Efficacy of short term dabigatran etexilate followed by aspirin monotherapy after LAA (left atrial appendage) device closure (the DEA-LAA study).

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LIST OF ABBREVIATIONS

ACP- Amplatzer cardiac plug

AF- atrial fibrillation

ASA- aspirin

CTA- CT angiography

DAPT- dual anti platelet therapy

DAT- device associated thrombus

DEA- **D**abigatran **E**texilate followed by **A**spirin

DOAC- direct oral anticoagulant

DRT- device related thrombus

ICE- intra-cardiac echocardiography

LAA- left atrial appendage

LAAC- left atrial appendage closure

OAC- oral anticoagulation

TEE- trans-esophageal echocardiography

WAS- Watchman access sheath

1. Background and Study Rationale:

Two years after FDA approval of the first left atrial appendage (LAA) closure device for the prevention of embolic stroke in patients with non-valvular atrial fibrillation, over 13,000 Watchman (Boston Scientific, Inc., Natick, MA) devices have been successfully implanted in the US. Post-approval prospective registry data in 3,822 consecutive cases demonstrated implantation was successful in 3,653 (95.6%), with a median procedure time of 50 min with the majority of operators new to the procedure (71%). Complications included 39 pericardial tamponades (1.02%), 3 procedure-related strokes (0.078%); 9 device embolizations (0.24%), and 3 procedure-related deaths (0.078%) [1]. The early phase PROTECT-AF complications topped 10%, but clearly as expertise in trans-septal access, and improvements in the delivery system and technique have evolved, total complications post implant have dropped to <3% in the EWOLUTION registry [2].

With proper patient selection, routine use of ultrasound to guide venous access, and a continued trend to implant without bridging anti-coagulation, expert centers may be able to reduce total acute complications below 1%. As a stroke prevention strategy, this could position LAA closure as a cost-effective consideration, potentially as first line therapy for many patients. Several landmark clinical trials are ongoing in the LAA occlusion space and will provide prospective randomized trial data on over 5000 patients closed with a variety of methods. The Amulet (Abbott Medical, Inc.) versus Watchman IDE clinical trial (clinical trials.gov # NCT02879448) has rapidly enrolled since opening in 2017 with a target enrollment of 1400 subjects and 300 roll-in cases. Subjects eligible for a Watchman LAA closure device are randomized 1:1 to Amulet or Watchman and followed for a minimum of 18 months for the endpoint of stroke or systemic embolism. Additionally, the surgical LAAOS-III trial is studying over 4000 patients undergoing open heart surgery with a history of AF, and randomized 1:1 to LAA excision, or no intervention on the LAA.

Anti-coagulation regimen and anti-platelet therapy post Watchman implant in the Amulet IDE is according to the FDA labeling for Watchman subjects, with a more variable strategy in the Amulet arm, including even DAPT alone (ASA 81mg plus Plavix 75mg minimum of 6 months, followed by ASA 81mg alone). Traditional or standard of care anticoagulation management following Watchman LAA closure device implantation includes oral dose adjusted warfarin INR 2-3 for 45 days after implant (unclear if this requires initiation of warfarin pre-procedure in patients who were intolerant to OAC). In addition, ASA 81mg is to be taken to 45 days when a follow up TEE is performed to assess leaks, device position or thrombus formation. Typically (in PROTECT and PREVAIL over 92% of subjects stopped OAC at 45 days), the FDA labeling is to initiate ASA 325mg daily with clopidogrel 75mg daily for up to 180 days post implant, then indefinite ASA 325mg daily is recommended.

