Supplementary Material

of the paper

A randomized controlled trial comparing apixaban to the vitamin K-antagonist phenprocoumon in patients on chronic hemodialysis – the AXADIA-AFNET 8 study

by Reinecke et al.

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Supplemental Methods

Search strategy for articles concerning apixaban in hemodialysis patients (as presented in Table 3)

Pub Med key words: hemodialysis atrial fibrillation anticoagulation, search on 26 Sep 2022

Manual search for papers mentioned in reviews and literature

Search: **hemodialysis atrial fibrillation anticoagulation**

("haemodialysis"[All Fields] OR "renal dialysis"[MeSH Terms] OR ("renal"[All Fields] AND "dialysis"[All Fields]) OR "renal dialysis"[All Fields] OR "hemodialysis"[All Fields]) AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields]) AND ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields])

Translations

hemodialysis: "haemodialysis"[All Fields] OR "renal dialysis"[MeSH Terms] OR ("renal"[All Fields] AND "dialysis"[All Fields]) OR "renal dialysis"[All Fields] OR "hemodialysis"[All Fields]

atrial fibrillation: "atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields]

anticoagulation: "anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields]

Supplemental Table S1: Primary and stratified analysis of the primary safety outcome (all events).

	Events					
	N	**Apixaban**	**Phenpro-coumon**	**Hazard ratio**	**95% Confidence interval**	
Primary confirmatory analysis	97	22/48	25/49	0.931	0.525	1.651
Predefined PP analysis	96	21/47	25/49	0.895	0.501	1.599
Exploratory sensitivity PP analysis	89	19/41	25/48	0.941	0.518	1.710
Stratification						
No prior TE + prior anticoagulation	57	21/31	12/26	0.834	0.386	1.803
No prior TE + anticoagulation naïve	17	2/8	5/9	0.516	0.102	2.594
prior TE + prior anticoagulation	16	5/6	6/10	1.901	0.592	6.099
prior TE + anticoagulation naïve	7	3/3	2/4	1.118	0.264	4.740
Cox-proportional hazard model with stratification included as fixed effects						
	97	22/48	25/49	0.968	0.543	1.725

PP indicates per-protocol; TE, thromboembolism.

Supplemental Table S2: Patients excluded from the per-protocol analysis.

Patient	Randomized group	Safety event	Time to event / censoring	Reason
Excluded from the predefined PP analysis				
029-002	Apixaban	YES	126 days	CHA_2DS_2-VASc risk (<2) detected after randomization, violation of inclusion criterion.
Additionally excluded from the exploratory sensitivity PP analysis				
009-001	Phenprocoumon	NO (censored at end of FU)	259 days	Apixaban treatment for 22 days before end of follow-up
004-008	Apixaban	NO (censored at end of FU)	702 days	Phenprocoumon onset after stop of apixaban treatment. Onset was 16 days before end of FU.
004-011	Apixaban	NO (censored at end of FU)	79 days	Phenprocoumon onset after stop of apixaban treatment. Onset was 24 days before end of FU.
024-002	Apixaban	NO (censored at end of FU)	435 days	Phenprocoumon onset after stop of apixaban treatment. Onset was 28 days before end of FU.
033-003	Apixaban	NO (censored at end of FU)	932 days	Phenprocoumon onset after stop of apixaban treatment. Onset was 30 days before end of FU.
033-008	Apixaban	YES	355 days	Phenprocoumon onset after stop of apixaban treatment. Onset was 20 days before end of FU.
036-002	Apixaban	YES	296 days	Received phenprocoumon for 11 days during hospitalization outside of the study center.

FU indicates follow-up, PP, per-protocol.

Supplemental Table S3: Quality of oral anticoagulation

	Untreated patients	**Documented protocol conform intake**	**Pills per day**	**Median therapy duration, days**
Apixaban	0/48	44/48	0-1/day: 2 /48 1-2/day: 35/48 2-3/day: 9/48	355.5 (range: 3-1,337)
	Untreated patients	**TTR > 0.66**	**Median TTR**	
Phenprocomoun	0/49	14/49	0.507 (range: 0-1) N=3 patients never reached the target INR (INR 2-3)	

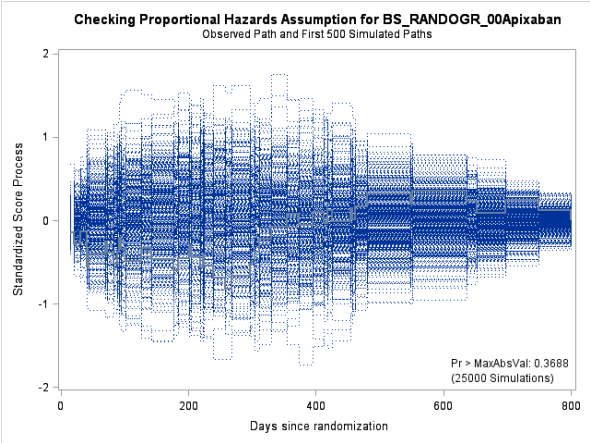
INR indicates international normalized ratio; TTR, Time in therapeutic range.

Supplemental Figure S1: Assessing the proportionality assumption of the Cox regression model

For the Cox model with only the randomized group as fixed effect:

Supremum Test for Proportionals Hazards Assumption

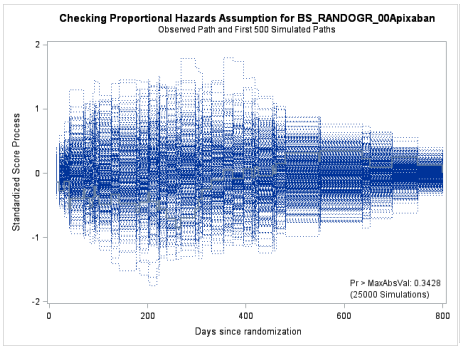
Variable	Maximum Absolute Value	Replications	Seed	Pr > MaxAbsVal
Randomized group	0.8213	25000	673730168	0.3688

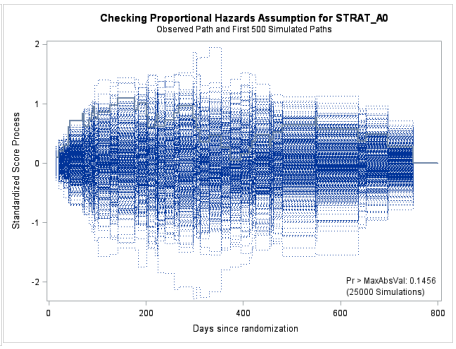


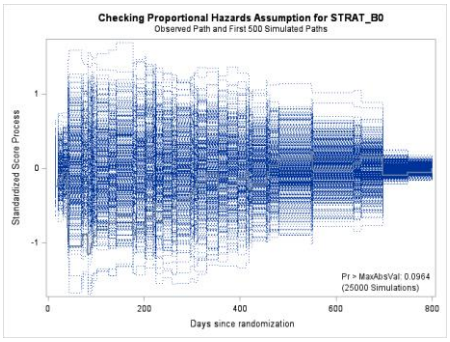
For the model also including stratification variables:

Supremum Test for Proportionals Hazards Assumption

Variable	Maximum Absolute Value	Replications	Seed	Pr > MaxAbsVal
Randomized group	0.8514	25000	1549440698	0.3428
Prior TE events	1.0926	25000	1549440698	0.1456
Prior anticoagulation	1.1492	25000	1549440698	0.0964

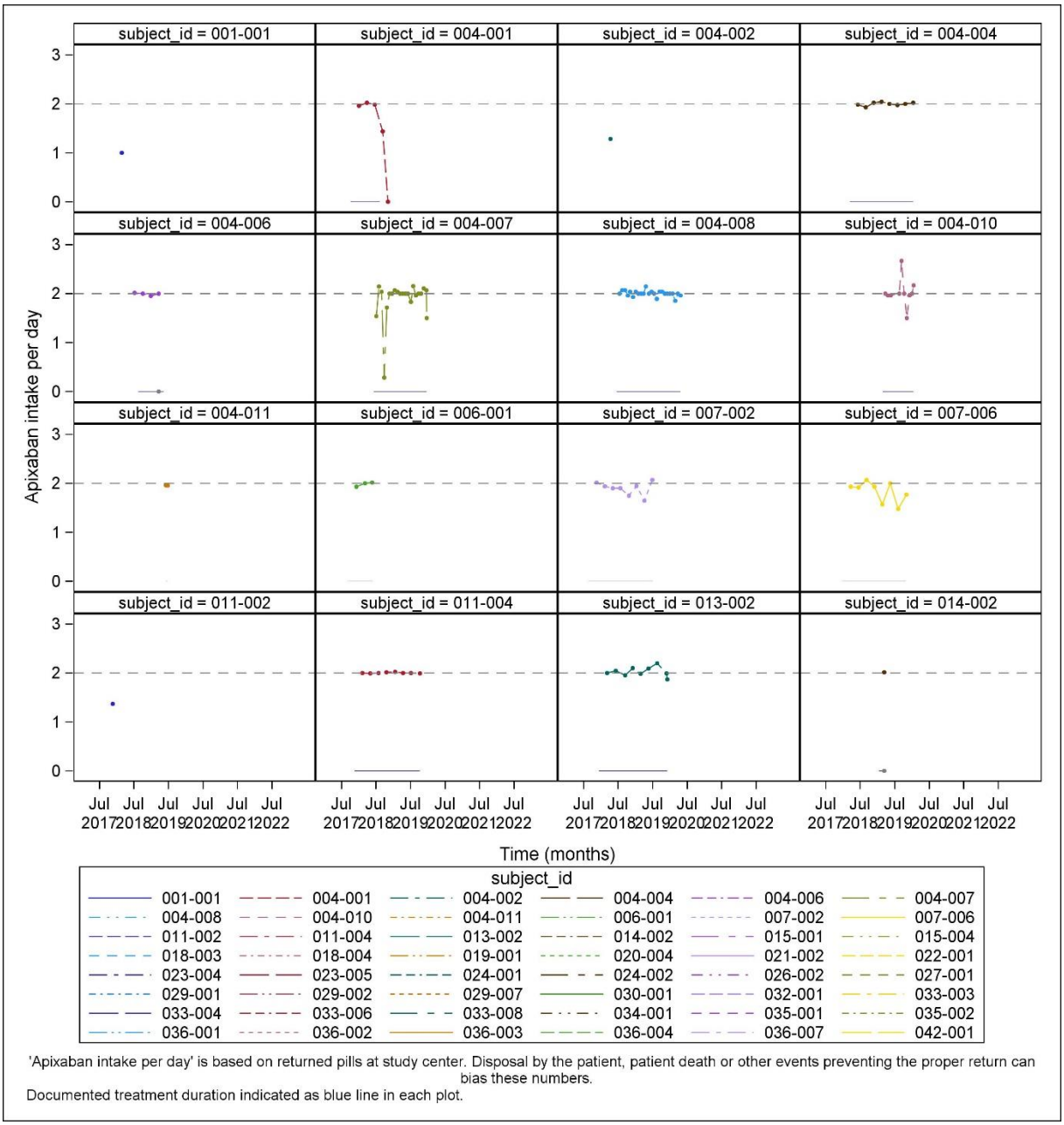






Hazard ratios were estimated in a Cox proportional regression model. We carefully checked the proportionality assumption by analyzing the model on 500 resampled paths and the Kolmogorov-type supremum test (n=25,000 repeated simulations). The supremum test did not indicate any clear violation of the proportionality assumption (p=0.369).

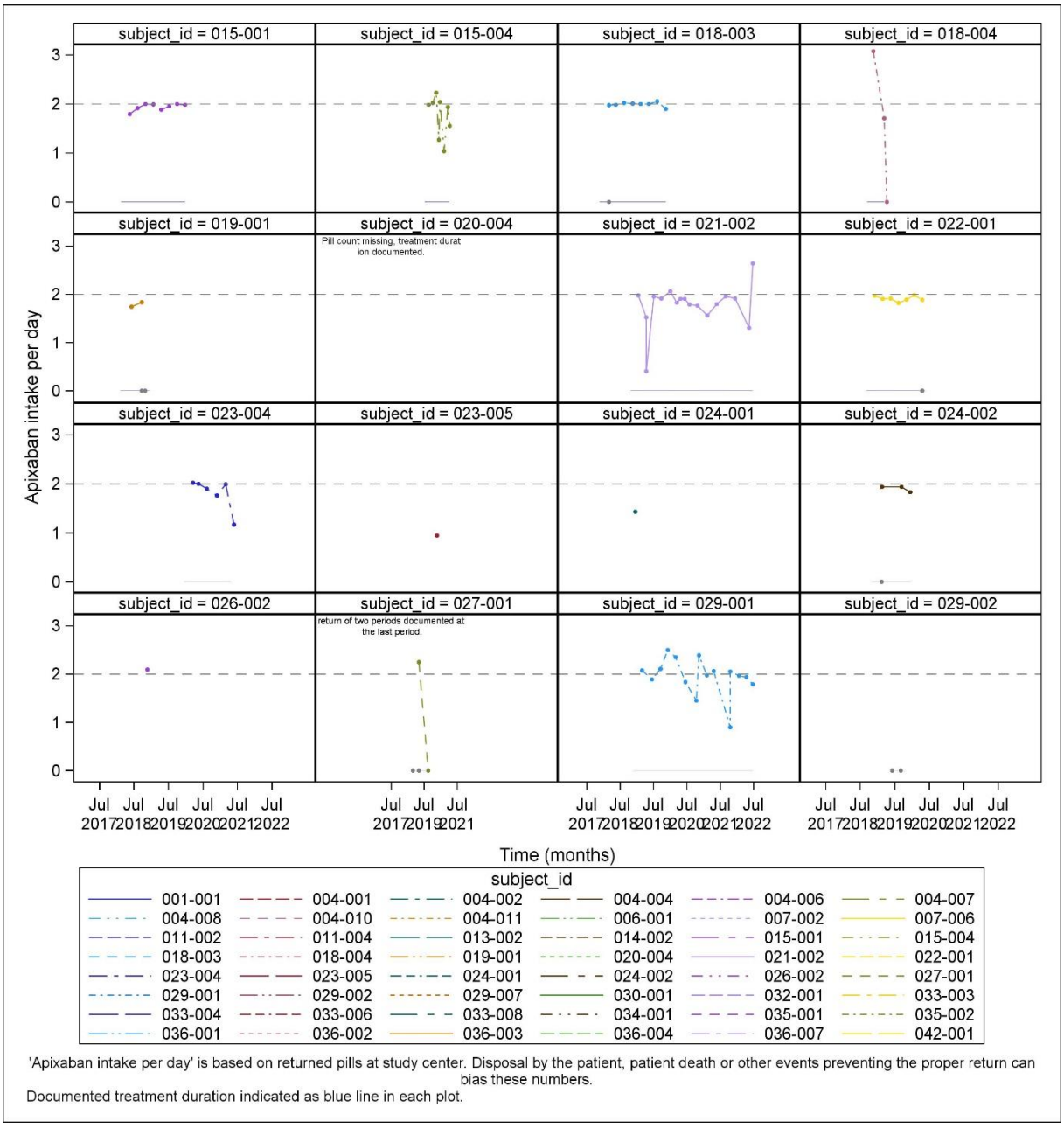
Supplemental Figure S2: Daily apixaban intake for all patients taking apixaban in the trial



'Apixaban intake per day' is based on returned pills at study center. Disposal by the patient, patient death or other events preventing the proper return can bias these numbers.

Documented treatment duration indicated as blue line in each plot.

Continued: Supplemental Figure S2: Daily apixaban intake for all patients taking apixaban in the trial



'Apixaban intake per day' is based on returned pills at study center. Disposal by the patient, patient death or other events preventing the proper return can bias these numbers.

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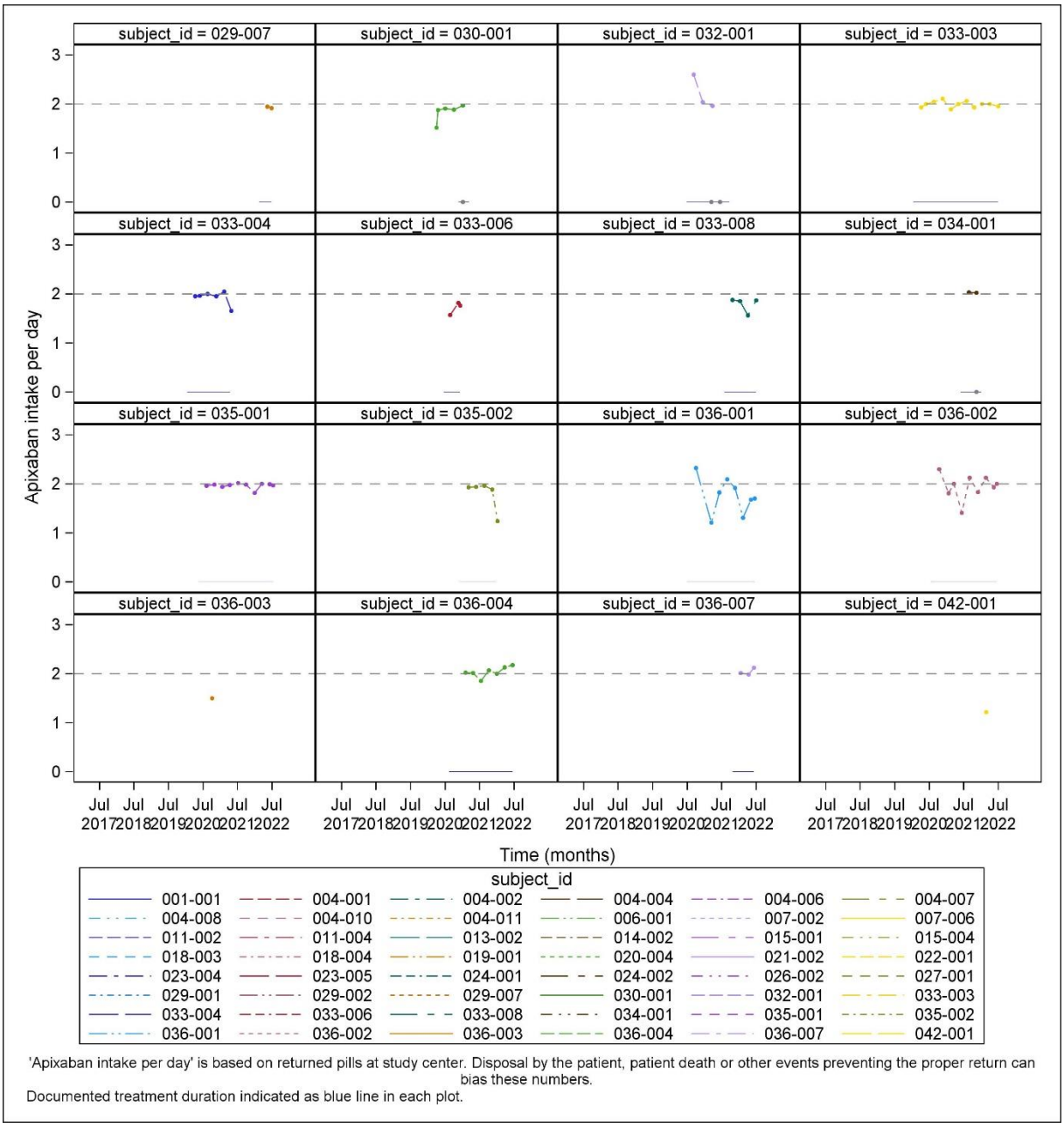
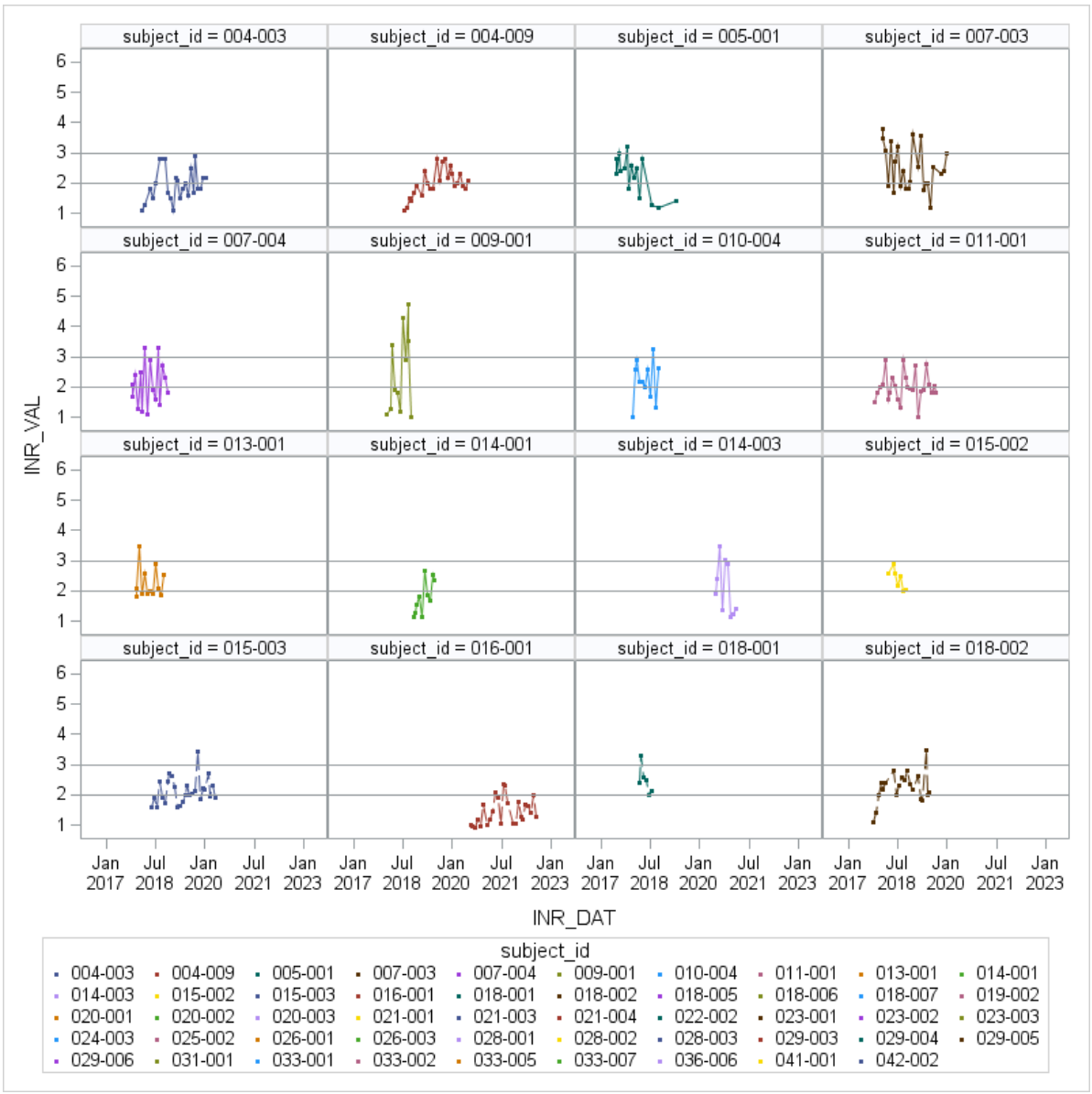
Continued: Supplemental Figure S2: Daily apixaban intake for all patients taking apixaban in the trial



