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Design and rationale of a randomized controlled trial comparing apixaban to phenprocoumon in patients with atrial fibrillation on chronic hemodialysis – the AXADIA - AFNET 8 study

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ABSTRACT

Introduction: Patients with end-stage kidney disease requiring maintenance hemodialysis treatment experience a dramatic cardiovascular morbidity and mortality. Due to the high athero- and arteriosclerotic burden and profound alterations in hemostasis, they frequently suffer and die from both thromboembolic and bleeding events. This is a particular concern in patients on hemodialysis with atrial fibrillation (AF). Controlled trials on the optimal anticoagulation in patients with AF on hemodialysis are not available. The randomized controlled phase IIIb AXADIA – AFNET 8 trial will evaluate the safety and efficacy of the factor Xa inhibitor apixaban in patients with AF requiring hemodialysis.

Methods and analysis: A total of 222 patients will be randomized in an open-labelled, 1:1 design to receive either apixaban 2.5 mg twice daily or dose-adjusted vitamin K antagonist therapy (VKA, target international normalized ratio 2.0-3.0). All patients will be treated and followed up for a minimum of 6 months up to a maximum of 24 months. The primary outcome is major or clinically relevant, non-major bleedings or death of any cause. Secondary outcomes include stroke, cardiovascular death, and other thromboembolic events, thus exploring the efficacy of apixaban. The first patient was randomized in June 2017.

Ethics and dissemination: The study protocol was approved by the Ethical Committee of the Landesaertzekammer, Westfalen-Lippe and the Medical Faculty of the University of Muenster, Muenster, Germany (reference number: 2016-598-f-A). Written informed consent will be obtained from all patients prior to study participation, including their consent for long-term follow-up. AXADIA – AFNET 8 is an investigator-initiated trial. Sponsor is AFNET, Muenster, Germany. Study findings will be disseminated to Bristol-Meyers Squibb, Munich, Germany, and Pfizer, Berlin, Germany, to the participating centers, at research conferences and in peer-reviewed journals.

Trial registration numbers: ClinicalTrails.gov: NCT02933697, EudraCT No. 2015-005503-84

Keywords: anticoagulation, atrial fibrillation, hemodialysis, cardiovascular morbidity and mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomized controlled phase IIIb trial will provide important information about the safety and efficacy of apixaban compared to Vitamin-K antagonist in patients on hemodialysis and with non-valvular atrial fibrillation.
- Although a larger cohort would have been desirable, the number of patients which will be enrolled in this study will be sufficient to determine a significant difference regarding the safety endpoints.
- This trial will provide evidence which type of anticoagulation shall be preferred in patients on hemodialysis and with non-valvular atrial fibrillation. The lack of a control arm without any oral anticoagulation is a limitation of the study design.

INTRODUCTION

More than 15 million people in the USA and more than 6 million people in Germany suffer from chronic kidney disease (CKD), with an expected increase in aging populations with more comorbidities such as diabetes or hypertension.[1-6] Approximately 120,000 patients are alive in CKD stage G4 in Germany, and 85,000 in stage G5D (end-stage kidney disease (ESKD) on peritoneal or hemodialysis).[5] CKD is an important driver of cardiovascular mortality,[4] illustrating the need for optimal cardiovascular protection in patients with CKD. Atrial fibrillation (AF) is common in CKD affecting ca 10-25% of patients with end-stage CKD.[7-10]

Patients with CKD are at high risk of thromboembolic events and bleedings.[7,8] Concordantly, ischemic and hemorrhagic stroke are typical and frequent complication in ESKD: data from the large US Renal Data System showed a stroke incidence of 15.1% in hemodialysis patients compared to 9.6% in other stages of CKD, and 2.6% in a control cohort without CKD; stroke-related 2-year mortalities of 74%, 55%, and 28%, respectively, have been reported from some analyses.[11] Oral anticoagulation with vitamin K antagonists (VKA) can prevent most thromboembolic events in patients with atrial fibrillation at risk of stroke.[12] Non vitamin-K antagonist oral anticoagulants (NOAC) have a similar effectiveness with lower risk of bleeding, particularly intracranial bleeds.[13]

The effectiveness and safety of VKA and NOACs in patients with non-valvular AF is well established, including in patients with mild or moderate CKD.[12-14] Unfortunately, there is very little evidence on the safety and efficacy of NOACs in patients with AF and end-stage CKD.

Bleeding rates in CKD patients on dialysis treated with vitamin K antagonists are high,[15-19] illustrating the need for safe anticoagulation in these patients.[20] In a retrospective analysis of the ARISTOTLE data,[21] the reduction in major bleedings was greatest in patients in advanced CKD on apixaban compared to patients on VKA. Apixaban or other NOACs have not been evaluated in patients with AF on hemodialysis. To address this evidence gap, the "Safety Study Assessing Oral **A**nticoagulation with Api**xa**ban versus Vitamin K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease (ESKD) on Chronic Hemo**dia**lysis Treatment" (AXADIA – AFNET 8) will compare the safety of apixaban to VKA therapy in CKD patients on dialysis.

METHODS AND ANALYSIS

Primary and secondary objective

The primary objective is to assess the safety of apixaban compared to VKA therapy (carried out using the local VKA phenprocoumon) in patients with AF and ESKD on maintenance hemodialysis treatment. The primary hypothesis of the study is that apixaban has a superior safety profile in patients with AF and ESKD on hemodialysis compared to phenprocoumon, while providing similar efficacy in reducing thromboembolic events. The secondary objective is to compare the efficacy of apixaban with VKA regarding prevention of thromboembolic events in patients with ESKD on hemodialysis and AF.

Patients, study design and randomization

AXADIA – AFNET 8 is an investigator-initiated, prospective, parallel-group, multi-center trial conducted in 25-30 German study sites (Supplements, Appendix A). Adult patients aged ≥18 years with ESKD on maintenance hemodialysis treatment 3 times a week and an indication for oral anticoagulation due to non-valvular AF will be centrally and electronically randomized into two treatment arms: apixaban or phenprocoumon. As phenprocoumon needs constant international normalized ratio (INR) control, the study will be performed with an open-label administration of the study drugs. The randomization will be stratified by two conditions: First, patients with a previous thromboembolism including any type of ischemic stroke that meet the above criteria, can be included after more than 3 months if they are not severely handicapped as indicated by a value of 0 or 1 on the modified Rankin scale[22] and will be stratified to assure equal distribution within the groups. For further details on inclusion and exclusion criteria see Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion criteria
• End-stage kidney disease with chronic hemodialysis treatment 3 times per week (with about 4 hours per dialysis)

- Chronic (i.e. repeated) paroxysmal, persistent or permanent atrial fibrillation documented by standard or Holter ECG on at least 2 separate days before (or apart from) hemodialysis procedures
- Increased risk of stroke or systemic embolism identified by a CHA_2DS_2-VASc score of 2 or more as an indication for oral anticoagulation
- Patients with a previous ischemic stroke that meet the above criteria, can be included after more than 3 months if not severely handicapped (modified Rankin scale 0 or 1 of 6[22])
- Males and females, aged 18 or older
- Signed written informed consent

Exclusion criteria at baseline

- AF or atrial flutter due to reversible causes (e.g., thyrotoxicosis, pericarditis)
- Patients with a new onset of hemodialysis within the last 3 months
- Clinically significant (moderate or severe) aortic and mitral stenosis
- Conditions other than AF that require chronic anticoagulation (e.g., a prosthetic mechanical heart valve).
- Active infective endocarditis
- Any planned interventional or surgical AF or atrial flutter ablation procedure
- Any active bleeding
- A serious bleeding event in the previous 6 months before screening
- Inadequately controlled (HbA1c levels >8.5%) or untreated diabetes
- History of malignant neoplasms at high risk of current bleeding (see summary of product characteristics of study drugs)
- Known indication for treatment with NSAIDs (ASA up to 100 mg per day is allowed)
- Impaired liver function e.g., caused by active infection with HIV, HBV or HCV, hepatitis or other liver damage
- Any type of stroke within 3 months prior to baseline
- Other indication for anticoagulation than AF
- Valvular heart disease requiring surgery
- A high risk of bleeding (e.g., active peptic ulcer disease, a platelet count of <100,000 per cubic millimeter or hemoglobin level of <8 g per deciliter)
- Documented hemorrhagic tendencies or blood dyscrasias
- Current alcohol or drug abuse
- Life expectancy of less than 1 year
- Indication for dual platelet inhibition at baseline (ASA ≤ 100 mg/day is allowed; clopidrogel is at baseline excluded at any dose, during trial allowed for up to 30 days).
- Any disease or circumstances on account of which the subject should not participate in the study in the opinion of the investigator
- Psychiatric condition that might limit the participation in the study and/or that lead to the assumption that the ability to completely understand the consequences of consent is missing
- Pregnant or breast-feeding women
- Documented intolerance to one or both active substances of the study drugs

AF indicates atrial fibrillation; ASA, acetylsalicylic acid; CHA_2DS_2-VASc score, **c**ongestive heart failure/LV dysfunction, **h**ypertension, **a**ge ≥75 years, **d**iabetes, previous **s**troke/transischemic attack/thrombo-embolism, **v**ascular disease, **a**ge 65-74, **s**ex **c**ategory (female); NSAID, non-steroidal anti-inflammatory drugs.

Second, patients actually on phenprocoumon therapy can also be randomized; however, their proportion will be limited to a maximum 50% of the entire cohort to ensure that AXADIA – AFNET 8 also provides safety information in anticoagulation-naïve patients. This condition will also be concerned as stratification in the randomization procedure. In overview, patient's recruitment and allocation is displayed in Figure 1 in accordance to the CONSORT standard.

Study procedures

Apixaban

Patients randomized to apixaban will be treated with apixaban 2.5 mg twice a day. Apixaban was chosen as its mode of excretion is mainly via the bile, theoretically enabling stable plasma levels independent of hemodialysis. In addition, a subanalysis of the effect of chronic kidney disease in the ARISTOTLE trial suggested that the relative bleeding risk of apixaban compared to VKA was lower in patients with advanced chronic kidney disease (eGFR 25-50 ml/h).[21] The study drug will be dispensed to the patient at the study site. The patient will be instructed to take the study drug with an approximately 12 hour gap apart. The compliance will be controlled by pill count and treatment interruptions will be documented and tracked centrally in the e-trial management system.

VKA

Patients randomized to VKA will be treated with phenprocoumon, the locally used vitamin K antagonist in Germany, with a target INR of 2-3. Patients will receive a prescription for phenprocoumon at the study site on the day of randomization. According to measured INR and the summary of product characteristics, the investigator will recommend an individually adjusted dose to the patient. Weekly INR controls will be carried out to ensure the compliance to the target INR.

The protocol provides detailed recommendations for anticoagulation during hemodialysis (Supplements, Appendix B).

All subjects will be treated with the study drug for at least 6 months. Subjects who are included early during the trial will stay under treatment in the study until the last subject has completed the treatment period of 6 months. This will probably lead to a study participation of about 24 months for the first subjects enrolled (Figure 2).

Timelines and follow-up

Screening period (up to 7 days before baseline visit): All patients must give full written informed consent during the screening period. Inclusion and exclusion criteria will be checked. Demographical and anthropometric data, renal status, concomitant diseases and medication, and data on hemodialysis will be documented. Blood count, INR evaluation, ECG recording, and risk stratification will be performed.

Baseline visit: Adherence to inclusion and exclusion criteria will be checked. Data on hemodialysis, and concomitant medication will be documented. If applicable, blood parameters, thromboembolic and bleeding events, adverse events, and events of special interest will be recorded. Patients will be randomized. EQ-5D questionnaire will be completed by the patient. For subjects randomized for phenprocoumon INR evaluation will be performed.

Follow-up visits: During the monthly follow-up visits, data on hemodialysis and INR evaluation (for subjects on phenprocoumon) will be documented. If applicable, changes in concomitant medication, blood parameters, thromboembolic and bleeding events, adverse events, and events of special interest will be documented. EQ-5D questionnaire will be completed on visit 6, 12, and 18 by the patient. Adherence to study drug will be performed on a quarterly basis.

End of treatment: Data on hemodialysis, concomitant medication, concomitant diseases, and adherence to study drug will be documented. ECG recording will be performed. EQ-5D questionnaire will be completed by the patient. For subjects on phenprocoumon INR will be measured. If

applicable, thromboembolic and bleeding events, adverse events, and events of special interest will be recorded.

End of study (30 days after end of treatment): Data on concomitant medication, blood parameters, thromboembolic and/or bleeding events, adverse events, and events of special interest will be documented.

Adverse event reporting: An adverse event (AE) is defined as any untoward medical occurrence or worsening of a pre-existing medical condition in the patient administered the study drug and that does not necessarily have a causal relationship with the study drug (i.e. apixaban or phenprocoumon). All AEs, regardless of related or not related to the study drug, which occur from screening to end of study will be collected and seriousness, severity, and causality will be assessed by the investigator. All AEs will be reported in detail in the electronic case report form (eCRF).

Primary, secondary, and other outcomes

Primary outcome is a composite of major and clinically relevant non-major bleeding in accordance to the *International Society of Thrombosis and Hemostasis* (ISTH) consensus[23] as well as shunt / fistula bleedings in dialysis patients on anticoagulation. The detailed list of all safety endpoints is given in Table 2.

Table 2: Endpoints

***Primary outcome**:* Composite of major and clinically relevant, non-major bleeding events and death of any cause

Major Bleeding events as defined by ISTH[23] and complemented by other serious bleeding events:

- Fatal bleeding
- Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more
- Bleeding leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding
- Bleeding that requires an operation or endoscopic intervention (arthroscopic, endovascular or a hemarthrosis)

Clinically relevant, non-major bleeding (according to ISTH consensus[23], complemented by relevant bleeding events in dialysis patients):

- Bleeding resulting in hospitalization or prolonged hospitalization
- Bleeding requiring medical or surgical treatment by a physician
- Bleeding leading to a modification of the given anticoagulant therapy
- Gastrointestinal bleeding proven by endoscopy or surgery
- Shunt- / catheter-induced bleeding
- Bleeding between dialysis sessions
- Prolonged bleeding requiring compression for more than 30 min after dialysis needle removal

***Efficacy events**:*

- Myocardial infarction
- Ischemic stroke
- All-cause death
- Cardiovascular death
- Deep vein thrombosis and/or pulmonary embolism

***Composite endpoint**:*

- Myocardial infarction
- Ischemic stroke
- All-cause death
- Deep vein thrombosis and/or pulmonary embolism

Events of special interest:

- Dialysis shunt thrombosis
- Clotting of dialysis membrane

***Pharmacokinetics** (sub-study in 28 apixaban patients)*

- Apixaban plasma level prior and after hemodialysis, see Figure 3

ISTH indicates International Society on Thrombosis and Haemostasis.

