Statistical Analysis Plan for
RENAL-AF

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RENal hemodialysis participants ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF) Randomized Clinical Trial

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ARB	Angiotensin II receptor blocker
AE	Adverse event
AF	Atrial fibrillation
β-hCG	Beta-human chorionic gonadotropin
BID	Bis in Die (i.e. twice a day)
BMI	Body mass index
BMS	Bristol-Myers Squibb
CBC	Complete blood count
CEC	Clinical events classification
CI	Confidence interval
CSR	Clinical study report
DBP	Diastolic blood pressure
DCRI	Duke clinical research institute
DMC	Data monitoring committee
eCRF	Electronic case report form
ESRD	End-stage renal disease
HR	Hazard ratio
INR	International normalized ratio
ISTH	International society of thrombosis and haemostasis
ITT	Intent-to-treat
KM	Kaplan-Meier
mITT	Modified intention to treat
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
NOAC	Non-vitamin K antagonist oral anticoagulants

NVAF	Non-valvular atrial fibrillation
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PROBE	Prospective, randomized, open-label, blinded end-point
PI	Principal investigator
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	System organ class
TBD	To be determined
TESAE	Treatment emergent serious adverse experiences
TIA	Transient ischemic attack
TTR	Time in therapeutic range
VKA	Vitamin K antagonists

1.0 Introduction

RENAL-AF is a prospective, randomized, open-label, blinded end-point evaluation trial (PROBE). The protocol states that a total of approximately 230 patients (randomized 1:1 in the apixaban and warfarin arms) will be enrolled at approximately 65 sites across the Unites States; however, due to slow enrollment, the trial was stopped early and a total of 155 participants were randomized at 42 sites within the United States. Due to the trial terminating early, duration of treatment will vary depending on when the participant was randomized. The plan at the time of the writing of this SAP is that all treatment will end within a week of July 5, 2019. Therefore, duration of treatment will be a maximum of 15 months, and the target is a mean follow-up of approximately 12 months with the last patient enrolled into the trial having a 6 months of follow-up. The study will assess the impact of apixaban compared to warfarin on the effect of major or clinically relevant non-major bleeding in participants with end-stage renal disease (ESRD) on hemodialysis with atrial fibrillation (AF), meaning atrial fibrillation without moderate or severe mitral stenosis. The reader of this Statistical Analysis Plan (SAP) is also encouraged to read the final clinical trial protocol (BMS Protocol CV185-450, Version 14 dated 12 September 2018) which provides detail on the conduct of the study, the operational aspects of clinical assessments and the timings of individual participant assessments. The reader is also encouraged to read the Clinical Endpoints Committee Charter (Version 4.0, Dated 07Feb2019) which outline the definitions of those endpoints that will be adjudicated.

This SAP contains definitions of analysis populations, derived variables and details on the statistical methods for the analyses and summaries of study data that are to be performed to help support the completion of the final statistical report for the RENAL-AF trial. Specifications of tables, figures, and data listings are contained in a separate document however, an initial table of contents can be found in Appendix II of this document.

A Data Monitoring Committee (DMC) will monitor this study based on a separate DMC Charter. A separate DMC SAP will be provided for monitoring safety of the participants by the DMC.

Outcomes that are adjudicated by a blinded clinical events classification (CEC) committee, the process for which is governed by CEC charter referenced in the protocol, will be referred to as "adjudicated" events in the SAP. The term "outcome" is used throughout this document as synonymous with the term "endpoint" used in the clinical trial protocol. The following outcomes are adjudicated by the blinded CEC committee in RENAL-AF: Bleeding (ISTH major, clinically relevant non-major, or minor), stroke (hemorrhagic, ischemic, or undetermined), transient ischemic attack (TIA), systemic embolism, and death (cardiovascular, non-cardiovascular, or undetermined). CEC data takes precedence over investigator data when both are available.

1.1. Study Objectives

Primary Objective

To assess the safety of apixaban versus warfarin regarding International Society of Thrombosis and Haemostasis (ISTH) major bleeding or clinically relevant non-major bleeding events in participants with NVAF and ESRD on hemodialysis.

Secondary Objectives

The secondary objectives are to:

1. Evaluate stroke and systemic embolism event rates with warfarin and apixaban in patients with NVAF and ESRD on hemodialysis.
2. Evaluate mortality rates with warfarin and apixaban in patients with NVAF and ESRD on hemodialysis.
3. Evaluate persistence (meaning the duration of time from initiation to discontinuation of therapy) of and adherence (meaning the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen) to warfarin and apixaban in patients with NVAF and ESRD on hemodialysis.
4. Evaluate the pharmacokinetics and pharmacodynamics of apixaban in ESRD NVAF patients on hemodialysis.

Other Objectives

Other objectives will include analysis of outcomes and treatment effect according to levels of cardiovascular biomarkers at baseline.

