Direct **O**ral Anticoagulant **T**herapy with the **H**eart**M**ate **3** LVAD: A Pilot Study

DOT-HM3 Study

Investigator initiated study

The study site:

Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Version 2.0 9/25/2022

TABLE of CONTENTS

TABLE of APPENDICES

Study organization

Expert Advisory Committee: Chair – Mandeep R. Mehra, MD, member - Jean M. Connors, MD (both BWH and Harvard Medical School, Massachusetts, U.S.A.)

Study Principal Investigator: Ivan Netuka, MD

Executive Committee (s): Expert Advisory Committee + CEC + DSMB – (TBD)

Study Site: Institute for Clinical and Experimental Medicine, Prague, Czech Republic

1 INTRODUCTION

HeartMate 3 (HM3) Left Ventricular Assist System (LVAS) is a centrifugal, fully magnetically levitated, continuous-flow pump designed to facilitate hemocompatibility by reducing shear stress on blood elements and to optimize pump washout by intrinsic pulsatility.

The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) trial 2-year data[1] demonstrated an absence of confirmed pump thrombosis requiring pump exchange and marked reduction in stroke rates. On the backdrop of conventional anticoagulation protocols used in the study, observed bleeding complication rates in HM 3 were reduced, yet there is a need for further improvement as the overall intensity of conventional anti-thrombotic therapy represents a major contributor to non-surgical bleeding-related outcomes.

The HM3 LVAS Instructions for Use (IFU) recommend maintaining patients on Warfarin and Aspirin for long-term anticoagulation therapy. Recent results of The Minimal AnticoaGulation EvaluatioN To aUgment heMocompatibility (MAGENTUM 1) pilot study[2] has demonstrated substantially lower-intensity anticoagulation (INR range 1.5 – 1.9) is achievable and supports the safety of lower targets with select patients implanted with the HeartMate 3 beyond 1 year with no thromboembolic complications or pump thrombosis. The observed outcomes were similar to those with the higher intensity anticoagulation targets and further support a signal of enhanced intrinsic thromboresistance of the HM3.

Direct oral anticoagulants (DOACs) are a class of drugs which directly exert therapeutic effect on specific coagulation factors. Broadly, they can be categorized as direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) or FXai. Warfarin, which inhibits vitamin K dependent synthesis of coagulation factors in a manner that prevents activation of these factors, has wide inter-individual variation in metabolism and a narrow therapeutic window, as well as both food-drug and drug-drug interactions; the result is that patients taking warfarin require frequent monitoring of the anticoagulant effect to maintain safety and efficacy. The DOAC directly enter the blood to bind to the activated coagulation factor target; they have predictable pharmacokinetics, little interindividual variation in metabolism, few drug-drug interactions, and no interactions with foods. The large phase 3 RCT in both AF and VTE established both efficacy and safety—without the need for monitoring. The FXai may provide better anticoagulation than the oral direct thrombin inhibitor due to their action earlier in the coagulation cascade prior to the generation of

thrombin which may ameliorate the likelihood of initiation of the feedback loop resulting in >1000-fold increase in thrombin production. Of the studied FXai , apixaban has the lowest major bleeding complication rate and has not been shown to increase GI-bleeding[3, 4, 5]. It also has the least dependence on renal clearance. Consequently, with the documented enhanced hemocompatibility of the HeartMate 3 and the potential for reduced major bleeding with apixaban in indicated patient populations, we provide the rationale that patients with the HM3 are in clinical equipoise to be randomized in a feasibility study of a new antithrombotic strategy testing apixaban with or without aspirin compared to the current standard of care warfarin and aspirin in a rigorously structured study to evaluate safety in stable patients with the HM3 device.

