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Official Title:	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 BAY 2976217
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Title Page

Protocol Title:

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 BAY 2976217

Protocol Number: 21170

Version Number 3.0

Amendment Number: Global Amendment 2

Compound Number: BAY 2976217

Study Phase: 2

Short Title: Ph 2 Safety, PK/PD of multiple doses of BAY 2976217 in ESRD

Acronym: RE-THINC ESRD

Sponsor Name:

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US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA

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Medical Monitor name and contact information will be provided separately.

Name: PPD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	07 JUL 2021
Amendment 1	29 SEP 2020
Original Protocol	09 MAR 2020

Amendment 2

This amendment is considered to be substantial, based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for the Amendment:

The rationale of this amendment is to implement the possibility of local laboratory safety assessments in case centrally provided laboratory kits are not available due to COVID-19-related logistical reasons.

Further it is to update the requirements for discontinuation of study intervention and the rules for prohibited medications intake. Minor corrections and clarifications were also added.

Key changes

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 4.4. End of study definition	Wording of the secondary safety endpoint was moved down together with a secondary objective.	Clarification for the analysis of the primary efficacy and safety outcomes. Wording was also updated to reflect changes that were carried out in a previous amendment on the analysis of TEAEs. Time windows for the analyses were also clarified, and end of study definition was updated to reflect the changes in the primary endpoints.
Section 1.3 Schedule of Activities (SoA)	Sentence requiring the procedures to be performed in the order they are indicated in the SoA was removed.	This previous requirement was removed to ease the study conduct at the sites.
Section 1.3 Schedule of Activities (SoA)	Measurement of Pre- & Post-HD weight, post-HD blood pressure, urea reduction ratio and Kt/V have been added to Visits FU2 and FU3, URR or Kt/V also to V8 and FU1	Addition of missing components of the renal replacement therapy procedure, and needed to assess successful dialysis procedure.
Section 3 Objectives and Endpoints Section 9.4.6.1. Exploratory efficacy endpoints	Exploratory endpoints have been updated as follows to include VTE into the composite endpoint	Based on expert opinion, the exploratory efficacy outcomes death due to MI, stroke, PE and SE, non-fatal stroke, non-fatal MI, major amputation of vascular etiology, and acute limb ischemia needs to be merged with the exploratory efficacy outcome VTE because of similar clinical importance.
Section 5.4 Screen failures	Section 5.4 has been changed to allow rescreening once, with no conditions.	The population under study has many comorbidities and may present transient laboratory abnormalities due to hemodialysis. Since screening period is short, by allowing rescreening, the investigator may choose to include a patient after clinical improvement or lab normalization.

Section # and Name	Description of Change	Brief Rationale
Section 6.5 Concomitant Therapy Section 7.1.1. Events Requiring Definitive Discontinuation of Study Intervention Section 7.1.2 Temporary discontinuation	If a prohibited concomitant medication is indicated, study intervention will be temporarily interrupted. Study intervention is permanently discontinued only in cases where the study intervention is interrupted for >56 days.	Participants make use of prohibited medication for a limited period to treat a specific condition. Once this has been resolved and the participant is no longer using the concomitant medication, the study intervention may be restarted.
Section 7.1.1 Events Requiring Definitive Discontinuation of Study Intervention Section 8.2.1.3 Recommendations for Surgeries Including Kidney Transplant	If participant discontinues during the main treatment period, the participant should conduct Visit 22 and then proceed to the follow-up period. If participant discontinues during the extended treatment period, the participant should conduct Visit 28, and then proceed to the follow-up period.	This change aims to minimize participant burden and, at the same time, secure participant safety and data acquisition as they will be followed for 20 weeks after the last dose. Full PK and PD sampling during follow up is important with view on interpretation of the data.
Section 8.2 Safety assessments	If the platelet value or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a local or central laboratory repeat blood specimen ~~must~~ may be re-drawn as soon as possible ~~(ideally at the next dialysis session, however, within no more than 7 days).~~	Patients are being seen 3 times a week, therefore one week has been perceived as too long.
Section 8.2.1.4: AV access bleeding	AV access bleeding assessment may be done prior to 15 minutes if the bleeding has already stopped.	Participant and site burden will be reduced without compromising the safety of the participant.
Section 9.4. statistical analyses	The investigator, study staff, participants, ~~blinded~~ monitors, ~~and members of the Sponsor's clinical operations team and data management team~~ and CIAC will remain blinded ~~throughout~~ until the end of the study.	Due to the planned snapshot, Sponsor's clinical team will need to be unblinded.
Section 9.4.1.1 Planned Methods of Analysis	All analyses and tabulations will be performed using SAS@ Version 9.2 or higher or if applicable, other software	In case of a software update, also other softwares apart from SAS Version 9.2 or higher may be used for the analyses.
Section 9.4.1.5 Definition of Baseline	The section was rewritten to reflect the change in definition of baseline. Reference to SAP for further details was added.	Baseline measurements are done at one timepoint only, and mean value will no longer be calculated
Section 9.4.1.6 On Treatment	Text was reorganized for better readability, and to not limit “on-treatment“ to the main treatment period.	Text was reorganized for better readability, and to not limit "on-treatment“ to the main treatment period.
Section 10.2 Appendix 2: Clinical Laboratory tests	Local laboratory results are allowed if due to logistical reasons central laboratory kits are not available, or in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation.	To enable the use of local laboratory for safety assessments, in case of shortage of central laboratory kits due to the COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
Section 10.3.2 Definition of SAE	Text in section f (other situations) was updated	Text was updated to reflect the changes implemented in protocol template update.

