**Magnetic VT study: a prospective, multicenter, post-market randomized controlled trial comparing VT ablation outcomes using remote magnetic navigation–guided substrate mapping and ablation versus manual approach in a low LVEF population**

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## Abstract

**INTRODUCTION** Patients with ischemic cardiomyopathy (ICM), a history of myocardial infarction, and implanted cardioverter defibrillators (ICD) consist of a significant population referred for ventricular tachycardia (VT) radiofrequency ablation. The success of ablation procedures depends on accurate arrhythmogenic substrate localization, followed by optimal delivery of energy provided by constant electrode-tissue contact. In contrast to conventional manual approach, magnetic navigation system (MNS) offers remote guidance of ablation catheters during ablation for cardiac arrhythmias by navigating the magnetic-tipped catheter precisely to the substrate targets. Despite impactful reports in MNS-guided VT ablations, the superior outcome evidence in ischemic VT in MNS is lacking from the prospective randomized study design, resulting in a major debate in the VT ablation field.

**OBJECTIVE** To demonstrate that ventricular tachycardia ablation using the Niobe® ES magnetic navigation system results in superior outcomes compared to a manual approach in subjects with ischemic scar VT in a low ejection fraction population.

**METHODS AND ANALYSIS DESIGN** This trial is a randomized, single-blind, prospective, multicenter post-market study. A total of 386 subjects (193 per group) will be enrolled and randomized 1:1 between treatment with the *Niobe* ES system and treatment via a manual procedure. Data will be collected to evaluate differences in VT ablation outcomes between patients treated in the *Niobe* system group and those in the manual control group. The study population will consist of patients at up to 20 sites who have sustained ischemic monomorphic VT, who have previously had an ICD implanted, and who have an LVEF of ≤35%. The primary study endpoint is freedom from any recurrence of VT through 12 months. The secondary endpoints are acute success (defined as non-inducibility of clinical VT and/or other monomorphic VT); freedom from any VT at 1 year in a large-scar subpopulation (defined as patients with a scar total surface area > the median scar total surface area for the total population as determined by electroanatomic mapping); procedure-related major adverse events (defined as death, cardiac tamponade, stroke, and bleeding requiring surgical intervention through 48 hours post-procedure, and progressive heart failure related to VT/VF recurrence within 48 hours post-ablation); and mortality rate through 12-month follow-up. Follow-up will consist of visits at 3, 6, 9, and 12 months, all of which will include ICD interrogation.

**ETHICS AND DISSEMINATION** All products in the study protocol are cleared for use in the country where they are being used. The study will not begin until the required approval/favorable opinion from the appropriate Institutional Review Board (IRB) or Medical Ethics Committee (MEC) or regulatory authority has been obtained, where appropriate. The protocol will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with all applicable local, country, federal, and Sponsor internal regulations. **Trial registration:** Clinicaltrials.gov identifier: NCT02637947.

**KEYWORDS** Ablation; Catheter; Electroanatomic mapping; Ischemic cardiomyopathy; Magnetic navigation; Ventricular tachycardia

**ABBREVIATIONS** **3D** = three dimensional; **AAD** = antiarrhythmic drug; **AE** = adverse event; **ATP** = adenosine triphosphate; **BIP** = bipolar voltage mapping; **CIP** = clinical investigation plan; **CMR** = cardiac magnetic resonance; **CRF** = case report form; **CRO** = contract research organization; **CVA** = cerebrovascular attack; **DAP** = dose area product; **DMC** = data monitoring committee; **DSMB** = Data and Safety Monitoring Board; **DVT** = deep vein thrombosis; **EAS** = electroanatomic scar; **EC** = ethics committee; **ECG** / **EKG** = electrocardiogram; **EF** = ejection fraction; **EP** = electrophysiology; **FMEA** = failure modes and effects analysis; **HIT** = heparin-induced thrombocytopenia; **IB** = investigator brochure; **ICD** = implantable cardioverter defibrillator; **ICM** = ischemic cardiomyopathy; **IFU** = Instructions for Use; **IRB** = institutional review board; **ITT** = intent to treat; **LAVA** = local abnormal ventricular activity; **LP** = late potential; **LV** = left ventricle; **LVAD/IABP** = left ventricular assist devices with intra-aortic balloon pump; **LVEF** = left ventricular ejection fraction; **MDD** = medical device directive; **MDR** = medical device reporting; **MEC** = medical ethics committee; **MI** = myocardial infarction; **MITT** = modified intent to treat; **MNS** = magnetic navigation system; **NSHNVT** = nonstructural heart disease ventricular tachycardia; **NYHA** = New York Heart Association; **PHI** = protected health information; **PI** = principal investigator; **PMVT** = polymorphic ventricular tachycardia; **RF** = radiofrequency; **RMN** = remote magnetic navigation; **RV** = right ventricle; **SBA** = substrate-based ablation; **SAE** = serious adverse event; **UNI** = unipolar voltage mapping; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