Secondary outcomes include thromboembolic events. Details of the secondary outcomes and other outcomes are given in Table 2.

Patient and public involvement

The outcome measures could have an impact on the patients' priorities and preferences. It will be a substantial improvement for patients to take a defined dose of oral anticoagulation twice a day. It can be expected that there will be less bleeding events under the study substance apixaban. However, no patients were involved in the design of this study, in the recruitment to and conduct of the study. The burden of the intervention will not be assessed by patients themselves. Study results will be disseminated to the patients by a circular letter.

Pharmacokinetic substudy

The dosing of apixaban with 2.5 mg twice daily was chosen based on pharmacokinetic modeling and based on the currently recommended dose for apixaban in patients with CKD stage G4 according to the European label.[24] Furthermore, results from a small pivotal study were published indicating that a dosage of 2.5 mg apixaban twice daily in dialysis-dependent patients will result in similar plasma levels as the higher dosage of 5 mg twice daily in healthy individuals.[25] To confirm these preliminary findings, a pharmacokinetic sub-study will be conducted in 28 patients randomized to apixaban to determine plasma serum levels of apixaban prior to and after hemodialysis, and also after a short (2 days), and a long (3 days) dialysis interval (Figure 3). In these patients two blood samples will be collected, one sample before and one after hemodialysis. Apixaban levels will be measured at a central laboratory in Richmond, VA, USA.

Sample Size Calculations

One recent publication reported bleeding rates in a similar (but not identical) setting in hemodialysis patients treated with dabigatran and rivaroxaban, acetylsalicylic acid (ASA) and VKAs.[26] Based on these data and using similar endpoint definitions especially for bleedings, it was assumed for the AXADIA – AFNET 8 study setting that apixaban would have comparable bleeding rates as ASA in dialysis patients. The latter assumption is supported by the AVERROES trial[27] in which apixaban and ASA were compared in a cohort of non-dialysis depended patients who were not considered suitable for oral anticoagulation due to a high bleeding risk: in that trial including patients with a comparable high risk as here, the rates of major and clinically relevant non-major bleedings were similar in the apixaban group and the ASA group. Based on these data, we expect a hazard rate for the combination of major and clinically relevant non-major bleedings of 0.0789 per months for apixaban and 0.131 for phenprocoumon. According to these figures, a total sample size of 166 patients will be sufficient to demonstrate superiority of apixaban treatment with 80% power with respect to the primary endpoint, and also with respect to clinically relevant non-major bleedings only. Including a 20% security margin and about 10% drop-outs, AXADIA – AFNET 8 will randomize 222 patients (Figure 1).

Statistics

The *full analysis* set will include all randomized patients with and without any kind of protocol violations, applying the intention-to-treat-principle. In the *per-protocol population*, patients with relevant protocol violations will be excluded. The *safety* set will consist of all patients who were randomized and received at least one dose of the study drug, applying the as-treated principle.

Continuous variables will be presented group-wise by means ± standard deviation and tested by t-tests for independent samples. Skewed data will be transformed towards normality or tested by non-parametric U-tests. Categorical variables will be presented by counts and percentages and compared by chi-square tests or Fisher's exact tests as appropriate.

In the primary statistical analysis, the treatments will be compared with respect to the primary safety endpoint time to first occurrence of a major or clinically relevant non-major bleeding or death of any

cause. Let HR denote the corresponding hazard ratio of the apixaban treatment versus VKA (phenprocoumon) treatment. Two statistical null hypotheses will be tested:

$H_0^{Superiority}$: HR≥1 versus $H_1^{Superiority}$: HR<1 (proof of superiority of apixaban)

$H_0^{Non\text{-}Inferiority}$: HR≥1.25 vs. $H_1^{Non\text{-}Inferiority}$: HR<1.25 (proof of non-inferiority of apixaban)

The multiple one-sided significance level is set to α=2.5%. A sequentially rejective multiple test procedure will be applied that controls the familywise error rate in the strong sense at pre-specified significance level α. The hypothesis $H_0^{Non\text{-}Inferiority}$ is defined to be the initial hypothesis and is assigned the local significance level $\alpha(H_0^{Non\text{-}Inferiority})$=2.5%. If the initial hypothesis $H_0^{Non\text{-}Inferiority}$ is rejected, subsequently the hypothesis $H_0^{Superiority}$ is tested on local significance level 2.5%. The primary statistical analysis provides confirmatory statistical evidence.

The superiority test will be performed in the full analysis set that consists of all randomized patients, including patients with any kind of protocol violations, applying the intention-to-treat principle. The non-inferiority test will additionally be performed in the per-protocol population, excluding patients with relevant protocol violations. Statistically significant non-inferiority will be claimed only if the result is supported both in the intention-to-treat analysis and the per-protocol analysis.

The primary analysis will be up to the first occurrence of the endpoint. Beyond the above primary statistical analysis of the primary endpoint, an extended analysis of the primary endpoint will additionally take recurrent events into regard and will be performed by fitting an Anderson-Gill model with robust estimation of coefficients and variance terms to the data. From all models, hazard ratios and two-sided 95% confidence limits will be calculated and discussed whether safety risks can be derived based on the results. Statistical analyses of the primary endpoint will be repeated in the safety population that consists of all patients who received at least one dose of the study drug, applying the as-treated principle.

The secondary endpoints, both events of special interest and the composite endpoint (Table 2) are the efficacy endpoints and will be analyzed on an intention-to-treat-basis by descriptive statistics only due to the small sample size which will probably not be sufficiently large enough to demonstrate superiority. Adjusted Cox proportional hazard models, Anderson-Gill models and the described sensitivity analyses will be performed as described above. No adjustment for multiplicity will be provided as the efficacy analysis is secondary behind the primary safety analysis.

The Data and Safety Monitoring Board will adjudicate the following safety and efficacy endpoints: major bleeding, clinically relevant, non-major bleeding, myocardial infarction, ischemic stroke, all-cause death, cardiovascular death, and deep vein thrombosis and/or pulmonary embolism (Table 2)

Ethicals and dissemination

AXADIA – AFNET 8 is an investigator-initiated trial which is conducted by the Kompetenznetz Vorhofflimmern e.V. (Atrial Fibrillation NETwork, AFNET), Muenster, Germany, as responsible sponsor. The study is financed by Bristol-Myers Squibb (BMS, Munich, Germany) and Pfizer (Berlin, Germany) (Supplements, Appendix C). AXADIA – AFNET 8 is registered at www.clinicaltrials.gov (NCT02933697) and at EudraCT (2015-005503-84). The study protocol was approved by the Ethical Committee of the Landesaerztekammer (Medical Association) Westfalen-Lippe and the Medical Faculty of the University of Muenster, Muenster, Germany (reference number: 2016-598-f-A) as lead ethics committee and by ethics committees at all participating sites. The design, conduct, and analysis of the study will be led by a steering committee (Supplements, Appendix D). A *Data and Safety Monitoring Board* will supervise this study (Supplements, Appendix E). All safety and efficacy endpoints will be evaluated by an independent *Endpoint Assessment Committee* blinded to treatment group, eCRF, e-trial system, data capture and monitoring (Supplements, Appendix F).

Study findings will be disseminated to Bristol-Meyers Squibb, Munich, Germany, and Pfizer, Berlin, Germany, to the participating centers, at research conferences, and in peer-reviewed journals.

DISCUSSION

Patients with CKD are well known to suffer from a high overall morbidity and mortality which is mainly driven by cardiovascular causes. This concerns especially patients in the advanced CKD stages G3 to G5 as demonstrated impressively by estimated 2.2 million deaths worldwide which are attributed only to patients in these stages.[4] These deleterious effects are caused on the one hand by the underlying diseases leading to kidney disease, on the other hand by alterations induced by CKD itself, which lead to rapid progress in athero- and arteriosclerosis but also to profound changes in hemostasis. Apart from these disease-related origins, the poor prognosis of patients with CKD - and especially those with ESKD – is, moreover, also attributed to a "therapeutic nihilism" of many treating physicians: Many AF patients with advanced CKD do not receive medications or treatments that have been proven or are at least considered to be beneficial in the general population.[28]

Oral anticoagulation in advanced kidney disease

This therapeutic nihilism is also of relevance in an ongoing, very controversial - in part highly emotional - debate about the value of oral anticoagulation in ESKD. Some of the protagonists accuse the others to harm the patients by administering a dangerous VKA, while their opponents point out that withholding the oral anticoagulation is not justified and actual harms the patients. In fact, currently no one has reliable and adequate data: While especially the large-sized trials with non-vitamin K antagonist oral anticoagulants have shown that oral anticoagulation is effective and safe even down to an eGFR of 25 or 30 ml/min,[29-32] below this threshold the available data are markedly limited regarding both quantity and quality.

Numerous small and retrospective studies have tried to assess the value of VKA in hemodialysis as summarized previously.[19, 33] However, all retrospective studies suffer from a significant selection bias of the patients treated with anticoagulation.[7] A meta-analysis of 11 observational studies with 25,407 AF patients with EKSD found warfarin to significantly lower stroke rate but to have no effect on mortality.[34]

Larger, unbiased observational information exists: In an analysis of the hospital data base of Denmark with more than 130,000 AF patients of whom 3,587 (2.7%) had non–end-stage chronic

kidney disease and 901 (0.7%) required renal-replacement therapy at the time of inclusion,[35] warfarin treatment was associated with a significantly decreased risk of stroke or systemic thromboembolism in patients with CKD and ESKD. Vitamin K antagonist mono-therapy and combination of VKA and ASA were associated with an increased risk of bleeding. Platelet inhibitors such as ASA did not reduce thromboembolic events but were associated with a high rate of adverse effects as also shown by others.[35, 36] Therefore, platelet inhibition does not seem to be a viable treatment in patients with AF and ESKD. A more recent report on an updated version of the same data set included meanwhile 150,000 patients[37] with an increased risk of stroke and systemic embolism (CHA_2DS_2-VASc score ≥2); their data showed that VKA therapy was significantly associated with lower all-cause mortality in patients with CKD (HR 0.64, 95% confidence interval 0.60-0.69) and in those with ESKD (HR 0.85, 95% confidence interval 0.72-0.99).

Another very recent publication from the same group has shown that time in therapeutic range (TTR) is of special importance in patients with reduced eGFR.[38] This aspect of TTR is included in AXADIA and the INR will be assessed and documented thoroughly.

All of these analyses do not allow an evidence-based decision how to treat hemodialysis patients to reduce their immense risk of stroke, systemic and venous thromboembolic events, bleedings and cardiovascular death. A recently started trial in the US (RENAL-AF, clinicaltrial.gov identifier NCT02942407) comparing apixaban (5 mg twice daily) with warfarin (INR 2-3) in patients with AF and ESKD on hemodialysis will add knowledge regarding safety and efficacy of apixaban in this critically ill patients' cohort.

Calciphylaxis with vitamin-K antagonists

Patients on maintenance hemodialysis treatment are often vitamin K-deficient which may be linked with advanced arterial calcifications due to a number of preclinical and few clinical studies.[39-42] However, a very recent clinical trial failed to demonstrate any negative impact of warfarin on calcification,[43] while also one older but large observational study from the US renal data system could not find any difference in overall survival between patients with and without warfarin.[44]

Although no explicit substudy regarding vascular calcifications is planned within AXADIA, major cardiovascular events due to calcifications are included in the efficacy endpoints of the trial and will be compared to patients receiving VKA and those under apixaban.

Limitations

With regard to the fact that this is an investigator-initiated trial, financial resources are spare and had to be applied thoroughly. Therefore, the number of patients which will be included to determine a significant difference regarding the safety endpoints is considered to be sufficient. A security margin of 20% should compensate the complete lack of any previous data in this field. Nevertheless, a larger cohort would have been desirable in order to identify differences concerning the efficacy endpoints.

The trial is adequately designed and powered to answer the question whether apixaban is non-inferior or possibly even superior to phenprocoumon regarding safety and maybe also regarding efficacy. However, since there is no control arm without any anticoagulation regime, the trial will provide evidence which type of anticoagulation to prefer if indicated (and if intended by the treating physician) - but not, whether any oral anticoagulation should be given at all in hemodialysis-dependent patients with AF.

Conclusion

The AXADIA trial will belong to the first randomized trials to compare two different regimens of anticoagulation in patients on maintenance hemodialysis. It will clarify if the novel direct factor Xa antagonist apixaban will be comparable or even be superior to a standard therapy with the VKA phenprocoumon in patients with paroxysmal, persistent or permanent AF. Finally, the AXADIA trial is a pilot study whose results shall provide the basis for a larger outcome study.

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Contributions

Holger Reinecke, Christoph Wanner, Rupert Bauersachs, Paulus Kirchhof, and Günter Breithardt conceived and designed the study; Holger Reinecke, Christoph Wanner, Rupert Bauersachs, Paulus Kirchhof, Günter Breithardt, and Sabine Jürgensmeyer contributed to protocol development; Joachim Gerß contributed to the statistical analysis; Holger Reinecke, Christiane Engelbertz, and Sabine Jürgensmeyer participated in the writing of the manuscript; all authors critically reviewed the manuscript and approved the final version.

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This investigator-initiated trial is conducted by the Kompetenznetz Vorhofflimmern e.V. (Atrial Fibrillation NETwork), Muenster, Germany. The study is financed by Bristol-Myers Squibb (BMS), Munich, Germany, and Pfizer, Berlin, Germany.

Conflict of interests

Holger Reinecke has received speaker honoraria from BMS, MedUpdate, NephroUpdate, and Pfizer. He has acted as a consultant for BMS, Pfizer and Pluristem receiving in part also financial compensations for this work. He has received research grants from the German Federal Ministry for Education and Research (BMBF). His division within the University Hospital of Muenster has taken or is still taking in multicenter trials of BARD, Bayer, BIOTRONIK, and Pluristem receiving patient fees and financial compensation for these efforts.

Paulus Kirchhof has received grants and non-financial support from the European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research and from several drug and device companies active in atrial fibrillation, and

has received honoraria from several such companies. He is listed as inventor on two patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

During preparation of this trial, Günter Breithardt has received speaker honoraria from BMS and Pfizer, he has been a member of the Scientific Advisory Boards for BMS and Pfizer, and Bayer Health Care. During his chairmanship of the Atrial Fibrillation NETwork, this institution has received funding for investigator-initiated trials from various companies (for details, please consult http://www.kompetenznetz-vorhofflimmern.de/en/research).

