Appendix 3

Study Report AXAFA-AFNET 5

Protocol Version Overview

Protocol versions

1) Final, dated 28th July 2014
2) Amended, dated 15th December 2014
3) Amended, dated 08th January 2015
4) Amended, dated 20th February 2015
5) Amended, dated 21st July 2016 (Final valid US Version)
6) Amended, dated 2nd November 2016 (Final valid EU version)

Summarised changes

2) Amendment dated 15.12.2014

- Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation or earlier when atrial thrombi have been excluded by a clinically indicated TEE. It was added that a TEE performed within 6 hours prior to randomisation is considered valid.
- A new appendix was added (Appendix VIII "List of strong inducers/inhibitors of P-gp and CYP3A4 which lead to contraindication for the combined use with apixaban") following a primary Ethics Committee's request.
- A new exclusion criterion was added (E14 "Documented atrial thrombi less than 3 months prior to randomisation.") following a primary Ethics Committee's request.
- Following a Competent Authority's request it was added that women of childbearing potential are required to perform a pregnancy test before first intake of the study medication. If clinical signs of pregnancy are present during intake of the study medication and up to an adequate interval after intake of study medication, a pregnancy test has to be performed.
- In accordance with the SmPC of apixaban and following a Competent Authority's request it was added that liver function parameters have to be assessed prior to first intake of study medication.
- More precise criteria for assessment of continuous effective anticoagulation in VKA patients prior to index catheter ablation (i.e. at least one INR value ≥2.0 prior to ablation and thereafter no value <2.0 prior to ablation).
- The list of conditions for which a patient is not to undergo MRI was extended following a primary Ethics Committee's request.

3) Amendment dated 08.01.2015

- Wording in section "Adverse Event Reporting" was adjusted following a Competent Authority's request.
- Further it was specified that in addition to serious adverse events (SAEs), also "AEs of special interest" will be MedDRA coded.

4) Amendment dated 20.02.2015

- Following a Competent Authority's request correction of reporting period for SAEs in accordance with ENTR/CT-3 (2011/C 172/01).

5) Amendment dated 21.07.2016

- The term "exploratory" in the context of primary outcome and secondary endpoints was deleted following a primary Ethics Committee's request.
- Protocol sections "Sample Size and Power Calculation" and "Interim Analyses, Reassessment of the Sample Size" have been described more in detail following a primary Ethics Committee's enquiries.
- Criteria for assessment of continuous effective anticoagulation in VKA patients prior to index catheter ablation was adapted: Because in clinical routine an INR value ≥2 directly prior to catheter ablation is

often not achieved, the reduction of the minimum value of the last INR required prior to the index catheter ablation to ≥1.8 represents clinical practice better. Further requirement of documenting all INR measurements (minimum of three) was added to ensure continuous anticoagulation.

- More concise description of the first intake of study medication was added in order to avoid misunderstandings.
- Clarification according to the definition of SAEs and AEs judged as medically important events.
- Modified Rankin Scale at baseline visit added and corresponding protocol appendix IX.
- Specification with regard to procedure assessing for pericardial effusion after catheter ablation, i.e. instead of a transthoracic echocardiography (TTE) also an intracardiac echocardiography (ICE) can be performed.

6) Amendment dated 02.11.2016

- Following a Competent Authority's objection the wording in section "Adverse Event Reporting" has again been formulated as in the version of amendment 08.01.2015.

CLINICAL TRIAL PROTOCOL

AXAFA - AFNET 5

*A*nticoagulation using the direct factor *X*a inhibitor apixaban during *A*trial *F*ibrillation catheter *A*blation: Comparison to vitamin K antagonist therapy.

An Investigator-driven, **P**rospective, Parallel-group, **R**andomised, **O**pen,
Blinded Outcom**e** Assessment (PROBE), Multi-centre Trial
to determine the optimal anticoagulation therapy for patients undergoing catheter ablation of atrial fibrillation

EudraCT number: 2014-002442-45
NCT number: XXX
ISRCTN87711003

Responsible Sponsor:
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Version control:
Final, dated 28th July 2014

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This protocol has been written in accordance with current applicable guidelines (ICH-GCP and EU-Directive 2001/20/EC) as well as all other relevant additional references, medical and legal ones.

Table of Contents

1 Summary

TITLE	**A**nticoagulation using the direct factor **X**a inhibitor apixaban during **A**trial **F**ibrillation catheter **A**blation: Comparison to vitamin K antagonist therapy (**AXAFA**)
INTERNATIONAL CHIEF INVESTIGATOR	Professor Paulus Kirchhof, Birmingham, UK and Münster, Germany
SPONSOR	Kompetenznetz Vorhofflimmern e.V. [Atrial Fibrillation Competence Network (AFNET) e.V.]
BACKGROUND AND RATIONALE	Factor Xa inhibitors and direct thrombin inhibitors are new, fixed dose oral anticoagulants that provide a much-needed alternative treatment to vitamin K antagonists (VKAs) for stroke prevention in atrial fibrillation (AF). Their use has been evaluated in several large clinical trials enrolling patients with non-valvular AF at increased risk for stroke. Three non-inferiority trials comparing apixaban, rivaroxaban, or dabigatran to warfarin have been reported, as well as one additional trial demonstrating superiority of apixaban to aspirin. Based on the outcome of these large trials, these three novel oral anticoagulants (NOACs) have been approved in the USA, Canada, and in Europe for stroke prevention in patients with AF and at least one additional risk factor for stroke. Furthermore, NOACs are recommended in current AF guidelines. Approximately 5-15% of the non-valvular AF population undergoes catheter ablation in recent surveys. While some of these patients require long-term anticoagulation because of their individual stroke risk, all patients require anticoagulation during and after the ablation procedure to reduce the risk of procedure-associated stroke. The use of NOACs in patients undergoing catheter ablation for symptomatic AF has not been tested in randomised controlled trials. Rather, retrospective small observational case series raised concerns about the peri-procedural use of NOACs in patients undergoing catheter ablation: The largest published experience exists with dabigatran, the NOAC which received approval first. Numerically, there were more severe events in patients undergoing catheter ablation with dabigatran than in those undergoing ablation while on VKAs, namely 18/409 patients with severe events on dabigatran (4.4%) compared to 8/371 patients with severe events on VKAs (2.1%). These numbers only represent serious events (such as pericardial tamponade, clinically overt stroke, death), as other major bleeding events were not collected. Although this observation is likely to reflect a play of chance rather than a biological difference, as suggested by more recent evidence from retrospective data, these data suggest to rather “choose the established treatment” of VKAs during ablation. In the absence of controlled trial data, this unequal distribution of serious complications is a cause of concern among ablationists. The international consensus statement on AF ablation was published before these reports on dabigatran. It suggests to perform AF ablation on continuous anticoagulation using either a VKA or a NOAC, while the focussed update of the ESC guidelines on AF, published after these reports on dabigatran became available, only mentions continuous peri-procedural anticoagulation using a VKA. Hence, there is a need for a well-designed, adequately powered trial to test whether NOACs can be used in the setting of catheter ablation of AF.

STUDY OBJECTIVE(S)	To demonstrate that anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of non-valvular AF in the prevention of peri-procedural complications.
STUDY DESIGN	Investigator-initiated, **p**rospective, parallel-group, **r**andomised, **o**pen, **b**linded outcom**e** assessment (PROBE) interventional multi-centre trial. Phase IV
STUDY POPULATION Medical condition / Main selection criteria	The following main criteria must be present for eligibility into the study: ▪ Non-valvular AF (ECG-documented) with a clinical indication for catheter ablation ▪ Clinical indication to undergo catheter ablation on continuous anticoagulant therapy ▪ Presence of at least one of the following $CHADS_2$ stroke risk factors: ✓ stroke or TIA ✓ age ≥ 75 years, ✓ hypertension, defined as chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mm Hg, ✓ diabetes mellitus, ✓ symptomatic heart failure (NYHA ≥ II). Patients not eligible for apixaban or with contraindications for oral anticoagulation are not suitable for AXAFA.
Number of patients	630 patients to be randomised (315 per group) and to undergo the index therapy of catheter ablation. However, to account for roughly 3% of patients who will not undergo the ablation procedure after randomisation, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e. randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort.
Expected number of sites	Approximately 25 ablation sites in Europe and 25 in the USA. All study sites will be routinely performing catheter ablation of AF.
INVESTIGATIONAL INTERVENTIONS	Investigational medicinal product: apixaban Comparator: locally used, marketed VKA Apixaban will be given 5 mg twice daily and compared to oral anticoagulation using the locally used VKA (aiming for an international normalized ratio (INR) of 2.0-3.0). The apixaban dose will be reduced to 2.5 mg twice daily at the time of randomisation according to the approved label. Study medication has to be administered effectively for at least 30 days prior to the planned catheter ablation procedure or during a shorter interval in patients undergoing a transesophageal echocardiogram (TEE) with exclusion of atrial thrombi. Study medication has to be effectively continued for three months after the ablation procedure. All patients will be treated following current guidelines (ESC focussed update of the AF guidelines, 2nd catheter ablation consensus statement) including continuous oral anticoagulation during ablation procedures (continuous apixaban, target INR 2.0-2.5 in the VKA group). All patients will receive peri-procedural heparin to assure an activated clotting time (ACT) >300 s.

	MRI sub-study: A subgroup of maximal 300 study patients will undergo brain magnetic resonance imaging study (MRI, without contrast agents) within 3-48 hours after the ablation procedure.
PRIMARY OUTCOME PARAMETERS	A composite of ▪ all-cause death, ▪ stroke (ischemic stroke, subarachnoid haemorrhage and haemorrhagic stroke), and ▪ major bleeding events, defined as BARC 2 or higher
SECONDARY OUTCOME PARAMETERS	▪ Any bleeding event ▪ Major bleeding events according to the ISTH and TIMI definitions ▪ Number of strokes, other systemic embolic events, and all-cause deaths ▪ Time from randomisation to ablation ▪ Nights spent in hospital after ablation ▪ Health-care related cost calculation ▪ Number of hospitalisations for cardiovascular reasons ▪ Treatment duration prior to ablation and total time on oral anticoagulation ▪ Number of patients with clinically indicated TEE ▪ ACT during ablation ▪ Time to recurrent AF ▪ Rhythm status at the end of follow-up ▪ Vascular access complications leading to prolongation of in-hospital stay or specific therapy ▪ Quality-of-life changes at month 3 compared to baseline ▪ Cognitive function change at month 3 compared to baseline ▪ Prevalence of clinically “silent” MRI-detected brain lesions within 48 hours after the ablation procedure (MRI sub-study), ▪ Impact of ablation-associated clinically overt strokes or MRI-detected but clinically “silent” acute brain lesions on cognitive function after ablation (MRI sub-study)
ASSESSMENT SCHEDULE	1. Enrolment and randomisation 2. Scheduled visit during ablation MRI sub-study: brain MRI within 3–48 hours after the ablation procedure 3. Scheduled follow-up at three months after ablation 4. Phone call 30 days after discontinuation of study drug
STATISTICAL CONSIDERATIONS	With respect to the primary outcome, the study is exploratory. The primary analysis is in the modified intention-to-treat population, consisting of all randomised patients who received at least one dose of study treatment and an ablation procedure for AF. Event rates at the end of follow-up will be compared between groups. An occurrence of the primary parameter is expected in 17-20% of the patients. The sample size will allow to detect a non-inferiority between the two random groups with a margin of 7.5%. Safety analysis will be performed with all patients randomised.
DURATION OF STUDY PERIOD (per patient)	Duration per patient: about 3 months for patients scheduled for ablation after exclusion of atrial thrombi by clinically indicated TEE, approximately 4 months in all other patients (depending on time of achieving therapeutic anticoagulation)

2 Abbreviations

ACC	American College of Cardiology
ACT	activated clotting time
ADC	apparent diffusion coefficient
AE	adverse event
AF	atrial fibrillation
AF-CHF	Atrial Fibrillation Congestive Heart Failure trial
AFNET	Atrial Fibrillation Network
ARWMC	Age Related White Matter Changes
AXAFA	Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy
BARC	Bleeding Academic Research Consortium
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-reactive protein
CV	Curriculum Vitae
CYP450 3A4	Cytochrome P450 3A4
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EC	Ethics Committee
ECG	electrocardiography
e-CRF	electronic case report form
EHRA	European Heart Rhythm Association
EQ-5D	Euroquol 5D questionnaire
ERC	Endpoint Review Committee
ESC	European Society of Cardiology
FLAIR	Fluid Attenuated Inversion Recovery
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HF	heart failure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IIT	Investigator Initiated Trial
INR	International Normalised Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention-to-treat
LA	left atrium
LBBB	left bundle branch block
LV	left ventricle
LVEF	left ventricular ejection fraction
MCA	middle cerebral artery
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MoCA	Montreal cognitive assessment
MRI	magnetic resonance imaging
mITT	modified intention-to-treat
NOAC	novel oral anticoagulant
NSTEMI	non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PE	physical examination
PI	principal investigator
PVI	pulmonary vein isolation
QoL	Quality-of-life
SAE	serious adverse event
SF-12	12-item Short-Form health survey
SOP	Standard Operating Procedure
TEE	Transesophageal echocardiogram
TIMI	thrombolysis in myocardial infarction
TTE	Transthoracic echocardiogram
VKA	vitamin K antagonist

The terms “trial” and “study” are being used interchangeably throughout this protocol.

3 Introduction

3.1 Background Information

Catheter ablation has become an important part of rhythm control therapy in AF patients (1, 2). There is growing evidence that catheter ablation procedures are best performed during continuous oral anticoagulation. This is reflected in current consensus statements and guidelines (2, 3). The published evidence illustrating the safety and efficacy of this approach was largely generated in patients undergoing catheter ablation during continuous treatment with VKAs (4-8). Emerging data further support a practice of continuous oral anticoagulation with a low-therapeutic anticoagulation level during ablation procedures.

Data on NOACs are inconclusive and even point towards a slightly higher peri-procedural risk for bleeding and strokes in uncontrolled, observational studies using the direct thrombin inhibitor dabigatran (9-13): In 409 patients receiving dabigatran peri-ablation, 3 strokes, 9 tamponades, and 7 further pericardial effusions were reported. In 371 patients receiving VKAs in the same series there were no strokes, 3 tamponades, and 5 pericardial effusions. Hence, serious events on NOACs (dabigatran) amount to 18/409 (4.4%) patients, while serious events on VKA were reported in 8/371 (2.1%) patients. More recent observational data are not sufficient to eliminate the safety concerns around the use of NOACs in patients undergoing catheter ablation (9). These and other studies furthermore report less severe bleeding events in 10-15% of the patients studied, based on a heterogeneous standard of reporting and heterogeneous definitions. Vascular access complications were not adequately reported and are likely to occur in 2-3% additional patients. Furthermore, around 10% of patients undergoing AF ablation are expected to suffer major, clinically relevant bleeding events (including a drop of haemoglobin and hematomas not requiring surgical intervention).

It is obvious that this imbalance in severe events is not statistically significant and likely prone to imbalanced patient distribution. Additionally, the peri-procedural dabigatran regime differed markedly between case series and centres. While some centres allowed to pause dabigatran for prolonged periods of time, others favoured a continuous therapy with dabigatran. This illustrates the uncontrolled and potentially suboptimal use of dabigatran in the published case series and calls for prospective validation of a reasonable anticoagulation strategy in patients undergoing AF ablation on NOACs (14).

This inconclusive evidence contrasts with the favourable efficacy and safety of dabigatran, rivaroxaban, and apixaban compared to the VKA warfarin in patients suffering from non-valvular AF (15-17). In these large randomised trials, severe bleeds were consistently similar or even less frequently reported with either of the NOACs, while the higher dose of dabigatran (150 mg twice daily) as well as apixaban also reduced stroke rates. Furthermore, all three NOACs reduced total deaths by 10-12%, and reduced intracranial bleeding events by 33-74% (15-17). It is surprising that NOACs that appear beneficial in general AF patients would prove to be detrimental in patients undergoing catheter ablation. On the other hand, each ablation procedure induces a risk for stroke and bleeding that may have a specific pathophysiology, e.g. bleeding secondary to venous vascular access complications or after transseptal puncture, and formation of thrombotic debris at the sheaths, catheter tip, or in the ablated, scarred regions. However, the current recommendations on peri-procedural anticoagulation may also generate potentially avoidable risk to patients: Patients who are in need for ablation and receiving a NOAC are often “switched” to VKAs for the procedure, which induces unstable anticoagulation and therefore cause a potential bleeding risk during the treatment change or may prolong the time to ablation. In other centres, the existing data on peri-procedural anticoagulation are interpreted as inconclusive and ablation procedures are performed under continuous anticoagulation with VKAs.

Hence, there is a need to test the peri-procedural use of NOACs in patients undergoing catheter ablation of AF in a controlled prospective trial.

Silent brain infarction is defined as cerebral infarction detected by brain imaging without matching clinical event. Clinically silent brain infarctions are detectable by magnetic resonance imaging (MRI) in 8-28% of the general population. They are more prevalent in patients with arterial hypertension and in the elderly (18).

Indeed, silent brain infarctions are quite common in AF cohorts undergoing MRI (37-75%) (19-21). Silent infarctions are often small subcortical (lacunar) infarcts. In the general population, silent brain infarcts are associated with a 2-4 fold risk of future clinically overt stroke, mortality, worsening of cognitive functions, and overt dementia in the long term (22, 23). There is growing evidence that AF per se and AF-related stroke associate with cognitive decline and dementia over time (19, 24-29). Therefore, it seems biologically plausible to assume that maintenance of sinus rhythm could prevent AF-related "silent" brain infarcts and subsequent slow cognitive decline (30, 31). On the other hand, catheter ablation is associated with clinically silent but MRI-detected acute brain lesions in 8-41% of all patients (32, 33, 36, 37). A recently published small case series reported MRI-detected silent brain lesions in 12-27% of all patients with peri-procedural VKA (33). It would be good to explore whether NOACs have the potential to reduce clinically silent brain lesions after catheter ablation of AF.

Blood-based biomarkers or specific ECG alterations could be useful to identify patients at risk for stroke and/or bleeding. This concept has never been applied to patients undergoing catheter ablation of AF, where bleedings requiring the attention of a health care professional are rather common (estimated at 15% of the patients undergoing ablation). Similarly, biomarkers may help to better identify patients at risk for recurrent AF after catheter ablation. AXAFA will provide a platform to explore these possibilities by collecting blood and a 12-lead resting ECG prior to ablation.

3.2 Study Rationale

One of the three NOACs is the direct, oral factor Xa inhibitor apixaban. Apixaban prevents strokes in AF patients significantly better compared to the VKA warfarin, and causes less major bleeding events. There are no data on apixaban in patients undergoing catheter ablation of AF. The AXAFA trial will compare peri-ablational treatment with apixaban to peri-ablational treatment with VKA in a randomised trial of patients undergoing catheter ablation of AF. This randomised trial will clarify the clinical utility of apixaban in the peri-ablational setting by systematically collecting data on clinically relevant ischemic and bleeding events in patients who will be prospectively followed in the context of a clinical trial.

3.3 Benefit-risk Assessment

General risk assessment of the AXAFA trial: All study drugs are market approved and will be used within the approved indications, only. All concomitant study procedures, e. g. the catheter ablation for AF, are standard care procedures according to applicable medical guidelines used within the recommended indications. All participating study sites have to document sufficient experience in the management of patients with AF in general and in catheter ablation of AF in detail. Thus, the overall risk level in this phase IV trial is expected to be low.

The additional brain MRIs being performed in about 300 sub-study patients will not add radiation risk to participating patients.

Assessment of the individual risk of study patients: The use of study drugs and concomitant procedures within AXAFA does not deviate from standard care procedures. The tested modification of the most common drug regime, treatment with a factor Xa inhibitor peri-ablation, is applying an approved medication within its approved label and in the approved population. There are several single-center reports that suggest safety of this approach, although a formal confirmation of its safety is lacking. Thus, the individual risk of study patients in both treatment arms will not differ from the risk of therapy in clinical routine.

General benefit of study patients: Patients in AXAFA will have the added benefit of careful standardised monitoring of their anticoagulant and interventional treatment by their study physicians as well as of additional quality management by the CRO, the sponsor and the Steering Committee. About 300 patients will additionally be able to participate in a MRI sub-study monitoring clinically "silent" brain lesions undetected in the regular clinical setting.

Individual benefit of study patients: Patients randomised to apixaban will receive a treatment that has been shown to be safer (reduced major bleeding events, especially intracranial bleeding) and slightly more effective than VKA in general AF populations (17, 50). Furthermore, apixaban treatment will be easier to use without the need of repetitive INR monitoring and frequently adapted dosing.

4 Study Objectives

To demonstrate that anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of non-valvular AF in the prevention of peri-procedural complications.

4.1 Primary Outcome Parameters

The primary outcome parameter of AXAFA is a composite of

- all-cause death,
- stroke, and
- major bleeding events.

Stroke comprises ischemic strokes as defined by the FDA (including ischemic infarction with (transient) clinical symptoms that resolve completely within 24 hours, but have a matching lesion on brain imaging as well as ischemic infarction interrupted by death within 24 hours), subarachnoid haemorrhage and haemorrhagic stroke. Major bleeding events will be defined according to the Bleeding Academic Research Consortium (BARC) definition as BARC 2 or higher (34), i.e. all bleeding events that require an action by a health care professional. This outcome parameter comprises all relevant bleeding events in a clinical setting and has been used to optimise arterial vascular procedures such as percutaneous coronary interventions (34, 35).

4.2 Secondary Outcome Parameters

4.2.1 Secondary efficacy outcome parameters

The secondary outcome parameters are defined as

- any bleeding event
- major bleeding events according to the ISTH and TIMI definitions,
- number of strokes, other systemic embolic events, and all-cause deaths,
- time from randomisation to ablation
- nights spent in hospital after ablation
- health-care related cost calculation estimated by quantification of interventions, nights spent in hospital, and the costs of outpatient treatment,
- number of hospitalisations (at least one over-night stay) for cardiovascular reasons ,
- treatment duration prior to ablation and total time on oral anticoagulation,
- number of patients with clinically indicated TEE
- ACT during ablation (assessed as mean, range, and number of ACT measurements within the target range)
- time to recurrent AF (determined clinically, and according to ECG and Holter ECG recording at the end of follow-up),
- rhythm status at the end of follow-up (assessed by Holter ECG),
- vascular access complications leading to prolongation of in-hospital stay or specific therapy,
- quality-of-life changes at month 3 compared to baseline (assessed by EQ-5D, SF-12 questionnaires, and by the Karnofsky scale),
- change of cognitive function at month 3 compared to baseline (assessed by Montreal Cognitive Assessment Scale; MoCA),

- MRI sub-study, only: Prevalence of clinically "silent" MRI-detected brain lesions within 48 hours after the ablation procedure,
- MRI sub-study, only: Impact of ablation-associated clinically overt strokes or MRI-detected but clinically "silent" acute brain lesions on cognitive function after ablation

4.2.2 Secondary safety outcome parameters

The major safety outcome parameter is a composite of all-cause death, stroke, cardiac tamponade, and major bleeding events defined as BARC 2 or higher. Furthermore, bleeding events requiring surgery or transfusion are part of this outcome.

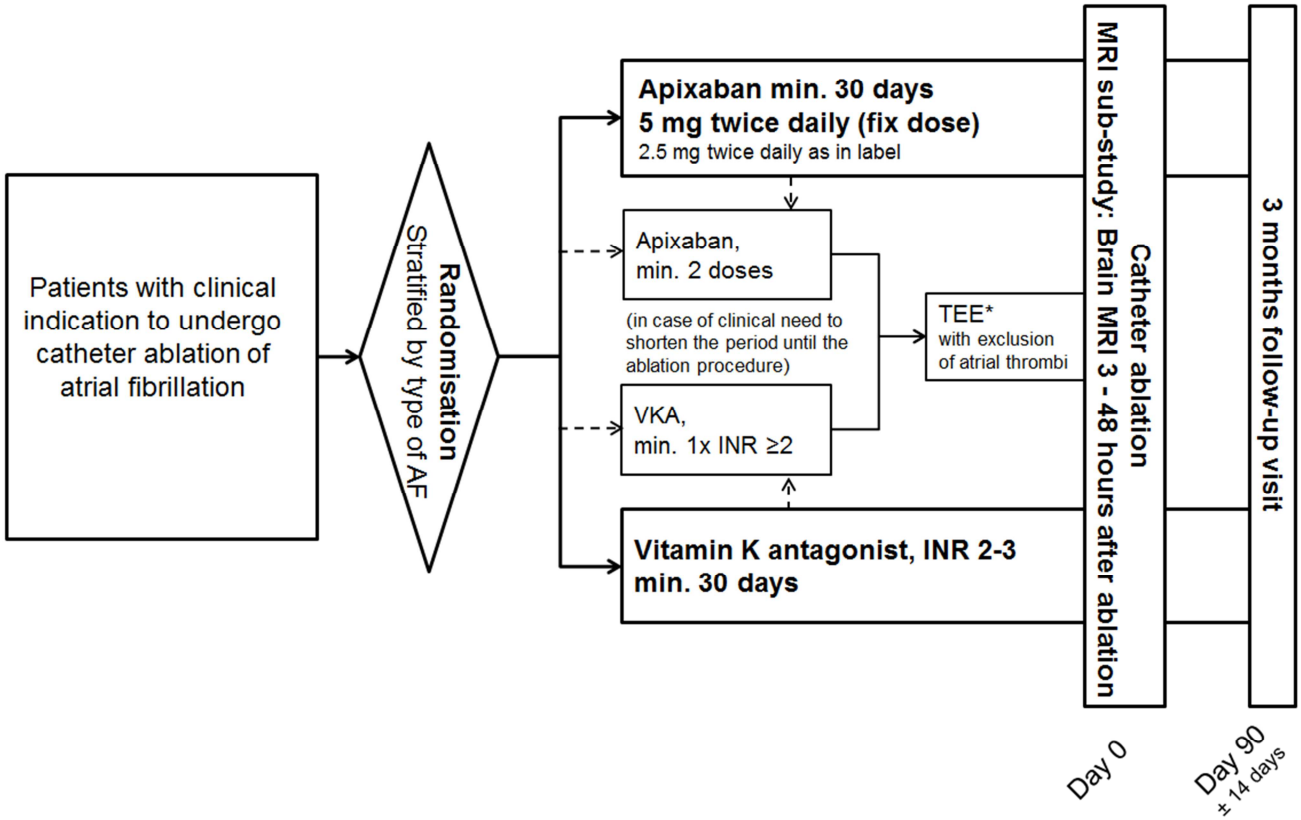
Other safety outcome parameters are the components of this composite, the number of serious adverse events (SAEs) of all types and all other bleeding events as well as vascular access complications leading to prolongation of in-hospital stay or specific therapy (such as surgery, supplementation of coagulant factors, intensive care).

All outcome events will be adjudicated centrally (blinded to study group, including blinding to INR) by the Endpoint Review Committee (ERC; refer to section 15.1.3).

5 Study Design

AXAFA is an investigator-initiated, prospective, parallel-group, randomised, open, blinded outcome assessment (PROBE) interventional multi-centre study. The trial tests whether peri-procedural anticoagulation therapy using the novel, oral, direct factor Xa inhibitor apixaban is a safe alternative to VKA therapy for patients undergoing catheter ablation of AF. The trial will be conducted in several European countries and in the USA (details of study sites are provided in a separate document).

5.1 Flow Chart



* TEE is a clinical decision by the treating physician.
Anticoagulation should be effective from randomisation until the end of the trial.

6 Selection of Patients

6.1 Informed Consent

A signed, ethics committee (EC) /institutional review board (IRB) approved informed consent form, written in accordance with country-specific applicable data privacy acts, the Declaration of Helsinki (appendix VI) and the applicable laws for research using medical devices and drugs, will be obtained from every patient prior to any study-related procedure. The valid national or local versions of the patient information and informed consent are part of the documents prepared for every submission to authorities or IRBs / ECs individually and will be kept as separate documents. All clinical data needed to evaluate the potential eligibility of a patient before study inclusion, e. g. recent laboratory results, ECG recordings or other technical parameters, are considered to be performed during clinical routine and are therefore not considered to be part of study related procedures.

The investigator or responsible medical staff will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information sheet. The patient will be given sufficient time to consider the study's implications before deciding whether to participate. The patient information sheet must be approved by the responsible EC / IRB before first use.

Should there be any amendments to the protocol, such that this would directly affect the patient's participation in the study, e.g. a change in any procedure, the informed consent form must be amended to incorporate this modification and the patients must agree to sign this amended form indicating that they re-consent to further participate in the modified study.

A signed copy of the patient's informed consent form must be maintained in the study file on site. The patient's permanent medical records should indicate the patient's study participation. A patient information sheet will be handed out to the patient unless declined by him/her.

6.2 Study Population

The intended population for this study is patients who are scheduled for catheter ablation of AF. Patients will be recruited by contracted study sites only, i.e. by approximately 50 sites performing catheter ablation for AF in clinical routine. Patient recruitment is expected to be completed after 25 months.

6.2.1 Number of Patients

630 patients will be randomised and undergo the index therapy of catheter ablation for AF. However, to account for roughly 3% of patients who will not undergo the ablation procedure, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e. randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort. The sample size may be re-estimated once in a blinded manner as described in the statistics section (refer to section 12).

6.2.2 Inclusion criteria

I1. Non-valvular AF (ECG-documented) with a clinical indication for catheter ablation

I2. Clinical indication to undergo catheter ablation on continuous anticoagulant therapy

I3. Presence of at least **one** of the $CHADS_2$ stroke risk factors

- Stroke or TIA
- age ≥ 75 years,
- hypertension, defined as chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mm Hg,
- diabetes mellitus,
- symptomatic heart failure (NYHA ≥ II).

I4. Age ≥ 18 years

I5. Provision of signed informed consent

6.2.3 Exclusion criteria

General exclusion criteria

E1. Any disease that limits life expectancy to less than 1 year

E2. Participation in another clinical trial, either within the past two months or still ongoing

E3. Previous participation in AXAFA

E4. Pregnant women or women of childbearing potential not on adequate birth control: only women with a highly effective method of contraception (oral contraception or intra-uterine device) or sterile women can be randomised.

E5. Breastfeeding women

E6. Drug abuse or clinically manifest alcohol abuse

E7. Any stroke within 14 days before randomisation

E8. Coadministration with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) or strong dual inducers of CYP3A4 and P-gp

Exclusion criteria related to a cardiac condition

E9. Valvular AF (as defined by the focussed update of the ESC guidelines on AF, i.e. severe mitral valve stenosis, mechanical heart valve). Furthermore, patients who underwent mitral valve repair are not eligible for AXAFA.

E10. Any previous ablation or surgical therapy for AF

E11. Cardiac ablation therapy for any indication (catheter-based or surgical) within 3 months prior to randomisation

E12. Clinical need for “triple therapy” (combination therapy of clopidogrel, acetylsalicylic acid, and oral anticoagulation)

E13. Other contraindications for use of VKA or apixaban

Exclusion criteria based on laboratory abnormalities

E14. Severe chronic kidney disease with an estimated glomerular filtration rate (GFR) < 15 ml/min

6.2.4 Randomisation

The patients will be randomised to one of two parallel study groups, designated as “Xa” and “VKA”. Randomisation will be stratified by the pattern of AF (paroxysmal vs. persistent / long-lasting persistent) as assessed by the responsible investigator at time of randomisation. Randomisation will be done by study site in blocks of variable size to allow minimising potential confounders related to different healthcare practice.

A randomisation list will be created by the responsible study statistician.

This list will be imported into the randomisation server of the electronic trial management system called MARVIN. During the trial, randomisation will be performed by MARVIN to the imported randomisation list. The investigator has to document several clinical items prior to randomisation to verify eligibility of the patient for randomisation and to determine the stratum. MARVIN displays the random group and asks for confirmation by authorised study personnel. The account ID of the person performing the randomisation in MARVIN and the corresponding time stamp will automatically be documented in an electronic audit trail.

7 Therapy

AXAFA is an open-label trial designed to evaluate the safety and efficacy of two types of anticoagulant therapy, VKA therapy and therapy with the direct factor Xa inhibitor apixaban, in patients undergoing scheduled catheter ablation for AF. All patients will undergo the ablation procedure after pre-treatment with an anticoagulant (either apixaban in the "Xa group" or a vitamin K antagonist in the "VKA group").

Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation. Ablation can be performed earlier when atrial thrombi have been excluded by a clinically indicated TEE. After TEE continuous effective anticoagulation must be ensured until the end of the trial.

Instructions with regard to change management of anticoagulants at start and discontinuation of study drug are described in appendix III.