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## Background

Ischemic cardiomyopathy (ICM) (1) patients with a history of myocardial infarction consist of a significant population referred for ventricular tachycardia (VT) radiofrequency (RF) ablation. Catheter ablation of VT is effective with recurrent sustained VT episodes and particularly useful in patients with implanted defibrillators. Most ICM patients have an arrhythmogenic substrate characterized by the formation of ventricular myocardial scar, likely results of necrosis caused by prior myocardial infarction and which can inhibit a patient's left ventricular ejection fraction (LVEF). Since scar-related reentry circuits are the most common mechanism for the ischemic VT population, current manual and remote magnetic navigation (RMN)–guided ablation strategies aim to identify a reentry circuit and to target a critical isthmus through activation and entrainment mapping during ongoing tachycardia. In the setting of non-inducibility of VT, hemodynamic intolerance of induced VT, or inducibility of non-clinical arrhythmias, a substrate-based approach is used to target electroanatomic scar (EAS) substrates. EAS, a rather new term, is a specific voltage-related definition that makes myocardial scar quantitatively measurable by three-dimensional (3D) mapping technology during the ablation.

Marchlinski et al. (2000) (2) defined reference values for endocardial EAS using 3D bipolar voltage mapping (BIP) still used in current studies. According to these definitions, normal endocardium has bipolar electrogram amplitudes greater than 1.5 mV, dense scar has voltages less than 0.5 mV, and border zone has voltages between 0.5 and 1.5 mV. The most common way to map EAS continues to be 3D BIP mapping, with task-specialized software programs like CARTO® (Biosense Webster, Diamond Bar, CA) and EnSite™ NavX™ (St. Jude Medical, St. Paul, MN). Other studies have offered their own ways of measuring and defining the extent of 3D EAS; for example, Hutchinson et al. (3) and others (4,5) have used 3D unipolar voltage mapping (UNI), where scar in the LV is defined as any tissue with a voltage below 8.3 mV. UNI

users claim that combining it with BIP results in a more comprehensive view of the scar tissue and results in more successful VT ablation procedures (3,5). Other techniques, like the use of surface electrocardiogram (ECG) and cardiac magnetic resonance (CMR), are common noninvasive ways to determine scar burden (6,7). For EAS, the most common use is endocardial areas with a bipolar voltage less than 1.5 mV (3).

3D EAS can be eliminated using one of many substrate-based ablation (SBA) strategies. One SBA strategy, called late potential abolition, targets scar areas with late potentials (LPs), defined as bipolar electrograms with an amplitude less than 1.5 mV and with high-amplitude electrical components appearing 20 ms or more after the end of the surface ECG reading's QRS component during SR pacing (8). LPs reveal the location of slow-conducting channels that cause VTs to occur through ventricular EAS (9). Another SBA strategy uses a high-density mapping catheter like the PentaRay® (Biosense Webster) to identify local abnormal ventricular activities, or LAVAs. LAVAs are similar to LPs in that they are both potentials distinct from the far-field ventricular electrogram and indicators of scar tissue, but LAVAs are high-frequency sharp potentials and can be identified at any time during the electrogram (10). Di Biase et al. (11) have also proposed the use of scar homogenization to target VT caused by scar tissue. Scar homogenization involves the ablation of the entirety of the border zone scar tissue so that it acts similarly to the dense scar tissue and thus prevents isthmuses from forming throughout the scar. All these strategies have proved beneficial to the treatment of patients with scar-related VT.