Apixaban Safety and Efficacy Data

Apixaban is a DOAC that directly inhibits Factor Xa (FXai) in the coagulation cascade. Its therapeutic effect is more consistent and predictable due to its mechanism of action, and it is not subject to the disadvantages inherent to Vitamin K antagonist (VKA) anticoagulants. In phase 3 clinical trial that resulted in FDA approval, involving 18,201 patients with non-valvular AF, Apixaban was shown to be non-inferior in antithrombotic effect and superior in terms of major bleeding relative to VKA anticoagulants (ARISTOTLE study; NCT00412984).[3] Major bleeding, per the International Society on Thrombosis and Haemostasis (ISTH) definition, was reduced with Apixaban relative to VKA, primarily due to a 58% reduction in intracranial hemorrhage (ICH) and 21% drop in locations other than the gastrointestinal (GI) tract.[3] Clinically relevant non-major bleeds were also significantly reduced in this study.[4] GI bleeding was not significantly different between Apixaban and warfarin.

In the AMPLIFY study (NCT00643201), the safety and efficacy of apixaban for the prevention of recurrent venous thromboembolic (VTE) events and death due to VTE were compared with warfarin in 5,395 patients with acute VTE. Apixaban was found to be non-inferior to warfarin preventing recurrent VTE events (RR: 0.84; 95% CI: 0.6 – 1.18), and major bleeding was reduced by 69% in the apixaban group.[6] In a meta-analysis of DOAC studies in the VTE population, FXa inhibitors were found to have 60 % lower rate of ICH and fatal bleeds compared to VKA.[7] In a retrospective study of Medicare beneficiaries, 36% fewer patients were hospitalized for upper-GI bleeding with apixaban than with warfarin.[8] In another post-market study, apixaban was compared with rivaroxaban and dabigatran using propensity-matched cohorts of Medicare beneficiaries, with non-valvular AF, in terms of safety and efficacy. Apixaban was found to have a lower risk of causing GI and major bleeds than the other DOACs.[5] No differences were seen between the three DOACs in strokes or systemic embolism.[8] Even in cancer patients in whom the risk of bleeding is higher than in other popualtions, treatment of VTE with apixaban showed no increase in major bleeding compared to dalteparin, unlike edoxaban and rivaroxaban, both of which had increased major bleeding compared to dalteparin.

The rationale for Apixaban use with the HeartMate 3

There have been no studies to date that have systematically evaluated the feasibility of using apixaban alone or combined with low dose aspirin in HM3 patients. All the primary phase 3 clinical trials assessing DOACs have focused on patients with non-valvular atrial fibrillation or venous thromboembolism with or without cancer. [7, 10] Within the literature, there are sparse reports of apixaban use with LVAD patients due to recurrent bleeding or non-compliance with warfarin.[32-35] These small sample size studies reported encouraging low rates of thromboembolic events. In all but one instance, aspirin was withheld due to the history of bleeding events. Patients in these studies either had the HeartMate II or HeartWare HVAD.

Reduction in bleeding and thromboembolic events with HeartMate 3 compared to the HeartMate II was demonstrated by the MOMENTUM 3 IDE Trial. Yet, bleeding complications remain a burdensome limitation while on support and represent a significant cause of rehospitalizations and morbidity. Independently, both a reduction in major bleeding events and stable anticoagulation intensity constitute a compelling potential benefit of a modified antithrombotic strategy with a direct oral anticoagulant. However, these apixaban associated benefits remain to be validated in advanced heart failure population supported with the HeartMate 3 LVAS. Therefore, the objective of this study is to assess safety and feasibility of apixaban use in HM3 supported patients.

2 STUDY OBJECTIVES

2.1 PRIMARY ENDPOINT

The primary endpoint to evaluate the safety and feasibility of apixaban with the HeartMate 3 LVAS is survival free of major HRAEs (hemocompatibility related adverse events) at 90 days post-enrollment. The primary analysis will compare the apixaban groups (n=30) to control (n=15). A separate analysis will compare the primary endpoint in patients randomized to receive aspirin (n=15) and no-aspirin (n=15) within the apixaban group.

Major HRAEs include:

- Stroke (ischemic/hemorrhagic)
- Pump thrombosis
- Severe bleeding (see Appendix II)
- Peripheral arterial thromboembolic events

HRAEs are influenced by several patient-specific risk factors, including anticoagulation, poor general health, altered circulation, the pump's hemocompatibility, and the presence of other comorbidities (e.g., AF, infections, etc.). In standard use, clinicians balance the risk of stroke and other thromboembolic (TE) events with the increased risk of bleeding when prescribing

anticoagulation or antiplatelet medications. Therefore, a composite endpoint comprising TE, bleeding, and pump-related events were chosen for the analysis.

