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Title page

Factor XI LICA to Reduce Thrombotic Events in End-Stage Renal Disease Patients on Hemodialysis: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Fesomersen

Acronym: RE-THINC ESRD

Bayer study drug	BAY 2976217*		
INN	Fesomersen		
Study purpose:	Safety		
Clinical study phase:	IIb	**Date:**	31 MAY 2022
Study No.:	21170	**Version:**	4.0
Authors:	PPD PPD (Version 1.0) PPD PPD (Version 1.0) PPD (from Version 2.0) PPD (from Version 2.0)		

***** The Drug Substance BAY 2976217 (ION-957943) is the icosasodium salt of a 20-base residue (20-mer) oligonucleotide conjugated at its 5′-end via an aminohexylphosphate linker to a GalNAc THA cluster. For the Drug Product, the label claim of 100 mg BAY 2976217 is defined on a free acid, anhydrous, solvent-free, and sodium acetate-free basis.

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AFib	Atrial fibrillation
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
ASO	Anti-sense oligonucleotide
AV	Arterio-venous
BMI	Body mass index: weight [kg] / (height [m])^2
CAD	Coronary artery disease
CHF	Congestive heart failure
CIAC	Central Independent Adjudication Committee
CNS	Central nervous system
C_{max}	Maximum concentration
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRNMB	Clinically relevant non-major bleeding
csRHR	Cause-specific relative hazard reduction
C_{trough}	Trough plasma concentration
CV	Cardiovascular
DM	Diabetes mellitus
DMC	Data monitoring committee
ECG	Electrocardiogram
EoT	End of treatment
EP	Extension period data scope
ESRD	End stage renal disease
F1.2	Prothrombin fragment 1 + 2
FAS	Full analysis set
FP	Follow up period data scope
FU	Follow-up
FXI	Coagulation factor XI
GalNAc	N-acetyl galactosamine
HD	Hemodialysis
ICH	International Council on Harmonization
INR	International normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
LLOQ	Lower limit of quantification
LMWH	Low molecular weight heparin
MACE	Major adverse cardiovascular event
MB	Major bleeding
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
OA	Data scope according to overall analysis principle
PAD	Peripheral arterial disease
PA	Data scope according to primary analysis principle
PD	Pharmacodynamics(s)
PE	Pulmonary embolism
PK	Pharmacokinetics
PT	Prothrombin time
RRT	Renal replacement therapy
SAE(s)	Serious adverse event(s)
SAF	Safety analysis set
SAP	Statistical analysis plan
SE	Systemic embolism

SOC	System organ class
SOP	Standard operating procedure
SQCS	Semi-quantitative clotting score
TA	Data scope according to total treatment analysis principle
TAT	Thrombin-antithrombin III complex
TEAE(s)	Treatment-emergent adverse event(s)
TIA	Transient ischemic attack
VTE	Venous thromboembolism
%CV	Percent coefficient of variation

1. Introduction

Patients with ESRD on hemodialysis are at a high risk for arterial and venous thromboembolic complications. However, because of the documented high risk for bleeding, no antithrombotic regimen has ever been evaluated in this group in a large clinical trial setting.

ESRD is associated with high CV comorbidity including CAD and PAD each associated with high mortality. Dialysis is associated with a prothrombotic state driven by inflammation, uremia-induced endothelial dysfunction and contact between blood and the dialysis circuit (Zoccali et al., 2003). Compared to the general population, patients receiving dialysis are at higher risk of thrombotic events including stroke (4-10x higher in dialysis patients) (Seliger et al., 2003), MI (CAD prevalence in dialysis patients is 5-10x higher) (Foley et al., 1998), and amputations, limb-ischemia and chronic skin ulcers related to PAD (PAD prevalence is as high as 40%) (United States Renal Data System, 2019). Only 40% of patients receiving HD are alive five years after onset (de Jager et al., 2009), and the mortality rate for that initiating dialysis is 15x higher than in matched controls from the general population (Mann et al., 2013). This high mortality is largely driven by CV causes (Mann et al., 2013).

The investigational agent, BAY 2976217 is a ligand conjugated antisense oligonucleotide (LICA) targeting FXI synthesis in the liver. CCI [redacted]

Given the multi-fold higher rates of CAD, PAD, stroke and AFib in patients with ESRD on hemodialysis coupled with an increased risk of bleeding versus the general population, there is a very high unmet need for therapies proven to address CV disease burden in these patients without increasing bleeding risk. Targeting FXI with GalNAc-conjugated FXI ASO (BAY2976217) may address this unmet need to reduce CV morbidity and mortality without increasing the risk of clinically significant bleeding (Von dem Borne et al., 1997).

As there is currently no accepted alternative therapy to reduce thrombotic events in this population except the use of low-dose ASA, the appropriate standard of care for the control arm of each cohort is placebo with or without low-dose ASA at the discretion of the investigator.

This statistical analysis plan (SAP) is based on the Global Clinical Study Protocol BAY 2976217/21170 version 3.0 dated 07 JUL 2021 and contains definitions of analysis sets, key derived variables and statistical methods for the LICA study. It provides a technical and detailed elaboration of the principal features of the planned analyses, e.g., derivation of the primary endpoints. Amendments and/or appendices to this core SAP may be used to add additional analysis and provide more details on the coding guidelines, data-handling, and output tables and figures.

Titles, mock-ups, and programming instructions for all statistical output (tables, figures, and listings (TLF)) are provided in a separate TLF specifications document.

2. Study Objectives

Objectives and endpoints are listed in Table 2-1.

Table 2-1: Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary	
• To evaluate the safety of Fesomersen as compared to placebo	Primary Endpoint • The incidence of major bleeding and clinically relevant non-major bleeding during the main treatment period and within the on-treatment time window, as assessed by blinded CIAC
Secondary	
• To evaluate the safety of Fesomersen as compared to placebo	• The incidence of the composite of major bleeding and clinically-relevant non-major bleeding during the main and extended treatment periods and within the on-treatment time window, as assessed by blinded CIAC • Incidence and severity of TEAEs during o the main treatment period and within the on-treatment time window o the main and extended treatment periods and within the on-treatment time window o the main and extended treatment periods and until 20 weeks after the last study intervention dose
• To evaluate the PK and PD of Fesomersen	Pharmacokinetic Endpoints • Trough concentrations for 3 dose levels of Fesomersen Pharmacodynamic Endpoints • Maximum change in FXI antigen levels during the main treatment period • Maximum change in FXI activity levels during the main treatment period
Exploratory	
• To evaluate the effect of Fesomersen on	Exploratory Efficacy Endpoints • Incidence of the composite and event types of death due to MI, stroke, PE and SE, and stroke,