The success of ablation depends on accurate arrhythmogenic substrate localization, followed by optimal delivery of energy provided by constant electrode-tissue contact. In contrast to conventional manual approach, magnetic navigation system (MNS) offers remote guidance of ablation catheters during ablation for cardiac arrhythmias by navigating the magnetic-tipped catheter precisely to the substrate targets. Recently, Bhaskaran et al. (2015) (11) reported that the latest MNS platform, *Niobe* ES, could produce larger lesion dimensions compared with manual approach in the presence of simulated wall motion in a bench-top model, consistent with greater catheter stability. MNS has provided important clinical advantages in safety because of the remote magnetic vector control, atraumatic catheter design, and less physical stress and radiation exposure for the operator. Numerous studies (12-15) have revealed significant advantages, mainly for the ablation of nonstructural heart disease VT (NSHDVT) when compared with conventional methods. A single-center study with consecutive case series (2015) (16) demonstrated a better long-term outcome of MNS in a heterogeneous VT (ischemic mixed with non-ischemic) cohort by the intention-to-treat analysis. Its better long-term outcome, more than 2 years, for the MNS group is likely linked to the higher acute success rate. A possible explanation for the higher acute success in MNS-guided VT ablation is enhanced maneuverability and improved catheter stability using the latest platform. However, despite these impactful reports in MNS-guided VT ablations, the superior outcome evidence in ischemic VT in MNS is lacking from randomized study design prospective. It remains a hot debate in the VT ablation field.

Recently, Di Biase et al. (17) retrospectively analyzed the two-central VT ablation data in 218 patients with ischemic cardiomyopathy and large EAS by comparing RMN with manual ablation. The data reports that MNS-guided VT ablations in ischemic cardiomyopathy subjects with large EAS (140 ± 61 $cm^2$) have an increased success rate at 1-year follow-up when compared with manual ablation. The better outcome might be due to the higher amount of time dedicated to RF ablations to achieve scar substrate homogenization rather than mapping.

The data along with other reports have triggered a study hypothesis: Is it possible that RMN-guided, substrate-based mapping and ablation is superior to manual catheter ablation in a low-EF population?

This report describes the study rationale, scientific merits and metrics for Magnetic-VT Clinical Trial NCT02637947.

## Methods

### Devices

The *Niobe* ES magnetic navigation system (*Niobe* or MNS) is a medical system manufactured by Stereotaxis, Inc. (St. Louis, MO, USA) for electrophysiological and interventional procedures in the heart and vasculature. The MNS facilitates the control of the distal tip of appropriately labeled compatible magnetic devices via magnetic fields. The physician uses the MNS to steer the distal tip of the catheter while the Cardiodrive® system provides the means for automated remote advancement or retraction. A companion x-ray system provides real-time guidance for the physician during the interventional procedure as well. The MNS is controlled by the Navigant® software system.

The *Niobe* system communicates with compatible Siemens and Philips digital fluoroscopy systems, with the CARTO® 3 electrophysiology (EP) navigation system, and with the *Cardiodrive* system where the *Niobe* system is installed.

Compatible magnetic EP catheters include the Biosense Webster NaviStar® RMT ThermoCool® and the Trignum Flux Gold-tip (Biotronik GMBH, Berlin, Germany). Designated introducer or guiding sheaths include the St. Jude Medical Fast-Cath™ 8.5F Guiding Introducer.

All products mentioned in this study are CE Marked and cleared for use in the country in which they are being used.

### Benefits

Potential benefits associated with the use of the *Niobe* ES system for VT treatment include:

- Elimination of ventricular tachycardia
- Faster, higher-density electroanatomic map of ventricular substrate, allowing physicians to more accurately delineate and homogenize scar
- Greater catheter maneuverability, not limited by preformed or evolved catheter curves, allowing physicians to more accurately position the catheter tip even in difficult anatomies, such as those encountered in cusp-related VT and papillary muscle originated VT
- More stable catheter-tissue contact, allowing for more controllable lesion formation
- Reduction in radiation exposure for both patient and physician
- Reduction in procedure-related complications

The *Niobe* ES system has been used in more than 80,000 magnetic-assisted electrophysiological and endovascular interventional cases, further supporting its comparable efficacy and superior safety profile. Based on a review of the current literature, regulatory status,

and clinical experience to date with the *Niobe* system, the potential benefits of use have been determined to outweigh any potential risks.

**Study Hypotheses**

The primary hypothesis is that RMN-guided, substrate-based mapping and ablation procedures will have a superior rate of VT freedom at 12 months in a low-EF patient population in comparison to that of manual catheter ablation procedures.