1.2. Study Design

The study is a prospective, randomized, open-label, blinded end-point evaluation trial. Participants with NVAF, ESRD, and a CHA2DS2-VASc (defined in Appendix 1 of CSP) of 2 or more will be randomized in a 1:1 ratio to apixaban or warfarin, stratified by investigative site and prior warfarin status (experienced versus naïve). Participants are considered warfarin naïve if they have never previously been on warfarin or if they have started warfarin within the last 30 days. Those participants randomized to apixaban who are >= 80 years old or dry body weight/hemodialysis target body weight ≤ 60 kg should receive 2.5 mg apixaban BID at any point during the trial at which they have met one of these characteristics; otherwise,

participants will receive 5 mg BID. If a study participant is taking apixaban 5 mg BID and is experiencing minor bleeding, the site investigator will be able to contact the study leadership to discuss temporary dose adjustments to 2.5 mg BID. Participants taking strong dual inhibitors of CYP3A4/P-gp (examples include ketoconazole, itraconazole, ritonavir, and clarithromycin) will be asked by the site investigator to reduce their dose of apixaban to 2.5mg twice daily based on the United States package insert.. Site investigators should consider dose reduction to 2.5 mg twice daily for participants taking dual inhibitors of CYP3A4/P-gp that are not strong inhibitors. If participants are already taking the 2.5-mg dose apixaban, the site investigator should avoid co-administration of these medications.

For those participants randomized to warfarin, the participant's prescribing provider (any provider caring for the patient with primary responsibility for warfarin management, including providers from a warfarin clinic or providers other than the study investigator) will select the warfarin dose. The goal INR will be 2.0-3.0, and the participant's provider should monitor the INR level and adjust the dose of warfarin accordingly. The frequency of INR measurements are at the discretion of the prescribing provider; however, it is recommended that the INR values are drawn at least once a month and more frequently at the time of warfarin initiation or around INR values out of the therapeutic range.

The primary outcome is ISTH major bleeding and clinically relevant non-major bleeding, adjudicated by a central blinded clinical events adjudication process.

Unless the participant specifically wrote a letter stating that they refused to allow any further information or data capture, including retrospectively through medical records, every effort will be made to obtain as much information as possible through the end of study/month 15 visit.

Samples will be obtained from a subset of patients randomized to apixaban, under versions 13 or earlier of the protocol, to characterize apixaban PK/PD levels in hemodialysis patients with atrial fibrillation. No patients enrolled under version 14 of the protocol will have PK/PD samples collected. On day 1, blood samples will be collected for PK analysis on all participants randomized to apixaban. A subset of no more than 50 participants randomized to apixaban will have additional PK/PD samples collected at Day 3 visit and Month 1 visit. Samples will be drawn pre-hemodialysis and post-hemodialysis. The PK/PD analysis is not within the scope of this SAP.

Selected biomarkers will be collected from a subset of patients at the day 1 visit, enrolled using versions 13 or earlier of the protocol, and stored for later analysis. If the biomarker sample is not able to be drawn at the Day 1 visit, it can be drawn at a subsequent visit. The biomarker analysis is not within the scope of this SAP.

1.3. Sample Size and Power

Due to a lower recruitment rate than anticipated in the early stage in the trial, the sample size was reduced from 760 (protocol version 13, section 12.1) to 230 patients providing a lack of statistical power thus making the analysis outlined in this SAP exploratory. The actual sample size, due to early termination of the trial due to slow enrollment, was 155.

Additional details can be found in the clinical study protocol (CSP).

1.4. Schedule of Major Assessments and Data Sources

Outcomes, serious adverse event and adverse events of special interest data are collected at day1, day 3 (day 3, 4, 5, or 6) and monthly through month 3 and then quarterly through end of study/month 15 visit. SAEs that occur any time after consent, including between consent and randomization, must be reported on the eCRF. All laboratory assessments will be performed according to the standard of care schedule for the patient. See Appendix I for a full schedule of procedures. All data for the final statistical report will be obtained from the IBM Clinical Development data base in which the eCRF was developed.

2.0 Analysis Populations

Those participants for whom no written informed consent was obtained will be excluded from all analyses.

2.1 Intent-to-treat (ITT) Population

The ITT population consists of all unique randomized participants regardless of their compliance with the study protocol. Participants are analyzed in the treatment group to which they were randomized. Unless otherwise noted, the ITT population will be utilized for the analysis outlined in this SAP.

2.3 Modified Intention to Treat (mITT) and Safety Populations

The "Safety population" is synonymous with the "Modified Intention to Treat (mITT) population" as defined in the CSP and may be utilized interchangeably throughout the final study SAP. The Safety population will consist of all randomized participants who received at least 1 dose of study medication. This population can be analyzed by randomized treatment or actual treatment received. "Actual treatment received" is defined as the initial treatment received.