Referrals for LAA closure for anti-coagulation failure (formation of thrombus in the LAA despite medical therapy, or recurrent embolic events or stroke while on OAC) are not

clearly outlined in any LAA closure clinical trial inclusion criteria. In our experience, these may actually be the patients who stand to benefit the most from removing or occluding the LAA. Two separate studies have shown over a 93% LAA closure efficacy rate, including a 2017 LAA closure study with long term CTA assessment on Atriclip (Atricure Inc., West Chester OH, USA) placed by thoracoscopic approach [4,5]. Prior formal studies of surgical methods have reached 60-70% closure rates at best, and incomplete surgical closure is associated with a higher rate of stroke [6]. Management immediately following LAA closure by an epicardial approach with Atriclip or surgical closure does not appear to require systemic anti-coagulation, though no prospective randomized data exists to support this claim.

Several retrospective studies were published in 2017 supporting the use of NOAC (novel oral anti-coagulant) or DOAC (direct oral anti-coagulant) for anti-coagulation post LAA device implant to reduce DAT. EWOLUTION reported a 1 year device associated thrombus rate of 3.7% with Watchman, independent of the post implant regimen, in which 73% of anti-coagulation 'contra-indicated' subjects were on anti-platelet regimens alone [2]. A separate study showed a 3.2% DAT rate with the Amplatzer Cardiac Plug (previous generation of the Amulet device under IDE trial in the US) [7]. While certainly not what the implanting physician hopes to see at the 45 days or 1 year follow up TEE, whether a DAT leads to clinical ischemic strokes as a whole has been difficult to determine. Standard practice has been to initiate short-term oral anti-coagulation and repeat the TEE in 6 weeks to ensure resolution, of a DAT, then return to anti-platelet therapy alone.

The process of complete endothelialization of a Watchman LAA closure device is poorly understood. Animal models suggest complete endothelialization may be complete within 6 weeks. Human autopsy examples show variable endothelialization at up to 9 months. A study in 2017 using CT angiography demonstrated contrast flow across 66% of LAA devices at 6 weeks, questioning if TEE at 6 weeks is really a suitable metric for 'closure' [8]. Likely this represents a slow leak through the fabric cap and not around the device, if the TEE shows no Doppler flow. We have seen several cases where follow up TEE missed a leak and an obvious gap with contrast filling a trabeculated LAA lobe was seen with CTA. Anti-coagulation was discontinued, but long-term studies are needed to evaluate the impact of this finding.

Event rates for bleeding after Watchman versus warfarin show superiority after 6 months when clopidogrel is discontinued. This is where the net clinical benefit of LAAC is seen, leading to improved long term outcomes and ultimately the rationale for FDA approval of the Watchman device. The role of dual anti-platelet therapy, or the use of 325mg ASA versus 81 mg ASA long term is not supported by any specific literature, and was carried over from previous trials with use of coronary stents, and PFO and ASD occluder devices. Once the LAA device has complete occlusion with no flow into the LAA and surface endothelialization, it is plausible that ASA 81mg is a sufficient recommendation long term. This has recently been established in European AF guidelines on LAA closure for patients contra-indicated to OAC, supporting single or dual anti-platelet therapy after implant.

However, this potentially sets up an increased risk of device associated thrombus (DAT). If an alternative post procedure regimen using 90 days of dabigatran plus 81mg ASA alone is employed, eliminating the use of clopidogrel, we may reduce both major bleeding events, and reduce device associated thrombus rates at 1 year follow up. It would not be expected to impact ischemic stroke rate, but this could be implied if fewer DAT are observed.

In conclusion, LAA closure is becoming a reasonable strategy for patients at high risk for stroke (CHADS 2 Vasc score 3-9) and high risk for bleeding on long term OAC (HAS BLED score 2-6). The FDA labeled strategy for medical management after Watchman implant is loosely supported scientifically, and still exposes patients to increased bleed risk up to 6 months after implant due to the use of DAPT. A shorter and simplified use of dabigatran BID for 90 days post LAAC with ASA 81mg, followed by ASA 81mg daily long term may reduce bleeding events, and have a beneficial impact on lowering the rate of DAT. Praxbind is a specific monoclonal anti-body available for dabigatran reversal. All study centers will have Praxbind available for use in the event of a major bleed, (i.e., subdural or intracranial bleed, or major bleed requiring transfusion), or in case of unexpected or emergent surgery.