Clarifications to the protocol

Section # and Name	Description of Change
Section 1.3 Schedule of Activities (SoA)	Informed consent form must be signed on V1 day, other assessments may be done at a later date. Sentence "Post-HD weight is to be measured after hemodialysis" was removed as unnecessary.
Section 2.3.2 Benefit assessment	Text was revised for better readability.
Section 3 Objectives and Endpoints	Link to estimand components for primary endpoint was removed as unnecessary in this section.
Section 4.1 Overall design	1)Clarification that ASA is not the only allowed antiplatelet therapy, but is only allowed, at doses below 150mg/day. 2)The primary analysis will be performed to expedite ~~management review and~~ Phase 3 dose selection. "Management review" was removed as it is part of the Phase 3 dose selection process.
Section 6.5 Concomitant Therapy	UFH or LMWH are also allowed to maintain patency of hemodialysis access
Section 7.1	Added a reference to section 7.1.1 to clarify the time participant will stay in the study in case the study intervention is withdrawn.
Section 7.1.1 Events Requiring Definitive Discontinuation of Study Intervention	The following paragraph was removed, as it does not belog to this section: ~~If consent is withdrawn, or the participant signs off dialysis without expected return of life-sustaining kidney function or without transferring to an alternative form of renal-replacement therapy, the Early Termination Visit will be conducted immediately (Section 7.2). See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.~~
Section 7.3 Lost to Follow Up	The survival status will be recorded in the eCRF, if no survival status is known, the contact attempt will be recorded.
Section 8.1 Efficacy assessments Section 8.3.6. Cardiovascular and Death Events	Clarification on how the adjudication process is triggered was added, as well as the location of further information on the adjudication process.
Section 8.2. Safety Assessments	Clinically significant changes in platelet count, ALT/AST are to be reported both as laboratory parameters as well as adverse events. Repeat samples for uninterpretable liver enzyme and platelet values samples may be done locally or centrally, and should be done as soon as possible. Specific time limit has been removed.
Section 8.2.1 Bleeding events	1) first paragraph: Clarification of text: bleeding event is an outcome, not an analysis, which is described in Section 9. 2)Third paragraph: no central laboratory samples are needed in case of bleeding events
Section 8.2.1 Bleeding events	Bleeding events are not adjudicated by the investigator, and the section has been revised accordingly.
Section 8.2.1.2: remedial treatment for bleeding	Clarification that remedial treatment for bleeding events is not considered rescue medication
Section 8.2.1.3: recommendations after surgeries	Modifications were made to to reflect the changes made in amendment 2 to the discontinuation and concomitant medication sections.
Section 8.2.1.4 AV access bleeding	A clarification was made that the AV access bleeding is assessed, at the end of the dialysis session.
Section 8.2.5 Clinical Safety Laboratory Assessments	Duplicated information on safety laboratory samples for ALT/AST was deleted, as this information is already available in Section 8.2
Section 8.3.10 Adjudication	Adjudication of an adverse event will only be carried out after randomization.

Section # and Name	Description of Change
Section 9.4.2 Primary Endpoints	1)Text was reorganized for better readability and correctness 2)Treatment policy strategy was removed from the protocol as the time windows are described later in this Section. 3)Description of primary and secondary safety analyses was further clarified, including time windows for the analyses.
Section 9.4.3 Secondary endpoints	Text was reorganized for better readability and consistency.
Section 9.4.6 Tertiary/exploratory endpoints	Text clarifying that further details on exploratory endpoints are described in the SAP was added.