2.2 SECONDARY ENDPOINTS

The secondary endpoints include an evaluation of the following adverse events per INTERMACS definitions (version 5.0) throughout the study period:

- Stroke (ischemic/hemorrhagic)
- Pump thrombosis
- Major bleeding
- GI Bleeding
- Peripheral arterial thromboembolic events
- Transient ischemic attack
- Hemolysis
- Venous thromboembolism
- Myocardial infarction
- Right heart failure
- Cardiac arrhythmias
- Liver and kidney dysfunction
- Death due to any cause

3 STUDY DESIGN

A prospective, single-center, randomized controlled trial of the feasibility and safety of apixaban in HeartMate 3 patients.

3.1 STUDY CENTER AND PATIENTS

Eligible patients implanted with HeartMate 3 LVAS and meeting predefined criteria will be included in this study. The study will be conducted at the Institute for Clinical and Experimental Medicine in Prague and will be made open to other selected centers. The study design anticipates 45 patients to be enrolled.

3.2 STUDY DURATION

Patients enrolled will be followed-up for 90 days post-transition to a designated antithrombotic regimen based on randomization. Provided the individual patients clinical course is uneventful regarding the primary endpoint, the patient's follow-up within the antithrombotic study protocol will be extended to the next pre-specified time point for analysis at 180 days.
After the 180 days timepoint is reached, the patients will be given a chance to prolong the study until 1 year. All apixaban subsets will be treated according to their original study arm, the patients from the Vitamin K antagonist and aspirin group will be randomized in a 1:1 manner to apixaban with or without aspirin

3.3 STUDY DESIGN

3.3.1 Study design

Stable HM3 patients who have not suffered a Major hemocompatibility-related adverse event after index hospitalization discharge and are at least 3 months post-implant will be screened for participation in the study. Upon meeting the study criteria and patient informed consent, the individuals will be randomized to either continued therapy with a Vitamin K antagonist and aspirin or conversion to apixaban 5 mg twice a day in a 2:1 manner (dose targeted to renal function); the apixaban group will be stratified further by 1:1 randomization to continued use of 100 mg aspirin once daily or cessation. Thus, 45 patients are planned to be enrolled and randomized in 3 subgroups of 15 patients in each arm (see Appendix I). After 180 days follow-up is reached, the Vitamin K antagonist and aspirin arm will be transitioned to apixaban and randomized in a 1:1 manner to groups with or without aspirin.

3.3.2 Adverse events adjudication and outcomes assessment

All suspected or confirmed HRAEs (safety surveillance see Appendix IV) will be promptly reported to and adjudicated by the Expert Advisory Committee to determine individual patient safety to continue with the assigned treatment arm and the overall study safety and eligibility for continuation. All adverse events will be periodically reported to the Institutional Ethics Committee.

4 PATIENT POPULATION

4.1 INCLUSION CRITERIA:

- The patient has been implanted with HeartMate 3 LVAS
- The patient is, at a minimum, 3 months post HeartMate 3 implant
- The patient is stable, ambulatory, and has been discharged home
- The patient provides written informed consent before any clinical investigation related procedure

4.2 EXCLUSION CRITERIA:

- Non-compliance with anticoagulation and antiplatelet medication, in the opinion of the investigator
- Weight ≤ 60 kgs. or age ≥ 80 years
- Poor kidney function with serum creatinine ≥ 221umol/L or creatinine clearance < 0.042 mL/s, or the need for chronic renal replacement therapy
- Total bilirubin > 43 umol/L, shock liver, or biopsy-proven liver cirrhosis
- Absence of an informed consent
- Presence of any mechanical prosthetic valve or any ancillary circulatory assist device system (other than the HM3)