2. Study design:

Single arm, prospective unblinded study on post Watchman LAA closure device implant anti-coagulation management at a primary center (Vanderbilt Medical Center) and up to 5 additional high volume LAA implant centers. This trial will be designed to evaluate the use of dabigatran for 90 days post implantation of an LAA closure device (Watchman LAA Closure Device, Boston Scientific Inc.). The drug will be initiated on the morning following device implantation, taken BID per package insert dosing and until follow-up 90-day post implant TEE. Aspirin monotherapy will be utilized in conjunction at 81 mg for up to 12 months, after which the patients will be exited from the study and further treatment decisions will be made by the following physician (see Schedule of Study Procedures at end of protocol). The objective of this trial is to evaluate safety and efficacy of a 90-day period of dabigatran etexilate following LAA closure to prevent device associated thrombus, while minimizing adverse bleeding by eliminating the need for clopidogrel. This is a single arm pilot study with the option (pending collaboration with additional funding source) to expand to a full single arm non-inferiority trial design with 80% power to detect a 1.4% difference with the non-inferiority margin 1% in absolute rate of DAT (control rate 3.9%).

Prospective, non-randomized single arm study. Comparison will be made to historical controls based on published one year DAT rates from PROTECT-AF, PREVAIL clinical trials, and EWOLUTION, and ACP/Amulet registries.

Echocardiography (TEE) will be performed at 90 days (3 months, +/- 2-week window), and again at 1-year post implant (+/- 4 weeks). Selected images will be interpreted by echo lab at coordinating center in an anonymous fashion (patient data de-identified). Ideal imaging will incorporate 0, 45, 90 and 135 degree angled views on the device at follow up.

Drug will be dispensed as part of the clinical trial supplied from the sponsor and each patient will receive a complete 90 days' supply up front. They will have a drug visit on the day of TEE with the research coordinator to hand back any remaining dabigatran, with clear instruction to stop the drug and only take ASA following confirmation of closure on TEE (no peri-device leak on Doppler of >5mm). A decision to continue anti-coagulation post closure 90day TEE will be made by the physician discretion based on TEE findings. If thrombus is found at the 90 days TEE, anti-coagulation may be extended another 6 weeks with repeat TEE imaging to confirm clot resolution at the discretion of the investigator. In the unlikely event of embolization or Doppler leak >5mm, decision on extending anti-coagulation, or re-implanting a device will be made by the following physician.

Additional baseline data collection: Patient demographics, medical history, age, sex, and prior use of anti-coagulants or anti-platelet medications will be collected. CHADS 2 Vasc, and HAS-BLED score calculated. Main indication for LAA closure must be documented. Baseline CBC and BMP required on day of implant or up to 1 week pre-procedure (typical standard of care labs at time of implant). This will include a recent calculation of Creatinine Clearance (using Cockroft Gault and using patients actual body weight) and dosing of study drug will be made in accordance (see below). Repeat PCV or hematocrit on the morning after Watchman LAAC implantation will be per hospital standard. PCV or hematocrit value pre-implant and at the post 90-day visit will be analyzed.

Calculation for dabigatran dosing:

CCr={ (l40–age) x weight in kg)/(72 x SCr) } x 0.85 (if female)

Implant procedure variables to collect include access site, sheath used for deployment (WAS), device size at implant and number of implant attempts. LA pressure mean if available. Presence of angiography contrast or Doppler Echo leak, thrombus, or pericardial effusion post implant will be recorded. At 90 days, TEE report findings and image review (standard of care) with drug dosing visit with research coordinator and return of any remaining study drug. 1 year TEE (standard of care) with a research exit visit with MD, physician extender, or research coordinator, with documentation of ASA tolerance, dosing, and any late bleeding episodes or hospitalizations (typically should be reported as AE/SAE when first knowledge of event is determined). TEE images will be sent to the primary study site (Vanderbilt University Medical Center) and core TEE lab will review to confirm presence or absence of DAT. In cases of CTA utilized for follow up, similarly images will be reviewed by chest radiology team at Vanderbilt.