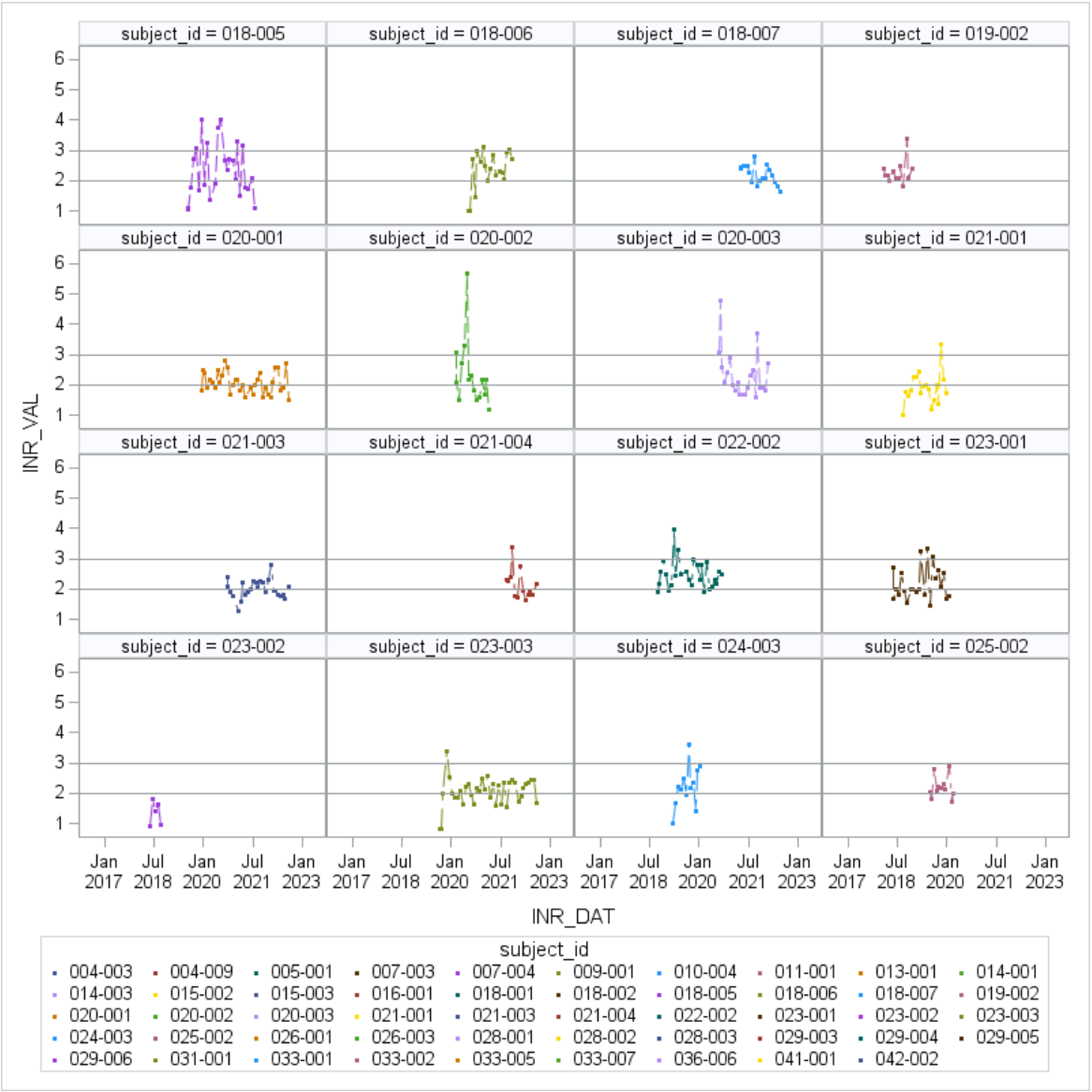
'Apixaban intake per day' is based on returned pills at study center. Disposal by the patient, patient death or other events preventing the proper return can bias these numbers.

Documented treatment duration indicated as blue line in each plot.

Supplemental Figure S3: INR values for all patients on phenprocoumon during study



Continued: Supplemental Figure S3: INR values for all patients on phenprocoumon during study



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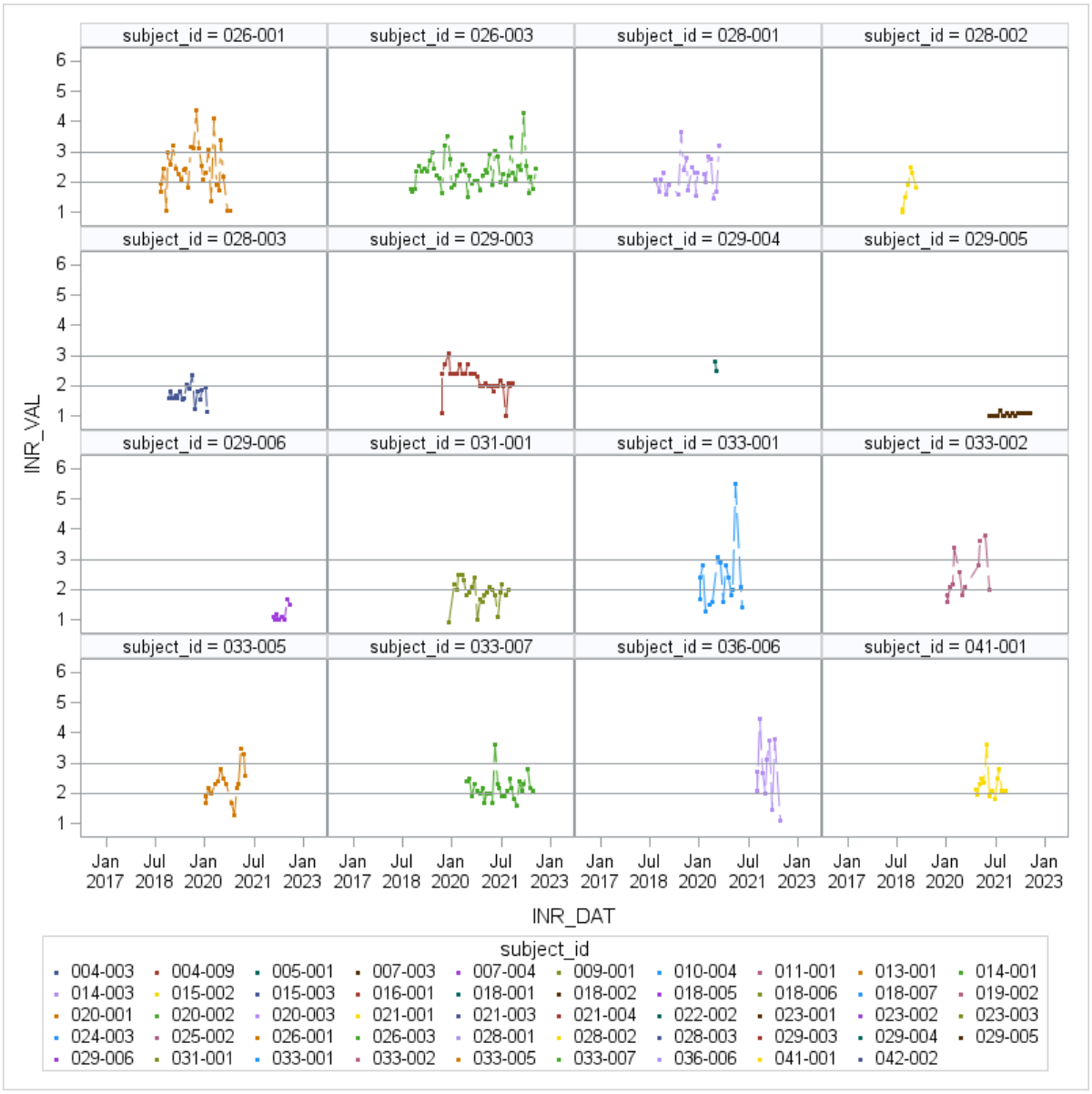

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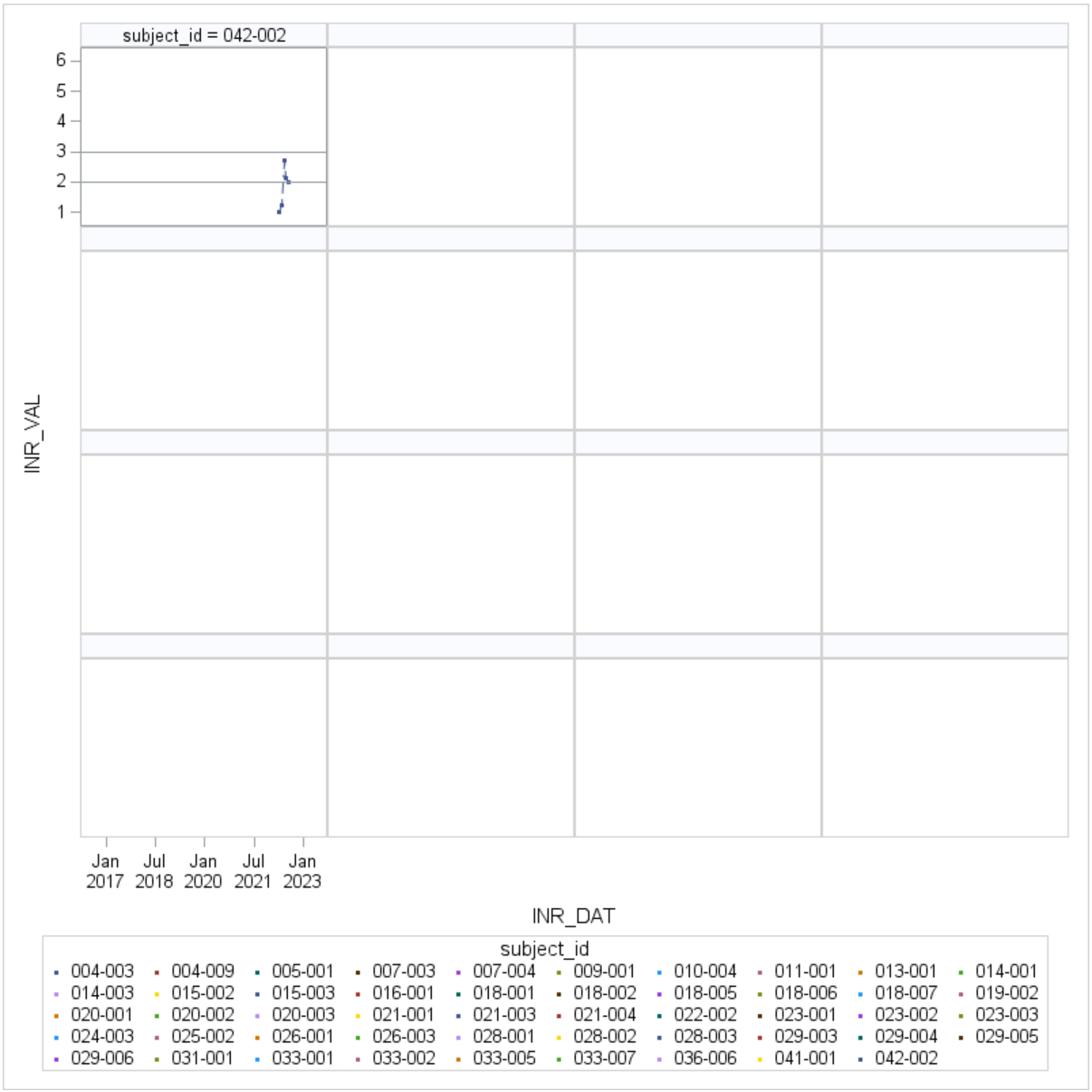

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Clinical Study Protocol
AXADIA-AFNET 8
EudraCT no. 2015-005503-84

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

Acronym: AXADIA – AFNET 8

PROTOCOL NUMBER: CV185-435

Phase of development: IIIb

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Legal sponsor according to the EU directive 2001/20/EC:

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Protocol Version: final 1.7

TABLE OF CONTENTS

	PROTOCOL SYNOPSIS
Protocol Title:	**A Safety Study Assessing Oral Anticoagulation with Apixaban versus Vitamin-K Antagonists in Patients with Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) on Chronic Hemodialysis Treatment**
Sites:	Approximately 30-35 sites in Germany are planned to be involved in the study. Co-ordinating Investigator Cardiology/ Head of the Trial Prof. Dr. med. H. Reinecke University Hospital Münster Department of Cardiology and Angiology Co-ordinating Investigator Nephrology/ Chief Investigator: Prof. Dr. med. C. Wanner University Hospital Würzburg Department of Internal Medicine Division of Nephrology
Research Hypothesis:	Administration of 2.5 mg apixaban twice daily is associated with a significant lower rate of major and clinically relevant non-major bleedings in patients with atrial fibrillation (AF) or atrial flutter (AFL) and end-stage kidney disease (ESKD) compared to oral vitamin-K antagonists (phenprocoumon), while it is non-inferior in preventing thromboembolic events.
Study Schema: **Drugs / Doses /** **Length of Treatment)**	Apixaban 2.5 mg twice daily or Phenprocoumon by INR (Target: 2.0-3.0) Planned duration of single patient participation is depending on event rate. Patients will be treated for at least 1 month and until termination of the study.
Study Objectives: **Primary:** **Secondary:**	Primary Objective: to assess the safety of the factor Xa inhibitor apixaban versus the vitamin-K antagonist (VKA) phenprocoumon in patients with ESKD on hemodialysis and AF. The safety will be assessed by means of the incidence of all-cause death, major and clinically relevant non-major bleedings on anticoagulation. Secondary Objective: to compare the efficacy of the factor Xa inhibitor apixaban with the VKA phenprocoumon regarding prevention of thromboembolic events in patients with ESKD on hemodialysis and AF. For further details please refer to “Criteria for Evaluation”.
Study Design:	Open-label, randomized controlled trial, phase IIIb

Accrual Goal: **(Total number of patients)**	Approximately 108 subjects planned to be allocated to the trial (randomized; 1:1 ratio). The total number of patients depends on the number of observed events. At least 75 subjects planned to be analyzed
Accrual Rate: **(Number of patients expected per month)**	1.8
First patient first visit (FPFV): **Last patient first visit (LPFV):** **Last patient last visit (LPLV):**	**Planned dates:** **FPFV**: 01. June 2017 **LPFV**: 01. June 2022 **LPLV**: 01. July 2022
Main Inclusion Criteria:	• End-stage kidney disease (ESKD) with chronic hemodialysis treatment 3 times per week (with a minimum of 3,5 hours per dialysis) • Chronic (i.e. repeated) paroxysmal, persistent or permanent atrial fibrillation (AF) and/ or atrial flutter (AFL) 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 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, i.e. no symptoms or no significant disability and able to carry out all usual activities, despite some symptoms (Farrell, Godwin, Richards, and Warlow (1991)) • Males and females, aged 18 years or older

Main Exclusion Criteria:	• AF or AFL 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 or AFL that require chronic anticoagulation (e.g., a prosthetic mechanical heart valve). • Active infective endocarditis • Any planned interventional or surgical AF or AFL 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 (SmPC) of study drugs) • Known indication for treatment with NSAIDs (see SmPC of study drugs) - acetylsalicylic acid (ASA) up to 100 mg per day is allowed • Known Antiphospholipid Syndrome requiring anticoagulation • Impaired liver function e.g., caused by active infection with HIV, HBV or HCV, hepatitis or other liver damage (No limits for ALT and AST values are defined in this study protocol, although mentioned in the SmPC because they are frequently elevated in dialysis patients. In case of clinically relevant increase of ALT or AST level, patient's eligibility is to be decided by the responsible investigator) • Any type of stroke within 3 months prior to baseline • Other indication for anticoagulation than AF or AFL • 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 excluded at any dose). • Active infection or symptoms suggestive of COVID-19 infection.

Criteria for Evaluation: (efficacy, safety, pharmacokinetics)	Primary safety events: All-cause death Major bleeding (as defined in the International Society on Thrombosis and Haemostasis (ISTH) consensus): • 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, 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 and outcomes • Myocardial infarction • Ischemic stroke • All-cause death • Cardiovascular death • Deep vein thrombosis and/or pulmonary embolism • Quality-of-life status Events of special interest • Dialysis shunt thrombosis • Clotting of dialysis membrane

	Composite endpoint: • Myocardial infarction • Ischemic stroke • All-cause death • Deep vein thrombosis and/ or pulmonary embolism
Statistics:	In the primary statistical analysis, the treatment arms 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. Two statistical hypotheses will be tested in order to prove superiority and/or non-inferiority of the apixaban versus phenprocoumon treatment (multiple one-sided significance level α=2.5%, accounting for multiple testing). Correspondingly, the primary statistical analysis comprises a superiority test and a non-inferiority test. The non-inferiority test and the superiority test will be performed in the safety population that consists of all randomized patients who received at least one dose of the study drug, including patients with any kind of protocol violations, applying the as-treated 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 this result is supported both in the as-treated analysis and the per-protocol analysis. The statistical analysis of the primary endpoint and the secondary endpoints will be performed 'on treatment', i.e. events are only counted during the period of receipt of study drug and 2 days after the last application, using Cox proportional hazard models with time-dependent covariates. Further safety analyses will include all events, including AEs and SAEs, which happen after randomization. The primary analysis will be up to the first occurrence of the endpoint. An extended analysis will additionally take recurrent events into regard using the Anderson-Gill model using robust variance estimates and a clock reset conditional risk set model (Prentice, Williams, and Peterson 1981). As a sensitivity analysis, statistical analyses will be repeated in the full analysis set that consists of all randomized patients, applying the intention-to-treat principle.

1 INTRODUCTION

Patients with chronic kidney disease (CKD) suffer from high cardiovascular morbidity and mortality. Moreover, their number is dramatically increasing. Thus, recent data provide evidence that more than 15 million people in the USA and more than 6 million people in Germany suffer from CKD - and their number appears to double every 10 years (Reinecke et al., 2006a), (Reinecke et al., 2006b). This is due to several causes, especially to the increasing prevalence of diabetes, hypertension, and a higher number of elderly people in general.

Of note, although about 6 million people suffer from CKD in Germany, only 120,000 are alive in CKD stage 4 and 85,000 in stage 5 (=end-stage kidney disease (ESKD) on peritoneal or hemodialysis). The reason for this phenomenon is the deleterious mortality in the advanced CKD stages 4 and 5. The dramatic cardiovascular morbidity and mortality of CKD patients has meanwhile received increasing attention, regarding myocardial infarction, chronic heart failure, and other cardiovascular conditions (Bode-Böger et al., 2006), (Heitmeyer et al., 2010).

In contrast, only little attention has been paid to the problem of atrial fibrillation (AF) in patients with CKD, although this arrhythmia is very frequent in this cohort due to the high prevalence of structural heart disease and hypertension as the major risk factors. A prevalence of AF of about 11-27%, e.g., in patients with ESKD on chronic hemodialysis treatment, has been reported while data on patients in other stages of CKD are very limited. For instance, in the randomized controlled 4D trial (type 2 diabetes mellitus hemodialysis patients), the incidence of documented AF was 11% (Wanner et al., 2005), (Krane et al., 2010).

Due to a large number of pathophysiological mechanisms involved, patients with CKD suffer from a high risk of both thromboembolic events and bleedings (Reinecke et al., 2009). Concordantly, ischemic (and hemorrhagic) stroke is a 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; the stroke-related 2-year mortality was 74%, 55%, and 28%, respectively.

ANTICOAGULATION IN PATIENTS WITH AF

In general, patients with AF and an increased risk for thromboembolism (as indicated by the $CHADS_2$- or the CHA_2DS_2-VASc-Score) should receive oral anticoagulation which reduces the risk of stroke or systemic embolism by about two thirds. Anticoagulation is, on the other hand, associated with an increased risk of bleedings, but the net benefit of anticoagulation prevails. While the evidence in favor of anticoagulation is completely consented for the general population and also for patients with mild CKD, there is only little evidence how to treat patients in more advanced stages of CKD who suffer from AF.

TYPES OF ANTICOAGULATION

Traditionally vitamin-K antagonists (warfarin and, especially in central Europe, phenprocoumon) have been considered as the established treatment modality. However, the need for repeated

assessment of their anticoagulant effect and the frequent interaction with other drugs as well as with food make them difficult to handle. Despite the evidence that vitamin-K antagonists (VKA) are also useful in the elderly, these patients who are at high risk of stroke as well as other high-risk patients are frequently undertreated. To overcome the limitations of VKAs, agents have been developed that target specific factors of the coagulation process. The factor Xa (FXa) is one of the two presently used targets for stroke prevention in AF. This factor plays a pivotal role in the coagulation cascade at the junction of the intrinsic and extrinsic pathways of the coagulation system. Inhibition of FXa exerts anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process, including fibrin formation and platelet activation.