Unless otherwise noted, the mITT population will be analyzed by randomized treatment.

3.0 BACKGROUND CHARACTERISTICS

3.1 Disposition of Participants

Disposition data will be summarized for all randomized participants by treatment group and overall.

Disposition data will include:

- Inclusion in each of the two study populations
- Participants completing study alive
- Participants who died during the study.
- Participants who were lost to follow up
- Participants who withdrew consent for further study participation
- Participants who were lost to follow-up for whom the primary outcome was evaluated.
- Participants who permanently discontinued assigned study drug and reason for permanent discontinuation.

3.2 Demographic and Baseline Characteristics

The demographic, baseline clinical and anthropometric characteristics collected in the study will be summarized by treatment and overall for ITT population.

Key demographic and baseline variables to be summarized include but are not limited to the following: age, sex, race/ethnicity, vintage (time since initiation of dialysis), height, dry body weight, Quételet's (body mass) index (BMI), vital signs, prior warfarin status (experienced versus naïve) and the following baseline medications: ACE inhibitor/ARB, amiodarone, beta-blocker, aspirin, clopidogrel, digoxin, calcium channel blocker, statin, and non- steroidal anti-inflammatory agent.

3.3 Medical History

Participant medical history, as collected on the eCRF, will be summarized by treatment and overall within ITT population. This summary will include, but not limited to, the following: prior warfarin status (experienced versus naïve), prior NOAC (experienced vs naïve), MI, clinically relevant or spontaneous bleeding, fall within previous year, type of atrial fibrillation, stroke, TIA, chronic heart failure, most recent left ventricular ejection fraction (normal, mild dysfunction, moderate dysfunction, or severe dysfunction), diabetes, chronic hypertension, and CHA2DS2-VASc score.

Renal and dialysis history will also be summarized by treatment and overall within ITT population.

4.0 METHODS OF ANALYSES

4.1 General Principles

All analyses included in this SAP will be performed using SAS v9.4 or higher (SAS Institute Inc., Cary, NC).

A safety follow-up will be performed 30 days after permanent treatment discontinuation, at which time, indicators as to whether or not events occurred as well as AE/SAEs are collected. If this safety follow-up occurs after the end of study/Month 15 visit, the information collected will not be used in the analysis outlined in this SAP but may be displayed as listings when indicated.

Descriptive statistics for categorical variables will be presented using counts and percentages per treatment group and overall. Percentages will be displayed through the first decimal place. Percentage

will be calculated based on number of participants with non-missing values for the variable. In the event that the summary displayed is for a subcategory ("child") of a main category ("parent"), the denominator for the "child" will be based on the non-missing observations for the "parent" (e.g., Anti-platelet (Y/N) is a 'parent' question and type of anti-platelet (e.g. aspirin) is a 'child' question. The denominator for aspirin will be number of participants who answered yes/no to the anti-platelet question).

Descriptive statistics for continuous variables will include the following: the number of participants, mean, standard deviation, median, 25thand 75th quartiles, minimum and maximum as appropriate and all summary data will be displayed through the 1st decimal place. In the event no meaningful information is available through the first decimal place (e.g., 0.01), the statistician in consultation with the PI or designee will determine the most relevant number of decimals to display. Summaries of continuous characteristics will be based on non-missing observations.

Unless otherwise specified in this document, relative study day is defined as the (assessment date of a measurement– randomization date) if assessment date is prior to randomization date and will be defined as (assessment date of measurement – randomization date) + 1 if assessment date is on/after date of randomization. Using this derivation, the day of randomization will be considered study day 1.

Data displayed by visit will utilize an "analysis visit" which will be derived based on windowing around the study day as agreed upon by the study PI or designee.

A baseline value is defined as the most recent assessment taken prior to/on day of randomization. When there is a missing assessment, it will not be imputed, thus, participants are excluded from any changes from baseline analysis for which they have a missing baseline value.

Due to the anticipated small number of events, stratification by site would produce sparse data and therefore, the baseline hazard within each stratum would be poorly estimated with such models. For this reason, sites will be pooled together and all Cox proportional hazards models will by adjusted for prior warfarin status (experienced vs naïve) only.

Unless otherwise specified, all Kaplan-Meier rates and Kaplan-Meier curves will be performed without adjustment of strata or covariates.

4.2 Time to Event Analyses

"On-treatment" time to event will be defined as ([event date – study drug initiation date] +1 where event occurs prior to/at 2 days after permanent study drug discontinuation and as [appropriate censoring date based on analytic population – study drug initiation date] +1 where event does not occur or occurs greater 2 days after permanent study drug discontinuation.

