

CLINICAL STUDY PROTOCOL

A PHASE 4, RANDOMIZED, OPEN LABEL, MULTICENTER
PROSPECTIVE COMPARATIVE STUDY TO EVALUATE THE
EFFICACY AND SAFETY OF
Edoxaban or Warfarin **T**herapy In **C**ardiovascular
Implantable **E**lectrical **D**evice Procedures in Patients with
Non-Valvular **A**trial **F**ibrillation
(“**ENTICED-AF Trial**”)

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I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study patients enrolled under my supervision and providing the Electrophysiology Research Foundation with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Title: A PHASE 4, RANDOMIZED, OPEN LABEL, MULTICENTER PROSPECTIVE COMPARATIVE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF **EDOXABAN** OR WARFARIN THERAPY IN CARDIOVASCULAR IMPLANTABLE ELECTRICAL DEVICE PROCEDURES IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION ("**ENTICED-AF TRIAL**").

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Number

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Protocol Synopsis:

TITLE	A phase 4, randomized, open label, multicenter prospective comparative study to evaluate the efficacy and safety of Edoxaban or Warfarin Therapy In Cardiovascular Implantable Electrical Device Procedures in Patients with Non-Valvular Atrial Fibrillation
SPONSOR	Electrophysiology Research Foundation
FUNDING ORGANIZATION	Daiichi-Sankyo Inc.
NUMBER OF SITES	20
RATIONALE	Perioperative bleeding is a risk of cardiovascular implantable device insertion or replacement procedures. Bleeding complications predispose patients to interruption of OAC therapy, use of reversal agents, infection, and re-operation and prolong hospital stays. In patients with non valvular atrial fibrillation, interrupted Edoxaban therapy may offer safety and efficacy that is non inferior to continuous Warfarin therapy during these procedures
STUDY DESIGN	This is a prospective randomized comparative evaluation of Edoxaban and Warfarin for safety and efficacy in perioperative use in patients with non-valvular atrial fibrillation undergoing clinically indicated implantation or replacement of cardiovascular implantable electrical devices. This study is a randomized, open label, active-controlled trial with an open-label safety extension, designed to compare local and systemic bleeding within 30 days of cardiac rhythm device implant among patients randomized to continuous Warfarin or interrupted (<24 hours) Edoxaban. The study will have three phases; a run in phase to establish stable Warfarin therapy, an acute open label 30-day phase when patients will be randomized in a 1:1 ratio to receive interrupted Edoxaban or continuous Warfarin, which will be followed by an open label follow up phase for an additional 5 months for safety monitoring. Drug transitions will be performed according to approved drug labeling.
PRIMARY OBJECTIVE	The primary objective is to compare the rates of local and systemic bleeding in patients randomized to Edoxaban compared to patients randomized to continuous Warfarin in within 30 days of cardiac rhythm device implant with concomitant non-valvular AF.
SECONDARY OBJECTIVES	The secondary objectives are to compare the rates of thrombotic events (embolism or stroke) and MACE events through 6 months following the procedure in the Edoxaban and Warfarin groups.

NUMBER OF PATIENTS	A maximum of 400 patients will be enrolled
PATIENT SELECTION CRITERIA	<p>a) Patients with established AF and bradycardia on long term (>3 weeks) therapeutic OAC with Warfarin or another OAC who are undergoing new pacemaker system implant or existing pacemaker system revision.</p> <p>b) Patients with newly detected bradycardia –tachycardia syndrome and AF who have been recently (less than 3 weeks) started on Warfarin, have a therapeutic INR and no thrombus on trans-esophageal echocardiogram (TEE) who are undergoing a new pacemaker system implant or revision.</p> <p>c) Patients with AF and ventricular tachyarrhythmias (VT or VF) or acquired structural heart disease who are candidates for ICD therapy and are on long term (>3 weeks) therapeutic OAC with Warfarin or another OAC who are undergoing new ICD system implant or existing ICD system revision.</p> <p>d) Patients with newly detected AF with VT or VF who have been recently (less than 3 weeks) started on Warfarin, have a therapeutic INR and no thrombus on TEE who are undergoing ICD system implant or revision</p> <p><u>Exclusion Criteria:</u></p> <p>a. Clinically significant valvular heart disease</p> <p>b. Patients requiring CIED lead extraction e.g. for device site infection, endocarditis, leads under advisory or other conditions warranting lead(s) system extraction.</p> <p>c. Recent (<1 month) myocardial infarction</p> <p>d. Documented LA thrombus on TEE</p> <p>e. Contraindications to anticoagulant therapy or adverse event with prior Warfarin or Edoxaban therapy</p> <p>f. Creatinine clearance <30ml/min or >95 ml/min</p> <p>g. Hepatic disease, advanced</p> <p>h. Recent stroke (<3 months) or thromboembolic event</p> <p>i. Recent (<3months) intracranial or other major bleeding event</p> <p>j. Use of concomitant dual antiplatelet therapy or other oral, subcutaneous or parenteral anticoagulant therapy</p> <p>k. Patients on Warfarin without therapeutic INR levels before study entry</p> <p>l. Patients with other clinically significant medical condition</p>