- Recent history of cardioembolic stroke
- Hemodynamically significant carotid arteries stenosis (documented by imaging investigation not older than 12 months)
- Need for antiplatelet therapy for reasons other than LVAD therapy
- Major HRAE event after HeartMate 3 index hospitalization discharge
- Known history of hyper- or hypo- coagulable disorder
- Anti-phospholipid syndrome positive patients with documented history of thrombotic/thromboembolic events
- Known hypersensitivity or allergy to apixaban or aspirin
- The patient is involved in another interventional study or any study that could potentially affect the functioning of the HM3 LVAD or the therapeutic effect of any of the study anticoagulants (warfarin, apixaban or aspirin), or could potentially confound the study results
- The patient is currently pregnant, breastfeeding, or intending to get pregnant during the study
- Presence of other anatomic or comorbid conditions, or other medical, social, non-compliance or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements or impact the scientific soundness of the clinical investigation results.

5 STUDY COURSE

5.1 ENROLLMENT PROCEDURES

Patients will sign an informed consent form at the time of the study enrollment. The consent form states that the data collected for this study will be used by authorized personnel only. The patient's privacy will be maintained according to local legislation and, patients will be identified by study specific code. The aggregate and/or de-identified patient specific data may be published or presented.

5.2 DATA COLLECTION & FOLLOW-UP ASSESSMENTS

The patient will be assessed at baseline. Lactate dehydrogenase (LDH) will be assessed once a week for 4 weeks, then once every 2 weeks for the next month and monthly thereafter; TTE ECHO follow–up will be performed at baseline, at 1 month and at 3 months, followed until study completion per site standard of care. A complete list of data fields to be collected is provided in Appendix II. A summary of the data collection is provided in Table 1 below, and follow-up assessments are further described in the following sections.

Table 1 – Summary of Patient Assessments and Data Collection

	Baseline[1]	**Once a week**[2]	**Once a month**[2]	**During regular ambulatory visits**	**At time of event**
Consent Form	X				
Demographics & Medical History	X				
Enrollment form	X				
Laboratory Assessment (study site standard of care)	X		X	X	X
LDH Assessment	X	X[3]	X[3]	X	X
ECHO assessment	X		X[4]	X	X
Anti-coagulation / anti-platelet regimen	X	X		X	X
Adverse Events: thrombosis, other adverse events					X
Rehospitalizations / Reoperations					X
Outcome					X

[1] Baseline is defined as the time point of the patient enrollment to the study.
[2] The follow-up assessments commence after the study enrollment.
[3] LDH assessment once a week for 4 weeks, then once every 2 weeks for the next month and monthly thereafter
[4] ECHO follow–up will be performed at baseline, at 1 month and at 3 months, followed by periodical 6-monthly examinations

5.2.1 Demographics

Patient demographics will be collected at baseline, including age, gender, height, weight, BMI, blood type, vital signs, etiology of heart failure, duration of mechanical circulatory support prior to study enrollment, Modified Rankin Score, INTERMACS Profile prior to HM3 implant, and therapeutic intent of HM3 support.

5.2.2 Medical History

The patient's medical history will be collected at baseline, including a history of cardiac arrhythmias, diabetes, smoking, hypertension, and cancer.

5.2.3 Enrollment form

Information will be captured on whether the patient met the study inclusion/exclusion criteria.

5.2.4 Laboratory Assessments and Diagnostics

LDH assessment will be performed once a week for 4 weeks after the randomization, then once every 2 weeks for the next month and monthly thereafter; other regular laboratory assessments will include standard of care work-up, including measurements of kidney and liver function and hemostasis. Desirably, the same local authorized laboratory facility should be used by the patients to ensure consistency of a laboratory follow-up.

5.2.4.1 Apixaban plasma concentration

Apixaban peak and trough levels will be performed using a commercially available anti-Xa assay with apixaban calibrators at 4 weeks visit per study protocol. Levels will also be drawn at the time of presentation with any HRAE.

5.2.5 Adverse Events

All INTERMACS adverse event definitions (version 5.0) will be used in this study for the evaluation of primary and secondary objectives. Laboratory values will be determined at the time of an adverse event.