For all other time to event analyses, unless otherwise specified in this document, time to event will be defined as ([event date – randomization date] +1 where event occurs and as [appropriate censoring date based on analytic population – randomization date] +1 where event does not occur)

Treatment differences will be evaluated using a Cox proportional hazards model that includes treatment as an indicator variable and adjusted for prior warfarin status (experienced vs naïve), unless specified otherwise. A subject will be classified as warfarin naïve if they have not previously received warfarin or another VKA or have initiated warfarin or another VKA within 30 days prior to randomization. Otherwise the subject will be classified as warfarin experienced. The data entry system will derive the appropriate stratum from information entered into the eCRF. The Breslow method [3] will be used for handling ties. P-value and confidence intervals for the HR will be based on the Wald statistic. In addition, the summary tables of these analyses will include the number (%) of participants with event, Kaplan-Meier rates as well as the 95% confidence interval by treatment monthly from randomization through the maximum follow-up. Competing risks are not taken into account for any of the Cox proportional hazards models. Competing risks may be taken into account as a sensitivity analysis if a considerable number of deaths are observed. Kaplan-Meier curves will be produced through maximum follow up available in the study, with number of participants at risk indicated below the plot at specific times.

4.3 Censoring

In this study we expect missing outcome data to be infrequent and every effort will be made to collect all information regarding the primary outcomes at the end of study/month 15 visit, even in those who have discontinued the study treatment. Information at the end of study/month 15 visit can be obtained from a source other than direct contact with the participant (e.g., medical record, family member, etc.). In the case of a medical record review, the end of study/month 15 date of assessment will be the date of most recent medical record reviewed.

In the primary and secondary time-to-event analyses in the ITT population, participants will be censored at the earliest of 1) maximum of (date of last contact where all elements of the outcome of interest were assessed (excluding the safety follow-up visit if it occurs after the end of study/month 15 visit), 2) end of study/month

15 date of assessment where all elements of the outcome of interest were assessed) and 3) death date (when death is not part of the outcome). Participants without any assessment of the outcome of interest will be censored at randomization.

In time-to-event analyses in the "mITT" population, participants who have not had the event of interest will be censored following same rules as detailed for the ITT population.

"On-treatment" time-to-event analyses will also be performed as sensitivity analyses. The censoring date for these analyses will be the earliest of 1) maximum of (date of last contact where all elements of the outcome of interest were assessed (excluding the safety follow-up visit if it occurs after the end of study/month 15 visit), 2) month 15 date of assessment where all elements of the outcome of interest were assessed), 3) death date (when death is not part of the outcome), and 4) 2 days after the permanent discontinuation of assigned study drug. Participants without any assessment of the outcome of interest will be censored at study drug initiation.

Unless otherwise specified, sensitivity analysis in the mITT population, if performed, will utilize the "on-treatment" time to event/censoring described above.

4.4 Handling of Missing Data

For the assessment of primary hypothesis, missing data relating to the indicator for the confirmed primary composite of major bleeding or clinically relevant non-major bleeding events and its components will not be imputed.

The CEC will make every attempt to provide a complete date for the confirmed primary composite of major bleeding or clinically relevant non-major bleeding events; however, in the instance when the dates are partially missing, imputation will be performed as follows:

Any partially missing date for a confirmed primary composite of major bleeding or clinically relevant non-major bleeding events, secondary outcomes (section 5.2), adverse events of special interest (section 5.3), other clinical events of special interest (section 5.4), study drug initiation and termination dates at the time of database lock will be imputed as follows:

- If the day is missing, then the 15th of the month will be used.
- If missing day and month, then June 15 of provided year will be used.
- If year is missing, no imputation will be performed.

The aforementioned dates specified above will never be completely missing as a year will always be required.

If the imputed portion of the date causes the date to be nonsensical (e.g. Prior to randomization or > last known alive date, etc.), the imputed date will be set to the appropriate boundary (e.g. randomization or last known alive, respectively). Details can be found in the analysis data set specifications.

If additional partially missing dates are required for analysis, they will be imputed as described above.

No other imputations for missing data will be performed.

4.5 Assessment of Model Assumptions

The validity of the proportional hazards assumption made in the primary analysis will be examined using a standard graphical methods such as Schoenfeld residual plots; if the assumption holds, the survival curves should be approximately parallel to each other.

An additional analytical method that includes the supremum test [1] as implemented by using the ASSESS statement in PROC PHREG in SAS version 9.4 may be utilized. A p-value of < 0.05 indicates violation of the proportional hazards assumption.

If there is evidence of non-proportionality, a time dependent covariate will be included in the model to account for this.

5.0 PRIMARY SAFETY AND ALL EFFICACY

Definitions for major bleeding, clinically relevant non-major bleeding, stroke, systemic embolism, transient ischemic attack, and cause of death are defined in the CEC charter. Unless specified otherwise, a 2-sided p-value of < 0.05 will be considered statistically significant.

5.1 Primary Outcome

The primary outcome is defined as the time from randomization to the onset of first adjudicated event in the composite of major bleeding/clinically relevant non-major bleeding in the ITT population or censoring date (as defined in section 4.3) If the event did not occur. Major bleeding includes hemorrhagic stroke as well as ischemic stroke with hemorrhagic transformation.