7.1 Xa group

Patients randomised to the Xa group will receive apixaban 5 mg twice daily throughout the study duration. Apixaban will be continued during the ablation procedure with twice daily dosing. The apixaban dose will be reduced to 2.5 mg twice daily in patients who fulfil two of the following criteria at the time of randomisation: chronic kidney disease (defined as serum creatinine ≥ 1.5 mg/dl [133 mM]), ≤ 60 kg body weight, or age ≥ 80 years. In case adaptation of apixaban dosage with regard to these criteria is deemed necessary after randomisation, this has to be documented in the e-CRF.

All patients randomised to the Xa group must have received at least two doses of apixaban prior to the ablation procedure.

7.1.1 Description of apixaban

Apixaban (or BMS-562247) has been tested in large trials and is approved for the prevention of strokes in AF patients. Apixaban will be applied in AXAFA within its approved indication and standard therapeutic dose.

Product description	Potency	Packaging/Label tupe	Appearance	Storage conditions
BMS-562247-01 Film Coated Tablet,	5 mg	200 tablets/bottle, open label	Reddish brown, plain, oval shaped, shallow bi-convex film coated tablet	Store at 2-30℃
BMS-562247-01 Film Coated Tablet,	2.5 mg	200 tablets/bottle, open label	Reddish brown, plain, oval shaped, shallow bi-convex film coated tablet	Store at 2-30℃

An adequate contract research organisation of the manufacturer is responsible for labelling, storage, and distribution to study sites on demand. Sufficient quantities of apixaban will be supplied.

7.1.2 Compliance with apixaban, dispensing and return of apixaban

Apixaban will be supplied to the study sites in sufficient quantity according to local needs, e. g. expected recruitment rate. The respective time of drug supply will be determined by the CRO but supply itself will be performed by the relabeling sub-contractor.

Logistics of apixaban study medication will be managed and tracked centrally in the e-trial management system MARVIN. Each apixaban study medication bottle will be supplied with a unique medication number

(numerical) together with a corresponding unique verifier (alpha-numerical) printed on study specific label. A list of all unique medication numbers together with the corresponding unique verifiers of the provided apixaban study medication will be hosted in the materials tool of the MARVIN system.

Labelling follows requirements as specified in Volume 4, EU Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products. National requirements will be taken into consideration. The subcontractor responsible for re-labelling and delivery of apixaban to study sites receives automated supply orders via e-mail from the MARVIN system detailed for amount of bottles with 5 mg or 2.5 mg tablets. Tracking of apixaban bottles to be sent to study sites will be performed by the subcontractor in MARVIN revealing information on medication numbers and verifiers, date of shipment and recipient (study site ID). Receipt of apixaban study medication has to be tracked by the receiving site staff by entering the verifier printed on each bottle label.

In case of randomisation of a new eligible patient to Xa group the MARVIN system displays the medication numbers of the two bottles (400 tablets) to be used depending on some medical items describing the patient's condition defining the use of 5 mg or 2.5 mg tablets. Site staff has to confirm drug dispense to the patient by entering the verifiers printed on each bottle label.

Prior to dispensing study medication to a patient, the investigator will document the patient's ID (automatically allocated by MARVIN), study site ID and the date of dispensing on the label. At the enrolment visit every patient randomised to Xa group will be handed out two bottles apixaban (5 mg or 2.5 mg depending on the patient's condition as described above). The consistent intake of apixaban is crucial for sufficient efficacy since no INR or other coagulation parameter monitoring will be performed in contrast to the VKA group. Patients will be asked to bring all unused or partly-used medication at each visit. The investigator will assess effective anticoagulation with apixaban by questioning the patient about medication intake and by pill count during the ablation visit and at the end of follow-up.

After a patient has terminated the study, any unused or part-used medication will be returned to the relabeling subcontractor. Returned apixaban medication will be tracked in the MARVIN system.

7.2 VKA group

Patients randomised to the VKA group will receive oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. VKAs will be prescribed as in clinical routine and dispensed by local hospital pharmacy. Costs will be reimbursed by sponsor. VKA therapy will be monitored by INR measurements according to applicable medical guidelines and to local routine policy, a minimum of three INR measurements is mandatory. The frequency and values of INR measurements will be collected in the e-CRF. Effective anticoagulation will be assessed by questioning the patient about medication intake and by INR measurements which need to be consistent within the therapeutic range (INR ≥2.0) in at least 30 days prior to catheter ablation. Any INR <2 resets this interval to 0 days or a TEE may be performed for exclusion of thrombi. In the latter case, there must be at least one INR value ≥2 prior to catheter ablation. It is recommended that the ablation procedure is performed while the INR is between 2 and 2.5.

Patients undergoing TEE with exclusion of atrial thrombi prior to the ablation procedure will be handled according to local routine, which may include heparin or low molecular weight heparins to achieve sufficient anticoagulation, e.g. in the initiation period of VKA therapy.

7.3 Concomitant Medication

The concomitant use of antiplatelet agents is discouraged in all study patients, because the concomitant use of an oral anticoagulant and antiplatelet agents increases the risk of bleeding without known benefits. All other concomitant medication can be used within the AXAFA trial. In the e-CRF, all antiarrhythmics,

anticoagulants, antithrombotic agents and other drugs administered for AF as well as for cardiovascular concomitant illnesses including statins and antidiabetics/insulin will be documented as well as medications known to interact with apixaban metabolism. No other medication neither any dosage will be documented in the e-CRF.

7.4 Catheter Ablation

7.4.1 Anticoagulation during the ablation procedure

All patients in AXAFA should undergo catheter ablation of AF while on continued oral anticoagulation as described above. The nature and conduct of the ablation procedure should not be influenced by the investigator's knowledge of the subject's treatment allocation. Based on published recommendations (2), a heparin bolus (100 IU/kg body weight) should be given in each patient either prior to or directly after transseptal puncture. Furthermore, an ACT > 300s needs to be maintained and documented during the ablation procedure. All other aspects of the ablation procedure and of peri-procedural management will follow local routine. The randomisation merely defines the type of anticoagulation therapy used.

7.4.2 Ablation procedure

The aim of catheter ablation in AF patients is isolation of the pulmonary veins (PVI) and additional procedures if deemed clinically necessary. PVI should be performed following local routine. Procedural safety is paramount in the context of AXAFA, and all means for a safe procedure should be taken. The study will be conducted in experienced centres on the plateau phase of their learning curve. Pre-study assessment of all centres will guarantee sufficient experience in PVI procedures. Evaluation of experimental or novel ablation devices is not permitted in the AXAFA trial. The exact ablation technique should follow local routine and adhere to the recommendations of the AFNET/EHRA/ECAS consensus statement on catheter ablation of AF, and to the locally applicable AF guidelines. Local routine should guide details of the procedure (e.g. the type of ablation and mapping system used, or the choice of ablation energy) within the limits of these recommendations. We encourage the use of irrigated tip catheters and flushing of all left atrial sheaths, as recommended in the AF ablation guidance document (2). Local PVI procedure policy will be documented prior to study start in each site and in case of relevant changes during the course of the trial. The technology and approach used will be documented in the e-CRF for every patient.

Usually, isolation of the pulmonary veins is the first and paramount target of catheter ablation in AF patients. In most cases, this will be achieved by circumferential, often antral, isolation of the left and right pulmonary veins in “two circles”. Sequential isolation of the ostia of each pulmonary vein is also permitted if the operator deems this procedure appropriate for a given patient. “Single shot” devices, e.g. using cryo-energy, may be used if there is sufficient experience with a given technique locally. Some patients may require more extensive ablation procedures targeting additional structures e.g. by linear lesions, ablation of ganglionated plexus and fractionated electrograms, or others. When sufficient local expertise and experience exists, such techniques can be applied to patients within AXAFA.

Adherence to usual technique and technology will be monitored to ensure a study close to clinical practice.

7.5 Post-study Treatment

After end of the study course in the individual patient (planned or premature study discontinuation), the investigator is free to decide, on which further anticoagulant medication to put the patient.

8 Adverse Event Reporting

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but only "Adverse Events of Special Interest" which are defined as described in section 8.1.

8.1 Adverse Events of Special Interest

Bleeding events: Any bleeding as classified BARC type 2–5 (refer to appendix IV) is considered major bleeding. Some bleeding events may meet the criteria of seriousness and would need to be reported as serious adverse event as described in section 8.2. All bleeding events will be classified according to the BARC scheme (refer to appendix IV).

Other complication of therapy: Any other event that is judged as causally related to the therapies applied within the trial, especially complications of ablation procedures (e.g. pulmonary vein stenosis, atrio-oesophageal fistula) and drug toxicity of the study medications.

Neurological abnormalities: All acute neurological deficits or other signs potentially indicating a stroke or TIA have to be investigated. Patients with suspected neurological deficit should be visited by a neurologist whenever feasible. In addition, it is desirable to obtain clinically indicated brain imaging (preferably brain MRI) to search for matching brain lesions and to be able to distinguish between ischemic or hemorrhagic stroke, respectively. The core imaging laboratory will centrally read such clinically indicated brain images.

Some of these events might fulfil the criteria for seriousness and in this case would need to be reported as serious adverse event as described in section 8.2.

Other non-serious adverse events will not be recorded in AXAFA.

8.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that

- results in death or,
- is life-threatening
  (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) or,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
  (defined as inpatient care of more than one calendar day [= at least one overnight stay]; see also **NOTE** below) or,
- results in persistent or significant disability/ incapacity or,
- is a congenital anomaly / birth defect, or
- is a medically important event
  (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation).
  Potential drug induced liver injury (DILI) is also considered an important medical event (refer to section 8.2.1 for the definition of potential DILI).

Additional study specific criteria for SAEs:

- pregnancy (refer to section 8.2.2 for reporting pregnancies),
- overdose (defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important),
- cancer diagnosed after randomisation.

More than one of the above criteria can be applicable to each event.

NOTE: The following hospitalisations are not considered SAEs:

- A visit to the emergency room or other hospital department without the necessity of an overnight stay that does not result in admission (unless considered an "important medical event" or a life-threatening event).
- Elective surgery planned before signing consent.
- Admissions as per protocol for a planned catheter ablation of AF or planned cardioversion of AF.
- Routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy).
- Any overnight hospital stay required only for diagnostic procedure (e.g. sleep laboratory).
- Medical or surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

8.2.1 Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation >3 times upper limit of normal (ULN)

AND

2. Total bilirubin >2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.2.2 Pregnancy

It is reminded that all means should be put in place to prevent pregnancy during the study. Before study enrolment, women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. In addition, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. The investigator must immediately notify the CRO of this event and record the

pregnancy on the Pregnancy Surveillance Form in the e-CRF. Initial information on a pregnancy must be reported immediately to the CRO, and the outcome information provided once the outcome is known.

8.3 Recording and Reporting Serious Adverse Events

Following the patient's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing of the study medications (apixaban or VKA). All SAEs occurring after the individual end of the follow-up period within the 30 days reporting period will be used for safety reporting, only. These SAEs will not add to any statistical analysis but will be considered descriptively, only.

The investigator should specify and report in the e-CRF the nature of the sign or symptom leading to the SAE, the date of onset of the sign or symptom, the date of resolution (duration) of the specific event (not of the underlying disease), the intensity, interventions performed (if any), the relationship to study treatment, and the outcome.

All SAEs, whether related or unrelated to investigational product, must be reported expeditiously to the CRO through the SAE section of the e-CRF within one working day of becoming aware of the event. An SAE form within the e-CRF should be completed for any event where doubt exists regarding its status of seriousness. As a minimum, the investigator has to fill out the following items of the internet-based SAE form:

- type of event,
- description (if mandatory),
- date of onset,
- criteria for seriousness,
- causal relationship to study therapy.

If the investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the related item of the form and be explained in the narrative section of the SAE form.

As soon as further information regarding the event is available (e.g. discharge letter), the investigator should complete the documentation in the e-CRF and sign it electronically. Copies of the discharge letter, of all reports regarding examinations carried out and/or diagnostic findings should be faxed to the CRO. For laboratory results, the laboratory normal ranges should be included. All documents should be sent to the CRO after adequate blinding of patient identifiers, only.

Follow-up of any SAE that is fatal or life threatening should be provided within one additional calendar week.

Any SAE reporting (initial reporting and follow-up information on e.g. changes of an ongoing SAE's intensity or relationship to the investigational product or outcome) is done through the SAE section of the e-CRF and an automated email notification system within MARVIN, i.e. no extra SAE form needs to be faxed but the CRO will receive an automated email containing all necessary information on the SAE at the same time of the data being documented or changes of relevant SAE data being made in the e-CRF.AFNET will via contracted CRO forward all SAEs within 48 hours of awareness to BMS Global Pharmacovigilance & Epidemiology (e-mail: Worldwide.safety@bms.com) to meet the needs of the market authorisation holder to periodically report SAEs within research projects using apixaban. The relevant SAE data according to the BMS "solicited and non-interventional research AE/SAE form" (version 10.12.2012) will be retrieved from clinical and SAE data documented by the investigator within the e-CRF and sent to BMS via e-mail form. Changes of relevant SAE data (including deletion of SAEs if relevant criteria are not met) will also be forwarded within 48 hours of awareness to BMS Global Pharmacovigilance & Epidemiology. Patient identifying data will consist of patient ID number, year of birth, gender and site ID number, only.

According to legal requirements and international standards, annual safety reports will be prepared by the CRO, reviewed and approved by the sponsor and chief international investigator and forwarded to responsible authorities of all participating countries and to all corresponding ECs / IRBs.

8.3.1 Definition of Intensity

Intensity	**Definition**
Mild	Patient is aware of signs and symptoms but they are easily tolerated
Moderate	Signs/symptoms cause sufficient discomfort to interfere with usual activities
Severe	Patient is incapable to work or perform usual activities
Very severe	Signs/symptoms are debilitating, significantly incapacitate patient despite symptomatic therapy

8.3.2 Definition of Causality

In accordance with the CIOMS group, causality of an event will be assessed as:

not related: No causal relationship exists between the study treatment and the event but an obvious alternative cause exists, e.g. the patient's underlying medical condition or concomitant therapy.

or

related: There is a reasonable / plausible possibility that the event may have been caused by the study treatment (e.g. the event cannot be explained by concomitant disease(s) or other drugs/treatments).

8.3.3 Adverse Event Follow-up Procedures

The investigator should take all appropriate measures to ensure the safety of the patients, notably he / she should follow-up the outcome of any AE of special interest as defined in section 8.1 or SAE (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the patient's condition.

In case of any SAE, the patient must be followed until clinical recovery is completed and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after termination of the trial, and that additional investigation may be requested by the CRO team.

8.4 Handling of Expedited Safety Reports

This applies to any SAE that is considered related to study therapy and the nature or severity is not consistent with the applicable product information (suspected unexpected serious adverse event; SUSAR). The expectedness of an adverse reaction will be determined by the sponsor, delegated to the CRO according to the summary of product characteristics in the version valid at the start of the trial.

The sponsor will act in strict compliance with all applicable laws and regulations and will ensure that any delegate strictly abides by the same. The CRO will notify the competent authorities, corresponding ECs / IRBs and all principal investigators concerned of any SUSAR in-line with applicable regulatory requirements.

9 Study Schedule

9.1 Visit Schedule

The timing and assessment of the study are outlined in the following table:

Assessment	**Enrolment and randomisation**	**Ablation** Day 0 of FU	**Follow-up Month 3*** Day 76 to 104 of FU	**Phone call****
Signed ICF	x			
Check inclusion & exclusion criteria	x			
Physical examination / medical history	x	x	x	
Laboratory parameters (blood sample)	x		x	
INR measurement (blood sample)[1]	x	x	x	
12 lead ECG	x	x	x	
24-hours Holter ECG			x	
Transesophageal echocardiogram (TEE)[2]	(x)			
Transthoracic echocardiogram (TTE; after ablation procedure)		x		
ACT measurement (blood sample)		x		
MRI sub-study, only: brain MRI (3-48 hours after ablation)		x		
Cognitive function test (MoCA)	x		x	
Quality-of-Life (EQ-5D, SF-12)	x		x	
Karnofsky score	x		x	
Supply of study medication	x			
Return of study medication			x	
Adverse event (AE) / serious adverse event (SAE)		x	x	x**

[1] In patients randomised to VKA-group, only.

[2] TEE is a clinical decision by the treating physician: in case of clinical need to shorten the period until the ablation procedure, a TEE must be performed to exclude atrial thrombi

* Time window ± 14 days (3 months = 90 days)

** 30 days after discontinuation of study drug (SAEs to be collected, only)

9.2 Baseline Visit

A patient meets eligibility criteria of the study if all inclusion and exclusion criteria are fulfilled as described in the sections above. Prior to any trial related procedure a signed informed consent form has to be obtained from every patient to be included in AXAFA and kept on file locally.

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent
- Document all inclusion and exclusion criteria
- Assess patients' medical history
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Perform a physical examination
- Obtain blood samples for laboratory assessments (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess quality-of-life (EQ-5D and SF-12 questionnaire)
- Assess performance status (Karnofsky score; refer to appendix V)
- Initiate study therapy and assure INR monitoring of therapy in case of VKA (refer to appendix III for instructions with regard to change of anticoagulants at start of study drug)
- In case of clinical need to shorten the period until the ablation procedure: perform TEE to exclude atrial thrombi

9.3 Follow-up

Every patient within AXAFA will undergo two scheduled in person follow-up visits, one at the time of the ablation procedure and another follow-up visit at the end of the study, three months after the ablation visit.

9.3.1 Index ablation visit

The time point of the ablation visit depends on the duration of effective anticoagulation:

Patients scheduled for ablation without exclusion of atrial thrombi by TEE will be treated for at least 30 days with the oral anticoagulant of their randomisation group prior to the ablation visit. This period can be longer according to clinical needs (e.g. scheduling and waiting list requirements, or insufficient or insufficiently documented oral anticoagulation). Effective anticoagulation (i.e. continuous medication intake in patients randomised to Xa, and INR between 2.0-3.0 in patients randomised to VKA) needs to be present for 30 days prior to ablation. Ineffective anticoagulation (e.g. failure to take medication in Xa group or INR <2.0 in VKA group) resets this interval to 0 days. Failure to take apixaban is defined as having missed more than one dose per week. In this case a TEE can be performed to avoid reset of anticoagulation interval to 0 days.

Patients scheduled for ablation after exclusion of atrial thrombi by TEE can undergo catheter ablation less than 30 days after initiation of anticoagulant study therapy provided that continuous effective anticoagulation is ensured between the TEE and the ablation (i.e. for patients in the Xa-group at least two doses of apixaban immediately prior to ablation, for patients in the VKA-group at least one INR value ≥2 prior to ablation).

In case TEE reveals evidence of atrial thrombi, no catheter ablation may be done (refer to section 9.4.1).

At the ablation visit, the investigator or designee will

- Assess and document adherence to study therapy by asking the patient and by reviewing INRs (VKA group patients) or by pill count (Xa group patients)
- Perform a physical examination
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Verify and document that there are no contra-indications for the ablation procedure
- Assess for clinical events and AEs or SAEs occurred since enrolment

Thereafter, the ablation procedure can be performed. During the ablation procedure, the study team will collect the procedural information including ACT measurements, details of the ablation technology used,

delivered energy, procedure time, rhythm at beginning and end of procedure, need for cardioversion during the procedure.

After the ablation procedure, the investigator or designee will

- Perform a TTE and assess especially for pericardial effusion
- Document any peri- or post-procedural difficulties or complications, especially potential primary outcome events and potential SAEs
- MRI sub-study, only: Perform a brain MRI according to the AXAFA imaging charter within 3-48 hours after the ablation and upload the MRI imaging data (technical details are described in a separate document).

9.3.2 Clinical follow-up visit (3 months after the ablation visit)

At this visit, the investigator or designee will

- Assess and document adherence to study therapy by reviewing INRs (VKA group patients) or by asking the patient and by pill count (Xa group patients)
- Perform a physical examination
- Document a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Obtain a 24 hour Holter ECG
- Obtain blood samples for laboratory assessments (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess performance status (Karnofsky score; refer to appendix V)
- Assess quality-of-life (EQ-5D and SF-12 questionnaires)
- Assess for clinical events and AEs or SAEs that occurred since the ablation procedure

9.3.3 Phone call (30 days after discontinuation of study drug)

30 days after discontinuation of study drug (whether at regular study end or at premature study termination) the investigator or designee will call the patient and assess for SAEs that occurred since discontinuation of study drug.

9.4 Premature Study Termination

9.4.1 Withdrawal prior to the ablation procedure

In case of patient's withdrawal of consent to further study participation prior to the ablation procedure or if the ablation procedure was not performed for medical reason, the investigator should contact the patient and

- Assess for clinical events and AEs respectively SAEs that occurred since enrolment
- Xa group patients, only: Ask for return of study medication and perform pill count.

These data will be documented in the e-CRF in a withdrawal visit. The extended 30 days-period of SAE reporting after discontinuation of study medications applies (refer to section 8.3.3) provided intake of at least one dose of study medication.

9.4.2 Withdrawal after ablation procedure

In case of patient's withdrawal of consent to further study participation after the ablation procedure, the investigator should contact the patient and ask him to come to the study site for a concluding visit. As far as the patient agrees, follow-up assessments as described in section 9.3.2 will be performed and documented

in the e-CRF. The extended 30 days-period of SAE reporting after discontinuation of study medications applies (refer to section 8.3.3).

9.5 Transthoracic Echocardiography

The main purpose of the TTE after the ablation procedure is the detection of pericardial effusion. This will be assessed by measuring the maximal separation between right ventricular wall and pericardium.

9.6 Electrocardiogram

All ECGs should be uploaded digitally onto a central server within the e-CRF. This requires an ECG machine capable of exporting an adequate digital format that can then be uploaded. Details regarding upload of ECGs are described in a separate ECG manual.

All patients will undergo 12-lead ECG at baseline, at the ablation visit and at the end of follow-up to determine rhythm. Operators recording ECGs should ensure that chest leads are placed in the proper position and electrodes make good skin contact to minimize artefacts. The reversal of limb leads and the switching of precordial leads are known to cause important alterations in ECGs.

The ECG recording should be annotated with the date of recording, patient ID and gender, only. No patient identifying annotations (e. g. last name, first name, date of birth) must be documented.

9.7 Blood Samples

Routine laboratory parameters are part of the screening procedures in order to verify the enrolment criteria and therefore not considered to be part of study related procedures. If these parameters can be assessed from a blood sample not older than 7 days at the date of inclusion, the blood sampling does not have to be repeated. Parameters include red blood cells, white blood cells, platelets, serum creatinine, aPTT, and INR. INR should be documented at least three times prior to the ablation visit in patients randomised to VKA therapy, and more often as clinically indicated. All INR measurements will be collected in the e-CRF. All blood parameters will be determined at the local laboratory of the study sites provided their analytical laboratories are certified. The e-CRF will collect laboratory values and information whether the value is normal or abnormal.

At baseline and at the end of follow-up, an additional blood sample will be collected (20ml whole blood in each case) and sent to a central laboratory for archiving for later analysis (analyses of factors and mechanisms of AF, stroke, and bleeding, including genetic markers). Patients will provide explicit signed informed consent to obtain this extra blood sample. Details regarding handling and shipment of these blood samples are described in a separate lab manual. Aim of these analyses is to evaluate the possible mechanisms of AF and thrombogenesis and to gain new knowledge regarding treatment of AF in the future.

9.8 Holter ECG

All patients will undergo 24-hour Holter ECG recording at the 3 months follow-up visit. The Holter ECG will be analysed locally, and the results will be documented in the e-CRF including burden of AF, i.e. total time in AF, number of AF episodes, and minimum and maximal time of AF episode.

9.9 MRI Sub-Study

It is well established that clinically “silent” strokes are associated with an increased risk of cognitive decline in the long-term (22). Silent strokes are accepted intermediate outcome parameters in neurology (23). Silent strokes are detected by MRI in 8-41% of all patients after catheter ablation (33, 36, 37). An increased number of patients with silent brain lesions already resulted in the redesign of one specific ablation catheter

technology (38). Silent brain lesions will therefore be assessed in this sub-study by brain MRI 3-48 hours after the ablation procedure.

It is expected that approximately 50% of the study sites will participate in this imaging sub-study. Study sites will have to decide on participation in the MRI sub-study at the time of site initiation at the latest. In study sites participating in the sub-study, all eligible patients will have to undergo MRI examination in order to avoid selection bias.

Patients are not eligible to undergo MRI examination if they have any non-MRI safe items in their body. Typical implants suspect to harm patients or at risk to be damaged during MRI examination are:

- Implanted pacemaker
- Implanted defibrillator
- Implantable pump
- Neurostimulator or transcutaneous electrical nerve stimulation
- Eye or ear implant
- Intrauterine device
- Artificial body parts
- Breast or penile implants
- Implanted shunts.

Patients might not be eligible to undergo MRI examination in case of any of these conditions:

- Problems lying on the back and holding still for 15 minutes
- Ever done metal grinding/welding as work or a hobby, or if ever seen a doctor about metal in the eyes
- Any metal in the body from an accident, gunshot, or military service wound
- Pregnancy
- Problems with claustrophobia.

Patients not eligible for MRI but recruited in study sites which decided to participate in the MRI sub-study are eligible to participate in the AXAFA main study.

Technical details regarding instructions for MRI examination and for digital upload of the MRI imaging data to a central system are described in a separate document.

All brain images will be centrally read for new brain lesions by core brain imaging centres. The core brain imaging centres will be blinded to therapy group for analysis of brain images. Details regarding central review of MRIs are described in a separate document.

10 Duration of Study Participation

10.1 Overall Duration of Study

With an expected screening and enrolment period of 25 months and a sliding initiation of sites over a period of nine months, and a maximum follow-up of four months per patient, overall study duration is calculated to be approximately 2.5 years (first-patient-in until last-patient-out). The total study duration might be adapted based on an interim analysis. Final data cleaning will require presumably three months after study closure. End of study is defined as last patient last visit (the 30-days SAE reporting period will exceed the official end of study date).

10.2 Individual Duration of the Study

According to the study protocol, the minimum follow-up time per patient is approximately three months. The total study duration per patient will depend on the duration of anticoagulation prior to the ablation procedure. For patients scheduled for catheter ablation of AF after exclusion of atrial thrombi by TEE the total study duration might be about three months, in all other patients it might be at least four months because these patients will have been anticoagulated for at least 30 days prior to catheter ablation. Difficulties in achieving therapeutic anticoagulation or irregular intake of study drug may prolong the follow-up period for some patients.

11 Stopping and Discontinuation Criteria

When the study is terminated, the nature of termination will be documented (scheduled end/discontinuation with justification). Discontinuation of the study will be communicated in writing according to the legal requirement. The decision to stop the study will be reached jointly by the sponsor and the SC.

11.1 Discontinuation Criteria related to the Study

Following a recommendation of the Data and Safety Monitoring Board (DSMB), the SC may decide discontinuation of the study due to efficacy criteria or adverse reactions in either study group. Discontinuation of the study can also be decided if patients cannot be recruited in sufficient numbers within a certain time period. Detailed criteria for a premature stopping of the entire trial based on safety concerns will be defined in the DSMB and SC charters.

Furthermore, the sponsor in collaboration with the international chief investigator has the right to close local study sites for enrolment of further patients if a major protocol violation occurs, the site does not comply with the study protocol or decisions of the committees or the international chief investigator or if the site remains inactive for several months. Such decisions will always be taken on a case-by-case basis, but may be taken e.g. if the study procedures and study therapy is not delivered according to protocol and after reminders to adhere to the protocol from the study team.

11.2 Discontinuation Criteria related to the Patient

The investigator is not able to decide about the discontinuation of study participation of any patient. The investigator has the option to discontinue study medication, however, the patient will continue to be followed during the study. Once a patient has been randomised the investigator has to follow this patient in-line with the intention-to-treat principle according to protocol. The patients will be advised in the informed consent forms that they have the right to withdraw from study participation at any time without statement of reasons. However, the investigator should try to find out the reason for patient’s withdrawal of consent and document these in the e-CRF.

In case a patient withdraws from study participation before an ablation procedure for AF was performed the withdrawal will be documented in the e-CRF. The initial ablation procedure for AF is the underlying intervention of the therapeutic concept of AXAFA. Analysis of outcome without performed ablation is scientifically useless in this concept.

Once a patient has been randomised and an ablation procedure for AF was performed and the first dose of study medication (apixaban or VKA) was taken, the treatment of the patient must not be discontinued. In case of patient's request or medical necessity of study treatment discontinuation (e.g. in case of major bleeding), patients will be followed according to study protocol. Any effort should be made to continue the allocated study medication as soon as clinically justifiable.

In case a protocol violation is noticed the patient will remain in the intention-to-treat group and will be followed according to protocol.

Patients will be followed according to the study protocol irrespective of whether they experience an outcome.

Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. The responsible investigator will take all acceptable measures to retrieve information on vital status of all patients enrolled in the trial.

12 Statistics

12.1 Statistical Methods

12.1.1 Analysis of the primary outcome

With respect to the primary outcome, the study is exploratory. The primary efficacy analysis will be based on composite endpoint of all-cause death, stroke or major bleeding in all randomised patients who undergo an ablation procedure for AF (i.e., modified intention-to-treat [mITT]). The efficacy composite endpoint is measured (in days) from the randomisation date to the day of the event (i.e., time-to-first event = event date - randomisation date +1). As a secondary analysis, time-to-event analysis will be conducted for the components of the primary composite endpoint.

The Kaplan-Meier (K-M) estimates of the survivor function and the log rank test statistic (44) will be used to assess the statistical significance of observed treatment differences in the time-to-event distributions between the treatment groups. The log-rank test statistics, p-values, K-M estimates, and life table estimates will be obtained from the SAS® V9.3 (or higher) procedure LIFETEST (SAS/STAT User's Guide, Version 9.3, Cary, NC: SAS Institute Inc. 2011).

Cox proportional hazards model will be used to obtain an estimate of the hazard ratio for Xa group to VKA therapy group. A 95% confidence interval (CI) will be computed for the hazard ratio. Stratified Cox proportional hazards model will be conducted using the stratification factors at randomisation as a strata statement in the model. In addition, the Cox proportional hazards model with clinically relevant baseline risk factors will be used to estimate the adjusted hazard ratio (95% CI).

As a sensitivity analysis, the per-protocol population will be used. Statistical models will be constructed to validate existing factors that predict outcome parameters, and to describe novel factors, e.g. blood- or ECG-based. Details of the statistical analysis will be defined in a statistical analysis plan.

12.1.2 Analysis of the secondary outcome

The secondary endpoints listed in section 4.2.1 that are measured as time-to-event will be analysed using the same statistical methods used for the primary efficacy endpoint (Section 12.1.1). Quality-of-life outcomes will be summarized by treatment groups for each component of the questionnaires (assessed by EQ-5D, SF-12 and by the Karnofsky scale), Total score quality of life outcomes from each assessment will be analysed as change from baseline at month 3 using analysis of covariance with the baseline values as a covariate in the model. Details of the statistical analysis will be defined in a statistical analysis plan.

MRI sub-study will develop a separate specific analytic plan prior to locking the main study database.

All the secondary endpoints analyses are exploratory in nature and will be tested at 0.05 significant level (i.e., no multiple comparisons adjustment).

12.1.3 Safety analysis

Safety data include adverse events as defined in section 8.1, primary safety endpoints, and data for other safety evaluations. Safety data will be collected on all randomised patients (i.e., ITT cohort) in this study.

The primary safety outcome in this study is a composite of all-cause death, stroke, cardiac tamponade and major bleeding events which will be analysed using time-to-event methodology as described in Section 12.1.1. Similar analyses and summary statistics will be provided for the components of this safety composite endpoint.

Serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment related SAEs will be summarized under each treatment group, by system organ class (SOC) and preferred term (PT). Comparisons between treatment groups will be made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term) of special interest. SAEs will be summarized by severity and relation to study treatment received.

12.1.4 Subgroup analysis

A list of subgroup criteria will be pre-specified in the statistical analysis plan.

12.2 Sample Size and Power Calculations

Assuming an overall event rate of the primary endpoint (composite of all-cause death, stroke or major bleeding) at day 90 to be 17%, a total of 630 patients (315 per group) will allow to detect a pre-specified margin of 7.5% (absolute difference) with 80% power using upper 1-sided 95% confidence interval (i.e., 2-sided 90% CI, (41)). The method of Farrington and Manning was used to compute sample size and power. To account for roughly 3% of patients who will not undergo the ablation procedure, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e., randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort.