ANTICOAGULATION IN CKD

Until November 2019, no data from randomized clinical trials on oral anticoagulation for AF in CKD 4 and ESKD patients with an increased risk of stroke or systemic embolism was available, and evidence for anticoagulation has been and is still discussed controversially (Reinecke et al., 2009), (Marinigh, Lane, & Lip, 2011), (Reinecke, Engelbertz, & Schabitz, 2013).

The current ESC (European Society for Cardiology) summarize therefore critically (Camm et al., 2012a): “AF patients with severe renal failure are at high risk for stroke, but are also at increased risk for death, coronary events and serious bleeding. These patients have not been adequately studied and have been excluded from clinical trials, and their risk assessment is complex. There is also the caveat that renal function may not remain static, especially in elderly AF patients with multiple co-morbidities and concomitant drug therapies.”

However, in November 2019 the data of the RENAL-AF trial were presented at the American Heart Association (AHA) congress as an oral presentation (Pokorney et al., 2019). Due to recruitment problems, RENAL-AF was stopped preliminary after 154 patients were enrolled (initially planned: 800 patients). Compared to AXADIA, RENAL-AF differs in two major aspects: First, the majority of analyzed patients in the apixaban arm received 5 mg bid apixaban according to the advice of the FDA as the regulatory agency. Second, the trial was solely performed in the USA, where different dialysis schemes are performed in comparison to Europe and especially in Germany (shorter session duration; and often not more than 3 times a week). Both issues affect the preliminary results of RENAL-AF markedly and severe doubts had been raised in advance whether the results of RENAL-AF can be applied to other countries. The following preliminary results reflect these problems very well:

- In regard to the primary endpoint, there was a trend to more bleedings in the apixaban arm, which must be contributed to the clearly higher dosage of 5 mg bid apixaban in the majority of participants (resulting in plasma levels of 200% according to confidential data of the pharmacokinetic department of BMS) while the administration of 2.5 mg bid apixaban lead to a plasma level of about 105% which is comparable to individuals without reduced kidney function receiving a dosage of apixaban 10 mg bid apixaban. In the present AXADIA trial the lower dosage of 2,5 mg bid is used throughout the entire trial.

On the other hand, the TTR in the warfarin arm was only 44% which represents subtherapeutic levels in a majority of cases. This even more enhances the impression that apixaban increases the risk of bleeding compared to VKA.

- The all-cause mortality in RENAL-AF was 22% (34 of 154 patients). Up to now the AXADIA trial shows a mortality of 8% (5 of 59 patients). This significant difference might be attributed mostly to the different dialysis schemes used in the USA.

RENAL-AF showed additional surprising differences between both treatment groups despite the number of 154 randomized patients: In the apixaban arm, more patients were >75 years (29 vs. 21%), females (42 vs. 31%), anticoagulation-naïve (12 vs. 5%) and had a bleeding events during the last year requiring hospitalization (10 vs. 3%). All these factors are well known to increase the risk for bleedings.

The present study should, therefore, examine the safety of oral anticoagulation in patients with ESKD, who suffer from progression of their renal disease while anticoagulated.

1.1 Overall Risk/ Benefit Assessment

During recent years, the effect of oral anticoagulation in advanced CKD has been assessed only in few, mostly small and retrospective (non-randomized) cohort studies of ESKD patients on hemodialysis. In these patients, anticoagulation was associated with a markedly reduced risk of stroke but was also associated with a 4- to 8-fold increased rate of bleeding (Olesen et al., 2012). However, these few retrospective studies suffered all from a significant bias when selecting patients for anticoagulation (Reinecke et al., 2009). They insofar do not allow an evidence-based decision how to treat these patients to reduce their high risk of stroke, systemic and venous thromboembolic events, bleeding and cardiovascular death.

Platelet inhibitors such as ASA did not reduce thromboembolic events but were associated with a high rate of adverse effects and bleedings (Chan, Lazarus, Thadhani, & Hakim, 2009), (Olesen et al., 2012). Therefore, platelet inhibition does not seem to be an adequate therapy in patients with AF and ESKD.

In regard to the general lack of data, RENAL-AF provides for the first time data in a randomized controlled trial on bleeding and embolic event rates in dialysis-dependent patients. Apart from the preliminary data from RENAL-AF, the only other study analyzing an overall benefit of oral anticoagulation in ESKD patients was another very recently published analysis based on the Danish registry data of 150,000 patients (Bonde et al., 2014) with an increased risk of stroke and systemic embolism (CHA_2DS_2-VASc score ≥2). Their data showed clearly that warfarin was significantly associated with lower all-cause mortality in patients with CKD (HR 0.64, 95%CI 0.60-0.69) and in those with ESKD (HR 0.85, 95%CI 0.72-0.99).

1.2 Research Hypothesis

The primary goal of this study is to assess the safety of two types of oral anticoagulants in patients with ESKD on hemodialysis with atrial fibrillation or atrial flutter. The novel FXa inhibitor apixaban (at a reduced dose of 2x 2.5 mg/day) will be compared to the vitamin-K antagonist (VKA) phenprocoumon (target range*:* International Normalized Ratio *(*INR) 2.0-3.0) regarding bleeding rates and all-cause mortality during chronic administration for prevention of stroke or systemic embolism.

The primary hypothesis of the study is that oral anticoagulation with apixaban will improve the safety by significantly reducing bleeding rates in patients with ESKD on hemodialysis and AF compared to the VKA phenprocoumon.

1.3 Study Rationale

Since there is no evidence-based treatment for patients with ESKD on hemodialysis and a need for anticoagulation, apixaban with its low renal clearance (<30% of total clearance) may offer a safe and effective alternative to VKA. Apixaban, belonging to the group of non-vitamin-K dependent oral anticoagulants, is a novel, orally active, potent, direct selective inhibitor of coagulation factor Xa. It reversibly binds to the active site of FXa and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin.

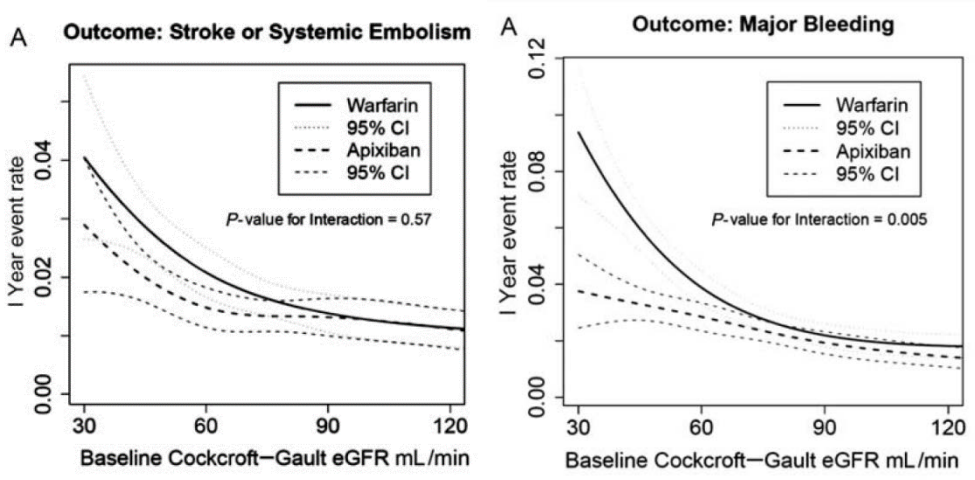

Figure 1: Data of ARISTOTLES trial (Hohnloser et al. 2012)

Data from the large randomized trial of apixaban and warfarin in patients with non-valvular AF (ARISTOTLE) represent a sound basis for using apixaban in these indications. In a retrospective analysis of the ARISTOTLE data (Hohnloser et al., 2012), treatment with apixaban reduced the rate of stroke, death, and major bleeding, regardless of renal function (see figure 1). Moreover,

those patients with advanced CKD had the greatest reduction in major bleedings with apixaban (figure, right box): the lower the eGFR, the larger the gap between the event rates of warfarin (bold line) and those of apixaban (dashed line) became, indicating a clear benefit for the use of apixaban. It is reasonable to speculate (although not proven) that with further decrease in eGFR below the limit of 30 mL/min as set in ARISTOTLE, this difference between warfarin and apixaban will further increase or at least be maintained (figure, left margin of right box).

On the other hand, recent administrative data from an US ESKD database (Chan, Edelman, Wenger, Thadhani, & Maddux, 2015) have shown that in dialysis patients with AF, the direct oral anticoagulants dabigatran and rivaroxaban, which both have a higher degree of renal elimination than apixaban, were associated with a higher risk of severe bleeding compared to warfarin. There were too few events in the study to detect meaningful differences in stroke and arterial embolism between the drug groups. Of note, these data as well are limited by their non-randomized nature and the potential to miss significant confounding factors that may have driven the decision to anticoagulate a patient on dialysis. Another major concern is that these data demonstrate that rivaroxaban and dabigatran have been readily used off-label in ESKD patients (Chan et al., 2015).

In this setting, it would therefore be of great interest and potential benefit for the patients to evaluate the impact of apixaban, because

- of its lower rates of bleeding with worsening of renal function, (Hohnloser et al., 2012) while effects on embolic events remain stable compared to warfarin;
- there is no need for laboratory controls of coagulation which is often considered one of the drawbacks of VKA;
- due to its low renal excretion, apixaban is relatively independent from any changes in the renal function which may occur over time in an individual. This appears to be advantageous in both patients with and without renal failure who may suffer from a decrease in renal function during a treatment with apixaban, and maybe even below a creatinine clearance of 25 mL/min (Hohnloser et al., 2012), (Reinecke et al., 2013). For the treating physicians this might turn out as an important benefit (less fear of bleedings, less need for creatinine controls) to prescribe apixaban instead of other drugs.
- in the AVERROES trial (Connolly et al., 2011) including patients not eligible for standard oral anticoagulation in part due to a high bleeding risk, the rates of major and clinically relevant non-major bleedings were similar with apixaban compared to platelet inhibition with acetylsalicylic acid.

Moreover, this study will add knowledge in a field where up to now only one other randomized clinical trial had evaluated the benefit of oral anticoagulation in ESKD but was stopped prematurely.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the safety of the factor Xa inhibitor apixaban versus a vitamin-K antagonist phenprocoumon in patients with AF and ESKD on hemodialysis.

The safety will be assessed by means of the incidence of all-cause death, major and clinically relevant, non-major bleeding as well as specific bleedings in dialysis patients (e.g., after shunt removal) on anticoagulation. A detailed definition of this safety endpoint is given in section 6.4.1.

2.2 Secondary Objective

The secondary objective of this study is to compare the efficacy of the factor Xa inhibitor apixaban with the VKA phenprocoumon regarding prevention of thromboembolic events in patients with ESKD on hemodialysis and AF. A detailed definition of efficacy endpoints is given in section 6.5.

3 ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC.

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment).

3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g.,

advertisements), and any other written information to be provided to subjects. The sponsor should also provide the IRB/IEC with a copy of the most recent SmPC labeling information to be provided to subjects, and any updates.

The sponsor should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to European or national regulatory requirements or institution procedures.

3.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical the study in which they volunteer to participate.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.

6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3.4 Insurance

All patients participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

The patients shall be given information about the settlement of the insurance contract and the provisions stipulated in it which concern them. A copy of the insurance terms and conditions should be handed out to the subject. Details concerning the insurance (e.g., insurance company, contact details, policy number etc.) will be itemized in the written patient information.

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

This safety study is initiated with EudraCT No. 2015- 005503-84. It is conducted in Germany as an investigator-driven, prospective, parallel-group, single country, multi-center phase IIIb trial to assess the safety of apixaban versus the vitamin-K antagonist phenprocoumon in patients with AF and ESKD on hemodialysis treatment.

The study is planned to be conducted in approximately 30-35 German study sites.

Male or female patients aged ≥ 18 years with ESKD on hemodialysis treatment 3 times a week, each with a duration of at least 3.5 hours, and with an indication for oral anticoagulation due to AF or AFL will be centrally randomized into 2 treatment arms: apixaban or phenprocoumon (1:1). Patients actually on phenprocoumon therapy can be randomized to either study drug treatment.

For a detailed description of the target population, please refer to section 4.2.

As phenprocoumon needs constant INR controls, the study is performed with open-label administration of study drugs.

For details regarding the study schedule (flow chart) and assessments conducted during the study, please refer to Table 2-1 in section 6.1. Details of safety evaluation criteria are given in section 6.4 and efficacy parameters are described in section 6.5.

A Data and Safety Monitoring Board will supervise this study, and safety and efficacy endpoints will additionally be evaluated by a blinded Endpoint Review Committee (refer to section 10.2).

All subjects will be treated with study drug until the end of the trial.

Planned TRIAL DURATION and SAMPLE SIZE

For detailed description, please refer to chapter 11.1.

AXADIA – AFNET 8 is an event-driven trial. We currently expect enrolment of up to 108 patients to achieve the required number of first primary outcome events (n= 64). Details are given in the section “sample size determination”(see 11.1). The end of the clinical study for each individual subject is defined as the End of Study (EoS) visit. End of recruitment will be announced either after the end of the recruitment period (60 month) or if 64 events have been reached, whatever comes first. At the end of the study, all subjects will be ordered to perform their individual End of

Treatment visit (EoT; for more details refer to section 5.4.2). The end of the clinical trial is defined as the last visit of the last subject in the study.

4.2 Study Population

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. For entry into the study, the following criteria MUST be met.

4.2.1 Inclusion Criteria

1) Signed Written Informed Consent

- Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

2) Target Population

- End-stage kidney disease (ESKD) with chronic hemodialysis treatment 3 times per week (at least 3.5 hours per dialysis)
- Chronic (i.e. repeated) paroxysmal, persistent or permanent atrial fibrillation (AF) or atrial flutter (AFL) 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, i.e. no symptoms or no significant disability and able to carry out all usual activities, despite some symptoms) (Farrell et al., 1991).

Age and Reproductive Status

- Males and Females, aged 18 or older
- Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24-48 hours prior to the start of study drug.
- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug for a total of 3 months (phenprocoumon treatment) or 3 days (apixaban treatment) post treatment completion.

- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug for a total of 5 months (phenprocoumon treatment) or 93 days (apixaban treatment) post treatment completion (including the 90 days duration of sperm turnover).

  Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

  Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

  At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

  Highly effective methods of contraception:

  - Male condoms with spermicide
  - Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) by WOCBP subject or male subject's WOCBP partner.
  - IUDs
  - Tubal ligation
  - Vasectomy
  - Complete Abstinence*

  *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

  WOMEN OF CHILD-BEARING POTENTIAL (WOCBP)

  A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

  Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal:

  - 1 week minimum for vaginal hormonal products (rings, creams, gels)
  - 4 week minimum for transdermal products
  - 8 week minimum for oral products

  Other parenteral products may require washout periods as long as 6 months.

4.2.2 Exclusion Criteria

1) Target Disease Exceptions

- AF or AFL 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 or AFL that require chronic anticoagulation (e.g., a prosthetic mechanical heart valve). Active infective endocarditis
- Any planned interventional or surgical AF ablation procedure

2) Medical History and Concurrent Diseases

- Any active bleeding
- A serious bleeding event in the previous 6 months before screening
- Active infective endocarditis
- Any active infection or symptoms suggestive of COVID-19 infection
- Inadequately controlled (HbA1c levels >8.5%) or untreated diabetes
- History of malignant neoplasms at high risk of current bleeding (see SmPC)
- Known indication for treatment with NSAIDs (see SmPC). However, 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 is excluded.
  (No explicit limits for ALT and AST values are defined in this study protocol, although mentioned in the SmPC of apixaban because these parameters are frequently elevated in dialysis patients. However, the treating dialysis doctors are experienced with this problem, and in case of clinically relevant increases of ALT or AST level patient's eligibility or exclusion should be decided by the responsible investigator.)
- Any type of stroke within 3 months prior to baseline visit (randomization)
- Other indication for anticoagulation than AF or AFL
- Known Antiphospholipid Syndrome requiring anticoagulation
- 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 excluded at any dose). Please act with precaution when combining different anticoagulation therapies (refer to section 5.6.2).
- 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 leads to the assumption that the ability to completely understand the consequences of consent is missing

3) Allergies and Adverse Drug Reactions

- Known allergies, sensitivities or adverse reactions to the active ingredient or to excipients of the study drugs.

4) Sex and Reproductive Status

- See section on WOCBP above (section 4.2.1, item # 3.)
- Pregnant or lactating subjects

5) Prohibited Treatments and/or Therapies

Medications or therapies listed below are prohibited at baseline (first study drug dose). If subject requires any of the prohibited therapies at baseline, subject should not be included in this trial.

<u>The use of the following medications or therapies is prohibited at baseline and patients taking these cannot be included:</u>

- Strong inhibitors of both CYP3A4 and P-glycoprotein (e.g., azole antifungals [itraconazole, voriconazole, posaconazole and ketoconazole], naproxene 500 mg or more, and protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir]) [in accordance to SmPC of apixaban ("Eliquis® 2,5 mg Filmtabletten," August 2020), (Heidbuchel et al., 2013) and (Kovacs et al., 2015)]

  (Moderate inhibitors of CYP3A4 and P-glycoprotein (e.g. diltiazem, amiodarone, verapamil, fluconazole, quinidine and naproxene <500 mg per day) are allowed and do not require study discontinuation)

- Platelet inhibitors, such as prasugrel, ticagrelor, clopidogrel (ASA up to 100 mg per day is allowed)
- Regular daily intake of NSAIDs or COX2 inhibitors (ASA up to 100 mg per day is allowed)

- Other antithrombotic agents (e.g., direct thrombin inhibitors, fondaparinux) GP IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban). If treatment with an agent above becomes necessary, study drug should be temporarily interrupted at the discretion of the treating physician, and restarted as soon as possible following discontinuation of the prohibited medication or therapy. (For further information please see section 5.6.1)

  Unfractionated heparin (UFH) and low-molecular weight heparin (LMWH) are allowed during hemodialysis according to site standard and at the discretion of the treating physician.

- Participation in another clinical trial, either within the last 30 days prior randomization or ongoing.

If a patient develops an indication for one of the therapies mentioned above throughout the treatment period, please refer to section 5.6.1 "prohibited and/or restricted treatments" for detailed instructions.

Instructions regarding restricted therapies used cautiously through the study are given in section 5.6.1 and 5.6.2.

The use of the following medications in a patient who is already included in the trial is **prohibited** and must lead to study discontinuation:

- Strong inhibitors of both CYP3A4 and P-glycoprotein (e.g., azole antifungals [itraconazole, voriconazole, posaconazole and ketoconazole], naproxene 500 mg or more, and protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir]) [in accordance to SmPC of apixaban ("Eliquis® 2,5 mg Filmtabletten," August 2020), (Heidbuchel et al., 2013) and (Kovacs et al., 2015)]

  (Moderate inhibitors of CYP3A4 and P-glycoprotein (e.g., diltiazem, amiodarone, verapamil, fluconazole, quinidine and naproxene <500 mg per day) are allowed and do not require study discontinuation)
- Regular intake of NSAIDs or COX2 inhibitors (ASA up to 100 mg per day is allowed)

The use of the following medications in a patient who is already included in the trial is restricted, but does not require study discontinuation:

- Dual platelet inhibition for up to 1 month after careful consideration of the treating physician
- Moderate inhibitors of CYP3A4 and P-glycoprotein (e.g., diltiazem, amiodarone, verapamil, quinidine and naproxene <500 mg per day) are allowed and do not require study discontinuation
- Strong inducers of CYP3A4 and P-glycoprotein (e.g., rifampicin, phenytoin, carbamazepin, phenobarbital or Hypericum perforatum) as they can reduce the apixaban exposition about 50 %
- Cytotoxic/myelosuppressive therapy

6) Other Exclusion Criteria

- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Employee of the study site or of the sponsor

4.2.3 Discontinuation of Subjects from Treatment

Subjects MUST discontinue the study drug for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Any kind of scheduled surgery or intervention which excludes a resumption of study therapy within 3 weeks afterwards
- Pregnancy
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Kidney transplantation scheduled in the next 3 days
- Use of prohibited medication, which must lead to study discontinuation (refer to section 5.6.1)

All subjects who discontinue should comply with protocol-specified follow-up procedures outlined in section 6.1.3. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).
In accordance with the legal requirements and ICH-GCP guideline, each patient can leave the study without giving reasons and without having disadvantages at any time.
If a subject withdraws before completing the study, the reason for withdrawal must be documented appropriately to the amount this information is available.

4.3 Premature Termination of the Study / of one Study Site

The sponsor retains the right to terminate the study at any time after carefully weighing the benefits against any possible risks. In case of premature discontinuation of the study, the sponsor will

promptly inform the investigators, regulatory authorities and IRB/IEC of the termination, giving the reason for premature discontinuation.

The sponsor has the right to close the whole study, and the sponsor has the right to close a single study site, at any time, although this should only occur after consultation between involved parties. The concerned ethics committee must be informed.

The following reasons may justify a premature termination of a single study site:

- The study site fails to comply with the requirements of the protocol
- The study site fails to comply with GCP standards
- The first patient fails to be recruited within a reasonable period after initiation of the study site
- The study site does not continue to recruit over a prolonged time interval.

In case of premature termination of recruitment at a given study site, patients who had been included in the trial before have to be managed according to the protocol and GCP standards until the end of the study.