Table 2-1: Objectives and Endpoints

Objectives	Estimands/Endpoints
thromboembolic events as compared to placebo	MI, VTE, major amputation of vascular etiology, and acute limb ischemia as assessed by the blinded CIAC • Incidence of thrombosis of the arterio-venous grafts or fistulas, assessed by the blinded CIAC
• To further evaluate the safety profile of Fesomersen as compared to placebo	<u>Other pre-specified Safety Endpoints</u> • Incidence and severity of AESIs- hepatic enzyme elevation, thrombocytopenia • Changes in vital signs and, laboratory assessments • Incidence and severity of bleeding of the arterio-venous grafts or fistulas
• To further evaluate the pharmacodynamics of Fesomersen as compared to placebo	<u>Other Pre-specified Pharmacodynamic Endpoints</u> • Maximum change in PT, INR and aPTT during the main treatment period • Extent and frequency of clotting on the dialysis filters & circuit • Changes in d-dimer • Thrombin-antithrombin complex (TAT) and Prothrombin fragment 1 + 2 (F1.2)
Other pre-specified	
• To further investigate Fesomersen (e.g. mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to cardiovascular and renal diseases and associated health problems • To evaluate potential associations between genotypic information and clinical efficacy and / or pharmacodynamics effects	• Various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

It is important to note, based on the current expert assessment of the COVID-19 Public Health Emergency, it is to be expected that only a very limited number of patients (<5) will suffer from confirmed COVID-19. Besides, as ESRD patients have to go to the hospital regularly, no increase in missing data is to be expected. For this reason, no intercurrent event linked to the COVID-19 Public Health Emergency is accounted for this study. However, any premature discontinuation will be summarized, and selected analyses will be repeated by confirmed COVID-19 (Yes/No) as reported by the investigator.

3. Study Design

This is a Phase 2 multicenter, double-blind, randomized, placebo-controlled study in ESRD patients who are stable on HD (including hemodiafiltration) ≥ 3 months for a minimum of 9 hours per week. Patients receiving therapeutic anticoagulation or antiplatelet therapy (other than ASA ≤ 150 mg/day) are excluded. Approximately 288 participants will be randomized. Participants will be allocated at randomization to 1 of 3 dose cohorts in a 1:1:1 ratio (Cohort A [40 mg], Cohort B [80 mg], and Cohort C [120 mg]), and within each cohort to receive SC treatment with either Fesomersen or matching placebo in a 3:1 ratio. Sponsor, participants and investigators are blinded with respect to active treatment versus matching placebo, but assignment to dose cohort will be known. The CIAC will be blinded to dose cohort allocation and treatment assignment. With an assumed attrition rate of 15% during the main treatment period, 288 randomized participants would allow for an estimated 240 evaluable participants.

All standard of care hemodialysis therapies as prescribed by their providers, including use of heparins to maintain dialysis circuit patency, will be continued.

- Cohort A: 40 mg Fesomersen or placebo SC (3:1) n~96
- Cohort B: 80 mg Fesomersen or placebo SC (3:1) n~96
- Cohort C: 120 mg Fesomersen or placebo SC (3:1) n~96

Participants will be stratified at randomization for use of ASA (yes/no). The use of ASA will remain at the discretion of the investigator. However, all efforts should be made during the treatment period to avoid change in ASA use or dose, unless clinically indicated. Additionally, participants will also be stratified based on the presence of selected CV risk factors. The investigator will evaluate the presence or absence of the following at the time of randomization:

(i) age >65 years,

(ii) history of DM type I or II,

(iii) history of MI,

(iv) history of stroke or TIA,

(v) history of CHF,

(vi) history of PAD,

(vii) history of Afib.

Strata 1 – zero or one risk factor, except the presence of DM or Afib; .

Strata 2 - either DM or Afib alone, or two or more risk factors.

All cohorts will consist of a 1-week screening period and a 24-week main treatment period (visit 5 to visit 22), the last 4 weeks of which are an evaluation period for certain PD and safety parameters.

The main treatment period consists of 24-weeks. Furthermore, the treatment will continue in an extended period, with up to an additional 24 weeks to collect additional long-term safety information. The participants will continue with study intervention (Fesomersen or placebo) according to their original randomization group assignment.

All participants who are in the extended treatment period will need to stop further treatment no later than when the last participant enrolled in the study has completed the 24-week main

treatment period (Visit 22). Participants in the extended treatment period will complete Visit 28, four weeks after their last dose and then move to the 16-week post-treatment follow-up period (FU1 to FU4). The sponsor reserves the discretion to halt further dosing in the extended treatment period earlier in anticipation of the least participant completing the main treatment period.

A participant is considered to be on treatment until 4 weeks after their last dose, whether they discontinue treatment early, complete only the main treatment period, or complete part or all the extended treatment period. Once the overall treatment period is completed, participants will have a 16-week post-treatment follow-up period.

The data and outcomes collected in the study will be summarized for below 4 groups:

- Pooled Placebo Group (from Cohorts A, B and C),
- 40 mg Dose Group (Fesomersen from Cohort A),
- 80 mg Dose Group (Fesomersen from Cohort B), and
- 120 mg Dose Group (Fesomersen from Cohort C).

All suspected bleeding, cardiovascular, and thromboembolic events occurring after randomization will be assessed by CIAC blinded to cohort and dose allocation.

An independent DMC will monitor the participant's safety and give recommendations to the Steering Committee. The DMC will review unblinded data from the study regularly, as outlined in the DMC Charter. At any time, if there is an unexpected finding(s) in Cohort C (the 120 mg dose cohort), the DMC may elect to modify the Cohort C to a 100 mg or 80 mg dose level. If recommended by the DMC, the change will be implemented by administrative letter and will not require a protocol amendment. All ongoing participants will have their dosing modified to 100 mg or 80 mg once monthly, and all new participants will be initiate dosing at 100 mg or 80 mg once monthly.

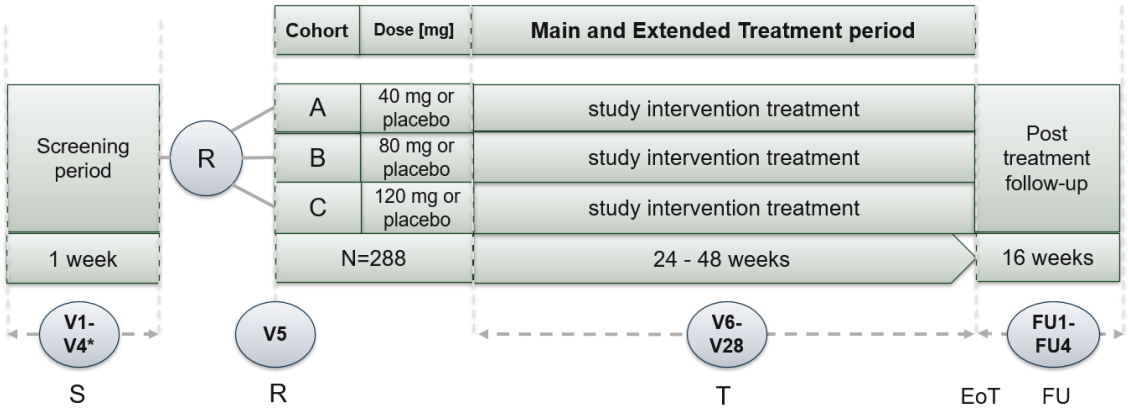
There will be an alternative PK&PD sampling group at selected sites. A target population of approximately 24 to 40 participants distributed among the three cohorts is sought for this group. Whereas all other participants will receive their first dose of study intervention on a dialysis day, participants in the alternative PK&PD sampling group will receive their first dose of study intervention on a non-dialysis day, preceding a scheduled dialysis day.