Medication administration with 90 days of dabigatran to be dispensed by pharmacy ideally one time (180 capsules).

3. Inclusion and Exclusion Criteria:

Patients over the age of 18 with renal function compatible with dosing of dabigatran and meeting all indications for watchman LAA closure device implantation as an alternative to long-term anticoagulation (CMS coverage criteria, CHADS 2 Vasc 3-9, and seeking suitable rationale for a non-pharmacologic stroke protection option). Lab testing and imaging will be part of standard of care for follow-up after LAA closure implantation including BMP, INR (when on warfarin) and baseline rhythm on day of implant, 90-day and 1-year transesophageal echo and when indicated CT angiography (subjects unable to undergo TEE at follow up). Images will be interpreted by the TEE operator, and an either independent radiologist or echocardiographer at Vanderbilt University Medical Center, the coordinating center.

Inclusion Criteria:

1. Male or female sex, age >18 years.
2. CHADS2 Vascular score of 3-9 and HAS BLED score 2 or higher meeting CMS coverage criteria for Watchman LAA closure device implantation.
3. Able to give informed consent.
4. Life expectancy of > 1year in the judgment of the implanting physician and shared decision-making physician.

To be eligible for enrollment, patients must NOT meet any of the following criteria.

Exclusion Criteria:

1. Unable to give informed consent
2. History of confirmed allergy to dabigatran etexilate
3. Active cerebral bleeding, or active non-cerebral bleeding requiring blood transfusions (any absolute contra-indications to anti-coagulation).
4. History of intraocular, spinal, retroperitoneal or a traumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired (e.g. by surgery)
5. Gastrointestinal (GI) haemorrhage within one month prior to screening, unless, in the opinion of the Investigator, the cause has been permanently eliminated (e.g. by surgery)
6. Major bleeding episode (reduction in the haemoglobin level of at least 2g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area

or organ) including life-threatening bleeding episode (symptomatic intracranial bleeding, bleeding with a decrease in the haemoglobin level of at least 5g/dL or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery) in one month prior to screening visit

7. Intolerance to dabigatran, if medication naïve, or other contra-indications as per the USPI, including ESRD on hemodialysis or GFR < 15ml/min, or concomitant use of rifampin.

8. History of non-compliance, inability to follow-up.

9. Pre-menopausal women (last menstruation ≤ 1 year prior to screening) who are not surgically sterile.

10. Ischemic stroke or hemorrhagic stroke within 90 days of LAA placement.

11. Anatomy unsuitable for LAA closure (incomplete surgical LAA ligation without suitable anatomy for Watchman placement. LAA ostial measurements >31mm, or <17mm in all views).

12. Requires long-term oral anticoagulation therapy for a condition other than atrial fibrillation.

13. ASA allergy, or confirmed allergy to nickel.

14. Prior PFO or ASD closure device or prosthetic or mechanical heart valve.

15. Acute MI within 90 days.

16. Platelets <50,000 at time of Watchman LAAC implantation.

17. Active endocarditis.

18. Planning for endocardial catheter AF or left atrial ablation within 90 days of Watchman implantation.

Dosing regimen of dabigatran will be by FDA and pharmacokinetic labeling for dabigatran 150mg BID dosing if Creatinine clearance >30mL/min, and 75mg BID dosing if 15-30mL/min. This will be based on calculated CC by baseline labs performed on day of implant. Additional dosing adjustments per package insert for patients taking dronedarone 400mg BID, or ketoconazole will be made consistent with drug label. The majority of subjects will be expected to be on 150 mg BID for 90 days. Subjects on 75 mg twice daily dosing may be enrolled if renal function is stable in the range of 15-30mL/min. Aspirin 81 mg a day will be taken along with oral anticoagulation for 90 days followed by longer-term aspirin 81 mg daily aspirin dose. At the 90 days TEE follow up (3 months) a PCV or CBC will be drawn and compared to baseline PCV pre-LAA closure implant as an assessment of

indolent blood loss (there is expected intra-procedural blood loss from back bleed on access sheaths estimated 25-125mL).