The complete study will be discontinued for the following reasons:

- Occurrence of new toxicological or pharmacological findings or SAEs, if these new findings invalidate the earlier risk benefit assessment and result in unacceptable patient risk
- Occurrence of severe study drug-related symptoms, if these new findings invalidate the earlier risk benefit assessment and result in unacceptable patient risk

The complete study may be discontinued for the following reasons:

- Information that is expected to be gathered by this study has already be gained by other means or studies
- Either of the presently marketed drugs is withdrawn from the market.
- The study proves not to meet the expected goal
- Other important or unforeseen circumstances

The decision to discontinue the study based on the reasons mentioned above will be made by the sponsor in agreement with the head of trial and the Steering Committee (SC) of the study.

5 TREATMENTS

5.1 Study Treatment / Investigational Product

In this study apixaban will be evaluated as an investigational product (IP) in patients with ESKD.

Besides, phenprocoumon will be defined as a non-investigational product since it will be used as a standard of care medication for above mentioned patient population.

An investigational product is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

A non-investigational product is defined: other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care. Any other drugs given to the patients are based on clinical indications as judged by the treating physician.

Both medications can be synonymously referred to as "study drug".

5.1.1 Identification

Subjects will receive either apixaban or phenprocoumon as study drug according to their randomization (refer to section 5.3). Dose and timing of study drug is displayed in section 5.4.

Table 1-1: Study Drugs

Product Description / Class and Dosage Form	**Potency**	**IP/ Non-IP**	**Blinded or Open Label**	**Packaging/ Appearance**	**Storage Conditions (per label)**
Apixaban	2.5 mg	IP	open	packaged in bottles of 200 tablets Reddish brown, plain, oval shaped, shallow biconvex film coated tablets	as per label
Phenprocoumon	3 mg	non-IP	open	not defined*	without any restrictions/ according to SmPC

* Subjects in the phenprocoumon group will be supplied with phenprocoumon by different manufacturing companies and therefore receive varying packaging sizes

5.1.2 Handling and Dispensing

Apixaban should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects in the apixaban treatment arm and only from official study sites by authorized personnel, as dictated by local regulations. If concerns regarding the quality or appearance of the IP arise, do not dispense the IP, and contact the sponsor immediately.

Apixaban will be dispensed to eligible patients after randomization at baseline (Day 1). Please refer to section 5.2.1 for supply and return information.

Phenprocoumon
The subjects in the phenprocoumon treatment arm will receive a standard prescription from the investigator as phenprocoumon is a standard of care drug and will be funded by the health insurance of the individual patient. The investigator is responsible for ensuring that only study subjects in the phenprocoumon treatment arm receive their prescribed phenprocoumon.

Both study drugs are tablets for oral intake and can be taken home by each patient and stored at home without any temperature restrictions.

5.2 Drug Ordering and Accountability

Apixaban

Bristol-Myers Squibb (BMS) will provide study-specific labeled apixaban at no cost for this study.

BMS or its collaborating drug supplier is responsible for labeling, storage and distribution of apixaban to study sites. Sufficient quantities of apixaban will be supplied. The sponsor will collaborate with the manufacturer on drug utilization in order to forecast or project demand needed. Sites will automatically be resupplied due to recruitment status.

Phenprocoumon

Phenprocoumon is a standard of care product and therefore funded by individual health insurance of participating subjects.

5.2.1 Supply and Return of Apixaban

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

Logistics of the apixaban study medication will be managed and tracked centrally in the e-trial management system set-up by the delegated CRO. Each apixaban study medication bottle will be supplied with a unique medication number (numerical) together with a corresponding unique

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

Labeling follows requirements as specified in Volume 4, EU Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products. National requirements will be taken into consideration. The subcontractor responsible for re-labeling and delivery of apixaban to the study sites receives automated supply orders via e-mail from the e-trial management system detailed for the amount of bottles with 2.5 mg tablets. Tracking of apixaban bottles to be sent to study sites will be performed by the subcontractor in the e-trial management system revealing information on medication numbers and verifiers, date of shipment and recipient (study site ID). Receipt of apixaban study medication has to be tracked by the receiving site staff and confirmed by fax at GCP services within 5 working days.

After a patient has terminated the study, any unused or part-used medication will be returned to and destroyed by the sponsor.

5.2.2 Accountability

Apixaban
Apixaban documentation must be maintained that includes all processes required to ensure drug is accurately administered.

This includes confirmation of receipt of the IP, recording quantities of the IPs dispensed and returned by each patient in accountability forms.

Site personnel and CRA will periodically check IP documentation and inventory of study medications held by the investigator to verify accountability of all apixaban used.

Phenprocoumon
As each individual subject will be supplied by local pharmacy different manufacturing companies and packaging options are possible for phenprocoumon. Consequentially, no drug accountability will be performed for phenprocoumon.

5.3 Method of Assigning Subjects to a Treatment Group

Eligible patients will be allocated in a centrally randomized fashion (1:1 ratio) to receive either apixaban or phenprocoumon.

- Phenprocoumon treatment group: 3 mg tablets, dosage depending on weekly INR controls
- Apixaban treatment group: 2.5 mg tablets, twice daily

To ensure the equal distribution of prognostic factors in the two treatment arms, patients will be centrally stratified according to the following parameters:

- Previous thromboembolism including any type of ischemic stroke as long as more than 3 months before baseline.
- Anticoagulation naïve patients.
  At least 50% of the subjects should be anticoagulation-naïve (=with a new indication for an oral anticoagulation). To ensure a homogenously distribution of anticoagulation naïve subjects in both treatment arms, this feature will be centrally coordinated during the randomization process.

Allocation of subjects to treatment groups will proceed through the use of an Interactive Web Response System (IWRS) that is accessible 24 hours a day, 365 days a year. The site personnel (i.e., study coordinator or specified designee) will be required to enter or select information that will include the user ID and password, the project and protocol number, the investigator site number, the fax number, the subject number, and the year of birth of the subject.

Also, the stratification prompts for this study (previous thromboembolism and anticoagulation naïve) must be answered.

The site personnel will then be provided with a subject randomization number and the treatment group assigned to the individual subject.

Once subject randomization numbers have been assigned, they cannot be reassigned. The IWRS will provide confirmation of the randomization number and treatment assignment to the site personnel. Site personnel will retain the confirmation reports via email.

Specific instructions for use of the IWRS will be provided.

Site personnel must record screen failures and withdrawals on the electronic Case Report Form (eCRF).

Each subject must be assigned a unique subject number. The subject must keep that number throughout the study even if he or she transfers to another site. A number must never be reassigned or reused for any reason. The investigator must maintain a subject master log linking the subject number to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor.

5.4 Selection and Timing of Dose for Each Subject

5.4.1 Dosing and Timing

Apixaban

Subjects randomized to the apixaban treatment group will receive 2.5 mg tablets twice daily for oral intake. This decreased dose was chosen due to the targeted study population with end stage renal disease. On one hand this is the dose recommended in the SmPC for AF patients with severe renal impairment (creatinine clearance 15 to 29 mL/min). On the other hand, there are available data from a small pilot study in dialysis patients which suggest that this dosage is most suitable for the benefit/risk ratio in patients on maintenance hemodialysis.

Patients will be instructed to take one tablet of 2.5 mg twice daily: one tablet in the morning and one in the evening at approximately the same time every day (with about 12 hours gap) irrespective of the time of dialysis. Most likely apixaban will not be administered during dialysis session. Apixaban can be taken with or without food.

Phenprocoumon

Phenprocoumon tablets for oral intake will be used as a reference of a given standard of care and will be dosed, taken and adjusted by responsible investigator as recommended in the appropriate SmPC of prescribed phenprocoumon.

Subjects in phenprocoumon treatment group will receive phenprocoumon individually adjusted to an INR of 2.0-3.0 as recommended in the appropriate SmPC for AF patients. The study drug can be taken with or without food.

Both study drugs should not be used if a patient has active pathological bleeding. If a dose of study drug is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and then continue with administration as before. The dose should not be doubled to make up for a missed dose.

5.4.2 Treatment Duration

For details refer to 4.1 and 11.1.

5.4.3 Dose Modifications

In this study, apixaban is used in the decreased dose of 2.5 mg twice daily to apply to the targeted study population with end stage renal disease. Therefore, no dose modifications of apixaban are foreseen during study participation.

Phenprocoumon will be adjusted according to the given standard of care to an INR of 2.0-3.0 (refer to appropriate SmPC). Therefore, INR values will be monitored on a regular basis and

phenprocoumon dose will be adjusted accordingly. Dose modifications are to be documented in the subject's study documents.

Under special circumstances, both study drugs can or should be discontinued temporarily or permanently (refer to section 5.4.4 and 5.4.5 for details).

5.4.4 Temporary Discontinuation of Study Drug

For any temporary discontinuation of study drug due to elective surgery or invasive procedures, investigator should contact the CRA in order to inform the CRA about reason and period of time for study drug discontinuation.

Discontinuing anticoagulants, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided, and if anticoagulation with apixaban or phenprocoumon must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

Any temporary discontinuation of study drug has to be documented in detail with dates, reason and outcome in study documents. In this study, interruptions for no longer than 3 weeks are accepted. Subjects who discontinue study drug treatment for more than 3 weeks are not allowed to resume study treatment (please refer to section 5.4.5 for details).

5.4.5 Permanent Discontinuation of Study Drug

If study drug treatment has to be discontinued permanently due to e.g., subject request, occurrence of AE or SAE, investigator decision or changes in therapy requirements, the reason for early permanent discontinuation of study drug must be documented appropriately to the amount this information is available. If applicable, any newly initiated antithromboembolic therapy replacing the study drug treatment has to be documented. Unused or part-used apixaban has to be returned, counted and documented accordingly.

Subjects who prematurely and permanently discontinue study drug treatment have to perform the End of Treatment (EoT) visit (see section 6.1.3).

After EoT subjects have to be followed for bleeding events, thromboembolic events and events of special interest as well as for all AEs and SAEs. A monthly documentation (see section 6.1.2.2) should be performed until End of Study (EoS, see section 6.1.5).

5.5 Blinding/Unblinding

This study will be conducted as an open label study due to required regular dose adjustments for phenprocoumon based on INR measurements.

In addition to the assessments performed and documented by the investigators, an assessment of outcomes blinded to study drug, is planned for this study (for details refer to section 10).

5.6 Concomitant Treatments

5.6.1 Prohibited and/or Restricted Treatments

Co-administration of both study drugs (apixaban or phenprocoumon) is not recommended with drugs that increase the risk of bleeding (e.g., daily administration of other anticoagulants or heparin, and any thrombolytic agents). It is recommended to interrupt anticoagulation therapy for any elective surgery. Prior to and after elective surgical interventions with an increased risk of thromboembolisms or bleedings, both study drugs should be administered with precaution and subjects should be closely monitored. For details please refer to appropriate SmPC.

The following medications or therapies are **prohibited** throughout the whole trial from baseline (first study drug dose) and must lead to study discontinuation:

- Strong inhibitors of both CYP3A4 and P-glycoprotein (e.g., azole antifungals [itraconazole, voriconazole, posaconazole and ketoconazole], naproxene 500 mg or more, and protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir]) in accordance to SmPC of apixaban ("Eliquis® 2,5 mg Filmtabletten," August 2020), (Heidbuchel et al., 2013) and (Kovacs et al., 2015)]

  (Moderate inhibitors of CYP3A4 and P-glycoprotein (e.g., diltiazem, amiodarone, verapamil, fluconazole, quinidine and naproxene <500 mg per day) are allowed and do not require study discontinuation)

- Regular intake of NSAIDs or COX2 inhibitors (ASA up to 100 mg per day is allowed)

The following medications or therapies are **restricted** throughout the whole trial from baseline (first study drug dose) but do not require study discontinuation:

The administration of the following agents in subjects on study drug should be done cautiously given the increased risk of bleeding. In such cases, consideration of interruption of the study drug may be warranted; this decision should be made after a careful assessment of the risks and potential benefits.

- Dual platelet inhibition for up to 1 month after careful consideration of the treating physician
- Moderate inhibitors of CYP3A4 and P-glycoprotein (e.g., diltiazem, amiodarone, verapamil, fluconazole, quinidine and naproxene <500 mg per day) are allowed and do not require study discontinuation
- Strong inducers of CYP3A4 and P-glycoprotein (e.g., rifampicin, phenytoin, carbamazepin, phenobarbital or Hypericum perforatum) as they can reduce the apixaban exposition about 50 %
- Cytotoxic/myelosuppressive therapy

The decision to employ dual anti-platelet therapy (with ASA and a thienopyridine such as clopidogrel or ticlopidine) in subjects on study drug may arise at the time of acute coronary

syndrome or percutaneous coronary intervention. The decision to employ concomitant dual anti-platelet therapy in subjects who are anticoagulated with study drug should be made by the investigator or treating physicians after careful consideration of the risks and potential benefits. In addition, if a subject is currently receiving an agent that is a potent inducer of CYP3A4, the investigator should carefully evaluate that subject's risk of thromboembolism, as the plasma concentration of apixaban may be lower than the one in subjects not receiving a potent inducer of CYP3A4.

5.6.2 Other Restrictions and Precautions

Apixaban should be discontinued 24 hours before procedures with a low risk of bleeding, and 48 hours prior to procedures with a moderate or high risk of bleeding. For the phenprocoumon treatment group refer to appropriate SmPC of prescribed phenprocoumon.

If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

The concomitant use of apixaban or phenprocoumon with antiplatelet agents increases the risk of bleeding. Those patients who will be adjusted from phenprocoumon to apixaban treatment will take the first dose of apixaban accordingly to INR measurement (<2.0).

In patients with AF and a condition that warrants mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy.

The concomitant use of IP and non-IP with caution when co-administered with COX2 inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs), including ASA.

5.6.3 Permitted Prior and Concomitant Treatment

All medication needed for treatment of concomitant diseases can be taken by the patient as long as treatment restrictions (refer to section 5.6.1 and 5.6.2) are kept. All medications taken by the patients through the entire study are to be documented in the study documents.

5.7 Treatment Compliance

<u>Apixaban</u>

Apixaban will be dispensed to participating subjects through the active treatment phase (baseline to End of Treatment). Each individual patient will be instructed to return all medication packages, either unused, partially used, or empty to the investigator every three monthly, the number of returned tablets will be recorded in the study documents and returned apixaban medication will be tracked in the e-trial management system according to section 5.2.1.

The individual subject's treatment compliance will be controlled by pill count: all dispensed and returned apixaban tablets will be counted and the individual treatment compliance will be documented. All treatment interruptions have to be documented in study documents accordingly including the dates and the reason for interruption (e.g., compliance or medical indication). A complete drug accountability for each patient in the apixaban group and in total will be documented in separate forms (refer to section 5.2.2).

Phenprocoumon

Subjects in the phenprocoumon group will be supplied with phenprocoumon by different manufacturing companies and therefore receive varying packaging sizes. No drug accountability will be performed for phenprocoumon.

For the subjects in the phenprocoumon arm INR values will be checked regularly to adjust the dose if necessary. Dose modifications are to be documented in the source data.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Schedule of Procedures

In this study there are no specific assessments defined as study assessments. Assessments will be conducted as needed by standard of care in the course of subjects' regular hemodialysis visits at the study site.

The study protocol defines several safety and efficacy parameters, which should be documented in the study documents (source data and eCRF). This means that assessments and parameters which must be documented in the course of this study are not necessarily study procedures.

The following sections itemize the assessments/parameters, which will be performed and/ or documented during the study course. A detailed description of all assessments and parameters is given in sections 6.4 to 6.6.

6.1.1 Screening

The following screening procedures will be performed and/or documented during screening period (up to 21 days before Baseline/Day 1):

- Obtain signed and personally dated written informed consent prior to any study related procedures
- Check of inclusion/exclusion criteria
- Documentation of demographics, patient's height and weight, and medical history/renal disease status and concomitant diseases
- Calculation and documentation of NYHA classification for chronic heart failure (see section 6.6.6)
- Calculation and documentation $CHADS_2$ & CHA_2DS_2-VASc Score (see section 6.6.6)
- Documentation of prior and concomitant medication
- Perform serum pregnancy test within 48 hours to baseline with results available prior to first study drug administration
- Evaluation and documentation of INR values
- Assessment of vital signs (blood pressure, mean heart rate)
- Standard 12-lead ECG: documentation of rhythm (clinically relevant findings at Screening are to be documented as concomitant disease)
- Assessment of atrial fibrillation and/or atrial flutter by an external medical physician (two ECGs to be sent by fax or scan prior randomization)
- Laboratory evaluation (blood chemistry, hematology and coagulation values): clinically relevant findings at Screening are to be documented as concomitant disease. Laboratory results of previous examinations (up to 14 days) can be used for screening visit.
- Documentation of key data of hemodialysis (see section 19.1)

The following documentation is only required, if applicable:

- AEs occurring since date of informed consent

Medical reports of each assessment performed at the time of screening as a standard of care procedure (e.g. ECG, CT, MRI, angiography etc.) will be sent to the sponsor or its delegated CRO in a pseudonymized manner on demand and will be provided to the Endpoint Review Committee for outcome analysis (see section 10.2).

6.1.2 Treatment Period

6.1.2.1 Baseline (Day 1) / Randomization Visit

The following procedures will be performed and/or documented at baseline:

- Check of inclusion/exclusion criteria

- Check of medical assessment for atrial fibrillation and/or atrial flutter documentation is finalized and subject is eligible.
- Randomization of eligible patients
- Study drug administration: Dispensation of apixaban or prescription for phenprocoumon. Those patients who will be adjusted from phenprocoumon to apixaban treatment will take first study drug according to INR measurement (< 2.0).
- Update concomitant diseases and concomitant medications
- Evaluation and documentation of INR values for subjects in the phenprocoumon treatment group
- Documentation of key data of hemodialysis (see section 19.1)
- Documentation of quality-of-life assessment by EQ-5D questionnaire. To be completed by the patient. (see section 19.2)

The following documentation is only required if applicable:

- Laboratory evaluation (blood chemistry, hematology and coagulation values) if not performed at screening visit. Clinically relevant changes are to be documented as AE, if the finding is to be categorized as event of grade 3-5 according to the NCI-CTCAE v 4.0 on a five-point scale. Results of previous examinations (up to 14 days) can be also used for documentation.
- AEs occurring since study start to be documented
- Bleeding events: events occurring since first dose of study drug to be categorized and documented (see section 6.4.1)
- Thromboembolic events: events occurring since first dose of study drug to be categorized and documented (see section 6.5.1)
- Events of special interest: events occurring since first dose of study drug to be categorized and documented (see section 6.5.1)

Medical reports of each assessment performed at the time of screening as a standard of care procedure (e.g., ECG, CT, MRI, angiography etc.) will be send to the sponsor or its delegated CRO in a pseudonymized manner on demand and will be provided to the Endpoint Review Committee for outcome analysis (see section10.2).

Update eCRF in a timely manner (within 5 days) after information becomes apparent.

6.1.2.2 Further documentation on a monthly basis/ Visit 1

The following procedures will be performed and/or documented through the active treatment period on a monthly basis.

- Evaluation and documentation of INR values for subjects in the phenprocoumon treatment group each month of treatment
- Documentation of key data of hemodialysis (see section 19) each month of treatment

The following documentation is only required if applicable:

- Compliance check for subjects in the apixaban treatment group
- Study drug: distribution of apixaban or phenprocoumon prescriptions and return of used apixaban packages and drug accountability on a quarterly basis (see sections 5.2.1 and 5.2.2)
- Update concomitant diseases and concomitant medication
- Laboratory evaluation (blood chemistry, hematology and coagulation values): Clinically relevant changes are to be documented as AE, if the finding is to be categorized as event of grade 3-5 according to the NCI-CTCAE v 4.0 on a five-point scale. Laboratory results of previous examinations (up to 14 days) can be also used for documentation.
- AEs occurring since baseline to be documented, still ongoing AEs since study start to be updated as applicable
- Bleeding events: new events occurring since first dose of study drug/baseline to be categorized and documented (see section 6.4.1)
- Thromboembolic events: new events occurring since first dose of study drug /baseline to be categorized and documented (see section 6.5.1)
- Events of special interest: new events occurring since first dose of study drug /baseline to be categorized and documented (see section 6.5.1)
- EQ-5D questionnaire will be completed by the patients every 6 months after Baseline (visit 6, visit 12, visit 18 and EoT)

Medical reports of each assessment performed during the treatment period as a standard of care procedure (e.g. CT, MRI, angiography, etc.) will be sent to the sponsor or its delegated CRO in a pseudonymized manner and will be provided to the Endpoint Review Committee for outcome analysis (see section 10.2).

Update eCRF in a timely manner (within 5 days) after information becomes apparent.

Subjects, who prematurely and permanently discontinued the study drug treatment have to be followed-up for bleeding events, thromboembolic events and events of special interest as well as for all AEs and SAEs for further 30 days until EoS. Therefore, the monthly documentation itemized above should be performed until End of Study.

6.1.3 End of Treatment (EoT)

The following procedures will be performed and/or documented at EoT:

- Return of apixaban study drug
- Compliance check and drug accountability for apixaban treatment group (see sections 5.2.1 and 5.2.2)
- Update concomitant diseases and concomitant medication
- Evaluation and documentation of INR values for subjects under phenprocoumon treatment

- Documentation of key data of hemodialysis (see section 19)
- Standard 12-lead ECG: documentation of rhythm (clinically relevant changes are to be documented as AE). A time window of +/- 5 days is allowed for ECG documentation. ECGs provided by external physicians are also permitted.
- EQ-5D questionnaire will be completed by the patient

The following documentation is only required if applicable:

- Laboratory evaluation (blood chemistry, hematology and coagulation values): Clinically relevant changes are to be documented as AE, if the finding is to be categorized as event of grade 3-5 according to the NCI-CTCAE v 4.0 on a five-point scale.
- New AEs to be documented; ongoing AEs to be updated as applicable
- New bleeding events to be categorized and documented (see section 6.4.1)
- New thromboembolic events to be categorized and documented (see section 6.5.1)
- New events of special interest to be categorized and documented (see section 6.5.1)

Medical reports of each assessment performed during the treatment period as a standard of care procedure (e.g., CT, MRI, angiography, etc.) will be sent to the sponsor or its delegated CRO in a pseudonymized manner and will be provided to the Endpoint Review Committee for outcome analysis (see section 10.2).