	<p>m. Patients with life expectancy < 1 year</p> <p>n. Lead extraction procedures</p>
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	<p>Edoxaban (30 mg tabs)</p> <p>Edoxaban 60 mg orally daily dose for creatinine clearance 50 to 95 ml/min and Edoxaban 30 mg orally for creatinine clearance of 30 to 49 ml/min.</p>
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Warfarin dose to maintain therapeutic INR, oral administration
DURATION OF PATIENT PARTICIPATION AND DURATION OF STUDY	<p>Screening: 7-26 days</p> <p>Treatment: 5 days of randomized therapy prior to procedure (which is a single day)</p> <p>Follow-up: 180 days</p>
CONCOMITANT MEDICATIONS	Allowed as per approved FDA guidelines
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	Major local or systemic bleeding as defined in the protocol at 30 days after implant procedure
SECONDARY ENDPOINTS	The secondary objectives are to compare the rates of thrombotic events (embolism or stroke) through 6 months following the procedure in the Edoxaban and Warfarin groups and the rates of MACE events through 6 months following the procedure in the Edoxaban and Warfarin groups
OTHER EVALUATIONS	The exploratory objectives are to compare rates of hemoglobin reductions from pre-procedure to 24-48 hours post procedure in the Edoxaban and Warfarin groups
SAFETY EVALUATIONS	Safety monitoring during the study will be performed by an independent data monitoring committee (DMC), as well as medical and clinical monitors

	and the coordinating center. Sites will be monitored by a clinical monitor at least once during this short trial. Clinical sites will be required to report all procedure related complications, deaths and major adverse events to the medical monitor within 24 hours of learning of the event. All events will be adjudicated by an independent events committee.
PLANNED INTERIM ANALYSES	When approximately 200 subjects have completed the study through the 30-day visit, an interim analysis for safety will be conducted by an independent data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study. Based on the primary outcome in these 200 subjects, the study may continue to enroll up to 200 additional subjects, or be terminated.
STATISTICS Primary Analysis Plan	This study contains an internal pilot, and the primary endpoint will be evaluated when 200 patients have reached 30-days post procedure or withdrawn. Based on the primary outcome in these 200 patients, the study may enroll up to 200 additional subjects, or be terminated. Bleeding rates will be compared for non-inferiority using a 1-sided exact test (Primary Endpoint). If non-inferiority of Edoxaban is demonstrated, superiority will be assessed using a 2-sided exact test (Secondary Endpoint).
Rationale for Number of Patients	The study is designed based on a non-inferiority hypothesis, with an overall type I error rate of 0.025 (1-sided) with a non-inferiority margin of 1.5%.

LIST OF ABBREVIATIONS

AE	Adverse event
CIED	Cardiovascular Implantable Electrical Device
CRF	Case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious adverse experience

1. Background

Non-valvular (NV) atrial fibrillation (AF) frequently coexists with bradyarrhythmias and tachyarrhythmias.^(1,2) NVAF patients frequently have cardiovascular implantable electrical devices (CIEDs) implanted for symptomatic bradycardias or tachycardias. In the elderly population, 30-40% of all patients with bradyarrhythmias and pacemakers (PM) have concomitant AF. In patients receiving implantable cardioverter-defibrillators (ICDs), 15 to 20% can have concomitant AF. Thus, insertion or revision of CIEDs is common in NVAF patients and requires management of concomitant anticoagulant therapy. Warfarin is the most commonly used oral anticoagulant (OAC) and is either bridged or continued for the CIED procedure. Bridging requires hospital admission for intravenous heparin therapy in many patients and continuous Warfarin therapy is now being increasingly employed. However, this approach is associated with significant peri-procedural bleeding complications during and after CIED procedures.

In the BRUISE control study AF patients with PM or ICD devices were studied using two different regimens for peri-procedural anticoagulation. Birnie et al reported “clinically significant” device pocket hematomas in 3.5% of on Warfarin and in 16% of patients on heparin bridging therapy.⁽³⁾ In another multi-center study, 9.8% of patients on heparin or Warfarin had significant pocket hematomas after pacemaker implantation.⁽⁴⁾ This is in contrast to the general CIED population, in whom this complication was observed only in 0.2% of implanted individuals in a nationwide experience from Denmark.⁽⁵⁾ Kutinsky et al reported even higher rates of hematoma formation in the presence of clopidogrel and aspirin with continued Warfarin therapy ranging from 9.5 to 24%.⁽⁶⁾ Bleeding complications predispose patients to interruption of OAC therapy, use of reversal agents, infection, and re-operation and prolong hospital stays. Bridging therapy may be associated with increased embolic events due to varying anticoagulation status.⁽³⁾

In contrast, in the MOST study performed in patients with only sick sinus syndrome at entry, bleeding complications with pacemaker implantation were <0.4%.⁽⁷⁾ Dewland et al reported major complication rates with ICD implants in the National Cardiovascular Device registry. They noted device related complications of approximately 1% exclusive of major bleeding and hematomas with ICD implants.⁽⁸⁾

2. Purpose and Rationale

The rationale of this study is based on the long half-life of Edoxaban and its potential for reduced bleeding risk in comparison to Warfarin in patients with non-valvular AF. Continuous Warfarin therapy has been advocated to avoid the need for bridging anticoagulation at the time of elective surgical procedures such as CIED insertions or revisions. Bridging can increase bleed rates and prolong hospital stay. However, clinical studies show major bleeding complications in 43.5% of such patients in the perioperative period. (3) It is proposed that Edoxaban 60 mg when administered up to 18 to 24 hours before after the CIED procedure and resumed 12 to 24 hours after the procedure could potentially reduce this bleeding risk without loss of efficacy in stroke prevention.

In patients with non-valvular AF on OAC therapy with concomitant bradyarrhythmias or tachyarrhythmias warranting insertion or replacement of a CIED, an interrupted Edoxaban regimen without bridging anticoagulation is hypothesized to show comparable safety and efficacy to continuous Warfarin therapy for peri-procedural anticoagulation.