The secondary hypothesis proposes (1) the acute success in the RMN arm is better than that of the manual arm and (2) the outcome at 12 months in the RMN arm will be superior to that of the manual arm in a large-scar population.

The study is intended to provide additional post-market data demonstrating improved patient outcomes of catheter ablation procedures guided by a *Niobe* ES magnetic navigation system for the treatment of ischemic ventricular tachycardia.

**Study Design**

It is a randomized, single-blind, prospective multicenter, post-market study. Subjects will be screened for study eligibility and asked to complete written informed consent before any study-specific testing assessments. Up to 386 subjects will be enrolled and randomized on a 1:1 basis to receive VT ablation treatment using either the *Niobe* system or standard manual catheter ablation treatment using commercially available products.

This will be the largest randomized VT study comparing outcomes from RMN with manually guided catheter ablation procedures. Subjects will be randomized according to a computer-generated randomization scheme. Randomization will be blocked at the study site level, and subjects will be blinded to group assignment. Since quality of life measurements will be collected during follow-up, this study is single-blinded to mitigate patient bias. Clinical evaluations will not be masked to the treating physician.

All subjects will be assessed for clinical follow-up at the following intervals:

- Baseline (pre-treatment)
- Procedure (time of VT mapping and ablation)
- Hospital discharge
- 3 months post-procedure
- 6 months post-procedure
- 9 months post-procedure
- 12 months post-procedure

This study is also an adaptive design: Interim analyses may be conducted to either (1) stop the trial early for efficacy or (2) re-estimate sample size. This type of design and analysis must be specified before the trial starts, it must be conducted by an independent party, and it will incur an alpha penalty, a statistical penalty for breaking blind by performing interim analyses (18). Use of adaptive design involves other disadvantages too; the advantages are (1) cost savings or (2) recovery from incorrect initial assumptions.

**Study Endpoints**

**Primary.** The primary clinical endpoint of this study is freedom from any VT at 12 months in the overall cohort. In a subanalysis, freedom from any VT will be compared between patient populations on antiarrhythmic drugs (AADs) and those off AADs.

**Secondary.** The following secondary endpoints will be collected to compare safety and treatment outcome between study arms.

Secondary *outcome* endpoints:

- Acute success as measured by non-inducibility of any VT (clinical VT or other sustained monomorphic VT) using typical stimulation protocol for induction, up to three extrastimuli brought in to ventricular refractoriness at two drive cycle lengths in two sites
- Freedom from VT at 12-month follow-up in a large scar subpopulation (patients with scar sizes/total surface areas > median scar sizes/total surface areas for the entire study population as determined via electroanatomic mapping)

Secondary *safety* endpoints:

- Rate of procedure-related major adverse events defined as death, cardiac tamponade, stroke, and bleeding requiring surgical intervention through 48 hours post-procedure, and progressive heart failure related to VT/VF recurrence within 48 hours post-ablation
- Mortality rate at 12-month follow-up

**Tertiary.** The following tertiary endpoints will be collected to provide additional product utilization data and compare treatment efficaciousness and cost effectiveness between arms.

Outcome Evaluation at 3-month, 6-month, 9-month, and 12-month follow-ups with respect to:

- Total number of appropriate ICD shocks
- Total number of anti-tachycardia pacing

Acute Procedural Efficiency measured by:

- Total procedure time
- Total fluoroscopy time
- Total fluoroscopy dose (dose area product; DAP)
- Total mapping time
- Total ablation time
- Total mapping points before ablation
- Total ablation energy delivery (watts x seconds / total scar surface area)
- Patient quality of life (SF-12): Medical Outcomes Study 12-item Short-Form Health Survey

**Study Participation**

Adult male and female subjects, age 18 or older, who have been diagnosed with ischemic monomorphic VT, are eligible for participation in this study. Each investigational center will screen patients for eligibility. If a subject meets all inclusion criteria and no exclusion criteria, the patient will be asked to participate. Study participation is wholly voluntary and the decision whether to participate will not affect the medical care provided to the patient.