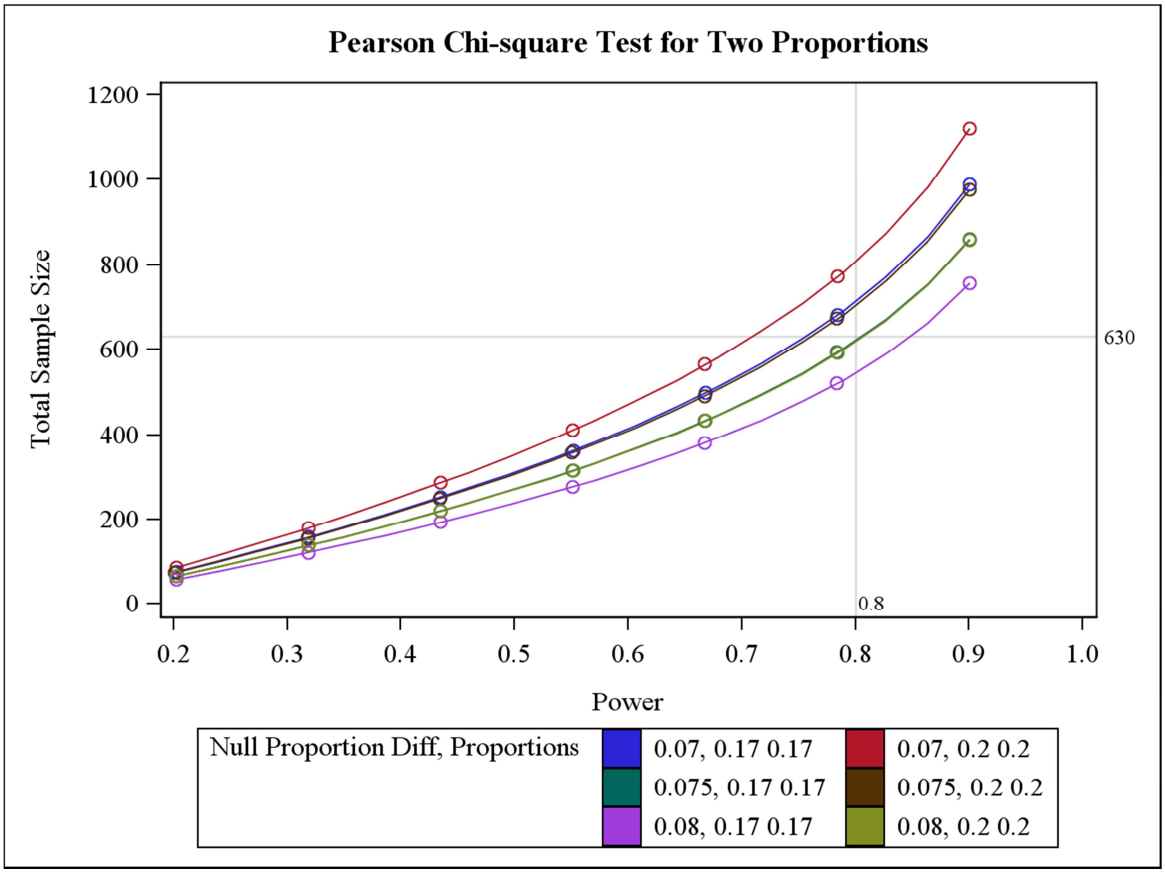


Figure: Power curves for several event rates and margin scenarios.

12.3 Interim Analyses, Reassessment of the Sample Size

There are two planned interim analyses to be conducted by the Data and Safety Monitoring Board (DSMB) after approximately 1/3 and 2/3 of patients underwent the catheter ablation procedure (i.e., roughly at 200 and 400 patients, respectively) who have completed 90 days (3 months) of study follow-up. The Haybittle–Peto boundary will be used as stopping rule guidance for the DSMB. The DSMB charter will provide further details on the conduct of the interim looks.

The Steering Committee could decide to conduct sample size re-estimation (sample size increase) during the interim looks using the observed aggregated event rate of the study primary endpoint. The re-estimation of the study size will be based on the current protocol assumptions (i.e., same study statistical power and the non-inferiority margin).

12.4 Patient Selection for Analyses

Under the mITT principle, all randomised patients who undergo an ablation procedure for AF will be included in the primary analysis and censoring mechanism will be applied to those patients without event at the end of the study follow-up. Patients without an event at the end of follow-up will have their efficacy measure censored at the end of follow-up. Patient without an event and who is lost to follow-up will be censored on the day of last contact with the patient. This concept will be applied to both treatment arms. In addition, a sensitivity (robustness) analysis will be conducted using per-protocol population (i.e., among those without major protocol violations).

The study sample size does account for those roughly 3% of patients who will not undergo the ablation procedure for AF. The initial ablation procedure for AF is the underlying intervention of the therapeutic concept of AXAFA. Safety analysis will be performed on all patients randomised (i.e., ITT cohort).

13 Access to Source Data / Documents

13.1 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

13.2 Source Documents

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes, memoranda, patient diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments) involved in this clinical study.

In case of data that are result of patient interrogation and will not be documented in clinical routine, the e-CRF is the source document, if the patients answer is documented there without prior documentation on paper (e.g. in case of central follow-up).

13.3 Direct Access

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

The investigator agrees that representatives or the designees of the sponsor such as monitors and auditors, and appropriate Regulatory Agencies will be given direct access to the regular clinical files of the patient.

14 Quality Control and Quality Assurance

14.1 Quality Control

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14.2 Initiation Visit

At each site an initiation visit will be performed by a representative of the CRO before enrolment of the first patient at this site.

14.3 Study Monitoring

Authorized, qualified representatives of the designated CRO will accomplish the monitoring of the study sites during the trial.

Data of a sufficient number of patients will be verified on site by source data validation checks for outcome and compliance with the protocol and consistency with data in the e-CRF.

It is important that the investigator and relevant personnel are available during the monitoring visits and that an appropriate location and sufficient amount of time is devoted to the process. During the monitoring visit a PC with internet connection should be available to the monitor for direct connection to the internet database of the study and to all the data of the patients if stored in the data system of the hospital or catheter lab.

The main duty of the monitor is to help the sponsor and the investigator to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the trial. At regular intervals during the study, the local site will be contacted through monitoring visits, letters/ emails or telephone calls by a monitor to review the progress of the study.

Further details are described in a separate monitoring manual.

14.4 Close Out Visit

Independent close out visits are not planned. In case of special requests by the sponsor, a separate close out visit may be performed at the end of the trial. The close out visit may be combined with the last monitoring visit.

14.5 Quality Assurance

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements.

The investigator should permit auditing by or on behalf of the sponsor and inspection by applicable regulatory authorities. The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during the audit or inspections.

14.5.1 Inspections

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsors and/or clinical research organisation facilities or at any other establishments deemed appropriate by the regulatory authorities.

14.5.2 Audits

An audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, designated Standard Operating Procedure (SOP), Good Clinical Practice (GCP) and the applicable regulatory requirements. An independent audit at the study site may take place at any time during or after the study.

15 Ethical and Legal Consideration

This is an investigator initiated (IIT), phase IV trial which meets all relevant ethical and regulatory standards (ICH-GCP). The trial will be conducted in accordance with the principles laid down in the Declaration of Helsinki in its version of October 2013 (Fortaleza).

Before initiating the study in each country, approval of the corresponding regulatory authority and Institutional Review Board/ Independent Ethics Committee will be obtained.

15.1 Ethical Consideration

15.1.1 Institutional Review Board/ Independent Ethics Committee (IRB / IEC)

It is intended to initially submit the study to the IRB / IEC of the national coordinator in Germany (“Leiter der klinischen Prüfung”, LKP). After the primary approval has been achieved, submission to other national and local IRB/ IECs will be performed.

Provided this is not contradictory to national law, the local investigator is responsible for submitting an application to the appropriate IRB / IEC. Furthermore the local investigator is required to forward to the sponsor a copy of the written and dated approval or favourable opinion of the local IRB/ IEC signed by the chairman and including information on the composition of the IRB / IEC. The trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, investigator’s CV, etc.) and the date of the review should be clearly stated on the written IRB/ IEC approval/ favourable opinion. The corresponding national coordinator together with the CRO will provide substantial support for any IRB / IEC submission. The sponsor is responsible to assure that approval of the local IRB / IEC in each country is obtained prior to study start in the respective study site or country in accordance with local requirements.

During the trial, any substantial amendment or modification to the clinical trial protocol should be submitted to the IRB / IEC. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the trial, in particular of any change in safety.

If requested, a progress report is sent to the IRB / IEC annually and a summary of the trial's outcome at the end of the study.

15.1.2 Steering Committee

The trial Steering Committee (SC) will consist of a small group of expert cardiologists, a neurologist, and an expert biostatistician (refer to appendix I). The functions of the SC are the following:

- Overall responsibility for the execution and scientific reporting of AXAFA.
- Advice on the scientific and clinical aspects of the study protocol and related documents.
- Responsibility for the conduct of the study according to the guidelines of good clinical practice (GCP) including the monitoring of patient recruitment.
- Reassessment of the sample size based on the blind review of the biostatistician.
- Reassessment of benefit/ risk ratio following the recommendations of the DSMB.
- Decisions on continuation or termination of the study based on the recommendations of the DSMB.

A SC charter providing operating procedures and responsibilities will be discussed and enacted latest at the second meeting. Meeting frequency will be defined by the committee and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings. Minutes of each meeting will be provided.

15.1.3 Endpoint Review Committee

The Endpoint Review Committee (ERC) will consist of three experts in cardiology, AF ablation, and stroke neurology. The committee will be blinded to therapy group and to INR values, although review of detailed laboratory parameters may in some cases suggest the type of anticoagulant therapy at the time of the event, and will centrally adjudicate all outcome events as well as any hospitalisation for other reason and any other SAE. Bleeding events not meeting the criteria of seriousness will not be adjudicated by ERC.

An ERC charter providing operating procedures and responsibilities will be discussed and enacted latest at the second meeting. Meeting frequency will be defined by the number of documented and cleaned SAEs and may vary depending. Meetings may be face-to-face meetings or conference calls. Minutes of each meeting will be provided.

15.1.4 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the SC and study investigators. It will consist of one statistician and two clinicians with expertise in clinical trials and in the management of AF patients. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. They regularly monitor the recruitment and conduct of trial, data quality and timeliness, the distribution of therapies within the study groups, the serious adverse events and further adverse events selected to their discretion during the course of the trial. DSMB will perform interim analyses after 1/3 and 2/3 of patients underwent the catheter ablation procedure (i.e., roughly at 200 and 400 patients, respectively) and give recommendations to the SC to continue or stop the trial. The Haybittle–Peto boundary (45, 46) will be implemented as stopping rule guidance for the DSMB.

A DSMB charter providing operating procedures and responsibilities will be discussed and enacted latest at the second meeting. Meeting frequency will be defined by the committee and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings and may have an open part with guests and a closed part. Minutes of each meeting will be provided. After each meeting, recommendations will be given to the SC in a written form.

15.1.5 National coordinators

National coordinators are selected experts that support submission to the competent authorities and IRB/IEC in their individual countries. The national coordinators provide their expertise regarding regulatory affairs in their countries. The national coordinators supervise and monitor the patient recruitment, and support recruitment measures on a national level. A national coordinator can also be a member of the SC.

15.2 Legal Consideration

The study will be notified to the competent authority of each participating country and approval obtained prior to study start in the respective country. Submission to relevant regulatory authorities in all participating countries lies within the sponsor's responsibility (if not required otherwise according to country specific requirements). The corresponding national coordinator will provide substantial support for any submission process. The study will be performed in accordance with the respective national legislation in each country.

15.3 Modification of Protocol

Any substantial amendment to the clinical trial protocol requires written approval/favourable opinion by the IRB / IEC prior to its implementation, unless there are overriding safety reasons that require immediate action. In some instances, an amendment may require a change to the informed consent form. In this case, the investigator must receive an IRB /IEC approval/favourable opinion concerning the revised informed consent form prior to implementation of the change.

Substantial amendments will be notified to the competent authorities too.

15.4 Financing and Insurance

The costs necessary to perform the study will be agreed upon with each investigator and will be documented in a separate financial agreement which will be signed by the investigator and the CRO on behalf of the sponsor, prior to the study commencing.

A patient insurance has been effected by the sponsor of the trial. Country specific requirements will be taken into account.

The insurance certificate as well as the insurance conditions will be handed out to all investigators. The insurance conditions have to be provided to the patients too.

15.5 Investigator's Information on IMP

Apixaban as well as VKAs are authority approved and marketed in all European countries and in the USA. The respective summary of product characteristics is publicly available in the internet.

15.6 Personal Data and Data Protection

All data obtained in the context of the clinical trial are subject to data protection. This applies to patients' data as well as to investigators' personal data which may be included in any database of the sponsor or the CRO.

The investigating physicians shall take care that patient documents (e.g. copies of reports on special findings) transmitted to the CRO or the sponsor contain no names, but only the year of birth and a relevant patient number. The storage of data for statistical analysis shall likewise be performed only under the patient's random/study number.

15.7 Data Handling and Record Keeping

15.7.1 Completion of Case Report Forms

All medical data in this trial are to be recorded directly in the e-CRFs. Documentation on paper will be restricted to exceptional circumstances only.

The investigator must ensure the accuracy, completeness and timeliness (and legibility in case of documentation on paper) of data.

15.7.2 Archiving

The investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. The investigator has to retain the study documents (i.e. investigator site file) after the completion or discontinuation of the study for the time period as required by national legislation. This especially applies to patients' signed informed consent forms and the patient identification list.

The investigator must notify the sponsor prior to destroying any essential study documents within the specified period following completion or discontinuation of the trial.

15.8 Confidentiality

All information disclosed or provided by the sponsor (or any company / institution acting on his behalf), or produced during the trial, including, but not limited to, the clinical trial protocol, the e-CRFs and the results obtained during the course of the trial, is confidential. The investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the sponsor. The sub-investigators shall be bound by the same obligation as the investigator. The investigator shall inform the sub-investigators of the confidential nature of the trial. Both, the investigator and the sub-investigators shall use the information solely for the purposes of the trial, to the exclusion of any use for their own or for a third party's account.

15.9 Responsibilities

The sponsor of this trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the trial with regard to ethical aspects, clinical trial protocol compliance, integrity and validity of the data recording.

16 Final Report and Publication Policy, Property Rights

The sponsor will be responsible for preparing the final study report that is to be signed by the SC. The sponsor will communicate the results of the trial to the investigators, authorities and IRBs/ECs.

The SC will be primarily responsible for the creation, review and submission of publications and presentations relating to the major aspects of the study within a timely fashion after completion of the study. All analyses will be the responsibility of the SC. Manuscripts for publication will be drafted by members of the SC or other interested investigators. All manuscripts will be subject to coordinated submission and review prior to submission. Coordination will be done by SC.

AXAFA is an investigator-initiated trial. Interested investigators and initiatives will be encouraged and supported as appropriate if they propose additional issues that may be studied within the main trial. These materials must be submitted to the SC for review and comment prior to publication or public dissemination. All relevant measures for transparency of clinical trials, and especially the recommendations of the editors of the major medical journals, will be met.

The publication rules are regulated separately and described in detail in a publication policy that is confirmed by the SC and part of the contract of the SC members.

All information and documents provided by the sponsor or its representatives are and remain the sole property of the sponsor. The investigator shall not mention any information for any other intellectual property rights.

All results, data, documents and inventions, which arise directly or indirectly from the trial in any form, shall be the immediate and exclusive property of the sponsor.

17 Definitions and Classifications

17.1 Protocol Violation

Protocol violations are any unapproved changes, deviations or departures from the study design or procedures of a research project that are under the investigator's control and that have not been reviewed and approved by the SC.

17.2 Major Protocol Violation

Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB- or Ethics Committee-approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Patients with major protocol violations will be excluded from the per protocol analysis. Some major protocol violations may be reported to regulatory authorities within defined time periods as mandated. Study specific definitions of major protocol violations will be given by the SC.

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19 Signatures

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Date	**Signature**
_____	_____ Paulus Kirchhof (chief international investigator)
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_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature local investigator
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Appendix I: Members of the Steering Committee

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Appendix II: Time Schedule

	Tasks	**Date**
Study planning	Draft Protocol, review and finalisation by Steering Committee	Nov 2013 to May 2014
Study preparation	Definition of drug supply mechanism	May to Jul 2014
	Set up of e-TMS (MARVIN), preparation of e-CRF; preparation of all other study relevant documentation	May to Jul 2014
	▪ Site selection, site contacts, site evaluation	May to Oct 2014
	▪ EC and CA submission	Aug 2014 to Mar 2015
Study initiation	▪ Site contracting	Sep 2014 to Apr 2015
	▪ Supply of the sites with study materials, initiation visits	Dec 2014 to Aug 2015
	▪ Recruitment period (FPI to LPI)	Jan 2015 – Jan 2017
Study duration	Treatment / Follow-up of last patient (LPI to LPO)	Feb to Jun 2017
	Mean follow-up period of all patients, assuming a linear patient recruitment	3.7 months
Interim analyses	▪ After 200 pts. have undergone AF ablation and completed the 3-months FU period	Estimated Feb 2016
	▪ After 400 pts. have undergone AF ablation and completed the 3-months FU period	Estimated Sep 2016
Study closure	Final data cleaning /study closure	Jul 2017
Final analysis	Statistical analysis, incl. review by Steering Committee	Aug to Sep 2017

Appendix III: Change management of anticoagulants at start and discontinuation of study drug

This appendix provides clinical guidance how to safely change patients from one anticoagulant to another anticoagulant which may be required at the time of enrolment (after randomisation) and at the end of study medication.

1. VKA to NOAC

- Discontinue the VKA and measure INR frequently (usually every day).
- Once INR is ≤2.0, the NOAC should be started without delay.
- If INR is >2.0, frequent INR measurements are needed (e.g. daily). NOAC treatment should be commenced when INR is ≤2.0.

2. NOAC to VKA

- Measure baseline INR.
- Initiate the VKA at the same time the patient is still on the NOAC, and continue the NOAC until INR is ≥2.
- The initial VKA dose will be an estimated daily dose if the INR is >1.5, and double the estimated daily dose if INR is ≤1.5. Thereafter, the expected daily maintenance dose of VKA is given.
- During concomitant administration of VKA and NOAC, take an INR measurement every day to decide when to discontinue the NOAC (i.e. when INR is ≥2).

3. NOAC to NOAC

When switching between NOACs, start the new NOAC at the time the next dose of the original NOAC is scheduled and terminate the original NOAC intake. Care should be taken in patients with impaired renal disease and in situations where higher-than therapeutic concentrations are expected.

4. Acetylsalicylic acid or clopidogrel to NOAC

Initiate the NOAC at the time of randomisation and terminate acetylsalicylic acid or clopidogrel intake.

5. Parenteral anticoagulant to NOAC

- Terminate intravenous unfractionated heparin (IV UFH) at the time of randomisation. Administer the first NOAC dose 2 hours after discontinuation of UFH in patients with normal kidney function (eGFR >60 ml/min) or 4 hours for patients with eGFR of 30-60 ml/min.
- Terminate the low-molecular weight heparin (LMWH) at the time of randomisation and start the NOAC at the time the next dose of LMWH is scheduled. Do not co-administer NOAC and LMWH ("NOAC replaces LMWH").

6. NOAC to parenteral anticoagulant

Start the parenteral anticoagulant (IV UFH, LMWH) at the time the next dose of the terminated NOAC is scheduled.

Appendix IV: Bleeding Academic Research Consortium (BARC) Classification of Bleeding Events

Table reproduced from (34).

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: ➢ requiring nonsurgical, medical intervention by a healthcare professional ➢ leading to hospitalisation or increased level of care, or ➢ prompting evaluation
Type 3	Type 3a Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed); Any transfusion with overt bleeding
	Type 3b Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed); Cardiac tamponade; Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid); Bleeding requiring intravenous vasoactive agents
	Type 3c Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal); Subcategories confirmed by autopsy or imaging or lumbar puncture; Intraocular bleed compromising vision
Type 4	Coronary artery bypass graft (CABG) related bleeding ➢ Perioperative intracranial bleeding within 48 h ➢ Reoperation after closure of sternotomy for the purpose of controlling bleeding ➢ Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period† ➢ Chest tube output ≥2 L within a 24-h period
Type 5	Fatal bleeding
	Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
	Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood =1 g/dL haemoglobin).
† Cell saver products are not counted.

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.

If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

Appendix V: Karnofsky Score

(Karnofsky DA, Burchenal JH. (1949). "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press. Page 196)

In medicine (oncology and other fields), performance status is an attempt to quantify patients' general well-being and activities of daily life.

The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is death. Although practitioners occasionally assign performance scores in between standard intervals of 10, there is no substantiated rationale for this and prognostication is not improved. This scoring system is named after Dr David A. Karnofsky, who described the scale with Dr Joseph H. Burchenal in 1949.

100% – normal, no complaints, no signs of disease

90% – capable of normal activity, few symptoms or signs of disease

80% – normal activity with some difficulty, some symptoms or signs

70% – caring for self, not capable of normal activity or work

60% – requiring some help, can take care of most personal requirements

50% – requires help often, requires frequent medical care

40% – disabled, requires special care and help

30% – severely disabled, hospital admission indicated but no risk of death

20% – very ill, urgently requiring admission, requires supportive measures or treatment

10% – moribund, rapidly progressive fatal disease processes

0% – death

Appendix VI: Declaration of Helsinki (Version Fortaleza, October 2013)

http://www.wma.net/en/30publications/10policies/b3/

Appendix VII: Definition of hospitalisation for cardiovascular reasons

Cardiovascular hospitalisations comprise all hospitalisations requiring at least one overnight stay in the hospital for cardiovascular reasons excluding stroke (ischemic stroke, subarachnoid haemorrhage and haemorrhagic stroke) and major bleeding (BARC 2-5).

The pre-specified main causes for cardiovascular hospitalisation are:

- acute coronary syndrome,
  (i.e. any hospitalisation that is due to new-onset or worsening chest pain is considered as an acute coronary syndrome when myocardial ischemia or coronary heart disease requiring therapy are found upon admission. Objective signs may consist of significant coronary stenosis upon angiography (usually requiring intervention), demonstration of acute ischemia by electrocardiogram or stress test (e.g. stress echocardiography, nuclear methods, or cardiac magnetic resonance imaging), or elevated cardiac biomarkers such as troponin I, troponin T, and/or creatine kinase with a cardiac origin. This outcome parameter comprises all myocardial infarctions (STEMI or NSTEMI).
- stable angina pectoris or atypical chest pain,
- worsening of heart failure
  (i.e. any hospitalisation for new-onset shortness of breath or worsening of exercise capacity that severely limits daily activities should raise the suspicion of worsening heart failure. Worsening of heart failure should be confirmed by adequate clinical findings or measures, e.g. severe peripheral oedema, dyspnoea at rest, biomarkers such as brain natriuretic peptide, or demonstration of lung edema on chest radiograph or worsening of left ventricular function, or by use of iv diuretics. Hospitalisations for acute cardiac decompensation due to AF are part of this outcome parameter),
- syncope,
- TIA,
- non-fatal cardiac arrest,
- ventricular arrhythmia,
- cardiac transplantation,
- any type of cardiovascular surgery,
- implantation of a pacemaker, ICD or any other cardiac device,
- percutaneous coronary, cerebrovascular or peripheral intervention,
- blood pressure related hospitalisation (hypotension, hypertension; except syncope),
- cardiovascular infection,
- pulmonary embolism or deep vein thrombosis,
- pulmonary vein stenosis,
- pericardial tamponade,
- atrio-oesophageal fistula,
- hospitalisation for AF
  (i.e. any hospitalisation for treatment of AF with at least one overnight stay, e.g. initiation of antiarrhythmic drug therapy, unplanned cardioversion or unplanned ablation of AF) and
- other cardiovascular reason.

19 Signatures

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
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AMENDMENT
TO THE
CLINICAL TRIAL PROTOCOL

AXAFA - AFNET 5

_A_nticoagulation using the direct factor _X_a inhibitor apixaban during _A_trial _F_ibrillation catheter _A_blation: Comparison to vitamin K antagonist therapy.

An Investigator-driven, **P**rospective, Parallel-group, **R**andomised, **O**pen,
Blinded Outcom**e** Assessment (PROBE), Multi-centre Trial
to determine the optimal anticoagulation therapy for patients undergoing catheter ablation of atrial fibrillation

EudraCT number: 2014-002442-45
NCT number: NCT02227550
ISRCTN87711003

Responsible Sponsor:
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Date of amendment:

15th December 2014
(amending protocol version dated 28th July 2014)

Prepared by Bianca-Maria Klein, CRI

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Rationale:

Minor editorial changes

6.2.3 Exclusion criteria

General exclusion criteria

Old version (28th July 2014):

E2. Participation in another clinical trial, either within the past two months or still ongoing.

E8. Coadministration with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) or strong dual inducers of CYP3A4 and P-gp

New version (15th December 2014):

E2. Participation in another clinical trial, either within the past 2 months or still ongoing.

E8. Coadministration with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) or strong dual inducers of CYP3A4 and P-gp (Appendix VIII)

Rationale:

Harmonisation of wording and reference to appendix.

Exclusion criteria related to a cardiac condition

Old version (28th July 2014):

not available

New version (15th December 2014):

E14 Documented atrial thrombi less than 3 months prior to randomisation

Rationale:

More detailed instructions for exclusion of patients before randomisation.

7 Therapy

Old version (28th July 2014):

…

Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation. Ablation can be performed earlier when atrial thrombi have been excluded by a clinically indicated TEE. After TEE continuous effective anticoagulation must be ensured until the end of the trial.

…

New version (15th December 2014):

…

Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation. Ablation can be performed earlier when atrial thrombi have been excluded by a clinically indicated TEE. A TEE performed within 6 hours prior to randomisation is considered valid. After TEE continuous effective anticoagulation must be ensured until the end of the trial.

…

Rationale:

More detailed instructions for inclusion of patients before randomisation.

8 Adverse Event Reporting

Old version (28th July 2014):

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but only "Adverse Events of Special Interest" which are defined as described in section 8.1.

New version (15th December 2014):

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but only "Adverse Events of Special Interest" (see 8.1) and adverse events judged as medically important by the Investigator, thus meeting criteria of seriousness (see 8.2).

Rationale:

Clarification Adverse Events, judged as medically important events, have to be documented, because they meet criteria of a serious adverse event.

8.2.1 Potential Drug-Induced Liver Injury (DILI)

Old version (28th July 2014):

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

…

New version (15th December 2014):

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event by reporting the liver function parameters. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

…

Rationale:

According to SmPC of apixaban.

8.2.2 Pregnancy

Old version (28th July 2014):

It is reminded that all means should be put in place to prevent pregnancy during the study. Before study enrolment, women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. In addition, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

…

New version (15th December 2014):

It is reminded that all means should be put in place to prevent pregnancy during the study. Before study enrolment, women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Women of childbearing potential are required to perform a pregnancy test before first intake of the study medication. During intake of the study medication up to an adequate interval after intake of study medication a pregnancy test has to be performed, if clinical signs of pregnancy are present. In addition, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

…

Rationale:

Vitamin-K antagonists may be associated with teratogenic or embryotoxic effects.

9.1 Visit Schedule

Old version (28th July 2014):

The timing and assessment of the study are outlined in the following table:

Assessment	**Enrolment and randomisation**	**Ablation** Day 0 of FU	**Follow-up Month 3*** Day 76 to 104 of FU	**Phone call****
Signed ICF	x			
Check inclusion & exclusion criteria	x			
Physical examination / medical history	x	x	x	
Laboratory parameters (blood sample)	x		x	
INR measurement (blood sample)[1]	x	x	x	
12 lead ECG	x	x	x	
24-hours Holter ECG			x	
Transesophageal echocardiogram (TEE)[2]	(x)			
Transthoracic echocardiogram (TTE; after ablation procedure)		x		
ACT measurement (blood sample)		x		
MRI sub-study, only: brain MRI (3-48 hours after ablation)		x		
Cognitive function test (MoCA)	x		x	
Quality-of-Life (EQ-5D, SF-12)	x		x	
Karnofsky score	x		x	
Supply of study medication	x			
Return of study medication			x	
Adverse event (AE) / serious adverse event (SAE)		x	x	x**

[1] In patients randomised to VKA-group, only.

[2] TEE is a clinical decision by the treating physician: in case of clinical need to shorten the period until the ablation procedure, a TEE must be performed to exclude atrial thrombi

***** Time window ± 14 days (3 months = 90 days)

****** 30 days after discontinuation of study drug (SAEs to be collected, only

New version (15th December 2014):

The timing and assessment of the study are outlined in the following table:

Assessment	**Enrolment and randomisation**	**Ablation** Day 0 of FU	**Follow-up Month 3*** Day 76 to 104 of FU	**Phone call****
Signed ICF	x			
Check inclusion & exclusion criteria	x			
Pregnancy Test[1]	x			
Physical examination / medical history	x	x	x	
Clinical routine laboratory parameters (blood sample)[2]	x		x	
Extra blood sample for central lab	x		x	
INR measurement (blood sample)[3]	x	x	x	
12 lead ECG	x	x	x	
24-hours Holter ECG			x	
Transesophageal echocardiogram (TEE)[4]	(x)			
Transthoracic echocardiogram (TTE; after ablation procedure)		x		
ACT measurement (blood sample)		x		
MRI sub-study, only: brain MRI (3-48 hours after ablation)		x		
Cognitive function test (MoCA)	x		x	
Quality-of-Life (EQ-5D, SF-12)	x		x	
Karnofsky score	x		x	
Supply of study medication	x			
Return of study medication			x	
Adverse event (AE) / serious adverse event (SAE)		x	x	x**

[1] Pregnancy test at enrolment and randomisation in all women with childbearing potential who are randomised to VKA treatment. During intake of VKA up to an adequate interval after intake of study medication a pregnancy test has to be performed, if clinical signs of pregnancy are present.

[2] Blood sample not older than 7 days at the date of inclusion

[3] In patients randomised to VKA-group, only.

[4] TEE is a clinical decision by the treating physician: in case of clinical need to shorten the period until the ablation procedure, a TEE must be performed to exclude atrial thrombi

* Time window ± 14 days (3 months = 90 days)

** 30 days after discontinuation of study drug (SAEs to be collected, only)

Rationale: Vitamin-K antagonists may be associated with teratogenic or embryotoxic effects.

9.2 Baseline Visit

Old version (28th July 2014):

A patient meets eligibility criteria of the study if all inclusion and exclusion criteria are fulfilled as described in the sections above. Prior to any trial related procedure a signed informed consent form has to be obtained from every patient to be included in AXAFA and kept on file locally.

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent
- Document all inclusion and exclusion criteria
- Assess patients' medical history
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Perform a physical examination
- Obtain blood samples for laboratory assessments (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess quality-of-life (EQ-5D and SF-12 questionnaire)
- Assess performance status (Karnofsky score; refer to appendix V)
- Initiate study therapy and assure INR monitoring of therapy in case of VKA (refer to appendix III for instructions with regard to change of anticoagulants at start of study drug)
- In case of clinical need to shorten the period until the ablation procedure: perform TEE to exclude atrial thrombi

New version (15th December 2014):

A patient meets eligibility criteria of the study if all inclusion and exclusion criteria are fulfilled as described in the sections above. Prior to any trial related procedure a signed informed consent form has to be obtained from every patient to be included in AXAFA and kept on file locally.

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent
- Document all inclusion and exclusion criteria
- Perform pregnancy test in all women with childbearing potential who are randomised to VKA treatment
- Assess patients' medical history
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Perform a physical examination
- Obtain blood samples for laboratory assessments, liver function parameters before first intake of study drug have to be documented in addition (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess quality-of-life (EQ-5D and SF-12 questionnaire)
- Assess performance status (Karnofsky score; refer to appendix V)
- Initiate study therapy and assure INR monitoring of therapy in case of VKA (refer to appendix III for instructions with regard to change of anticoagulants at start of study drug)
- In case of clinical need to shorten the period until the ablation procedure: perform TEE to exclude atrial thrombi

Rationale: According to SmPC of apixaban.

9.3.1 Index ablation visit

Old version (28th July 2014):

…

Patients scheduled for ablation after exclusion of atrial thrombi by TEE can undergo catheter ablation less than 30 days after initiation of anticoagulant study therapy provided that continuous effective anticoagulation is ensured between the TEE and the ablation (i.e. for patients in the Xa-group at least two doses of apixaban immediately prior to ablation, for patients in the VKA-group at least one INR value ≥2 prior to ablation).