3. Objectives

3.1 Primary Objective

The primary objective is to compare the rates of bleeding (local or systemic) in patients randomized to Edoxaban compared to patients randomized to continuous Warfarin in within 30 days of cardiac rhythm device implant for non-valvular AF.

3.2 Secondary Objective

The secondary objectives are:

1. To compare the rates of thrombotic events (embolism or stroke) through 6 months following the procedure in the Edoxaban and Warfarin groups
2. To compare the rates of MACE events through 6 months following the procedure in the Edoxaban and Warfarin groups

MACE components include:

- Cardiovascular hospitalization
- Stroke

- Myocardial infarction
- Heart failure
- Vascular events
- Death

3.3 Exploratory Objectives

The exploratory objectives are:

1. To compare rates of hemoglobin reductions of ≥ 2 g/L from pre-procedure to 24-48 hours post procedure in the Edoxaban and Warfarin groups
2. To compare change in hemoglobin from pre-procedure to 24-48 hours post procedure in the Edoxaban and Warfarin groups
3. To compare the rates of other events of interest, including
 - Hemoglobin decrease of 1.5Gm% or greater after 24 to 48 hrs
 - Other cardiac procedures
 - Hematoma requiring no intervention
 - Device Infection
 - Device explanation
 - Major intracranial hemorrhage
 - Vascular events
 - Myocardial Infarction (MI)
 - Cardiovascular Hospitalization
 - Hospitalization after procedure discharge and prior to study conclusion
 - Stroke and death composite

4. Study Design

4.1 Overview

This study is a randomized, open label, active-controlled trial with a safety extension (follow-up phase). It is designed to compare bleeding, local or systemic, within 30 days of cardiac rhythm device implant (acute phase) for non-valvular AF among patients randomized to continuous Warfarin or interrupted

Edoxaban. Randomization will be stratified by device type and HAS-BLED score (≤ 2 or ≥ 3). Patients will be randomized in a 1:1 ratio to receive interrupted Edoxaban or continuous Warfarin. This study contains an internal pilot opportunity to adjust the sample size or terminate the study, and there will be an interim analysis of the primary endpoint when 200 patients have reached 30-days post procedure or withdrawn. Based on the primary outcome in these 200 patients, the study may:

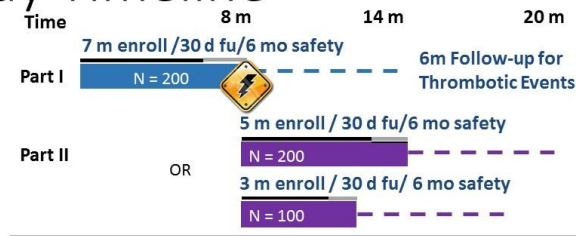
- Enroll 200 additional patients (pacemaker capped at 100 patients, ICD capped at 150 patients)
- Enroll 100 additional patients
- Be terminated


The study design is outlined in Figure 1.

Figure 1:

Study Design Flow Chart

Study Timeline



- Seamless design, enrollment does not stop between phases
-  Opportunity to stop if Part I objectives are not met
- Minimal resource commitment to Part II if Part I objectives not met
- For Part II, all sites enrolling, experience should lead to improved data quality compared to Part I
- Phases analyzed separately (primary) and combined

Eligible subjects must be stable on a therapeutic dose of Warfarin (INR 2-3) for three weeks prior to randomization. If potential patients are taking an anticoagulant besides Warfarin, or otherwise not meeting this criteria, must be switched to Warfarin and complete 3 weeks of dosing with INRs in the therapeutic range (run-in period) at randomization.

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The final INR should be performed on the day of randomization, and the procedure should be scheduled a minimum of 5 days and at most 15 days after randomization. Once eligibility has been confirmed and informed consent has been obtained, patients will be randomized via an interactive secure web randomization system. Patients will be randomized in a 1:1 ratio to Edoxaban or Warfarin. Randomization will be blocked by HAS-BLED score, and based on a randomization list, which will be created prior to commencement of the study.

At randomization, subjects will be provided with a drug kit containing either open-label Edoxaban or Warfarin for 30 days at a randomization visit. Patients randomized to Warfarin will take Warfarin on the day of procedure and patients randomized to Edoxaban will receive no drug on the day of the procedure.

Routine clinical care will be implemented with patients being scheduled for discharge within 24 hours of admission to maintain ambulatory procedural status. Patients requiring longer lengths of stay will have documentation of conditions warranting such care.

The routine standard of care (SOC) is instituted after the procedure, with a pre-discharge visit (4 to 24 hours after procedure), wound care visit (usually 1 to 2 weeks after the procedure) and standard device clinical follow-up procedures. These can include one month, three month or six month visits or remote monitoring as clinically employed in the study.

In the event of an acute procedural bleed, blood products or vitamin K may be administered. In this case, the patient will be counted as having met the primary endpoint. The primary outcome of major bleed will be assessed at the 30-day visit. The medical monitor will confirm that the primary endpoint has been assessed.

After the 30-day assessment, patients will continue to take the randomized anticoagulant unless it becomes medically necessary to change it. The MACE components will be collected at the time of the 6-month in-clinic visit.

There will be a telephone follow-up at 3 months after the CIED procedure for MACE and hospitalizations and vital status. There will be a face to face visit at 6 months which will result in study follow up completion and final patient assessment for safety endpoints, hospitalizations and vital status.