Rupert Bauersachs has received consulting / lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer.

Christoph Wanner does not report conflicts of interest in respect to the present work. Outside this area of research he has received speaker honoraria from Amgen, Boehringer-Ingelheim, Genzyme-Sanofi and Shire.

All other authors have nothing to disclose.

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Figure legends

Figure 1:

Patient's enrollment and allocation in accordance to the CONSORT stand is displayed. Of note, two stratifications are implemented in the randomization procedure: First, for patients who suffered from a previous stroke or systemic thromboembolic event which must have occurred at least 3 months before enrolment without residual limitations (only value of 0 or 1 on the modified rankin scale). Second, for patients who were already assigned to an oral anticoagulation whose proportion will be limited to 50% of the entire study cohort.

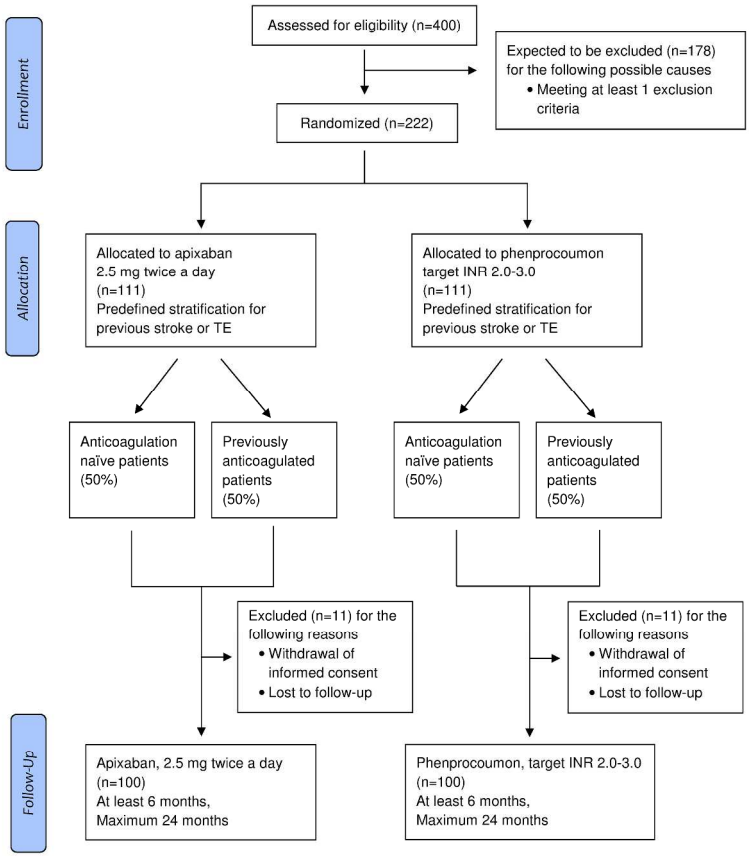
Figure 2:

Timelines and regular visits during the study period are presented. After screening visit, 2 qualifying ECGs showing atrial fibrillation must be sent to a central appraisal and, if all other inclusion and exclusion criteria match, randomization and inclusion can be performed within 7 days. Afterwards, monthly visits during the regular dialysis sessions will have to be documented. When the last recruited patient has been on treatment for 6 months the study will be terminated (*end of treatment*). All patients will be followed-up for another 30 days after which the study will be completed (*end of study*).

Figure 3:

The design of a pharmacokinetic (PK) substudy is given here. In total 28 patients who must give additional written informed consent will be examined regarding their apixaban levels before and after dialysis. Of these, apixaban levels will be assessed in 14 patients after the 3 day-long dialysis-free interval, and in another 14 patients after the short 2 day dialysis-free interval. Since patients on hemodialysis are regularly treated in 2 shifts (AM and PM), the 14 patients will be splitted again and apixaban levels will be assessed in 7 patients of the AM shift and another 7 patients of the PM shift. This might be of interest since patients will be instructed to take their apixaban between 7-8 AM and

PM, independent from the start of their dialysis shifts, so plasma levels may vary between the groups.



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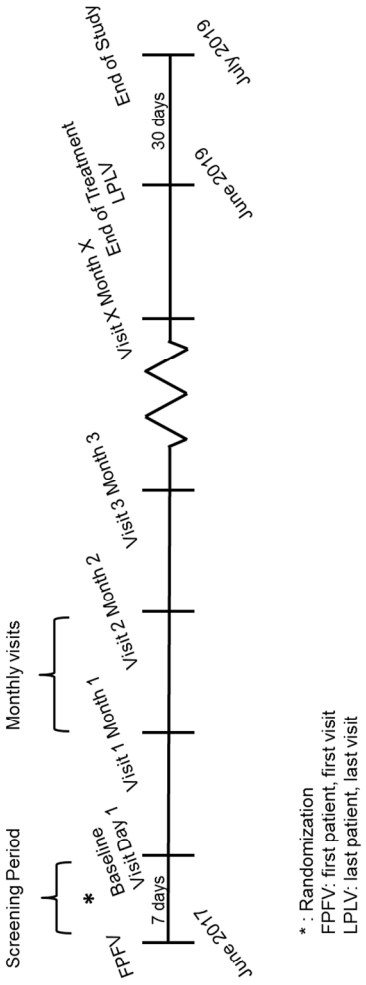

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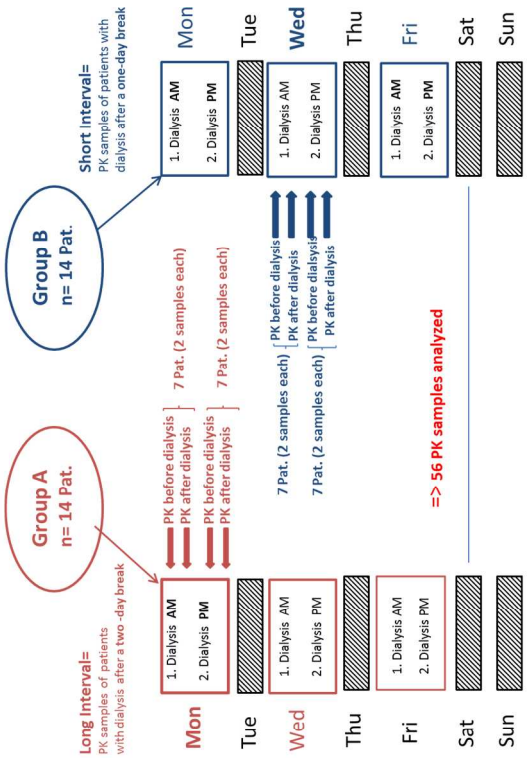

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Supplements

Appendix A: Participating centers (by status of 15th February 2018; more sites will be submitted to EC until summer 2018)

Site	Investigator
Robert-Bosch-Krankenhaus Stuttgart Allgemeine Innere Medizin und Nephrologie Stuttgart, Germany	Prof. Dr. Dominik Alscher
Klinikum Coburg Nephrologische Klinik Coburg, Germany	Prof. Dr. Markus Ketteler
KfH-Nierenzentrum Berlin-Neukölln Berlin, Germany	Prof. Dr. Christiane Erley
Zentrum für Nierenerkrankungen Hannover, Germany	Dr. Hans Schmidt-Gürtler
KfH-Nierenzentrum Bottrop Bottrop, Germany	Dr. Maria Lusch
KfH-Nierenzentrum Dülmen Dülmen, Germany	Dr. Wolfgang Bagnewski
Klinik für Nierenheilkunde und Bluthochdruck, Mühlenkreiskliniken Minden, Germany	Prof. Dr. Jörg Radermacher

Universitätsklinikum Münster Department für Kardiologie und Angiologie Münster, Germany	Prof. Dr. Holger Reinecke
KfH Nierenzentrum Bonn Universitätsklinikum Bonn Bonn, Germany	Prof. Dr. Rainer Woitas
Universitätsklinikum des Saarlandes Klinik für Innere Medizin IV Homburg/Saar, Germany	Prof. Dr. Gunnar Heine
KfH-Nierenzentrum Bischofswerda Bischofswerda, Germany	Dr. Kirsten Anding-Rost
Klinikum Lüdenscheid Klinik für Nephrologie und Dialyseverfahren Lüdenscheid, Germany	Prof. Dr. Jan Galle
Nierenzentrum Wiesbaden/Rheumatologie Wiesbaden, Germany	Prof. Dr. Frank Strutz
KfH-Nierenzentrum Wismar Wismar, Germany	Priv.-Doz. Dr. Heiko Hickstein
Nephrocare Berlin-Weissensee GmbH Berlin, Germany	Dr. Joachim Groll

Appendix B: Suggestions for anticoagulation during hemodialysis

No-heparin hemodialysis was developed for use in the patient at high risk of bleeding. Here, a pretreating of both the dialyzer and the blood lines will be washed with a solution of 2000 - 5000 units of heparin in one liter of NaCl. The heparinized NaCl solution is flushed from the extracorporeal lines prior to dialysis treatment. Extracorporeal blood flows are rapidly increased to 250 to 500 mL/min and maintained throughout the treatment. 25 to 30 mL NaCl flushes are administered every 15 to 30 min to the arterial limb (predialyzer) in order to minimize hemoconcentration and to wash any fibrin strands out of the kidney.

The use of minimum-dose heparin has been shown to reduce bleeding complications in high-risk patients when compared with regional heparinization and protamine neutralization. Here, a bolus of 500 units heparin will be administered every 30 min in order to keep the activated clotting time between 150 and 200 seconds. Alternatively, a continuous infusion of heparin with frequent monitoring of ACT can be used to achieve the same degree of anticoagulation.

Appendix C: Funding

The sponsor of the trial is Atrial Fibrillation NETwork, Muenster, Germany. The entire trial will be funded by Bristol-Myers Squibb, Munich, Germany, and Pfizer, Berlin, Germany.

Appendix D: Members of the steering committee

Holger Reinecke, MD, chief physician cardiology, Muenster, Germany; Christoph Wanner, MD, chief physician nephrology, Wuerzburg, Germany; Rupert Bauersachs, MD, senior consultant hemosteology, Darmstadt, Germany; Guenter Breithardt, MD, senior consultant cardiology, Muenster, Germany; Joachim Gerß, PhD, chief statistician, Muenster, Germany; Paulus Kirchhof, MD, Professor of Cardiovascular medicine, University of Birmingham, Birmingham, United Kingdom (represening AFNET); Martin Sommer, MD, and Michael Krekler, MD (representing Pfizer and BMS, nonvoting).

Appendix E: Members of the data Safety monitoring Board

Joachim Hoyer, MD, nephrologist, Marburg, Germany; Thomas Klingenheben, MD, cardiologist, Bonn, Germany; Guido Knapp, PhD, statistician, Dortmund, Germany.

Appendix F: Members of the endpoints assessment committee

Karl Georg Haeusler, MD, neurologist, Berlin, Germany; Kristina Wasmer, MD, cardiologist, Division of Rhythmology, Hospital of the University of Muenster, Germany; Christian Rump, MD, nephrologist, Duesseldorf, Germany.

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Design and rationale of a randomized controlled trial comparing apixaban to phenprocoumon in patients with atrial fibrillation on chronic hemodialysis – the AXADIA - AFNET 8 study

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	atrial fibrillation, hemodialysis, cardiovascular morbidity, cardiovascular mortality, Anticoagulation < HAEMATOLOGY

Design and rationale of a randomized controlled trial comparing apixaban to phenprocoumon in patients with atrial fibrillation on chronic hemodialysis – the AXADIA - AFNET 8 study

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ABSTRACT

Introduction: Patients with end-stage kidney disease requiring maintenance hemodialysis treatment experience a dramatic cardiovascular morbidity and mortality. Due to the high athero- and arteriosclerotic burden and profound alterations in hemostasis, they frequently suffer and die from both thromboembolic and bleeding events. This is a particular concern in patients on hemodialysis with atrial fibrillation (AF). Controlled trials on the optimal anticoagulation in patients with AF on hemodialysis are not available. The randomized controlled phase IIIb AXADIA – AFNET 8 trial will evaluate the safety and efficacy of the factor Xa inhibitor apixaban in patients with AF requiring hemodialysis.

Methods and analysis: A total of 222 patients will be randomized in an open-labelled, 1:1 design to receive either apixaban 2.5 mg twice daily or dose-adjusted vitamin K antagonist therapy (VKA, target international normalized ratio 2.0-3.0). All patients will be treated and followed up for a minimum of 6 months up to a maximum of 24 months. The primary outcome is major or clinically relevant, non-major bleedings or death of any cause. Secondary outcomes include stroke, cardiovascular death, and other thromboembolic events, thus exploring the efficacy of apixaban. The first patient was randomized in June 2017.

Ethics and dissemination: The study protocol was approved by the Ethical Committee of the Landesaertzekammer, Westfalen-Lippe and the Medical Faculty of the University of Muenster, Muenster, Germany (reference number: 2016-598-f-A). Written informed consent will be obtained from all patients prior to study participation, including their consent for long-term follow-up. AXADIA – AFNET 8 is an investigator-initiated trial. Sponsor is AFNET, Muenster, Germany. Study findings will be disseminated to Bristol-Meyers Squibb, Munich, Germany, and Pfizer, Berlin, Germany, to the participating centers, at research conferences and in peer-reviewed journals.

Trial registration numbers: ClinicalTrails.gov: NCT02933697, EudraCT No. 2015-005503-84

Keywords: anticoagulation, atrial fibrillation, hemodialysis, cardiovascular morbidity and mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomized controlled phase IIIb trial will provide important information about the safety of apixaban compared to Vitamin-K antagonist in patients on hemodialysis and with non-valvular atrial fibrillation.
- The secondary outcome will evaluate the efficacy of apixaban compared to Vitamin-K antagonist in preventing thromboembolic events.
- A pharmacokinetic substudy enrolling 28 patients will investigate whether a reduced dosage of 2.5 mg apixaban in hemodialysis patients results in similar plasma levels of apixaban as the recommended 5 mg dose for patients without renal insufficiency, as preliminary findings suggest.
- This trial will provide evidence which type of anticoagulation shall be preferred in patients on hemodialysis and with non-valvular atrial fibrillation. The lack of a control arm without any oral anticoagulation is a limitation of the study design.