Central lab results for PD parameters, including coagulation parameters, will not be provided to the sites, as these are potentially unblinding. Investigators will also avoid local testing of coagulation parameters, as these may be unblinding, unless clinically indicated.

The primary analysis will be performed after all participants have completed the main treatment period (primary completion). A full analysis will be performed after the last participant has completed the 16-weeks post treatment follow-up period (study completion).

The end of the study is defined as the date the last participant completes the last protocol-defined visit/contact.

Figure 3–1: Study Design



S = screening, R = randomization, T = treatment, EoT = end of treatment, FU = follow-up

4. General Statistical Considerations

4.1 General Principles

For continuous variables, descriptive summary statistics including number of patients, mean, standard deviation, median, upper and lower quartiles (25th percentile, 75th percentile), and minimum and maximum values will be presented. For categorical variables, counts and percentages will be presented in frequency tables. For continuous variables collected at multiple time points, the descriptive statistics will be provided at each time point. All statistical tests will be conducted using 2-sided tests with 10% Type I error rate unless otherwise stated.

Placebo-treated patients will be pooled and analyzed as a single placebo group. Therefore, four treatment groups will be included and presented in the analysis as 40 mg, 80 mg, 120 mg, and placebo. Patients who are Fesomersen-treated may be pooled and summarized as the pooled treatment group.

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA) or if applicable, other software.

4.2 Handling of Dropouts

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

4.2.1 Permanent Discontinuation of Study Intervention

A randomized subject who permanently discontinues Fesomersen or placebo before their planned Visit 28 + 5 days window (extended treatment period) or before the last scheduled dose for primary completion, is defined as having had a permanent discontinuation of study intervention (including subjects who were randomized but never started taking any study intervention). The reason for the discontinuation of study intervention will be recorded in the eCRF and source documentation.

The investigator may temporarily discontinue study intervention. If the discontinuation remains necessary > 56 days from the last dose, the participant will be permanently discontinued from study intervention and will enter the post-treatment follow-up period.

The number of subjects who permanently discontinue study intervention and the reason for discontinuation will be displayed by treatment groups. Baseline characteristics will be displayed by permanently discontinue study intervention (yes/no). All data collected until the discontinuation will be presented.

Participants whose discontinuation reason is recorded as COVID-19 will be included and presented here with the reason entered in eCRF.

4.2.2 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The investigator should make all efforts to determine the survival (vital status) of any participant who would otherwise be lost to follow-up during the treatment period or post-

treatment follow-up period, whether by direct contact or indirect contact with a reliable source (family-member, health-care provider, etc.). A participants survival status will be recorded in the eCRF. If no survival status is known, the contact attempt will be recorded.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the eCRF.

Additional descriptive analyses in the presence of missing data

The number of subjects who prematurely discontinue the study and study intervention for any reason, as well as the reasons for premature discontinuation of study and study intervention, will be reported.

Kaplan-Meier plots for "lost to follow up" will be provided if there are any such incidences.

All dropouts will be carefully evaluated with respect to:

- baseline characteristics,
- potential differences between the treatment groups in the proportion of patient withdrawals or the timing of withdrawals, and
- the reasons for premature discontinuation of study and/or study intervention and potential dropout patterns will be described.

The number, timing, pattern, and reasons for missing values of all relevant efficacy and safety variables will be displayed by means of descriptive statistics and visualized if applicable.

4.4 Interim Analyses and Data Monitoring

No formal interim analysis is planned.

An independent Data Monitoring Committee (DMC) will monitor the safety of the participants. A DMC will frequently review safety data to ensure the safety of the participants in the ongoing study. Further details can be found in the DMC charter.

4.5 Data Rules

4.5.1 Analysis Dates

For the study, the following date and time window are of relevance for the analysis:

- End of Study Date

  The end of the study is defined as the date the last participant completes the last protocol-defined visit/contact.

- Primary Completion Date

  The primary completion date is the date when the last participant completes the main treatment period . See the below period definitions for data collection in each period.

- Main Treatment Period (actual)

  The main treatment period includes a total of 24 weeks

For subjects who ***did not*** enter the extension period the main treatment period is defined as the period from first dose of study intervention to the last date of dose +28 days.
For subjects who ***did*** enter the extension period the main treatment period is defined as the period from first dose of study intervention to the administration of study intervention (and hence commencement of the extension period), at visit 22.

- Extended Treatment Period (actual)

  The extended treatment period includes a total of up to 24 weeks, from study intervention administration on visit 22 until the date of last dose +28 days or date of last contact (whichever comes first).

- Post-Treatment Follow-up Period (actual)

  The post-treatment follow-up period includes a total of 16 weeks. For subjects who ***did not*** enter the extension period, the follow up is defined as the period from the end of the main treatment period +1 day to the last contact date.
  For subjects who ***did*** enter the extension period, the follow up is defined as the period from the end of extension period + 1 day to the last contact date.

For each subject, the following individual dates are of relevance for analysis:

- Randomization date:

  The date of randomization as recorded in the IxRS system.

- Date of the first dose of study intervention:

  The date of the first dose of Fesomersen or placebo will be used from the appropriate eCRF page capturing the study intervention.

  Date of the earliest logically possible dose of study intervention administration will be used, in cases where the date of the first dose is missing or incomplete.

- Date of the last dose of study intervention:

  The date of the last dose of Fesomersen or placebo will be used from the appropriate eCRF page capturing the study intervention.

  Date of the latest logically possible dose of study intervention administration will be used, in cases where the date of the last dose is missing or incomplete.

  Incomplete dates will be imputed for the analysis as appropriate based on available information.

4.5.2 Data Scopes

All analyses are based on two elements:

1) analysis set, which specifies which subjects will be included in an analysis; and

2) data scope, which defines the time window within which data will be included in the analysis.

This section describes the coverage of the event data scopes used for the statistical analyses. Analysis sets are described in Section 5.

The below data scopes are based on the 3 periods of the study, main treatment, extension treatment and follow up, as defined in section 4.5.1:

Data scope according to primary analysis principle (PA)

The PA data scope includes outcome events observed from the date of first administration of study intervention until the end of the main treatment period. Events occurring after the main treatment period will not be counted for primary analysis data scope.

Data scope according to total treatment analysis principle (TA)

The TA data scope includes outcome events observed from the date of first administration of study intervention until the end of the extension treatment period. Events occurring after the extension treatment period will not be counted for total treatment analysis data scope.

Data scope according to overall analysis principle (OA)

The OA data scope includes outcome events observed from the date of first administration of study intervention until the end of post-treatment follow-up period.

4.5.2.1 Exploratory data scopes

Extension period data scope (EP)

The EP data scope includes outcome events observed from the start of the extension period until the end of the extension period.