In the unlikely event that two or more confirmed outcomes occur on the same day, the following hierarchy will be used to ascribe the primary component of the composite:

- Major bleed
- Clinically relevant non-major bleed

Event rates of the primary outcome for the ITT and mITT populations will be estimated using Cox proportional hazards model and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of the primary outcome/censored date in case of no event.by treatment group . Participants at risk at quarterly time points will be displayed.

5.1.1 Non-inferiority Exploratory Analysis of Primary Outcome

Due to lack of statistical power because of a small sample size, the current analytic plan has been changed from a formal non-inferiority testing followed by superiority testing, as described in draft SAP version 3.5, dated 06DEC2017, to an exploratory analytic plan.

The primary exploratory hypothesis is defined as:

H0: $HR \geq 1.4$ vs. H1: $HR < 1.4$

The above hypothesis will be tested at a 1-sided significance level of 0.025 in the ITT population. A 2-sided 95% confidence interval (CI) for the hazard ratio (apixaban vs. warfarin) will be established as well as the p-value will be provided using the Cox Proportional Hazards model that includes treatment as a covariate and adjusted for prior warfarin status. If the upper limit of the 2-sided 95% CI for the estimated hazard ratio (HR) from the Cox model is below the non-inferiority margin of 1.40 then this will be considered evidence of non- inferiority of apixaban.

The analysis, as described above, will constitute the primary exploratory analyses from which treatment differences will be interpreted.

Additionally, the aforementioned analyses will be performed in the 'mITT' population as a sensitivity analysis.

5.1.2 Key Supportive Analysis for Exploratory Analysis of Non-inferiority of Primary Outcome

As a sensitivity analysis similar to the method described in Section 5.1.1, including Kaplan-Meier curves, will be conducted among mITT populations. The 'on-treatment' time to event (section 4.2) and censoring scheme (section 4.3) will be utilized for this populations. This analysis will compare randomized treatment groups.

5.1.3 Superiority Exploratory Analysis of Primary Outcome

Time from randomization to the onset of first adjudicated primary composite outcome will be analyzed using hazard ratios, 95% confidence intervals and p-values as in Section 5.1.1. If the upper limit of the 2-sided 95% CI is below 1, then this will be considered evidence of superiority of apixaban.

5.1.4 Covariate Adjusted Analysis of Primary Outcome

The primary analysis, excluding Kaplan-Meier curves, will be repeated in the ITT populations after adjusting for the following covariates: CHA2DS2-VASc score and baseline hemoglobin. No missing data imputation will be utilized for the aforementioned covariates as complete data is anticipated.

5.1.5 Subgroup Analysis

Subgroup analyses will be performed for the primary outcome among the ITT population in order to explore whether treatment effects on the risk of experiencing major/clinically non-relevant bleeds are consistent across subgroups.

Pre-specified subgroups are detailed below. For each potential modifier of treatment effect, the interaction of the potential modifier with randomized treatment will be examined using the Cox proportional hazards model adjusted for prior warfarin use. Potential modifiers expressed as continuous or ordinal variables will be treated as such in the Cox model. The corresponding hazard ratios, 95% CIs, and appropriate summary statistics will be provided. Lack of a significant interaction will imply that the differences in treatment HRs across subgroups are within the realm of chance and that the overall response-rates and overall HR are the most appropriate estimates of treatment effect within all subgroups for that factor. It is recognized that testing many subgroups can yield spurious false positive outcomes.

Forest plots will be provided with estimated hazard ratios and 95% CIs; the CIs usually will be much wider and the power to detect a true difference will be low within any one subgroup owing to the smaller number

of participants and events. In addition, when sample sizes for subgroups are small, treatment effects cannot be estimated precisely.

The following subgroups determined by baseline characteristics will be examined:

- Age >= 80 and/or body weight (kg) <=60
- Prior use of warfarin
- Age: a) < 65 yrs. vs >= 65 yrs., b) < 80 yrs. vs >= 80 yrs.
- Sex
- Myocardial infarction
- Peripheral arterial disease
- Type of atrial fibrillation: permanent persistent or paroxysmal
- Prior stroke or TIA
- Diabetes
- Heart failure
- Hypertension
- CHA2DS2-VASc score: 2 vs >=3
- Race: a) White vs African American/Black vs Other and b) African American vs Other,
- Aspirin use within 24 hours prior to randomization
- Amiodarone use within 24 hours prior to randomization
- History of prior clinically relevant spontaneous bleeding
- Hemoglobin
- Time since dialysis initiation
- Time in therapeutic range prior to baseline (for participants previously treated with Warfarin)

5.2 Secondary Outcomes

The secondary outcomes are defined as follows:

- Any bleed (major, clinically relevant non-major, or minor bleed)
- Stroke
  - Ischemic stroke
  - Hemorrhagic stroke
  - Stroke of unknown cause
- Systemic embolism
- All-cause mortality

- Composite of stroke or systemic embolism
- Composite of stroke, systemic embolism, major bleeding, and all-cause mortality

5.2.1 Analysis of Secondary Outcomes

The analysis as described below for the following secondary outcomes will be performed in the ITT population: 1) Any bleed, 2) all-cause mortality, and 3) composite of stroke, systemic embolism, major bleeding, and all-cause mortality:

A hazard ratio, 2-sided 95% confidence interval for the hazard ratio (apixaban vs warfarin), and p-value will be provided using the Cox Proportional Hazards model that includes treatment as the independent variable adjusted for prior warfarin.

Kaplan-Meier event rates as well as the 95% confidence interval by treatment will be displayed quarterly from randomization through maximum follow-up.

Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of the secondary outcome of interest/censored date in case of no event (in months), by treatment group at randomization. Participants at risk at each time point will be displayed.

If the analysis for above cannot be performed due to small event counts, counts and percentages as well as a p-value from a chi-square test or fisher's mid-p test, whichever is appropriate, will be displayed.

- Additionally, the counts and percentages of the CEC adjudicated events from randomization through end of study visit/month 15 in the ITT population will be calculated for the following: stroke, type of stroke, systemic embolism, and composite of stroke or systemic embolism. P-values from a chi-square test or fisher's mid-p test, whichever is appropriate, will be displayed.

It is recognized that results should be interpreted with caution when a relatively small number of events occur.

Partial/missing event dates will be imputed in the same manner as the primary outcome described in section 4.4.

A listing of events that occur after end of study/month 15 will be displayed, if applicable.

5.3 Events of Special Interest

The following events are clinical events of special interest that were investigator reported:

- Thrombosis of fistula, graft, or access catheter
- Thrombosis of extracorporeal dialysis circuit
- Access site bleeding that does not meet the criteria for acute clinically overt bleeding (defined in Section 12.3 of CSP)
- Other clinically overt bleeding that does not meet the criteria for major or clinically relevant non-major bleeding (defined in Section 12.3 of CSP))
- Red blood cell transfusion(s)

The counts and percentages for the ITT population will be calculated for the events of special interest which occurred from randomization through end of study/month 15.

A listing of events that occur after the end of study/month 15 visit will be displayed, if applicable.

5.4 Other Clinical Outcomes of Interest

The other clinical outcomes of interest (investigator reported except for TIA) are as follows:

- Myocardial infarction
- Atrial fibrillation with rapid ventricular response
- Heart failure or fluid overload
- Pulmonary edema
- Transient ischemic attack
- Acute severe hypertension
- Infections (including but not limited to cellulitis, osteomyelitis, and pneumonia)

The counts and raw percentages from randomization through end of study/month 15 in the ITT population will be calculated for the outcomes described above.

A listing of events that occur after end of study/month 15 will be displayed, if applicable.

Outcomes that are expected to occur in patients on hemodialysis as part of the disease process that are not clinically relevant to the trial are not collected or reported thus will not be analyzed: hyperkalemia , hypoglycemia in patients with diabetes, bradycardia, peripheral arterial disease or gangrene, chronic obstructive pulmonary disease, constipation, hypotension, or long bone fracture such as femur fracture.
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6.0 Pharmacokinetics (PK) and Pharmacodynamics (PD) of Apixaban

The PK/PD analysis of Apixaban will be described in a separate analysis plan.

7.0 Safety and Tolerability Analysis

There are no a priori hypotheses to be tested for safety. Safety and tolerability will be assessed within the ITT population.

7.1 Adverse Events (AEs)/Serious Adverse Experiences (SAEs)

All Serious Adverse Events (SAEs) that occur following the subject's written consent through 30 days after permanent study drug discontinuation will be collected.

The original term used by investigators to identify SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent serious adverse experiences (TESAE) are defined as those SAEs that have a start date after the date of first study medication administration. Outcomes defined in section 5 of the SAP (i.e., primary outcomes, secondary outcomes, events of special interest, and other clinical outcomes) are not regarded as SAEs for the safety analysis. Upon summarizing serious adverse events, participants will be counted only once for each preferred term.

A subject level summary by treatment and overall will be displayed for treatment emergent serious adverse events, including the number of SAEs reported after the end of study/month 15 visit.

The number and percentage of participants experiencing the types of AE/SAEs listed below as well as the number of events will be tabulated by system organ class (SOC) and preferred term (PT).