5.2.6 Changes to the antithrombotic regimen

Any changes to the designated antithrombotic regimen based on randomization algorithm will be documented during the follow-up visits or with the occurrence of an adverse event.

5.2.7 Rehospitalizations/Reoperations

Once a patient is admitted to the hospital, details will be collected on the admission date and the reason for the rehospitalization and date of discharge and antithrombotic therapy status.

Reoperations will also be captured, including the date and reason for the reoperation.

5.2.8 Outcome

The patient's outcome (transplanted, expired, explanted or withdrew) and date of outcome will be captured.

5.2.9 Completion of study follow up

Upon completion of study follow up, patients will be transitioned back to their pre-study anticoagulation regimen (e.g. warfarin with aspirin).

5.3 DATA ANALYSIS AND STATISTICAL ISSUES

Survival free of a hemocompatibility-related endpoint 90 days will be evaluated. The prevalence (percent of patients with events) and incidence (event rates in events per pt-year) of adverse events and rehospitalizations will be determined.

6 ETHICAL AND REGULATORY CONSIDERATIONS

6.1 INFORMED CONSENT/PATIENT AUTHORIZATION

The patient, before study enrollment, must provide informed consent. The informed consent form, where patient informed consent is captured, must have prior approval from the Ethics Review Board (ERB).

6.2 ETHICS REVIEW BOARD (ERB)

ERB approval will be obtained prior to enrolling any patients in this study. ERB will maintain oversight of the study in accordance with local policies and procedures.

7 DATA REPORTING AND RECORD-KEEPING

7.1 DATA REPORTING

The data to be collected are identified in Appendix I. These will be captured by investigators and entered into a Microsoft Office Excel sheet in anonymized form according to local regulatory standards. The investigator must ensure that the study required observations and findings are recorded correctly and completely and in a timely manner. Source data will be maintained by the study site (e.g. in the form of patient medical records) for verification of data listed in the study data tables.

7.2 CONFIDENTIALITY

Patient Confidentiality will be enforced as per General Data Protection Regulation (GDPR) of the EU Directive no. 2016/679 (effective since 25th May 2018).

The patient will be made aware (via the patient authorization) that certain personally identifiable information will be collected as part of this study and will be disclosed outside the hospital. This information will include date of birth, date of death, admission and discharge dates, and dates of treatment. Except when required by law or except by the patient's authorization, the patient will not be

identified by name, address or telephone number in the study records disclosed outside of the hospital. In the study records disclosed outside of the hospital the patient will be assigned a unique study code.

7.3 MAINTENANCE OF STUDY DOCUMENTATION

The following study documents will be maintained by the study site and be available for periodic review by Abbott or the expert advisory committee per explicit request:

- Copy of the Study Protocol
- Ethics Committee Approvals and Correspondence: a copy of all Ethics Committee approvals and any significant correspondence will also be provided Abbott.
- Ethics Committee approved Patient Authorization/Informed Consent Forms: a copy will also be provided to Abbott.
- Signature Verification Form: all study site individuals approved by the investigator to participate in this study and/or complete data entry must sign the Signature Verification Form. This form will be maintained on site.
- Study Agreement: the Investigator and the Institution will complete a Study Agreement prior to patient enrollment. The agreement will identify the investigator's legal and ethical commitments with respect to the conduct of this study.
- Patient Authorization/Informed Consents for each patient enrolled in the study
- Source documentation (such as patient clinic charts, medical records, lab records)