4.2 Justification of key elements of study design

4.2.1 Primary Endpoint

Peri-procedural bleeding and major local bleeding is of clinical concern for patients who require anticoagulation. Though catastrophic bleeding is rare, bleeding requiring clinical intervention is more frequent and can be studied in a modestly sized trial. Unlike strict use of change in hemoglobin, the need for intervention with vitamin K or blood products is recognizable to patients. Reduction in the need to administer an intervention for a procedural bleed should also result in lower health care resource utilization and costs.

Major local or systemic bleeding is defined as one of the following events:

- Significant hematoma requiring further surgery, resulting in prolongation of hospitalization, or requiring interruption of oral anticoagulation therapy
- Blood transfusion (permitted if hemoglobin is below 8 gm%, or 9 gm% in patients with active myocardial ischemia e.g. acute coronary syndrome)
- Surgical or interventional procedure to control bleeding that is symptomatic (shock, severe hypotension (90 mm hg systolic) or angina or myocardial infarction, which is not amenable to conservative measures (pressure dressing, ice packs) or volume expansion with intravenous fluids)
- Use of reversal agent injection to control bleeding leading to clinically manifest shock (e.g. hypotension requiring pressors, oliguria etc.) or death, severe and symptomatic hypotension (90 mm hg systolic or lower) or angina or hemoglobin decline to below 8 gm% not amenable to conservative measures (pressure dressing, ice packs or volume expansion with intravenous fluids)
- Hemorrhage leading to stroke or eventual fatality

(INR- guidelines for vitamin K injection or blood products will be established- see guideline below).

(aPTT or anti- factor Xa assay may or may not be available for Edoxaban to guide reversal – clinical and Hemoglobin guidelines as established above will be employed to guide use of reversal with blood products or transfusion).

Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving VKAs

Condition	Suggested Intervention
INR less than 4.5 but above	Hold or reduce Warfarin dose. Resume Warfarin when INR is therapeutic.

therapeutic	
INR 4.5 to 10 with no evidence of bleeding	<p>Hold Warfarin. Resume Warfarin when INR is therapeutic.</p> <p>Vitamin K not routinely recommended if no evidence of bleeding.</p> <p>Vitamin K can be used if urgent surgery needed (less than 5 mg, with additional 1 to 2 mg in 24 hrs. if needed) or bleeding risk is high (1 to 2.5 mg).</p>
INR greater than 10 with no evidence of bleeding	<p>Hold Warfarin therapy and administer vitamin K 2.5 mg to 5 mg orally.</p> <p>Monitor INR.</p> <p>Resume Warfarin at lower dose when INR therapeutic.</p>
Serious bleeding at any elevation of INR or Life-threatening bleeding	<p>Consult Hematology.</p> <p>Hold Warfarin.</p> <p>Administer intravenous vitamin K 5 mg to 10 mg by slow infusion or administer blood products as appropriate.</p>

*In patients with mild to moderately elevated INRs without major bleeding, give vitamin K or blood products as appropriate. Adapted from ACCP Evidence-Based Clinical Practice Guideline *Chest* 2012; 141(Suppl 2): e154S-88s.

4.2.2 Choice of continuous Warfarin as a comparator

Heparin bridging was standard of care until the BRUISE-CONTROL study showed a reduction of bleeds with continuous Warfarin compared to heparin combined with bridging therapy. No robust studies of other anticoagulants in procedural settings have been performed to date, so continuous Warfarin is the only suitable comparator.

4.2.3 Timing of primary endpoint evaluation

Other studies in cardiovascular medicine such as those for interventions during acute myocardial infarction or chronic ischemic heart disease consider bleeding events through 30-days post-procedure, and so it is a commonly used clinical timeframe. Because this trial is examining a surgical intervention, there is potential for bleeds and other acute complications. If this happens, the open label design allows investigators to make appropriate treatment decisions as quickly as possible. As always, open-label designs have an increased risk of bias. To combat this risk, we have defined a primary endpoint with minimal patientivity (see section 4.2.1). We will also have a blinded adjudication committee review each potential primary endpoint event to confirm that the study definition has been met.

4.2.4 Secondary endpoint evaluation

The secondary endpoint of superiority for peri-procedural bleeds will be assessed using the same methodology as the primary endpoint, except that the test will be for superiority. If the study does not meet the non-inferiority endpoint, superiority will not be assessed. The overarching goal is to reduce peri-procedural bleeds without causing an increase in stroke. Thrombi may form slowly though clinical presentation may occur months later. Considering events through 6 months post procedure helps to ensure that the interruption of Edoxaban for the procedure does not result in an increase in late-occurring thrombi or other safety issues.

5. Study Population

5.1 Device case mix

The case mix in electrophysiology programs currently is approximately 60% ICD procedures and 40% permanent pacemaker procedures. Of these, new implants constitute approximately 50% and device replacement procedures constitute 50%. Based on the BRUISE control study data, the bleeding rates differ between these groups (de novo implants versus replacement of generator; ICDs versus pacemaker). In addition, significant proportions (20%) of patients have additional lead revision, or lead insertion for device upgrade procedures that can add to the complexity of the procedure and impact the bleed rates. Lead extraction procedures are not permitted in this case mix. The pacemaker component will be capped at 100 subjects and ICD patients at 150 subjects in the first phase of the study. Subjects for potential enrollment in the study will be identified based on their medical and device history, chart review of the outpatient pacemaker clinic or scheduling for device procedures and then undergo evaluation for possible study inclusion criteria and subsequent enrollment.