General Inclusion Criteria

1. Patient is 18 years of age or older

2. Patient has provided written informed consent
3. Patient has an implantable cardioverter defibrillator (ICD) previously implanted
4. Drug refractory monomorphic VT
5. Patient is a candidate for ischemic VT RF ablation
6. Patient has had a myocardial infarction
7. LVEF ≤ 35%

General Exclusion Criteria

1. Non-ischemic VT
2. History of stroke within 1 month before enrollment
3. Acute MI within 30 days before enrollment
4. Unstable angina
5. Cardiac surgery within 60 days before enrollment
6. Patient is pregnant or nursing
7. Limited life expectancy of 1 year or less (Subjects requiring LVAD/IABP intraprocedural support may be enrolled as long as life expectancy is at least 1 year following the ablation procedure.)
8. Patient is unable or unwilling to cooperate with the study procedures
9. Known presence of intracardiac thrombi determined by echocardiography
10. Major contraindication to anticoagulation therapy or coagulation disorder
11. Previous pericarditis or cardiac tumor
12. Previous thoracic radiation therapy
13. Any other reason the investigator considers the subject ineligible

Once enrolled in the study, a subject can exit early only as a withdrawal. To limit the number of withdrawals before treatment, subjects will be enrolled, randomized, and treated as close together as possible.Study Procedures

**Table 1** is an overall summary of required procedures and evaluations, or study schema. All study data will be documented on the standardized Case Report Forms.

| **Time Periods and Assessments** | **Preoperative** | **Operative** | **Discharge** | **3 mos** | **6 mos** | **9 mos** | **12 mos** |
|---|---|---|---|---|---|---|---|
| **Physical Exam** | **X** | | **X** | **X** [1] | **X** | **X** [1] | **X** |
| **Medical History** | **X** | | | | | | |
| **Demographics** (age, gender) | **X** | | | | | | |
| **Current Medications** (AADs, other relevant cardiovascular drugs) | **X** | | **X** | **X** | **X** | **X** | **X** |
| **Electrocardiogram (EKG)** | **X** | | **X** | **X** [1] | **X** | **X** [1] | **X** |
| **ICD Interrogation** | **X** | | **X** | **X** | **X** | **X** | **X** |
| **Quality of Life Instruments** (SF-12) | **X** | | | **X** | **X** | **X** | **X** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Diagnosis and Etiology** | **X** | | | | | | |
| **2D Echocardiography and Doppler** | **X** [2] | | | | | | **X** |
| **Procedural Data** | | **X** | | | | | |
| **Intraoperative Criteria** | | **X** | | | | | |
| **Concomitant Procedures** | | **X** | | | | | |
| **Adverse Events** | | **X** | **X** | **X** | **X** | **X** | **X** |

[1] Only if follow-up is conducted in person; it is not needed if remote monitoring follow-up occurs.
[2] Pre-op echo must be performed within 6 months of planned implant date.

**Screening.** Patients who have been diagnosed with ischemic cardiomyopathy–induced monomorphic VT with prior ICD implantation and who are treated at a participating study center are eligible for study inclusion.

**Informed consent.** Patients who meet the general inclusion and exclusion criteria and agree to participate in the study will complete a written Informed Consent Form before undergoing any study-specific testing. Subjects will be given ample time to read the Informed Consent, to discuss potential risks and benefits with the study investigator before providing consent. Additional information will be provided to subjects as needed.

If during the course of the preoperative evaluations, the patient is found not to be eligible for inclusion in the study, the patient will be notified and the reason for ineligibility documented on the appropriate Case Report Form.

**Preoperative evaluations and data requirements.** Pre-operative echocardiographic data must be collected within 6 months of the planned VT ablation procedure date before enrollment. Since the protocol will allow remote monitoring follow-ups for clinical evaluations, a subject should have an ICD with remote monitoring system capability.

**Operative procedures and data requirements.** Subjects will be prepped and a standard approach used for VT ablation. Investigators will be advised of the *Niobe* system use techniques per the Instructions for Use (IFU) during site initiation and or other account support training.

All subjects will undergo electroanatomic mapping to determine the extent and location of dense scar and border zone tissue. Total scar surface area will be measured and documented in $cm^2$. Locations of scar will also be documented using the diagram in **Figure 1**, which details segmentation of the left ventricle as defined by the American Heart Association (19).