Corrections of inconsistencies and minor corrections (editorial corrections not detailed)**:**

Section # and Name	Description of Change
Section 1.1 Synopsis	A sentence was deleted that was not needed.
Section 1.3 Schedule of Activities (SoA)	Erroneous plus sign at visit window for V1 was corrected to a minus sign
Section 1.3 Schedule of Activities (SoA)	Erroneous ** at Screening (1 Week) was removed
Section 8.6.1 Secondary pharmacodynamic parameters Section 8.6.2 Other pharmacodynamic parameters	Secondary and Other pharmacodynamic parameters were aligned with protocol section 3.
Section 9.4.1.3 Inter-current event Section 9.4.2 Primary endpoints	Unblinding to study intervention: the study will allow unblinding of the treatment assignment if the investigator deemed it necessary ~~after~~ <u>related to</u> a bleeding event or AE
Section 9.4.2 Primary endpoints	Intercurrent events were separated to different bullet points. The order of primary safety endpoints was changed to reflect the improtance of each endpoint, with the most important now on top.
Throughout	The term combination of MB and CRNMB Bleeding has been changed to composite of MB and CRNMB Bleeding
Throughout	As vital signs comprise only post HD BP measurements, the term “vital signs“ has been replaced by post HD BP where appplicable.
Throughout	Observation period was deleted as observation period has been removed from the study in previous amendment.

Administrative changes

Section # and Name	Description of Change
Title page	Protocol version number was removed from the header and placed on the protocol title page
Throughout	Protocol version number was deleted from the header, and protocol date as added.

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1. Protocol Summary

1.1 Synopsis

Study 21170 is a Phase 2 trial designed to evaluate the safety, pharmacokinetics and pharmacodynamics of BAY 2976217 in a population of patients with ESRD on HD treatment. The investigational agent, BAY 2976217 is a ligand conjugated antisense oligonucleotide (LICA) targeting coagulation factor XI synthesis. BAY 2976217 is ligand-conjugated to GalNAc [redacted] It is designed to inhibit synthesis of FXI in the liver with low circulating blood levels of the drug and the potential for reduced systemic effects.

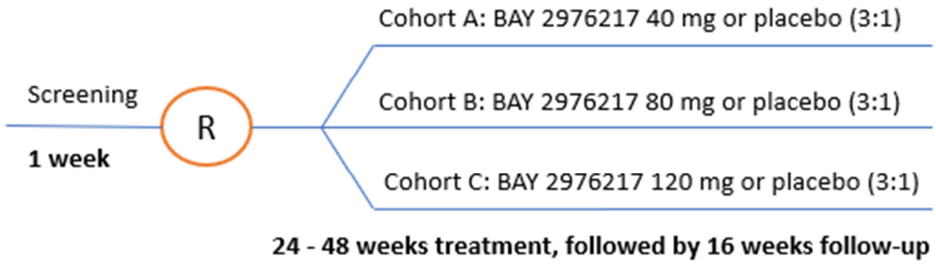
The participant population for this trial, ESRD patients on HD, are at high risk for both arterial and venous thrombosis and thromboembolism. However, treatment with antithrombotics in order to reduce the thrombosis risk has been complicated by increased risk of bleeding in this participant population. The study intervention BAY 2976217 is expected to reduce thrombotic events with minimal bleeding complications, a profile which may be ideal in this participant population. The action and tolerability of BAY 2976217 is supported by pre-clinical studies and Phase 1 human trials. The effects of targeting FXI have been evaluated with the unconjugated FXI ASO (BAY 2306001), that shares the same nucleotide sequence with BAY 2976217 and has an identical mechanism of action, in ESRD patients on HD in two Phase 2 placebo-controlled studies that enrolled 256 participants. Dose-dependent decreases in circulating FXI antigen and FXI activity were observed, there was no increase in clinically significant bleeding over placebo, and clotting of the dialysis circuit was reduced in a dose-dependent manner.

Study 21170 is a parallel group treatment study design with 3 dose cohorts that is participant and investigator blinded to assignment to active treatment versus placebo, in ESRD patients who are on HD ≥ 3 months, and are receiving hemodialysis for a minimum of 9 hours per week. Participants receiving therapeutic anticoagulation or antiplatelet other than ASA ≤ 150 mg/day are excluded. Approximately 288 randomized participants (to achieve an estimated 240 evaluable participants) with ESRD on HD are randomly assigned in a 3:1 fashion to receive SC treatment with one of 3 dose levels of BAY 2976217 or matching placebo. Following a 1-week screening, participants will be treated for 24 weeks, with the final 4 weeks of the main treatment period as an evaluation period for certain PD and safety parameters. To collect additional long-term safety information, participants will continue to be treated as randomized in the extended treatment period, with up to 24 weeks of additional treatment with study intervention. Once the overall treatment period is complete, participants will have a 16-week post-treatment follow-up period.