INTRODUCTION

More than 15 million people in the USA and more than 6 million people in Germany suffer from chronic kidney disease (CKD), with an expected increase in aging populations with more comorbidities such as diabetes or hypertension.[1-6] Approximately 120,000 patients are alive in CKD stage G4 in Germany, and 85,000 in stage G5D (end-stage kidney disease (ESKD) on peritoneal or hemodialysis).[5] CKD is an important driver of cardiovascular mortality,[4] illustrating the need for optimal cardiovascular protection in patients with CKD. Atrial fibrillation (AF) is common in CKD affecting ca 10-25% of patients with end-stage CKD.[7-10]

Patients with CKD are at high risk of thromboembolic events and bleedings.[7,8] Concordantly, ischemic and hemorrhagic stroke are typical and frequent complication in ESKD: data from the large US Renal Data System showed a stroke incidence of 15.1% in hemodialysis patients compared to 9.6% in other stages of CKD, and 2.6% in a control cohort without CKD; stroke-related 2-year mortalities of 74%, 55%, and 28%, respectively, have been reported from some analyses.[11] Oral anticoagulation with vitamin K antagonists (VKA) can prevent most thromboembolic events in patients with atrial fibrillation at risk of stroke.[12] Non vitamin-K antagonist oral anticoagulants (NOAC) have a similar effectiveness with lower risk of bleeding, particularly intracranial bleeds.[13]

The effectiveness and safety of VKA and NOACs in patients with non-valvular AF is well established, including in patients with mild or moderate CKD.[12-14] Unfortunately, there is very little evidence on the safety and efficacy of NOACs in patients with AF and end-stage CKD.

Bleeding rates in CKD patients on dialysis treated with vitamin K antagonists are high,[15-19] illustrating the need for safe anticoagulation in these patients.[20] In a retrospective analysis of the ARISTOTLE data,[21] the reduction in major bleedings was greatest in patients in advanced CKD on apixaban compared to patients on VKA. Apixaban or other NOACs have not been evaluated in patients with AF on hemodialysis. To address this evidence gap, the "Safety Study Assessing Oral **A**nticoagulation with Api**xa**ban versus Vitamin K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease (ESKD) on Chronic Hemo**dia**lysis Treatment" (AXADIA – AFNET 8) will compare the safety of apixaban to VKA therapy in CKD patients on dialysis.

METHODS AND ANALYSIS

Primary and secondary objective

The primary objective is to assess the safety of apixaban compared to VKA therapy (carried out using the local VKA phenprocoumon) in patients with AF and ESKD on maintenance hemodialysis treatment. The primary hypothesis of the study is that apixaban has a superior safety profile in patients with AF and ESKD on hemodialysis compared to phenprocoumon, while providing similar efficacy in reducing thromboembolic events. The secondary objective is to compare the efficacy of apixaban with VKA regarding prevention of thromboembolic events in patients with ESKD on hemodialysis and AF.

Patients, study design and randomization

AXADIA – AFNET 8 is an investigator-initiated, prospective, parallel-group, multi-center trial conducted in 25-30 German study sites (Supplement, Appendix A). Adult patients aged ≥18 years with ESKD on maintenance hemodialysis treatment 3 times a week and an indication for oral anticoagulation due to non-valvular AF will be centrally and electronically randomized into two treatment arms: apixaban or phenprocoumon (1:1 allocation). As phenprocoumon needs constant international normalized ratio (INR) control, the study will be performed with an open-label administration of the study drugs. The randomization will be stratified by two conditions: First, patients with a previous thromboembolism including any type of ischemic stroke that meet the above criteria, can be included after more than 3 months if they are not severely handicapped as indicated by a value of 0 or 1 on the modified Rankin scale[22] and will be stratified to assure equal distribution within the groups. For further details on inclusion and exclusion criteria see Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion criteria
• End-stage kidney disease with chronic hemodialysis treatment 3 times per week (with about 4 hours per dialysis)

- Chronic (i.e. repeated) paroxysmal, persistent or permanent atrial fibrillation documented by standard or Holter ECG on at least 2 separate days before (or apart from) hemodialysis procedures
- Increased risk of stroke or systemic embolism identified by a CHA_2DS_2-VASc score of 2 or more as an indication for oral anticoagulation
- Patients with a previous ischemic stroke that meet the above criteria, can be included after more than 3 months if not severely handicapped (modified Rankin scale 0 or 1 of 6[22])
- Males and females, aged 18 or older
- Signed written informed consent

Exclusion criteria at baseline

- AF or atrial flutter due to reversible causes (e.g., thyrotoxicosis, pericarditis)
- Patients with a new onset of hemodialysis within the last 3 months
- Clinically significant (moderate or severe) aortic and mitral stenosis
- Conditions other than AF that require chronic anticoagulation (e.g., a prosthetic mechanical heart valve).
- Active infective endocarditis
- Any planned interventional or surgical AF or atrial flutter ablation procedure
- Any active bleeding
- A serious bleeding event in the previous 6 months before screening
- Inadequately controlled (HbA1c levels >8.5%) or untreated diabetes
- History of malignant neoplasms at high risk of current bleeding (see summary of product characteristics of study drugs)
- Known indication for treatment with NSAIDs (ASA up to 100 mg per day is allowed)
- Impaired liver function e.g., caused by active infection with HIV, HBV or HCV, hepatitis or other liver damage
- Any type of stroke within 3 months prior to baseline
- Valvular heart disease requiring surgery
- A high risk of bleeding (e.g., active peptic ulcer disease, a platelet count of <100,000 per cubic millimeter or hemoglobin level of <8 g per deciliter)
- Documented hemorrhagic tendencies or blood dyscrasias
- Current alcohol or drug abuse
- Life expectancy of less than 1 year
- Indication for dual platelet inhibition at baseline (ASA ≤ 100 mg/day is allowed; clopidrogel is at baseline excluded at any dose, during trial allowed for up to 30 days).
- Any disease or circumstances on account of which the subject should not participate in the study in the opinion of the investigator
- Psychiatric condition that might limit the participation in the study and/or that lead to the assumption that the ability to completely understand the consequences of consent is missing
- Pregnant or breast-feeding women
- Documented intolerance to one or both active substances of the study drugs

AF indicates atrial fibrillation; ASA, acetylsalicylic acid; CHA_2DS_2-VASc score, **c**ongestive heart failure/LV dysfunction, **h**ypertension, **a**ge ≥75 years, **d**iabetes, previous **s**troke/transischemic attack/thrombo-embolism, **v**ascular disease, **a**ge 65-74, **s**ex **c**ategory (female); NSAID, non-steroidal anti-inflammatory drugs.

Second, patients actually on phenprocoumon therapy can also be randomized; however, their proportion will be limited to a maximum 50% of the entire cohort to ensure that AXADIA – AFNET 8 also provides safety information in anticoagulation-naïve patients. This condition will also be concerned as stratification in the randomization procedure. In overview, patient's recruitment and allocation is displayed in Figure 1 in accordance to the CONSORT standard.

Study procedures

Treatment with apixaban

Patients randomized to apixaban will be treated with apixaban 2.5 mg twice a day. Apixaban will be provided to the study sites by Bristol-Myers Squibb in specific labeled bottles of 200 tablets. Apixaban was chosen as its mode of excretion is mainly via the bile, theoretically enabling stable plasma levels independent of hemodialysis. In addition, a subanalysis of the effect of chronic kidney disease in the ARISTOTLE trial suggested that the relative bleeding risk of apixaban compared to VKA was lower in patients with advanced chronic kidney disease (eGFR 25-50 ml/h).[21] The study drug will be dispensed to the patient at the study site. The patient will be instructed to take the study drug with an approximately 12 hour gap apart. The compliance will be controlled by pill count and treatment interruptions will be documented and tracked centrally in the e-trial management system.

Treatment with phenprocoumon

Patients randomized to VKA will be treated with phenprocoumon, the locally used vitamin K antagonist in Germany, with a target INR of 2.0-3.0. Patients will receive a prescription for phenprocoumon at the study site on the day of randomization. According to measured INR and the summary of product characteristics, the investigator will recommend an individually adjusted dose to the patient. Weekly INR controls will be carried out to ensure the compliance to the target INR.

The protocol provides detailed recommendations for anticoagulation during hemodialysis (Supplement, Appendix B).

All subjects will be treated with the study drug for at least 6 months. Subjects who are included early during the trial will stay under treatment in the study until the last subject has completed the treatment period of 6 months. This will probably lead to a study participation of about 24 months for the first subjects enrolled (Figure 2).

Timelines and follow-up

Screening period (up to 7 days before baseline visit): In presence of the study staff, all patients must give full written informed consent during the screening period (Supplement, Appendix C). Insurance information covering any harm resulting from the study drug are handed out to the participant. Inclusion and exclusion criteria will be checked. Demographical and anthropometric data, renal status, concomitant diseases and medication, and data on hemodialysis will be documented. Blood count, INR evaluation, ECG recording, and risk stratification will be performed.

Baseline visit: Adherence to inclusion and exclusion criteria will be checked. Data on hemodialysis, and concomitant medication will be documented. If applicable, blood parameters, thromboembolic and bleeding events, adverse events, and events of special interest will be recorded. Patients will be randomized. EQ-5D questionnaire will be completed by the patient. For subjects randomized for phenprocoumon INR evaluation will be performed.

Follow-up visits: During the monthly follow-up visits, data on hemodialysis and INR evaluation (for subjects on phenprocoumon) will be documented. If applicable, changes in concomitant medication, blood parameters, thromboembolic and bleeding events, adverse events, and events of special interest will be documented. EQ-5D questionnaire will be completed on visit 6, 12, and 18 by the patient. Adherence to study drug will be performed on a quarterly basis.

End of treatment: Data on hemodialysis, concomitant medication, concomitant diseases, and adherence to study drug will be documented. ECG recording will be performed. EQ-5D questionnaire

will be completed by the patient. For subjects on phenprocoumon INR will be measured. If applicable, thromboembolic and bleeding events, adverse events, and events of special interest will be recorded.

End of study (30 days after end of treatment): Data on concomitant medication, blood parameters, thromboembolic and/or bleeding events, adverse events, and events of special interest will be documented.

Adverse event reporting: An adverse event (AE) is defined as any untoward medical occurrence or worsening of a pre-existing medical condition in the patient administered the study drug and that does not necessarily have a causal relationship with the study drug (i.e. apixaban or phenprocoumon). All AEs, regardless of related or not related to the study drug, which occur from screening to end of study will be collected and seriousness, severity, and causality will be assessed by the investigator. All AEs will be reported in detail in the electronic case report form (eCRF).

Primary, secondary, and other outcomes

Primary outcome is a composite of major and clinically relevant non-major bleeding in accordance to the *International Society of Thrombosis and Hemostasis* (ISTH) consensus[23] as well as shunt / fistula bleedings in dialysis patients on anticoagulation. The detailed list of all safety endpoints is given in Table 2.

Table 2: Endpoints

***Primary outcome**:* Composite of major and clinically relevant, non-major bleeding events and death of any cause

Major Bleeding events as defined by ISTH[23] and complemented by other serious bleeding events:

- Fatal bleeding
- Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more
- Bleeding leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding
- Bleeding that requires an operation or endoscopic intervention (arthroscopic, endovascular or a hemarthrosis)

Clinically relevant, non-major bleeding (according to ISTH consensus[23], complemented by relevant bleeding events in dialysis patients):

- Bleeding resulting in hospitalization or prolonged hospitalization
- Bleeding requiring medical or surgical treatment by a physician
- Bleeding leading to a modification of the given anticoagulant therapy
- Gastrointestinal bleeding proven by endoscopy or surgery
- Shunt- / catheter-induced bleeding
- Bleeding between dialysis sessions
- Prolonged bleeding requiring compression for more than 30 min after dialysis needle removal

***Efficacy events**:*

- Myocardial infarction
- Ischemic stroke
- All-cause death
- Cardiovascular death
- Deep vein thrombosis and/or pulmonary embolism

***Composite endpoint**:*

- Myocardial infarction
- Ischemic stroke
- All-cause death
- Deep vein thrombosis and/or pulmonary embolism

Events of special interest:

- Dialysis shunt thrombosis
- Clotting of dialysis membrane

***Pharmacokinetics** (sub-study in 28 apixaban patients)*

- Apixaban plasma level prior and after hemodialysis, see Figure 3

ISTH indicates International Society on Thrombosis and Haemostasis.

Secondary outcomes include thromboembolic events. Details of the secondary outcomes and other outcomes are given in Table 2.

Study discontinuation

In accordance to the SmPC of apixaban[24], the following medications are prohibited throughout the whole trial and will lead to study discontinuation: Strong inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein. Furthermore, regular intake of nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 (COX-2) inhibitors, except for acetyl salicylic acid up to 100 mg/day, lead also to study discontinuation.

Other reason for discontinuation are: Elective surgical interventions which demands interruption of study drug intake for more than three weeks; planned kidney transplantation within the next three days; pregnancy; any adverse event or clinical relevant change in blood parameters because of which the responsible physician does not consider a study drug continuation as beneficial for the patient.

All patients who prematurely discontinue the study drug treatment are asked to perform the end of treatment visit.

Data management and auditing

An interactive web response system (IWRS) will be used to allocate patients to the two treatment groups. Study staff will record patients' data on the eCRF. All study-related information about participants will be stored securely and kept strictly confidential. All study sites will be supervised by a monitor throughout the entire study duration. One visit takes place before enrolment of the first patient to clarify all prerequisites and assure the medical and formal instruction of investigators and the knowledge to the protocol. On-site monitoring takes place on a regular basis and includes review of protocol compliance, check of the complete and correct entry into the eCRF, and correct handling and storage of the study drug.

Patient and public involvement

Neither public nor patients were involved in the design or conduct of the study. Study results will be disseminated to the patients by a circular letter.

Pharmacokinetic substudy

The dosing of apixaban with 2.5 mg twice daily was chosen from pharmacokinetic modeling from plasma levels of some individuals with dialysis-dependent renal failure. Moreover, it based on the currently recommended dose for apixaban in patients with CKD stage G4 according to the European label.[24] Furthermore, results from a small pivotal study were published indicating that a dosage of 2.5 mg apixaban twice daily in dialysis-dependent patients will result in similar plasma levels as the higher dosage of 5 mg twice daily in healthy individuals.[25] To confirm these preliminary findings, a pharmacokinetic sub-study will be conducted in this trial with 28 patients randomized to apixaban to determine plasma serum levels of apixaban prior to and after hemodialysis, and also after a short (2 days), and a long (3 days) dialysis interval (Figure 3). The study staff will obtain written consent from patients willing to participate in the substudy. In these patients two blood samples will be collected, one sample before and one after hemodialysis. Apixaban levels will be measured at a central laboratory in Richmond, VA, USA.