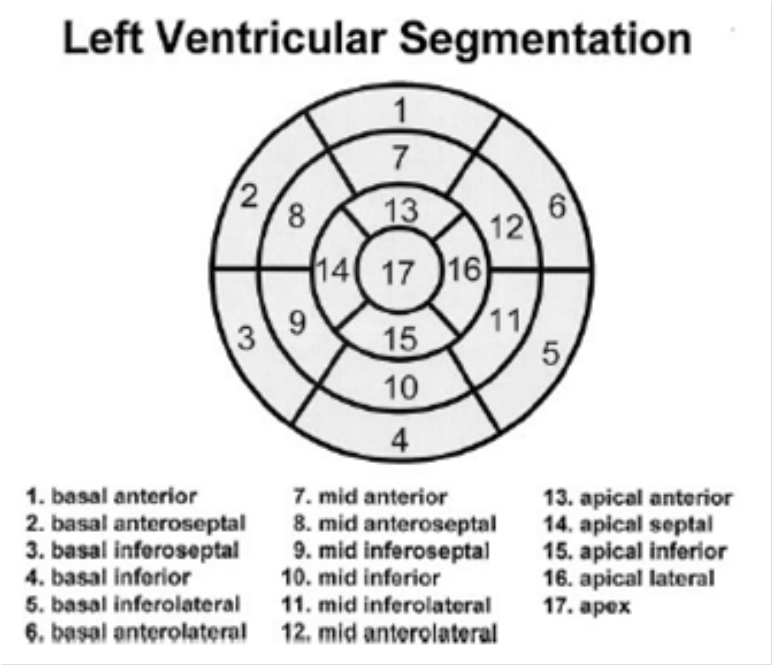


**Figure 1.** Segmentation of left ventricle to be used to document scar location

In addition, subjects will undergo substrate-based mapping and ablation through one of the following options:

- Mapping and ablation of late potentials (LPs)
- Mapping and ablation of local abnormal ventricular activities (LAVAs) / homogenization of entire scar (extensive ablation of entire scar)

With these options, the acute procedural endpoints will be one of the following:

- Complete elimination of LPs
- Complete elimination of LAVAs
- Completion of scar homogenization (extensive ablation of entire scar)

Conventional activation and entrainment mapping can be a part of the overall ablation strategy for stable, mappable VTs, but one of the substrate-based mapping and ablation strategies above must also be included per each institutional standard.

Acute success will be measured by the non-inducibility of any VT, defined as clinical VTs (based on similar cycle length, if known) as well as other sustained monomorphic VTs. Polymorphic ventricular tachycardia (PMVT) and ventricular fibrillation can be inducible through post-procedural programmed stimulation. The occurrence of PMVT/VF would be accepted as a positive EP study, and no further stimulation to achieve ventricular refractoriness is required per the study protocol.

**Crossover Subjects.** If the physician decides to stop treating with the current catheter and use the alternate catheter (from the other arm) to complete the ablation procedure, the occurrence will be documented on the operative procedure case report form.

**Re-intervention.** If a study subject experiences complications or otherwise requires additional unplanned re-interventions regardless of relationship to the index VT ablation procedure, all data will be captured on the Re-Intervention and Adverse Event forms where applicable.

**Hospital discharge.** Before hospital discharge, study subjects will undergo a clinical evaluation. A discharge EKG will be required.

### Follow-up Visits

Study-required clinical evaluations will be performed at 3, 6, 9, and 12 months. For all follow-up procedures, subjects are to be evaluated for recurrence of any VTs, defined as the documentation of sustained VT or ventricular fibrillation, including the evidence of appropriate ICD therapy such as antitachycardia pacing.

Antiarrhythmic drugs (AADs) will be discontinued at 3 months post-procedure. If the study subject is on AADs pre-procedure, the same drugs continue through 3 months after ablation. If the subject is not on AADs pre-procedure, the physician is not permitted to add AADs post-procedure.

**Three (3) month, Six (6) month, Nine (9) month, and Twelve (12) month follow-up visits are required per the protocol (see Table 1).**

### Study Administration

**Study subject removal.** Although all subjects are informed of their right to withdraw from the clinical study at any time, all patients are expected to continue in the study up to 12 months. A patient will not be considered lost to follow-up until the 12-month visit. “Lost to follow-up” will be documented on the Case Report Form when the following criterion has been met: After the 12-month visit, documentation of three unsuccessful attempts on 3 different days over a 2-month period by the Investigator or his/her designee to contact the patient or next of kin.

**Protocol deviations.** A protocol deviation is a failure to comply with the requirements specified within the study plan. Examples of protocol deviations may include (1) enrollment of a study patient who does not meet all inclusion/exclusion criteria and (2) a participant who missed study visits without documentation. All deviations are reviewed and assessed for their impact on patient safety by the Sponsor. Each investigative center will receive notifications of its deviations at least annually. Sponsor will report all deviations as part of the study annual report.