Follow up period data scope (FP)

The FP data scope includes outcome events observed from the start of the post-treatment follow-up period until the end of the post-treatment follow up period

4.6 Blind Review

There will be two data assessment lists. The first one will occur after primary completion and the second one will occur after end of study. The results of both data lists will be documented in separate lists of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis sets. Pharmacodynamic and pharmacokinetic values to be excluded from statistical analysis will be documented and respective flags will be incorporated in the clinical database.

4.7 Sample Size Determination

No formal statistical sample size estimates were performed.

The sample size was selected based on prior experience in ESRD with the unconjugated ASO. This study is planned to ensure the safety, tolerability, and PK/PD relationships are assessed adequately while minimizing unnecessary participant exposure. There is no plan for statistical hypothesis testing for this study. In this study, the number of subjects is considered based on the ISIS 416858-CS5 study design.

Approximately 288 participants (96 [72 active+24 placebo] per cohort) will be randomly assigned to study intervention so that an estimated 240 participants will complete the main treatment period. All participants will be randomized to 1 of 3 dose cohorts in a 1:1:1 ratio (Cohort A, Cohort B, and Cohort C). Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive treatment with either Fesomersen or placebo. Considering an approximately 15% dropout rate, an estimated total of 60 participants per intervention group and the placebo group will complete the main treatment period. A participant will be evaluated once he/she was randomized and received at least one dose of study intervention. The number of evaluable and randomized participants is assumed to be similar.

Table 4-1 summarizes 95% expected range for the true population proportion of participants with a composite of MB and CRNMB bleeding. For example, with 60 participants, if 5% of them had a composite of MB and CRNMB bleeding during the main treatment period and the desired confidence level is 95%, the corresponding confidence interval would be ± 5.51, i.e. the range of 0.0 % to 10.51%. If multiple samples were drawn from the same population and a 95% CI calculated for each sample, we would expect the true population proportion to be found within 95% of these CIs.

Table 4-1: Confidence Interval for proportion of participants with a composite of MB and CRNMB Bleeding

Sample Size	Observed Proportion *	Desired Confidence level	Corresponding two-sided confidence interval	Range for the true population proportion
60	2%	95%	±3.54	0.0% to 5.54%
	3%	95%	±4.32	0.0% to 7.32%
	4%	95%	±4.96	0.0% to 8.96%
	5%	95%	±5.51	0.0 % to 10.51%
	6%	95%	±6.01	0.0% to 12.01%
	7%	95%	±6.46	0.54% to 13.46%
	8%	95%	±6.86	1.14% to 14.86%

CRNMB = clinically relevant non-major bleeding, MB = major bleeding

* The range of observed proportion is considered based on the Interim report of ISIS 416858-CS5 study where the composite of MB and CRNMB bleeding proportion for Placebo was 5.7% and for total ISIS treated= 4.5% (ISIS treated with 200mg, 250mg and 300 mg doses were 3.8%, 5.6% and 4.0% respectively)

5. Analysis Sets

5.1 Assignment of Analysis Sets

All subjects who have been randomized in the study are valid for assignment to analysis sets.

The following populations are defined:

Table 5-1: Populations

Population	Description
Enrolled	All participants who sign the ICF
Full analysis set (FAS)	All participants randomized who have received at least 1 dose of study intervention. Participants will be analyzed according to the intervention they were randomized.
Safety analysis set (SAF)	All participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants will be analyzed according to the intervention they received. If a participant was administered, in error, a different dose to that which they were randomized to, they will be analyzed according to the intervention received most frequently (i.e. at > 50% of visits), in cases where 2 different doses were administered for the same number of visits, the participant would be excluded from the safety analysis set.
Pharmacokinetic set (PK)	All Fesomersen-treated participants with at least 1 PK sample in accordance with the PK sampling schedule (Section 8.5.1 of the study protocol) and without deviation from the protocol that would interfere with the evaluation of the PK data will be included in the PK analysis.
Pharmacodynamic set (PD)	All participants with at least 1 PD sample in accordance with the PD sampling schedule and without deviation from the protocol that would interfere with the evaluation of the PD data will be included in the PD analysis.
Listing only set	All participants who signed consent but are not randomized.

If the safety and full analysis sets are identical, i.e. all subjects received the treatment to which they were randomized, the full analysis set will not be used.

The planned analyses for the primary, secondary, exploratory, and PK-PD endpoints are summarized in but not limited to Table 5-2 below

Table 5-2: Sketch of the planned analyses on the endpoints

Endpoints	Analysis Type	Analysis set	Data Scope
Primary Endpoint(s)	Main	SAF	PA [a)]
	Additional	SAF	TA [a)]
	Exploratory	SAF	OA [b)]
	Subgroup	SAF	PA [a)]
		SAF	TA [a)]
Secondary Endpoint(s)	Main	SAF	PA [a)]
	Additional	SAF	TA [a)]
	Exploratory	SAF	OA [b)]
Exploratory Endpoint(s)	Main	SAF	PA [a)]
	Additional	SAF	TA [a)]
	Exploratory	SAF	OA [b)]
		FAS	PA [b)]
		FAS	TA [b)]
	Subgroup	SAF	PA [a)]
		SAF	TA [a)]
PK, PD Endpoint(s)			
Trough concentrations	Main	PK	OA
Maximum change in FXI antigen levels	Main	PD	OA
Maximum change in FXI activity levels	Main	PD	OA

PA: Data scope according to primary analysis principle, TA: Data scope according to total treatment analysis principle, OA: Data scope according to overall analysis principle.
a) on-treatment estimand
b) treatment policy estimand

6. Statistical Methodology

The primary safety and efficacy variables will be analyzed descriptively for the following groups:

- Pooled Placebo Group (from Cohorts A, B and C),
- 40 mg Dose Group (Fesomersen from Cohort A),
- 80 mg Dose Group (Fesomersen from Cohort B), and
- 120 mg Dose Group (Fesomersen from Cohort C).

For selected analyses the pooled Fesomersen treatment arms will be presented in addition.

Incidence rates and cumulative incidences will be calculated only for endpoints with at least 1 event in a treatment arm. Hazard ratios (cause specific and sub distribution), log-rank test and Gray's test will only be calculated if there is at least 1 event in each of the compared treatment arms.

6.1 Population Characteristics

6.1.1 Disposition

The following will be tabulated overall and/or by treatment group:

- Study sample sizes (All enrolled subjects)
- Study sample sizes by region, country, and site
- Subject disposition (by treatment group and overall)
- Number of subjects and primary reasons for screening failures
- Number of subjects and primary reasons for permanent discontinuation of study intervention (by treatment group and overall)

6.1.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics include:

- Dialysis and ESRD disease characteristics obtained before the first study intervention administration
- Age groups
    - <60 years,
60-75
>75years
    - <50yrs
>=50-<60yrs
>=60-<65yrs
>=65-<70yrs
>=70-<80yrs
>=80yrs
    - <=65 years
>65 years)

- BMI groups
    - Below 18.5 = underweight;
      18.5 to <25.0 = healthy weight;
      25.0 to <30.0 = overweight;
      >= 30.0 = obesity
        - 30 to <35: obesity class 1;
          35 to <40: obesity class 2;
          >=40: obesity class 3
- Age, Weight, Height, BMI as continuous variables
- Gender, Ethnicity, Race
- Time since the start date for renal replacement therapy,

The continuous variables will be summarized using descriptive statistics, while counts and percentages will be provided for categorical variables. All analyses will be presented overall and by treatment group in both the FAS and SAF analysis sets. Other baseline characteristics may be added as deemed appropriate. No statistical tests will be performed to compare these characteristics across treatment groups.