5.2 Study Inclusion criteria

1. Subjects must be willing and able to give written informed consent
2. Outpatients \geq 18 years of age, male or post-menopausal female patients; premenopausal female patients who are on and will maintain continuous birth control therapy during the study.
3. Subjects must satisfy one of the following four inclusion criteria
 - e) Patients with established AF and bradycardia on long term (>3 weeks) therapeutic OAC with Warfarin or another OAC who are undergoing new pacemaker system implant or existing pacemaker system revision (single chamber, dual chamber or cardiac resynchronization device).

- f) Patients with newly detected bradycardia –tachycardia syndrome and AF who have been recently (less than 3 weeks) started on Warfarin, have a therapeutic INR and no thrombus on trans-esophageal echocardiogram (TEE) who are undergoing a new pacemaker system implant or revision (single chamber, dual chamber or cardiac resynchronization device).
 - g) Patients with AF and ventricular tachyarrhythmias (VT or VF) or acquired structural heart disease who are candidates for ICD therapy and are on long term (>3 weeks) therapeutic OAC with Warfarin or another OAC who are undergoing new ICD system implant or existing ICD system revision (single chamber, dual Chamber or cardiac resynchronization device).
 - h) Patients with newly detected AF with VT or VF who have been recently (less than 3 weeks) started on Warfarin, have a therapeutic INR and no thrombus on TEE who are undergoing ICD system implant or revision (single chamber, dual chamber or cardiac resynchronization device).
- 4. Subjects must be candidates for long-term OAC therapy based on clinical practice guidelines for treatment of NVAf. In subjects on OAC other than Warfarin entering the study, Warfarin therapy must be established with therapeutic INR levels before the procedure.
 - 5. Subjects are candidates for either Warfarin or Edoxaban therapy as per FDA drug approval guidelines. Guidelines for GFR as established for Edoxaban will be applicable to all subjects regardless of randomized drug choice.

5.3 Study Exclusion criteria

- 1. Clinically significant valvular heart disease (defined as atrial fibrillation in a patient with moderate to severe stenosis or regurgitation of one or more cardiac valves and without any other associated comorbidity that can contribute to the development of the arrhythmia).
- 2. Patients requiring CIED lead extraction e.g. for device site infection, endocarditis, leads under advisory or other conditions warranting lead(s) system extraction.
- 3. Recent (<1 month) myocardial infarction
- 4. Documented LA thrombus on TEE
- 5. Contraindications to anticoagulant therapy or adverse event with prior Warfarin or Edoxaban therapy
- 6. Creatinine clearance <30ml/min or >95ml/min
- 7. Advanced hepatic disease

8. Recent stroke (<3 months) or thromboembolic event
9. Recent (<3months) intracranial or other major bleeding event
10. Use of concomitant dual antiplatelet therapy or other oral, subcutaneous or parenteral anticoagulant therapy
11. Patients on Warfarin without therapeutic INR levels before study entry
12. Patients with other clinically significant medical condition
13. Patients with life expectancy < 1 year
14. Lead extraction procedures
15. Premenopausal female patients, who are not on continuous birth control therapy or are likely to discontinue it at any time during the entire duration of study enrollment.
16. Pregnant patients

6. Study Treatments

6.1 Investigational and control drugs

There are only two FDA approved drugs in this study, Edoxaban and Warfarin. No investigational drugs are anticipated.

6.1.1 Run-in Phase

Warfarin may be taken once per day. The allowable doses are 1- 20 mg per day. Subjects should be reminded of dietary and other interactions relevant to Warfarin.

6.1.2 Acute Open Label Phase

Subjects eligible for randomization will have maintained INR values in the therapeutic range based on a patient-specific dose of Warfarin – or baseline Warfarin therapeutic dose. From randomization to assessment of the primary endpoint, the study will be open label in design. In subjects randomized to Edoxaban in accordance with drug labeling, the transition from Warfarin and initiating Edoxaban should be performed when the INR has decreased below 2.5 after the discontinuation of Warfarin.

6.1.3 Follow-up Open Label Phase

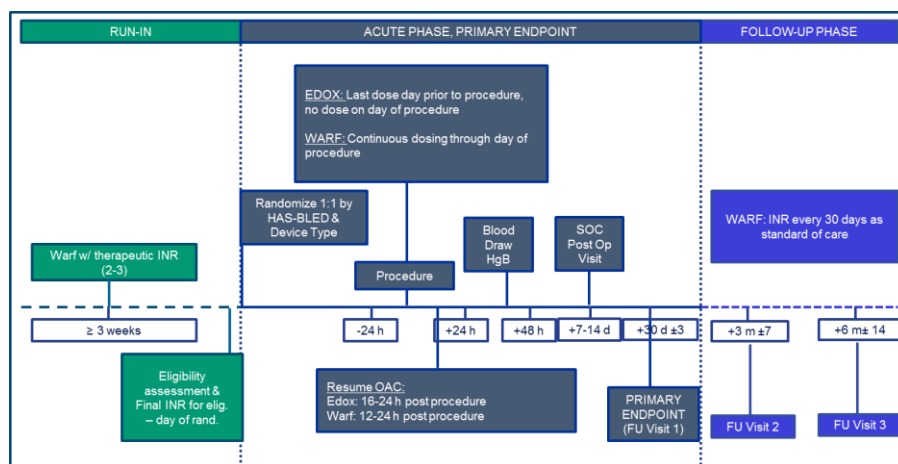
Subjects randomized to continuous Warfarin should have an INR in the first month, and continue monthly INRs as per standard practice guideline recommendations. Warfarin dosage should be adjusted according to standard practice to keep patients in the therapeutic range. Subjects randomized to Edoxaban should take it once daily per package dosing instructions (Edoxaban 60 mg daily dose for

creatinine clearance 50 to 95 ml/min and Edoxaban 30 mg for creatinine clearance of 30 to 49 ml/min). Subjects will be followed for an additional five months with a phone follow up at 3 months (± 1 week) and final follow up visit at 6 months (± 1 week). After the final follow up visit or after the subject is terminated from the study, subjects on Edoxaban transitioning to Warfarin should be maintained on Edoxaban until the INR is 2.0 or higher before Edoxaban discontinuation in accordance with drug labeling.