### Adverse Events

Adverse events will be identified and captured throughout the duration of the study and summarized in the final report. In addition, a DSMB will review adverse events and will adjudicate events for their relationship to the study device(s) and/or procedures and assess event rates for safety purposes. In this post-market study, adverse events will be reported in accordance with FDA Medical Device Reporting (21 CFR Part 803) requirements or per the European Medical Device Directive (93/42/EEC) and all applicable national regulations, Ethics Committee requirements, and Sponsor’s internal procedures.

**Adverse Event (AE) definition.** An AE is considered any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the device under evaluation/related procedure.

**Serious Adverse Event (SAE) definition.** An SAE is considered an adverse event that:

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

**Notification.** Investigators will immediately notify the Sponsor of any potential adverse events occurring at US or EU study sites. The Sponsor will submit a report to the FDA or the National Competent Authority within the required timeframe, if the event is reportable in accordance with the associated body's regulation or standard.

### Statistical Considerations and Data Analysis

**General considerations.** This prospectively randomized controlled single blind study with 386 patients is being randomized 1:1 to receive VT ablation treatment with either the magnetic navigation system (*Niobe* ES MNS) or a conventional manual catheter ablation approach (control). Continuous variables will be summarized using descriptive statistics, specifically the sample size, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

*Primary analyses.* The primary analyses will be performed on the modified intent-to-treat (MITT) population, which consists of all randomized patients who complete an ablation procedure. This group excludes any patients who were randomized but exited the study before completing their procedure, even if the procedure had been started. In analyses based on the MITT population, subjects will be analyzed according to the study arm to which they were randomized (regardless of the actual intervention received).

*Secondary analyses.* Secondary analyses will be performed on the per-protocol (PP) population, which consists of all randomized patients who complete the study with no major protocol deviations. All subject data in the PP population will be analyzed according to the treatment received during the study. The analyses based on the PP population will be conducted only if the MITT and PP populations differ.

*Major protocol deviation.* A major protocol deviation is defined as any protocol deviation that affects the primary endpoints. The study subjects to be excluded from the PP analysis set and the reasons for their exclusion will be determined and documented before statistical analysis of the treatment arms. These decisions will not be outcome-data driven.

The significance level for all statistical tests will be set to 0.05. Unless otherwise noted, no imputation for missing data will be performed, and data will be pooled across all study centers. No adjustments for multiplicity will be performed for any of the endpoint analyses.

**Interim analysis plan.** *It* specified before the start of this study the option to analyze the available data if a significant difference in treatment means is reached so that the trial can be stopped early. For instance, if an interim analysis is conducted when 50% of the subjects have

reached their 12-month endpoint of treatment success/failure and the magnetic device shows superior efficacy, the trial may be halted at this point.

As another example, an analysis of the available data can be conducted at a specific point in the trial to re-estimate sample size. For instance, the original sample size calculations assumed the treatment success rate for the control group was 68.8% and 81.2% for the magnetic device group. When 50% of the efficacy data is available, an analysis is conducted and we find that the control group rate is actually 75%. Since a smaller gap exists between the two treatment group proportions, a larger sample size is required to detect a statistically significant difference. A computation of conditional power will give the required increase in sample size to bring the overall power back up to 80%.

*Sample size.* The required sample size was calculated based on the following specifications (20):

1. Endpoint: Freedom from ventricular tachycardia through 12 months
2. Two-sided chi-square test
3. Alpha = 0.05
4. True percentage for control treatment: 68.8%
5. True percentage for RMN: 81.2%
6. 1:1 allocation of patients
7. Power = 80%

Based on the above specifications, the required sample size is 191 subjects per treatment group (a total of 382 subjects). However, an interim analysis on the primary endpoint will be conducted after 60% of the subjects have completed the 12-month follow up. The conduct of one interim analysis based on O'Brien-Fleming stopping boundaries will require an inflation of the sample size by a factor of 1.008 (21). Taking this adjustment factor in account, a total of 386 subjects is required for the study.

Sample size re-estimation is proposed as the protocol adaptive design (22) to make midcourse modifications of the maximum information or duration, which is defined as:

1. Done when 1-year outcomes are known for 60% to 75% of patients
2. Sample size increased, if needed, based on conditional power
3. Pre-specified maximum increase in sample size up to 100%

The study incurs no statistical penalty if results are "promising" at the time of the sample size re-estimation.