Drug required for study: Initially start with 100 subject pilot study on therapy for 90 days, with option to expand to full non-inferiority study if collaborative funding is secured (IF study expands beyond pilot, estimate 262 subjects, 90 days on therapy). Estimate 80% or more subjects on 150mg BID dosing, and up to 20% subjects on 75mg BID dosing. With either the 100-subject pilot study, or optional expanded single arm study (262 patients) the objective is to establish a device associated thrombus (DAT) rate at 3 months and 1 year within 1.5% or less deviation from published DAT rates at 3.9% (Saw, J., et al). Comparison will be made to published data on Watchman LAA closure utilizing the 45-day warfarin after implant followed by six-month dual antiplatelet regimen, or registry data from European experience on Watchman and Amulet/ACP LAA closure systems.

Patients can be consented for the trial on the day of implantation or up to one month prior in clinic during consultation for LAA closure. This is an unblinded, single arm prospective study. Study exit visit will be coordinated with final twelve-month follow-up imaging after LAA closure implantation.

Endpoints:

Primary endpoint: Device associated thrombus (DAT) at 1-year follow-up imaging by either transesophageal echocardiogram or CT angiography depending on the patient tolerance for TEE (TEE preferred).

Secondary endpoints: Includes ischemic stroke, peripheral thrombo-embolic events, major bleeding requiring intervention (blood transfusion, or surgical or non-operative intervention, i.e., pericardial effusion, vascular access repair etc.).

Statistical Methods/Calculations:

Statistical sample size calculation to establish comparable DAT rate with the prescribed regimen:

Available data for background on DAT;

Overall incidence of DAT was 3.9% (82 DAT for 2118 implanted devices)

Lempereur et al. Meta-Analysis [ref 19]: 30 studies describing DAT events were included in the analysis. The overall incidence of DAT was 3.9% (82 DAT for 2118 implanted devices). The median time from procedure to diagnosis of DAT was 1.5 months (IQR: 0-2.9). Most cases were diagnosed with transesophageal echocardiogram (TEE). The treatment consisted of low molecular weight heparin (LMWH) in 45.5% of cases, and oral anticoagulation (OAC) or other treatment modalities in 54.5%. Complete thrombus resolution was achieved in 95.0% of cases (100% with LMWH and 89.5% with OAC). Treatment duration varied greatly with a median treatment duration of 45 days (IQR: 14-

135). Clinical events related to DAT consisted of neurologic events namely two transient ischemic attacks (2.4%) and four ischemic strokes (4.9%).

Saw et al [ref 7]. 339 analyzable TEE in follow up. Patients' mean age was 74.4 ± 7.5 years, and 67.3% were men. The mean CHADS2 score was 2.7 ± 1.3, the mean CHA2DS2-VASc score was 4.3 ± 1.5, and the mean HAS-BLED score was 3.0 ± 1.2. Peri-procedural major adverse events occurred in 2.4%. Median clinical follow-up duration was 355 days (range 179 to 622 days). Follow-up transesophageal echocardiography was performed after a median of 134 days (range 88 to 227 days). Device-associated thrombus was observed in 3.2% Independent predictors of device-associated thrombus were smoking (odds ratio: 5.79; p = 0.017) and female sex (odds ratio: 4.22; p = 0.027).