7. Study Visits

This study consists of three parts: a run-in or eligibility phase, an acute phase and a follow-up phase. Figure 2 for shows a diagram of study activities. Table 2 and Appendix A show visits.

Figure 2: Study events



Eligibility will be assessed when subjects have completed 3 weeks of Warfarin dosing. The procedure should be scheduled 5 to 15 days after randomization so that subjects are adequately anticoagulated with Warfarin or Edoxaban. The last dose of Edoxaban will be administered less than 24 hours prior to the procedure. Randomization will be obtained via IVRS once eligibility has been confirmed and the procedure has been scheduled.

On the day of the procedure, Warfarin will be continued and Edoxaban will be interrupted. Edoxaban dosing will resume a minimum of 16 and a maximum of 24 hours following the procedure. During and after the procedure, subjects will be assessed for safety and efficacy endpoints for bleeding and

embolism respectively as well as major adverse cardiovascular events (MACE). Edoxaban subjects will in general be discharged on the same day as the procedure, whereas Warfarin subjects will have their discharge timing determined on an individual basis by the investigator.

After discharge, subjects must return to the lab that drew the pre-procedure sample for another blood sample. This post-procedure blood draw should occur 24 to 48 hours after the procedure. The subjects will then resume the standard of care (SOC) follow-up. The SOC includes a pre-discharge visit (4 to 24 hours after procedure), wound care visit (usually 1 to 2 weeks after the procedure) and standard device clinical follow-up procedures. These can include one month, three month or six month visits or remote monitoring as clinically employed in the study.

The primary outcome assessment visit should be 30-days post procedure \pm 3 days. Assessments including focused H&P, concomitant medications, NYHA class, adverse events and hospitalizations will be collected. If a bleeding event has occurred, details including the date, time, required intervention and outcome should be recorded. Documentation of intervention may include the hospital order for vitamin K or blood products.

There will be a telephone follow-up at 3 months after the CIED procedure for MACE and hospitalizations and vital status. The final safety visit should be scheduled 6 months \pm 14-days post procedure or at the time of discontinuation if possible. Assessments including focused H&P, concomitant medications, NYHA class, adverse events and hospitalizations will be collected. If the investigator suspects that a MACE event has occurred, a MACE CRF should be completed.

Table 2: Schedule of study procedures and visits

Time point	Pre-procedure	Procedure (PM or ICD)	Post-procedure					
			Blood Draw	SOC Post Op	1	2	3	
								24-48 h
Demographics								
Medical & AF History	+							
Focused H & P					+			+
Con Meds	+				+			+
NYHA Class	+				+			+
Hemoglobin	+		+					
Procedure Details	PM or ICD							
Adverse Events	+	+		+	+	+	+	+
Hospitalizations	+				+			+

* Phone call

8. Assessment of Safety and Monitoring

Safety monitoring during the study will be performed by medical and clinical monitors and the coordinating center. Sites will be monitored by a clinical monitor at least once during this short trial. At the time of the site visit, the monitors will review implant procedure reports for all cases enrolled. Any issues or problems discovered will be discussed with the investigator; corrective action will be taken as necessary. Any findings will be documented in the monitoring reports and follow-up correspondence.

Clinical sites will be required to report all procedure related complications, deaths and major adverse events (AE) to the medical monitor within 24 hours of learning of the event. The medical monitor will review the case within 24 hours of notification and confer with the local physician as appropriate. The study principal investigator will be notified if the complication is serious or if it appears that the complication or implant failure may have been due to a deficiency of the operator or support facility and personnel. In this case, or if a clinical site reports implant failure or serious complications in conjunction

with two consecutive cases, the clinical site may be suspended from enrolling additional patients until a full examination of the complications and their probable cause can be determined and any problems have been rectified. All adverse events and procedure related complications will be recorded on CRFs and coded using MedDRA and included in tabular reports to the DSMB.

8.1 Adverse events

An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after randomization, regardless of the relationship to randomized treatment, procedures, underlying disease or comorbidities. All adverse events that occur or worsen after randomization should be reported on the CRF. When possible, the diagnosis or cause of the event should be reported instead of reporting symptoms. When multiple symptoms are related to a cause or diagnosis, only the cause or diagnosis should be reported.

Investigators should follow up with adverse events until they have resolved, the subject dies or withdraws from the study, or until the study is concluded.

8.2 Serious adverse event reporting

Serious adverse events (SAEs) are adverse events where at least one of the following is true:

- The event results in death
- The event is life-threatening
- The event requires or prolongs hospitalization
- The event results in permanent disability or incapacity
- The event is a congenital abnormality / birth defect
- The event is medically important

In the case of a serious adverse event, the investigator must immediately fax the signed and dated Serious Adverse Event case report form, accompanied by copies of all examinations, to the designated medical monitor.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in *other* situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the above definition.