- Treatment emergent SAEs (TESAEs). This will be displayed by SOC and PT
- Treatment emergent AEs that result in discontinuation of study drug

- Treatment emergent SAEs (TESAEs) resulting in a fatal outcome. This will be displayed by SOC and PT

All SAEs, including those collected during a 30-day safety follow-up which occurred after the participant's final study visit, will be listed, indicating the site number, participant ID, assigned treatment group, age, gender, and race, randomization date, treatment start date, apixaban dosage, preferred term, onset date, day of onset relative to randomization, resolution date, duration, date of last study drug dose, day of last study drug dose relative to randomization date, intensity, relationship, action taken and outcome. Additionally, separate listings will also be presented for participants who 1) experienced a fatal SAE and 2) any AEs resulting in study drug discontinuation.

7.2 Laboratory Data

Descriptive statistics will be provided by treatment for hematocrit values at each assessment time point and for changes from baseline.

Laboratory data will be summarized for the ITT population.

7.3 Extent of Study Medication Exposure

Extent of study medication exposure utilizing persistence, adherence, and self-compliance measures will be summarized for the ITT population.

7.3.1 Study Medication Persistence

Persistence is defined as the duration of time from initiation to permanent discontinuation of therapy. Persistence to study medication for the ITT population during the study period will be summarized by treatment and overall. Persistence is calculated as the number of days from the date of first dose of study drug to the date of last dose of study drug, inclusively ((date of last dose of study drug – date of first dose of study drug) + 1). This duration will not be adjusted for any period the participant may have been temporarily off of study drug. Descriptive statistics will be presented by treatment group and overall.

7.3.2 Self-reported Compliance

The answers to two self-reported compliance questions are obtained quarterly and each will be summarized by visit, treatment and overall in the ITT population. The two questions are as follows:

- Out of the past 7 days, did you miss a dose of your blood thinner?
- Over the last 30 days, how often have you taken your blood thinner: less than 20% (5 days or fewer), 20-80% (6 days to 23 days), or greater than 80% (24 days or more) of the time?

7.3.3 Apixaban Adherence

Apixaban adherence will be summarized in the ITT population.
Pill counts and apixaban dispensation will occur quarterly.
Adherence to apixaban will be calculated as follows:

Numerator: # pills taken from randomization to last dose of assigned study drug.
This will be ascertained by taking the number of pills originally in the container when dispensed and subtracting the number of pills remaining in the container at the quarterly visit and summing this value across the quarterly visits.

Denominator: # of pills expected to be taken from randomization to last dose of assigned study drug.
This will be ascertained as follows: 2 pills a day * number of days that the participant was on assigned study drug

The number of days that the participant is on assigned study drug is derived as follows: (date of last dose of assigned study drug – date of first dose of assigned study drug) + 1,

Adherence = (numerator/denominator) * 100

7.3.4 Warfarin Adherence

The time in therapeutic range (TTR) will be determined by the modified Rosendaal method of linear interpolation between each pair of measured INR values [2]. The proportion of time (counted from first INR value recorded on or after dosing on Day 3 until the day of discontinuation of study drug without considering interruptions) in which participants have an INR in the following ranges will be summarized in the ITT population:

- INR < 2.0, 2.0 ≤ INR ≤ 3.0, INR > 3.0

The frequency of participants with INR in the 2.0-3.0 range for ≥ 60%, ≥ 65%, ≥ 70%, ≥ 75%, or ≥ 80% of time will also be summarized in the ITT population.

Only participants who have received study drug every day for the first 3 days from study drug initiation will be included in these time-related summaries. The INR control measure, proportion of time in each INR interval, is calculated using Rosendaal's method which assumes that the INR value between two measurements varies linearly from the first value to the second value

- let INR_i and INR_{i+1} be the two consecutive INR values
- let D_i and D_{i+1} be the dates associated with these two consecutive INR values,

  $[(D_{i+1} - D_i) = k, k>1]$
- assuming the linear increase or decrease between the two consecutive INR measurements, the unit change per day in INR is $m=(INR_{i+1} - INR_i)/ (D_{i+1} - D_i)$
- the estimated INR value for the date after D_i (D_i+1) will be $INR_i + (m*1)$
- Similarly, the estimated INR value for the date (D_i+2) will be $INR_i + (m*2)$, etc.; the estimated INR value on the date immediately prior to D_{i+1} will be $INR_i + (m*(k-1))$.

The estimated INR will be set to missing between D_{i+1} and D_i if $D_{i+1} - D_i > 56$.

Using Rosendaal's method, each participant will have an INR measurement every day, either actual or by estimation through linear interpolation. The proportion of time participants have an INR within an interval is the number of days with INR in the interval divided by the total number of days.

7.4 Medications

Medications taken at/prior to randomization will be summarized by treatment and overall. Indication of medication usage will be retrieved from the screening/randomization visit page.

Medications taken after randomization will be summarized by treatment and overall. Indication of medication usage will be retrieved from the follow-up medication visit page. If a participant took the same medication

more than once post-randomization, the participant will only be counted one time. A participant must have an answer as to whether or not a medication was taken on at least one post-randomization form to be included in the denominator.