Kaneko et al. [ref 20] 78 patients (50 males, 72 ± 8 years, average CHA2DS2-VASc score of 4.3 + 1.8) who had undergone WATCHMAN implantation. WATCHMAN was successfully implanted in all patients and four (5%) developed DRT. Patients with DRT were more often female (75 vs. 34%, p = 0.094). CHA2DS2-VASc score was higher for patients with DRT (6.3 ± 2.5 vs. 4.2 ± 1.7, p = 0.022). Chronic kidney disease (100% vs. 43%, p = 0.024) and deep implantation of the device, which was defined as implant position below the LAA ostial plane (75 vs. 24%, p = 0.026), were more common in patients with DRT. HAS-BLED score (4.5 ± 1.0 vs. 3.5 ± 1.1, p = 0.074) was higher and oral anticoagulants (50 vs. 84%, p = 0.086) were less commonly prescribed for patients with DRT. Multivariable logistic regression analysis showed that higher CHA2DS2-VASc score (p = 0.022, OR 2.8) and deep implantation (p = 0.032, OR 24.7) were associated with DRT. These results suggest the possible role of CHA2S2-VASc scores and implantation depth in the development of DRT after percutaneous LAA closure using the WATCHMAN device.

With a single arm non-inferiority trial design to show the absolute rate of DAT is less than the control rate of 3.9% by a non-inferiority margin of 1% having a power 80% to detect a 1.4% difference at 0.05 level of significance, we would need 262 total subjects enrolled and reaching imaging endpoint evaluation. The initial study will begin with pilot to 100 subjects (with 46% power) with an option to expand if additional funding source is obtained.

Data Management:

Data will be stored in a HIPPA-compliant manner in a REDCap database accessible to only the PI and key study personnel at each participating center, and site coordinating center monitoring team (Vanderbilt University Medical Center). Uploaded files and patient data will be identifiable in raw form but de-identified chart and subject ID in REDCap with access restricted to implant sites and coordinating center.

Safety Reporting:

Adverse events (AE) related to the drug or the procedure during the course of the study will be reported in the patient's record, and the investigator will give his or her opinion as to the relationship of the adverse event to study drug treatment.(i.e., the relationship will be reported as "related" or "unrelated" to the study drug administration). . If the adverse event is serious, it will be reported to Boehringer Ingelheim Pharmaceuticals, Inc. (BI), and IRB by the coordinating center and trial PI. All serious adverse events will be followed until resolution or stabilization. Results of the follow-up will be reported to BI and the IRB.

Definitions of Adverse Events:

"An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product"

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Acute minor or major complications following the implant procedure will be reported. Intra-operative major bleeding or device related (embolization, stroke, hemorrhage, etc.), will be reported as a procedural complication which is not study drug related. After the AM dosing of dabigatran post-operative day #1, and up to 90 days post procedure, AE's potentially related to study drug will need to be reported. Adverse events include events such as those described above that occur at any time from informed consent until 90 days post implant of the LAA closure Watchman device.

Recording of Adverse Events:

All AEs will be documented. A description of the event, including its date of onset and resolution, whether it constitutes a serious adverse event (SAE) or not, any action taken (e.g., changes to administration), and outcome, will be provided, along with the investigator's assessment of causality (i.e., the relationship to the study treatment[s]) and determination of severity (e.g., mild, moderate, severe). For an AE to be a suspected treatment-related event, there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE.

Bleeding events

Patients will be carefully assessed for signs and symptoms of bleeding at each visit. Bleeding will be classified as major or minor using the following guidelines. Major bleeds will be further sub classified as either life-threatening or other major bleeds.

Major Bleeds:

Bleeding associated with a transfusion of at least 2 units of blood or packed cells.

Symptomatic bleeding in a critical area or organ requiring surgical or non-operative intervention: Intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.

Minor Bleeds:

Minor bleeds are clinical bleeds that do not fulfill the criteria for major bleeds. Minor bleeds are classified as associated with study medication discontinuation (temporary or permanent) or not.