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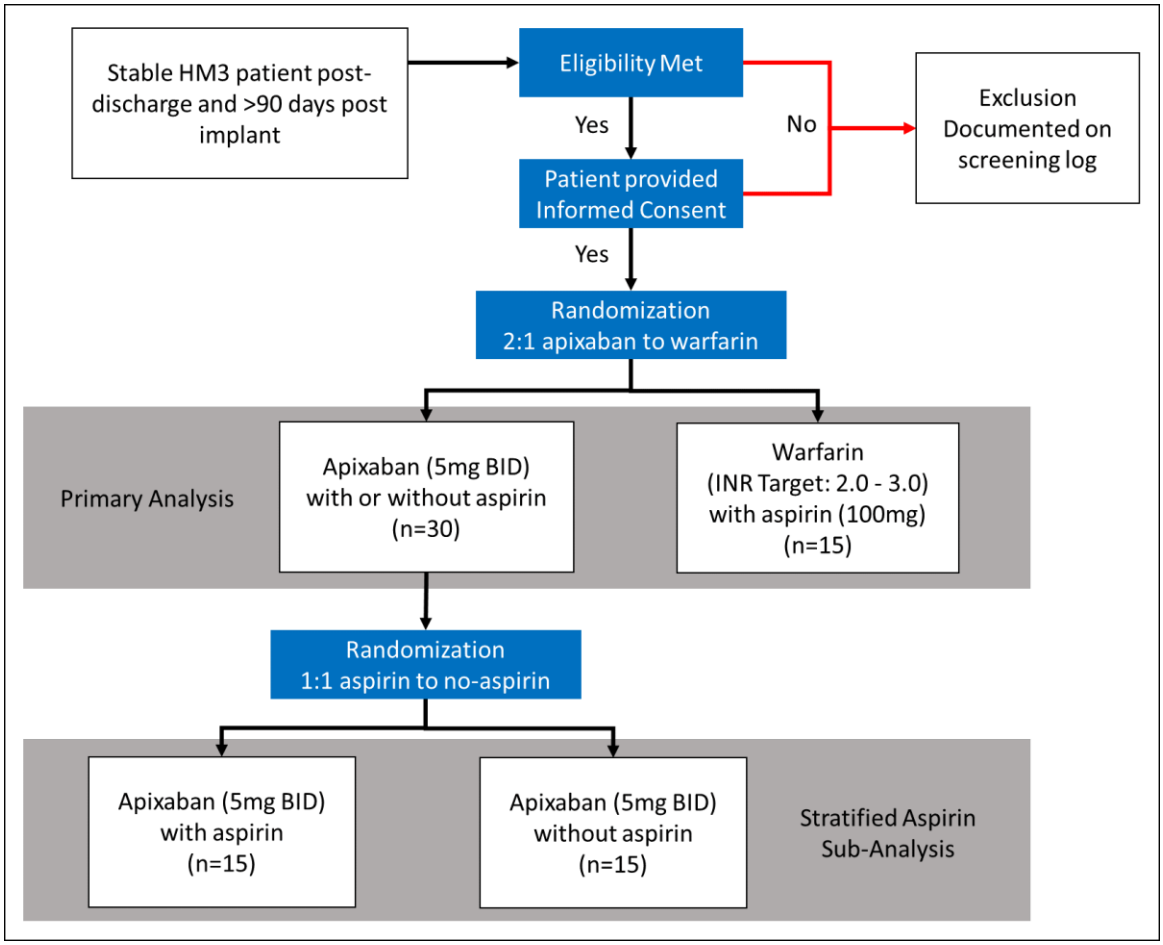
Appendix I: Study design flow chart



Appendix II: Severe Bleeding Definition

SEVERE BLEEDING:

Type A: (Meets any of the below)

- Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL(30-50g/L) (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type B: (Meets any of the below)

- Overt bleeding plus hemoglobin drop 5 g/dL (50g/L) or greater (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental, nasal, skin, or hemorrhoid)
- Hypotension attributable to bleeding and requiring intravenous vasoactive agents for hemodynamic support
- Intracranial Hemorrhage that does not meet the definition of hemorrhagic stroke

Type C1: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type C2: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Appendix III: Data Collection spreadsheet