Update eCRF in a timely manner (within 5 days) after information becomes apparent.

6.1.4 Early Discontinuation of Study Drug Treatment

Subjects who prematurely and permanently discontinue study drug treatment prior to official End of Trial should perform the End of Treatment (EoT) visit, as itemized above at date of permanent study drug discontinuation.

These subjects have to be followed for bleeding events, thromboembolic events and events of special interest as well as for all AEs and SAEs until EoS (for further details see section 6.1.5). A monthly documentation should be performed (see section 6.1.2.2).

The reason for early and permanent discontinuation of study drug must be documented appropriately to the amount this information is available. If applicable, any newly initiated antithromboembolic therapy replacing the study drug treatment has to be documented.

6.1.5 End of Study (EoS)

All subjects have to perform their EoS visit 30 days after End of Treatment (EoT) visit - or 30 days after their last dose of study drug - whatever occurs last.

The following documentation is required, if applicable:

- Laboratory evaluation (blood chemistry, hematology and coagulation values): Clinically relevant changes are to be documented as AE, if the finding is to be categorized as event of grade 3-5 according to the NCI-CTCAE v 4.0 on a five-point scale.
- New AEs to be documented
- New bleeding events: to be categorized and documented (see section 6.4.1)
- New thromboembolic events: to be categorized and documented (see section 6.5.1)
- New events of special interest to be categorized and documented (see section 6.5.1)

SAEs present at EoS are to be followed for 30 days or to resolution/ stabilization - whatever occurs first.

6.1.6 Study Flow Chart

The following study flow chart (table 2-1) displays, which assessments are to be performed and which patient data are to be recorded during the course of the study.

Table 2-1: Study flow chart - documentation required during study

Study Procedures	**Screening period**	**Active treatment period (until last patient has completed treatment period)**		**End of Treatment (EoT)/** early discontinuation[d]	**End of Study[h] (EoS)/** 30 days after EoT
	Screening/ Day -21 to Randomization Visit	Baseline/ Randomization Visit, Day 1	Further documentation[g] on a monthly basis[f,] Visit1/ Month 1		
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographics, height, weight	X				
Prior/ Concomitant medication	X	X	X	X	X
Concomitant disease	X	X	X	X	
Medical history/renal disease status	X				
NYHA classification for chronic heart failure	X				
$CHADS_2$ & CHA_2DS_2-VASc Score	X				
Vital signs (blood pressure, pulse)	X				
Standard 12-lead ECG[i]	X			X	
INR evaluation [a]	X	X	X	X	
Key data of hemodialysis[b]	X	X	X	X	
Serum pregnancy test[c]	X				
Randomization		X			
Study drug administration[k]		X	X		
Study drug accountability, compliance check (apixaban group only)			X	X	
Laboratory evaluation[l]	X	X	X	X	X
Bleeding events		X	X		X

Table 2-1: Study flow chart - documentation required during study

Study Procedures	**Screening period**	**Active treatment period (until last patient has completed treatment period)**		**End of Treatment (EoT)/** early discontinuation[d]	**End of Study[h] (EoS)/** 30 days after EoT
	Screening/ Day -21 to Randomization Visit	Baseline/ Randomization Visit, Day 1	Further documentation[g] on a monthly basis[f,] Visit1/ Month 1		
(according to ISTH)[e]				X	
Thromboembolic events[e]		X	X	X	X
Events of special interest[e]		X	X	X	X
Adverse events[e]	X	X	X	X	X
EQ-5D questionnaire[j]		X	X	X	

a. For subjects under phenprocoumon treatment only
b. Detailed documentation of dialysis duration and parameters (see Appendix 19.1) Duration of hemodialysis session should last at least 3,5 hours.
c. For women of childbearing potential (WOCBP) only, serum pregnancy tests must be performed within 24-48 hours to baseline with results available prior to first study drug administration
d. Subjects who prematurely and permanently discontinue study drug are to be followed for bleeding events, thromboembolic events and events of special interest as well as for all AEs and SAEs until EoS (see section 6.1.5). A monthly documentation should be performed (see section 6.1.2.2). The reason for early discontinuation and any new antithromboembolic therapy must be documented appropriately.
e. Documentation will be done from the signing of the informed consent form until EoS, e.g. at least 2 days after EOT. All SAEs present at EoS have to be followed for another 30 days.
f. Month = 28 days. For visits a time window of +/- 2 days are allowed.
g. Documentation of procedures performed as given by the standard of care is required on a monthly basis
h. End of Treatment for the entire study population will be announced officially after recruitment period has been completed or if 64 events have been observed, whatever comes first. Then, all subjects have to perform EoT followed by the EoS visit, 30 days after the official EoT - or 30 days after their last dose of study drug - whatever occurs last.
i. Atrial fibrillation or atrial flutter should be documented on two separate ECGs. Both ECGs will be used for randomization and could be performed prior study start, e.g. from an external physician. Prior randomization ECGs will be sent by fax or scan to external medical assessment. For EoT visit a time window of +/- 5 days is allowed for ECG documentation as well as ECGs provided by external physicians are also permitted.
j. EQ-5D questionnaire will be completed at baseline visit and afterwards every 6 months (baseline, Visit 6, Visit 12, Visit 18 and, EoT) by patients.
k. Study drug administration and return will be on a quarterly basis after randomization. Those patients who will be adjusted from phenprocoumon to apixaban treatment will take first dosis of apixaban after INR < 2.0.
l. Laboratory results of previous examinations can be used for screening, baseline and monthly visits up to 14 days prior actual visit date.

6.1.7 Pandemic situation: re-initiation or discontinuation of enrollment

Under a pandemic situation all sites are obliged to perform a risk assessment for the continuation or discontinuation of study recruitment under the actual conditions at the local study site, taking into account the local guidance for research and patient care as well as governmental requirements. In case of a discontinuation of enrollment or planned re-initiation, the sponsor needs to be immediately informed by sending the risk assessment questionnaire (see Appendix 19.3) to the following e-mail address: info-axadia@af-net.eu

In general, every study center shall evaluate whether the safety requirements can be met under present conditions. The recruitment of new patients should be critically evaluated depending on the local situation and governmental and other regulatory requirements. It is of highest importance to ensure the patient's safety at any time.

6.2 End of Trial

The **official End of Trial** for the entire study population will be announced after:

- required number of events has been observed or
- whole study period has been reached (maximum of 5 years recruitment).

6.3 Study Materials

All information regarding study drug is integrated in section 5.1.

6.4 Safety Assessments

Among subjects on hemodialysis with an indication for anticoagulation, frequent assessments of hematology, blood chemistry and coagulation are standard of care. Therefore, this study protocol specifies no assessments and procedures to be performed which means that all assessments will be conducted as targeted by standard of care.

Although the study protocol defines safety parameters and medical information, which should be documented in the study documents during the course of the study, these parameters and medical information are not necessarily study procedures.

6.4.1 Bleeding Events

All assessments which are clinically indicated to screen for bleeding events (e.g., coagulation parameter, CT, MRI, sonography) are performed as standard of care.

The assessments have to be documented in the study documents including results and outcome.

All bleeding events have to be categorized and documented in detail in study documents according to International Society on Thrombosis and Haemostasis **(ISTH) c**onsensus (Schulman et al., 2010) and the most recent apixaban SmPC as follows:

Major Bleeding (as defined in the ISTH consensus):

- Fatal bleeding.
- Bleeding that is symptomatic and occurs in a critical area or organ, such 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 mmmol/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, 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

All bleeding events have to be documented in the bleeding event documentation in the eCRF according to ISTH criteria and as AEs in the AE section of eCRF (please refer to section 7 for details to AEs).

Copies of pseudonymized medical reports are transferred to the sponsor or its delegated CRO and will be provided to the blinded Endpoint Review Committee for additional outcome analysis.

6.4.2 Laboratory Evaluation

Laboratory parameters (blood chemistry, hematology and coagulation parameters) are measured as standard of care procedures during the entire study.

In this study, the following parameters are of special interest:

- Complete blood count

- Creatinine
- Parathyroid hormone (PTH)
- AST/GOT
- ALT/GPT
- GGT
- Bilirubin
- Calcium
- Phosphate
- Coagulation parameter

Clinically relevant findings at Screening of these laboratory values are to be documented as concomitant disease. Clinically relevant changes are to be documented as AE.

Clinically relevant is defined as follows: finding is to be categorized as event of grade 3-5. Severity of finding will be graded to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 on a five-point scale. These cases need to be reported in detail on the AE section of the eCRF.

Moreover, the following laboratory abnormalities should be captured on the AE section and reported as appropriate:

- Any laboratory test result that meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

6.4.3 International Normalized Ratio (INR)

INR values will be regularly determined as a route of routine and documented for patients in the phenprocoumon treatment group on a monthly basis.

6.4.4 Vital Signs

Screening period: Systolic and diastolic blood pressure and pulse rate will be measured on dialysis days before dialysis, and documented in study documents.

6.5 Efficacy Assessments

In this study most assessments defined as efficacy assessments will be conducted as targeted by standard of care in the course of subjects' regular hemodialysis visits at the study site.

Although the study protocol defines efficacy parameters and medical information which should be documented in the study documents (source data and eCRF) during the course of the study, most of these parameters and medical information are not necessarily study procedures.

The assessment of Quality-of-life (EQ-5D, see section 6.5.3) is the only study-specific procedure that is not conducted as targeted by standard of care.

6.5.1 Thromboembolic and other Events

The incidence of thromboembolic and major other events will be recorded through the entire study categorized according to following single and composite endpoints:

Thromboembolic events

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

Events of special interest

- Dialysis shunt thrombosis
- Clotting of dialysis membrane

Composite endpoint:

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

All these events have to be recorded in the event documentation and as AE in the AE section of eCRF (please refer to section 7 for details to AEs).

Assessments which are clinically indicated and are performed as a standard of care to screen for events listed above (e.g., angiography, CT, MRI, sonography) have to be documented in source data. Copies of pseudonymized medical reports will be transferred to the sponsor or its delegated CRO and will be provided to the blinded Endpoint Review Committee for additional endpoint assessment.

6.5.2 ECG

At Screening and EoS, rhythm parameters (sinus rhythm or AF or AFL, mean HR) in the ECG performed as a standard of care procedure have to be documented in the source data and eCRF. Qualifying ECGs will be reviewed externally by a medical expert and will be sent by fax.

Clinically relevant findings (other than target disease) are to be documented as concomitant disease or AE.

6.5.3 Quality-of-life

Quality of life will be assessed using the EuroQoL EQ-5D questionnaire. The EQ-5D is a self-administered, validated, generic preference-based measure of health status that comprises a 5-question multi-attribute questionnaire and a visual analogue self-rating scale (Herdmann et al. 2011). Patients are asked to rate severity of their current problems according to 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). Patients can therefore be classified into 3, 125 possible health states which can be converted into an EQ-5D index score. On the visual analogue scale patients are asked to rate their own health state relative to full health (score=100) or worst imaginable health state (score=0).

6.6 Other Assessments

6.6.1 Key Data of Hemodialysis:

Patients are eligible for this study if they are on hemodialysis 3 times a week with at least 3.5 hours per dialysis. Parameter of hemodialysis (e.g., Hb, weight, complete duration, time and number of performed dialysis therapies) should be documented pre- and post-dialysis on a monthly basis in the source data and eCRF. Any event (e.g., shunt thrombosis or clotting of dialysis membrane) during dialysis therapy is to be documented accordingly as event of special interest or bleeding or thromboembolic event and AE during the whole study until EoS (see section 6.1 and 6.1.5).

6.6.2 Concomitant Medication

All medications taken by the patients in the period from signing the informed consent form / Screening to End of Study will be documented classified by drug generic name / trade name or active substance (in case no generic name is available) on the appropriate eCRF page, i.e., any medication for treatment of concomitant diseases (e.g., diabetes, hypertension, cardiovascular disease and hyperlipidemia) or AEs.

All medications taken from first dosing of study drug (baseline/Day 1) to End of Study will be documented as concomitant medication on the appropriate eCRF page.

Any medication taken during the interval from signing the informed consent form / Screening to the date of the baseline visit (Day1) if stopped before the first use of the study drug, is classified as 'prior medication'. Medications which are taken during the study conduct at least once after the first use of study drug are classified as 'concomitant medication'. Note, that a medication classified as 'concomitant' could already be taken prior to first application of study drug.

Concomitant treatments which are prohibited or restricted during study participation are described in section 5.6.

6.6.3 Medical History/ Concomitant Diseases

Clinically relevant information on medical and surgical history and all concomitant diseases will be obtained and documented at Screening by diagnosis and time of diagnosis. During each following study visit, the investigator will document any relevant changes in the patient's health status. The occurrence of new concomitant diseases, not present at Screening, or a worsening in the concomitant diseases will be documented as AE.

The following information is predetermined as relevant medical history information and to be documented in the study documents:

- Patients height and weight
- Diabetes mellitus
- Underlying renal disease/cause for ESKD
- History of myocardial infarction or unstable angina
- History of stroke or transient ischemic attack (TIA)
- History of hypertension, hypertensive crisis or hypertensive encephalopathy
- History of hyperlipidemia
- History of cardio vascular disease (individual and family history)
- Previous thromboembolism or bleeding events
- History of liver injury or infection
- Active malignancy within the last 5 years (except superficial basal cell and superficial squamous (skin) cell, or carcinoma in situ of the cervix or breast),
- Prior valvular heart disease or valvular transplants
- History of coronary interventions, coronary bypass or vascular surgery
- Pacemaker or ICD implantation

- Prior cardiac arrest necessitating defibrillation
- Peripheral artery occlusive disease (Fontaine criteria)
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to day 1 (baseline), or anticipation of need for major surgical procedure during the course of the study.
- History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess or active gastrointestinal bleeding
- Serious, non-healing wound, active ulcer, or untreated bone fracture.

6.6.4 Renal Disease Status

The following details of the renal disease status will be assessed at Screening and documented in the study documents:

- Start (date of diagnosis) and reason of renal disease
- Start and reason of hemodialysis
- Previous or planned kidney transplantation

6.6.5 Pregnancy Test

A serum pregnancy test will be performed within 24-48 hours before baseline with results available prior to first treatment and at the End of Study Visit for each woman of childbearing potential.

6.6.6 Demographics and Baseline characteristics

[NYHA, CHADS2, Quality-of-life (EQ-5D)]

- Demographic information (age, gender and ethnic origin) will be recorded at Screening
- **NYHA** classification for chronic heart failure will be assessed at Screening

  The New York Heart Association (NYHA) developed a functional classification for patients with heart disease.

  Patients will be classified according to the following parameters:

  - (1) Limitations on physical activity
  - (2) Symptoms (undue fatigue palpitations dyspnea and/or anginal pain) with ordinary physical activity
  - (3) Status at rest

Table 3-2: NYHA - classification			
Limitations on physical activity	**Symptoms with ordinary physical activity**	**Status at rest**	**Class**
None	None	Comfortable	I
Slight	Symptomatic with ordinary activities	Comfortable	II
Marked	Symptomatic at less than ordinary levels of activity	Comfortable	III
Unable to perform any activity	Discomfort with any activity	Symptomatic at rest	IV

- **$CHADS_2$ and CHA_2DS_2-VASc Scores** estimate patient's risk of stroke (Camm et al., 2012b). They will be assessed at Screening.

  The **$CHADS_2$** and **CHA_2DS_2-VASc** scores are clinical prediction rules for estimating the risk of stroke in patients with AF. A high $CHADS_2$ or **CHA_2DS_2-VASc** score corresponds to a greater risk of stroke, while a low score corresponds to a lower risk of stroke.

The **$CHADS_2$** score is calculated based on following criteria:

Table 3-3: $CHADS_2$ - Scoring		
	Condition	**points**
C	Congestive heart failure	1
H	Hypertension (blood pressure consistently above 140/90 mmHg or treated hypertension on medication)	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S_2	Prior stroke, TIA or thromboembolism	2

The **CHA_2DS_2-VASc** score is a refinement of $CHADS_2$ score and extends the latter by including additional common stroke risk factors.

Table 3-4: CHA_2DS_2-VASc – Scoring		
	Condition	**Points**
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

Quality-of-life: for details refer to 6.5.3.

6.6.7 Treatment Compliance

Apixaban treatment compliance will be measured by the number of applications of apixaban based on the drug accountability performed on site (refer to section 5.7).

Patient's compliance rate will be calculated considering the duration of treatment phase, the number of tablets to be taken and the missed applications.

For the phenprocoumon treatment arm no drug accountability will be performed. Individual treatment compliance can only be estimated over changes in INR throughout the study.

7 ADVERSE EVENTS

In this study an **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered one of the study drugs (i.e. apixaban or phenprocoumon) and that does not

necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The following laboratory abnormalities should be captured as AEs and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (e.g., use the term anemia rather than low hemoglobin value).

Following the subject's written consent to participate in the study, all AEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. Investigators will seek information on AEs at each patient contact. All AEs must be collected that occur from screening until the end of study. For subjects who prematurely discontinue study drug treatment all AEs have to be collected until EoS (except for patients who withdrew informed consent).

For each AE, the investigator will make an assessment of seriousness (see section 8.1) severity, and causality. Severity of all AEs will be graded according to the NCI-CTCAE v 4.0 on a five-point scale (Grade 1 to 5).

  - Grade 1: Mild; asymptomatic or mild symptoms; or clinical or diagnostic observations only; or intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; or limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
  - Grade 3: Severe or medically significant but not immediately life-threatening; or hospitalization or prolongation of hospitalization indicated; or disabling; or limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
  - Grade 4: Life-threatening consequences; or urgent intervention indicated.
  - Grade 5: Death related to AE.

All AEs need to be reported in detail on the appropriate page of the eCRF.

During the study all AEs should be followed to resolution or stabilization or reported as SAEs if they become serious.

All non-serious AEs are to be followed for at least 2 days after last dose of study drug. A non-serious adverse event is any AE that is not classified as serious.

SAEs present at EoS are to be followed for additional 30 days or to resolution/ stabilization – whatever occurs first (see 6.1.5).

- The causal relationship to study drug is determined by a physician at the trial site and should be applied to assess all adverse events (AEs). The causal relationship can be one of the following:
    - Reasonable possibility: There is a reasonable causal relationship between study drug administration and the AE.
    - No reasonable possibility: There is not a reasonable causal relationship between study drug administration and the AE.
- The term "reasonable causal relationship" means there are facts (evidence) or arguments to suggest a causal relationship.
- The investigator will also document whether the event results in study discontinuation or other actions taken concerning the study drug.
- Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events). Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious adverse event, as appropriate, and reported accordingly.

7.1 Adverse events of special interest

In this study, the following adverse events of special interest are to be handled like SAEs, regardless of whether these reports are classified as serious or unexpected:

- Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

8 SERIOUS ADVERSE EVENTS

A **Serious Adverse Event (SAE)** is any AE/untoward medical occurrence that:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- requires inpatient hospitalization or causes prolongation of existing hospitalization (see ***NOTE****: below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.
- suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.
- although adverse events of special interest, pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs – see below. An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

***NOTE:** The following hospitalizations are not considered as SAEs:*

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

8.1 Serious Adverse Event Collecting and Reporting by the investigators

Following the subject's written consent to participate in the study, all SAEs as defined above, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur from

Screening until the End of Study. All SAEs that are present at the EoS visit are to be followed for additional 30 days or to resolution/stabilization – whatever occurs first.

For each SAE, the investigator will make an assessment of seriousness, severity, and causality. Severity of all SAEs will be graded according to the NCI-CTCAE v 4.0 on a five-point scale (Grade 1 to 5). All SAEs need to be recorded in the eCRF and source documents, additionally being reported on the SAE form.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. After the official end of trial will have been announced, such reports should be sent to the sponsor AFNET, no longer to the addressees as outlined below.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), this should be specified on the SAE Form.

SAEs must be reported on the SAE Form, pregnancies on the Pregnancy Surveillance Form. The forms should be completed in English, with as much information as possible. Relevant information must be entered on the form. Medical reports or copies of results should not be attached, only on explicit request. The investigator should not wait for full details before making the initial report.

Minimum information to be included in any initial SAE report:

1. Subject number
2. SAE details (where possible a diagnosis rather than a list of symptoms)
3. Details about administration of study drug
4. Causality assessment of SAE to study drug
5. Contact information of reporting investigator

Personal data have to be replaced by the subject number before forwarding any information.

SAEs and pregnancies must be reported by fax, within 24 hours after becoming aware of the event, on the respective form to:

1. **ZKS Münster Safety Desk** (sponsor's delegate for SAE management)

   SAE Fax Number, Germany: 0251 83 57112

2. **Bristol-Myers Squibb** (as per contract)

   SAE Fax Number, USA: 001 609-818-3804

Both fax numbers are available on each form. The report should not be sent by unprotected email, for reasons of data protection. Fax transmission confirmations for both reports should be filed together with any SAE or Pregnancy Surveillance Form.

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available (e.g. diagnosis, outcome), a follow-up SAE report should be sent within 24 hours to the ZKS Münster Safety Desk and to BMS using the same procedure used for transmitting the initial SAE report. The investigator should answer any query from the Safety Desk or BMS as soon as possible.

In case of death, the investigator has to supply the competent authority and the Ethics Committee with any details if requested by them.

All SAEs should be followed to resolution or stabilization.

8.1.1 Assessment and Reporting Requirements of the Sponsor

The ZKS Münster Safety Desk will document each SAE, check it and query additionally required information, if any. A Coordinating Investigator or a named delegate will review each SAE again for seriousness and relatedness. The Coordinating Investigator or delegate will also assess whether a serious adverse event, considered related to an investigational medicinal product, is expected or unexpected according to the applicable Product Information (current version of the German Summary of Product Characteristics for the investigational medicinal product apixaban: "Eliquis® 2,5 mg Filmtabletten") and whether any SAE might influence the benefit-risk-ratio or might require changes in the conduct of the trial.

