronization. The objectives with the AXONE system are clearly superior to that of a regular single LV lead implantation, and should be compared with at least what one expects from a cardiac resynchronization procedure with 2 separate LV leads. Besides pacing at 2 separate LV sites, one could envision to pace at sites that are not reachable with a regular 4 to 5 French LV lead. In light of these objectives, the results regarding handling assessment of the Fastrack and AXONE lead are clearly acceptable.
However, one should focus our efforts on pacing capabilities of the lead that appeared below expected thresholds. This point should clearly be improved for future evaluation.

It can also be observed that the median protocol-related procedure time was slightly above the predefined value (21 vs 20 min). This and the feedback of participating investigators suggest that the time duration allowed to the AXONE procedure was too short. Especially while doing very gentle and delicate maneuvers like navigating in the coronary sinus venous network with a small guidewire, having to rush to complete the procedure is not desirable. It should be reminded here, that placing the AXONE lead in a cross vein position amounts to insert two separate left ventricular leads. With that in mind, one could envision to extend the time duration dedicated to the AXONE lead placement to a value corresponding to the implantation time of 2 separate LV leads (ie, 35 min or so). Modification of the protocol accordingly could have a beneficial impact, not only on the safety side of the procedure but also, it could offer the opportunity to improve the pacing threshold results.

7. ETHICS

The study was initially approved by Ethics Committee (CPP Ile-de-France 2, réf: 2017-12-09) on 05 Feb 2018 and by Competent Authority (ANSM, réf: 2017-A02803-50) on 25 Jun 2018. Amendment n°1 related to modification of the Investigator Brochure was reviewed and approved by CA on 18 Sep 2018. Amendment n°1 was not applicable for EC.

8. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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9. DATA QUALITY ASSURANCE

The Sponsor monitored the study for CIP compliance verifying the following, but not limited to:

- The safety and rights of subjects were being protected
- The study was conducted in accordance with the currently approved CIP and any other study agreements, ICH-E6 GCP guidelines, ISO 14155 and all applicable regulatory requirements
- Data were authentic, accurate, and complete

Fully validated data management applications in accordance with ICH-E6: Good Clinical Practice (GCP): Consolidated Guidance guidelines were used for all data handling, verification of the data and conduct of statistical analyses activities. Electronic edit checks and manual queries from clinical data reviews were generated to the sites. All queries were resolved prior to database lock (07 Feb 2019) to ensure data integrity.

All data collected through the 1 month follow-up visit were 100% Source Data Verified.

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11. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE: Adverse Event
CIP: Clinical Investigation Plan
CRT: Cardiac Resynchronization Therapy
CSR: Clinical Study Report
EC: Ethic Committee
ITT: Intention to Treat
LV: Left Ventricular
SAE : Serious Adverse Event

12. SIGNATURE PAGE

See section Signature Page, on Page 2.

13. APPENDICES

13.1. APPENDIX 1 : LIST OF ADVERSE EVENTS

Final diagnosis	ventricular disorders during standard LV lead implant patient performed ventricular tachycardia	Poket haematoma patient came to hospital due to pain and haematoma at the poket	Coronary sinus dissection no symptoms, no signs	At the location of the defibrillator descending under the scar. bruise and blood flow from a stitch	Throat pain oral drought (pharyngitis)
Subject ID	101	103	302	305	407
Seriousness	Non-Serious	Non-Serious	Non-Serious	Non-Serious	Non-Serious
Relationship to the protocol	Not related	Not related	Not related	Not related	Not related
Device	L	S	none	S	L
LV dysfunction etiology	Cardiomyopathy + Valvular Heart Disease	Cardiomyopathy + Valvular Heart Disease	Cardiomyopathy + Valvular Heart Disease	Cardiomyopathy + Valvular Heart Disease	
Intervention date	09/08/2018	04/09/2018	22/08/2018	19/10/2018	13/11/2018
Date of AE occurence	09/08/2018	11/09/2018	22/08/2018	22/10/2018	NK/11/2018
Timing	during	after	during	after	after ?
Outcome	Resolved	Resolved	Resolved	Resolved	Resolved
Resolution date	09/08/2018	04/10/2018	22/08/2018	05/12/2018	13/12/2018

Final diagnosis	Patient hospitalized due to palpitations. Atrial fibrillation on ecg. Minimal pericardial effusion.	Thorax dyspnea since 13 sepmteber 2018 of sudden onset. The patient went to the emergency room, without any cardiac cause. The general practitioner did not see any pleural effusion on the x-ray. Cardiologist has scheduled a pneumology's consultation quickly	Cardiac disorder during operation blood pressure drop with 16mm pericarditis resulting in percutaneous drainage	Sternal pain intense chest pain. Pericardal effusion	Implantation of an epicardial vg lead no symptom
Subject ID	106	201	203	401	402
Seriousness	Serious	Serious	Serious	Serious	Serious
Relationship to the protocol	Unknown	Not related	Not related	Not related	Not related
Device	S+XS	S	none	S	L+XS
LV dysfunction etiology	Cardiomyopathy + Valvular Heart Disease	Cardiomyopathy	Cardiomyopathy + Valvular Heart Disease	Cardiomyopathy	Cardiomyopathy
Intervention date	07/11/2018	10/09/2018	24/10/2018	22/08/2018	22/08/2018
Date of AE occurence	23/11/2018	13/09/2018	24/10/2018	23/08/2018	17/09/2018
Timing	after	after	during	after	after
Outcome	Resolved	Ongoing or chronic	Resolved	Resolved	Resolved
Resolution date	26/11/2018		01/11/2018	25/08/2018	25/09/2018