	Baseline	At regular ambulatory visits	Once a week	Once a month	At the time of the event
Baseline info:					
Patient identifier	x				
Date of birth	x				
Gender	x				
Ethnicity	x				
Race	x				
Etiology	x				
Current device strategy	x				
Blood type	x				
Assessment of routine tests done to evaluate the prothrombotic state	x				
Medical History					
INTERMACS Profile at time of implant	x				
Coronary artery disease	x				
Arrhythmia: atrial/ventricular; Afib (yes/no)	x				
Ventricular pacing	x				
Cancer	x				
ICD	x				
Stents, location	x				
Myocardial infarction	x				
Diabetes	x				
Smoking history	x				
Diverticular disease or diagnosed AVMs	x				
GI Ulcer	x				
Significant carotid stenosis (or if last examination > 12 months old)	x				
AEs since pump implant:	x				
Enrollment Form	x				
Date enrolled	x				
Incl/excl criteria (yes/no)	x				
Date of study therapy initiation	x				

	Baseline	At regular ambulatory visits	Once a week	Once a month	At the time of the event
Physical Exam					
Heart rate	x				x
Height in cm	x				x
Weight in kg	x				x
BP_MEAN – Doppler	x				x
Pump parameters (speed, flow, PI, power)	x	x			x
Laboratory tests					
Creatinine	x	x			x
Urea	x	x			x
Total Bilirubin	x	x			x
Hgb	x	x			x
Hct	x	x			x
WBC (leucocytes)	x	x			x
PLT	x	x			x
Verify-now test	x	x			x
INR	x	x			x
Fibrinogen	x	x			x
aPTT	x	x			x
LDH	x	x	x[1]	x	x
Plasma free hemoglobin	x	x			x
BNP (or NT Pro BNP)	x	x			x
Anti Xa apixaban		x[3]			x
Baseline diagnostics					
ECG (date, rhythm)	x	x			x
Echocardiography	x			x[2]	x
Carotid ultrasound (if more than 12 months since last examination)	x				
Implant information					
Date implanted	x				
Follow-up					
Reoperation for bleeding/thrombosis? Date, reason	x				x
Date of initial discharge post LVAD implant	x				

	Baseline	At regular ambulatory visits	Once a week	Once a month	At time of event
Current anticoagulation regimen (date, medication, dosages)	x	x			x
Re-hospitalization for thrombosis/other AE? Admission date, reason, treatment, discharge					x
HRAE					x
Onset date					x
Is event stroke, TIA, or device thrombosis					x
If stroke, is it ischemic or hemorrhagic?					x
If stroke, head CT examination					x
If device thrombosis: Hemolysis seen? Thrombolytics given? Increase in pump power? Pump replaced? Other clinical symptoms?					x
Collect laboratory tests listed above					x
Current anticoag/antiplt medications					x
Any change to anticoag/antiplt meds? If yes, what					x
Infection requiring antibx or + BC					x
Describe event and treatment					x
Resolution date					x
Other AE					
Onset date					x
Type of event					x
Examination incl. imaging methods					x
Laboratory tests					x
Rehospitalisation/reoperation					x
Treatment					x
Outcome					
Date					x

	Baseline	At regular ambulatory visits	Once a week	Once a month	At time of event
Type of outcome (expired, explanted, transplanted)					x
If expired, cause of death					x

[1] LDH assessment once a week for 4 weeks, then once every 2 weeks for the next month and monthly thereafter

[2] ECHO follow–up will be performed at baseline, at 1 month and at 3 months, followed by periodical 6-monthly examinations

[3] Performed at 4 weeks visit after the anticoagulation transition in patient on apixaban only

Appendix IV: Therapeutic efficacy adjustments and safety monitoring

Advanced Pump Thrombosis Monitoring Protocol

- Monitor LDH at baseline and after initiation of determined antithrombotic therapy based on randomization algorithm once a week during first 4 weeks, then once every 2 weeks for the next month and monthly after that
- If LDH rises more than 1.2x baseline:
    - repeat LDH within the next 1-3 business days
    - monitor plasma free hemoglobin (pf-Hb) and haptoglobin if available; and total bilirubin
    - complete evaluation with the team to rule out other reasons for LDH rise
    - echocardiogram to evaluate for aortic insufficiency
    - prompt study team to review within 48 hours
    - retrospective data log files analysis (particularly rotor noise and rotor displacement trends) followed by prospective analysis 2 weeks post event

Appendix V: Apixaban effect reversal protocol

In case of need of reversal of the effect of apixaban, following protocol will be executed.