Serious Adverse Event Reporting to BI Pharmacovigilance

Adverse events classified by the treating investigator as serious require expeditious handling and reporting. Serious adverse events may occur at any time from informed consent until 30 days post cessation of dabigatran etexilate administration. BI must be notified of all SAEs containing at least one (1) fatal or immediately life-threatening event within five calendar days of the first knowledge of the event by the treating physician or research personnel. BI must be notified of all other SAEs within ten calendar days of the first knowledge of the event by the treating physician or research personnel. The SAE reports shall include all SAEs and non-serious AEs occurring in the same time and/or which are medically related and, in particular, the following information:

(i) the listedness of the reported events based on BI Investigator's Brochure for the dabigatran etexilate,

(ii) PI causal assessment as to whether the event(s) is/are related to the use of the dabigatran etexilate, and

(iii) the seriousness of each AE.

Causality should be assessed for each event as either "yes" or "no". No other variation should be reported. In case, according to the physician's causal assessment the association between an event and the patient's exposure to the dabigatran etexilate is classified as "unknown", the event will be considered "related" to the Study Drug for regulatory reporting purposes. If the SAE report forwarded to the BI was also submitted to a regulatory authority, this shall be indicated in the cover letter.

Supporting documentation for each of the reported SAEs, if requested by BI, will be provided to BI. Supporting documentation shall include, but is not limited to, lab reports, autopsy reports etc. SAEs, during and after pregnancy, will be reported to BI. To report an SAE, a BI SAE Reporting Form will be completed with the necessary information as available, and faxed using the following contact information:

Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road. Ridgefield, CT. Fax: **1-203-837-4329**.

Follow-up information for SAEs and information on non-serious AEs that become serious will also be reported to BI as soon as it is available; these reports will be submitted using the BI SAE Reporting Form. Serious adverse events occurring more than 30 days after study drug administration need only be reported if a relationship to the dabigatran etexilate administration is suspected.

The investigator does not need to actively monitor participants for adverse events once the clinical trial has ended However, if the investigator becomes aware of an SAE(s) that occurred after the participant has completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if the investigator considers it as relevant to the use of the BI study drug dabigatran.

SAE Reporting to Regulatory Bodies: Regardless of causality, all SAEs will be documented and reported to regulatory bodies, including the IRB as required by the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP). Follow-up information for SAEs and information for non-serious AEs that become serious will also be reported in the same manner. SAE's will be reported to the Vanderbilt Human Research Protection Program according to their policies and procedures.

Study duration and timelines:

From completion of the protocol, approval of contract and site initiation at Vanderbilt University Medical Center, study duration would be as follows: Estimated rate of enrollment is 2-3 subjects per site per month. Estimated time to complete enrollment of 100

subjects is 12 months once all sites are open, followed by 1 year of follow up to reach 1 year post implant imaging. Estimate completion of study in 24 months.

Publications:

Target Journals for publication of American College of Cardiology, Heart Rhythm, or Circulation Arrhythmia and Electrophysiology.

Schedule of Study Procedures:

	Baseline Visit	Procedure Day (+/- 3 days)	POD 1	90 Days Post Procedure (+/- 14 days)	1 Year Post Procedure (+/- 14 days)	AE/Other (e,g, DAT, study medication continued beyond 90 days)
Demographics	X					
H and P (including vital signs, height and weight)	X	X		X	X	X
I/E criteria (confirm eligibility)	X	X				
Informed Consent [(a)]	X	X				
CBC/BMP		X	X	X	X	X
Creat Cl	X	X	X	X	X	X
AE review	X	X	X	X	X	X
TEE		X (intra-operative)		X	X	X
Dispense Study Medication			X			X (as needed)
Pill Count/medication termination (planned)				X		X (as needed)
Exit					X	

[(a)] Informed Consent may be completed anytime up to one month prior to implant.

References:

Additional References Regarding LAA and LAA Device Associated Thrombus:

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