Age for each participant will be defined as the number of years between informed consent date and birth date.

For summarizing race, if multiple races are recorded in the database, then 'multiple race' will be used in the summary table.

6.1.3 Definition of Baseline

In general, a baseline assessment will be the last non-missing value prior to the first administration of study intervention (Fesomersen or placebo) on Day 1. If Day 1 values are not available, last screening values will be used. Furthermore, if there is more than one assessment at the same timepoint, the baseline value will be the mean of the recorded measurements prior to the administration of study intervention.

6.1.4 Medical History

Medical history will be presented by the pre-specified terms, as collected in the eCRF using MedDRA Primary System Organ Class / Preferred Term. The summary of medical history data will be presented in frequency tables, showing the number of subjects with medical history findings (i.e., listed conditions of previous diagnoses, diseases, or surgeries) that started before signing of the informed consent and that are considered relevant to the study.

6.1.5 Protocol Deviations

Frequency tables will present a summary of protocol deviations related to inclusion and exclusion criteria, as well as important protocol deviations; these will be presented by visit and treatment. The summary will be based on SAF analysis set.

6.1.6 Prior and Concomitant Medications

The dictionary used for coding concomitant medications is the World Health Organization Drug Registration and Listing. Frequency tables displaying frequency of subjects for each drug category summarized by Anatomical Therapeutic Chemical (ATC) class and coded terms will be used to summarize the number and percentage of subjects with prior and

concomitant medications. The following definitions for prior and concomitant medications will be used:

- Prior medication: medication stopped prior to the date of randomization
- Concomitant medication in main treatment period (PA), extension period (EP), follow-up period (FP), total treatment analysis principle (TA), overall analysis principle (OA) (i.e. at least one dose was administered within the respective period)
- Concomitant medication started in main treatment period (PA), extension period (EP), follow-up period (FP), total treatment analysis principle (TA), overall analysis principle (OA) (i.e. first administration of concomitant medication occurred within the respective period)

The frequency tables of concomitant medications will be presented by treatment group and time period.

Additionally, frequency tables and listings of subjects taking prohibited concomitant medications (see study protocol section 6.5) will be provided.

6.1.7 Extent of Exposure and Compliance

All summaries related to exposure to the study intervention will be presented by treatment group based on SAF analysis set.

The treatment duration (date of last study intervention - date of first study intervention+1 day) will be summarized descriptively. Additionally, the number of subjects by treatment duration category will be given (≤4 weeks, >4-≤8 weeks, >8-≤12 weeks, >12-≤24 weeks, >24 weeks).

The time on study intervention (treatment duration excluding days off study intervention) will be calculated and summarized descriptively.

Compliance will be presented by visits as entered in the eCRF and summarized based on FAS analysis set. The number of subjects with at least 80% compliance will be presented.

$$Study\ Drug\ Compliance = 100 \times \frac{\text{Total number of doses with injections given}}{\text{Total number of doses with injections expected}}$$

If a patient discontinued the study intervention, the total number of doses with injections expected is counted, per the schedule of injections, up to the last attended study visit during the total treatment period.

6.1.8 Baseline Renal Replacement Therapy

Information on the renal replacement therapy at baseline will be evaluated similar to the other baseline characteristics. In this context the use of unfractionated heparins and LMWH for dialysis maintenance at baseline will be descriptively summarized by treatment groups and overall.

6.2 Efficacy

6.2.1 Analysis of Exploratory Efficacy Variable(s)

Two exploratory efficacy variables will be considered.

First exploratory efficacy composite endpoint consisting of the following components:

- Death due to MI, ischemic stroke, pulmonary embolism (PE), non-CNS systemic embolism (SE) and undetermined - presumed cardiovascular death

- Stroke (ischemic or undetermined type)
- MI
- Major amputation of vascular etiology
- Acute limb ischemia
- Symptomatic VTE
- Systemic embolism

Second exploratory efficacy endpoint:

- Thrombosis of the arterio-venous grafts or fistulas

The frequency and percentage of participants with an exploratory efficacy event will be reported where the denominator will be total number of participants in each treatment group, within the SAF analysis set and PA data scope. The corresponding exact binomial two-sided 95% confidence interval calculated using Blaker's method will be provided.

Exposure adjusted incidence rate (100 person-years) analysis will be performed by treatment group and overall. In addition, the analysis of the exploratory efficacy variable will be conducted as a descriptive time to first event analysis separately for the three Fesomersen dose groups and placebo, similar to the primary safety analysis (i.e. only treatment emergent efficacy events which occurred during the main treatment period will be considered). Thus, the descriptive analysis focuses on estimating the efficacy under constant BAY2976217 concentration during chronic treatment. This analysis will be based on SAF analysis set and the PA data scope.

6.2.1.1 Other Exploratory Efficacy Analyses

Efficacy Analysis by Component

The single components of the main efficacy variable will be analyzed in a similar way to the main efficacy analysis in section 6.2.1.

Analysis of Death Events

The main efficacy analysis will be repeated for overall death and for its components (Death due to MI, stroke, pulmonary embolism (PE) and systemic embolism (SE), CV death, Non-CV death, Undetermined death, and other reasons).

Pre-Treatment Efficacy Summary

Pre-treatment events between randomization and first dose of study intervention will be listed.

6.2.2 Sensitivity and Supplementary Efficacy Analysis

The exploratory efficacy endpoints will be analyzed using the same method described in Section 6.2.1based on:

- SAF analysis set and TA data scope,
- SAF analysis set and OA data scope,
- FAS analysis set and PA data scope,
- FAS analysis set and TA data scope

6.2.2.1 Stratified Efficacy Analysis

The main efficacy analysis with Cox regression will be repeated incorporating all factors considered in the randomization as stratification factors without interaction terms. if the model converges.

6.2.2.2 Competing Risk Model Analysis

The exploratory variables will be analyzed using a competing risk event model similar to the primary safety endpoint (see section 6.4.1.1). Death due to reasons other than MI, stroke, PE and SE is considered a competing event for the efficacy analysis.

6.2.2.3 Subgroup Analysis

The analysis for the exploratory efficacy variables will be repeated by the following subgroups:

- Age groups
    - <60 years,
      60-75
      >75years
    - <50yrs
      >=50-<60yrs
      >=60-<65yrs
      >=65-<70yrs
      >=70-<80yrs
      >=80yrs
- BMI groups
    - Below 18.5 = underweight;
      18.5 to <25.0 = healthy weight;
      25.0 to <30.0 = overweight;
      >= 30.0 = obesity
        - 30 to <35: obesity class 1;
          35 to <40: obesity class 2;
          >=40: obesity class 3
- Gender,
- Previous CV events (MI or stroke or TIA or VTE)
- Previous MACE (MACE is defined as: prior myocardial infarction, prior stroke from the medical history database.)
- History of DM,
- History of Afib,
- Race,
- Time since the start date for renal replacement therapy (<1 year; >=1 year),
- Use of low dose ASA,
- History of COVID-19,

- COVID-19 during the study

The analyses for the subgroups will be repeated for the exploratory endpoints based on SAF analysis set and PA data scope and SAF analysis set and TA data scope. The results will be presented descriptively with forest plots.