…

New version (15th December 2014):

…

Patients scheduled for ablation after exclusion of atrial thrombi by TEE can undergo catheter ablation less than 30 days after initiation of anticoagulant study therapy provided that continuous effective anticoagulation is ensured between the TEE and the ablation (i.e. for patients in the Xa-group at least two doses of apixaban immediately prior to ablation, for patients in the VKA-group at least one INR value ≥2.0 prior to ablation and thereafter no value <2.0 prior to ablation).

…

Rationale:

More detailed instructions for assessment of continuous effective anticoagulation prior to catheter ablation.

9.7 Blood Samples

Old version (28th July 2014):

Routine laboratory parameters are part of the screening procedures in order to verify the enrolment criteria and therefore not considered to be part of study related procedures. If these parameters can be assessed from a blood sample not older than 7 days at the date of inclusion, the blood sampling does not have to be repeated. Parameters include red blood cells, white blood cells, platelets, serum creatinine, aPTT, and INR. INR should be documented at least three times prior to the ablation visit in patients randomised to VKA therapy, and more often as clinically indicated. All INR measurements will be collected in the e-CRF. All blood parameters will be determined at the local laboratory of the study sites provided their analytical laboratories are certified. The e-CRF will collect laboratory values and information whether the value is normal or abnormal.

…

New version (15th December 2014):

Routine laboratory parameters are part of the screening procedures in order to verify the enrolment criteria and therefore not considered to be part of study related procedures. If these parameters can be assessed from a blood sample not older than 7 days at the date of inclusion, the blood sampling does not have to be repeated. Parameters include red blood cells, white blood cells, platelets, serum creatinine, aPTT, and INR. INR should be documented at least three times prior to the ablation visit in patients randomised to VKA therapy, and more often as clinically indicated. All INR measurements will be collected in the e-CRF. Before first intake of study drug liver function parameters have to be documented. All blood parameters will be determined at the local laboratory of the study sites provided their analytical laboratories are certified. The e-CRF will collect laboratory values and information whether the value is normal or abnormal.

…

Rationale:

According to SmPC of apixaban.

9.9 MRI Sub-Study

Old version (28th July 2014):

…

Patients might not be eligible to undergo MRI examination in case of any of these conditions:

- Problems lying on the back and holding still for 15 minutes
- Ever done metal grinding/welding as work or a hobby, or if ever seen a doctor about metal in the eyes
- Any metal in the body from an accident, gunshot, or military service wound
- Pregnancy
- Problems with claustrophobia.

…

New version (15th December 2014):

Patients might not be eligible to undergo MRI examination in case of any of these conditions:

- Problems lying on the back and holding still for 15 minutes
- Ever done metal grinding/welding as work or a hobby, or if ever seen a doctor about metal in the eyes
- Any metal in the body from an accident, gunshot, or military service wound
- Pregnancy
- Problems with claustrophobia
- Documented epilepsy
- Severe noise sensitivity or tinnitus
- Head trauma associated with commotio cerebri ≤ 6 weeks prior to study start

Rationale:

Completion of exclusion criteria for study related brain MRI.

15.1.1 Institutional Review Board/ Independent Ethics Committee (IRB / IEC)

Old version (28th July 2014):

It is intended to initially submit the study to the IRB / IEC of the national coordinator in Germany ("Leiter der klinischen Prüfung", LKP). After the primary approval has been achieved, submission to other national and local IRB/ IECs will be performed.

Provided this is not contradictory to national law, the local investigator is responsible for submitting an application to the appropriate IRB / IEC. Furthermore the local investigator is required to forward to the sponsor a copy of the written and dated approval or favourable opinion of the local IRB/ IEC signed by the chairman and including information on the composition of the IRB / IEC.

New version (15th December 2014):

It is intended to initially submit the study to the IRB / IEC of the national coordinator in Germany ("Leiter der klinischen Prüfung", LKP). After the primary approval has been achieved, submission to other national and local IRB/ IECs will be performed.

Provided this is not contradictory to national law, the principal investigator is responsible for submitting an application to the appropriate IRB / IEC. Furthermore the principal investigator is required to forward to the sponsor a copy of the written and dated approval or favourable opinion of the local IRB/ IEC signed by the chairman and including information on the composition of the IRB / IEC.

Rationale:

Harmonisation of wording.

18 References

Old version (28th July 2014):

…

46. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44(526):793-7.

47. Connolly S, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser S, Diaz R, Talajic M, Jun Z, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Meighem W, Lip GYH, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, o'Donnel M, Lawrence J, Lewis GD, Afzal R, Yusuf S. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806-17

New version (15th December 2014):

…

46. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44(526):793-7.

47. Connolly S, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser S, Diaz R, Talajic M, Jun Z, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Meighem W, Lip GYH, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, o'Donnel M, Lawrence J, Lewis GD, Afzal R, Yusuf S. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806-17

48. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm A J, Kirchhof P. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15:625-651.

Rationale:

New literature citation for more detailed information on the use of apixaban.

19 Signatures

Old version (28th July 2014):

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	**Signature**
…	
_____	_____ Signature local investigator
	_____ (Name local investigator; printed)

New version (15th December 2014):

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	**Signature**
…	
_____	_____ Signature principal investigator
	_____ (Name principal investigator; printed)

Rationale:

Harmonisation of wording.

Appendix VIII: List of strong inducers/inhibitors of P-gp and CYP3A4 which lead to contraindication for the combined use with apixaban (Practical Guide Use of NOACs (48)).

Old version (28th July 2014):

not available

New version (15th December 2014):

- Ketoconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Rifampicin
- St John's wort
- Carbamazephine
- Phenytoin
- Phenobarbital
- HIV protease inhibitors:
  - Ritonavir
  - Saquinavir
  - Indinavir
  - Lopinavir
  - Fosamprenavir
  - Atazanavir
  - Tipranavir
  - Darunavir

Rationale:

More detailed information on the use of apixaban

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	**Signature**
_____	_____ Paulus Kirchhof (chief international investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

_____	_____ Signature principal investigator
	_____ (Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	Signature
Dec 16 2014	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
Dec 16, 2014	Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	**Signature**
	Paulus Kirchhof (chief international investigator)
January 2nd, 2015	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	**Signature**
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
12/16/14	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	**Signature**
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
17.12.2014	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	**Signature**
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
05.01.2015	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

05.01.2015	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	**Signature**
_____	_____ Paulus Kirchhof (chief international investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
18.12.2014	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

_____	_____ Signature principal investigator
	_____ (Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	Signature
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
12/23/2014	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	**Signature**
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
23/12/2014	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to it.

Date	Signature
_____	_____ Paulus Kirchhof (chief international investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
16 Dec 2014	Hussein R. Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)

The undersigned has read this protocol amendment and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

_____ _____ Signature principal investigator

_____ (Name principal investigator; printed)

AMENDMENT
TO THE
CLINICAL TRIAL PROTOCOL

AXAFA - AFNET 5

*A*nticoagulation using the direct factor *X*a inhibitor apixaban during *A*trial *F*ibrillation catheter *A*blation: Comparison to vitamin K antagonist therapy.

An Investigator-driven, **P**rospective, Parallel-group, **R**andomised, **O**pen,
Blinded Outcom**e** Assessment (PROBE), Multi-centre Trial
to determine the optimal anticoagulation therapy for patients undergoing catheter ablation of atrial fibrillation

EudraCT number: 2014-002442-45
NCT number: NCT02227550
ISRCTN87711003

Responsible Sponsor:
Kompetenznetz Vorhofflimmern e.V. (AFNET e.V.)
[German Atrial Fibrillation Competence NETwork]
Mendelstraße 11
48149 Münster, Germany

Date of amendment:

08th January 2015
(amending protocol version 28th July 2014,
amending amendment version 15th December 2014)

Prepared by Bianca-Maria Klein, CRI

8 Adverse Event Reporting

Old version (15th December 2014):

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but only "Adverse Events of Special Interest" (see 8.1) and adverse events judged as medically important by the Investigator, thus meeting criteria of seriousness (see 8.2).

New version (8th January 2015):

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but

a) "Adverse Events of Special Interest" (see 8.1),
b) adverse events judged as medically important by the Investigator, and
c) serious adverse events (see 8.2).

Adverse events a) to c) will be part of the safety analysis (see 12.1.3).

Rationale:

Clarification to assure that adverse events judged as medically important events have to be documented, even if they do not meet criteria of “Adverse Events of Special Interest”.

12.1.3 Safety analysis

Old version (28th July 2014):

Safety data include adverse events as defined in section 8.1, primary safety endpoints, and data for other safety evaluations. Safety data will be collected on all randomised patients (i.e., ITT cohort) in this study.

The primary safety outcome in this study is a composite of all-cause death, stroke, cardiac tamponade and major bleeding events which will be analysed using time-to-event methodology as described in Section 12.1.1. Similar analyses and summary statistics will be provided for the components of this safety composite endpoint.

Serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment related SAEs will be summarized under each treatment group, by system organ class (SOC) and preferred term (PT). Comparisons between treatment groups will be made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term) of special interest. SAEs will be summarized by severity and relation to study treatment received.

New version (8th January 2015):

Safety data include adverse events as defined in section 8 and 8.1, primary safety endpoints, and data for other safety evaluations. Safety data will be collected on all randomised patients (i.e., ITT cohort) in this study.

The primary safety outcome in this study is a composite of all-cause death, stroke, cardiac tamponade and major bleeding events which will be analysed using time-to-event methodology as described in Section 12.1.1. Similar analyses and summary statistics will be provided for the components of this safety composite endpoint.

Adverse events as defined in section 8 and 8.1 and serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment related SAEs will be summarized under each treatment group, by system organ class (SOC) and preferred term (PT). Comparisons between treatment groups will be made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term) of special interest. SAEs will be summarized by severity and relation to study treatment received.

Rationale:

Clarification to assure that adverse events judged as medically important events are included in the safety analysis.

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	**Signature**
_____	_____ Paulus Kirchhof (chief international investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature local investigator
	_____ (Name local investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	**Signature**
8 Jan 2015	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)
	Signature local investigator
	(Name local investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
January, 13 2015 01/11/15	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
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	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)
	Signature local investigator
	(Name local investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
1/8/15	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
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	Hussein Al-Khalidi (study statistician)
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Date	Signature
_____	_____ Paulus Kirchhof (chief international investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
9.1.2015	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature local investigator
	_____ (Name local investigator; printed)

CHARITÉ
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Signatures

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Date	Signature
_____	_____ Paulus Kirchhof (chief international investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
12.01.2015	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature local investigator
	_____ (Name local investigator; printed)

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	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
09/1-15	Jens Cosedis Nielsen
	Jonathan Piccini
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	Hussein Al-Khalidi (study statistician)
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	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
1/9/2015	Jonathan Piccini
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	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
9/1/2015	Lluis Mont
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_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
Jan 9, 2015	H. R. Al-Khalidi Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature local investigator
	_____ (Name local investigator; printed)

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Date	Signature
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	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
Jan 8.2015	Günter Breithardt (sponsor representative)
	Signature local investigator
	(Name local investigator; printed)

AMENDMENT
TO THE
CLINICAL TRIAL PROTOCOL

AXAFA - AFNET 5

*A*nticoagulation using the direct factor *X*a inhibitor apixaban during *A*trial *F*ibrillation catheter *A*blation: Comparison to vitamin K antagonist therapy.

An Investigator-driven, **P**rospective, Parallel-group, **R**andomised, **O**pen,
Blinded Outcom**e** Assessment (PROBE), Multi-centre Trial
to determine the optimal anticoagulation therapy for patients undergoing catheter ablation of atrial fibrillation

EudraCT number: 2014-002442-45
NCT number: NCT02227550
ISRCTN87711003

Responsible Sponsor:
Kompetenznetz Vorhofflimmern e.V. (AFNET e.V.)
[German Atrial Fibrillation Competence NETwork]
Mendelstraße 11
48149 Münster, Germany

Date of amendment:

20th February 2015
(amending protocol version 28th July 2014,
amending amendment version 15th December 2014,
amending amendment version 08th January 2015)

Prepared by Bianca-Maria Klein, CRI

8.3 Recording and Reporting Serious Adverse Events

Old version (28th July 2014):

All SAEs, whether related or unrelated to investigational product, must be reported expeditiously to the CRO through the SAE section of the e-CRF within one working day of becoming aware of the event.

New version (20th February 2015):

All SAEs, whether related or unrelated to investigational product, must be reported expeditiously to the CRO through the SAE section of the e-CRF within 24 hours of becoming aware of the event.

Rationale:

Clarification according to the EC guidance document 2011/C 172/01 (CT-3), Section 4.3, paragraph 29.

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	**Signature**
21 Feb 2015	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)
	Signature local investigator
	(Name local investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
	Paulus Kirchhof (chief international investigator)
February 20th, 2015	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
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	(Name local investigator; printed)

Signatures

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Date	**Signature**
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
2/20/15	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)
	Signature local investigator
	(Name local investigator; printed)

Signatures

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Date	Signature
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
20.2.2015	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)
	Signature local investigator
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Date	Signature
	Paulus Kirchhof (chief international investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
2015-02-23	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)
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_____	_____ Paulus Kirchhof (chief international investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
24. FEB 2015	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature local investigator
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	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
2/20/2015	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Günter Breithardt (sponsor representative)
	Signature local investigator
	(Name local investigator; printed)

Signatures

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Date	Signature
	Paulus Kirchhof (chief international investigator)
February 20th, 2015	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
23/2/2015	Lluis Mont
	Hussein Al-Khalidi (study statistician)
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_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
Feb 20, 2015	Hussein R. Al-Khalidi Hussein Al-Khalidi (study statistician)
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature local investigator
	_____ (Name local investigator; printed)

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	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
Feb 20, 2015	Günter Breithardt (sponsor representative)
	Signature local investigator
	(Name local investigator; printed)

AMENDMENT
TO THE
CLINICAL TRIAL PROTOCOL

AXAFA - AFNET 5

Anticoagulation using the direct factor **X**a inhibitor apixaban during **A**trial **F**ibrillation catheter **A**blation: Comparison to vitamin K antagonist therapy.

An Investigator-driven, **P**rospective, Parallel-group, **R**andomised, **O**pen,
Blinded Outcom**e** Assessment (PROBE), Multi-centre Trial
to determine the optimal anticoagulation therapy for patients undergoing catheter ablation of atrial fibrillation

EudraCT number: 2014-002442-45
NCT number: NCT02227550
ISRCTN87711003

Responsible Sponsor:
Kompetenznetz Vorhofflimmern e.V. (AFNET)
[Atrial Fibrillation NETwork]
Mendelstraße 11
48149 Münster, Germany

Version of amendment:

21st July 2016
(amending protocol version 28th July 2014 valid in Belgium, Denmark, Italy,
amending protocol version 08th January 2015 valid in Germany, the Netherlands,
amending protocol version 20th February 2015 valid in Austria, Great Britain, Spain, the USA)

Prepared by Bianca-Maria Klein, CRI

Preamble

An amendment version 15.12.2014 was submitted, but never approved, due to findings of a central ethics committee. This version was never in force in any participating country.

Abbreviations

AT = Austria
BE = Belgium
DK = Denmark
ES = Spain
DE = Germany
GB = Great Britain
IT = Italy
NL = The Netherlands
US = The United States of America

Address and name of the Sponsor

Old version 28.07.2014 valid in BE, DK, IT:

Kompetenznetz Vorhofflimmern e.V. (AFNET e.V.)
[German Atrial Fibrillation Competence NETwork]
Albert-Schweitzer-Campus 1, Gebäude D11
Domagkstraße 11
48149 Münster, Germany
Email: info@kompetenznetz-vorhofflimmern.de
Phone: +49-251-834 5340
Fax: +49-251-834 5343

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Kompetenznetz Vorhofflimmern e.V. (AFNET e.V.)
[German Atrial Fibrillation Competence NETwork]
Mendelstraße 11
48149 Münster, Germany
Email: info@kompetenznetz-vorhofflimmern.de
Phone: +49-251-834 5340
Fax: +49-251-834 5343

New version:

Kompetenznetz Vorhofflimmern e.V. (AFNET ~~e.V.~~)
[~~German~~ Atrial Fibrillation ~~Competence~~ NETwork]
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48149 Münster, Germany
Email: info@kompetenznetz-vorhofflimmern.de
Phone: +49-251-~~834 5340~~ 980 1340
Fax: +49-251-~~834 5343~~ 980 1349

Rationale:

Administrative change.

1 Summary

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

STUDY POPULATION - Expected number of sites

Approximately 25 ablation sites in Europe and 25 in the USA. All study sites will be routinely performing catheter ablation of AF.

INVESTIGATIONAL INTERVENTIONS

Apixaban will be given 5 mg twice daily and compared to oral anticoagulation using the locally used VKA (aiming for an international normalized ratio (INR) of 2.0-3.0). The apixaban dose will be reduced to 2.5 mg twice daily at the time of randomisation according to the approved label. Study medication has to be administered effectively for at least 30 days prior to the planned catheter ablation procedure or during a shorter interval in patients undergoing a transesophageal echocardiogram (TEE) with exclusion of atrial thrombi. Study medication has to be effectively continued for three months after the ablation procedure.

STATISTICAL CONSIDERATIONS

With respect to the primary outcome, the study is exploratory. The primary analysis is in the modified intention-to-treat population, consisting of all randomised patients who received at least one dose of study treatment and an ablation procedure for AF. Event rates at the end of follow-up will be compared between groups. An occurrence of the primary parameter is expected in 17-20% of the patients. The sample size will allow to detect a non-inferiority between the two random groups with a margin of 7.5%.

Safety analysis will be performed with all patients randomised.

New version:

STUDY POPULATION - Expected number of sites

Approximately 50 ablation sites in Europe and ~~25~~ in the USA. All study sites will be routinely performing catheter ablation of AF.

INVESTIGATIONAL INTERVENTIONS

Apixaban will be given 5 mg twice daily and compared to oral anticoagulation using the locally used VKA (aiming for an international normalized ratio (INR) of 2.0-3.0). The apixaban dose will be reduced to 2.5 mg twice daily at the time of randomisation in applicable patients according to the approved label. Study medication has to be administered effectively for at least 30 days prior to the planned catheter ablation procedure or during a shorter interval in patients undergoing a transesophageal echocardiogram (TEE) with exclusion of atrial thrombi. Study medication has to be effectively continued for three months after the ablation procedure.

STATISTICAL CONSIDERATIONS

~~With respect to the primary outcome, the study is exploratory.~~ The primary analysis is in the modified intention-to-treat population, consisting of all randomised patients who received at least one dose of study treatment and an ablation procedure for AF. Event rates at the end of follow-up will be compared between

groups. An occurrence of the primary parameter is expected in 17-20% of the patients. The sample size will allow to detect a non-inferiority between the two random groups with a margin of 7.5%.

Safety analysis will be performed with all patients randomised.

Rationale:

The expected regional distribution of participating sites has to be adjusted. More sites will participate in Europe and less in the USA.

More precision is added to clarify that the apixaban dose will be reduced to 2.5 mg only for patients, who fulfil the requirements of dose reduction according to the dosage recommendation in the SmPC.

Due to objections by the central Ethics Committee for Italy “Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo” and the local Italian Ethics Committee “Comitato Etico per la Sperimentazione di Padova”, it was agreed with the central Ethics Committee for Italy “Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo” that the expression “exploratory” will no longer be applied in the entire study protocol.

Non-substantial change.

2 Abbreviations

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Not available

New version:

CIOMS Council for International Organization of Medical Sciences

ICE Intracardiac echocardiogram

Rationale:

Addition of abbreviation.

It was agreed by the Steering Committee, that the use of transthoracic echocardiogram (TTE) **or** intracardiac echocardiogram (ICE) is possible for checking for pericardial effusion after the ablation procedure, because intracardiac echocardiography (ICE) is an emerging technique for imaging of intracardiac structures in clinical routine and may serve as an alternative for the transoesophageal approach (see Dairywala IT, Li P, Liu Z, et al. Catheter-based interventions guided solely by a new phased-array intracardiac imaging catheter: in vivo experimental studies. J Am Soc Echocardiogr 2002;15:150–8.).

Non-substantial change.

5 Study Design

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

The trial tests whether peri-procedural anticoagulation therapy using the novel, oral, direct factor Xa inhibitor apixaban is a safe alternative to VKA therapy for patients undergoing catheter ablation of AF.

New version:

The trial tests whether peri-procedural anticoagulation therapy using the novel, oral, direct factor Xa inhibitor apixaban is not less safe than VKA therapy for patients undergoing catheter ablation of AF.

Rationale:

Due to objections by the central Ethics Committee for Italy “Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo” and the local Italian Ethics Committee “Comitato Etico per la Sperimentazione di Padova”, it was agreed with the central Ethics Committee for Italy “Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo” that the expression “safe alternative” will be replaced by “not less safe” in the entire study protocol.

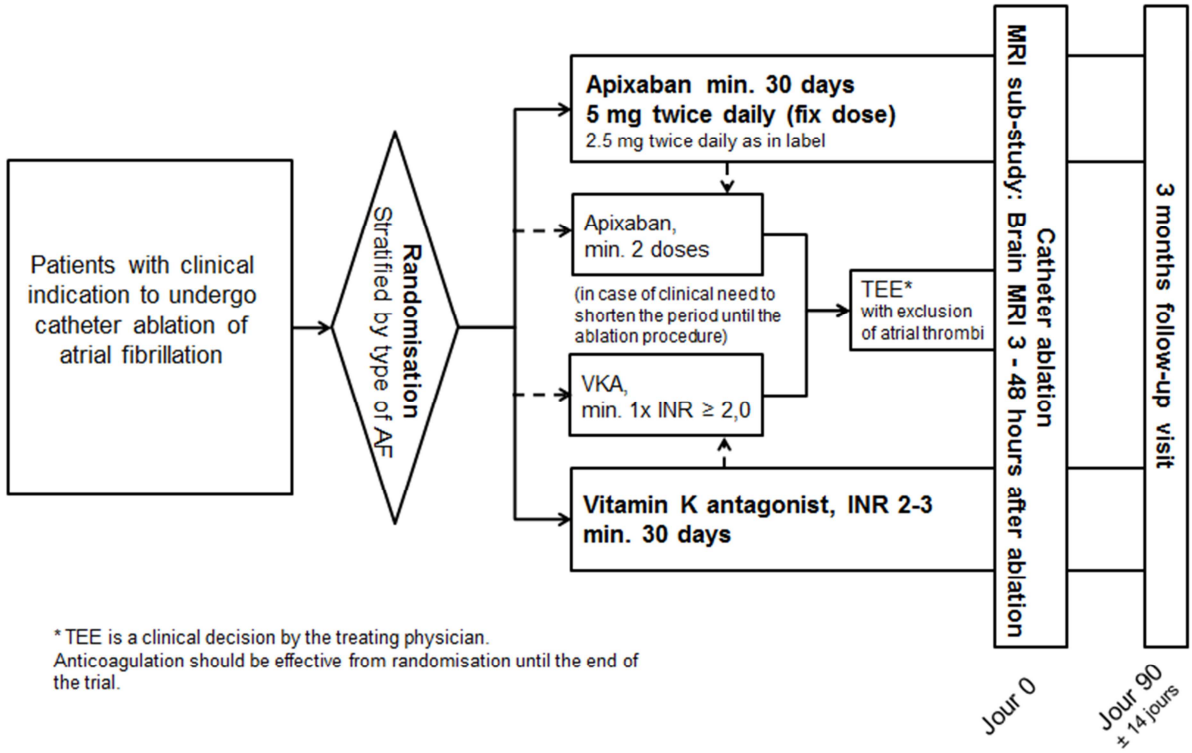
Non-substantial change.

5.1 Flow Chart

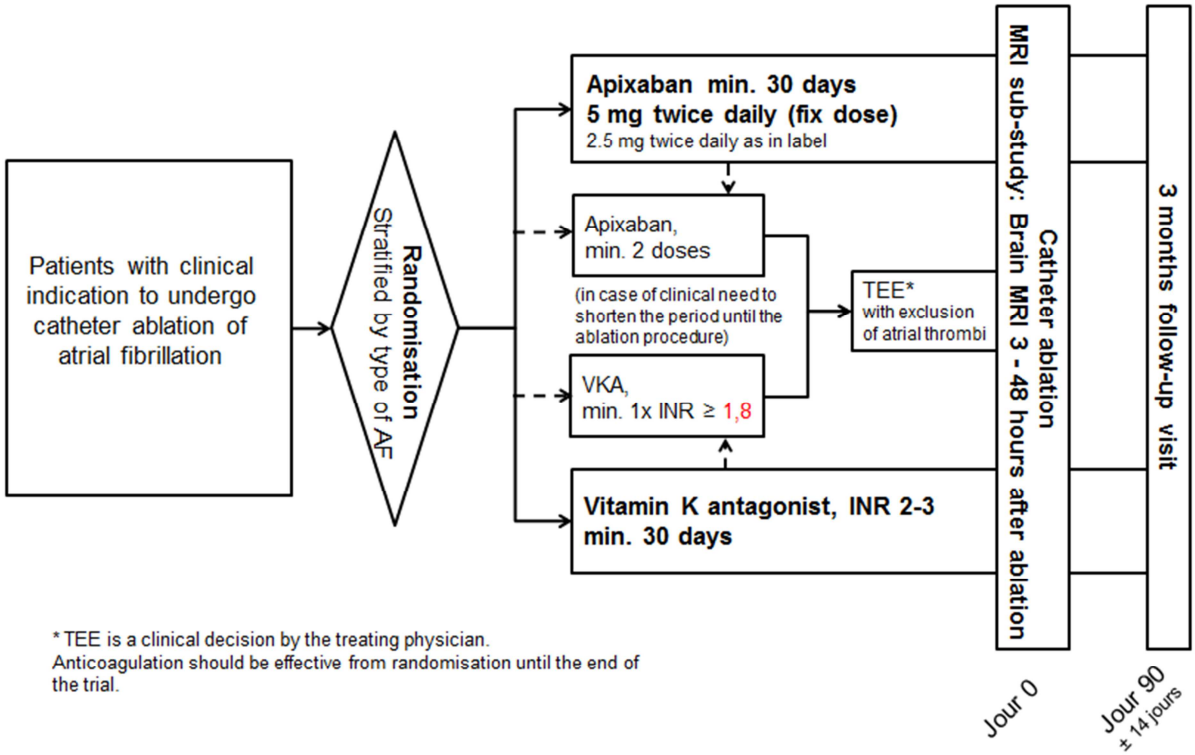
Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:



New version:



Rationale:

As in clinical routine an INR value ≥2 prior to catheter ablation is rarely achieved, the reduction of the minimum value of the last INR required prior to the index catheter ablation to ≥1.8 represents clinical practice better and is still safe as described.

Non-substantial change.

6.2.3 Exclusion criteria

Old version 28.07.2014 valid in BE, DK, IT:

General exclusion criteria

[…]

E8. Coadministration with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) or strong dual inducers of CYP3A4 and P-gp

Exclusion criteria related to a cardiac condition

[…]

Not available

Exclusion criteria based on laboratory abnormalities

E14. Severe chronic kidney disease with an estimated glomerular filtration rate (GFR) < 15 ml/min

New version (and versions 08.01.2015 valid in DE, NL, and 20.02.2015 valid in AT, ES, GB, US):

General exclusion criteria

[…]

E8. Coadministration with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) or strong dual inducers of CYP3A4 and P-gp (Appendix VIII)

Exclusion criteria related to a cardiac condition

[…]

E14. Documented atrial thrombi less than 3 months prior to randomisation

Exclusion criteria based on laboratory abnormalities

E15. Severe chronic kidney disease with an estimated glomerular filtration rate (GFR) < 15 ml/min

Rationale:

Addition of reference to appendix.

More detailed instructions for exclusion of patients before randomisation to better reflect clinical practice. Implicitly included in the old version as given in the medical guidelines of catheter ablation of atrial fibrillation.

Substantial change.

7 Therapy

Old version 28.07.2014 valid in BE, DK, IT:

Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation. Ablation can be performed earlier when atrial thrombi have been excluded by a clinically indicated TEE. After TEE continuous effective anticoagulation must be ensured until the end of the trial.

New version (and versions 08.01.2015 valid in DE, NL, and 20.02.2015 valid in AT, ES, GB, US:

Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation. Ablation can be performed earlier when atrial thrombi have been excluded by a clinically indicated TEE. A TEE performed within 6 hours prior to randomisation is considered valid. After TEE continuous effective anticoagulation must be ensured until the end of the trial.

Rationale:

More detailed instructions for inclusion of patients before randomisation to better reflect clinical routine procedures.

Non-substantial change.

7.1.2 Compliance with apixaban, dispensing and return of apixaban

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Prior to dispensing study medication to a patient, the investigator will document the patient's ID (automatically allocated by MARVIN), study site ID and the date of dispensing on the label. At the enrolment visit every patient randomised to Xa group will be handed out two bottles apixaban (5 mg or 2.5 mg depending on the patient's condition as described above). The consistent intake of apixaban is crucial for sufficient efficacy since no INR or other coagulation parameter monitoring will be performed in contrast to the VKA group. Patients will be asked to bring all unused or partly-used medication at each visit. The investigator will assess effective anticoagulation with apixaban by questioning the patient about medication intake and by pill count during the ablation visit and at the end of follow-up.

New version:

Prior to dispensing study medication to a patient, the investigator will document the patient's ID (automatically allocated by MARVIN), study site ID and the date of dispensing on the label. First intake of study medication needs to be ensured at study enrolment (taking into consideration the change management instructions). Every patient randomised to Xa group will be handed out two bottles of apixaban (5 mg or 2.5 mg depending on the dosage recommendations described above). The consistent intake of apixaban is crucial for sufficient efficacy since no INR or other coagulation parameter monitoring will be performed in contrast to the VKA group. Patients will be asked to bring all unused, ~~or~~ partly-used, or empty medication at each visit. The investigator will assess effective anticoagulation with apixaban by questioning the patient about medication intake and by pill count during the ablation visit and at the end of follow-up.

Rationale:

A more concise description of the first intake of study medication is added in order to avoid misunderstandings.

A more concise description of the visit procedures assuring the understanding that even empty bottles need to be weight and verified.

Non-substantial change.

7.2 VKA group

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Patients randomised to the VKA group will receive oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. VKAs will be prescribed as in clinical routine and dispensed by local hospital pharmacy. Costs will be reimbursed by sponsor. VKA therapy will be monitored by INR measurements according to applicable medical guidelines and to local routine policy, a minimum of three INR measurements is mandatory. The frequency and values of INR measurements will be collected in the e-CRF. Effective anticoagulation will be assessed by questioning the patient about medication intake and by INR measurements which need to be consistent within the therapeutic range (INR ≥2.0) in at least 30 days prior to catheter ablation. Any INR <2 resets this interval to 0 days or a TEE may be performed for exclusion of thrombi. In the latter case, there must be at least one INR value ≥2 prior to catheter ablation. It is recommended that the ablation procedure is performed while the INR is between 2 and 2.5.

Patients undergoing TEE with exclusion of atrial thrombi prior to the ablation procedure will be handled according to local routine, which may include heparin or low molecular weight heparins to achieve sufficient anticoagulation, e.g. in the initiation period of VKA therapy.

New version:

Patients randomised to the VKA group will receive oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. First intake of study medication needs to be ensured at study enrolment (taking into consideration the change management instructions). VKAs will be prescribed as in clinical routine and dispensed by local hospital pharmacy. Costs will be reimbursed by sponsor. VKA therapy will be monitored by INR measurements according to applicable medical guidelines and to local routine policy~~, a minimum of three INR measurements is mandatory~~. The frequency and all values of INR measurements will be collected in the e-CRF. A minimum of three INR measurements is mandatory between the baseline visit and the ablation visit, and between the index ablation visit and the 3 month follow-up visit. Effective anticoagulation will be assessed by questioning the patient about medication intake and by INR measurements which need to be consistent within the therapeutic range (INR ≥2.0) in at least 30 days prior to catheter ablation. Any INR <2 within the 30 days period prior to catheter ablation resets this interval to 0 days or a TEE may be performed for exclusion of thrombi (49). If atrial thrombi were excluded by TEE, or all measured INR values were ≥2.0 for 30 days, the last measured INR value prior to index ablation needs to be ≥1.8. ~~In the latter case, there must be at least one INR value ≥2 prior to catheter ablation. It is recommended that the ablation procedure is performed while the INR is between 2 and 2.5.~~

~~Patients undergoing TEE with exclusion of atrial thrombi prior to the ablation procedure will be handled according to local routine, which may include heparin or low molecular weight heparins to achieve sufficient anticoagulation, e.g. in the initiation period of VKA therapy.~~

Rationale:

A more concise description of the first intake of study medication is added in order to avoid misunderstandings.