Sample Size Calculations

One recent publication reported bleeding rates in a similar (but not identical) setting in hemodialysis patients treated with dabigatran and rivaroxaban, acetylsalicylic acid (ASA) and VKAs.[26] Based on these data and using similar endpoint definitions especially for bleedings, it was assumed for the AXADIA – AFNET 8 study setting that apixaban would have comparable bleeding rates as ASA in dialysis patients. The latter assumption is supported by the AVERROES trial[27] in which apixaban and ASA were compared in a cohort of non-dialysis depended patients who were not considered suitable for oral anticoagulation due to a high bleeding risk: in that trial including patients with a

comparable high risk as here, the rates of major and clinically relevant non-major bleedings were similar in the apixaban group and the ASA group. Based on these data, we expect a hazard rate for the combination of major and clinically relevant non-major bleedings of 0.0789 per months for apixaban and 0.131 for phenprocoumon. According to these figures, a total sample size of 166 patients will be sufficient to demonstrate superiority of apixaban treatment with 80% power with respect to the primary endpoint, and also with respect to clinically relevant non-major bleedings only. Including a 20% security margin and about 10% drop-outs, AXADIA – AFNET 8 will randomize 222 patients (Figure 1).

Statistics

The *full analysis* set will include all randomized patients with and without any kind of protocol violations, applying the intention-to-treat-principle. In the *per-protocol population*, patients with relevant protocol violations will be excluded. The *safety* set will consist of all patients who were randomized and received at least one dose of the study drug, applying the as-treated principle.

Continuous variables will be presented group-wise by means ± standard deviation and tested by t-tests for independent samples. Skewed data will be transformed towards normality or tested by non-parametric U-tests. Categorical variables will be presented by counts and percentages and compared by chi-square tests or Fisher's exact tests as appropriate.

In the primary statistical analysis, the treatments will be compared with respect to the primary safety endpoint time to first occurrence of a major or clinically relevant non-major bleeding or death of any cause. Let HR denote the corresponding hazard ratio of the apixaban treatment versus VKA (phenprocoumon) treatment. Two statistical null hypotheses will be tested:

$H_0^{\text{Superiority}}$: HR≥1 versus $H_1^{\text{Superiority}}$: HR<1 (proof of superiority of apixaban)

$H_0^{\text{Non-Inferiority}}$: HR≥1.25 vs. $H_1^{\text{Non-Inferiority}}$: HR<1.25 (proof of non-inferiority of apixaban)

The multiple one-sided significance level is set to α=2.5%. A sequentially rejective multiple test procedure will be applied that controls the familywise error rate in the strong sense at pre-specified significance level α. The hypothesis $H_0^{\text{Non-Inferiority}}$ is defined to be the initial hypothesis and is assigned the local significance level $\alpha(H_0^{\text{Non-Inferiority}})$=2.5%. If the initial hypothesis $H_0^{\text{Non-Inferiority}}$ is rejected, subsequently the hypothesis $H_0^{\text{Superiority}}$ is tested on local significance level 2.5%. The primary statistical analysis provides confirmatory statistical evidence.

The superiority test will be performed in the full analysis set that consists of all randomized patients, including patients with any kind of protocol violations, applying the intention-to-treat principle. The non-inferiority test will additionally be performed in the per-protocol population, excluding patients with relevant protocol violations. Statistically significant non-inferiority will be claimed only if the result is supported both in the intention-to-treat analysis and the per-protocol analysis.

The primary analysis will be up to the first occurrence of the endpoint. Beyond the above primary statistical analysis of the primary endpoint, an extended analysis of the primary endpoint will additionally take recurrent events into regard and will be performed by fitting an Anderson-Gill model with robust estimation of coefficients and variance terms to the data. From all models, hazard ratios and two-sided 95% confidence limits will be calculated and discussed whether safety risks can be derived based on the results. Statistical analyses of the primary endpoint will be repeated in the safety population that consists of all patients who received at least one dose of the study drug, applying the as-treated principle.

The secondary endpoints, both events of special interest and the composite endpoint (Table 2) are the efficacy endpoints and will be analyzed on an intention-to-treat-basis by descriptive statistics only due to the small sample size which will probably not be sufficiently large enough to demonstrate superiority. Adjusted Cox proportional hazard models, Anderson-Gill models and the described sensitivity analyses will be performed as described above. No adjustment for multiplicity will be provided as the efficacy analysis is secondary behind the primary safety analysis.

The Data and Safety Monitoring Board will adjudicate the following safety and efficacy endpoints: major bleeding, clinically relevant, non-major bleeding, myocardial infarction, ischemic stroke, all-cause death, cardiovascular death, and deep vein thrombosis and/or pulmonary embolism (Table 2)

Ethics and dissemination

AXADIA – AFNET 8 is an investigator-initiated trial which is conducted by the Kompetenznetz Vorhofflimmern e.V. (Atrial Fibrillation NETwork, AFNET), Muenster, Germany, as responsible sponsor. The study is financed by Bristol-Myers Squibb (BMS, Munich, Germany) and Pfizer (Berlin, Germany) as specified in the Supplement (Appendix D).

AXADIA – AFNET 8 is registered at www.clinicaltrials.gov (NCT02933697, registration date October 14, 2016) and at EudraCT (2015-005503-84).

The study protocol (CV185-435, version 1.2, August 18, 2017) was approved by the Ethical Committee of the Landesaerztekammer (Medical Association) Westfalen-Lippe and the Medical Faculty of the University of Muenster, Muenster, Germany (reference number: 2016-598-f-A) as lead ethics committee and by ethics committees at all participating sites. Protocol amendments will be communicated to the study sites by the sponsor.

The design, conduct, and analysis of the study as well as decisions on publication of study results will be led by a steering committee (Supplement, Appendix E). The steering committee has full access to the dataset. A *Data and Safety Monitoring Board* will supervise this study and will be blinded to treatment groups (Supplement, Appendix F). All safety and efficacy endpoints will be evaluated by an independent *Endpoint Assessment Committee* blinded to treatment group, eCRF, e-trial system, data capture and monitoring (Supplement, Appendix G). The trial sponsor has no role in collection, analysis and interpretation of data, or decision to submit results.

Study findings will be disseminated to Bristol-Meyers Squibb, Munich, Germany, and Pfizer, Berlin, Germany, to the participating centers, at research conferences, and in peer-reviewed journals.

DISCUSSION

Patients with CKD are well known to suffer from a high overall morbidity and mortality which is mainly driven by cardiovascular causes. This concerns especially patients in the advanced CKD stages G3 to G5 as demonstrated impressively by estimated 2.2 million deaths worldwide which are attributed only to patients in these stages.[4] These deleterious effects are caused on the one hand by the underlying diseases leading to kidney disease, on the other hand by alterations induced by CKD itself, which lead to rapid progress in athero- and arteriosclerosis but also to profound changes in hemostasis. Apart from these disease-related origins, the poor prognosis of patients with CKD - and especially those with ESKD – is, moreover, also attributed to a "therapeutic nihilism" of many treating physicians: Many AF patients with advanced CKD do not receive medications or treatments that have been proven or are at least considered to be beneficial in the general population.[28]

Oral anticoagulation in advanced kidney disease

This therapeutic nihilism is also of relevance in an ongoing, very controversial - in part highly emotional - debate about the value of oral anticoagulation in ESKD. Some of the protagonists accuse the others to harm the patients by administering a dangerous VKA, while their opponents point out that withholding the oral anticoagulation is not justified and actual harms the patients. In fact, currently no one has reliable and adequate data: While especially the large-sized trials with non-vitamin K antagonist oral anticoagulants have shown that oral anticoagulation is effective and safe even down to an eGFR of 25 or 30 ml/min,[29-32] below this threshold the available data are markedly limited regarding both quantity and quality.

Numerous small and retrospective studies have tried to assess the value of VKA in hemodialysis as summarized previously.[19, 33] However, all retrospective studies suffer from a significant selection bias of the patients treated with anticoagulation.[7] A meta-analysis of 11 observational studies with 25,407 AF patients with EKSD found warfarin to significantly lower stroke rate but to have no effect on mortality.[34]

Larger, unbiased observational information exists: In an analysis of the hospital data base of Denmark with more than 130,000 AF patients of whom 3,587 (2.7%) had non–end-stage chronic

kidney disease and 901 (0.7%) required renal-replacement therapy at the time of inclusion,[35] warfarin treatment was associated with a significantly decreased risk of stroke or systemic thromboembolism in patients with CKD and ESKD. Vitamin K antagonist mono-therapy and combination of VKA and ASA were associated with an increased risk of bleeding. Platelet inhibitors such as ASA did not reduce thromboembolic events but were associated with a high rate of adverse effects as also shown by others.[35, 36] Therefore, platelet inhibition does not seem to be a viable treatment in patients with AF and ESKD. A more recent report on an updated version of the same data set included meanwhile 150,000 patients[37] with an increased risk of stroke and systemic embolism (CHA_2DS_2-VASc score ≥2); their data showed that VKA therapy was significantly associated with lower all-cause mortality in patients with CKD (HR 0.64, 95% confidence interval 0.60-0.69) and in those with ESKD (HR 0.85, 95% confidence interval 0.72-0.99).

Another very recent publication from the same group has shown that time in therapeutic range (TTR) is of special importance in patients with reduced eGFR.[38] This aspect of TTR is included in AXADIA and the INR will be assessed and documented thoroughly.

All of these analyses do yet not allow an evidence-based decision how to treat hemodialysis patients to reduce their immense risk of stroke, systemic and venous thromboembolic events, bleedings and cardiovascular death. A recently started trial in the US (RENAL-AF, clinicaltrial.gov identifier NCT02942407) comparing apixaban (5 mg twice daily) with warfarin (INR 2-3) in patients with AF and ESKD on hemodialysis will add knowledge regarding safety and efficacy of apixaban in this critically ill patients' cohort.

Calciphylaxis with vitamin-K antagonists

Patients on maintenance hemodialysis treatment are often vitamin K-deficient which may be linked with advanced arterial calcifications due to a number of preclinical and few clinical studies.[39-42] However, a very recent clinical trial failed to demonstrate any negative impact of warfarin on calcification,[43] while also one older but large observational study from the US renal data system could not find any difference in overall survival between patients with and without warfarin.[44]

Although no explicit substudy regarding vascular calcifications is planned within AXADIA, major cardiovascular events due to calcifications are included in the efficacy endpoints of the trial and will be compared to patients receiving VKA and those under apixaban.

Limitations

With regard to the fact that this is an investigator-initiated trial, financial resources are spare and had to be applied thoroughly. Therefore, the number of patients which will be included to determine a significant difference regarding the safety endpoints is considered to be sufficient. A security margin of 20% should compensate the complete lack of any previous data in this field. Nevertheless, a larger cohort would have been desirable in order to identify differences concerning the efficacy endpoints.

The trial is adequately designed and powered to answer the question whether apixaban is non-inferior or possibly even superior to phenprocoumon regarding safety and maybe also regarding efficacy. However, since there is no control arm without any anticoagulation regime, the trial will provide evidence which type of anticoagulation to prefer if indicated (and if intended by the treating physician) - but not, whether any oral anticoagulation should be given at all in hemodialysis-dependent patients with AF.

Fistula-bleeding events may be induced either by puncturing for dialysis procedure or by anticoagulation. No differentiation will be made with regard to the underlying cause of this outcome measure. Therefore, bleeding events may be overestimated. But due to the randomized design of the trial, fistula bleedings are expected to occur with equal distribution in both trial arms.

Finally, the trial is designed as an open-label trial due to required regular dose adjustments for phenprocoumon based on INR measurements.

Conclusion

The AXADIA trial will belong to the first randomized trials to compare two different regimens of anticoagulation in patients on maintenance hemodialysis. It will clarify if the novel direct factor Xa antagonist apixaban will be comparable or even be superior to a standard therapy with the VKA

phenprocoumon in patients with paroxysmal, persistent or permanent AF. Finally, the AXADIA trial is a pilot study whose results shall provide the basis for a larger outcome study.

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Contributions

Holger Reinecke, Christoph Wanner, Rupert Bauersachs, Paulus Kirchhof, and Günter Breithardt conceived and designed the study; Holger Reinecke, Christoph Wanner, Rupert Bauersachs, Paulus Kirchhof, Günter Breithardt, and Sabine Jürgensmeyer contributed to protocol development; Joachim Gerß contributed to the statistical analysis; Holger Reinecke, Christiane Engelbertz, and Sabine Jürgensmeyer participated in the writing of the manuscript; all authors critically reviewed the manuscript and approved the final version.

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Conflict of interests

Holger Reinecke has received speaker honoraria from BMS, MedUpdate, NephroUpdate, and Pfizer. He has acted as a consultant for BMS, Pfizer and Pluristem receiving in part also financial compensations for this work. He has received research grants from the German Federal Ministry for Education and Research (BMBF). His division within the University Hospital of Muenster has taken or

is still taking in multicenter trials of BARD, Bayer, BIOTRONIK, and Pluristem receiving patient fees and financial compensation for these efforts.

Paulus Kirchhof has received grants and non-financial support from the European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research and from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies. He is listed as inventor on two patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

During preparation of this trial, Günter Breithardt has received speaker honoraria from BMS and Pfizer, he has been a member of the Scientific Advisory Boards for BMS and Pfizer, and Bayer Health Care. During his chairmanship of the Atrial Fibrillation NETwork, this institution has received funding for investigator-initiated trials from various companies (for details, please consult http://www.kompetenznetz-vorhofflimmern.de/en/research).

Rupert Bauersachs has received consulting / lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer.

Christoph Wanner does not report conflicts of interest in respect to the present work. Outside this area of research he has received speaker honoraria from Amgen, Boehringer-Ingelheim, Genzyme-Sanofi and Shire.

All other authors have nothing to disclose.

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Figure legends

Figure 1:

Patient's enrollment and allocation in accordance to the CONSORT stand is displayed. Of note, two stratifications are implemented in the randomization procedure: First, for patients who suffered from a previous stroke or systemic thromboembolic event which must have occurred at least 3 months before enrolment without residual limitations (only value of 0 or 1 on the modified rankin scale). Second, for patients who were already assigned to an oral anticoagulation whose proportion will be limited to 50% of the entire study cohort.