6.2.3 Analysis of COVID-19 Patients

Analysis to evaluate the COVID-19 impact on the study exploratory efficacy endpoint will be performed by comparing the descriptive statistics among COVID-19 versus non-COVID-19 patient population. COVID-19 cases will be recorded as adverse events in the eCRF, participants with a documented adverse event of COVID-19 during the study will form the COVID-19 population, all other participants will be included in the non-COVID-19 population. Additional analysis on the COVID-19 will be described in the future SAP revision if needed.

6.3 Pharmacokinetics/Pharmacodynamics.

Plasma and dialysate samples will be collected for measurement of plasma Fesomersen-eq. concentrations and dialysate concentrations of Fesomersen and its metabolites, respectively. PK- and PD- samples will be collected in all participants. A subset of at approximately 24-40 participants will be participating in an alternative PK&PD sampling group with the first dose on a non-dialysis day

There may be some inaccuracies in the actual sampling times compared to planned sampling. These deviations can be relevant for the interpretation of pharmacokinetic and pharmacodynamic data. Accepted time windows are prespecified in the guidance documents for PK and PD validity for study #21170 and will be referenced in the final blind review report. Accepted time windows for the assessment of pharmacokinetic concentrations will be handled analogously.

All valid results will be included in the listings and graphical displays of individual data, which are displayed using actual times. Measurements taken outside the predefined time windows will be flagged by the pharmacokinetic and pharmacodynamic experts to be excluded from the calculation of summary statistics (with respect to planned times) in order to avoid biased results. Samples flagged for other reasons, as defined in respective guidance documents for PK and PD validity for study #21170, will be excluded from statistics accordingly (see also section 4.6).

6.3.1 Pharmacokinetics Analysis

Plasma Fesomersen-eq. concentrations and dialysate concentrations of Fesomersen and its metabolites, respectively, will be summarized by visit and planned sampling time intervals, separated according to actual dose cohort. Descriptive statistics [geometric mean and percent coefficient of variation (%CV), arithmetic mean and %CV, median and range] will be presented by treatment group and time in tabular form. Analysis comparing regular and alternative PK sampling group will be done. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Box-plots for Fesomersen-eq. trough (C_{trough}) plasma concentrations will be provided by actual dose cohort and visit.

For all treatments where at least one subject with at least one confirmed ADA formation is included, the individual concentrations of Fesomersen in plasma will be displayed including supplemental information about the ADA titer. Individual subjects with confirmed ADA formation will be indicated by different colors and symbols.

Pharmacokinetic and exposure-response analysis using population approaches (popPK and popPK/PD, e.g., by non-linear mixed effect modeling) will be reported under separate document, if applicable.

6.3.2 Pharmacodynamic Analysis

Analysis comparing regular and alternative PD sampling will be done.

6.3.2.1 The PD profile

The effect of Fesomersen on PD profile will be assessed on maximum change in FXI activity levels, FXI antigen levels, PT, INR, aPTT, d-dimer, TAT, and F1.2 levels during the main treatment period by treatment group in PD analysis set.

Change and percent change from baseline FXI activity levels, FXI antigen levels, PT, INR, aPTT, d-dimer, TAT, and F1.2 levels will be summarized by treatment and visit separately. Individual results will be presented in data listings by treatment. Figures of the mean levels of all PD parameters (FXI activity and antigen, PT, INR, aPTT, d-dimer, TAT and F1.2) as well as change and percent change from baseline will be provided by treatment group, and scheduled visit.

Change and percent change from baseline in FXI activity levels, FXI antigen levels, PT, INR, and aPTT will be compared between each of the study intervention group and pooled placebo group using the Wilcoxon Rank Sum test.

Frequency and percent of patients with average FXI activity ≤0.1, ≤0.2, ≤0.3, ..., ≤1.0 U/mL during each visit with PK/PD measurements up to last dose + 28 days will also be provided.

The incidence and events for any aPTT>160s will be summarized by treatment and visit.

For all treatments where at least one subject with at least one confirmed ADA formation is included, the PD parameters. in plasma will be displayed including supplemental information about the ADA titer. Individual subjects with confirmed ADA formation will be indicated by different colors and symbols.

6.3.2.2 SQCS Analysis

The effect of Fesomersen on the clotting in the dialysis circuit will be assessed by the SQCS.

The clotting assessment will be conducted on the PD analysis set and will be presented according to treatment group. Clotting scores will be assigned as follows:

Table 6-1: Clotting scale score

Clotting score	Definition
Clotting Score 0	Clean filter and no visible clots in the drip chambers
Clotting Score 1	For traces of coagulation in the filter and/or in the drip chambers
Clotting Score 2	Intermediate state between 1 and 3
Clotting Score 3	Fully clotted extracorporal system resulting in an interruption of the hemodialysis session

Adequate anticoagulation is defined by an SQCS of less or equal "1".

The summary of each clotting score category will be presented in frequency and the percentage of patients by visits.

The overall score for individual subjects, which is the highest clotting score from all visits per data scope, will also be summarized. The overall clotting score will be analyzed for treatment comparison between each Fesomersen dose groups and placebo group using the Wilcoxon Rank Sum test.

The difference in the mean of SQCSs during the main treatment period between each of the Fesomersen groups and the placebo group will be displayed together with the corresponding 90% (and 95%) confidence intervals applying ANOVA with treatment group as factor.

Furthermore, the difference in the proportion of hemodialysis sessions with adequate anticoagulation during the main treatment period between each of the Fesomersen dose groups and the placebo group will be summarized with the corresponding 90% (and 95%) confidence intervals using the unstratified exact method with the standardized test statistic and inverting a two-sided test (Agresti and Min, 2000) as exploratory analysis.

Frequency of dialyzer filters usage will be analyzed through descriptive statistics.

Most severe clotting category

In order to examine the correlation of FXI activity level and clotting, a separate summary on the most severe clotting category will be provided for patients with average FXI activity ≤0.1, ≤0.2, ≤0.3, ..., ≤1.0 U/mL for Fesomersen treated patients only.

6.4 Safety

The primary objective is to assess the safety of the three different doses of Fesomersen given once a month, which is expected to be maintained during chronic treatment. The primary analysis of the unblinded data snapshot, will be conducted after all participants complete the 24-week main treatment period to assess the safety and PK/PD, and exploratory efficacy of the results. . An unblinding plan additional to this SAP will detail the unblinding process and contain the study team members who will be unblinded at the time of the primary analysis.

Additional tables, including participant's extended treatment period up until primary completion, will be presented. No formal interim report will be written.