In this context the following definitions apply:

- An adverse reaction is any untoward and unintended response to an investigational medicinal product related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
- In this trial, the definition adverse reaction will apply to both study drugs.
- All adverse events judged by either the reporting investigator or on side of the sponsor as having a reasonable causal relationship to a study drug qualify as adverse reactions.
- "Unexpected" means that the nature, severity or outcome of the adverse reaction is not consistent with the applicable product information for an investigational medicinal product. The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events. Examples include:
    - A more specific reaction than labelled ("acute renal failure" is a labelled adverse reaction, a new report of "interstitial nephritis" is more specific and therefore unexpected).

  - An increase in the rate of occurrence of an expected adverse reaction, which is judged to be clinically important, is considered as unexpected.
  - An expected adverse reaction with fatal outcome has to be considered as unexpected as long as the fatal outcome is not explicitly mentioned in the applicable product information.

- A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that has been judged to be unexpected.

It is the duty of the Safety Desk to ensure that the leading Ethics Committee, the competent authority and all participating investigators are informed of all suspected unexpected serious adverse reactions (SUSARs) in accordance with legal requirements (fatal or life threatening SUSAR within 7 days, detailed follow-up information within an additional 8 days, if any; all other SUSARs within 15 days after initial receipt of the minimum case information at the Safety Desk; electronic report or CIOMS-1 form, as appropriate). SUSAR follow-up reports will be submitted as required.

The Coordinating Investigators are responsible for the ongoing safety evaluation of the trial. In case of safety relevant issues (besides SUSARs) which require expedited reporting, the Coordinating Investigators will ensure to submit an appropriate report in due time. The Safety Desk may advice on the reporting procedures and provide support, as required. This includes issues which might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial as well as urgent safety measures to protect the subjects against any immediate hazard.

Annual safety reports will be prepared and submitted in accordance with legal requirements (Development Safety Update Report, DSUR). The Coordinating Investigators are responsible for providing the updated benefit-risk assessment and passages requiring medical assessment. The Safety Desk is responsible for preparing the template with as much information as possible, SAE listings, and for finalizing the report and submitting it to the competent authority and ethics committee in due time. The report will be prepared annually from the date of the initial clinical trial authorization and submitted within 60 days of data lock point (day before anniversary of initial authorization). Additional reports will be prepared on request by the competent authority or ethics committee.

The Safety Desk will concurrently provide copies for SUSARs and annual safety reports to BMS, according to stipulation.

The Safety Desk will provide information on SAEs for the Data and Safety Monitoring Board on request.

Details of all AEs will be reported by the sponsor or its designated CRO to the competent authorities on request.

Non-serious adverse events and laboratory test abnormalities are provided to BMS by the sponsor or its designated CRO via annual safety reports (if applicable), and interim or final study reports.

8.1.2 SAE Reconciliation

The sponsor or its delegated medical advisor will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Reconciliation will occur every three months and once just prior to database lock/Final Study Report (FSR) between the sponsor or collaborating CRO. The sponsor´s CRO will request a safety data reconciliation report to aepbusinessprocess@bms.com. BMS GPV&E will e-mail upon request from the sponsor, the GPV&E reconciliation report. The data elements listed on the GPV&E safety data reconciliation report will be used for case identification purposes. If the sponsor determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

8.1.3 Health Authority Reporting (Worldwide)

The sponsor must adhere to local Health Authority Reporting Requirements and timelines. For studies conducted under a local health authority:

- Adverse drug reactions that are Serious, Unexpected, and at least Possibly Related to the drug (Suspected Unexpected Serious Adverse Reaction, SUSAR) and that have not previously been reported in the Investigators' Brochure, or reference safety information document will be reported promptly, within local reporting timelines, to the health authority in writing by the sponsor.
- A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.
- The sponsor shall notify the health authority of any unexpected fatal or life threatening experience associated with the use of the drugs as soon as possible but no later than 7 calendar days after initial receipt of the information.

All SAEs and SUSARs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology

Bristol-Myers Squibb Company

Fax Number: 609-818-3804

Email: Worldwide.safety@bms.com

8.1.4 Non-Serious Events

A nonserious adverse event is an AE not classified as serious.

8.1.5 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Nonserious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

Nonserious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

9 PREGNANCY

If, following initiation of the study drug (i.e. the IP apixaban or the standard of care medication phenprocoumon), it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study drug exposure, including during at least 5 half-lives after product administration, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

The investigator must immediately notify the ZKS Münster Safety Desk and BMS of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form. The Project Managers ensure that this is covered by informed consent of the patient and the patient’s partner, as applicable.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

10 COMMITTEES

10.1 Data Safety and Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the sponsor and the Steering Committee (SC). It will consist of one statistician and two clinicians with expertise in clinical studies and in cardiology and nephrology. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. They regularly monitor the recruitment and conduct of the study, data quality and timelines, the distribution of therapies within the study groups, the serious adverse events and further adverse events selected to their discretion during the course of the trial. The DSMB will give recommendations to the sponsor and the SC to continue or stop the study.

A DSMB charter providing operating procedures and responsibilities will be enacted. Meeting frequency will be defined by the sponsor and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings.

10.2 Endpoint Review Committee

In addition to the study assessments performed and documented by the investigators, a blinded assessment of outcomes is planned for this study following the FDA guidance for clinical trial sponsors for Establishment and Operation of Clinical Trial Data Monitoring Committees (FDA, 2006).

Such committees are particularly valuable when endpoints are subjective and/or require the application of a complex definition, and when the intervention is not delivered in a blinded fashion.

The blinded endpoint assessment will be performed by a blinded Endpoint Review Committee consisting of 3 specialized physicians from the following fields: neurology, cardiology and nephrology.

Details and procedures of this blinded assessment will be described separately in a detailed charter describing the standard operation procedures of this committee.

10.3 Steering Committee

The trial Steering Committee (SC) will consist of a small group of experts in cardiology, nephrology, hemosteology and an expert biostatistician (refer to section 16). The functions of the SC are the following:

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

A SC charter providing operating procedures and responsibilities will be discussed and enacted latest at the second meeting. Meeting frequency will be defined by the committee and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings. Minutes of each meeting will be provided. A list of members of the SC is given in section 20.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size Determination

The primary (safety) endpoint of the AXADIA-AFNET8 trial is the time to first occurrence of a major or clinically relevant non-major bleeding or death of any cause.

Until the very recent presentation of the RENAL-AF trial in November 2019 at the AHA congress, only one other publication reported bleeding rates in a similar – but definitely not comparable – setting in hemodialysis patients with new oral anticoagulants (NOACs), ASA and VKAs (Chan et al., 2015).

The statistical assumptions of the original application were based on these data from Chan et al. using similar (but not identical – see below) endpoint definitions especially for bleedings, it is assumed that apixaban would have similar bleeding rates as ASA in dialysis patients.

Our assumption was based on the AVERROES trial (Connolly et al., 2011) in which apixaban and ASA were compared in a cohort of patients who were considered unsuitable for oral anticoagulation due to multiple risks including an expected increased bleeding risk: in this trial with patients with a comparable high risk as here, the rates of major and clinically relevant non-major bleedings were similar in the apixaban and ASA arm. Based on this assumption of similar bleeding event rates on ASA and apixaban, and with the given event rates in dialysis patients

from Chan et al. (Chan et al., 2015), we calculated (based on their figures in tables 2 and 3 for major bleedings, minor bleedings and a composite of both) the following sample sizes for a log-rank test according to Lakatos (Lakatos, 1988). However, because the study from Chan was a retrospective, file-based cohort study it appears reasonable in comparison to other studies (Vasquez, 2003, Wiesholzer, 2001) to assume that in a prospective trial more events will be recorded: especially major bleedings in the Chan study were only recorded if they led to hospitalization or death and not according to the ISTH consensus. So they definitely missed numerous bleedings requiring, e.g., ambulatory transfusions or drops in hemoglobin of >20g/L. Similarly, minor bleedings were also only retrieved retrospectively from the patients' files and are expected to be more complete (and higher) in our trial.

Endpoint	**Hazard rate/ month apixaban**	**Hazard rate/ month VKA.**	**Hazard Ratio Apixaban/Vit. K.Antag.**	**Accrual/ Total Time (months)**	**Alpha 1sided**	**Power (non-inferiority)**	**Total N/ Events**
Deaths	.0054	.0054	1	-	-	-	-
Major bleeds	.0299	.0393	.761	60/ 61	.025	.80	217/ 128
Clinically relevant, non-major bleeds	.0490	.0917	.535	60/ 61	.025	.80	58/ 44
Combination of death, major an clinically relevant non-major bleeds	.0843	.1364	.618	60/ 61	.025	.80	75/ 64

According to these figures, recruitment will be stopped when n= 64 events have been observed or the maximal recruitment duration of 60 months has been reached. This will be sufficient to demonstrate non-inferiority of apixaban treatment with 80% power with respect to the primary endpoint (combination of death, major and clinically-relevant non-major bleedings) and also with respect to clinically relevant non-major-bleedings only.

The calculations shown above do not take into account dropout rate. Because of our uncertainty regarding dropout distribution due to withdrawals or non-bleeding events leading to the early termination of treatment for a patient, we plan to monitor "information time" and stop recruitment based on the observation of the required number of events or on reaching the maximal recruitment duration, as stated above.

Based on a dropout rate of approximately 30%, incorporating early withdrawal, we plan to randomize approximately 108 patients.

11.2 Populations for Analyses

The full analysis set consists of all randomized patients, including patients with any kind of protocol violations. In the per-protocol population, patients with relevant protocol violations are

excluded. The safety population consists of all patients who were randomized and received at least one dose of the study drug.

11.3 Endpoint Definitions

Primary Safety Endpoints:

The primary endpoint of the study is the first occurrence of a major or clinically relevant non-major bleeding (see section 6.4.1) or death of any cause.

Secondary Endpoints

As secondary endpoints will be recorded thromboembolic and major other events, and a composite of these as well as events of special interest and Quality-of-life (EQ-5D index score) through the entire study (see section 6.5.1).

11.4 Analyses

11.4.1 Demographics and Baseline Characteristics

Continuous variables are presented group wise as means and standard deviation (SD) 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 as counts and percentages and compared by chi-square tests or Fisher's exact test as appropriate.

11.4.2 Safety Analyses

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 is applied that controls the familywise error rate (FWER) 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 primary non-inferiority and superiority tests will be performed in the safety population that consists of all patients who were randomized and received at least one dose of the study drug, applying the as-treated 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 this result is supported both in the as-treated analysis and the per-protocol analysis.

As outlined in section 11.1, apixaban treatment is expected to be superior to phenprocoumon treatment. Assuming a treatment effect of HR=0.618, non-inferiority of apixaban is demonstrated with 80% power, if the primary analysis is performed when 64 events with respect to the primary endpoint have emerged in total across both treatment groups.

The primary endpoint and the secondary endpoints will be analyzed 'on treatment' including all randomized patients who received at least one dose of the study drug. In these analyses, patients are considered at risk and events are counted only in the time period from receipt of the study drug until 2 days after intake of the last dose (exposure time). A crossover from one study arm to the other is discouraged. The exposure time will be reduced in case of cross-over, but last at least for 2 days after last intake. Beyond 21 days into a study drug interruption/discontinuation the patient is not considered at risk and events are not counted unless the patient resumes his study drug. Technically, this is realized by use of a Cox regression model. For increase of the statistical power, significant prognostic baseline characteristics, medical history and medication will be included into the model as factors and covariates. ASA use will be modeled with a time-dependent covariate. Details will be given in a statistical analysis plan, based on a pooled (and thus blind) analysis of the baseline data of the recruited patients.

The primary analysis will be up to the first occurrence of the endpoint. An extended analysis 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. As a sensitivity analysis, a clock reset conditional risk set model according to Prentice, Williams, and Peterson (1981) will be fitted to the data (Prentice, Williams, & Peterson, 1981).

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.

As a sensitivity analysis, statistical analyses will be repeated in the full analysis set that consists of all randomized patients, applying the intention-to-treat principle. For that analysis, all events will be counted and patients will be considered at risk regardless of whether the patient was 'on treatment' or not.

11.4.3 Efficacy Analyses

The secondary endpoints, including events of special interest, the composite endpoint (see section 6.5.1) and Quality-of-life (EQ-5D index score, see section 6.5.1) are the efficacy endpoints and will be analyzed on an as-treated-basis by descriptive statistics only due to the small sample size which will probably not sufficient to demonstrate superiority. Adjusted Cox proportional hazard models, Anderson-Gill models and the described sensitivity analyses will be supplied where applicable as described above. No adjustment for multiplicity will be provided as the efficacy analysis is secondary behind the safety analysis.

11.4.4 Other Analyses

Further baseline characteristics will be added to the previously defined models.

12 STUDY MANAGEMENT

12.1 Compliance with the Protocol

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by the sponsor.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to sponsor.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, the sponsor must inform relevant IRB(s)/IEC(s).

12.2 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by Sponsor, whichever is longer.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IEC/IRB). Notice of such transfer will be given in writing to the sponsor.

12.2.1 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (i.e. apixaban)is maintained at each study site where apixaban is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label ID number or batch number
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Non-study disposition (e.g., lost, wasted)
- Amount returned to the sponsor
- Amount destroyed at sponsor
- Dates and initials of person responsible for IP dispensing/accountability, as per the delegation of authority form.

12.3 Destruction of Study Drug

It is the sponsor's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

13 DATA HANDLING AND QUALITY MANAGEMENT

13.1 Data Recording

The eCRFs will be provided by the sponsor's designated CRO and the study personnel will be instructed how to fill in the eCRFs.

Data required according to this protocol are to be recorded on the eCRFs as soon as possible but within 5 days after information become apparent.

The documentation will be kept in such way, that it is possible to easily reconstruct the course of the study at a later date (in accordance with the details given in the protocol). Access to eCRFs should be available at all times for monitoring visits.

Study data include all findings, measurements, or other individual data. All data stored in electronic data retrieval systems during the study are to be made available for monitoring and archiving purposes in hard copies initialed and dated by responsible study staff.

13.2 Monitoring

Monitoring procedures include one or more visit(s) designed to clarify all prerequisites and to assure the medical and formal instruction of investigators as to the procedures and activities to be performed for this trial before the study commences.

Interim monitoring visits will take place on a regular basis according to a schedule fixed by mutual agreement. During these visits, the CRA will review protocol compliance, check the eCRFs for completeness, accuracy, plausibility and clarity, and crosscheck the data with the source documents (medical records). He / she will also verify the correct handling, use and storage of the study drugs.

Additionally, the CRA will check whether all SAEs have been appropriately reported within the time periods required and will collect appropriate copies of the completed forms (as applicable).

The investigators participating in the trial must allow the monitor to make regular visits and to check the entries by comparison with the original patient documents.

All details concerning the type and extent of source data verification are specified in the monitoring manual.

13.3 Data Processing

Subject data will be entered into the eCRF by authorized site staff. Queries resulting from online checks implemented in the system are automatically generated during data entry and directly handled by site staff prior to review by data management.

The CRA posts manual queries into the eCRF regarding issues detected during source data verification. The data managers post manual queries into the eCRF based on the data review performed in accordance with the data cleaning plan.

All queries, whether generated by the system or by a user, will be in the discrepancy database of the system.

An eCRF documentation in accordance with the CRF completion guideline by site staff as well as the careful data review and query management performed by data management will ensure that a clean and consistent database is provided prior to the statistical analysis being performed.

The database will be closed, after all data are entered and source verified, all queries are solved, all investigator´s electronic signatures are available, coding of medical terms is complete and the SAE reconciliation is finalized.

13.4 Auditing

The investigator will permit study related audits, IEC/IRB review, and regulatory inspections, providing direct access to source data / documents.

A visit may be arranged by the sponsor or its designees in order to audit the study site and the study documents, which originate there. The auditor(s) will usually be accompanied by the CRA or the project manager. The investigator will be informed about the outcome of the audit.

In addition, inspections by health authority representatives, including foreign authorities, are possible at any time. The investigator should notify the sponsor of any such inspection immediately.

14 FINAL REPORT AND PUBLICATION POLICY, PROPERTY RIGHTS

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

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

AXADIA-AFNET8 is an investigator-initiated trial. Interested investigators and initiatives will be encouraged and supported as appropriate if they propose additional issues. These materials must be submitted to the SC for review and comment prior to publication or public dissemination. All relevant measures for transparency of clinical trials, and especially the recommendations of the editors of the major medical journals, will be met.

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

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

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

15 FINANCING

Expenses arising in connection with the study, the remuneration of the investigators for performance of the study will be reimbursed by the sponsor in accordance with the respective contracts. The respective financing agreements are addressed in a separate document.

16 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Legal sponsor according to the EU directive 2001/20/EC This project is financially supported by BMS an Pfizer	Kompetenznetz Vorhofflimmern e.V. Atrial Fibrillation NETwork (AFNET) Phone: +49 (0)251 – 980 1330 Fax: +49 (0)251 – 980 1349	Mendelstraße 11 48149 Münster Germany
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Steering Committee (SC)	The SC consists of the following members: • 1 representative of the Sponsor (Prof. Dr. Kirchhof) • 2 representatives of the funding Companies BMS and Pfizer (Dr. Sommer, Dr. Krekler) - non voting • 1 PI Cardiology (Prof. Dr. Reinecke) • 1 PI Nephrology (Prof. Dr. Wanner) • 1 Senior Consultant Hemosteology (Prof. Dr. Bauersachs) • 1 Senior Consultant Cardiology (Prof. Dr. Dr. Breithardt) • 1 Head Biometrician (Dr. J. Gerß) • 1 AFNET network office representative, guest – non voting	
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No. of study sites (planned)*	Approximately 30-35 sites in Germany	
Study sites *		
Investigators *		
Monitoring *	*pro**innovera*** GmbH	Wienburgstrasse 207 48159 Münster Germany

* Will be addressed and updated in a separate document.

17 LIST OF ABBREVIATIONS

AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
AFNET	Kompetenznetz Vorhofflimmern e.V. / Atrial Fibrillation NETwork
AHA	American Heart Association
ALT	Alanine transaminase
ASA	Acetyl Salicyl Acid
AST	Aspartate Transaminase
AT	Amino Transaminase
BMS	Bristol-Myers Squibb
CHADS	**C**ongestive heart failure; **H**ypertension; **A**ge; **D**iabetes mellitus; **S**troke
CKD	Chronic Kidney Disease
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Potential Drug-Induced Liver Injury
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiography
EoS	End of Study (for patients)
EoT	End of (study drug) Treatment
EQ-5D	Quality of Life Questionnaire (5D)
ERC	Endpoint Review Committee
ESKD	End Stage Kidney Disease
ESC	European Society of Cardiology
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase

GOT	Aspartate Transaminase
GPT	Alanine Transaminase
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
FXa	Factor Xa
HCG	Human Chorionic Gonadotropin
HRT	Hormone Replacement Therapy
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
i.e.	Id est
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ISR	Investigator-Sponsored Research
ISTH	International Society on Thrombosis and Haemostasis
IWRS	Interactive Web Response System
LMWH	Low-molecular weight heparin
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NOAC	New oral Anticoagulants
NSAE	Non-Serious Adverse Event
NSAID	Non-Steroidale Anti-Inflammatory Drug
NYHA	New York Heart Association
SAE	Serious Adverse Event
SC	Steering Committee
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTR	Time in Therapeutic Range

UFH	Unfractionated Heparin
ULN	Upper Limit of Normal
VKA	Vitamin-K Antagonist
WOCBP	Women of Child-Bearing Potential
ZKS-MS	Zentrum für Klinische Studien Münster

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19 APPENDICES

19.1 Suggestions for hemodialysis in patients with oral anticoagulation

Anticoagulation in routine hemodialysis consists of a standard dose of heparin given as a bolus at the start of the dialysis treatment, with a mid-treatment dose to maintain suitable anticoagulation. Alternatively, heparin modeling can be performed using an initial bolus followed by a constant fixed infusion of heparin to maintain an activated clotting time (ACT) of 200 to 250 seconds (normal = 90 to 140 seconds).

Some protocols use higher heparin doses with decreasing infusion rates as the treatment proceeds to minimize postdialysis bleeding from venipuncture sites they are, however, unsuitable for patients with significant bleeding risks.

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.

19.2 Quality of Life questionnaire (EQ-5D)

Gesundheitsfragebogen

Deutsche Version für Deutschland

(German version for Germany)

Bitte kreuzen Sie unter jeder Überschrift DAS Kästchen an, das Ihre Gesundheit HEUTE am besten beschreibt.