To ensure continuous anticoagulation, documentation of all INR measurements (minimum of three) is necessary.

As in clinical routine an INR value ≥2 prior to catheter ablation is rarely achieved, the reduction of the minimum value of the last INR required prior to the index catheter ablation to ≥1.8 represents clinical practice better and is still safe as described.

Deletion of the last sentence, as the procedures described correspond to clinical routine and, therefore, this is redundant information.

Non-substantial change.

8 Adverse Event Reporting

Old version 28.07.2014 valid in BE, DK, IT:

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but only "Adverse Events of Special Interest" which are defined as described in section 8.1.

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but

a) "Adverse Events of Special Interest" (see 8.1),
b) adverse events judged as medically important by the Investigator, and
c) serious adverse events (see 8.2).

Adverse events a) to c) will be part of the safety analysis (see 12.1.3).

New version:

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but

a) "Adverse Events of Special Interest" (see 8.1), and
b) “Serious Adverse Events”, including adverse events judged as medically important by the investigator (see 8.2).

Adverse events a) and b) will be part of the safety analysis (see 12.1.3).

Rationale:

Clarification according to the definition of “Serious Adverse Events”: adverse events judged as medically important events meet the criteria of seriousness.

Non-substantial change.

8.2.1 Potential Drug-Induced Liver Injury (DILI)

Old version 28.07.2014 valid in BE, DK, IT:

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

New version (and versions 08.01.2015 valid in DE, NL, and 20.02.2015 valid in AT, ES, GB, US:

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event by reporting the liver function parameters. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Rationale:

Text adapted to SmPC of apixaban.

Non-substantial change.

8.2.2 Pregnancy

Old version 28.07.2014 valid in BE, DK, IT:

It is reminded that all means should be put in place to prevent pregnancy during the study. Before study enrolment, women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. In addition, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

It is reminded that all means should be put in place to prevent pregnancy during the study. Before study enrolment, women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Women of childbearing potential are required to perform a pregnancy test before first intake of the study medication. During intake of the study medication up to an adequate interval after intake of study medication a pregnancy test has to be performed, if clinical signs of pregnancy are present. In addition, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

New version:

It is reminded that all means should be put in place to prevent pregnancy during the study. Before study enrolment, women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Women of childbearing potential are required to perform a pregnancy test before first intake of the study medication. If clinical signs of pregnancy are present during intake of the study medication and up to an adequate interval after intake of study medication, a pregnancy test has to be performed. In countries where legally required (e.g. Austria) monthly pregnancy tests need to be performed for all women of childbearing potential. In addition, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Rationale:

Clarification to assure adequate pregnancy test procedures during intake of study medication in women of childbearing potential, as study medication may be associated with teratogenic or embryotoxic effects. There are no data yet on the effects of apixaban on pregnancy and lactation.

Substantial change.

8.2.2 Pregnancy

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

If, following initiation of the investigational product, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. The investigator must immediately notify the CRO of this event and record the pregnancy on the Pregnancy Surveillance Form in the e-CRF. Initial information on a pregnancy must be reported immediately to the CRO, and the outcome information provided once the outcome is known.

New version:

If, following initiation of the investigational product, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. The investigator must immediately notify the CRO of this event and record the pregnancy on the Pregnancy Surveillance Form ~~in the e-CRF~~. Initial information on a pregnancy must be reported immediately to the CRO, and the outcome information provided once the outcome is known.

Rationale:

Result of pregnancy tests will not be documented as a single item in the eCRF, but on a separate “Pregnancy Surveillance Form”, filed in the Investigator Site File.

Non-substantial change.

8.3. Recording and Reporting Serious Adverse Events

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

All SAEs, whether related or unrelated to investigational product, must be reported expeditiously to the CRO through the SAE section of the e-CRF within one working day of becoming aware of the event.

New version (and version 20.02.2015 valid in AT, ES, GB, US):

All SAEs, whether related or unrelated to investigational product, must be reported expeditiously to the CRO through the SAE section of the e-CRF within 24 hours of becoming aware of the event.

Rationale:

Clarification according to the EC guidance document 2011/C 172/01 (CT-3), Section 4.3, paragraph 29.

Non-substantial change.

9.1 Visit Schedule

Old version 28.07.2014 valid in BE, DK, IT:

Assessment	**Enrolment and randomisation**	**Ablation** Day 0 of FU	**Follow-up Month 3*** Day 76 to 104 of FU	**Phone call****
Signed ICF	x			
Check inclusion & exclusion criteria	x			
Physical examination / medical history	x	x	x	
Laboratory parameters (blood sample)	x		x	
INR measurement (blood sample)[1]	x	x	x	
12 lead ECG	x	x	x	
24-hours Holter ECG			x	
Transesophageal echocardiogram (TEE)[2]	(x)			
Transthoracic echocardiogram (TTE; after ablation procedure)		x		
ACT measurement (blood sample)		x		
MRI sub-study, only: brain MRI (3-48 hours after ablation)		x		
Cognitive function test (MoCA)	x		x	
Quality-of-Life (EQ-5D, SF-12)	x		x	
Karnofsky score	x		x	
Supply of study medication	x			
Return of study medication			x	
Adverse event (AE) / serious adverse event (SAE)		x	x	x**

[1] In patients randomised to VKA-group, only.

[2] TEE is a clinical decision by the treating physician: in case of clinical need to shorten the period until the ablation procedure, a TEE must be performed to exclude atrial thrombi

***** Time window ± 14 days (3 months = 90 days)

****** 30 days after discontinuation of study drug (SAEs to be collected, only

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Assessment	**Enrolment and randomisation**	**Ablation** Day 0 of FU	**Follow-up Month 3*** Day 76 to 104 of FU	**Phone call****
Signed ICF	x			
Check inclusion & exclusion criteria	x			
Pregnancy Test[1]	x			
Physical examination / medical history	x	x	x	
Clinical routine laboratory parameters (blood sample)[2]	x		x	
Extra blood sample for central lab	x		x	
INR measurement (blood sample)[3]	x	x	x	
12 lead ECG	x	x	x	
24-hours Holter ECG			x	
Transesophageal echocardiogram (TEE)[4]	(x)			
Transthoracic echocardiogram (TTE; after ablation procedure)		x		
ACT measurement (blood sample)		x		
MRI sub-study, only: brain MRI (3-48 hours after ablation)		x		
Cognitive function test (MoCA)	x		x	
Quality-of-Life (EQ-5D, SF-12)	x		x	
Karnofsky score	x		x	
Supply of study medication	x			
Return of study medication			x	
Adverse event (AE) / serious adverse event (SAE)		x	x	x**

[1] Pregnancy test at enrolment and randomisation in all women with childbearing potential who are randomised to VKA treatment. During intake of VKA up to an adequate interval after intake of study medication a pregnancy test has to be performed, if clinical signs of pregnancy are present.

[2] Blood sample not older than 7 days at the date of inclusion

[3] In patients randomised to VKA-group, only.

[4] TEE is a clinical decision by the treating physician: in case of clinical need to shorten the period until the ablation procedure, a TEE must be performed to exclude atrial thrombi

* Time window ± 14 days (3 months = 90 days)

** 30 days after discontinuation of study drug (SAEs to be collected, only)

New version:

Assessment	**Enrolment and randomisation**	**Ablation** Day 0 of FU	**Follow-up Month 3*** Day 76 to 104 of FU	**Phone call****
Signed ICF	x			
Check inclusion & exclusion criteria	x			
Pregnancy Test[1]	x	x[1]	x[1]	
Physical examination / medical history	x	x	x	
Clinical routine laboratory parameters (blood sample)[2]	x		x	
Extra blood sample for central lab	x		x	
INR measurement (blood sample)[3]	x	x	x	
12 lead ECG	x	x	x	
24-hours Holter ECG			x	
Transesophageal echocardiogram (TEE)[4]	(x)			
Transthoracic echocardiogram (TTE; after ablation procedure) or Intracardiac echocardiogram (ICE; after ablation procedure)[5]		x		
ACT measurement (blood sample)		x		
MRI sub-study, only: brain MRI (3-48 hours after ablation)		x		
Cognitive function test (MoCA)	x		x	
Quality-of-Life (EQ-5D, SF-12)	x		x	
Karnofsky Scale	x		x	
Modified Rankin Scale	x	x	x	
Supply of study medication	x			
Return of study medication			x	
Adverse event (AE) / serious adverse event (SAE)		x	x	x**

[1] Pregnancy test at enrolment and randomisation in all women with childbearing potential ~~who are randomised to VKA treatment~~. Where legally required (e.g. Austria) monthly pregnancy tests need to be performed for all women of childbearing potential.

[2] Blood sample not older than 7 days at the date of inclusion

[3] In patients randomised to VKA-group, only.

[4] TEE is a clinical decision by the treating physician: in case of clinical need to shorten the period until the ablation procedure, a TEE must be performed to exclude atrial thrombi

[5] Check for pericardial effusion by transthoracic echocardiogram (TTE) or intracardiac echocardiogram (ICE) performed after ablation procedure.

***** Time window ± 14 days (3 months = 90 days)
** 30 days after discontinuation of study drug (SAEs to be collected, only)

Rationale:

Update of the Visit Schedule Table to changes (listed and explained in previous sections) to the protocol text.

Non-substantial change.

9.2 Baseline Visit

Old version 28.07.2014 valid in BE, DK, IT:

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent
- Document all inclusion and exclusion criteria
- Assess patients' medical history
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Perform a physical examination
- Obtain blood samples for laboratory assessments (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess quality-of-life (EQ-5D and SF-12 questionnaire)
- Assess performance status (Karnofsky score; refer to appendix V)
- Initiate study therapy and assure INR monitoring of therapy in case of VKA (refer to appendix III for instructions with regard to change of anticoagulants at start of study drug)
- In case of clinical need to shorten the period until the ablation procedure: perform TEE to exclude atrial thrombi

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent
- Document all inclusion and exclusion criteria
- Perform pregnancy test in all women with childbearing potential who are randomised to VKA treatment
- Assess patients' medical history
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Perform a physical examination
- Obtain blood samples for laboratory assessments, liver function parameters before first intake of study drug have to be documented in addition (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess quality-of-life (EQ-5D and SF-12 questionnaire)
- Assess performance status (Karnofsky score; refer to appendix V)
- Initiate study therapy and assure INR monitoring of therapy in case of VKA (refer to appendix III for instructions with regard to change of anticoagulants at start of study drug)
- In case of clinical need to shorten the period until the ablation procedure: perform TEE to exclude atrial thrombi

New version:

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent
- Document all inclusion and exclusion criteria
- Perform pregnancy test in all women with childbearing potential ~~who are randomised to VKA treatment~~
- Assess patients' medical history
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Perform a physical examination
- Obtain blood samples for laboratory assessments, liver function parameters before first intake of study drug have to be documented in addition (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess quality-of-life (EQ-5D and SF-12 questionnaire)
- Assess performance status (Karnofsky Scale; refer to appendix V)
- Assess degree of disability (modified Rankin Scale; refer to appendix IX)
- Initiate study therapy and assure INR monitoring of therapy in case of VKA (refer to appendix III for instructions with regard to change of anticoagulants at start of study drug)
- In case of clinical need to shorten the period until the ablation procedure: perform TEE to exclude atrial thrombi

Rationale:

Update of the visit procedures to changes (listed and explained in previous section) to the protocol text.

Non-substantial change.

9.3.1 Index ablation visit

Old version 28.07.2014 valid in BE, DK, IT:

Patients scheduled for ablation without exclusion of atrial thrombi by TEE will be treated for at least 30 days with the oral anticoagulant of their randomisation group prior to the ablation visit. This period can be longer according to clinical needs (e.g. scheduling and waiting list requirements, or insufficient or insufficiently documented oral anticoagulation). Effective anticoagulation (i.e. continuous medication intake in patients randomised to Xa, and INR between 2.0-3.0 in patients randomised to VKA) needs to be present for 30 days prior to ablation. Ineffective anticoagulation (e.g. failure to take medication in Xa group or INR <2.0 in VKA group) resets this interval to 0 days. Failure to take apixaban is defined as having missed more than one dose per week. In this case a TEE can be performed to avoid reset of anticoagulation interval to 0 days.

[…]

Not available

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Patients scheduled for ablation after exclusion of atrial thrombi by TEE can undergo catheter ablation less than 30 days after initiation of anticoagulant study therapy provided that continuous effective anticoagulation is ensured between the TEE and the ablation (i.e. for patients in the Xa-group at least two doses of apixaban immediately prior to ablation, for patients in the VKA-group at least one INR value ≥2.0 prior to ablation and thereafter no value <2.0 prior to ablation). Effective anticoagulation (i.e. continuous medication intake in patients randomised to Xa, and INR between 2.0-3.0 in patients randomised to VKA) needs to be present for 30 days prior to ablation. Ineffective anticoagulation (e.g. failure to take medication in Xa group or INR <2.0 in VKA group) resets this interval to 0 days. Failure to take apixaban is defined as having missed more than one dose per week. In this case a TEE can be performed to avoid reset of anticoagulation interval to 0 days.

[…]

Not available

New version:

Patients scheduled for ablation after exclusion of atrial thrombi by TEE can undergo catheter ablation less than 30 days after initiation of anticoagulant study therapy provided that continuous effective anticoagulation is ensured between the TEE and the ablation (i.e. for patients in the Xa-group at least two doses of apixaban immediately prior to ablation, for patients in the VKA-group at least one INR value ≥2.0 prior to ablation and the last INR value after TEE and prior to index ablation needs to be ≥1.8). Effective anticoagulation needs to be present for 30 days prior to ablation (i.e. continuous medication intake in patients randomised to Xa. In patients randomised to VKA an INR between 2.0-3.0 is mandatory, with a minimum of three INR measurements). Ineffective anticoagulation (e.g. failure to take medication in Xa group or INR <2.0 in VKA group) resets this interval to 0 days. Failure to take apixaban is defined as having missed more than one dose per week. In this case a TEE can be performed to avoid reset of anticoagulation interval to 0 days.

[…]

- Assess degree of disability (modified Rankin Scale; refer to appendix IX)

Rationale:

Update of the visit procedures to changes (listed and explained in previous section) to the protocol text. Non-substantial change.

9.3.1 Index ablation visit

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

- Perform a TTE and assess especially for pericardial effusion

New version:

- Perform a TTE or ICE and assess especially for pericardial effusion

Rationale:

Update of the visit procedures to changes (listed and explained in previous section) to the protocol text.

Non-substantial change.

9.3.2 Clinical follow-up visit (3 month after the ablation visit)

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

- Assess and document adherence to study therapy by reviewing INRs (VKA group patients) or by asking the patient and by pill count (Xa group patients)
- Assess performance status (Karnofsky score; refer to appendix V)

Not available

New version:

- Assess and document adherence to study therapy by reviewing INRs (VKA group patients) or by asking the patient and by pill count (Xa group patients). A minimum of three INR measurements is mandatory between the index ablation visit and the three month follow-up visit.
- Assess performance status (Karnofsky Scale; refer to appendix V)
- Assess degree of disability (modified Rankin Scale; refer to appendix IX)

Rationale:

Update of the visit procedures to changes (listed and explained in previous section) to the protocol text.

Non-substantial change.

9.5 Transthoracic/intracardiac Echocardiography

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

9.5 Transthoracic Echocardiography

The main purpose of the TTE after the ablation procedure is the detection of pericardial effusion. This will be assessed by measuring the maximal separation between right ventricular wall and pericardium.

New version:

9.5 Transthoracic/intracardiac Echocardiography

The main purpose of the TTE or ICE after the ablation procedure is the detection of pericardial effusion. This will be assessed by measuring the maximal separation between right ventricular wall and pericardium.

Rationale:

Update of the visit procedures to changes (listed and explained in previous section) to the protocol text.

Non-substantial change.

9.6 Electrocardiogram

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

All ECGs should be uploaded digitally onto a central server within the e-CRF. This requires an ECG machine capable of exporting an adequate digital format that can then be uploaded. Details regarding upload of ECGs are described in a separate ECG manual.

New version:

All ECGs should be uploaded digitally onto a central server within the e-CRF. This requires an ECG machine capable of exporting an adequate digital format that can then be uploaded. ~~Details regarding upload of ECGs are described in a separate ECG manual.~~

Rationale:

A separate ECG manual is not necessary, as the ECG devices at the study sites have their specific ECG manual.

Non-substantial change.

9.7 Blood Samples

Old version 28.07.2014 valid in BE, DK, IT:

Routine laboratory parameters are part of the screening procedures in order to verify the enrolment criteria and therefore not considered to be part of study related procedures. If these parameters can be assessed from a blood sample not older than 7 days at the date of inclusion, the blood sampling does not have to be repeated. Parameters include red blood cells, white blood cells, platelets, serum creatinine, aPTT, and INR. INR should be documented at least three times prior to the ablation visit in patients randomised to VKA therapy, and more often as clinically indicated. All INR measurements will be collected in the e-CRF. All blood parameters will be determined at the local laboratory of the study sites provided their analytical laboratories are certified. The e-CRF will collect laboratory values and information whether the value is normal or abnormal.

At baseline and at the end of follow-up, an additional blood sample will be collected (20ml whole blood in each case) and sent to a central laboratory for archiving for later analysis (analyses of factors and mechanisms of AF, stroke, and bleeding, including genetic markers). Patients will provide explicit signed informed consent to obtain this extra blood sample. Details regarding handling and shipment of these blood samples are described in a separate lab manual. Aim of these analyses is to evaluate the possible mechanisms of AF and thrombogenesis and to gain new knowledge regarding treatment of AF in the future.

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Routine laboratory parameters are part of the screening procedures in order to verify the enrolment criteria and therefore not considered to be part of study related procedures. If these parameters can be assessed from a blood sample not older than 7 days at the date of inclusion, the blood sampling does not have to be repeated. Parameters include red blood cells, white blood cells, platelets, serum creatinine, aPTT, and INR. INR should be documented at least three times prior to the ablation visit in patients randomised to VKA therapy, and more often as clinically indicated. All INR measurements will be collected in the e-CRF. Before first intake of study drug liver function parameters have to be documented. All blood parameters will be determined at the local laboratory of the study sites provided their analytical laboratories are certified. The e-CRF will collect laboratory values and information whether the value is normal or abnormal.

At baseline and at the end of follow-up, an additional blood sample will be collected (20ml whole blood in each case) and sent to a central laboratory for archiving for later analysis (analyses of factors and mechanisms of AF, stroke, and bleeding, including genetic markers). Patients will provide explicit signed informed consent to obtain this extra blood sample. Details regarding handling and shipment of these blood samples are described in a separate lab manual. Aim of these analyses is to evaluate the possible mechanisms of AF and thrombogenesis and to gain new knowledge regarding treatment of AF in the future.

New version:

Routine laboratory parameters are part of the screening procedures in order to verify the enrolment criteria and therefore not considered to be part of study related procedures. If these parameters can be assessed from a blood sample not older than 7 days at the date of inclusion, the blood sampling does not have to be repeated. Parameters include red blood cells, white blood cells, platelets, serum creatinine, aPTT, and INR. INR should be documented at least three times prior to the ablation visit in patients randomised to VKA therapy, and more often as clinically indicated. All INR measurements will be collected in the e-CRF. Before

first intake of study drug liver function parameters have to be documented. All blood parameters will be determined at the local laboratory of the study sites provided their analytical laboratories are certified. The e-CRF will collect laboratory values and information whether the value is normal or abnormal.

At baseline and at the end of follow-up, an additional blood sample will be collected (20ml whole blood in each case) and sent to central laboratory for archiving for later analysis (analyses of factors and mechanisms of AF, stroke, and bleeding, including genetic markers). Patients will provide explicit signed informed consent to obtain this extra blood sample. ~~Details regarding handling and shipment of these blood samples are described in a separate lab manual.~~ Aim of these analyses is to evaluate the possible mechanisms of AF and thrombogenesis and to gain new knowledge regarding treatment of AF in the future.

Rationale:

A separate lab manual is not available, but a form “Overview Biosampling” filed in the Investigator Site File providing detailed explanation for handling of the extra blood withdrawal.

Non-substantial change.

9.9 MRI Sub-Study

Old version 28.07.2014 valid in BE, DK, IT:

Patients might not be eligible to undergo MRI examination in case of any of these conditions:

- Problems lying on the back and holding still for 15 minutes
- Ever done metal grinding/welding as work or a hobby, or if ever seen a doctor about metal in the eyes
- Any metal in the body from an accident, gunshot, or military service wound
- Pregnancy
- Problems with claustrophobia.

New version (and versions 08.01.2015 valid in DE, NL, and 20.02.2015 valid in AT, ES, GB, US:

Patients might not be eligible to undergo MRI examination in case of any of these conditions:

- Problems lying on the back and holding still for 15 minutes
- Ever done metal grinding/welding as work or a hobby, or if ever seen a doctor about metal in the eyes
- Any metal in the body from an accident, gunshot, or military service wound
- Pregnancy
- Problems with claustrophobia
- Documented epilepsy
- Severe noise sensitivity or tinnitus
- Head trauma associated with commotio cerebri ≤ 6 weeks prior to study start

Rationale:

Completion of exclusion criteria for study related brain MRI according to clinical routine standards.

Substantial change.

12.1.1 Analysis of the primary outcome

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

With respect to the primary outcome, the study is exploratory. The primary efficacy analysis will be based on composite endpoint of all-cause death, stroke or major bleeding in all randomised patients who undergo an ablation procedure for AF (i.e., modified intention-to-treat [mITT]). The efficacy composite endpoint is measured (in days) from the randomisation date to the day of the event (i.e., time-to-first event = event date - randomisation date +1). As a secondary analysis, time-to-event analysis will be conducted for the components of the primary composite endpoint.

New version:

~~With respect to the primary outcome, the study is exploratory.~~ The primary efficacy analysis will be based on composite endpoint of all-cause death, stroke or major bleeding in all randomised patients who undergo an ablation procedure for AF (i.e., modified intention-to-treat [mITT]). The efficacy composite endpoint is measured (in days) from the randomisation date to the day of the event (i.e., time-to-first event = event date - randomisation date +1). As a secondary analysis, time-to-event analysis will be conducted for the components of the primary composite endpoint.

Rationale:

Due to objections by the central Ethics Committee for Italy “Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo” and the Italian local Ethics Committee “Comitato Etico per la Sperimentazione di Padova”, it was agreed with the central Ethics Committee for Italy “Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo” that the expression “exploratory” will no longer be applied in the entire study protocol.

Non-substantial change.

12.1.2 Analysis of the secondary outcome

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

All the secondary endpoints analyses are exploratory in nature and will be tested at 0.05 significant level (i.e., no multiple comparisons adjustment).

New version:

All the secondary endpoints analyses ~~are exploratory in nature and~~ will be tested at 0.05 significant level (i.e., no multiple comparisons adjustment).

Rationale:

Due to objections by the central Ethics Committee for Italy “Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo” and the Italian local Ethics Committee “Comitato Etico per la Sperimentazione di Padova”, it was agreed with the central Ethics Committee for Italy “Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo” that the expression “exploratory” will no longer be applied in the entire study protocol.

Non-substantial change.

12.1.3 Safety analysis

Old version 28.07.2014 valid in BE, DK, IT:

Safety data include adverse events as defined in section 8.1, primary safety endpoints, and data for other safety evaluations. Safety data will be collected on all randomised patients (i.e., ITT cohort) in this study.

The primary safety outcome in this study is a composite of all-cause death, stroke, cardiac tamponade and major bleeding events which will be analysed using time-to-event methodology as described in Section 12.1.1. Similar analyses and summary statistics will be provided for the components of this safety composite endpoint.

Serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment related SAEs will be summarized under each treatment group, by system organ class (SOC) and preferred term (PT). Comparisons between treatment groups will be made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term) of special interest. SAEs will be summarized by severity and relation to study treatment received.

New version (and versions 08.01.2015 valid in DE, NL, and 20.02.2015 valid in AT, ES, GB, US:

Safety data include adverse events as defined in section 8 and 8.1, primary safety endpoints, and data for other safety evaluations. Safety data will be collected on all randomised patients (i.e., ITT cohort) in this study.

The primary safety outcome in this study is a composite of all-cause death, stroke, cardiac tamponade and major bleeding events which will be analysed using time-to-event methodology as described in Section 12.1.1. Similar analyses and summary statistics will be provided for the components of this safety composite endpoint.

Adverse events as defined in section 8 and 8.1 and serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment related SAEs will be summarized under each treatment group, by system organ class (SOC) and preferred term (PT). Comparisons between treatment groups will be made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term) of special interest. SAEs will be summarized by severity and relation to study treatment received.

Rationale:

Clarification of sections describing adverse events judged as medically meeting the criteria of "Serious Adverse Events".

Non-substantial change.

12.2 Sample Size and Power Calculations

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Assuming an overall event rate of the primary endpoint (composite of all-cause death, stroke or major bleeding) at day 90 to be 17%, a total of 630 patients (315 per group) will allow to detect a pre-specified margin of 7.5% (absolute difference) with 80% power using upper 1-sided 95% confidence interval (i.e., 2-sided 90% CI, (41)). The method of Farrington and Manning was used to compute sample size and power. To account for roughly 3% of patients who will not undergo the ablation procedure, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e., randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort.

New version:

Assuming an overall event rate of the primary endpoint (composite of all-cause death, stroke or major bleeding) at day 90 to be 17%, a total of 630 patients (315 per group) will allow to detect a pre-specified margin of 7.5% as an absolute difference (i.e. 1.44 relative risk) with 80% power using upper 1-sided 95% confidence interval (i.e., 2-sided 90% CI, (41)). The method of Farrington and Manning was used to compute sample size and power. To account for roughly 3% of patients who will not undergo the ablation procedure, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e., randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort.

Rationale:

More detailed information is provided due to the remarks by the central Ethics Committee in the Netherlands “Medisch Ethische Toetsingscommissie Universitair Medisch Centrum Groningen”, that “non-inferiority spectrum of 7.5% may negatively influence the clinical relevance”.

Non-substantial change.

12.3 Interim Analyses, Reassessment of the Sample Size

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

There are two planned interim analyses to be conducted by the Data and Safety Monitoring Board (DSMB) after approximately 1/3 and 2/3 of patients underwent the catheter ablation procedure (i.e., roughly at 200 and 400 patients, respectively) who have completed 90 days (3 months) of study follow-up. The Haybittle–Peto boundary will be used as stopping rule guidance for the DSMB. The DSMB charter will provide further details on the conduct of the interim looks.

New version:

There are two planned interim analyses to be conducted by the Data and Safety Monitoring Board (DSMB) after approximately 1/3 and 2/3 of patients who underwent the catheter ablation procedure (i.e., roughly at 200 and 400 patients, respectively) and had a minimum 90 days (3 months) of completed study follow-up. The Haybittle–Peto boundary will be used as stopping rule guidance for the DSMB. The Haybittle–Peto boundary is chosen to preserve the type I error (alpha) at 5% for the final analysis. There is no plan to stop the study during the interim looks, unless there is a safety concern. The DSMB charter will provide further details on the conduct of the interim looks.

Rationale:

More detailed information is provided due to further enquiries by the central Ethics Committee in the Netherlands “Medisch Ethische Toetsingscommissie Universitair Medisch Centrum Groningen” regarding the Haybittle Peto boundary, and the question about the rationale for interim analyses after 2/3 of patients underwent the catheter ablation procedure.

Non-substantial change.

12.4 Patient Selection for Analyses

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Under the mITT principle, all randomised patients who undergo an ablation procedure for AF will be included in the primary analysis and censoring mechanism will be applied to those patients without event at the end of the study follow-up. Patients without an event at the end of follow-up will have their efficacy measure censored at the end of follow-up. Patient without an event and who is lost to follow-up will be censored on the day of last contact with the patient. This concept will be applied to both treatment arms. In addition, a sensitivity (robustness) analysis will be conducted using per-protocol population (i.e., among those without major protocol violations).

New version:

In order to reduce bias toward the null hypothesis in non-inferiority testing of the primary endpoint, a modified intent-to-treat (mITT) population will be used. Under the mITT principle, all randomised patients who undergo an ablation procedure for AF will be included in the primary analysis and censoring mechanism will be applied to those patients without event at the end of the study follow-up. Patients without an event at the end of follow-up will have their efficacy measure censored at the end of follow-up. Patients without an event and who are lost to follow-up will be censored on the day of last contact with the patient. This concept will be applied to both treatment arms. In addition, a sensitivity (robustness) analysis will be conducted using per-protocol population (i.e., among those without major protocol violations).

Rationale:

Further precision is provided based on the requests for clarification by the central Ethics Committee of England ‘National Research Authority NRES Committee of England – Cambridge South’ on the use of a modified intention to treat analysis rather than an intention to treat analysis.

Non-substantial change.

15.1.4 Data and Safety Monitoring Board

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the SC and study investigators. It will consist of one statistician and two clinicians with expertise in clinical trials and in the management of AF patients. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. They regularly monitor the recruitment and conduct of trial, data quality and timeliness, the distribution of therapies within the study groups, the serious adverse events and further adverse events selected to their discretion during the course of the trial. DSMB will perform interim analyses after 1/3 and 2/3 of patients underwent the catheter ablation procedure (i.e., roughly at 200 and 400 patients, respectively) and give recommendations to the SC to continue or stop the trial. The Haybittle–Peto boundary (45, 46) will be implemented as stopping rule guidance for the DSMB.

New version:

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the SC and study investigators. It will consist of one statistician and two clinicians with expertise in clinical trials and in the management of AF patients. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. They regularly monitor the recruitment and conduct of trial, data quality and timeliness, the distribution of therapies within the study groups, the serious adverse events and further adverse events selected to their discretion during the course of the trial. DSMB will perform interim analyses after 1/3 and 2/3 of patients underwent the catheter ablation procedure (i.e., roughly at 200 and 400 patients, respectively, and have completed 90 days [3 months] of study follow-up) and give recommendations to the SC to continue or stop the trial. The Haybittle–Peto boundary (45, 46) will be implemented as stopping rule guidance for the DSMB.

Rationale:

Further precision is provided in accordance to preceding text (chapter 12.3)

Non-substantial change.

18 References

Old version 28.07.2014 valid in BE, DK, IT:

[…]

46. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44(526):793-7.

47. Connolly S, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser S, Diaz R, Talajic M, Jun Z, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Meighem W, Lip GYH, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, o'Donnel M, Lawrence J, Lewis GD, Afzal R, Yusuf S. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806-17

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

[…]

46. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44(526):793-7.

47. Connolly S, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser S, Diaz R, Talajic M, Jun Z, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Meighem W, Lip GYH, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, o'Donnel M, Lawrence J, Lewis GD, Afzal R, Yusuf S. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806-17

48. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm A J, Kirchhof P. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15:625-651.

New version:

[…]

46. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44(526):793-7.

47. Connolly S, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser S, Diaz R, Talajic M, Jun Z, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Meighem W, Lip GYH, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, o'Donnel M, Lawrence J, Lewis GD, Afzal R, Yusuf S. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806-17

48. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm A J, Kirchhof P. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15:625-651.

49. Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. Circulation. 2014; 129(25):2638-44.

Rationale:

New literature citation for more detailed information on the use of apixaban.

Addition of a new reference (no. 36) due to changes in section 7.2 VKA group.

Non-substantial change.

19 Signatures

Old version 28.07.2014 valid in BE, DK, IT:

Date	**Signature**
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature local investigator
	_____ (Name local investigator; printed)

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Date	**Signature**
_____	_____ Günter Breithardt (sponsor representative)
_____	_____ Signature principal investigator
	_____ (Name principal investigator; printed)

New version:

Date	**Signature**
_____	_____ Ulrich Schotten (sponsor representative)
_____	_____ Signature principal investigator
	_____ (Name principal investigator; printed)

Rationale:

Prof. Günter Breithardt has resigned from his position at Kompetenznetz Vorhofflimmern e.V. and Prof. Ulrich Schotten was elected as new sponsor representative for the AXAFA trial.

Non-substantial change.

Appendix I Members of the Steering Committee

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Günter Breithardt (non-voting)
Kompetenznetz Vorhofflimmern e.V.
Albert-Schweitzer-Campus 1, Building D11, Domagkstraße 11, 48149 Münster, Germany
Email: g.breithardt@uni-muenster.de

New version:

Ulrich Schotten (non-voting)
Kompetenznetz Vorhofflimmern e.V.
University Maastricht, Department of Physiology, PO Box 616, 6200 MD Maastricht, Netherlands
Email: schotten@maastrichtuniversity.nl

Rationale:

Prof. Günter Breithardt has resigned from his position at Kompetenznetz Vorhofflimmern e.V. and Prof. Ulrich Schotten was elected as new sponsor representative for the AXAFA trial.