The final data analysis will be conducted once all participants complete the follow-up period (the last participant's last follow-up visit). At the end of the study completion, statistical analysis will include all data, including the main treatment period, extension period, and the follow-up period as well as distinctive period analysis appropriately.

6.4.1 Analysis of the Primary Safety Variable

The primary analysis is based on a descriptive proportion of subjects with primary endpoints (independently adjudicated) based on SAF analysis set and PA data scope. For each treatment and bleeding category, participants reporting more than one bleeding event will be counted only once using the highest severity. The frequency and percentage of participants with bleeding will be reported where the denominator will be total number of participants in each treatment group.

Estimand for the Primary Safety Endpoint:

The five attributes of the estimand are as follows:

- **Population:** The population consists of ESRD patients as described by the inclusion/exclusion criteria given in study protocol.
- **Variable:** The incidence of the composite of MB, CRNMB, events during the main treatment period, as assessed by the CIAC
- **Treatment:** Three dose groups of Fesomersen or placebo on top of standard of care
- **Intercurrent events:**
    - Unblinding to study intervention: the study allows unblinding of treatment assignment if the investigator deems necessary when related a bleeding or major surgery occur regardless of whether such an event occurs (treatment-policy strategy)
    - Early definitive discontinuation of study intervention or death or kidney transplant: until the occurrence of the intercurrent event (while on treatment strategy)
    - Dose reduction: regardless of whether such an event occurs (treatment-policy strategy).
- **Population-level summary:** Incidence proportion of subjects with an event by study intervention group and differences between Fesomersen treatment groups and placebo group. For the incidence proportions the exact binomial two-sided 95% confidence interval using Blaker's method will be provided. For the difference in incidence proportions the two-sided 95% confidence interval will be presented using the unstratified exact method with the standardized test statistic and inverting a two-sided test (Agresti and Min, 2000).

6.4.1.1 Additional Primary Safety Endpoint(s) Analysis:

Estimand for Time to Event Safety Endpoint:

The attributes constituting the estimand for this endpoint are the following:

- **Population:** The population consists of ESRD patients as described by the inclusion/exclusion criteria given in study protocol.
- **Variable**:
    - Time from first dose of intervention to MB and CRNMB events (in alignment with ISTH guidelines) up until 28 days after last study intervention
- **Treatment:** Three dose groups of Fesomersen or placebo on top of standard of care
- **Intercurrent events**: Of interest is the response to treatment while the participant is
    - alive (intercurrent event "death") and
    - exposed to study intervention (intercurrent event "premature discontinuation of treatment"),

i.e., both intercurrent events are handled using the same strategy "while alive" or "while on treatment".

Population-level summary:

Death and premature end of exposure to assigned treatment (last administration of assigned treatment plus 28 days) considered a competing event for the safety analysis.

The cumulative incidence function for the event-of-interest as well as the associated competing event(s) together with the corresponding confidence interval will be estimated for each treatment arm using Aalen-Johansen estimators.

The cumulative incidence, i.e. the probability of having a specific event, E, at or before a timepoint, t, $P(T \leq t, E = 1)$, will be estimated for time-to-event endpoints by Aalen-Johansen estimators with the competing event.

The difference of the Aalen-Johansen estimators between 40mg Fesomersen and placebo and 80mg Fesomersen and placebo and 120mg Fesomersen and placebo will be presented with a 90% confidence interval.

As the Aalen-Johansen estimator is approximately normal distributed (Aalen, Borgan and Gjessing 2008), the difference of Aalen-Johansen estimators is approximately normal distributed. Thus, the two-sided 90% confidence interval is obtained via:

$$\left[(\widehat{AJ}^{TRT}(day) - \widehat{AJ}^{Control}(day)) \pm z_{0.95} \sqrt{\sigma^2(\widehat{AJ}^{TRT}(day)) + \sigma^2(\widehat{AJ}^{Control}(day))} \right],$$

with $\widehat{AJ}^{TRT}(day)$ the Aalen-Johansen estimator for Fesomersen (TRT) at study day, $z_{0.95}$ the 95% quantile of the standard normal distribution and $\sigma^2(\widehat{AJ}^{TRT}(day))$ and $\sigma^2(\widehat{AJ}^{Control}(day))$ are the estimated variances of the Aalen-Johansen estimators at study day, estimated with the Aalen method.

Rates

Cause-specific incidence rates will be calculated for each treatment arm with an 90% confidence interval.

The on-treatment incidence rate will be expressed a "subjects with an event – per 100 participant years". For that the following formula is used:

$$IR_{adj} = \frac{\#Participants\ with\ an\ event}{\sum time\ under\ treatment\ (in\ days)/(100 * 365.25)}$$

The 90% confidence interval for the exposure-adjusted IR will be computed as

$$\left[\frac{IR_{adj} * \chi^2(0.05; 2e)}{2e}; \frac{IR_{adj} * \chi^2(0.95; 2e)}{2e} \right],$$

with $\chi^2(q; 2e)$ the q quantile of a chi square distribution with 2e degrees of freedoms and e the number of participants with an event. (Nelson 1982)

Hazard ratios

With respect to the cause-specific hazards for the respective safety variable, each of the Fesomersen groups will be compared to the placebo group using two-sided log-rank tests. Due to the explorative nature of these analyses, no multiplicity adjustment will be done.

The cause-specific hazard function $h_k(t)$ is the chance that an individual experiences an event of the primary safety outcome in the next instant in time, given that the individual has not had such an event or a competing event up to time t. Cause-specific hazard ratios, cause-specific relative hazard reduction (csRHR; csRHR = 100 × [1 – cause-specific hazard ratio]%), and corresponding 2-sided 90% and 95% confidence intervals, comparing the hazards for the event-of-interest in each of the Fesomersen groups with the placebo group will be estimated based on three separate cause-specific Cox proportional hazards models as exploratory amalysis. Censoring will be assumed to be independent form the study intervention. For example, for the comparison of the 120 mg Fesomersen group with the placebo group, the

corresponding cause-specific Cox proportional hazards model can be described by the following equation:

$$H_k(t,x_i) = h_{0,k}(t) \exp(\beta_k x_i),$$

where

$h_k(.)$ cause-specific hazard function for primary safety outcome, as a function of time and subject's covariates

$h_{0,k}(.)$ unspecified underlying baseline hazard function for primary safety outcome; hazard of an individual with $x_i = 0$

t time (in days) relative to the date of first administration

x_i treatment group of subject i
(0 corresponds to "placebo group" and
1 corresponds to "120mg Fesomersen group")

β_k unknown parameter (to be estimated); cause-specific hazard ratio = $\exp(\beta_k)$

k type of event

Probability

As a supportive analysis, the cumulative incidence functions for the respective event-of-interest will be compared using the Fine and Grays subdistribution hazards model as well as using the Gray's test.

6.4.2 Analysis of Secondary Safety Variable(s)

The secondary safety analysis is based on secondary endpoints incidence and severity of TEAE by treatment and overall with SAF analysis set and PA data scope.