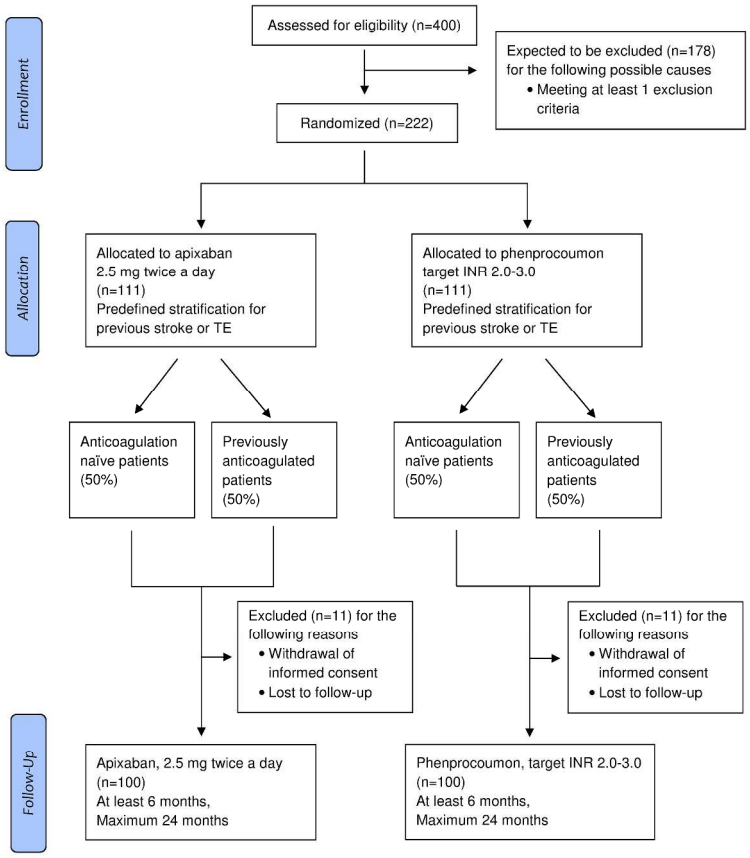
Figure 2:

Timelines and regular visits during the study period are presented. After screening visit, 2 qualifying ECGs showing atrial fibrillation must be sent to a central appraisal and, if all other inclusion and exclusion criteria match, randomization and inclusion can be performed within 7 days. Afterwards, monthly visits during the regular dialysis sessions will have to be documented. When the last recruited patient has been on treatment for 6 months the study will be terminated (*end of treatment*). All patients will be followed-up for another 30 days after which the study will be completed (*end of study*).

Figure 3:

The design of a pharmacokinetic (PK) substudy is given here. In total 28 patients who must give additional written informed consent will be examined regarding their apixaban levels before and after dialysis. Of these, apixaban levels will be assessed in 14 patients after the 3 day-long dialysis-free interval, and in another 14 patients after the short 2 day dialysis-free interval. Since patients on hemodialysis are regularly treated in 2 shifts (AM and PM), the 14 patients will be splitted again and apixaban levels will be assessed in 7 patients of the AM shift and another 7 patients of the PM shift. This might be of interest since patients will be instructed to take their apixaban between 7-8 AM and

PM, independent from the start of their dialysis shifts, so plasma levels may vary between the groups.



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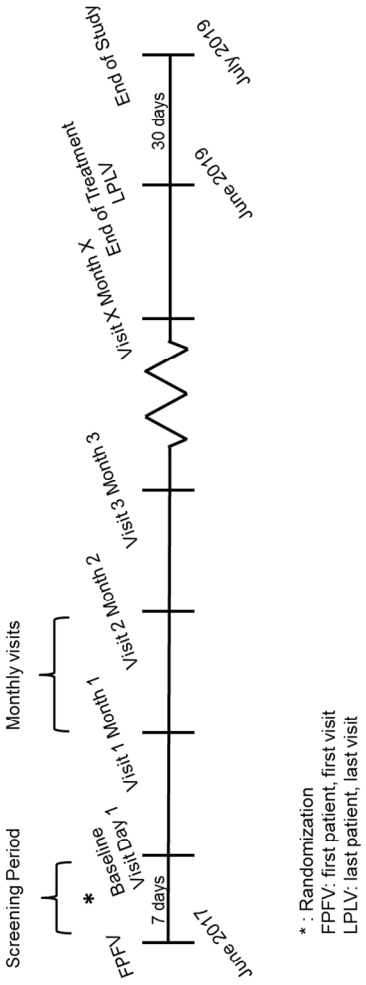

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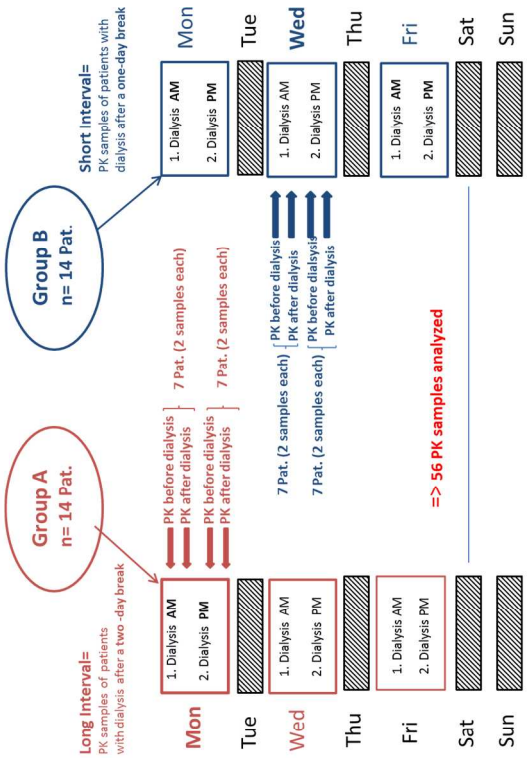

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297x420mm (300 x 300 DPI)

Supplements

Appendix A: Participating centers (by status of 15th Mai 2018; more sites will be submitted to EC until summer 2018)

Site	Investigator
Robert-Bosch-Krankenhaus Stuttgart Allgemeine Innere Medizin und Nephrologie Stuttgart, Germany	Prof. Dr. Dominik Alscher
Klinikum Coburg Nephrologische Klinik Coburg, Germany	Prof. Dr. Markus Ketteler
KfH-Nierenzentrum Berlin-Neukölln Berlin, Germany	Prof. Dr. Christiane Erley
Zentrum für Nierenerkrankungen Hannover, Germany	Dr. Hans Schmidt-Gürtler
KfH-Nierenzentrum Bottrop Bottrop, Germany	Dr. Maria Lusch
KfH-Nierenzentrum Dülmen Dülmen, Germany	Dr. Wolfgang Bagnewski
Klinik für Nierenheilkunde und Bluthochdruck, Mühlenkreiskliniken Minden, Germany	Prof. Dr. Jörg Radermacher
Universitätsklinikum Münster Klinik für Kardiologie I: Koronare Herz-krankheit, Herzinsuffizienz und Angiologie	Prof. Dr. Holger Reinecke

Münster, Germany	
KfH Nierenzentrum Bonn Universitätsklinikum Bonn Bonn, Germany	Prof. Dr. Rainer Woitas
Universitätsklinikum des Saarlandes Klinik für Innere Medizin IV Homburg/Saar, Germany	Prof. Dr. Gunnar Heine
KfH-Nierenzentrum Bischofswerda Bischofswerda, Germany	Dr. Kirsten Anding-Rost
Klinikum Lüdenscheid Klinik für Nephrologie und Dialyseverfahren Lüdenscheid, Germany	Prof. Dr. Jan Galle
Universitätsklinik Marien-Hospital Herne Herne, Germany	Prof. Dr. Timm Westhoff
Nierenzentrum Wiesbaden/Rheumatologie Wiesbaden, Germany	Prof. Dr. Frank Strutz
KfH-Nierenzentrum Wismar Wismar, Germany	Priv.-Doz. Dr. Heiko Hickstein
Nephrocare Berlin-Weissensee GmbH Berlin, Germany	Dr. Joachim Groll
Nephrologisches Zentrum Villingen-Schwenningen, Germany	Dr. Thomas Weinreich
Ev.-Luth. Diakonissenanstalt zu Flensburg	Dr. Wolfgang Ries

Medizinische Klinik Flensburg, Münster	

Appendix B: Suggestions for anticoagulation during hemodialysis

No-heparin hemodialysis was developed for use in the patient at high risk of bleeding. Here, a pretreating of both the dialyzer and the blood lines will be washed with a solution of 2000 - 5000 units of heparin in one liter of NaCl. The heparinized NaCl solution is flushed from the extracorporeal lines prior to dialysis treatment. Extracorporeal blood flows are rapidly increased to 250 to 500 mL/min and maintained throughout the treatment. 25 to 30 mL NaCl flushes are administered every 15 to 30 min to the arterial limb (predialyzer) in order to minimize hemoconcentration and to wash any fibrin strands out of the kidney.

The use of minimum-dose heparin has been shown to reduce bleeding complications in high-risk patients when compared with regional heparinization and protamine neutralization. Here, a bolus of 500 units heparin will be administered every 30 min in order to keep the activated clotting time between 150 and 200 seconds. Alternatively, a continuous infusion of heparin with frequent monitoring of ACT can be used to achieve the same degree of anticoagulation.

Appendix C: Informed Consent

Protokoll Nummer: CV185-435 EudraCT-Nr. **2015-005503-84**

Name des Patienten, Geburtsdatum: _____

Prüfarzt (Name): .....

Prüfstelle, Adresse und Telefon: .....
.....
.....
.....
.....

Patienteninformation

Klinische Studie zur Überprüfung der Sicherheit des oralen Antikoagulans Apixaban gegenüber einem Vitamin-K Antagonisten bei dialysepflichtigen Patienten mit chronischem Nierenversagen und Vorhofflimmern.

(A Safety Study Assessing Oral Anticoagulation with Apixaban versus Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease (ESKD) on Chronic Hemodialysis Treatment)
(AXADIA – AFNET 8)

Sehr geehrte Patientin, sehr geehrter Patient,

wir möchten Sie fragen, ob Sie bereit sind, an der nachfolgend beschriebenen klinischen Prüfung (Studie) teilzunehmen.

Klinische Prüfungen sind notwendig, um Erkenntnisse über die Wirksamkeit und Verträglichkeit von Arzneimitteln zu gewinnen oder zu erweitern. Deshalb schreibt der Gesetzgeber im Arzneimittelgesetz vor, dass neue Arzneimittel klinisch geprüft werden müssen. Die klinische Prüfung, die wir Ihnen hier vorstellen, wurde – wie es das Gesetz verlangt – von der zuständigen Ethikkommission zustimmend bewertet und von der zuständigen Behörde genehmigt. Dabei hat die Ethik-Kommission die in dieser Patienteninformation und Einwilligungserklärung dargestellten Informationen geprüft und dem Prüfarzt eine positive Stellungnahme übermittelt. Wir möchten Sie bitten die Informationen in diesen Unterlagen zu überdenken und zu entscheiden, ob Sie an der Studie teilnehmen wollen.
Diese klinische Prüfung wird in Deutschland an mehreren Orten durchgeführt; es sollen insgesamt ungefähr 222 Personen daran teilnehmen. Die Studie wird veranlasst und organisiert durch das Kompetenznetz Vorhofflimmern e.V. (AFNET), Münster, den Sponsor dieser Studie (www.kompetenznetz-vorhofflimmern.de) und finanziert durch die Firmen Bristol-Myers Squibb GmbH&KGaA, Arnulfstrasse 29, 80636 München, Deutschland und Pfizer Deutschland GmbH, Linkstr. 10, 10785 Berlin. Das Prüfzentrum erhält für Ihre Teilnahme im Rahmen dieser klinischen Prüfung eine finanzielle Entschädigung.

Ihre Teilnahme an dieser klinischen Prüfung ist freiwillig. Sie werden in diese Prüfung also nur dann einbezogen, wenn Sie dazu schriftlich Ihre Einwilligung erklären. Sofern Sie nicht

an der klinischen Prüfung teilnehmen oder später aus ihr ausscheiden möchten, entstehen Ihnen daraus keine Nachteile.

Sie wurden bereits auf die Studie angesprochen. Der nachfolgende Text soll Ihnen die Ziele und den Ablauf erläutern. Anschließend wird ein Prüfarzt das Aufklärungsgespräch mit Ihnen führen. Bitte zögern Sie nicht, alle Punkte anzusprechen, die Ihnen unklar sind. Sie werden danach ausreichend Bedenkzeit erhalten, um über Ihre Teilnahme zu entscheiden.

1. Warum wird diese Prüfung durchgeführt?

Es ist bekannt, dass Patienten mit der Herzrhythmusstörung Vorhofflimmern ein erhöhtes Risiko haben, durch die Verschleppung eines Blutgerinnsels, zum Beispiel an einem Schlaganfall zu erkranken. Um dieses Risiko zu verringern, werden solchen Patienten häufig „Blutverdünnungsmittel“, im Fachjargon: orale Antikoagulanzien, verschrieben.

Apixaban (Eliquis®) und Phenprocoumon sind bereits zugelassene blutverdünnende Medikamente, die bei Patienten mit der Herzrhythmusstörung Vorhofflimmern eingesetzt werden. Die Zulassung gilt jedoch nicht für chronisch nierenkranke Patienten, die eine schwere Nierenfunktionsstörung aufweisen.

Die vorliegende klinische Studie zielt deshalb darauf ab, nachzuweisen, ob das blutverdünnende Medikament, Apixaban, bei dialyseabhängigen Patienten mit Vorhofflimmern gegenüber einem anderen blutverdünnenden Medikament, z.B. Marcumar®, hinsichtlich der Verminderung von Blutungen sicher und wirksam ist.

Weiterhin soll mit dieser Studie gezeigt werden, ob die Einnahme der beiden Antikoagulanzien bei dialyseabhängigen Patienten mit Vorhofflimmern, das Auftreten von Schlaganfällen oder systemischen Embolien (Gefäßverschlüssen) verringern kann.

2. Erhalte ich das Prüfpräparat auf jeden Fall?

In dieser klinischen Prüfung werden die beiden Prüfpräparate Phenprocoumon (z.B. Marcumar®) und Apixaban (Eliquis®) miteinander verglichen. Beide Medikamente sind für die Behandlung von z.B. Schlaganfällen bei bestimmten Herzrhythmusströungen bereits zugelassen.

Im Falle Ihrer Teilnahme werden Sie entweder Phenprocoumon oder Apixaban erhalten. Welches Prüfpräparat Sie erhalten, entscheidet ein zuvor festgelegtes Zufallsverfahren; dieses Verfahren wird Randomisierung genannt. Die Wahrscheinlichkeit entweder das Prüfpräparat Phenprocoumon oder das Prüfpräparat Apixaban zu erhalten, beträgt jeweils 50 %.