Non-substantial change.

Appendix II Time Schedule

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

	Tasks	**Date**
Study planning	Draft Protocol, review and finalisation by Steering Committee	Nov 2013 to May 2014
Study preparation	Definition of drug supply mechanism	May to Jul 2014
	Set up of e-TMS (MARVIN), preparation of e-CRF; preparation of all other study relevant documentation	May to Jul 2014
	▪ Site selection, site contacts, site evaluation	May to Oct 2014
	▪ EC and CA submission	Aug 2014 to Mar 2015
Study initiation	▪ Site contracting	Sep 2014 to Apr 2015
	▪ Supply of the sites with study materials, initiation visits	Dec 2014 to Aug 2015
	▪ Recruitment period (FPI to LPI)	Jan 2015 – Jan 2017
Study duration	Treatment / Follow-up of last patient (LPI to LPO)	Feb to Jun 2017
	Mean follow-up period of all patients, assuming a linear patient recruitment	3.7 months
Interim analyses	▪ After 200 pts. have undergone AF ablation and completed the 3-months FU period	Estimated Feb 2016
	▪ After 400 pts. have undergone AF ablation and completed the 3-months FU period	Estimated Sep 2016
Study closure	Final data cleaning /study closure	Jul 2017
Final analysis	Statistical analysis, incl. review by Steering Committee	Aug to Sep 2017

New version:

	Tasks	**Date**
Study planning	Draft Protocol, review and finalisation by Steering Committee	Nov 2013 to Jul 2014
Study preparation	Definition of drug supply mechanism	May to Jul 2014

	Set up of e-TMS (MARVIN), preparation of e-CRF; preparation of all other study relevant documentation	May to Dec 2014
	▪ Site selection, site contacts, site evaluation	May to Oct 2014
	▪ EC and CA submission	Aug 2014 to Jul 2016
Study initiation	▪ Site contracting	Sep 2014 to Jul 2016
	▪ Supply of the sites with study materials, initiation visits	Dec 2014 to Jul 2016
	▪ Recruitment period (FPI to LPI)	Feb 2015 – Jan 2017
Study duration	Treatment / Follow-up of last patient (LPI to LPO)	Feb to Jun 2017
	Mean follow-up period of all patients, assuming a linear patient recruitment	3.7 months
Interim analyses	▪ After 200 pts. have undergone AF ablation and completed the 3-months FU period	Estimated Apr 2016
	▪ After 400 pts. have undergone AF ablation and completed the 3-months FU period	Estimated Nov 2016
Study closure	Final data cleaning /study closure	Jul 2017
Final analysis	Statistical analysis, incl. review by Steering Committee	Aug to Sep 2017

Rationale:

As agreed with the Steering Committee, the time schedules needs to be adapted as the contract negotiations with some sites were lasting longer than expected.

Non-substantial change.

Appendix VIII: List of strong inducers/inhibitors of P-gp and CYP3A4 which lead to contraindication for the combined use with apixaban (Practical Guide Use of NOACs (48)).

Old version 28.07.2014 valid in BE, DK, IT:

Not available

New version (and versions 08.01.2015 valid in DE, NL, and 20.02.2015 valid in AT, ES, GB, US:

Appendix VIII: List of strong inducers/inhibitors of P-gp and CYP3A4 which lead to contraindication for the combined use with apixaban (Practical Guide Use of NOACs (48)).

- Ketoconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Rifampicin
- St John's wort
- Carbamazephine
- Phenytoin
- Phenobarbital
- HIV protease inhibitors:
  - Ritonavir
  - Saquinavir
  - Indinavir
  - Lopinavir
  - Fosamprenavir
  - Atazanavir
  - Tipranavir
  - Darunavir

Rationale:

More detailed information on the use of apixaban.

Substantial change.

Appendix IX Modified Rankin Scale

Old version 28.07.2014 valid in BE, DK, IT:

Old version 08.01.2015 valid in DE, NL:

Old version 20.02.2015 valid in AT, ES, GB, US:

Not available

New version:

Appendix IX Modified Rankin Scale

The Modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It has become the most widely used clinical outcome measure for stroke clinical trials.

The scale was originally introduced in 1957 by Dr. John Rankin of Stobhill Hospital, Glasgow, Scotland, and then modified to its currently accepted form by Prof. C. Warlow's group at Western General Hospital in Edinburgh for use in the UK-TIA study in the late 1980s. The first publication of the current modified Rankin Scale was in 1988 by van Swieten, et al., who also published the first interobserver agreement analysis of the modified Rankin Scale.

Interobserver reliability of the mRS can be improved by using a structured questionnaire during the interview process and by having raters undergo a multimedia training process. The multimedia mRS training system which was developed by Prof. K. Lees' group at the University of Glasgow is available online. The mRS is frequently criticized for its subjective nature which is viewed as skewing results, but is used throughout hospital systems to assess rehabilitation needs and outpatient course. These criticisms were addressed by researchers creating structured interviews which ask simple questions both the patient and/or the caregiver can respond to.

More recently, several tools have been developed to more systematically determine the mRS, including the mRS-SI, the RFA, and the mRS-9Q. The mRS-9Q is in the public domain and a free web calculator is available at www.modifiedrankin.com.

The scale runs from 0-6, running from perfect health without symptoms to death.

0 - No symptoms.
1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3 - Moderate disability. Requires some help, but able to walk unassisted.
4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6 - Dead.

Rationale:

Update of the visit procedures to changes to the protocol text.

Non-substantial change.

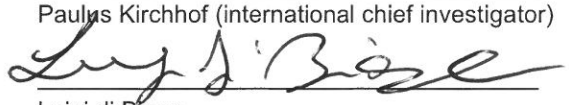
Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
8 July 2016	Paulus Kirchhof (international chief investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Ulrich Schotten (sponsor representative)
	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	**Signature**
	Paulus Kirchhof (international chief investigator)
08/18/16	 Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Ulrich Schotten (sponsor representative)
	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
	Paulus Kirchhof (international chief investigator)
	Luigi di Biase
8/12/16	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Ulrich Schotten (sponsor representative)
	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
	Paulus Kirchhof (international chief investigator)
	Luigi di Biase
	David Callans
28/07/2016	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Ulrich Schotten (sponsor representative)
	Signature principal investigator
	(Name principal investigator; printed)

Signatures

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Date	**Signature**
_____	_____ Paulus Kirchhof (international chief investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
05.08.2016	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Ulrich Schotten (sponsor representative)
_____	_____ Signature principal investigator
	_____ (Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
	Paulus Kirchhof (international chief investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
08.08.2016	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Ulrich Schotten (sponsor representative)
	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
	Paulus Kirchhof (international chief investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
8-23-2016	Jonathan Piccini
	Lluis Mont
	Hussein Al-Khalidi (study statistician)
	Ulrich Schotten (sponsor representative)
	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
_____	_____ Paulus Kirchhof (international chief investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
Lluis Mont 1 August 2016	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
_____	_____ Ulrich Schotten (sponsor representative)
_____	_____ Signature principal investigator
	_____ (Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
	Paulus Kirchhof (international chief investigator)
	Luigi di Biase
	David Callans
	Karl Georg Häusler
	Gerhard Hindricks
	Jens Cosedis Nielsen
	Jonathan Piccini
	Lluis Mont
July 27, 2016	Hussein R. Al-Khalidi (study statistician)
	Ulrich Schotten (sponsor representative)
	Signature principal investigator
	(Name principal investigator; printed)

Signatures

The undersigned have read this protocol amendment and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	**Signature**
_____	_____ Paulus Kirchhof (international chief investigator)
_____	_____ Luigi di Biase
_____	_____ David Callans
_____	_____ Karl Georg Häusler
_____	_____ Gerhard Hindricks
_____	_____ Jens Cosedis Nielsen
_____	_____ Jonathan Piccini
_____	_____ Lluis Mont
_____	_____ Hussein Al-Khalidi (study statistician)
26-7-2016	_____ Ulrich Schotten (sponsor representative)
_____	_____ Signature principal investigator
	_____ (Name principal investigator; printed)

CLINICAL TRIAL PROTOCOL

AXAFA - AFNET 5

*A*nticoagulation using the direct factor *X*a inhibitor apixaban during *A*trial *F*ibrillation catheter *A*blation: Comparison to vitamin K antagonist therapy.

An Investigator-driven, **P**rospective, Parallel-group, **R**andomised, **O**pen, **B**linded Outcom**e** Assessment (PROBE), Multi-centre Trial
to determine the optimal anticoagulation therapy for patients undergoing catheter ablation of atrial fibrillation

EudraCT number: 2014-002442-45
NCT number: NCT02227550
ISRCTN87711003

Responsible Sponsor:
Kompetenznetz Vorhofflimmern e.V. (AFNET)
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This protocol has been written in accordance with current applicable guidelines (ICH-GCP and EU-Directive 2001/20/EC) as well as all other relevant additional references, medical and legal ones.

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1 Summary

TITLE	**A**nticoagulation using the direct factor **X**a inhibitor apixaban during **A**trial **F**ibrillation catheter **A**blation: Comparison to vitamin K antagonist therapy (**AXAFA**)
INTERNATIONAL CHIEF INVESTIGATOR	Professor Paulus Kirchhof, Birmingham, UK and Münster, Germany
SPONSOR	Kompetenznetz Vorhofflimmern e.V. (AFNET) [Atrial Fibrillation NETwork]
BACKGROUND AND RATIONALE	Factor Xa inhibitors and direct thrombin inhibitors are new, fixed dose oral anticoagulants that provide a much-needed alternative treatment to vitamin K antagonists (VKAs) for stroke prevention in atrial fibrillation (AF). Their use has been evaluated in several large clinical trials enrolling patients with non-valvular AF at increased risk for stroke. Three non-inferiority trials comparing apixaban, rivaroxaban, or dabigatran to warfarin have been reported, as well as one additional trial demonstrating superiority of apixaban to aspirin. Based on the outcome of these large trials, these three novel oral anticoagulants (NOACs) have been approved in the USA, Canada, and in Europe for stroke prevention in patients with AF and at least one additional risk factor for stroke. Furthermore, NOACs are recommended in current AF guidelines. Approximately 5-15% of the non-valvular AF population undergoes catheter ablation in recent surveys. While some of these patients require long-term anticoagulation because of their individual stroke risk, all patients require anticoagulation during and after the ablation procedure to reduce the risk of procedure-associated stroke. The use of NOACs in patients undergoing catheter ablation for symptomatic AF has not been tested in randomised controlled trials. Rather, retrospective small observational case series raised concerns about the peri-procedural use of NOACs in patients undergoing catheter ablation: The largest published experience exists with dabigatran, the NOAC which received approval first. Numerically, there were more severe events in patients undergoing catheter ablation with dabigatran than in those undergoing ablation while on VKAs, namely 18/409 patients with severe events on dabigatran (4.4%) compared to 8/371 patients with severe events on VKAs (2.1%). These numbers only represent serious events (such as pericardial tamponade, clinically overt stroke, death), as other major bleeding events were not collected. Although this observation is likely to reflect a play of chance rather than a biological difference, as suggested by more recent evidence from retrospective data, these data suggest to rather “choose the established treatment” of VKAs during ablation. In the absence of controlled trial data, this unequal distribution of serious complications is a cause of concern among ablationists. The international consensus statement on AF ablation was published before these reports on dabigatran. It suggests to perform AF ablation on continuous anticoagulation using either a VKA or a NOAC, while the focussed update of the ESC guidelines on AF, published after these reports on dabigatran became available, only mentions continuous peri-procedural anticoagulation using a VKA. Hence, there is a need for a well-designed, adequately powered trial to test whether NOACs can be used in the setting of catheter ablation of AF.

STUDY OBJECTIVE(S)	To demonstrate that anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of non-valvular AF in the prevention of peri-procedural complications.
STUDY DESIGN	Investigator-initiated, **p**rospective, parallel-group, **r**andomised, **o**pen, **b**linded outcom**e** assessment (PROBE) interventional multi-centre trial. Phase IV
STUDY POPULATION Medical condition / Main selection criteria	The following main criteria must be present for eligibility into the study: ▪ Non-valvular AF (ECG-documented) with a clinical indication for catheter ablation ▪ Clinical indication to undergo catheter ablation on continuous anticoagulant therapy ▪ Presence of at least one of the following $CHADS_2$ stroke risk factors: ✓ stroke or TIA ✓ age ≥ 75 years, ✓ hypertension, defined as chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mm Hg, ✓ diabetes mellitus, ✓ symptomatic heart failure (NYHA ≥ II). Patients not eligible for apixaban or with contraindications for oral anticoagulation are not suitable for AXAFA.
Number of patients	630 patients to be randomised (315 per group) and to undergo the index therapy of catheter ablation. However, to account for roughly 3% of patients who will not undergo the ablation procedure after randomisation, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e. randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort.
Expected number of sites	Approximately 50 ablation sites in Europe and in the USA. All study sites will be routinely performing catheter ablation of AF.
INVESTIGATIONAL INTERVENTIONS	Investigational medicinal product: apixaban Comparator: locally used, marketed VKA Apixaban will be given 5 mg twice daily and compared to oral anticoagulation using the locally used VKA (aiming for an international normalized ratio (INR) of 2.0-3.0). The apixaban dose will be reduced to 2.5 mg twice daily at the time of randomisation in applicable patients according to the approved label. Study medication has to be administered effectively for at least 30 days prior to the planned catheter ablation procedure or during a shorter interval in patients undergoing a transesophageal echocardiogram (TEE) with exclusion of atrial thrombi. Study medication has to be effectively continued for three months after the ablation procedure. All patients will be treated following current guidelines (ESC focussed update of the AF guidelines, 2nd catheter ablation consensus statement) including continuous oral anticoagulation during ablation procedures (continuous apixaban, target INR 2.0-2.5 in the VKA group). All patients will receive peri-procedural heparin to assure an activated clotting time (ACT) >300 s.

	MRI sub-study: A subgroup of maximal 300 study patients will undergo brain magnetic resonance imaging study (MRI, without contrast agents) within 3-48 hours after the ablation procedure.
PRIMARY OUTCOME PARAMETERS	A composite of ▪ all-cause death, ▪ stroke (ischemic stroke, subarachnoid haemorrhage and haemorrhagic stroke), and ▪ major bleeding events, defined as BARC 2 or higher
SECONDARY OUTCOME PARAMETERS	▪ Any bleeding event ▪ Major bleeding events according to the ISTH and TIMI definitions ▪ Number of strokes, other systemic embolic events, and all-cause deaths ▪ Time from randomisation to ablation ▪ Nights spent in hospital after ablation ▪ Health-care related cost calculation ▪ Number of hospitalisations for cardiovascular reasons ▪ Treatment duration prior to ablation and total time on oral anticoagulation ▪ Number of patients with clinically indicated TEE ▪ ACT during ablation ▪ Time to recurrent AF ▪ Rhythm status at the end of follow-up ▪ Vascular access complications leading to prolongation of in-hospital stay or specific therapy ▪ Quality-of-life changes at month 3 compared to baseline ▪ Cognitive function change at month 3 compared to baseline ▪ Prevalence of clinically “silent” MRI-detected brain lesions within 48 hours after the ablation procedure (MRI sub-study), ▪ Impact of ablation-associated clinically overt strokes or MRI-detected but clinically “silent” acute brain lesions on cognitive function after ablation (MRI sub-study)
ASSESSMENT SCHEDULE	1. Enrolment and randomisation 2. Scheduled visit during ablation MRI sub-study: brain MRI within 3–48 hours after the ablation procedure 3. Scheduled follow-up at three months after ablation 4. Phone call 30 days after discontinuation of study drug
STATISTICAL CONSIDERATIONS	The primary analysis is in the modified intention-to-treat population, consisting of all randomised patients who received at least one dose of study treatment and an ablation procedure for AF. Event rates at the end of follow-up will be compared between groups. An occurrence of the primary parameter is expected in 17-20% of the patients. The sample size will allow to detect a non-inferiority between the two random groups with a margin of 7.5%. Safety analysis will be performed with all patients randomised.
DURATION OF STUDY PERIOD (per patient)	Duration per patient: about 3 months for patients scheduled for ablation after exclusion of atrial thrombi by clinically indicated TEE, approximately 4 months in all other patients (depending on time of achieving therapeutic anticoagulation)

2 Abbreviations

ACC	American College of Cardiology
ACT	activated clotting time
ADC	apparent diffusion coefficient
AE	adverse event
AF	atrial fibrillation
AF-CHF	Atrial Fibrillation Congestive Heart Failure trial
AFNET	Atrial Fibrillation Network
ARWMC	Age Related White Matter Changes
AXAFA	Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy
BARC	Bleeding Academic Research Consortium
CIOMS	Council for International Organization of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-reactive protein
CV	Curriculum Vitae
CYP450 3A4	Cytochrome P450 3A4
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EC	Ethics Committee
ECG	electrocardiography
e-CRF	electronic case report form
EHRA	European Heart Rhythm Association
EQ-5D	Euroquol 5D questionnaire
ERC	Endpoint Review Committee
ESC	European Society of Cardiology
FLAIR	Fluid Attenuated Inversion Recovery
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HF	heart failure
ICE	Intracardiac echocardiogram
ICF	informed consent form

ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IIT	Investigator Initiated Trial
INR	International Normalised Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention-to-treat
LA	left atrium
LBBB	left bundle branch block
LV	left ventricle
LVEF	left ventricular ejection fraction
MCA	middle cerebral artery
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MoCA	Montreal cognitive assessment
MRI	magnetic resonance imaging
mITT	modified intention-to-treat
NOAC	novel oral anticoagulant
NSTEMI	non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PE	physical examination
PI	principal investigator
PVI	pulmonary vein isolation
QoL	Quality-of-life
SAE	serious adverse event
SF-12	12-item Short-Form health survey
SOP	Standard Operating Procedure
TEE	Transesophageal echocardiogram
TIMI	thrombolysis in myocardial infarction
TTE	Transthoracic echocardiogram
VKA	vitamin K antagonist

The terms “trial” and “study” are being used interchangeably throughout this protocol.

3 Introduction

3.1 Background Information

Catheter ablation has become an important part of rhythm control therapy in AF patients (1, 2). There is growing evidence that catheter ablation procedures are best performed during continuous oral anticoagulation. This is reflected in current consensus statements and guidelines (2, 3). The published evidence illustrating the safety and efficacy of this approach was largely generated in patients undergoing catheter ablation during continuous treatment with VKAs (4-8). Emerging data further support a practice of continuous oral anticoagulation with a low-therapeutic anticoagulation level during ablation procedures.

Data on NOACs are inconclusive and even point towards a slightly higher peri-procedural risk for bleeding and strokes in uncontrolled, observational studies using the direct thrombin inhibitor dabigatran (9-13): In 409 patients receiving dabigatran peri-ablation, 3 strokes, 9 tamponades, and 7 further pericardial effusions were reported. In 371 patients receiving VKAs in the same series there were no strokes, 3 tamponades, and 5 pericardial effusions. Hence, serious events on NOACs (dabigatran) amount to 18/409 (4.4%) patients, while serious events on VKA were reported in 8/371 (2.1%) patients. More recent observational data are not sufficient to eliminate the safety concerns around the use of NOACs in patients undergoing catheter ablation (9). These and other studies furthermore report less severe bleeding events in 10-15% of the patients studied, based on a heterogeneous standard of reporting and heterogeneous definitions. Vascular access complications were not adequately reported and are likely to occur in 2-3% additional patients. Furthermore, around 10% of patients undergoing AF ablation are expected to suffer major, clinically relevant bleeding events (including a drop of haemoglobin and hematomas not requiring surgical intervention).

It is obvious that this imbalance in severe events is not statistically significant and likely prone to imbalanced patient distribution. Additionally, the peri-procedural dabigatran regime differed markedly between case series and centres. While some centres allowed to pause dabigatran for prolonged periods of time, others favoured a continuous therapy with dabigatran. This illustrates the uncontrolled and potentially suboptimal use of dabigatran in the published case series and calls for prospective validation of a reasonable anticoagulation strategy in patients undergoing AF ablation on NOACs (14).

This inconclusive evidence contrasts with the favourable efficacy and safety of dabigatran, rivaroxaban, and apixaban compared to the VKA warfarin in patients suffering from non-valvular AF (15-17). In these large randomised trials, severe bleeds were consistently similar or even less frequently reported with either of the NOACs, while the higher dose of dabigatran (150 mg twice daily) as well as apixaban also reduced stroke rates. Furthermore, all three NOACs reduced total deaths by 10-12%, and reduced intracranial bleeding events by 33-74% (15-17). It is surprising that NOACs that appear beneficial in general AF patients would prove to be detrimental in patients undergoing catheter ablation. On the other hand, each ablation procedure induces a risk for stroke and bleeding that may have a specific pathophysiology, e.g. bleeding secondary to venous vascular access complications or after transseptal puncture, and formation of thrombotic debris at the sheaths, catheter tip, or in the ablated, scarred regions. However, the current recommendations on peri-procedural anticoagulation may also generate potentially avoidable risk to patients: Patients who are in need for ablation and receiving a NOAC are often “switched” to VKAs for the procedure, which induces unstable anticoagulation and therefore cause a potential bleeding risk during the treatment change or may prolong the time to ablation. In other centres, the existing data on peri-procedural anticoagulation are interpreted as inconclusive and ablation procedures are performed under continuous anticoagulation with VKAs.

Hence, there is a need to test the peri-procedural use of NOACs in patients undergoing catheter ablation of AF in a controlled prospective trial.

Silent brain infarction is defined as cerebral infarction detected by brain imaging without matching clinical event. Clinically silent brain infarctions are detectable by magnetic resonance imaging (MRI) in 8-28% of the general population. They are more prevalent in patients with arterial hypertension and in the elderly (18).

Indeed, silent brain infarctions are quite common in AF cohorts undergoing MRI (37-75%) (19-21). Silent infarctions are often small subcortical (lacunar) infarcts. In the general population, silent brain infarcts are associated with a 2-4 fold risk of future clinically overt stroke, mortality, worsening of cognitive functions, and overt dementia in the long term (22, 23). There is growing evidence that AF per se and AF-related stroke associate with cognitive decline and dementia over time (19, 24-29). Therefore, it seems biologically plausible to assume that maintenance of sinus rhythm could prevent AF-related "silent" brain infarcts and subsequent slow cognitive decline (30, 31). On the other hand, catheter ablation is associated with clinically silent but MRI-detected acute brain lesions in 8-41% of all patients (32, 33, 36, 37). A recently published small case series reported MRI-detected silent brain lesions in 12-27% of all patients with peri-procedural VKA (33). It would be good to explore whether NOACs have the potential to reduce clinically silent brain lesions after catheter ablation of AF.

Blood-based biomarkers or specific ECG alterations could be useful to identify patients at risk for stroke and/or bleeding. This concept has never been applied to patients undergoing catheter ablation of AF, where bleedings requiring the attention of a health care professional are rather common (estimated at 15% of the patients undergoing ablation). Similarly, biomarkers may help to better identify patients at risk for recurrent AF after catheter ablation. AXAFA will provide a platform to explore these possibilities by collecting blood and a 12-lead resting ECG prior to ablation.

3.2 Study Rationale

One of the three NOACs is the direct, oral factor Xa inhibitor apixaban. Apixaban prevents strokes in AF patients significantly better compared to the VKA warfarin, and causes less major bleeding events. There are no data on apixaban in patients undergoing catheter ablation of AF. The AXAFA trial will compare peri-ablational treatment with apixaban to peri-ablational treatment with VKA in a randomised trial of patients undergoing catheter ablation of AF. This randomised trial will clarify the clinical utility of apixaban in the peri-ablational setting by systematically collecting data on clinically relevant ischemic and bleeding events in patients who will be prospectively followed in the context of a clinical trial.

3.3 Benefit-risk Assessment

General risk assessment of the AXAFA trial: All study drugs are market approved and will be used within the approved indications, only. All concomitant study procedures, e. g. the catheter ablation for AF, are standard care procedures according to applicable medical guidelines used within the recommended indications. All participating study sites have to document sufficient experience in the management of patients with AF in general and in catheter ablation of AF in detail. Thus, the overall risk level in this phase IV trial is expected to be low.

The additional brain MRIs being performed in about 300 sub-study patients will not add radiation risk to participating patients.

Assessment of the individual risk of study patients: The use of study drugs and concomitant procedures within AXAFA does not deviate from standard care procedures. The tested modification of the most common drug regime, treatment with a factor Xa inhibitor peri-ablation, is applying an approved medication within its approved label and in the approved population. There are several single-center reports that suggest safety of this approach, although a formal confirmation of its safety is lacking. Thus, the individual risk of study patients in both treatment arms will not differ from the risk of therapy in clinical routine.

General benefit of study patients: Patients in AXAFA will have the added benefit of careful standardised monitoring of their anticoagulant and interventional treatment by their study physicians as well as of additional quality management by the CRO, the sponsor and the Steering Committee. About 300 patients will additionally be able to participate in a MRI sub-study monitoring clinically "silent" brain lesions undetected in the regular clinical setting.

Individual benefit of study patients: Patients randomised to apixaban will receive a treatment that has been shown to be safer (reduced major bleeding events, especially intracranial bleeding) and slightly more effective than VKA in general AF populations (17, 50). Furthermore, apixaban treatment will be easier to use without the need of repetitive INR monitoring and frequently adapted dosing.

4 Study Objectives

To demonstrate that anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of non-valvular AF in the prevention of peri-procedural complications.

4.1 Primary Outcome Parameters

The primary outcome parameter of AXAFA is a composite of

- all-cause death,
- stroke, and
- major bleeding events.

Stroke comprises ischemic strokes as defined by the FDA (including ischemic infarction with (transient) clinical symptoms that resolve completely within 24 hours, but have a matching lesion on brain imaging as well as ischemic infarction interrupted by death within 24 hours), subarachnoid haemorrhage and haemorrhagic stroke. Major bleeding events will be defined according to the Bleeding Academic Research Consortium (BARC) definition as BARC 2 or higher (34), i.e. all bleeding events that require an action by a health care professional. This outcome parameter comprises all relevant bleeding events in a clinical setting and has been used to optimise arterial vascular procedures such as percutaneous coronary interventions (34, 35).

4.2 Secondary Outcome Parameters

4.2.1 Secondary efficacy outcome parameters

The secondary outcome parameters are defined as

- any bleeding event
- major bleeding events according to the ISTH and TIMI definitions,
- number of strokes, other systemic embolic events, and all-cause deaths,
- time from randomisation to ablation
- nights spent in hospital after ablation
- health-care related cost calculation estimated by quantification of interventions, nights spent in hospital, and the costs of outpatient treatment,
- number of hospitalisations (at least one over-night stay) for cardiovascular reasons ,
- treatment duration prior to ablation and total time on oral anticoagulation,
- number of patients with clinically indicated TEE
- ACT during ablation (assessed as mean, range, and number of ACT measurements within the target range)
- time to recurrent AF (determined clinically, and according to ECG and Holter ECG recording at the end of follow-up),
- rhythm status at the end of follow-up (assessed by Holter ECG),
- vascular access complications leading to prolongation of in-hospital stay or specific therapy,
- quality-of-life changes at month 3 compared to baseline (assessed by EQ-5D, SF-12 questionnaires, and by the Karnofsky Scale),
- change of cognitive function at month 3 compared to baseline (assessed by Montreal Cognitive Assessment Scale; MoCA),

- MRI sub-study, only: Prevalence of clinically "silent" MRI-detected brain lesions within 48 hours after the ablation procedure,
- MRI sub-study, only: Impact of ablation-associated clinically overt strokes or MRI-detected but clinically "silent" acute brain lesions on cognitive function after ablation

4.2.2 Secondary safety outcome parameters

The major safety outcome parameter is a composite of all-cause death, stroke, cardiac tamponade, and major bleeding events defined as BARC 2 or higher. Furthermore, bleeding events requiring surgery or transfusion are part of this outcome.

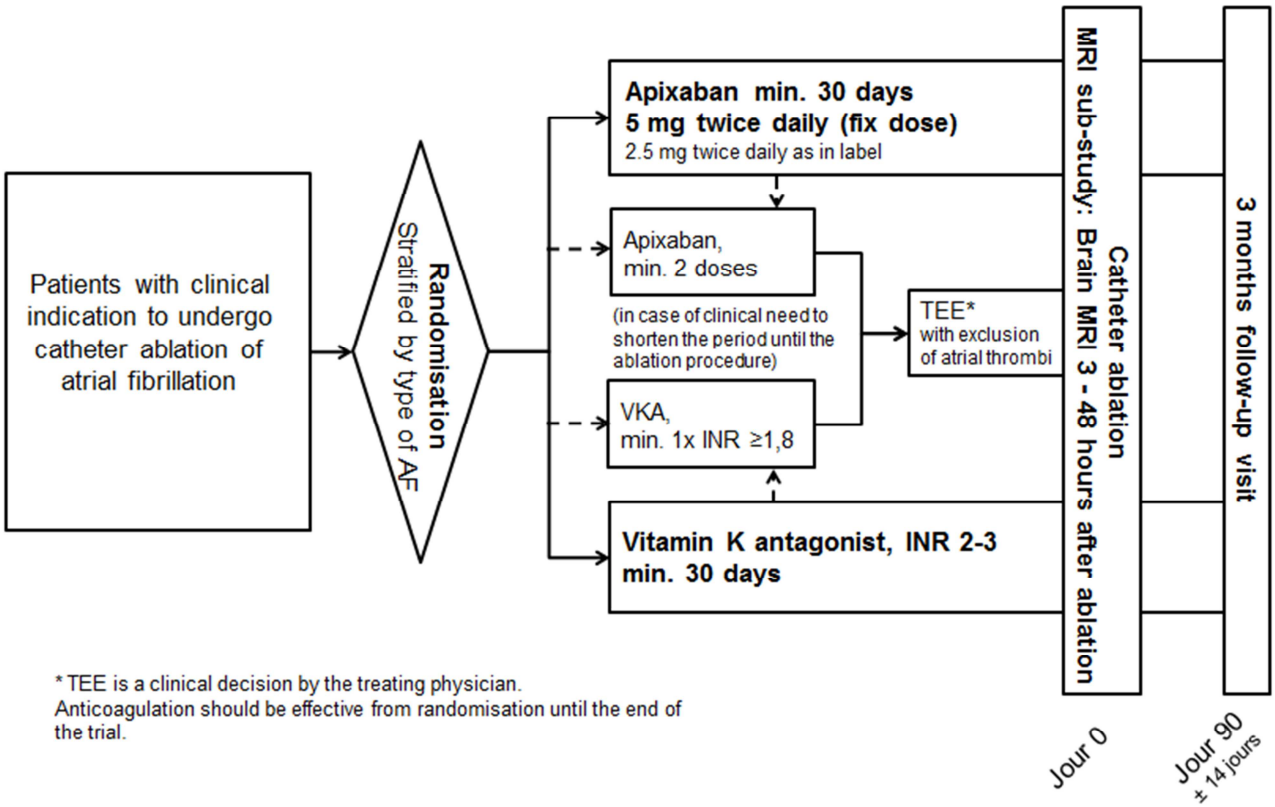
Other safety outcome parameters are the components of this composite, the number of serious adverse events (SAEs) of all types and all other bleeding events as well as vascular access complications leading to prolongation of in-hospital stay or specific therapy (such as surgery, supplementation of coagulant factors, intensive care).

All outcome events will be adjudicated centrally (blinded to study group, including blinding to INR) by the Endpoint Review Committee (ERC; refer to section 15.1.3).

5 Study Design

AXAFA is an investigator-initiated, prospective, parallel-group, randomised, open, blinded outcome assessment (PROBE) interventional multi-centre study. The trial tests whether peri-procedural anticoagulation therapy using the novel, oral, direct factor Xa inhibitor apixaban is not less safe than VKA therapy for patients undergoing catheter ablation of AF. The trial will be conducted in several European countries and in the USA (details of study sites are provided in a separate document).

5.1 Flow Chart



6 Selection of Patients

6.1 Informed Consent

A signed, ethics committee (EC) /institutional review board (IRB) approved informed consent form, written in accordance with country-specific applicable data privacy acts, the Declaration of Helsinki (appendix VI) and the applicable laws for research using medical devices and drugs, will be obtained from every patient prior to any study-related procedure. The valid national or local versions of the patient information and informed consent are part of the documents prepared for every submission to authorities or IRBs / ECs individually and will be kept as separate documents. All clinical data needed to evaluate the potential eligibility of a patient before study inclusion, e. g. recent laboratory results, ECG recordings or other technical parameters, are considered to be performed during clinical routine and are therefore not considered to be part of study related procedures.