The original terms used by investigators to report AEs via the CRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The summary of all adverse events will be tabulated by the primary system organ class (SOC) and preferred term (PT) by treatment arm. A total column will be included in all safety summaries.

The version number of MedDRA used for the analyses will be stored in the clinical database. Tables and/or listings of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

Treatment emergent adverse events (TEAEs)

Overall study TEAEs are defined as AEs that occurred or worsened after first dosing until 20 weeks after the last study intervention dose.

Main treatment period TEAE:

The main treatment period TEAEs will be defined as those AEs that occurred after first dosing and those existing pre-dose AEs that worsened severity post-dose treatment period until 28 days after the last dose of the study drug during the main treatment period. The most conservative approach will be used to determine if the event occurs during the main treatment period.

TEAE during overall treatment period:

For the overall TEAE analysis the event which occurred during the main and extension treatment period and during the post treatment follow-up period will be considered.

All TEAEs, all TEAEs potentially related to study intervention, all TEAEs potentially related to ESRD or the hemodialysis procedure, all TESAEs, and all TESAEs potentially related to study intervention will be summarized by treatment group and by MedDRA SOC and PT terms.

TEAEs and TESAEs leading to discontinuation and AEs of special safety interest (if applicable) will be listed. The date, relative date (to start of study intervention) and phase of the study (during treatment, post-treatment) will be included.

Frequency tables, showing an overall summary of number of events, number of subjects with AEs, serious adverse events (SAEs) and adverse events of special interest (AESIs) will be given, and will include the following information.

- if AE (/SAE/AESI) occurred with causal relationship to study drug;
- if AE (/SAE/AESI) occurred with causal relationship to study procedures (renal replacement therapy);
- maximum intensity for any AE / any study-drug related AE;
- AE related deaths;
- AE resulting in permanent discontinuation of study drug.

6.4.3 Sensitivity and Supplementary Safety Analysis

To support the primary study results and to assess the robustness of the analysis, several additional sensitivity and supplementary analyses will be performed.

The primary safety endpoint will be analyzed using the same method described in Section 6.4.1.1 based on SAF analysis set and both TA and OA data scope.

In addition, analysis will be performed with additional bleeding events on SAF analysis set with PA data scope, and SAF analysis set with TA data scope:

- Minor bleeding
    - Minor bleeding will be further categorized as injection site and non-injection site bleeding events.

Additional analysis on the secondary safety endpoints will be performed based on SAF analysis set and TA data scope.

6.4.3.1 Stratified Safety Analysis

The primary safety endpoints analysis will be repeated incorporating all stratification factors, both with and without interaction terms.

6.4.4 Analysis of Other Pre-Specified Safety Variable(s)

The additional safety endpoints analysis is based on a descriptive proportion of subjects by treatment group and overall with pre-specified safety endpoints based on SAF analysis set.

- Incidence proportion of adverse events of special interests (AESIs) and severity will be summarized by treatment group and overall.
- Vital sign measures (including ECG) and the change from baseline will be summarized by treatment group and overall.

- Laboratory tests variables will be summarized by study visits, by treatment group, and overall. It will also be presented as change and percentage change from baseline over time after study intervention administration, as appropriate. In addition, the number of subjects who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group and overall.
- Bleeding of the arterio-venous grafts or fistulas will be summarized by treatment group and overall. Additionally, assessment of the severity of bleeding at the dialysis access following the hemodialysis procedure will be done at specified visits. Severity of bleeding at the dialysis access will be assessed approximately 15 minutes (10 – 20 minutes) after removal of the dialysis needle(s) from the AV access according to the following categories (exploratory bleeding score):
  i. "0" no access bleeding;
  ii. "1" slow oozing;
  iii. "2" overt bleeding

Proportion of the participants with the bleeding at the dialysis access following the hemodialysis procedure will be summarized by treatment group according to the above bleeding score categories.

6.4.5 Subgroup Analysis

The subgroup analyses based on baseline and demographic characteristics are planned for the treatment groups comparisons of the primary safety endpoints, the subgroups for the safety analysis are the same as those listed in section 6.2.2.3:

The analyses for the subgroups will be performed based on SAF analysis set and PA data scope and SAF analysis set and TA data scope. The results will be presented descriptively with forest plots.

6.4.6 Analysis of COVID-19 Patients

Analysis to evaluate the COVID-19 impact on the study primary safety endpoint will be performed by comparing the descriptive statistics among COVID-19 versus non-COVID-19 patient population. Additional analysis on the COVID-19 will be described in the future SAP revision if needed.

6.5 Data affected by the war in Ukraine

Data ‘affected’ by the war in the Ukraine will be assessed during the final Blind Review Meeting and will be documented in the Blind Review Report. As the war started after the primary analysis was completed, it is expected that only data in the post study intervention follow-up period will be affected, the impact of the war is considered to be minor/not substantial on the statistical analysis and on interpretation on the study results.
Any missingness due to the war is considered as not related to the outcomes of the study i.e. the missingness is likely noninformative. The EMA guidance “Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials” released by the Biostatistics Working Party will be taken into account.

7. Document History and Changes in the Planned Statistical Analysis

- Approval of the SAP version 1.0 dated 25 AUG 2020
- The following changes were made in the SAP Version 2.0 dated 15 DEC 2021:
    - Updated the data scope definitions to cover the follow up and extension periods alone.
    - Updated the concomitant medication period definitions
    - Adapted the safety and efficacy outcome variable sections with the exploratory competing risk analysis including with cause-specific and sub-distribution hazard models
    - Clarified definition of the subgroup of subjects with COVID-19
    - General updates based on new version of the protocol
    - Updates to the PK/PD sections based on expert opinion and review
    - Updated BAY 2976217 to 'Fesomersen'.
    - Removed the following subgroups as they do not make sense
        - Medical condition that likely led to RRT
        - Time since the start date for most recent Hemodialysis (including hemodiafiltration)
    - Removed text from section 6.4.3 due to repetition and referenced the text in section 6.4.1.
    - Updated the safety analysis set definition to clarify how subjects who were mis-dosed would be handled
- The following changes were made in the SAP version 3.0 dated 01 FEB 2022:
    - Added undetermined- presumed cardiovascular death to efficacy composite
    - Updated analysis periods and data scopes so they no longer depend on visits
    - Aligned the subgroups across safety and efficacy analyses
- The following changes were made in the SAP version 4.0 dated 31MAY2022:
    - Added section 6.5 relating to the handling of data affected by the war in Ukraine.

8. References

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Statistical Analysis Plan (Amendment/Supplement) Approval Form

Study Number (Bay No./IMP no.)	21170
Statistical Analysis Plan (SAP) Version and Date	Version 4.0 31st May 2022

I have read and approve the SAP/SAP Amendment referred above.

	Name	Signature and Date
Author:		
Study Statistician	PPD	PPD
Approved by:		
Statistical Project Lead	PPD	PPD
Clinical Lead	PPD	PPD
Study Medical Expert	PPD	PPD

Study Statistical Analyst	PPD	PPD
Global safety lead	PPD	PPD
Medical Writer	PPD	PPD
PK lead	PPD	PPD
PD lead	PPD	PPD