**Final analysis plans**

*Endpoints.* The primary effectiveness endpoint is Chronic Success, defined as freedom from any recurrence of VT through 1 year. AADs will be discontinued at 3 months post-procedure, unless AADs were used to treat unrelated arrhythmias. If the study subject is on AADs pre-procedure, the same drugs will continue through 3 months post-ablation. If the study subject is not on AADs pre-procedure, the physician is not permitted to add AADs post-procedure. However, AAD therapy after the ablation is at discretion of the treating physician. The Kaplan-Meier method will be used to estimate the true Chronic Success proportion and the corresponding 95% confidence interval for each treatment group. A two-sided normal approximation test will be used to test for a difference in proportions between treatments. For these analyses, subjects requiring re-intervention before 1 year will be considered failures for this endpoint at the time of re-intervention. Subjects who drop out of the study or are lost to follow-up before 12 months will be

censored as of the time of dropout or loss to follow-up if they have not experienced recurrence of VT before the time of dropout or loss to follow-up.

The secondary effectiveness endpoints were defined in the Study Design section of this paper. Acute Success will be summarized by treatment group using frequencies and percentages and a 95% exact (Clopper-Pearson) confidence interval for the true percentage. The proportion of subjects achieving acute success, the proportion of subjects with procedure related adverse events, and the proportion of subjects with heart failure related to VT/VF recurrence within 48 hours post-ablation will be compared between treatments using a two-sided chi-square test. The second secondary effectiveness endpoint as well as both of the secondary safety endpoints will each be analyzed in a manner analogous to that used for Chronic Success, except that for death through 12-month follow-up and stroke through 12-month follow-up subjects requiring re-intervention will be considered censored observations, rather than failures, as of the time of re-intervention. The tertiary outcomes, also listed in the Study Design section, will be summarized using descriptive statistics and will be analyzed using a two-sided, two-sample t-test to test for a difference in means between treatments.

## Discussion

### Clinical implications

The purpose of this post-market study is to demonstrate that ischemic scar ventricular VT ablation using the *Niobe* ES system results in superior outcomes when compared with a manual approach in subjects with ischemic VT in a low-EF population. As indicated earlier, it is the first study to prospectively compare MNS-guided substrate-based mapping and ablation to manual catheter ablation in this special VT population with a superiority design input. The proposed primary endpoints by Magnetic VT are similar to Smash-VT or V-Tach, but different to that of Vanish trial (Table 3). If the study is successful, the results could provide further evidence as the standard of care concerning the remote navigation guided ablation choice for the VT treatment, using the substrate base strategy in low EF cohorts and/or in a large scar VT sub-population. Magnetic VT should provide significant scientific merits and benefits to the treatment of patients with scar-related VT.

**Table 3** Comparison between the MAGNETIC-VT study design and other published VT ablation clinical trials in ischemic VT populations

| Study | Reddy et al. 2007 (SMASH-VT) (23) | Kuck et al. 2010 (V-TACH) (24) | Sapp et al. 2016 (VANISH) (25) | Natale et al 2016 MAGNETIC-VT |
|---|---|---|---|---|
| Major inclusion criteria | Spontaneous VT/VF, prior MI, and ICD | VT, prior MI, EF ≤ 50%, and ICD | ICM, drug refractory VT, and ICD | Drug refractory ischemic VT, prior MI, EF ≤ 35%, and ICD |
| Design | Randomized, prospective<br>N=128 (64:64) | Randomized, prospective<br>N=110 (54: 56) | Randomized, controlled<br>N= 259 (132: 127) | Randomized, prospective<br>N= 386 ( 193:193) |

| | | | | |
|---|---|---|---|---|
| | Catheter ablation plus ICD vs. ICD alone | Catheter ablation plus ICD vs. ICD alone | Catheter ablation with continuation of antiarrhythmic drugs vs. escalated drug therapy | Catheter ablation with magnetic navigation vs. manual catheter ablation |
| Primary endpoints | VT recurrence | Survival free from ICD therapy | Death, first occurrence of VT storm, or first occurrence of ICD therapy | Freedom from VT |

**Study limitations:** It is a large-sample size, randomized clinical study, which could face lengthy enrollment challenges.

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