BEWEGLICHKEIT / MOBILITÄT

- Ich habe keine Probleme herumzugehen ❑
- Ich habe leichte Probleme herumzugehen ❑
- Ich habe mäßige Probleme herumzugehen ❑
- Ich habe große Probleme herumzugehen ❑
- Ich bin nicht in der Lage herumzugehen ❑

FÜR SICH SELBST SORGEN

- Ich habe keine Probleme, mich selbst zu waschen oder anzuziehen ❑
- Ich habe leichte Probleme, mich selbst zu waschen oder anzuziehen ❑
- Ich habe mäßige Probleme, mich selbst zu waschen oder anzuziehen ❑
- Ich habe große Probleme, mich selbst zu waschen oder anzuziehen ❑
- Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ❑

ALLTÄGLICHE TÄTIGKEITEN *(z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)*

- Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
- Ich habe leichte Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
- Ich habe mäßige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
- Ich habe große Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
- Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ❑

SCHMERZEN / KÖRPERLICHE BESCHWERDEN

- Ich habe keine Schmerzen oder Beschwerden ❑
- Ich habe leichte Schmerzen oder Beschwerden ❑
- Ich habe mäßige Schmerzen oder Beschwerden ❑
- Ich habe starke Schmerzen oder Beschwerden ❑
- Ich habe extreme Schmerzen oder Beschwerden ❑

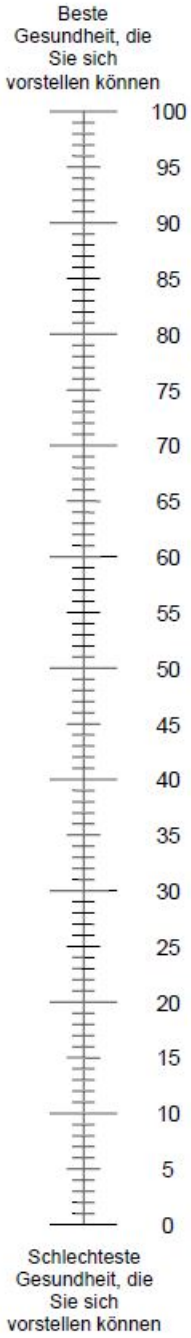
ANGST / NIEDERGESCHLAGENHEIT

- Ich bin nicht ängstlich oder deprimiert ❑
- Ich bin ein wenig ängstlich oder deprimiert ❑
- Ich bin mäßig ängstlich oder deprimiert ❑
- Ich bin sehr ängstlich oder deprimiert ❑
- Ich bin extrem ängstlich oder deprimiert ❑

2

- Wir wollen herausfinden, wie gut oder schlecht Ihre Gesundheit HEUTE ist.
- Diese Skala ist mit Zahlen von 0 bis 100 versehen.
- 100 ist die beste Gesundheit, die Sie sich vorstellen können. 0 (Null) ist die schlechteste Gesundheit, die Sie sich vorstellen können.
- Bitte kreuzen Sie den Punkt auf der Skala an, der Ihre Gesundheit HEUTE am besten beschreibt.
- Jetzt tragen Sie bitte die Zahl, die Sie auf der Skala angekreuzt haben, in das Kästchen unten ein.

IHRE GESUNDHEIT HEUTE = ☐



3

19.3 Site risk assessment questonnaire

Zentrumsspezifische Risiko-Abschätzung zur Patientenrekrutierung im Pandemiefall

Sehr geehrte Prüferinnen und Prüfer der AXADIA-AFNET 8 Studie,

auch wenn die COVID-19 Pandemie uns alle weiterhin vor große Herausforderungen stellt, möchten wir gemeinsam mit Ihnen alles daran setzen, die AXADIA-AFNET 8 Studie auch im Sinne unserer Patientinnen/en zum Erfolg zu führen. Die Sicherheit der Studienteilnehmer und des Studienpersonals soll auch unter den aktuellen Umständen höchste Priorität haben.

Wir möchten daher im Pandemiefall jede klinische Prüfstelle bitten, vor der Einstellung, bzw. vor Wiederaufnahme der Patientenrekrutierung eine sorgfältige Risiko-Nutzen-Abwägung entsprechend der Situation vor Ort durchzuführen.

Die im Folgenden aufgeführten Fragen sollen Ihnen dafür als Orientierung dienen:

Prüfstelle:

1. Wie ist die Infektionslage in der lokalen Region/Einzugsgebiet Ihrer Prüfstelle? Gibt es regulatorische Gründe, die gegen eine Wiederaufnahme der Patientenrekrutierung sprechen?

   ☐ Ja, bitte spezifizieren:
   _____
   ☐ Nein

   Infektionslage:
   _____

2. Ist ein ausreichender zeitlicher und räumlicher Abstand zu anderen Patienten gewährleistet?

   ☐ Ja ☐ Nein

3. Können die am Zentrum durchgeführten Studienvisiten vom üblichen Klinikbetrieb räumlich separiert durchgeführt werden?

☐ Ja ☐ Nein

4. Ist ausreichend persönliche Schutzausrüstung vorhanden, um die Studienvisiten für Personal und Patient sicher durchführen zu können?

   ☐ Ja ☐ Nein

5. Ist ausreichend Studienpersonal verfügbar, um SAEs zeitgerecht zu melden, die Studienvisiten zeitgerecht durchzuführen, die Dateneintragungen im eCRF vorzunehmen und die Studie protokollgerecht durchzuführen?

   ☐ Ja ☐ Nein

6. Kann ein Vor-Ort Monitoring unter Einhaltung der geforderten Hygienestandards (vom üblichen Klinikbetrieb separierter Raum, Mindestabstand) durchgeführt werden?

   ☐ Ja ☐ Nein

Nach sorgfältiger Risiko-Nutzen Abwägung kann die Patientenrekrutierung für die AXADIA-AFNET 8 Studie an unserer Prüfstelle

☐ fortgesetzt werden. **☐ nicht fortgesetzt werden.**

Sollte sich meine Einschätzung der Situation ändern, werde ich die Studienleitung hierüber umgehend informieren.

_____ _____

Ort, Datum Name des Prüfers

_____

Unterschrift des Prüfers

Bitte zurücksenden per E-Mail: info-axadia@af-net.eu oder per Fax: 0251 980 1349

20 SIGNATURES

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

Date	**Signature**
11 JAN 2021	**Prof. Holger Reinecke** Co-ordinating investigator cardiology (Head of the Trial)
	Prof. Christoph Wanner Co-ordinating investigator nephrology (Chief of the Trial)
	Prof. Paulus Kirchhof Chairman of the Board of the Sponsor (Atrial Fibrillation NETwork, AFNET)
	Dr. Joachim Gerß Study Statistician

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	Prof. Holger Reinecke Co-ordinating investigator cardiology (Head of the Trial)
13. Jan. 2021	**Prof. Christoph Wanner** Co-ordinating investigator nephrology (Chief of the Trial)
	Prof. Paulus Kirchhof Chairman of the Board of the Sponsor (Atrial Fibrillation NETwork, AFNET)
	Dr. Joachim Gerß Study Statistician

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Date	**Signature**
	Prof. Holger Reinecke Co-ordinating investigator cardiology (Head of the Trial)
	Prof. Christoph Wanner Co-ordinating investigator nephrology (Chief of the Trial)
Hamburg, 11 Jan 2021	**Prof. Paulus Kirchhof** Chairman of the Board of the Sponsor (Atrial Fibrillation NETwork, AFNET)
	Dr. Joachim Gerß Study Statistician

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	Prof. Christoph Wanner Co-ordinating investigator nephrology (Chief of the Trial)
	Prof. Paulus Kirchhof Chairman of the Board of the Sponsor (Atrial Fibrillation NETwork, AFNET)
11 January 2021	**Dr. Joachim Gerß** Study Statistician

AXADIA - 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

Statistical Analysis Plan

Version: 01
Date: 08.07.2022

Sponsor protocol code: CV185-435

EudraCT number: 2015-005503-84

ClinicalTrials.gov identifier: NCT02933697

Acronym: AXADIA – AFNET 8

Sponsor
Kompetenznetz Vorhofflimmern e.V.
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Biostatistician / author
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Münster 12.7.2022
Place, date

H. Reinecke
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Würzburg 20.7.2022
Place, date

Signature

Chairmen of the Board of the Sponsor
Name:
Prof. Dr. med. Paulus Kirchhof
Affiliation:
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Schmeddingstrasse 56
48149 Münster

Münster, 8.7.2022
Place, date

J. Gerß
Signature

1 Background of the Study

This statistical analysis plan (SAP) was written based on the protocol version 1.7, effective since January 2021. Furthermore, the study design was published in Reinecke, H., Jürgensmeyer, S., Engelbertz, C., Gerss, J., Kirchhof, P., Breithardt, G., Bauersachs, R., & Wanner, C. (2018). Design and rationale of a randomised controlled trial comparing apixaban to phenprocoumon in patients with atrial fibrillation on chronic haemodialysis: the AXADIA-AFNET 8 study. BMJ open, 8(9), e022690. https://doi.org/10.1136/bmjopen-2018-022690

The study protocol had several amendments, with two changes in the sample size estimation. The underlying statistical design was not changed and especially the preselected null-hypotheses nor the preselected testing procedures were affected. Amendments with respect to sample size were based on improved assessment of the expected hazard ratio of the primary safety outcome and additional calculations were made to adjust for modified recruitment schedules. In 2020 an updated accrual time and total study time was amended and respectively taken into account for a sample size. In 2021 a further slight change to the accrual time was introduced and an update expected drop-out rate (now 30%) was considered. The study finally stopped recruiting in June 2022 due to reaching 60 months (maximal recruitment time).

This SAP was written before unblinding of the study statistician and database lock, but after end of recruitment.

1.1 Study objectives

The primary goal of this study is to assess the safety of two types of oral anticoagulants in patients with End-stage kidney disease (ESKD) on hemodialysis with atrial fibrillation (AF) or atrial flutter (AFL). The novel FXa inhibitor apixaban (at a reduced dose of 2x 2.5 mg/day) will be compared to the vitamin-K antagonist (VKA) phenprocoumon (target range: International Normalized Ratio (INR) 2.0-3.0) regarding bleeding rates during chronic administration for prevention of stroke or systemic embolism. The primary hypothesis of the study is that oral anticoagulation with apixaban will improve the safety by significantly reducing bleeding rates in patients with ESKD on hemodialysis and AF compared to the VKA phenprocoumon.

1.2 General study design and plan

The study is conducted in Germany as an investigator-driven, prospective, parallel-group, single country, multi-center phase IIIb trial to assess the safety of apixaban versus the vitamin-K antagonist phenprocoumon in patients with AF and ESKD on hemodialysis treatment. The study is conducted in 30-35 German study sites. Male or female patients aged ≥ 18 years with ESKD on hemodialysis treatment 3 times a week, each with a duration of at least 3.5 hours, and with an indication for oral anticoagulation due to AF or AFL are centrally randomized into 2 treatment arms: apixaban or phenprocoumon (1:1). Patients previously on phenprocoumon therapy can be randomized to either study drug treatment. As phenprocoumon needs constant INR controls, the study is performed with open-label administration of study drugs.

2 Analysis populations

2.1 Treated population (primary analysis population) / Safety population

The treated population consists of all patients who were randomized and received at least one dose of study drug. This population will be the primary analysis population. This population coincides with the safety population.

2.2 Full analysis set

The full analysis set consists of all randomized patients, including patients with any kind of protocol violations.

2.3 Per protocol population

In the per-protocol population, patients with relevant major protocol violations are excluded.

Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB- or Ethics Committee-approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Patients with major protocol violations will be excluded from the per-protocol analysis. Study specific definitions of major protocol violations are found in 13.4.5 and will not be repeated here.

3 Endpoints and variables

3.1 Primary confirmatory safety outcome parameter

The primary confirmatory safety outcome parameter of the trial is the time from the first dose of the study drug to the first occurrence of a major or clinically relevant non-major bleeding or death of any cause. All bleeding events were centrally adjudicated.

All bleeding events have to be categorized and documented in detail in study documents according to International Society on Thrombosis and Haemostasis (ISTH) consensus (Schulman et al., 2010) and the most recent apixaban SmPC ("Apixaban [Eliquis]) as follows:

Major Bleeding (as defined in the ISTH consensus):

- 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 mmmol/ 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, 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

3.2 Primary efficacy outcome parameter

The primary efficacy outcome parameter is a composite of myocardial infarction, ischemic stroke, deep vein thrombosis, pulmonary embolism, and all-cause death. This outcome captures a composite of thromboembolic complications and death.

3.3 Secondary outcomes

The incidence of thromboembolic and major other events is recorded throughout the entire study categorized according to following single and composite outcomes:

Thromboembolic events

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

Events of special interest

- Dialysis shunt thrombosis
- Clotting of dialysis membrane

For the Quality-of-life EQ-5D index questionnaire, see study protocol Section 19.2.

3.4 Details on exposure time

The primary endpoint and the secondary endpoints will be analyzed 'on treatment' including all randomized patients who received at least one dose of the study drug. In these analyses, patients are considered at risk and events are counted only in the time period from receipt of the study drug until 2 days after intake of the last dose (exposure time). A cross-over from one study arm to the other is discouraged. The exposure time will be reduced in case of cross-over, but last at least for 2 days after last intake. Beyond 21 days into a study drug interruption/discontinuation the patient is not considered at risk and events are not counted unless the patient resumes his study drug.

3.5 Variables to be analyzed descriptively

3.5.1 Subject disposition

3.5.2 Demographic and Baseline Variables

- Age in years
- Sex
- Ethnicity
- Childbearing
- INR
- Height / Weight / BMI
- Heart frequency (HF)
- Blood pressure (sys/dia)
- ECG at screening (HF, QRS duration, rhythm, QT and QTc(Bazett) interval, PQ interval, left/right bundle branch block) [one to three ECGs may be documented at screening]
- Hemodialysis [at screening, at baseline and monthly]
- Blood laboratory [at screening, at baseline and monthly] (see also 3.4.5)
- Risk at screening (risk items(n=15), CHADS2, CHA2DS2-VASc, HAS-BLED) [at screening]
- Quality of life [at baseline and monthly]
- COVID-19 test

3.5.3 Concurrent and Prior Illnesses and Medications

Medical history comprises

- Hypertension
- Coronary heart disease
- Angina pectoris
- Family history of heart diseases

- Diabetes mellitus
- Smoking status
- Hyperlipidemia
- Peripheral arterial disease
- Heart valve disease
- Myocard infarct
- Percutaneous coronary intervention / Bypass surgery / and other heart surgery
- Pacemaker / Defibrilator
- Prior reanimation
- Cardiomypathy
- Nephropathy (vascular / interstitial / glomular / diabetic)
- Date of first dialysis
- Planned kidney transplantation
- Invasive coronary angiography and/or ventriculography
- Echo cardiography
- MRI / PET
- Physical status

Concomitant medication (Listing of substances, dose, frequency and duration) will be provided as listing (see 13.3)

Concomitant diseases (diagnosis, duration, status at end of treatment) will be provided as listing (see 13.3)

3.5.4 Treatment Compliance and Extent of Exposure

Variable reported under this section were documented in the end of treatment (EOT) CRF.

- Date of first intake / of last intake / Duration of treatment
- Study medication was taken in compliance with the protocol
- Early termination of drug intake / reasons

Further analyses will be made from the drug accountability data set.

3.5.5 Laboratory parameters

- Leukocytes
- Erythrocytes
- Platelets
- Haemoglobine
- Creatinine
- PTH (parathormone)
- AST/GOT
- ALT/GPT
- gammaGT
- Bilirubine
- Calcium
- Phosphate

3.5.6 Vital parameters

- Height / Weight / BMI
- Heart frequency (HF)
- Blood pressure (sys/dia)
- ECG at screening (HF, QRS duration, rhythm, QT and QTs interval, PQ interval, left/right bundle block)

3.5.7 Adverse Events

Adverse events will be listed individually by patient (see section 13.3). Additionally, the total frequency and severity of adverse events will be reported as well as the, outcome of AEs.

The occurrence of embolisms will be compared between the two study arms.

4 Statistical Methods

4.1 Summary of study data

Continuous variables are summarized using mean, standard deviation, quartiles, minimum and maximum and compared via t-tests, possibly after a transformation towards normality, or by non-parametric U tests.
Categorical variables will be presented as counts and percentages (based on the non-missing sample size) and compared by chi-square tests or Fisher's exact test as appropriate.
To perform a survival analysis for a comparison of groups with respect to a censored survival time a log-rank test will be performed. To illustrate the results, Kaplan-Meier plots will be provided. Time-to-event outcomes will be characterized by median times and 1-year percentages (e.g. 1-year survival times).

4.2 Primary confirmatory safety analysis

In the primary statistical analysis, the treatments will be compared with respect to the primary safety outcome and with respect to the primary efficacy outcome. Let Hazard Ratio (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 is applied that controls the familywise error rate (FWER) in the strong sense at pre-specified significance level α for the primary safety outcome. 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 superiority test will be performed in the treated population (safety population) that consists of all randomized and treated patients, including patients with any kind of protocol violations, applying the intention-to-treat principle. The non-inferiority test will be performed in the per-protocol population, excluding patients with relevant major protocol violations and the treated population (safety population). Statistical significant non-inferiority ($H_0^{\text{Non-Inferiority}}$) will be claimed only if this result is supported by both, the intention-to-treat analysis and the per-protocol analysis.

The primary safety analyses provides confirmatory statistical evidence.

As a sensitivity analysis, statistical analyses will be repeated in the full analysis set that consists of all randomized patients, applying the intention-to-treat principle. For that analysis, all events will be counted and patients will be considered at risk regardless of whether the patient was 'on treatment' or not.

From all models, hazard ratios and two-sided 95% confidence limits will be calculated.

4.3 Analysis of the primary efficacy outcome

The primary efficacy outcome will be analyzed according to the primary safety analysis described in 4.2. This analysis was prespecified and all considerations with respect to superiority, non-inferiority, multiplicity and the selected alpha-level will be chosen identically. The results of the primary efficacy outcome will be considered noticeable when the p-value of the statistical test is below the selected alpha.

4.4 Secondary analyses

The secondary endpoints, including events of special interest, the composite endpoint (see protocol section 6.5.1, SAP section 3.2) and Quality-of-life (EQ-5D index score, see section protocol section 6.5.1, SAP section 3.2) are the efficacy endpoints and will be analyzed on an as-treated-basis by descriptive statistics only due to a probable small sample size which will probably not sufficient to demonstrate superiority.

No adjustment for multiplicity will be provided as the efficacy analysis is considered secondary behind the primary analyses. Results with p-values below level alpha will be denoted noticeable.

An extended analysis will take recurrent primary or secondary events into regard and will be performed by fitting an Anderson-Gill model with robust estimation of coefficients and variance terms to the data. As a sensitivity analysis, a clock reset conditional risk set model according to Prentice, Williams, and Peterson (1981) will be fitted to the data (Prentice et al., 1981).

5 Power calculation

The primary (safety) endpoint of the AXADIA-AFNET8 trial is the time to first occurrence of a major or clinically relevant non-major bleeding or death of any cause. Until the very recent presentation of the RENAL-AF trial in November 2019 at the AHA congress, only one other publication reported bleeding rates in a similar – but definitely not comparable – setting in hemodialysis patients with new oral anticoagulants (NOACs), ASA and VKAs (Chan et al., 2015). The statistical assumptions of the original application were based on these data from Chan et al. using similar (but not identical – see below) endpoint definitions especially for bleedings, it is assumed that apixaban would have similar bleeding rates as ASA in dialysis patients. Our assumption was based on the AVERROES trial (Connolly et al., 2011) in which apixaban and ASA were compared in a cohort of patients who were considered unsuitable for oral anticoagulation due to multiple risks including an expected increased bleeding risk: in this trial with patients with a comparable high risk as here, the rates of major and clinically relevant nonmajor bleedings were similar in the apixaban and ASA arm. Based on this assumption of similar bleeding event rates on ASA and apixaban, and with the given event rates in dialysis patients from Chan et al. (Chan et al., 2015), we calculated (based on their figures in tables 2 and 3 for major bleedings, minor bleedings and a composite of both) the following sample sizes for a log-rank test according to Lakatos (Lakatos, 1988). However, because the study from Chan was a retrospective, file-based cohort study it appears reasonable in comparison to other studies (Vasquez, 2003, Wiesholzer, 2001) to assume that in a prospective trial more events will be recorded: especially major bleedings in the Chan study were only recorded if they led to hospitalization or death and not according to the ISTH consensus. So they definitely missed numerous bleedings requiring, e.g., ambulatory transfusions or drops in hemoglobin of >20g/L. Similarly, minor bleedings were also only retrieved retrospectively from the patients' files and are expected to be more complete (and higher) in our trial.

Endpoint	Hazard rate/ month apixaban	Hazard rate/ month VKA.	Hazard Ratio Apixaban/Vit. K.Antag.	Accrual/ Total Time (months)	Alpha 1sided	Power (non-inferiority)	Total N/ Events
Deaths	.0054	.0054	1	-	-	-	-
Major bleeds	.0299	.0393	.761	60/ 61	.025	.80	217/ 128
Clinically relevant, non-major bleeds	.0490	.0917	.535	60/ 61	.025	.80	58/ 44
Combination of death, major an clinically relevant non-major bleeds	.0843	.1364	.618	60/ 61	.025	.80	75/ 64

According to these figures, recruitment will be stopped **when n= 64 events have been observed or the maximal recruitment duration of 60 months has been reached.**
This will be sufficient to demonstrate non-inferiority of apixaban treatment with 80% power with respect to the primary endpoint (combination of death, major and clinically-relevant non-major bleedings) and also with respect to clinically relevant non-major-bleedings only. The calculations shown above do not take into account dropout rate. Because of our uncertainty regarding dropout distribution due to withdrawals or non-bleeding events leading to the early termination of treatment for a patient, we plan to monitor "information time" and stop recruitment based on the observation of the required number of events or on reaching the maximal recruitment duration, as stated above. Based on a dropout rate of approximately 30%, incorporating early withdrawal, we plan to randomize approximately 108 patients

6 Randomization and Blinding

Eligible patients were allocated in a centrally randomized fashion (1:1 ratio) to receive either apixaban or phenprocoumon. To ensure the equal distribution of prognostic factors in the two treatment arms, patients were centrally stratified according to the following parameters:

- Previous thromboembolism including any type of ischemic stroke as long as more than 3 months before Baseline.
- Anticoagulation naïve patients.

At least 50% of the subjects should be anticoagulation-naïve (= with a new indication for an oral anticoagulation). To ensure a homogenously distribution of anticoagulation naïve subjects in both treatment arms, this feature was centrally coordinated during the randomization process.

The study is open-label.

7 Treatment of missing values and outliers

7.1 Missing values

Missing value will not be imputed.

7.2 Outliers

Outliers will not be detected or analyzed in a specific manner.

8 Subgroup analyses

Not prespecified.

9 Stopping rules

Stopping rules are not applicable within the scope of this SAP.

10 Summary of changes to the protocol

This is the first version of this document.

11 Software

Analysis is performed using SAS version 9.4 or later.