8.3 Follow-up of Adverse Events and Serious Adverse Events

The investigator should take all appropriate measures to ensure the safety of the subjects. The outcome of any adverse event (clinical signs, laboratory values, etc.) should be followed up until they return to normal or until stabilization of the patient's condition

9. Quality Control and Data management

Data management will be performed by the Data Coordinating Center. Subject identifiers will be eliminated and study subject numbers only will be used during data collection in the electronic case report forms to ensure compliance with study confidentiality and HIPAA standards. All study data will be maintained in strict confidentiality at the Data Coordinating Center. Quality control will be performed by both Coordinating and Data Management Centers. GCP standards will be followed. Monitors will evaluate data collection procedures, and data entry procedures will be defined by the Data Coordinating Center. Details on data collection and cleaning are shown in subsequent section. A Data Monitoring Committee (DMC) and a charter will be established. Any published data will remove all patient identifiers and patients will only be numerically listed in study reports.

9.1 Data Collection and Database Management

Data will be collected on standardized Case Report Forms (CRFs) using an online electronic data capture system (eCRFs). Individually assigned user IDs and passwords will be required to gain access to the system and access will be controlled based on role in the study. Extensive online data edits will be programmed as part of the electronic data captures system. Other data cleaning procedures will be applied as appropriate.

Adverse events will be coded using the most current version of MedDRA.

Concomitant medication use will be collected by drug class for commonly prescribed cardiovascular medications.

A separate Data Management Plan will provide details of the data collection, coding, cleaning and archival processes.

9.2 Site training and monitoring

Prior to study initiation, all investigators and research coordinators will be trained in the study protocol at a central investigators meeting. Each clinical site will be visited by trained clinical monitors at least once during the study to make sure that study protocol procedures are being followed, consent is being

obtained per regulation and data are being collected contemporaneously and accurately. Clinical monitoring visits will be scheduled as needed thereafter. Any serious complications of the implant procedure will be reviewed by the DMC and a summary of the failures and complications will be presented to the DMC at each meeting.

10. Assessment of Non-Inferiority Hypothesis and Data Analysis

This study was designed based on a non-inferiority hypothesis, with an overall type I error rate of 0.025 (1-sided). The non-inferiority margin is 1.5%.

10.1 Expected event rates

See section 5.1 for case mix assumptions. For Warfarin, the 30-day primary event rate is estimated to be 3.51 % based on the continuous Warfarin arm of the BRUISE control study⁽³⁾. For Edoxaban, we estimate the primary endpoint rate to be 0.5%. In the Danish study by Kirkfeldt⁽⁴⁾, major perioperative hematomas requiring re-intervention was 0.2% for new implants and 0.1% for generator changes. In this study, 26.6% of implants were ICDs and 73.4% were pacemakers. In the report by Dewland from the NCDR registry, ICD hematoma rates were estimated at 0.8% for new implants. Using the case mix assumptions in section 5.1, 30% new ICDs, 20% new pacemaker implants, 30% generator changes only, and 20% pulse generator changes and lead revisions, the estimate is more conservative (lower).

Details of this calculation and comparison to other studies can be found in Appendix A

10.2 Sample size calculation (Appendix B)

It is possible, due to the low event rate in the Edoxaban arm and small sample size, that we could see no events in this arm. Thus, these sample size calculations are based on absolute risk differences rather than relative risk differences. Assuming event rates for Warfarin and Edoxaban of 3.51% and 0.5%, respectively, 300 total patients provides approximately 80% power to detect non-inferiority (margin 1.5%).

This study is a randomized, open label, active-controlled trial with an open-label safety extension, designed to compare local or systemic bleeding within 30 days of cardiac rhythm device implant for non-valvular AF among patients randomized to continuous Warfarin or interrupted Edoxaban. The DMC will review a formal interim analysis of the first 200 patients. Based on this analysis the DMC will make a recommendation about whether the study should be stopped or continued as planned. They may recommend that the study:

1. Be terminated for futility
2. Enroll an additional 100 patients in part II
3. Enroll an additional 200 patients in part II

Details about the criteria for this decision will be included in an interim statistical analysis plan and/or the DMC charter prior to the first data safety review. Because there is no opportunity to stop for efficacy after the first 200 patients, no type I error adjustment for the final analysis is necessary.

10.3 Analysis of the primary objective

The primary comparison of rates will be based on the Exact test. If appropriate given the event distribution, the Cochran–Mantel–Haenszel test will be performed as a supportive analysis, including the stratification factors.

10.4 Analysis of secondary objectives

The assessment of superiority of Edoxaban will be assessed if the primary endpoint analysis shows non-inferiority. In this case, the test will use the same methodology but will test the hypothesis that the difference in bleed rates (Warfarin – Edoxaban) is significantly different from zero rather than significantly greater than -1.5%.

With the exception of continuous change in hemoglobin, all remaining secondary endpoints are binary. They will be summarized with the number and percent in each group, and as rates based on the total patient-years of follow-up. The treatments will be compared as for the primary endpoint. If there are sufficient numbers of events, survival analysis techniques will also be used.

Continuous change in hemoglobin will be compared using ANCOVA, adjusted for baseline and trial stratification factors.

A statistical analysis plan (SAP) containing more information about end of study statistical analyses will be finalized prior to database lock.

10.5 Populations for analysis

The main populations for analysis will be as follows:

- The **intention-to-treat** population will include all randomized subjects, grouped by randomized treatment assignment. Since randomization occurs on the day of the procedure, all randomized subjects are expected to undergo device implant.

The primary and secondary endpoints will be evaluated in the intention-to-treat population. Adverse events and other safety information will be reported for all subjects where the implant procedure was started.

10.6 Handling of missing data values/censoring/discontinuations

Sensitivity analyses will be performed using multiple imputation and other techniques to determine the impact of missing data. The algorithms used for data imputation will be described in the SAP and finalized prior to database lock.