The investigator or responsible medical staff will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information sheet. The patient will be given sufficient time to consider the study's implications before deciding whether to participate. The patient information sheet must be approved by the responsible EC / IRB before first use.

Should there be any amendments to the protocol, such that this would directly affect the patient's participation in the study, e.g. a change in any procedure, the informed consent form must be amended to incorporate this modification and the patients must agree to sign this amended form indicating that they re-consent to further participate in the modified study.

A signed copy of the patient's informed consent form must be maintained in the study file on site. The patient's permanent medical records should indicate the patient's study participation. A patient information sheet will be handed out to the patient unless declined by him/her.

6.2 Study Population

The intended population for this study is patients who are scheduled for catheter ablation of AF. Patients will be recruited by contracted study sites only, i.e. by approximately 50 sites performing catheter ablation for AF in clinical routine. Patient recruitment is expected to be completed after 25 months.

6.2.1 Number of Patients

630 patients will be randomised and undergo the index therapy of catheter ablation for AF. However, to account for roughly 3% of patients who will not undergo the ablation procedure, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e. randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort. The sample size may be re-estimated once in a blinded manner as described in the statistics section (refer to section 12).

6.2.2 Inclusion criteria

I1. Non-valvular AF (ECG-documented) with a clinical indication for catheter ablation.

I2. Clinical indication to undergo catheter ablation on continuous anticoagulant therapy.

I3. Presence of at least **one** of the $CHADS_2$ stroke risk factors

- Stroke or TIA,
- age ≥ 75 years,
- hypertension, defined as chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mm Hg,
- diabetes mellitus,
- symptomatic heart failure (NYHA ≥ II).

I4. Age ≥ 18 years.

I5. Provision of signed informed consent.

6.2.3 Exclusion criteria

General exclusion criteria

E1. Any disease that limits life expectancy to less than 1 year.

E2. Participation in another clinical trial, either within the past 2 months or still ongoing.

E3. Previous participation in AXAFA.

E4. Pregnant women or women of childbearing potential not on adequate birth control: only women with a highly effective method of contraception (oral contraception or intra-uterine device) or sterile women can be randomised.

E5. Breastfeeding women.

E6. Drug abuse or clinically manifest alcohol abuse.

E7. Any stroke within 14 days before randomisation.

E8. Coadministration with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) or strong dual inducers of CYP3A4 and P-gp (Appendix VIII).

Exclusion criteria related to a cardiac condition

E9. Valvular AF (as defined by the focussed update of the ESC guidelines on AF, i.e. severe mitral valve stenosis, mechanical heart valve). Furthermore, patients who underwent mitral valve repair are not eligible for AXAFA.

E10. Any previous ablation or surgical therapy for AF.

E11. Cardiac ablation therapy for any indication (catheter-based or surgical) within 3 months prior to randomisation.

E12. Clinical need for “triple therapy” (combination therapy of clopidogrel, acetylsalicylic acid, and oral anticoagulation)

E13. Other contraindications for use of VKA or apixaban.

E14. Documented atrial thrombi less than 3 months prior to randomisation.

Exclusion criteria based on laboratory abnormalities

E15. Severe chronic kidney disease with an estimated glomerular filtration rate (GFR) < 15 ml/min.

6.2.4 Randomisation

The patients will be randomised to one of two parallel study groups, designated as “Xa” and “VKA”. Randomisation will be stratified by the pattern of AF (paroxysmal vs. persistent / long-lasting persistent) as assessed by the responsible investigator at time of randomisation. Randomisation will be done by study site in blocks of variable size to allow minimising potential confounders related to different healthcare practice.

A randomisation list will be created by the responsible study statistician.

This list will be imported into the randomisation server of the electronic trial management system called MARVIN. During the trial, randomisation will be performed by MARVIN to the imported randomisation list. The investigator has to document several clinical items prior to randomisation to verify eligibility of the patient for randomisation and to determine the stratum. MARVIN displays the random group and asks for confirmation by authorised study personnel. The account ID of the person performing the randomisation in MARVIN and the corresponding time stamp will automatically be documented in an electronic audit trail.

7 Therapy

AXAFA is an open-label trial designed to evaluate the safety and efficacy of two types of anticoagulant therapy, VKA therapy and therapy with the direct factor Xa inhibitor apixaban, in patients undergoing scheduled catheter ablation for AF. All patients will undergo the ablation procedure after pre-treatment with an anticoagulant (either apixaban in the “Xa group” or a vitamin K antagonist in the “VKA group”).

Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation. Ablation can be performed earlier when atrial thrombi have been excluded by a clinically indicated TEE. A TEE performed within 6 hours prior to randomisation is considered valid. A TEE performed within 6 hours prior to randomisation is considered valid. After TEE continuous effective anticoagulation must be ensured until the end of the trial.

Instructions with regard to change management of anticoagulants at start and discontinuation of study drug are described in appendix III.

7.1 Xa group

Patients randomised to the Xa group will receive apixaban 5 mg twice daily throughout the study duration. Apixaban will be continued during the ablation procedure with twice daily dosing. The apixaban dose will be reduced to 2.5 mg twice daily in patients who fulfil two of the following criteria at the time of randomisation: chronic kidney disease (defined as serum creatinine ≥ 1.5 mg/dl [133 mM]), ≤ 60 kg body weight, or age ≥ 80 years. In case adaptation of apixaban dosage with regard to these criteria is deemed necessary after randomisation, this has to be documented in the e-CRF.

All patients randomised to the Xa group must have received at least two doses of apixaban prior to the ablation procedure.

7.1.1 Description of apixaban

Apixaban (or BMS-562247) has been tested in large trials and is approved for the prevention of strokes in AF patients. Apixaban will be applied in AXAFA within its approved indication and standard therapeutic dose.

Product description	Potency	Packaging/Label tupe	Appearance	Storage conditions
BMS-562247-01 Film Coated Tablet,	5 mg	200 tablets/bottle, open label	Reddish brown, plain, oval shaped, shallow bi-convex film coated tablet	Store at 2-30℃
BMS-562247-01 Film Coated Tablet,	2.5 mg	200 tablets/bottle, open label	Reddish brown, plain, oval shaped, shallow bi-convex film coated tablet	Store at 2-30℃

An adequate contract research organisation of the manufacturer is responsible for labelling, storage, and distribution to study sites on demand. Sufficient quantities of apixaban will be supplied.

7.1.2 Compliance with apixaban, dispensing and return of apixaban

Apixaban will be supplied to the study sites in sufficient quantity according to local needs, e. g. expected recruitment rate. The respective time of drug supply will be determined by the CRO but supply itself will be performed by the relabeling sub-contractor.

Logistics of apixaban study medication will be managed and tracked centrally in the e-trial management system MARVIN. Each apixaban study medication bottle will be supplied with a unique medication number (numerical) together with a corresponding unique verifier (alpha-numerical) printed on study specific label. A list of all unique medication numbers together with the corresponding unique verifiers of the provided apixaban study medication will be hosted in the materials tool of the MARVIN system.

Labelling follows requirements as specified in Volume 4, EU Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products. National requirements will be taken into consideration. The subcontractor responsible for re-labelling and delivery of apixaban to study sites receives automated supply orders via e-mail from the MARVIN system detailed for amount of bottles with 5 mg or 2.5 mg tablets. Tracking of apixaban bottles to be sent to study sites will be performed by the subcontractor in MARVIN revealing information on medication numbers and verifiers, date of shipment and recipient (study site ID). Receipt of apixaban study medication has to be tracked by the receiving site staff by entering the verifier printed on each bottle label.

In case of randomisation of a new eligible patient to Xa group the MARVIN system displays the medication numbers of the two bottles (400 tablets) to be used depending on some medical items describing the patient's condition defining the use of 5 mg or 2.5 mg tablets. Site staff has to confirm drug dispense to the patient by entering the verifiers printed on each bottle label.

Prior to dispensing study medication to a patient, the investigator will document the patient's ID (automatically allocated by MARVIN), study site ID and the date of dispensing on the label. First intake of study medication needs to be ensured at study enrolment (taking into consideration the change management instructions). Every patient randomised to Xa group will be handed out two bottles of apixaban (5 mg or 2.5 mg depending on the dosage recommendations described above). The consistent intake of apixaban is crucial for sufficient efficacy since no INR or other coagulation parameter monitoring will be performed in contrast to the VKA group. Patients will be asked to bring all unused, partly-used, or empty medication at each visit. The investigator will assess effective anticoagulation with apixaban by questioning the patient about medication intake and by pill count during the ablation visit and at the end of follow-up.

After a patient has terminated the study, any unused or part-used medication will be returned to the relabeling subcontractor. Returned apixaban medication will be tracked in the MARVIN system.

7.2 VKA group

Patients randomised to the VKA group will receive oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. First intake of study medication needs to be ensured at study enrolment (taking into consideration the change management instructions). VKAs will be prescribed as in clinical routine and dispensed by local hospital pharmacy. Costs will be reimbursed by sponsor. VKA therapy will be monitored by INR measurements according to applicable medical guidelines and to local routine policy. The frequency and all values of INR measurements will be collected in the e-CRF. A minimum of three INR measurements is mandatory between the baseline visit and the ablation visit, and between the index ablation visit and the 3 month follow-up visit. Effective anticoagulation will be assessed by questioning the patient about medication intake and by INR measurements which need to be consistent within the therapeutic range (INR ≥2.0) in at least 30 days prior to catheter ablation. Any INR <2 within the 30 days period prior to catheter ablation resets this interval to 0 days or a TEE may be performed for exclusion of thrombi (49). If atrial thrombi were excluded by TEE, or all measured INR values were ≥2.0 for 30 days, the last measured INR value prior to index ablation needs to be ≥1.8.

7.3 Concomitant Medication

The concomitant use of antiplatelet agents is discouraged in all study patients, because the concomitant use of an oral anticoagulant and antiplatelet agents increases the risk of bleeding without known benefits. All

other concomitant medication can be used within the AXAFA trial. In the e-CRF, all antiarrhythmics, anticoagulants, antithrombotic agents and other drugs administered for AF as well as for cardiovascular concomitant illnesses including statins and antidiabetics/insulin will be documented as well as medications known to interact with apixaban metabolism. No other medication neither any dosage will be documented in the e-CRF.

7.4 Catheter Ablation

7.4.1 Anticoagulation during the ablation procedure

All patients in AXAFA should undergo catheter ablation of AF while on continued oral anticoagulation as described above. The nature and conduct of the ablation procedure should not be influenced by the investigator's knowledge of the subject's treatment allocation. Based on published recommendations (2), a heparin bolus (100 IU/kg body weight) should be given in each patient either prior to or directly after transseptal puncture. Furthermore, an ACT > 300s needs to be maintained and documented during the ablation procedure. All other aspects of the ablation procedure and of peri-procedural management will follow local routine. The randomisation merely defines the type of anticoagulation therapy used.

7.4.2 Ablation procedure

The aim of catheter ablation in AF patients is isolation of the pulmonary veins (PVI) and additional procedures if deemed clinically necessary. PVI should be performed following local routine. Procedural safety is paramount in the context of AXAFA, and all means for a safe procedure should be taken. The study will be conducted in experienced centres on the plateau phase of their learning curve. Pre-study assessment of all centres will guarantee sufficient experience in PVI procedures. Evaluation of experimental or novel ablation devices is not permitted in the AXAFA trial. The exact ablation technique should follow local routine and adhere to the recommendations of the AFNET/EHRA/ECAS consensus statement on catheter ablation of AF, and to the locally applicable AF guidelines. Local routine should guide details of the procedure (e.g. the type of ablation and mapping system used, or the choice of ablation energy) within the limits of these recommendations. We encourage the use of irrigated tip catheters and flushing of all left atrial sheaths, as recommended in the AF ablation guidance document (2). Local PVI procedure policy will be documented prior to study start in each site and in case of relevant changes during the course of the trial. The technology and approach used will be documented in the e-CRF for every patient.

Usually, isolation of the pulmonary veins is the first and paramount target of catheter ablation in AF patients. In most cases, this will be achieved by circumferential, often antral, isolation of the left and right pulmonary veins in “two circles”. Sequential isolation of the ostia of each pulmonary vein is also permitted if the operator deems this procedure appropriate for a given patient. “Single shot” devices, e.g. using cryo-energy, may be used if there is sufficient experience with a given technique locally. Some patients may require more extensive ablation procedures targeting additional structures e.g. by linear lesions, ablation of ganglionated plexus and fractionated electrograms, or others. When sufficient local expertise and experience exists, such techniques can be applied to patients within AXAFA.

Adherence to usual technique and technology will be monitored to ensure a study close to clinical practice.

7.5 Post-study Treatment

After end of the study course in the individual patient (planned or premature study discontinuation), the investigator is free to decide, on which further anticoagulant medication to put the patient.

8 Adverse Event Reporting

As all treatments in AXAFA are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). Therefore, in the context of AXAFA, not all adverse events will be recorded, but

a) "Adverse Events of Special Interest" (see 8.1),

b) “Adverse Events” judged as medically important by the investigator, and

c) “Serious Adverse Events” (see 8.2).

Adverse events a) to c) will be part of the safety analysis (see 12.1.3).

8.1 Adverse Events of Special Interest

Bleeding events: Any bleeding as classified BARC type 2–5 (refer to appendix IV) is considered major bleeding. Some bleeding events may meet the criteria of seriousness and would need to be reported as serious adverse event as described in section 8.2. All bleeding events will be classified according to the BARC scheme (refer to appendix IV).

Other complication of therapy: Any other event that is judged as causally related to the therapies applied within the trial, especially complications of ablation procedures (e.g. pulmonary vein stenosis, atrio-oesophageal fistula) and drug toxicity of the study medications.

Neurological abnormalities: All acute neurological deficits or other signs potentially indicating a stroke or TIA have to be investigated. Patients with suspected neurological deficit should be visited by a neurologist whenever feasible. In addition, it is desirable to obtain clinically indicated brain imaging (preferably brain MRI) to search for matching brain lesions and to be able to distinguish between ischemic or hemorrhagic stroke, respectively. The core imaging laboratory will centrally read such clinically indicated brain images.

Some of these events might fulfil the criteria for seriousness and in this case would need to be reported as serious adverse event as described in section 8.2.

Other non-serious adverse events will not be recorded in AXAFA.

8.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that

- results in death or,
- is life-threatening
  (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) or,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
  (defined as inpatient care of more than one calendar day [= at least one overnight stay]; see also **NOTE** below) or,
- results in persistent or significant disability/ incapacity or,
- is a congenital anomaly / birth defect, or
- is a medically important event
  (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not

result in hospitalisation).
Potential drug induced liver injury (DILI) is also considered an important medical event (refer to section 8.2.1 for the definition of potential DILI).

Additional study specific criteria for SAEs:

- pregnancy (refer to section 8.2.2 for reporting pregnancies),
- overdose (defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important),
- cancer diagnosed after randomisation.

More than one of the above criteria can be applicable to each event.

NOTE: The following hospitalisations are not considered SAEs:

- A visit to the emergency room or other hospital department without the necessity of an overnight stay that does not result in admission (unless considered an "important medical event" or a life-threatening event).
- Elective surgery planned before signing consent.
- Admissions as per protocol for a planned catheter ablation of AF or planned cardioversion of AF.
- Routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy).
- Any overnight hospital stay required only for diagnostic procedure (e.g. sleep laboratory).
- Medical or surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

8.2.1 Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event by reporting the liver function parameters. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation >3 times upper limit of normal (ULN)

AND

2. Total bilirubin >2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.2.2 Pregnancy

It is reminded that all means should be put in place to prevent pregnancy during the study. Before study enrolment, women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Women of childbearing potential are required to perform a pregnancy test before first intake of the study medication. If clinical signs of pregnancy are present during intake of the study medication and up to an adequate interval after intake of study medication, a pregnancy test has to be performed. In countries where legally required (e.g. Austria)

monthly pregnancy tests need to be performed for all women of childbearing potential. In addition, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. The investigator must immediately notify the CRO of this event and record the pregnancy on the Pregnancy Surveillance Form. Initial information on a pregnancy must be reported immediately to the CRO, and the outcome information provided once the outcome is known.

8.3 Recording and Reporting Serious Adverse Events

Following the patient's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing of the study medications (apixaban or VKA). All SAEs occurring after the individual end of the follow-up period within the 30 days reporting period will be used for safety reporting, only. These SAEs will not add to any statistical analysis but will be considered descriptively, only.

The investigator should specify and report in the e-CRF the nature of the sign or symptom leading to the SAE, the date of onset of the sign or symptom, the date of resolution (duration) of the specific event (not of the underlying disease), the intensity, interventions performed (if any), the relationship to study treatment, and the outcome.

All SAEs, whether related or unrelated to investigational product, must be reported expeditiously to the CRO through the SAE section of the e-CRF within 24 hours of becoming aware of the event. An SAE form within the e-CRF should be completed for any event where doubt exists regarding its status of seriousness. As a minimum, the investigator has to fill out the following items of the internet-based SAE form:

- type of event,
- description (if mandatory),
- date of onset,
- criteria for seriousness,
- causal relationship to study therapy.

If the investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the related item of the form and be explained in the narrative section of the SAE form.

As soon as further information regarding the event is available (e.g. discharge letter), the investigator should complete the documentation in the e-CRF and sign it electronically. Copies of the discharge letter, of all reports regarding examinations carried out and/or diagnostic findings should be faxed to the CRO. For laboratory results, the laboratory normal ranges should be included. All documents should be sent to the CRO after adequate blinding of patient identifiers, only.

Follow-up of any SAE that is fatal or life threatening should be provided within one additional calendar week.

Any SAE reporting (initial reporting and follow-up information on e.g. changes of an ongoing SAE's intensity or relationship to the investigational product or outcome) is done through the SAE section of the e-CRF and an automated email notification system within MARVIN, i.e. no extra SAE form needs to be faxed but the CRO will receive an automated email containing all necessary information on the SAE at the same time of the data being documented or changes of relevant SAE data being made in the e-CRF. AFNET will via contracted CRO forward all SAEs within 48 hours of awareness to BMS Global Pharmacovigilance &

Epidemiology (e-mail: Worldwide.safety@bms.com) to meet the needs of the market authorisation holder to periodically report SAEs within research projects using apixaban. The relevant SAE data according to the BMS "solicited and non-interventional research AE/SAE form" (version 10.12.2012) will be retrieved from clinical and SAE data documented by the investigator within the e-CRF and sent to BMS via e-mail form. Changes of relevant SAE data (including deletion of SAEs if relevant criteria are not met) will also be forwarded within 48 hours of awareness to BMS Global Pharmacovigilance & Epidemiology. Patient identifying data will consist of patient ID number, year of birth, gender and site ID number, only.

According to legal requirements and international standards, annual safety reports will be prepared by the CRO, reviewed and approved by the sponsor and chief international investigator and forwarded to responsible authorities of all participating countries and to all corresponding ECs / IRBs.

8.3.1 Definition of Intensity

Intensity	**Definition**
Mild	Patient is aware of signs and symptoms but they are easily tolerated
Moderate	Signs/symptoms cause sufficient discomfort to interfere with usual activities
Severe	Patient is incapable to work or perform usual activities
Very severe	Signs/symptoms are debilitating, significantly incapacitate patient despite symptomatic therapy

8.3.2 Definition of Causality

In accordance with the CIOMS group, causality of an event will be assessed as:

not related: No causal relationship exists between the study treatment and the event but an obvious alternative cause exists, e.g. the patient's underlying medical condition or concomitant therapy.

or

related: There is a reasonable / plausible possibility that the event may have been caused by the study treatment (e.g. the event cannot be explained by concomitant disease(s) or other drugs/treatments).

8.3.3 Adverse Event Follow-up Procedures

The investigator should take all appropriate measures to ensure the safety of the patients, notably he / she should follow-up the outcome of any AE of special interest as defined in section 8.1 or SAE (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the patient's condition.

In case of any SAE, the patient must be followed until clinical recovery is completed and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after termination of the trial, and that additional investigation may be requested by the CRO team.

8.4 Handling of Expedited Safety Reports

This applies to any SAE that is considered related to study therapy and the nature or severity is not consistent with the applicable product information (suspected unexpected serious adverse event; SUSAR). The expectedness of an adverse reaction will be determined by the sponsor, delegated to the CRO according to the summary of product characteristics in the version valid at the start of the trial.

The sponsor will act in strict compliance with all applicable laws and regulations and will ensure that any delegate strictly abides by the same. The CRO will notify the competent authorities, corresponding ECs / IRBs and all principal investigators concerned of any SUSAR in-line with applicable regulatory requirements.

9 Study Schedule

9.1 Visit Schedule

The timing and assessment of the study are outlined in the following table:

Assessment	**Enrolment and randomisation**	**Ablation** Day 0 of FU	**Follow-up Month 3*** Day 76 to 104 of FU	**Phone call****
Signed ICF	x			
Check inclusion & exclusion criteria	x			
Pregnancy Test[1]	x	x[1]	x[1]	
Physical examination / medical history	x	x	x	
Clinical routine laboratory parameters (blood sample)[2]	x		x	
Extra blood sample for central lab	x		x	
INR measurement (blood sample)[3]	x	x	x	
12 lead ECG	x	x	x	
24-hours Holter ECG			x	
Transesophageal echocardiogram (TEE)[4]	(x)			
Transthoracic echocardiogram (TTE; after ablation procedure) or Intracardiac echocardiogram (ICE; after ablation procedure)[5]		x		
ACT measurement (blood sample)		x		
MRI sub-study, only: brain MRI (3-48 hours after ablation)		x		
Cognitive function test (MoCA)	x		x	
Quality-of-Life (EQ-5D, SF-12)	x		x	
Karnofsky Scale	x		x	
Modified Rankin Scale	x	x	x	
Supply of study medication	x			
Return of study medication			x	
Adverse event (AE) / serious adverse event (SAE)		x	x	x**

1 Pregnancy test at enrolment and randomisation in all women with childbearing potential. Where legally required (e.g. Austria) monthly pregnancy tests need to be performed for all women of childbearing potential.

2 Blood sample not older than 7 days at the date of inclusion

3 In patients randomised to VKA-group, only.

4 TEE is a clinical decision by the treating physician: in case of clinical need to shorten the period until the ablation procedure, a TEE must be performed to exclude atrial thrombi
5 Check for pericardial effusion by transthoracic echocardiogram (TTE) or intracardiac echocardiogram (ICE) performed after ablation procedure.
* Time window ± 14 days (3 months = 90 days)
** 30 days after discontinuation of study drug (SAEs to be collected, only)

9.2 Baseline Visit

A patient meets eligibility criteria of the study if all inclusion and exclusion criteria are fulfilled as described in the sections above. Prior to any trial related procedure a signed informed consent form has to be obtained from every patient to be included in AXAFA and kept on file locally.

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent
- Document all inclusion and exclusion criteria
- Perform pregnancy test in all women with childbearing potential
- Assess patients' medical history
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Perform a physical examination
- Obtain blood samples for laboratory assessments, liver function parameters before first intake of study drug have to be documented in addition (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess quality-of-life (EQ-5D and SF-12 questionnaire)
- Assess performance status (Karnofsky Scale; refer to appendix V)
- Assess degree of disability (modified Rankin Scale; refer to appendix IX)
- Initiate study therapy and assure INR monitoring of therapy in case of VKA (refer to appendix III for instructions with regard to change of anticoagulants at start of study drug)
- In case of clinical need to shorten the period until the ablation procedure: perform TEE to exclude atrial thrombi

9.3 Follow-up

Every patient within AXAFA will undergo two scheduled in person follow-up visits, one at the time of the ablation procedure and another follow-up visit at the end of the study, three months after the ablation visit.

9.3.1 Index ablation visit

The time point of the ablation visit depends on the duration of effective anticoagulation:

Patients scheduled for ablation after exclusion of atrial thrombi by TEE can undergo catheter ablation less than 30 days after initiation of anticoagulant study therapy provided that continuous effective anticoagulation is ensured between the TEE and the ablation (i.e. for patients in the Xa-group at least two doses of apixaban immediately prior to ablation, for patients in the VKA-group at least one INR value ≥2.0 prior to ablation and the last INR value after TEE and prior to index ablation needs to be ≥1.8). Effective anticoagulation needs to be present for 30 days prior to ablation (i.e. continuous medication intake in patients randomised to Xa. In patients randomised to VKA an INR between 2.0-3.0 is mandatory, with a minimum of three INR measurements). Ineffective anticoagulation (e.g. failure to take medication in Xa group or INR <2.0 in VKA group) resets this interval to 0 days. Failure to take apixaban is defined as having missed more than one dose per week. In this case a TEE can be performed to avoid reset of anticoagulation interval to 0 days.

In case TEE reveals evidence of atrial thrombi, no catheter ablation may be done (refer to section 9.4.1).

At the ablation visit, the investigator or designee will

- Assess and document adherence to study therapy by asking the patient and by reviewing INRs (VKA group patients) or by pill count (Xa group patients)
- Perform a physical examination
- Obtain a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Verify and document that there are no contra-indications for the ablation procedure
- Assess degree of disability (modified Rankin Scale; refer to appendix IX)
- Assess for clinical events and AEs or SAEs occurred since enrolment

Thereafter, the ablation procedure can be performed. During the ablation procedure, the study team will collect the procedural information including ACT measurements, details of the ablation technology used, delivered energy, procedure time, rhythm at beginning and end of procedure, need for cardioversion during the procedure.

After the ablation procedure, the investigator or designee will

- Perform a TTE or ICE and assess especially for pericardial effusion
- Document any peri- or post-procedural difficulties or complications, especially potential primary outcome events and potential SAEs
- MRI sub-study, only: Perform a brain MRI according to the AXAFA imaging charter within 3-48 hours after the ablation and upload the MRI imaging data (technical details are described in a separate document).

9.3.2 Clinical follow-up visit (3 months after the ablation visit)

At this visit, the investigator or designee will

- Assess and document adherence to study therapy by reviewing INRs (VKA group patients) or by asking the patient and by pill count (Xa group patients) . A minimum of three INR measurements is mandatory between the index ablation visit and the three month follow-up visit.
- Perform a physical examination
- Document a 12-lead ECG (should be collected digitally; refer to section 9.6)
- Obtain a 24 hour Holter ECG
- Obtain blood samples for laboratory assessments (refer to section 9.7)
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.7)
- Assess cognitive function (MoCA test)
- Assess performance status (Karnofsky Scale; refer to appendix V)
- Assess degree of disability (modified Rankin Scale; refer to appendix IX)
- Assess quality-of-life (EQ-5D and SF-12 questionnaires)
- Assess for clinical events and AEs or SAEs that occurred since the ablation procedure

9.3.3 Phone call (30 days after discontinuation of study drug)

30 days after discontinuation of study drug (whether at regular study end or at premature study termination) the investigator or designee will call the patient and assess for SAEs that occurred since discontinuation of study drug.

9.4 Premature Study Termination

9.4.1 Withdrawal prior to the ablation procedure

In case of patient's withdrawal of consent to further study participation prior to the ablation procedure or if the ablation procedure was not performed for medical reason, the investigator should contact the patient and

- Assess for clinical events and AEs respectively SAEs that occurred since enrolment
- Xa group patients, only: Ask for return of study medication and perform pill count.

These data will be documented in the e-CRF in a withdrawal visit. The extended 30 days-period of SAE reporting after discontinuation of study medications applies (refer to section 8.3.3) provided intake of at least one dose of study medication.

9.4.2 Withdrawal after ablation procedure

In case of patient's withdrawal of consent to further study participation after the ablation procedure, the investigator should contact the patient and ask him to come to the study site for a concluding visit. As far as the patient agrees, follow-up assessments as described in section 9.3.2 will be performed and documented in the e-CRF. The extended 30 days-period of SAE reporting after discontinuation of study medications applies (refer to section 8.3.3).

9.5 Transthoracic/intracardiac Echocardiography

The main purpose of the TTE or ICE after the ablation procedure is the detection of pericardial effusion. This will be assessed by measuring the maximal separation between right ventricular wall and pericardium.

9.6 Electrocardiogram

All ECGs should be uploaded digitally onto a central server within the e-CRF. This requires an ECG machine capable of exporting an adequate digital format that can then be uploaded.

All patients will undergo 12-lead ECG at baseline, at the ablation visit and at the end of follow-up to determine rhythm. Operators recording ECGs should ensure that chest leads are placed in the proper position and electrodes make good skin contact to minimize artefacts. The reversal of limb leads and the switching of precordial leads are known to cause important alterations in ECGs.

The ECG recording should be annotated with the date of recording, patient ID and gender, only. No patient identifying annotations (e. g. last name, first name, date of birth) must be documented.

9.7 Blood Samples

Routine laboratory parameters are part of the screening procedures in order to verify the enrolment criteria and therefore not considered to be part of study related procedures. If these parameters can be assessed from a blood sample not older than 7 days at the date of inclusion, the blood sampling does not have to be repeated. Parameters include red blood cells, white blood cells, platelets, serum creatinine, aPTT, and INR. INR should be documented at least three times prior to the ablation visit in patients randomised to VKA therapy, and more often as clinically indicated. All INR measurements will be collected in the e-CRF. Before first intake of study drug liver function parameters have to be documented. All blood parameters will be determined at the local laboratory of the study sites provided their analytical laboratories are certified. The e-CRF will collect laboratory values and information whether the value is normal or abnormal.

At baseline and at the end of follow-up, an additional blood sample will be collected (20ml whole blood in each case) and sent to a central laboratory for archiving for later analysis (analyses of factors and

mechanisms of AF, stroke, and bleeding, including genetic markers). Patients will provide explicit signed informed consent to obtain this extra blood sample. Aim of these analyses is to evaluate the possible mechanisms of AF and thrombogenesis and to gain new knowledge regarding treatment of AF in the future.

9.8 Holter ECG

All patients will undergo 24-hour Holter ECG recording at the 3 months follow-up visit. The Holter ECG will be analysed locally, and the results will be documented in the e-CRF including burden of AF, i.e. total time in AF, number of AF episodes, and minimum and maximal time of AF episode.

9.9 MRI Sub-Study

It is well established that clinically "silent" strokes are associated with an increased risk of cognitive decline in the long-term (22). Silent strokes are accepted intermediate outcome parameters in neurology (23). Silent strokes are detected by MRI in 8-41% of all patients after catheter ablation (33, 36, 37). An increased number of patients with silent brain lesions already resulted in the redesign of one specific ablation catheter technology (38). Silent brain lesions will therefore be assessed in this sub-study by brain MRI 3-48 hours after the ablation procedure.

It is expected that approximately 50% of the study sites will participate in this imaging sub-study. Study sites will have to decide on participation in the MRI sub-study at the time of site initiation at the latest. In study sites participating in the sub-study, all eligible patients will have to undergo MRI examination in order to avoid selection bias.

Patients are not eligible to undergo MRI examination if they have any non-MRI safe items in their body. Typical implants suspect to harm patients or at risk to be damaged during MRI examination are:

- Implanted pacemaker
- Implanted defibrillator
- Implantable pump
- Neurostimulator or transcutaneous electrical nerve stimulation
- Eye or ear implant
- Intrauterine device
- Artificial body parts
- Breast or penile implants
- Implanted shunts.

Patients might not be eligible to undergo MRI examination in case of any of these conditions:

- Problems lying on the back and holding still for 15 minutes
- Ever done metal grinding/welding as work or a hobby, or if ever seen a doctor about metal in the eyes
- Any metal in the body from an accident, gunshot, or military service wound
- Pregnancy
- Problems with claustrophobia
- Documented epilepsy
- Severe noise sensitivity or tinnitus
- Head trauma associated with commotio cerebri ≤ 6 weeks prior to study start

Patients not eligible for MRI but recruited in study sites which decided to participate in the MRI sub-study are eligible to participate in the AXAFA main study.

Technical details regarding instructions for MRI examination and for digital upload of the MRI imaging data to a central system are described in a separate document.

All brain images will be centrally read for new brain lesions by core brain imaging centres. The core brain imaging centres will be blinded to therapy group for analysis of brain images. Details regarding central review of MRIs are described in a separate document.

10 Duration of Study Participation

10.1 Overall Duration of Study

With an expected screening and enrolment period of 25 months and a sliding initiation of sites over a period of nine months, and a maximum follow-up of four months per patient, overall study duration is calculated to be approximately 2.5 years (first-patient-in until last-patient-out). The total study duration might be adapted based on an interim analysis. Final data cleaning will require presumably three months after study closure. End of study is defined as last patient last visit (the 30-days SAE reporting period will exceed the official end of study date).