12 References

Chan, K. E., Edelman, E. R., Wenger, J. B., Thadhani, R. I., & Maddux, F. W. (2015). Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation, 131(11), 972-979. doi:10.1161/CIRCULATIONAHA.114.014113

Connolly, S. J., Eikelboom, J., Joyner, C., Diener, H. C., Hart, R., Golitsyn, S., Yusuf, S. (2011). Apixaban in patients with atrial fibrillation. N Engl J Med, 364(9), 806-817. doi:10.1056/NEJMoa1007432

Lakatos, E. (1988). Sample sizes based on the log-rank statistic in complex clinical trials. Biometrics, 44(1), 229-241.

Prentice, R. L., Williams, B. J., & Peterson, A. V. (1981). On the regression analysis of multivariate failure time data. Biometrika, 68 (2), 373-379.

13 Appendix

13.1 Reference ranges of laboratory parameters

Does not apply.

13.2 Tables to be created (examples/templates)

Table x. Descriptive statistics

Parameter	Apixaban (N=xxx)	Phenprocoumon (N=xxx)
Age [years], mean (SD)		
Sex, n(%)		
Ethnicity, n(%)		
Height [cm], mean(SD)		
Weight [kg], mean (SD)		
...	...	...

Table x. Descriptive statistics on protocol violations

Protocol violation	Apixaban (N=xxx)	Phenprocoumon (N=xxx)
IN-1		
IN-2		
...		
EX-1		
EX-2		
...	...	...
...		

Violations, which did not occur, will not be listed.

Table x. Result of the primary safety analysis.

Study arm	Kaplan-Meier estimate at 1 year	Median Kaplan-Meier estimate	Hazard ratio (95%CI)	$p_{non\text{-}inf}$	$p_{superiority}$
Treated Population/Safety population[a]					
Apixaban	xx.xx%	xx months	x.xx (x.xx; x.xx)	0.xxxx[†]	0.xxxx[‡]
Phenprocoumon	xx.xx%	xx months			
Per protocol population[b]					
Apixaban	xx.xx%	xx months	x.xx (x.xx; x.xx)	0.xxxx[†]	0.xxxx[d]
Phenprocoumon	xx.xx%	xx months			
Full analysis set[c]					
Apixaban	xx.xx%	xx months	x.xx (x.xx; x.xx)	0.xxxx[d]	0.xxxx[d]
Phenprocoumon	xx.xx%	xx months			

[a] all randomized patients, at least one dose, ITT, "on-treatment events"
[b] all randomized patients, at least one dose, per-protocol, "on-treatment events"
[c] all randomized patients, ITT, all events
[†] Statistical significant non-inferiority will be claimed only if this result is supported by both, the intention-to-treat analysis and the per-protocol analysis
[‡] Primary confirmatory analysis of superiority
[d] Sensitivity analyses

Table x. Result of the primary efficacy analysis.

Study arm	Kaplan-Meier estimate at 1 year	Median Kaplan-Meier estimate	Hazard ratio (95%CI)	$p_{non-inf}$	$p_{superiority}$
Treated Population/Safety population[a]					
Apixaban	xx.xx%	xx months	x.xx (x.xx; x.xx)	0.xxxx[†]	0.xxxx[‡]
Phenprocoumon	xx.xx%	xx months			
Per protocol population[b]					
Apixaban	xx.xx%	xx months	x.xx (x.xx; x.xx)	0.xxxx[†]	0.xxxx[d]
Phenprocoumon	xx.xx%	xx months			
Full analysis set[c]					
Apixaban	xx.xx%	xx months	x.xx (x.xx; x.xx)	0.xxxx[d]	0.xxxx[d]
Phenprocoumon	xx.xx%	xx months			

[a] all randomized patients, at least one dose, ITT, "on-treatment events"
[b] all randomized patients, at least one dose, per-protocol, "on-treatment events"
[c] all randomized patients, ITT, all events
[†] Statistical noticeable non-inferiority will be claimed only if this result is supported by both, the intention-to-treat analysis and the per-protocol analysis
[‡] Analysis of superiority of the primary efficacy endpoint
[d] Sensitivity analyses

Table x. Cross table for binary outcome.

Group, N(%)	Not present (0)	Present (1)	Totals
Apixaban	Xx (Xx%)	Xx (xx%)	Xx (xx%)
Phenprocoumon	Xx (xx%)	Xx (xx%)	Xx (Xx%)
Totals	Xx	Xx	Xx (100%)

Percentages are within-group.

13.3 Lists of data to be created

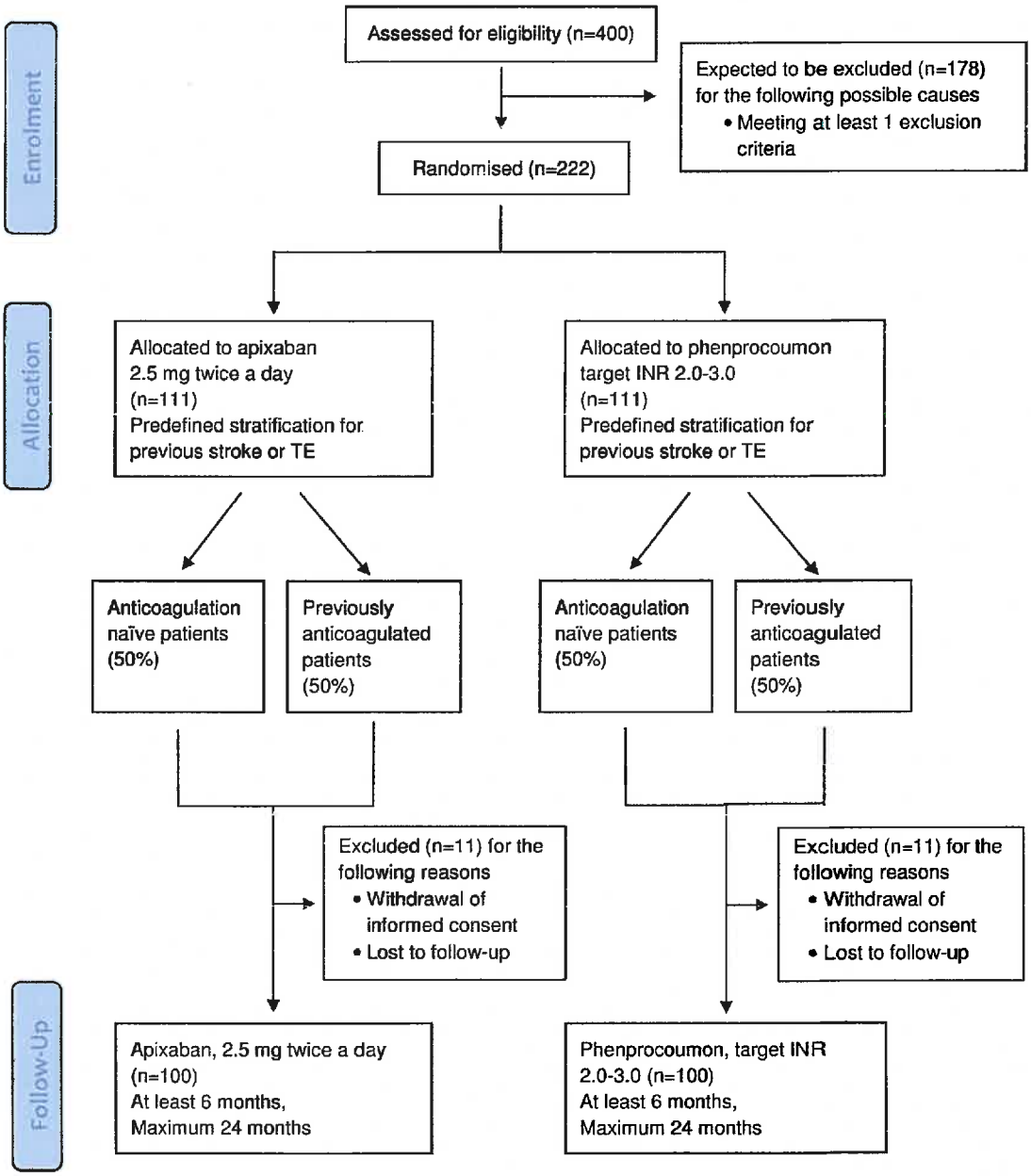
All of the following listings will provide the patient identifier, center, randomized group and the respective information of the specific listing.

13.3.1 Discontinued patients
13.3.2 Protocol deviations
13.3.3 Patients excluded from the efficacy analysis
13.3.4 Demographic data
13.3.5 Concomitant medication (CONMED)
13.3.6 Concomitant diseases (CONDIS)
13.3.7 Compliance and/or Drug Concentration Data (if available)
13.3.8 Individual Primary and Secondary Outcome data
13.3.9 Adverse event listings (per patient)

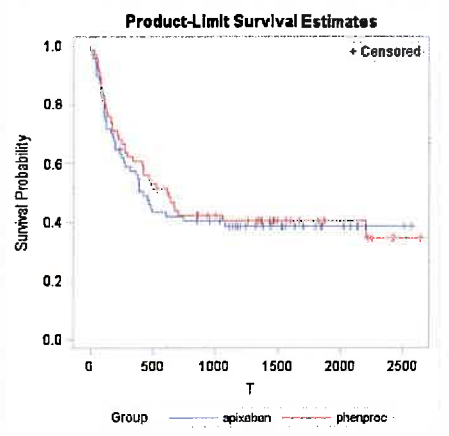
13.4 Graphics to be created (examples)

13.4.1 CONSORT patient flow chart (according to Reinecke et al, BMJ Open 2018)

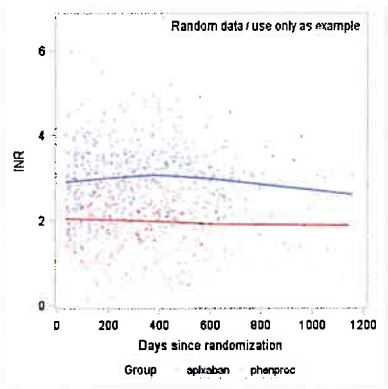
Note: This template contains the initially planned recruitment numbers. In the statistical report these will be replaced by the actual recruitment numbers. Numbers of patients who "received at least one dose of study drug" will be reported in the allocation boxes.



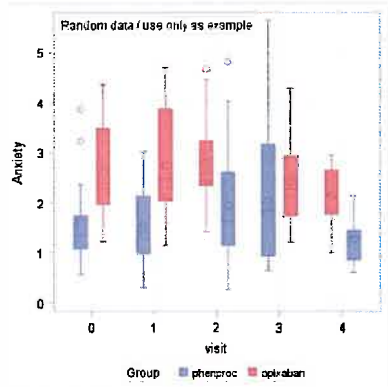
13.4.2 Kaplan-Meier plots for time to event outcomes



13.4.3 Time courses of regularly measured laboratory values (example)



13.4.4 Time course of continuous outcomes at discrete time points (example)



13.4.5 Classification of protocol violation

According to study protocol major protocol violations are defined as any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB- or Ethics Committee-approved protocol that may affect

1. the participant's rights, safety or well-being, or
2. the completeness, accuracy and reliability of the study data.

Patients with major protocol violations will be excluded from the per protocol analysis but included in the ITT analysis.

Study specific definition and classification of protocol violations are described in the following and have been agreed on by the Steering Committee.

Protocol violations that may have been documented within the study data and are not classified one of the described categories have to be classified by the Steering Committee into either one of the existing categories or, if not possible, into a new category. Furthermore, for these new protocol violations, the decision if the new violation represents a major violation (i.e. the patient has to be excluded from the per protocol set) has to be made.

Violation related to inclusion criteria

As a matter of principle, any violation of inclusion criteria is a major protocol violation.

The randomization tool QCTMS IRT does not allow randomisation of a patient not fulfilling all inclusion criteria. Thus, protocol violations related to inclusion criteria – if any – have been detected by the CRA during source data verification after randomisation, only, and documented retrospectively in the eCRF.

Violation	Description	Major (yes/no)	Comment
IN-01	No End-stage kidney disease (ESKD) documented: Hemodialysis treatment less than 3 times per week with a duration less than 3,5 hours per dialysis session.	Yes	
IN-02	AF/ AFL with a clinical indication for anticoagulation not present	Yes	
IN-03	No $CHADS_2$ stroke risk factor present	Yes	
IN-04	Patients with ischemic stroke which are severely handicapped (modified Rankin scale 0 or 1 of	Yes	

	6, i.e. no symptoms or no significant disability and able to carry out all usual activities, despite some symptoms		
IN-05	Patients who had an ischemic stroke that was no more than 3 months ago	Yes	
IN-06	Males and females which are younger than 18 years	Yes	

Violation related to exclusion criteria

As a matter of principle, any violation of exclusion criteria is a major protocol violation. Exemptions may be defined with regard to time-related criteria (e.g. extended time interval). QCTMS IRT does not allow randomisation of a patient with exclusion criteria present. Thus, protocol violations related to exclusion criteria – if any – have been detected by the CRA during source data verification after randomisation, only, and documented retrospectively in the eCRF. Any situation described as exclusion criteria, occurring only after randomisation is not considered protocol violation related to exclusion criteria.

Violation	Description	Major (yes/no)	Comment
EX-1	Documented AF or AFL due to reversible causes (e.g., thyrotoxicosis, pericarditis	Yes	
EX-2	Documented new onset of hemodialysis within the last 3 months	Yes	
EX-3	Documented clinically significant (moderate or severe) aortic and mitral stenosis	Yes	
EX-3	Conditions other than AF or AFL that require chronic anticoagulation (e.g., a prosthetic mechanical heart valve)	Yes	
EX-4	Documented active infective endocarditis	Yes	
EX-5	Any planned interventional or surgical AF or AFL ablation procedure	Yes	
EX-6	Documented active bleeding	Yes	
EX-7	Documented serious bleeding event in the previous 6 months before screening	Yes	
EX-8	Documented inadequately controlled (HbA1c levels >8.5%) or untreated diabetes	Yes	

Violation	Description	Major (yes/no)	Comment
EX-9	Documented history of malignant neoplasms at high risk of current bleeding (see summary of product characteristics (SmPC) of study drugs	Yes	
EX-10	Documented indication for treatment with NSAIDs (see SmPC of study drugs)	Yes	
EX-11	Documented Antiphospholipid Syndrome requiring anticoagulation	Yes	
EX-12	Documented impaired liver function e.g., caused by active infection with HIV, HBV or HCV, hepatitis or other liver damage (No limits for ALT and AST values are defined in this study protocol, although mentioned in the SmPC because they are frequently elevated in dialysis patients. In case of clinically relevant increase of ALT or AST level, patient's eligibility is to be decided by the responsible investigator)	Yes	
EX-13	Documented valvular heart disease requiring surgery	Yes	
EX-14	Patients with 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	Yes	
EX-15	Documented hemorrhagic tendencies or blood dyscrasias	Yes	
EX-16	Patients with a current alcohol or drug abuse	Yes	
EX-17	Patients with a life expectancy of less than 1 year	Yes	
EX-18	Patients with an indication for dual platelet inhibition at baseline	Yes	
EX-19	Pregnant or lactating women	Yes	
EX-20	Paticipation in another clinical trial, either 30 days prior randomization or ongoing.	Yes	
EX-21	Prisoners or subjects who are involuntarily incarcerated	Yes	
EX-22	Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness	Yes	

Violation	Description	Major (yes/no)	Comment
EX-23	Employee of the study site or of the Sponsor's company	Yes	
EX-24	Any active infection or symptoms suggestive of COVID-19 infection	Yes	

Violation related to study therapy

Medications or therapies listed below are prohibited at baseline (first study drug dose). If subject requires any of the prohibited therapies at baseline, subject should not be included in this trial. In addition, the use of the following medications in a patient who is already be included in the trial is prohibited and must lead to study discontinuation.

Violation	Description	Major (yes/no)	Comment
THERAPY-01	Intake of strong inhibitors of both CYP3A4 and P-glycoprotein (e.g., azole antifungals [itraconazole, voriconazole, posaconazole and ketoconazole], naproxene 500 mg or more, and protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir])	No	
THERAPY-02	Intake of platelet inhibitors, such as prasugrel, ticagrelor, clopidogrel	No	
THERAPY-03	Daily intake of NSAIDs or COX2 inhibitors	No	
THERAPY-04	Intake of other antithrombotic agents (e.g., direct thrombin inhibitors, fondaparinux) GP IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban)	No	
THERAPY-05	Planned kidney transplantation scheduled in the next 3 days	No	

Violation related to study drug

Violation	Description	Major (yes/no)	Comment
DRUG-01	Any kind of scheduled surgery or intervention which excludes a resumption of study therapy within 3 weeks afterwards	No	
DRUG-02	Dosis modification: subjects who took more than daily dosis (2.5 mg, BID) of apixaban during study course	No	
DRUG-03	Dosis modification: subjects who took less than dialys dosis (2.5 mg, BID) of apixaban during study course over a time period of more than 3 weeks	No	
DRUG-04	Dosis modification: subjects who received more than the given standard of care of phenprocoumon (INR 2.0-3.0) dosis during study course	No	
DRUG-05	Dosis modification: subjects who received less than the given standard of care dosis of phenprocoumon (INR 2.0-3.0) 3 weeks or longer	No	
DRUG-06	Subjects who interrupted study drug for more than 3 weeks and resumed study drug afterwards	No	
DRUG-07	Subjects who took apixaban less than 24 hours before procedures with a low risk of bleeding	No	
DRUG-08	Subjects who took apixaban less than 48 hours before procedures with a high risk of bleeding	No	
DRUG-09	Subjects who switched from phenprocoumon to apixaban treatment without INR evaluation (<2,0) previously	No	
DRUG-10	Subjects who were not compliant with the intake of their study drug	No	

DRUG-11	Study drug which was not administered every 3 month	No	
DRUG-12	Used study drug which was not returned by subject	No	

Violation related to assigning subjects to a treatment group

Violation	Description	Major (yes/no)	Comment
GROUP-01	Subjects who were wrongly allocated to either anticoagulation naïve or anticoagulation treated treatment group	Yes	
GROUP-02	Subjects who were wrongly allocated to either the existence of thromboembolism events or not	yes	

Violation related to Hemodialysis

Violation	Description	Major (yes/no)	Comment
DIA-01	Duration of a hemodialysis session was less than 3.5 hours	No	
DIA-02	Number of hemodialysis sessions were less than 3 times a week for one subject	No	

Violation related to study procedures

Violation	Description	Major (yes/no)	Comment
PROC-01	Serum pregnancy test was not performed or >24-48 hours prior to Baseline visit	No	
PROC-02	Monthly visits, EoS and EoT which were not performed within 28 days and a time window of +/ - 2 days	No	
PROC-03	AF/ AFL which were not documented on two separate ECGs prior randomization	No	

Violation	Description	Major (yes/no)	Comment
PROC-04	AF/ AFL which were not confirmed by external physician prior randomization	No	
PROC-05	Laboratory results which were evaluated >14 days prior screening, baseline, monthly visit and EoT	No	
PROC-06	Quality of life: EQ-5D evaluation was not performed every 6 month	No	
PROC-07	Samples for pharmacokinetic analysis which were taken prior 30 treatment period for subjects allocated to the apixaban group	No	
PROC-08	Monthly visit was not performed	No	
PROC-09	End of treatment visit was not performed	No	
PROC-10	End of study visit was not performed	No	
PROC-11	NYHA classification was not performed on screening/ baseline visit	No	
PROC-12	$CHADS_2$ & CHA_2DS_2-VASc Score was not evaluated on screening/ baseline visit	No	
PROC-13	Vital signs were not determined on screening/ baseline visit	No	
PROC-14	12-lead ECG was not performed on screening/ baseline visit	No	
PROC-15	12-lead ECG was not performed on EoT visit	No	
PROC-16	INR evaluation was not performed on screening, baseline for subjects who were treated with phenprocoumon prior randomization	No	

Violation	Description	Major (yes/no)	Comment
PROC-17	INR evaluation was not performed on monthly visits and EoT for subjects which are allocated to phenprocoumon group	No	
PROC-18	Documentation of key data of hemodialysis session is not performed on screening, baseline, monthly visit and EoT	No	
PROC-19	Study drug which was not administered after randomization	No	
PROC-20	Study drug which was not administered on a quarterly basis on monthly visits	No	
PROC-21	Study drug was not checked on a quarterly basis after return from subject	No	
PROC-22	Laboratory evaluation was not performed on screening/ baseline visit	No	
PROC-23	Laboratory evaluation was not performed on monthly visit	No	
PROC-24	Laboratory evaluation was not performed on EoT visit	No	
PROC-25	Laboratory evaluation was not performed on EoS visit	No	
PROC-26	Evaluation of bleeding events was not performed on baseline visit	No	
PROC-27	Evaluation of bleeding events was not performed on monthly visit	No	
PROC-28	Evaluation of bleeding events was not performed on EoT visit	No	
PROC-29	Evaluation of bleeding events was not performed on EoS visit	No	

Violation	Description	Major (yes/no)	Comment
PROC-30	Evaluation of thromboembolic events was not performed on baseline visit	No	
PROC-31	Evaluation of thromboembolic events was not performed on monthly visit	No	
PROC-32	Evaluation of thromboembolic events was not performed on EoT visit	No	
PROC-33	Evaluation of thromboembolic events was not performed on EoS visit	No	
PROC-34	Evaluation of events of special interest was not performed on baseline visit	No	
PROC-35	Evaluation of events of special interest was not performed on monthly visit	No	
PROC-36	Evaluation of events of special interest was not performed on EoT visit	No	
PROC-37	Evaluation of events of special interest was not performed on EoS visit	No	
PROC-38	Documentation of hemodialysis parameters was not performed on screening/ baseline visit	No	
PROC-39	Documentation of hemodialysis parameters was not performed on monthly visit	No	
PROC-40	Documentation of hemodialysis parameters was not performed on EoT visit	No	