Die vorliegende Studie ist eine sogenannte offene Studie, bei der sowohl Sie als Patient, als auch Ihr behandelnder Arzt wissen, welches Prüfpräparat Sie erhalten („open-label“ Anwendung).

3. Wie ist der Ablauf der Studie und was muss ich bei Teilnahme beachten?

Die Gesamtdauer der Studie beträgt maximal 24 Monate. Die Untersuchungen, die im Rahmen der Studie stattfinden, sind, bis auf die Beantwortung eines Gesundheitsfragebogens, identisch mit den Untersuchungen eines Ihnen bekannten Dialysebesuches. Sie müssen keine zusätzlichen Termine für die Studie wahrnehmen.
Nachdem Sie Ihr schriftliches Einverständnis zur der Studie gegeben haben, wird die Vorgeschichte Ihrer Krankheit erhoben und Sie werden einer ärztlichen Untersuchung unterzogen. Dazu gehört insbesondere eine körperliche Untersuchung, die Erhebung Ihrer Vitalparameter, wie z.B. Blutdruck- und Pulsmessung, die Erstellung von einem Elektrokardiogramm (EKG) und einer Blutabnahme zur Bestimmung Ihrer Blutparameter und Ihres Gerinnungswertes. Außerdem wird Ihr Arzt bei Ihnen ein mögliches Risiko hinsichtlich des Auftretens eines Schlaganfalls und/ oder eines Herzinfarktes, einstufen. Weiterhin wird Ihr Arzt mit Ihnen die momentane Einnahme von Medikamenten besprechen und dokumentieren. Ihr Arzt wird Ihnen außerdem einen Lebensqualitätsfragebogen (EQ-5D), der fünf Fragen über ihre momentane Einschätzung zu Ihrer Gesundheit beinhaltet, aushändigen. Hierbei sollen Sie Ihren Gesundheitszustand anhand einer Skala von 0 (sehr schlecht) bis 100 (sehr gut) beurteilen. Es ist wichtig, dass Sie die fünf Fragen und Ihre momentane Einschätzung Ihres Gesundheitsstatus selbstständig angeben, denn nur Sie können am besten beurteilen, wie es Ihnen momentan geht. Die Beantwortung der Fragen wird ca. fünf Minuten in Anspruch nehmen.
Beim Abschluss des ersten Studienbesuches werden Sie in eine der beiden Medikationsgruppen aufgenommen (Apixaban oder Phenprocoumon). Sie erhalten die Prüfmedikation von Ihrem Prüfarzt in dem Fall, dass Sie Apixaban einnehmen werden. Falls Sie zuvor Phenprocoumon eingenommen haben, müssen Sie Phenrprocomoun absetzen und die erste Tablette von Apixaban dann einnehmen, wenn ihr INR Wert kleiner 2.0 ist. Dies kann einige Tage dauern, sodass Sie in diesem Zeitraum keine blutverdünnende Medikation erhalten.
Für den Fall, dass Sie an der Behandlungsgruppe mit Phenprocoumon teilnehmen, wird Ihnen Ihr Prüfarzt die Medikation verschreiben.

Einen Monat nach Studienbeginn werden wieder Daten zu Ihrer Blutgerinnung, der Art der Dialyse und Ihren Blutwerten erhoben und registriert. Außerdem wird Ihr Arzt Sie nach Blutungs- und/ oder anderen thromboembolischen Ereignissen (Gefäßverschluss), anderen Arztbesuchen sowie Änderungen in der Einnahme Ihrer Medikamente befragen. Hierbei sollten Sie alle Änderungen, die seit Ihres letzten Besuches aufgetreten sind, angeben.

Nach jedem dritten Monat erhalten Sie neue Studienmedikation. Falls Sie Apixaban einnehmen, bringen Sie bitte jede leere und ggf. jede angefangene Medikamentenflasche zu dem Studienbesuch mit. Die Tabletteneinnahme wird durch Ihren Arzt kontrolliert, dokumentiert und die Medikationsflaschen werden zurückgenommen.

Halbjährlich und beim Abschluss der Studie, wird Ihr Arzt Sie wieder bitten, den Fragebogen zur Einschätzung Ihrer Lebensqualität (EQ-5D), den Sie bereits aus der Einschlussuntersuchung kennen, auszufüllen.

Beim Abschlussbesuch der Studie werden alle diejenigen Untersuchungen durchgeführt, die Sie beim Einschluss, zu Beginn der Studie, schon kennengelernt haben. Dazu gehört insbesondere eine körperliche Untersuchung, die Erhebung Ihrer Vitalparameter, wie z.B. Blutdruck- und Pulsmessung, die Erstellung von einem Elektrokardiogramm (EKG) und eine Blutabnahme zur Bestimmung Ihrer Blutparameter und Ihrem Gerinnungswert. Außerdem wird Ihr Arzt die Studienmedikation zurücknehmen und Ihre Medikamenteneinnahme innerhalb der letzten drei Monate dokumentieren. Sie werden beim Abschlussbesuch keine neue Studienmedikation erhalten.

30 Tage nach dem Abschlussbesuch werden nochmals Ihre Blutwerte überprüft und Sie werden ein letztes Mal zu dem Auftreten von unerwünschten, insbesondere zu Blutungs-

oder anderweitigen thromboembolischen, Ereignissen befragt. Ihr Arzt wird im Anschluss frei über die weitere Therapie entscheiden.

Wenn Sie von weiteren Ärzten behandelt werden, müssen Sie diese über Ihre Teilnahme an der klinischen Prüfung informieren. Umgekehrt sollten Sie Ihren Prüfarzt ebenfalls über jede medizinische Behandlung, die Sie durch einen anderen Arzt erfahren, informieren. Sie erhalten einen Studienausweis, den Sie für den Notfall immer mit sich führen sollten.
Die Studienmedikamente sollten Sie so sicher aufbewahren, dass sie für Kinder oder andere Personen nicht erreichbar sind. Die Abgabe an Dritte ist untersagt.

4 Welchen persönlichen Nutzen habe ich von der Teilnahme an der Studie?

Vorstudien mit Apixaban haben gezeigt, dass Apixaban das Blutungsrisiko bei Patienten mit Vorhofflimmern und einer Nierenfunktionseinschränkung verringert. Aus diesem Grund kann durch die Einnahme von Apixaban bei Ihnen das Blutungsrisiko im Vergleich zu der sonst üblichen Therapie mit Phenprocoumon verringert werden; bei gleich gutem Schutz gegen Blutgerinnselbildung.

Außerdem würden Sie von der einfachen Anwendung bei Apixaban profitieren, da im Vergleich zur Einnahme von Phenprocoumon (z.B. Marcumar®), keine regelmäßigen INR Kontrollen durch Ihren Arzt notwendig sind.

Es kann jedoch auch sein, dass Sie durch die Teilnahme an dieser Studie vielleicht keinen persönlichen Gesundheitsnutzen haben. Die Ergebnisse der Studie können aber möglicherweise dazu beitragen, die Behandlung von dialysepflichtigen Patienten mit Vorhofflimmern zukünftig zu verbessern.

5. Welche Risiken sind mit der Teilnahme an der Studie verbunden?

Das Prüfpräparat Apixaban ist ein bereits auf dem Markt befindliches, zugelassenes Präparat, das auch bei Patienten mit nicht-valvulärem Vorhofflimmern und mindestens einem weiteren Risikofaktor eingesetzt wird. Die bislang beobachteten Nebenwirkungen und Beschwerden sind in der nachfolgenden Tabelle 1 zusammengefasst.

Tabelle 1

Häufige Nebenwirkungen (*kann bis zu **1 von 10** Behandelten betreffen*)	**Gelegentliche Nebenwirkungen** *(kann bis zu **1 von 100** Behandelten betreffen)*	**Seltene Nebenwirkungen** *(kann bis zu **1 von 1.000** Behandelten betreffen)*
Blutungen einschließlich: • Einblutungen in das Auge • Magen- oder Darmblutungen oder dunkles/schwarzes Blut im Stuhl • Nachweis von Blut im Urin bei Labortests • Nasenbluten • Rektalbluten, Zahnfleischbluten • Blutergüsse und Schwellungen	Blutungen einschließlich: • im Gehirn oder in der Wirbelsäule • im Mund oder Blut im Speichel beim Husten • im Bauch, in den Enddarm (Mastdarm) oder vaginale Blutungen • helles/rotes Blut im Stuhl • Blutungen nach einer Operation einschließlich Blutergüssen und Schwellungen, Austritt von Blut oder Flüssigkeit aus der Operationswunde/dem Operationsschnitt (Wundsekretion) oder der Injektionsstelle • Juckreiz, Hautausschlag • allergische Reaktionen (Überempfindlichkeitsreaktionen), die Schwellungen des Gesichts, der Lippen, des Mundes, der Zunge und/oder des Rachens und Atemprobleme verursachen können.	Blutungen einschließlich: • Blutungen in Lunge und Rachen • Blutungen in den Raum hinter der Bauchhöhle

Letztlich wäre durch die medikamentöse Blutverdünnung sogar eine lebensgefährliche Blutung bzw. ein Verbluten möglich. Weitere Nebenwirkungen umfassen eine Erhöhung der Leberwerte, die sich aber nach Absetzen des Medikaments im Regelfall wieder komplett zurückbilden.

Alle oben beschriebenen Nebenwirkungen können bei der Einnahme von Phenprocoumon (z.B. Marcumar®) ebenfalls auftreten.

Bedenken Sie bitte, dass bei der Behandlung im Rahmen dieser klinischen Prüfung auch bisher unbekannte Nebenwirkungen/ Risiken auftreten können.

Falls bei Ihnen Beschwerden, Erkrankungen oder Verletzungen im Verlauf der klinischen Prüfung auftreten, teilen Sie diese bitte den Studienmitarbeitern mit. Insofern diese schwerwiegend sind, melden Sie sich bitte umgehend, z.B. telefonisch.

6. Welche anderen Behandlungsmöglichkeiten gibt es außerhalb der Studie?

Bei dialyseabhängigen Patienten mit Vorhofflimmern wird manchmal aufgrund der erhöhten Blutungskomplikationen überhaupt kein Antikoagulans zur Vorbeugung von thromboembolischen Ereignissen (z.B. Schlaganfällen) verschrieben, sodass derzeit auf keine andere Behandlungsmöglichkeit zurückgegriffen werden kann. Entsprechend sind die Herzinfarkt- und Schlaganfallraten bei unbehandelten Patienten höher, als bei behandelten Patienten.

7. Wer darf an dieser klinischen Prüfung nicht teilnehmen?

An dieser klinischen Prüfung dürfen Sie nicht teilnehmen, wenn Sie gleichzeitig an anderen klinischen Prüfungen (außer Registerstudien) teilnehmen oder zuvor (< 30 Tage) an einer anderen klinischen Studie teilgenommen haben.

Schwangere und stillende Frauen dürfen an dieser klinischen Prüfung **nicht teilnehmen**, da die Risiken von Apixaban für einen Embryo, Fötus oder ein zu stillendes Kind noch unbekannt sind.

Zu Beginn der klinischen Prüfung müssen sich deshalb alle Frauen einem Schwangerschaftstest (Serumtest) unterziehen. Davon ausgenommen sind Frauen nach den Wechseljahren oder solche, die operativ sterilisiert wurden.

Gilt nur für Frauen im gebärfähigen Alter: Im Falle Ihrer Teilnahme an unserer klinischen Prüfung müssen Sie zuverlässige Maßnahmen zur Schwangerschaftsverhütung anwenden. Dieses ist für Frauen die Benutzung von hormonellen Methoden, wie z.B. der Pille, Vaginalring, intrauterine Spirale oder der Verzicht auf Geschlechtsverkehr während der gesamten Studiendauer.

Sollten Sie während der klinischen Prüfung schwanger werden oder den Verdacht haben, dass Sie schwanger geworden sind, müssen Sie umgehend den Prüfarzt darüber informieren.

Wenn Sie ein heterosexuell aktiver und zeugungsfähiger Mann sind, müssen Sie sich damit einverstanden erklären, ab dem Zeitpunkt der Unterzeichnung dieses Dokuments sichere Maßnahmen zur Schwangerschaftsverhütung (z.B. mit Spermizid behandelte Kondome) anzuwenden. Weiterhin sollten Sie adäquate Verhütungsmethoden auch für mindestens 5 Monate nach Einnahme von Phenprocoumon und 3 Monate nach Einnahme von Apixaban benutzen.

8. Entstehen für mich Kosten durch die Teilnahme an der klinischen Prüfung? Erhalte ich eine Aufwandsentschädigung?

Durch Ihre Teilnahme an dieser klinischen Prüfung entstehen für Sie keine zusätzlichen Kosten und Sie müssen das Studienmedikament sowie eventuelle Untersuchungen und medizinischen Versorgungen im Rahmen der Studie nicht bezahlen.

Sie erhalten keine Aufwandsentschädigung für Ihre Studienteilnahme.

9. Bin ich während der klinischen Prüfung versichert?

Bei der klinischen Prüfung eines Arzneimittels sind alle Studienteilnehmer gemäß dem Arzneimittelgesetz versichert.

Der Versicherungsschutz erstreckt sich nach den Allgemeinen Versicherungsbedingungen für versicherungspflichtige klinische Prüfungen von Arzneimitteln auf Gesundheitsschädigungen, die als Folge der klinischen Prüfung während und im Zeitraum bis zu 5 Jahren nach Abschluss Ihrer Studienteilnahme eintreten und nicht länger als 10 Jahre nach Beendigung Ihrer Studienteilnahme dem Versicherer gemeldet werden.

Entsprechend den Allgemeinen Versicherungsbedingungen beträgt die Versicherungssumme höchstens 500.000 EUR pro Person.

Wenn Sie vermuten, dass durch die Teilnahme an der klinischen Prüfung Ihre Gesundheit geschädigt oder bestehende Leiden verstärkt wurden, müssen Sie dies unverzüglich dem Versicherer

Name und Anschrift der Versicherung: CNA Insurance Company Limited
Im Mediapark 8
50670 Köln
Telefon: 0221-94 99-86 0
Fax: 0221-94 99-86 99

Versicherungsnummer: 10202564

direkt anzeigen, gegebenenfalls mit Unterstützung durch Ihren Prüfarzt, um Ihren Versicherungsschutz nicht zu gefährden. Sofern Ihr Prüfarzt Sie dabei unterstützt, erhalten Sie eine Kopie der Meldung. Sofern Sie Ihre Anzeige direkt an den Versicherer richten, informieren Sie bitte zusätzlich Ihren Prüfarzt.