Concomitant medications will be summarized in the ITT population.

7.5 Investigator reported events

The following investigator reported events will be summarized by treatment in the ITT population and include the following:

- Any bleed composite (major bleed, clinically relevant non-major bleed, or minor bleed) and components as follows:
  - Major bleed
  - Clinically relevant non-major bleed
  - Minor bleed
- Mortality
- Stroke
- Systemic embolism

Descriptive statistics will be provided for investigator reported events by treatment and overall.

8.0 DMC AND INTERIM ANALYSIS

The data monitoring committee (DMC) will monitor the safety aspects of this study. The DMC is expected to meet at least every 6-months. The DMC charter will provide details on monitoring roles and responsibilities.

While the DMC will review frequencies of bleeding events, no formal interim analysis is planned for this trial so no adjustment for multiple looks at the data is necessary.

9.0 REFERENCES

1. Lin, D. Y., Wei, L. J., and Ying, Z. Checking the Cox Model with Cumulative Sums of Martingale-Based Residuals. Biometrika 1993; 80:557–572.

2. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69(3):236-9.

3. Breslow, N. E. Covariance Analysis of Censored Survival Data. Biometrics 1974;30:89–9

Appendix I: Schedule of Procedures

Procedure	(Screening & Randomization)	Day 1[1]	Day 3[2] (Day 3, 4, 5, or 6)	Month 1 (± 4 days)	Month 2 (± 4 days)	Month 3, 6, 9, 12 (± 4 days)	Month 15 (+ 4 days) or Final Visit
Informed Consent	X						
Eligibility review	X						
Medical History Review	X						
Vital signs[3]	X	X	X	X	X	X	X
Height	X						
Dry body weight or hemodialysis target body weight	X						X
ECG[4]	X						
SAE, AEs of special interest, and bleeding event assessment	X[5]	X	X	X	X	X	X
Con med assessment	X	X	X	X	X	X	X
Pregnancy prevention counseling	X						

Procedure	(Screening & Randomization)	Day 1[1]	Day 3[2] (Day 3, 4, 5, or 6)	Month 1 (± 4 days)	Month 2 (± 4 days)	Month 3, 6, 9, 12 (± 4 days)	Month 15 (+ 4 days) or Final Visit
Randomize in EDC system	X						
Dispense or prescribe and instruct on use of drug	X					X	
Medication Compliance Assessment						X	X
Record start and stop time of hemodialysis session		X	X	X	X	X	X
Record time of apixaban dose		X	X	X			
CBC[6]	X			X	X	X	X
BMP	X						
INR[7]	X			X	X	X	X
Urine or serum β-hCG[8]	X						
Pharmacokinetic Sample[9]		X	X	X			

Procedure	(Screening & Randomization)	Day 1[1]	Day 3[2] (Day 3, 4, 5, or 6)	Month 1 (± 4 days)	Month 2 (± 4 days)	Month 3, 6, 9, 12 (± 4 days)	Month 15 (+ 4 days) or Final Visit
Biomarker Sample[10]		X					

[1] Visit should occur within 3 days of randomization or as soon as the INR value is < 2.0 in the case of patients on warfarin at the time of enrollment, who were randomized to apixaban

[2] Visit may occur on Day 3, 4, 5, or 6 depending on hemodialysis session

[3] Resting blood pressure, pulse, respiratory rate, and temperature

[4] After resting for ≥ 5 minutes, at enrollment or within 30 days of enrollment. May include a single lead rhythm strip such as AliveCor.

[5] SAEs that occur anytime after consent, including between consent and randomization, must be reported

[6] Includes hematocrit, hemoglobin (Hb), platelet count, red blood cell count (RBC), red cell distribution width (RDW). Results from most recent standard of care draw may be used, if results are not > 30 days old.

[7] Includes International Normalized Ration (INR). INR should be performed at least monthly for patients randomized to warfarin, and at screening and randomization for all patients.

[8] If positive, patient is not eligible to participate. If patient is anuric, a serum pregnancy test can be performed.

[9] At Day 1 visit, PK samples are to be collected for all patients randomized to apixaban: at the start of the hemodialysis session and at the end of the hemodialysis session. A sub-set of 50 patients randomized to the apixaban arm will have additional PK samples, and a PD sample, drawn at the Day 3 (between day 3 and day 6) and Month 1 visits. Samples are to be collected at the start of the hemodialysis session, and at the end of the hemodialysis session. This is only for patients enrolled using versions 13 or earlier of the protocol. No samples will be collected for patients enrolled using version 14 of the protocol.

[10] If the biomarker sample is not able to be drawn at the Day 1 visit, it can be drawn at a subsequent visit. This is only for patients enrolled using versions 13 or earlier of the protocol. No samples will be collected for patients enrolled using version 14 of the protocol.

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Additional listings may be created as needed for CSR