10.2 Individual Duration of the Study

According to the study protocol, the minimum follow-up time per patient is approximately three months. The total study duration per patient will depend on the duration of anticoagulation prior to the ablation procedure. For patients scheduled for catheter ablation of AF after exclusion of atrial thrombi by TEE the total study duration might be about three months, in all other patients it might be at least four months because these patients will have been anticoagulated for at least 30 days prior to catheter ablation. Difficulties in achieving therapeutic anticoagulation or irregular intake of study drug may prolong the follow-up period for some patients.

11 Stopping and Discontinuation Criteria

When the study is terminated, the nature of termination will be documented (scheduled end/discontinuation with justification). Discontinuation of the study will be communicated in writing according to the legal requirement. The decision to stop the study will be reached jointly by the sponsor and the SC.

11.1 Discontinuation Criteria related to the Study

Following a recommendation of the Data and Safety Monitoring Board (DSMB), the SC may decide discontinuation of the study due to efficacy criteria or adverse reactions in either study group. Discontinuation of the study can also be decided if patients cannot be recruited in sufficient numbers within a certain time period. Detailed criteria for a premature stopping of the entire trial based on safety concerns will be defined in the DSMB and SC charters.

Furthermore, the sponsor in collaboration with the international chief investigator has the right to close local study sites for enrolment of further patients if a major protocol violation occurs, the site does not comply with the study protocol or decisions of the committees or the international chief investigator or if the site remains inactive for several months. Such decisions will always be taken on a case-by-case basis, but may be taken e.g. if the study procedures and study therapy is not delivered according to protocol and after reminders to adhere to the protocol from the study team.

11.2 Discontinuation Criteria related to the Patient

The investigator is not able to decide about the discontinuation of study participation of any patient. The investigator has the option to discontinue study medication, however, the patient will continue to be followed during the study. Once a patient has been randomised the investigator has to follow this patient in-line with the intention-to-treat principle according to protocol. The patients will be advised in the informed consent

forms that they have the right to withdraw from study participation at any time without statement of reasons. However, the investigator should try to find out the reason for patient's withdrawal of consent and document these in the e-CRF.

In case a patient withdraws from study participation before an ablation procedure for AF was performed the withdrawal will be documented in the e-CRF. The initial ablation procedure for AF is the underlying intervention of the therapeutic concept of AXAFA. Analysis of outcome without performed ablation is scientifically useless in this concept.

Once a patient has been randomised and an ablation procedure for AF was performed and the first dose of study medication (apixaban or VKA) was taken, the treatment of the patient must not be discontinued. In case of patient's request or medical necessity of study treatment discontinuation (e.g. in case of major bleeding), patients will be followed according to study protocol. Any effort should be made to continue the allocated study medication as soon as clinically justifiable.

In case a protocol violation is noticed the patient will remain in the intention-to-treat group and will be followed according to protocol.

Patients will be followed according to the study protocol irrespective of whether they experience an outcome.

Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. The responsible investigator will take all acceptable measures to retrieve information on vital status of all patients enrolled in the trial.

12 Statistics

12.1 Statistical Methods

12.1.1 Analysis of the primary outcome

The primary efficacy analysis will be based on composite endpoint of all-cause death, stroke or major bleeding in all randomised patients who undergo an ablation procedure for AF (i.e., modified intention-to-treat [mITT]). The efficacy composite endpoint is measured (in days) from the randomisation date to the day of the event (i.e., time-to-first event = event date - randomisation date +1). As a secondary analysis, time-to-event analysis will be conducted for the components of the primary composite endpoint.

The Kaplan-Meier (K-M) estimates of the survivor function and the log rank test statistic (44) will be used to assess the statistical significance of observed treatment differences in the time-to-event distributions between the treatment groups. The log-rank test statistics, p-values, K-M estimates, and life table estimates will be obtained from the SAS® V9.3 (or higher) procedure LIFETEST (SAS/STAT User's Guide, Version 9.3, Cary, NC: SAS Institute Inc. 2011).

Cox proportional hazards model will be used to obtain an estimate of the hazard ratio for Xa group to VKA therapy group. A 95% confidence interval (CI) will be computed for the hazard ratio. Stratified Cox proportional hazards model will be conducted using the stratification factors at randomisation as a strata statement in the model. In addition, the Cox proportional hazards model with clinically relevant baseline risk factors will be used to estimate the adjusted hazard ratio (95% CI).

As a sensitivity analysis, the per-protocol population will be used. Statistical models will be constructed to validate existing factors that predict outcome parameters, and to describe novel factors, e.g. blood- or ECG-based. Details of the statistical analysis will be defined in a statistical analysis plan.

12.1.2 Analysis of the secondary outcome

The secondary endpoints listed in section 4.2.1 that are measured as time-to-event will be analysed using the same statistical methods used for the primary efficacy endpoint (Section 12.1.1). Quality-of-life outcomes will be summarized by treatment groups for each component of the questionnaires (assessed by EQ-5D, SF-12 and by the Karnofsky Scale), Total score quality of life outcomes from each assessment will be analysed as change from baseline at month 3 using analysis of covariance with the baseline values as a covariate in the model. Details of the statistical analysis will be defined in a statistical analysis plan.

MRI sub-study will develop a separate specific analytic plan prior to locking the main study database.

All the secondary endpoints analyses will be tested at 0.05 significant level (i.e., no multiple comparisons adjustment).

12.1.3 Safety analysis

Safety data include adverse events as defined in section 8 and 8.1, primary safety endpoints, and data for other safety evaluations. Safety data will be collected on all randomised patients (i.e., ITT cohort) in this study.

The primary safety outcome in this study is a composite of all-cause death, stroke, cardiac tamponade and major bleeding events which will be analysed using time-to-event methodology as described in Section 12.1.1. Similar analyses and summary statistics will be provided for the components of this safety composite endpoint.

Adverse events as defined in section 8 and 8.1 and serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment related SAEs will be summarized under each treatment group, by system organ class (SOC) and preferred term (PT). Comparisons between treatment groups will be made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term) of special interest. SAEs will be summarized by severity and relation to study treatment received.

12.1.4 Subgroup analysis

A list of subgroup criteria will be pre-specified in the statistical analysis plan.

12.2 Sample Size and Power Calculations

Assuming an overall event rate of the primary endpoint (composite of all-cause death, stroke or major bleeding) at day 90 to be 17%, a total of 630 patients (315 per group) will allow to detect a pre-specified margin of 7.5% as an absolute difference (i.e. 1.44 relative risk) with 80% power using upper 1-sided 95% confidence interval (i.e., 2-sided 90% CI, (41)). The method of Farrington and Manning was used to compute sample size and power. To account for roughly 3% of patients who will not undergo the ablation procedure, the study will enrol a total of 650 patients (325 per group) in order to maintain 630 evaluable patients (i.e., randomised and have undergone the index therapy of catheter ablation) for the primary analysis using mITT cohort.

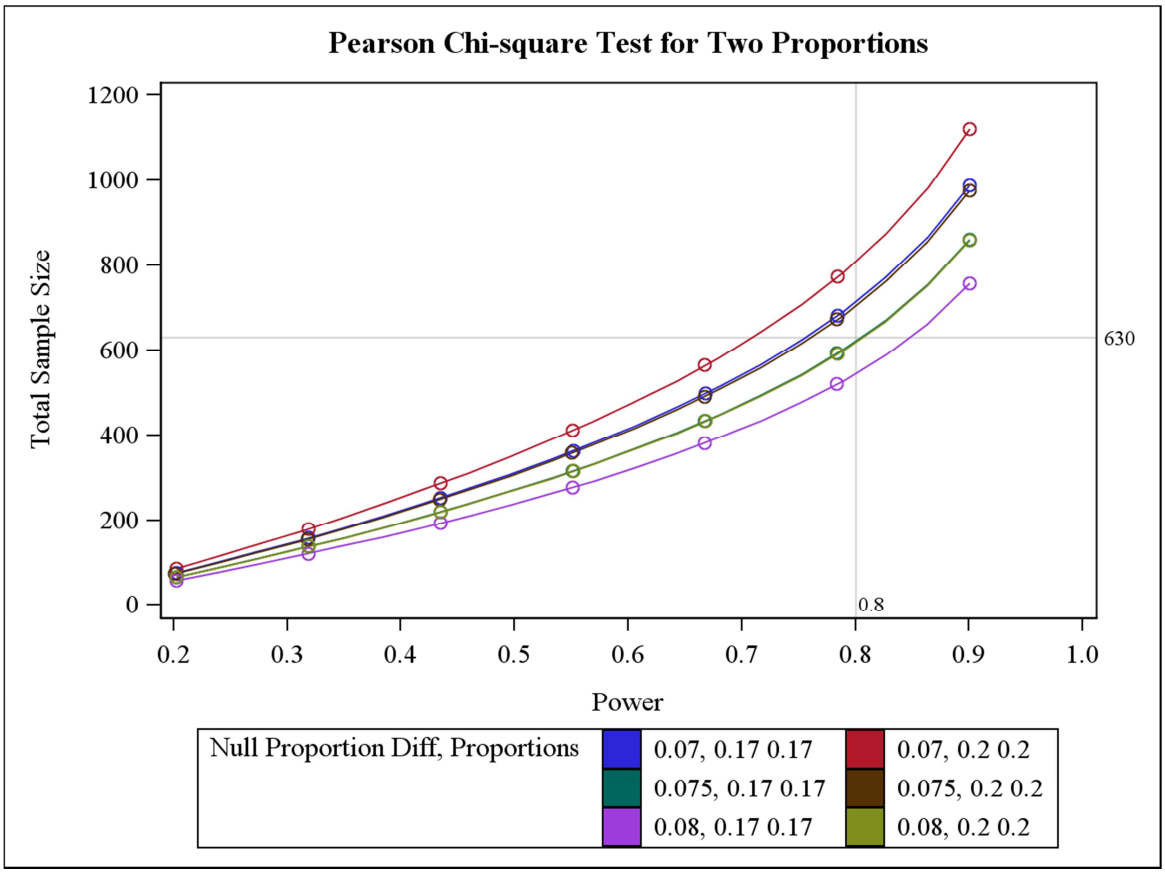


Figure: Power curves for several event rates and margin scenarios.

12.3 Interim Analyses, Reassessment of the Sample Size

There are two planned interim analyses to be conducted by the Data and Safety Monitoring Board (DSMB) after approximately 1/3 and 2/3 of patients who underwent the catheter ablation procedure (i.e., roughly at 200 and 400 patients, respectively) and had a minimum 90 days (3 months) of completed study follow-up. The Haybittle–Peto boundary will be used as stopping rule guidance for the DSMB. The Haybittle–Peto boundary is chosen to preserve the type I error (alpha) at 5% for the final analysis. There is no plan to stop the study during the interim looks, unless there is a safety concern. The DSMB charter will provide further details on the conduct of the interim looks.

The Steering Committee could decide to conduct sample size re-estimation (sample size increase) during the interim looks using the observed aggregated event rate of the study primary endpoint. The re-estimation of the study size will be based on the current protocol assumptions (i.e., same study statistical power and the non-inferiority margin).

12.4 Patient Selection for Analyses

In order to reduce bias toward the null hypothesis in non-inferiority testing of the primary endpoint, a modified intent-to-treat (mITT) population will be used. Under the mITT principle, all randomised patients who undergo an ablation procedure for AF will be included in the primary analysis and censoring mechanism will be applied to those patients without event at the end of the study follow-up. Patients without an event at the end of follow-up will have their efficacy measure censored at the end of follow-up. Patient without an event and who is lost to follow-up will be censored on the day of last contact with the patient. This concept will be applied to both treatment arms. In addition, a sensitivity (robustness) analysis will be conducted using per-protocol population (i.e., among those without major protocol violations).

The study sample size does account for those roughly 3% of patients who will not undergo the ablation procedure for AF. The initial ablation procedure for AF is the underlying intervention of the therapeutic concept of AXAFA. Safety analysis will be performed on all patients randomised (i.e., ITT cohort).

13 Access to Source Data / Documents

13.1 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

13.2 Source Documents

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes, memoranda, patient diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments) involved in this clinical study.

In case of data that are result of patient interrogation and will not be documented in clinical routine, the e-CRF is the source document, if the patients answer is documented there without prior documentation on paper (e.g. in case of central follow-up).

13.3 Direct Access

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

The investigator agrees that representatives or the designees of the sponsor such as monitors and auditors, and appropriate Regulatory Agencies will be given direct access to the regular clinical files of the patient.

14 Quality Control and Quality Assurance

14.1 Quality Control

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14.2 Initiation Visit

At each site an initiation visit will be performed by a representative of the CRO before enrolment of the first patient at this site.

14.3 Study Monitoring

Authorized, qualified representatives of the designated CRO will accomplish the monitoring of the study sites during the trial.

Data of a sufficient number of patients will be verified on site by source data validation checks for outcome and compliance with the protocol and consistency with data in the e-CRF.

It is important that the investigator and relevant personnel are available during the monitoring visits and that an appropriate location and sufficient amount of time is devoted to the process. During the monitoring visit a PC with internet connection should be available to the monitor for direct connection to the internet database of the study and to all the data of the patients if stored in the data system of the hospital or catheter lab.

The main duty of the monitor is to help the sponsor and the investigator to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the trial. At regular intervals during the study, the local site will be contacted through monitoring visits, letters/ emails or telephone calls by a monitor to review the progress of the study.

Further details are described in a separate monitoring manual.

14.4 Close Out Visit

Independent close out visits are not planned. In case of special requests by the sponsor, a separate close out visit may be performed at the end of the trial. The close out visit may be combined with the last monitoring visit.

14.5 Quality Assurance

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements.

The investigator should permit auditing by or on behalf of the sponsor and inspection by applicable regulatory authorities. The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during the audit or inspections.

14.5.1 Inspections

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsors and/or clinical research organisation facilities or at any other establishments deemed appropriate by the regulatory authorities.

14.5.2 Audits

An audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, designated Standard Operating Procedure (SOP), Good Clinical Practice (GCP) and the applicable regulatory requirements. An independent audit at the study site may take place at any time during or after the study.

15 Ethical and Legal Consideration

This is an investigator initiated (IIT), phase IV trial which meets all relevant ethical and regulatory standards (ICH-GCP). The trial will be conducted in accordance with the principles laid down in the Declaration of Helsinki in its version of October 2013 (Fortaleza).

Before initiating the study in each country, approval of the corresponding regulatory authority and Institutional Review Board/ Independent Ethics Committee will be obtained.

15.1 Ethical Consideration

15.1.1 Institutional Review Board/ Independent Ethics Committee (IRB / IEC)

It is intended to initially submit the study to the IRB / IEC of the national coordinator in Germany ("Leiter der klinischen Prüfung", LKP). After the primary approval has been achieved, submission to other national and local IRB/ IECs will be performed.

Provided this is not contradictory to national law, the principal investigator is responsible for submitting an application to the appropriate IRB / IEC. Furthermore the principal investigator is required to forward to the sponsor a copy of the written and dated approval or favourable opinion of the local IRB/ IEC signed by the chairman and including information on the composition of the IRB / IEC. The trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, investigator's CV, etc.) and the date of the review should be clearly stated on the written IRB/ IEC approval/ favourable opinion. The corresponding national coordinator together with the CRO will provide substantial support for any IRB / IEC submission. The sponsor is responsible to assure that approval of the local IRB / IEC in each country is obtained prior to study start in the respective study site or country in accordance with local requirements.

During the trial, any substantial amendment or modification to the clinical trial protocol should be submitted to the IRB / IEC. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the trial, in particular of any change in safety.

If requested, a progress report is sent to the IRB / IEC annually and a summary of the trial's outcome at the end of the study.

15.1.2 Steering Committee

The trial Steering Committee (SC) will consist of a small group of expert cardiologists, a neurologist, and an expert biostatistician (refer to appendix I). The functions of the SC are the following:

- Overall responsibility for the execution and scientific reporting of AXAFA.
- Advice on the scientific and clinical aspects of the study protocol and related documents.
- Responsibility for the conduct of the study according to the guidelines of good clinical practice (GCP) including the monitoring of patient recruitment.
- Reassessment of the sample size based on the blind review of the biostatistician.
- Reassessment of benefit/ risk ratio following the recommendations of the DSMB.
- Decisions on continuation or termination of the study based on the recommendations of the DSMB.

A SC charter providing operating procedures and responsibilities will be discussed and enacted latest at the second meeting. Meeting frequency will be defined by the committee and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings. Minutes of each meeting will be provided.

15.1.3 Endpoint Review Committee

The Endpoint Review Committee (ERC) will consist of a minimum of three experts in cardiology, AF ablation, and stroke neurology. The committee will be blinded to therapy group and to INR values, although review of detailed laboratory parameters may in some cases suggest the type of anticoagulant therapy at the time of the event, and will centrally adjudicate all outcome events as well as any hospitalisation for other reason and any other SAE. Bleeding events not meeting the criteria of seriousness will not be adjudicated by ERC.

An ERC charter providing operating procedures and responsibilities will be discussed and enacted latest at the second meeting. Meeting frequency will be defined by the number of documented and cleaned SAEs and may vary depending. Meetings may be face-to-face meetings or conference calls. Minutes of each meeting will be provided.

15.1.4 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the SC and study investigators. It will consist of one statistician and two clinicians with expertise in clinical trials and in the management of AF patients. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. They regularly monitor the recruitment and conduct of trial, data quality and timeliness, the distribution of therapies within the study groups, the serious adverse events and further adverse events selected to their discretion during the course of the trial. DSMB will perform interim analyses after 1/3 and 2/3 of patients underwent the catheter ablation procedure (i.e., roughly at 200 and 400 patients, respectively, and have completed 90 days [3 months] of study follow-up) and give recommendations to the SC to continue or stop the trial. The Haybittle–Peto boundary (45, 46) will be implemented as stopping rule guidance for the DSMB.

A DSMB charter providing operating procedures and responsibilities will be discussed and enacted latest at the second meeting. Meeting frequency will be defined by the committee and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings and may have an open part with guests and a closed part. Minutes of each meeting will be provided. After each meeting, recommendations will be given to the SC in a written form.

15.1.5 National coordinators

National coordinators are selected experts that support submission to the competent authorities and IRB/IEC in their individual countries. The national coordinators provide their expertise regarding regulatory affairs in their countries. The national coordinators supervise and monitor the patient recruitment, and support recruitment measures on a national level. A national coordinator can also be a member of the SC.

15.2 Legal Consideration

The study will be notified to the competent authority of each participating country and approval obtained prior to study start in the respective country. Submission to relevant regulatory authorities in all participating countries lies within the sponsor's responsibility (if not required otherwise according to country specific requirements). The corresponding national coordinator will provide substantial support for any submission process. The study will be performed in accordance with the respective national legislation in each country.

15.3 Modification of Protocol

Any substantial amendment to the clinical trial protocol requires written approval/favourable opinion by the IRB / IEC prior to its implementation, unless there are overriding safety reasons that require immediate action. In some instances, an amendment may require a change to the informed consent form. In this case, the investigator must receive an IRB /IEC approval/favourable opinion concerning the revised informed consent form prior to implementation of the change.

Substantial amendments will be notified to the competent authorities too.

15.4 Financing and Insurance

The costs necessary to perform the study will be agreed upon with each investigator and will be documented in a separate financial agreement which will be signed by the investigator and the CRO on behalf of the sponsor, prior to the study commencing.

A patient insurance has been effected by the sponsor of the trial. Country specific requirements will be taken into account.

The insurance certificate as well as the insurance conditions will be handed out to all investigators. The insurance conditions have to be provided to the patients too.

15.5 Investigator's Information on IMP

Apixaban as well as VKAs are authority approved and marketed in all European countries and in the USA. The respective summary of product characteristics is publicly available in the internet.

15.6 Personal Data and Data Protection

All data obtained in the context of the clinical trial are subject to data protection. This applies to patients' data as well as to investigators' personal data which may be included in any database of the sponsor or the CRO.

The investigating physicians shall take care that patient documents (e.g. copies of reports on special findings) transmitted to the CRO or the sponsor contain no names, but only the year of birth and a relevant patient number. The storage of data for statistical analysis shall likewise be performed only under the patient's random/study number.

15.7 Data Handling and Record Keeping

15.7.1 Completion of Case Report Forms

All medical data in this trial are to be recorded directly in the e-CRFs. Documentation on paper will be restricted to exceptional circumstances only.

The investigator must ensure the accuracy, completeness and timeliness (and legibility in case of documentation on paper) of data.

15.7.2 Archiving

The investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. The investigator has to retain the study documents (i.e. investigator site file) after the completion or discontinuation of the study for the time period as required by national legislation. This especially applies to patients' signed informed consent forms and the patient identification list.

The investigator must notify the sponsor prior to destroying any essential study documents within the specified period following completion or discontinuation of the trial.

15.8 Confidentiality

All information disclosed or provided by the sponsor (or any company / institution acting on his behalf), or produced during the trial, including, but not limited to, the clinical trial protocol, the e-CRFs and the results

obtained during the course of the trial, is confidential. The investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the sponsor. The sub-investigators shall be bound by the same obligation as the investigator. The investigator shall inform the sub-investigators of the confidential nature of the trial. Both, the investigator and the sub-investigators shall use the information solely for the purposes of the trial, to the exclusion of any use for their own or for a third party's account.

15.9 Responsibilities

The sponsor of this trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the trial with regard to ethical aspects, clinical trial protocol compliance, integrity and validity of the data recording.

16 Final Report and Publication Policy, Property Rights

The sponsor will be responsible for preparing the final study report that is to be signed by the SC. The sponsor will communicate the results of the trial to the investigators, authorities and IRBs/ECs.

The SC will be primarily responsible for the creation, review and submission of publications and presentations relating to the major aspects of the study within a timely fashion after completion of the study. All analyses will be the responsibility of the SC. Manuscripts for publication will be drafted by members of the SC or other interested investigators. All manuscripts will be subject to coordinated submission and review prior to submission. Coordination will be done by SC.

AXAFA is an investigator-initiated trial. Interested investigators and initiatives will be encouraged and supported as appropriate if they propose additional issues that may be studied within the main trial. These materials must be submitted to the SC for review and comment prior to publication or public dissemination. All relevant measures for transparency of clinical trials, and especially the recommendations of the editors of the major medical journals, will be met.

The publication rules are regulated separately and described in detail in a publication policy that is confirmed by the SC and part of the contract of the SC members.

All information and documents provided by the sponsor or its representatives are and remain the sole property of the sponsor. The investigator shall not mention any information for any other intellectual property rights.

All results, data, documents and inventions, which arise directly or indirectly from the trial in any form, shall be the immediate and exclusive property of the sponsor.

17 Definitions and Classifications

17.1 Protocol Violation

Protocol violations are any unapproved changes, deviations or departures from the study design or procedures of a research project that are under the investigator’s control and that have not been reviewed and approved by the SC.

17.2 Major Protocol Violation

Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator’s control and not in accordance with the IRB- or Ethics Committee-approved protocol that may affect the participant’s rights, safety or well-being, or the completeness, accuracy and

reliability of the study data. Patients with major protocol violations will be excluded from the per protocol analysis. Some major protocol violations may be reported to regulatory authorities within defined time periods as mandated. Study specific definitions of major protocol violations will be given by the SC.

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19 Signatures

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
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Appendix II Time Schedule

	Tasks	**Date**
Study planning	Draft Protocol, review and finalisation by Steering Committee	Nov 2013 to Jul 2014
Study preparation	Definition of drug supply mechanism	May to Jul 2014
	Set up of e-TMS (MARVIN), preparation of e-CRF; preparation of all other study relevant documentation	May to Dec 2014
	▪ Site selection, site contacts, site evaluation	May to Oct 2014
	▪ EC and CA submission	Aug 2014 to Mar 2016
Study initiation	▪ Site contracting	Sep 2014 to Jul 2016
	▪ Supply of the sites with study materials, initiation visits	Dec 2014 to Jul 2016
	▪ Recruitment period (FPI to LPI)	Feb 2015 – Jan 2017
Study duration	Treatment / Follow-up of last patient (LPI to LPO)	Feb to Jun 2017
	Mean follow-up period of all patients, assuming a linear patient recruitment	3.7 months
Interim analyses	▪ After 200 pts. have undergone AF ablation and completed the 3-months FU period	Estimated Apr 2016
	▪ After 400 pts. have undergone AF ablation and completed the 3-months FU period	Estimated Nov 2016
Study closure	Final data cleaning /study closure	Jul 2017
Final analysis	Statistical analysis, incl. review by Steering Committee	Aug to Sep 2017

Appendix III Change management of anticoagulants at start and discontinuation of study drug

This appendix provides clinical guidance how to safely change patients from one anticoagulant to another anticoagulant which may be required at the time of enrolment (after randomisation) and at the end of study medication.

1. VKA to NOAC

- Discontinue the VKA and measure INR frequently (usually every day).
- Once INR is ≤2.0, the NOAC should be started without delay.
- If INR is >2.0, frequent INR measurements are needed (e.g. daily). NOAC treatment should be commenced when INR is ≤2.0.

2. NOAC to VKA

- Measure baseline INR.
- Initiate the VKA at the same time the patient is still on the NOAC, and continue the NOAC until INR is ≥2.
- The initial VKA dose will be an estimated daily dose if the INR is >1.5, and double the estimated daily dose if INR is ≤1.5. Thereafter, the expected daily maintenance dose of VKA is given.
- During concomitant administration of VKA and NOAC, take an INR measurement every day to decide when to discontinue the NOAC (i.e. when INR is ≥2).

3. NOAC to NOAC

When switching between NOACs, start the new NOAC at the time the next dose of the original NOAC is scheduled and terminate the original NOAC intake. Care should be taken in patients with impaired renal disease and in situations where higher-than therapeutic concentrations are expected.

4. Acetylsalicylic acid or clopidogrel to NOAC

Initiate the NOAC at the time of randomisation and terminate acetylsalicylic acid or clopidogrel intake.

5. Parenteral anticoagulant to NOAC

- Terminate intravenous unfractionated heparin (IV UFH) at the time of randomisation. Administer the first NOAC dose 2 hours after discontinuation of UFH in patients with normal kidney function (eGFR >60 ml/min) or 4 hours for patients with eGFR of 30-60 ml/min.
- Terminate the low-molecular weight heparin (LMWH) at the time of randomisation and start the NOAC at the time the next dose of LMWH is scheduled. Do not co-administer NOAC and LMWH ("NOAC replaces LMWH").

6. NOAC to parenteral anticoagulant

Start the parenteral anticoagulant (IV UFH, LMWH) at the time the next dose of the terminated NOAC is scheduled.

Appendix IV Bleeding Academic Research Consortium (BARC) Classification of Bleeding Events

Table reproduced from (34).

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: ➢ requiring nonsurgical, medical intervention by a healthcare professional ➢ leading to hospitalisation or increased level of care, or ➢ prompting evaluation
Type 3	Type 3a Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed); Any transfusion with overt bleeding
	Type 3b Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed); Cardiac tamponade; Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid); Bleeding requiring intravenous vasoactive agents
	Type 3c Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal); Subcategories confirmed by autopsy or imaging or lumbar puncture; Intraocular bleed compromising vision
Type 4	Coronary artery bypass graft (CABG) related bleeding ➢ Perioperative intracranial bleeding within 48 h ➢ Reoperation after closure of sternotomy for the purpose of controlling bleeding ➢ Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period† ➢ Chest tube output ≥2 L within a 24-h period
Type 5	Fatal bleeding
	Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
	Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood =1 g/dL haemoglobin).
† Cell saver products are not counted.

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.

If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

Appendix V Karnofsky Scale

(Karnofsky DA, Burchenal JH. (1949). "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press. Page 196)

In medicine (oncology and other fields), performance status is an attempt to quantify patients' general well-being and activities of daily life.

The Karnofsky Scale runs from 100 to 0, where 100 is "perfect" health and 0 is death. Although practitioners occasionally assign performance scores in between standard intervals of 10, there is no substantiated rationale for this and prognostication is not improved. This scoring system is named after Dr David A. Karnofsky, who described the scale with Dr Joseph H. Burchenal in 1949.

100% – normal, no complaints, no signs of disease

90% – capable of normal activity, few symptoms or signs of disease

80% – normal activity with some difficulty, some symptoms or signs

70% – caring for self, not capable of normal activity or work

60% – requiring some help, can take care of most personal requirements

50% – requires help often, requires frequent medical care

40% – disabled, requires special care and help

30% – severely disabled, hospital admission indicated but no risk of death

20% – very ill, urgently requiring admission, requires supportive measures or treatment

10% – moribund, rapidly progressive fatal disease processes

0% – death

Appendix VI Declaration of Helsinki (Version Fortaleza, October 2013)

http://www.wma.net/en/30publications/10policies/b3/

Appendix VII Definition of hospitalisation for cardiovascular reasons

Cardiovascular hospitalisations comprise all hospitalisations requiring at least one overnight stay in the hospital for cardiovascular reasons excluding stroke (ischemic stroke, subarachnoid haemorrhage and haemorrhagic stroke) and major bleeding (BARC 2-5).

The pre-specified main causes for cardiovascular hospitalisation are:

- acute coronary syndrome,
  (i.e. any hospitalisation that is due to new-onset or worsening chest pain is considered as an acute coronary syndrome when myocardial ischemia or coronary heart disease requiring therapy are found upon admission. Objective signs may consist of significant coronary stenosis upon angiography (usually requiring intervention), demonstration of acute ischemia by electrocardiogram or stress test (e.g. stress echocardiography, nuclear methods, or cardiac magnetic resonance imaging), or elevated cardiac biomarkers such as troponin I, troponin T, and/or creatine kinase with a cardiac origin. This outcome parameter comprises all myocardial infarctions (STEMI or NSTEMI).
- stable angina pectoris or atypical chest pain,
- worsening of heart failure
  (i.e. any hospitalisation for new-onset shortness of breath or worsening of exercise capacity that severely limits daily activities should raise the suspicion of worsening heart failure. Worsening of heart failure should be confirmed by adequate clinical findings or measures, e.g. severe peripheral oedema, dyspnoea at rest, biomarkers such as brain natriuretic peptide, or demonstration of lung edema on chest radiograph or worsening of left ventricular function, or by use of iv diuretics. Hospitalisations for acute cardiac decompensation due to AF are part of this outcome parameter),
- syncope,
- TIA,
- non-fatal cardiac arrest,
- ventricular arrhythmia,
- cardiac transplantation,
- any type of cardiovascular surgery,
- implantation of a pacemaker, ICD or any other cardiac device,
- percutaneous coronary, cerebrovascular or peripheral intervention,
- blood pressure related hospitalisation (hypotension, hypertension; except syncope),
- cardiovascular infection,
- pulmonary embolism or deep vein thrombosis,
- pulmonary vein stenosis,
- pericardial tamponade,
- atrio-oesophageal fistula,
- hospitalisation for AF
  (i.e. any hospitalisation for treatment of AF with at least one overnight stay, e.g. initiation of antiarrhythmic drug therapy, unplanned cardioversion or unplanned ablation of AF) and
- other cardiovascular reason.

Appendix VIII List of strong inducers/inhibitors of P-gp and CYP3A4 which lead to contraindication for the combined use with apixaban (Practical Guide Use of NOACs (48))

- Ketoconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Rifampicin
- St John's wort
- Carbamazephine
- Phenytoin
- Phenobarbital
- HIV protease inhibitors:
  - Ritonavir
  - Saquinavir
  - Indinavir
  - Lopinavir
  - Fosamprenavir
  - Atazanavir
  - Tipranavir
  - Darunavir

Appendix IX Modified Rankin Scale

The Modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It has become the most widely used clinical outcome measure for stroke clinical trials.

The scale was originally introduced in 1957 by Dr. John Rankin of Stobhill Hospital, Glasgow, Scotland, and then modified to its currently accepted form by Prof. C. Warlow's group at Western General Hospital in Edinburgh for use in the UK-TIA study in the late 1980s. The first publication of the current modified Rankin Scale was in 1988 by van Swieten, et al., who also published the first interobserver agreement analysis of the modified Rankin Scale.

Interobserver reliability of the mRS can be improved by using a structured questionnaire during the interview process and by having raters undergo a multimedia training process. The multimedia mRS training system which was developed by Prof. K. Lees' group at the University of Glasgow is available online. The mRS is frequently criticized for its subjective nature which is viewed as skewing results, but is used throughout hospital systems to assess rehabilitation needs and outpatient course. These criticisms were addressed by researchers creating structured interviews which ask simple questions both the patient and/or the caregiver can respond to.

More recently, several tools have been developed to more systematically determine the mRS, including the mRS-SI, the RFA, and the mRS-9Q. The mRS-9Q is in the public domain and a free web calculator is available at www.modifiedrankin.com.

The scale runs from 0-6, running from perfect health without symptoms to death.

0 - No symptoms.
1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3 - Moderate disability. Requires some help, but able to walk unassisted.
4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6 - Dead.