11. Discontinuation of the Study

This study is a randomized, open label, active-controlled trial with an open-label safety extension, designed to compare local or systemic bleeding within 30 days of cardiac rhythm device implant for non-valvular AF among patients randomized to continuous Warfarin or interrupted Edoxaban. The study may be terminated for futility. It may also be terminated for safety if a statistically higher than expected adverse event or local and systemic bleeding rate is encountered in either arm. These safety boundaries will be defined prospectively by the DMC.

12. Ethical considerations

12.1 Ethical compliance

The study and all its processes and procedures must comply with the Declaration of Helsinki, ICH-GCP and conformity with other international standards. If these guidelines are in conflict, the guideline that affords the most protection to the individual patient should be followed.

For studies conducted in the USA, the investigator will additionally ensure adherence to the basic principles of “Good Clinical Practice” as outlined in 21 CFR, subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Patients”, and part 56, “Institutional Review Boards”.

12.2 Informed consent procedures

The investigator or a person designated by the investigator should fully inform the subject of all pertinent aspects of the clinical trial including the written information approved by the local IRB/IEC/REC. Prior to assessment of eligibility, subjects may only be included in the study after providing written, IRB/IEC/REB-approved informed consent. The informed consent must be consistent with local

legal and site requirements, and must be signed and dated by the patient prior to any study-specific procedures occur.

12.3 Institutional Review Board/ Independent Ethics Committee / Research Ethics Board

The investigator must submit this protocol to the appropriate IRB/ REB. He or she is required to forward to the Data Coordinating Center a copy of the written and dated approval opinion by the Chair of the IRB/IEC/REB composition. Where allowed, a central IRB (Western IRB) will be used and the Data Coordinating Center will facilitate the application.

The study (protocol number, protocol title and version number), the documents reviewed (protocol, Informed Consent Form, etc.) and the date of the review should be clearly stated on the written IRB/IEC/REB approval opinion. During the clinical trial, any amendment or modification to the protocol should be sent to the IRB/IEC/REB. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the study, in particular any change in safety.

12.4 Responsibilities of the investigator and IRB/IEC/REB

The investigators undertake full responsibility to perform the study in accordance with this protocol, Good Clinical Practice and the applicable regulatory requirements.

The investigator is required to ensure adherence with the visit schedule and procedures as required by the protocol. The investigator agrees to provide all information requested in the Case Report form in an accurate manner.

13. Publication strategy

13.1 Publication of results

The design of this study will be posted in a publicly accessible database such as www.clinicaltrials.gov. In addition, upon study completion, database lock and unblinding, the results of this trial will be submitted for publication in a peer-reviewed journal and the Late Breaking Clinical Trials at a major national meeting. All study data will remain at the DCC, and all analyses will be conducted and validated at the DCC.

13. REFERENCES

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Appendix A: Schedule of Visits and Visit Elements

Time point	Pre-procedure	Procedure (PM or ICD)	Post-procedure				
			Blood Draw	SOC Post Op	1	2	3
			24-48 h	1-7 d	1 m	3 m*	6 m
Demographics							
Medical & AF History	+						
Focused H & P					+		+
Con Meds	+				+		+
NYHA Class	+				+		+
Hemoglobin	+		+				
Procedure Details	PM or ICD						
Adverse Events	+	+		+	+	+	+
Hospitalizations	+				+		+

* Phone call

Abbreviations: Con – concomitant; NYHA – New York Heart Association; PM – pacemaker; ICD – implantable cardioverter-defibrillator

Appendix B: Details of event rate assumptions

Calculation of Major Bleed Rate Assumption							
BRUISE-CONTROL Continuous Warfarin							
	Patients	% mITT	% ITT	Bleeds	% of Row		
N - ITT	343			12	3.50%		
Did not have procedure	8			0	0.00%		
Had procedure (mITT)	335	100.00%	97.67%	12	3.58%		
						Assumed Distribution	Weight Comp.
New Implant	156	46.57%	45.48%	5	3.21%	50%	
ICD	98	29.25%	28.57%	4	4.08%	30%	1.22%
PM	58	17.31%	16.91%	1	1.72%	20%	0.34%
Replacement / Revision	179	53.43%	52.19%	7	3.91%	50%	
Pulse generator change only	106	31.64%	30.90%	2	1.89%	30%	0.57%
Pulse generator change - plus*	73	21.79%	21.28%	5	6.85%	20%	1.37%
						Weighted Average Total	3.51%
<i>*Additional procedure including repositioning or adding a lead, device pocket revision, upgrade from PM to ICD</i>							
RE-LY							
	D110		D150		Warfarin		
	# surgeries	# bleed	# surgeries	# bleed	# surgeries	# bleed	% bleed
Urgent surgery	107	19	141	25	111	24	21.62%
Major surgery	473	29	511	33	498	39	7.83%
Elective surgery	1380	38	1405	53	1447	48	3.32%
Minor surgery	424	8	435	14	436	8	1.83%
Total	2384		2492		2492		
Major + Minor + Elective					2381	95	3.99%
Other trial overall major bleed rates							
	Bleed Rate	N	% Total Pts	Wt. Comp.			
RE-LY	4.6%	1558	19.0%	0.0088			
Yokoshiki	5.1%	59	0.7%	0.0004			
Denmark - haematoma	2.3%	5918	72.3%	0.0169			
Kutinsky (no drug)	8.7%	630	7.7%	0.0067			
Milic	4.8%	20	0.2%	0.0001			
Total (Weighted Average %)		8185		3.28%			