Bei der Aufklärung der Ursache oder des Umfangs eines Schadens müssen Sie mitwirken und alles unternehmen, um den Schaden abzuwenden und zu mindern.

Während der Dauer der klinischen Prüfung dürfen Sie sich einer anderen medizinischen Behandlung – außer in Notfällen – nur nach vorheriger Rücksprache mit dem Prüfarzt unterziehen. Von einer erfolgten Notfallbehandlung müssen Sie den Prüfarzt unverzüglich unterrichten.

Sie erhalten ein Exemplar der Versicherungsbedingungen. Wir weisen Sie insbesondere auf Punkt 1.4 (zu den Ausschlüssen), Punkt 3.1 (zum Umfang der Leistungen) und Punkt 4.3 sowie Punkt 4.4. (zu Ihren Obliegenheiten) hin. Bei Verletzung Ihrer Obliegenheiten droht der Verlust des Versicherungsschutzes.

Patienten, die an der Substudie teilnehmen, sind über die oben angegebene Versicherung zusatzversichert.

10. Werden mir neue Erkenntnisse während der klinischen Prüfung mitgeteilt?

Sie werden umgehend und vollständig über neue Erkenntnisse, die in Bezug auf diese klinische Prüfung bekannt werden und die für Ihre Bereitschaft zur weiteren Teilnahme wesentlich sein können, informiert. Auf dieser Basis können Sie dann Ihre Entscheidung zur weiteren Teilnahme an dieser klinischen Prüfung zu jeder Zeit überdenken.

11. Wer entscheidet, ob ich aus der klinischen Prüfung ausscheide?

Sie können jederzeit, auch ohne Angabe von Gründen, Ihre Teilnahme beenden, ohne dass Ihnen dadurch irgendwelche Nachteile bei Ihrer medizinischen Behandlung entstehen.

Unter gewissen Umständen ist es aber auch möglich, dass der Prüfarzt oder der Sponsor entscheidet, Ihre Teilnahme an der klinischen Prüfung vorzeitig zu beenden, ohne dass Sie auf die Entscheidung Einfluss haben. Die Gründe hierfür können z. B. sein:

- Ihre weitere Teilnahme an der klinischen Prüfung ist ärztlich nicht mehr vertretbar;
- die gesamte klinische Prüfung wird abgebrochen.

Sofern Sie sich dazu entschließen, vorzeitig aus der klinischen Prüfung auszuscheiden, oder Ihre Teilnahme aus einem anderen der genannten Gründe vorzeitig beendet wird, ist es für Ihre eigene Sicherheit wichtig, dass Sie sich einer abschließenden Kontrolluntersuchung unterziehen.
Der Prüfarzt wird mit Ihnen besprechen, wie dann Ihre weitere Behandlung stattfindet.

12. Was geschieht mit meinen Daten?

Während der klinischen Prüfung werden medizinische Befunde und persönliche Informationen von Ihnen erhoben und in der Prüfstelle in Ihrer persönlichen Akte niedergeschrieben oder elektronisch gespeichert. Die für die klinische Prüfung wichtigen Daten werden zusätzlich in pseudonymisierter Form gespeichert, ausgewertet und gegebenenfalls weitergegeben.

Pseudonymisiert bedeutet, dass keine Angaben von Namen oder Initialen verwendet werden. Es wird ein Nummerncode vergeben, evtl. mit Angabe des Geburtsjahres.

Die Daten sind gegen unbefugten Zugriff gesichert. Eine Entschlüsselung erfolgt nur unter den vom Gesetz vorgeschriebenen Voraussetzungen. Ohne Ihre Zustimmung zur Verarbeitung Ihrer Daten können Sie nicht an der oben genannten klinischen Prüfung teilnehmen.

Das Arzneimittelgesetz enthält nähere Vorgaben für den erforderlichen Umfang der Einwilligung in die Datenerhebung und -verwendung. **Einzelheiten, insbesondere zur Möglichkeit eines Widerrufs, entnehmen Sie bitte der Einwilligungserklärung, die im Anschluss an diese Patienteninformation abgedruckt ist.**

13. Was geschieht mit meinen Blutproben?

Die Blutproben werden ausschließlich für diese klinische Prüfung verwendet. Etwaiges Restmaterial wird bei Abschluss der Prüfung vernichtet. Die Blutproben werden in gleicher Weise verschlüsselt wie Ihre persönlichen Daten.

14. An wen wende ich mich bei weiteren Fragen?

Beratungsgespräche an der Prüfstelle

Sie haben stets die Gelegenheit zu weiteren Beratungsgesprächen mit dem auf Seite 1 genannten oder einem anderen Prüfarzt.

Kontaktstelle

Es existiert außerdem eine Kontaktstelle bei der zuständigen Bundesoberbehörde. Teilnehmer an klinischen Prüfungen, ihre gesetzlichen Vertreter oder Bevollmächtigten können sich an diese Kontaktstelle wenden:

Bundesinstitut für Arzneimittel und Medizinprodukte
Fachgebiet Klinische Prüfung / Inspektionen
Kurt-Georg-Kiesinger-Allee 3
53175 Bonn

Telefon: 0228 / 207-4318 Fax: 0228 / 207-4355
e-mail: klinpruefung@bfarm.de

Protokoll Nummer: CV185-435 EudraCT-Nr. **2015-005503-84**

Prüfarzt (Name): ……

Prüfstelle, Adresse Und Telefon: ……
……
……
……

EudraCT-Nr. **2015-005503-84**

Klinische Studie zur Überprüfung der Sicherheit des oralen Antikoagulans Apixaban gegenüber einem Vitamin-K Antagonisten bei dialysepflichtigen Patienten mit chronischem Nierenversagen und Vorhofflimmern.

(**AXADIA – AFNET 8 Studie**)

Einwilligungserklärung

……
Name des Patienten in Druckbuchstaben

Teilnehmer-Nr. ……

Ich bin in einem persönlichen Gespräch durch den Prüfarzt

……
Name der Ärztin/des Arztes

ausführlich und verständlich über das Prüfmedikament und die Vergleichstherapie sowie über Wesen, Bedeutung, Risiken und Tragweite der klinischen Prüfung aufgeklärt worden. Ich habe darüber hinaus den Text der Patienteninformation sowie die hier nachfolgend abgedruckte Datenschutzerklärung gelesen und verstanden. Ich hatte die Gelegenheit, mit dem Prüfarzt über die Durchführung der klinischen Prüfung zu sprechen. Alle meine Fragen wurden zufrieden stellend beantwortet.

Möglichkeit zur Dokumentation zusätzlicher Fragen seitens des Patienten oder sonstiger Aspekte des Aufklärungsgesprächs:

_____

_____

_____

_____

Ich hatte ausreichend Zeit, mich zu entscheiden.

Protokoll Nummer: CV185-435 EudraCT-Nr. **2015-005503-84**

Mir ist bekannt, dass ich jederzeit und ohne Angabe von Gründen meine Einwilligung zur Teilnahme an der Prüfung zurückziehen kann (mündlich oder schriftlich), ohne dass mir daraus Nachteile für meine medizinische Behandlung entstehen.

Datenschutz:

Mir ist bekannt, dass bei dieser klinischen Prüfung personenbezogene Daten, insbesondere medizinische Befunde über mich erhoben, gespeichert und ausgewertet werden sollen. Die Verwendung der Angaben über meine Gesundheit erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der klinischen Prüfung folgende freiwillig abgegebene Einwilligungserklärung voraus, das heißt ohne die nachfolgende Einwilligung kann ich nicht an der klinischen Prüfung teilnehmen.

1. Ich erkläre mich damit einverstanden, dass im Rahmen dieser klinischen Prüfung personenbezogene Daten, insbesondere Angaben über meine Gesundheit, über mich erhoben und in Papierform sowie auf elektronischen Datenträgern in der Prüfstelle aufgezeichnet werden. Soweit erforderlich, dürfen die erhobenen Daten pseudonymisiert (verschlüsselt) weitergegeben werden:
   a) an den Sponsor, Kompetenznetz Vorhofflimmern e.V. (AFNET), oder eine von diesem beauftragte Stelle zum Zwecke der wissenschaftlichen Auswertung,
   b) im Falle eines Antrags auf Zulassung: an den Antragsteller und die für die Zulassung zuständige Behörde (Bundesamt für Arzneimittel und Medizinprodukte) und an andere Behörden außerhalb der Europäischen Union,
   c) im Falle unerwünschter Ereignisse: an das Kompetenznetz Vorhofflimmern e.V. (den Sponsor), an Bristol-Myers Squibb, an die jeweils zuständige Ethik-Kommission und die zuständige Bundesoberbehörde, (Bundesinstitut für Arzneimittel und Medizinprodukte) sowie von dieser an die Europäische Datenbank,
   d) an Niederlassungen von Bristol-Myers Squibb und Pfizer in der EU, in den Vereinigten Staaten von Amerika oder in anderen Ländern. Insofern die Daten in Länder außerhalb der EU weitergegeben werden, gelten die Europäischen Datenschutzrichtlinien nicht mehr.
2. Außerdem erkläre ich mich damit einverstanden, dass autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Sponsors und Bristol-Myers Squibb sowie die zuständigen Überwachungsbehörden in meine beim Prüfarzt vorhandenen personenbezogenen Daten, insbesondere meine Gesundheitsdaten, Einsicht nehmen, soweit dies für die Überprüfung der ordnungsgemäßen Durchführung der Studie notwendig ist. Für diese Maßnahme entbinde ich den Prüfarzt von der ärztlichen Schweigepflicht.
3. Die Einwilligung zur Erhebung und Verarbeitung meiner personenbezogenen Daten, insbesondere der Angaben über meine Gesundheit, ist unwiderruflich. Ich bin bereits darüber aufgeklärt worden, dass ich jederzeit die Teilnahme an der klinischen Prüfung beenden kann. Im Fall eines solchen Widerrufs meiner Einwilligung, an der Studie teilzunehmen, erkläre ich mich damit einverstanden, dass die bis zu diesem Zeitpunkt gespeicherten Daten weiterhin verwendet werden dürfen, soweit dies erforderlich ist, um
   a) Wirkungen des zu prüfenden Arzneimittels festzustellen,
   b) sicherzustellen, dass meine schutzwürdigen Interessen nicht beeinträchtigt werden,
   c) der Pflicht zur Vorlage vollständiger Zulassungsunterlagen zu genügen.
4. Ich erkläre mich damit einverstanden, dass meine Daten nach Beendigung oder Abbruch der Prüfung mindestens zehn Jahre aufbewahrt werden, wie es die Vorschriften über die klinische Prüfung von Arzneimitteln bestimmen. Danach werden meine personenbezogenen Daten gelöscht, soweit nicht gesetzliche, satzungsmäßige oder vertragliche Aufbewahrungsfristen entgegenstehen.
5. Ich bin über folgende gesetzliche Regelung informiert: Falls ich meine Einwilligung, an der Studie teilzunehmen, widerrufe, müssen alle Stellen, die meine personenbezogenen Daten, insbesondere Gesundheitsdaten, gespeichert haben, unverzüglich prüfen, inwieweit die gespeicherten Daten für die in Nr. 3 a) bis c) genannten Zwecke noch erforderlich sind.

   Nicht mehr benötigte Daten sind unverzüglich zu löschen.
6. Ich bin damit einverstanden, dass Gesundheitsdaten bei mitbehandelnden Ärzten erhoben oder eingesehen werden, soweit dies für die ordnungsgemäße Durchführung und Überwachung der Studie notwendig ist. Insoweit entbinde ich diese Ärzte von der Schweigepflicht. (Falls nicht gewünscht, bitte streichen.)
7. Ich bin damit einverstanden, dass mein Hausarzt

   .....
   Name

   über meine Teilnahme an der klinischen Prüfung informiert wird (falls nicht gewünscht, bitte streichen).

Protokoll Nummer: CV185-435 EudraCT-Nr. **2015-005503-84**

**Ich erkläre mich bereit,
an der oben genannten klinischen Prüfung
freiwillig teilzunehmen.**

Ein Exemplar der Patienten-Information und -Einwilligung habe ich erhalten. Ein Exemplar verbleibt im Prüfzentrum.

.....
Name des Patienten in Druckbuchstaben

....
Datum (eigenhändige Datierung durch Patienten) eigenhändige Unterschrift des **Patienten**

Ich habe das Aufklärungsgespräch geführt und die Einwilligung des Patienten eingeholt.

.....
Name des Prüfarztes/der Prüfärztin in Druckbuchstaben

....
Datum Unterschrift des aufklärenden **Prüfarztes/der Prüfärztin**

Appendix D: Funding

The sponsor of the trial is Atrial Fibrillation NETwork, Muenster, Germany. The entire trial will be funded by Bristol-Myers Squibb, Munich, Germany, and Pfizer, Berlin, Germany.

Appendix E: Members of the steering committee

Holger Reinecke, MD, chief physician cardiology, Muenster, Germany; Christoph Wanner, MD, chief physician nephrology, Wuerzburg, Germany; Rupert Bauersachs, MD, senior consultant hemosteology, Darmstadt, Germany; Guenter Breithardt, MD, senior consultant cardiology, Muenster, Germany; Joachim Gerß, PhD, chief statistician, Muenster, Germany; Paulus Kirchhof, MD, Professor of Cardiovascular medicine, University of Birmingham, Birmingham, United Kingdom (represening AFNET); Martin Sommer, MD, and Michael Krekler, MD (representing Pfizer and BMS, nonvoting).

Appendix F: Members of the data safety monitoring board

Joachim Hoyer, MD, nephrologist, Marburg, Germany; Thomas Klingenheben, MD, cardiologist, Bonn, Germany; Guido Knapp, PhD, statistician, Dortmund, Germany.

Appendix G: Members of the endpoints assessment committee

Karl Georg Haeusler, MD, neurologist, Berlin, Germany; Kristina Wasmer, MD, cardiologist, Division of Rhythmology, Hospital of the University of Muenster, Germany; Christian Rump, MD, nephrologist, Duesseldorf, Germany.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 15
	2b	All items from the World Health Organization Trial Registration Data Set	1-19, Supplement
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	1,19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19, Supplement
	5b	Name and contact information for the trial sponsor	1, 19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15, Supplement

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5, Supplement
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-8, Figure 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, 9, Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5, 11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5, 11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5, 11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	unblinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9, Table 2
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12-14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14, Supplement

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not planned
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19, 20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.