As this is a Phase 2 safety trial, the primary endpoint is the incidence of major bleeding and clinically relevant non-major bleeding as assessed by a CIAC. Additional study endpoints include the incidence and frequency of TEAEs, AESIs, changes in vital signs and laboratory findings, trough levels of BAY 2976217, maximum change in FXI activity levels during the main treatment period and coagulation parameters and clotting in the dialysis filters and circuit.

The study is graphically illustrated in Figure 1–1.

Figure 1–1: Study design



Protocol Title: 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 BAY 2976217

Short Title: Ph 2 Safety, PK/PD of multiple doses of BAY 2976217 in ESRD

Rationale:

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.

Patients with congenital deficiency of FXI and agents used to inhibit or decrease production of FXI have shown promise in reducing thrombotic events without increasing clinically significant bleeding, making it an attractive candidate for use in the ESRD patient on HD. An unconjugated FXI ASO (BAY 2306001) was studied in clinical trials. Pre-operative reduction of the synthesis of FXI levels by the unconjugated FXI ASO in patients who had elective primary unilateral total knee arthroplasty was highly effective for prevention of venous thrombosis and was not associated with increased peri-operative or subsequent bleeding. Two Phase 2 studies were conducted in ESRD patients, that showed that the reduction of the synthesis of FXI levels by the ASO was associated with less clotting of the dialysis circuit without an increase in bleeding risk.

However, the unconjugated FXI ASO requires higher doses with relatively high injection volumes, and a long loading phase to achieve adequate liver delivery to reduce FXI levels, and was associated with certain adverse events such as thrombocytopenia and injection site reactions. Therefore, the GalNAc-conjugated FXI ASO BAY 2976217 was developed [redacted]

Animal studies as well as a Phase 1 human trial of BAY 2976217 have confirmed significant dose-dependent reduction in FXI activity with lower doses of the drug, and no evidence of injection site reactions or platelet effects. [redacted] rogression to a Phase 2 trial in ESRD patients on HD is reasonable as there is a high unmet medical need to reduce thrombotic events without increasing bleeding in this population. As there is currently no accepted alternative therapy proven to reduce thrombotic events in this population, the use of low-dose ASA is recommended and widely accepted (1).

Objectives and Endpoints:

Objectives	Estimands/Endpoints
Primary	
• To evaluate the safety of BAY 2976217as compared to placebo	Primary Endpoint • The incidence of composite 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 BAY 2976217as compared to placebo	• The incidence of 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 BAY 2976217	Pharmacokinetic Endpoints • Trough concentrations for 3 dose levels of BAY 2976217 Pharmacodynamic Endpoints • Maximum change in FXI antigen levels during the main treatment period • Maximum change in FXI activity levels during the main treatment period

Overall Design

This is a multicenter, double-blind, randomized, parallel group treatment study with 3 dose cohorts tested against placebo, in ESRD patients who are on HD (including hemodiafiltration) ≥ 3 months, and are receiving hemodialysis for a minimum of 9 hours per week. Participants receiving therapeutic anticoagulation or antiplatelet other than ASA ≤ 150 mg/day are excluded. Approximately 288 participants will be randomized in this study. Participants will be stratified at randomization for use of ASA (yes/no) and CV risk factors (stratum 1 / stratum 2), and will then be randomized 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]). Within each cohort participants will be randomized to receive either BAY 2976217 or matching placebo (administered at equivalent dose volumes) in a 3:1 ratio. Sponsor, participants and investigators are blinded with respect to active treatment versus matching placebo, but not blinded to dose cohort. With an assumed attrition rate of approximately 15% during the main treatment period, approximately 288 randomized participants would allow for an estimated 240 participants. All standard of care

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

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 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

Stratum 1- zero or one risk factor, except the presence of DM or Afib;

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

All cohorts will consist of up to 1-week screening period and a 24-week main treatment period, the last 4 weeks of which are an evaluation period, an up to 24-week extended treatment period, followed by a 16-week post-treatment follow-up period.

The data and outcomes collected in the study will be analyzed by 4 groups: Pooled placebo group (from Cohorts A, B and C), 40 mg dose group (BAY 2976217 from Cohort A), 80 mg dose group (BAY 2976217 from Cohort B), and 120 mg dose group (BAY 2976217 from Cohort C). All suspected bleeding, cardiovascular and thrombosis events will be assessed by CIAC blinded to treatment allocation. An independent DMC will monitor the participant's safety and give recommendations to the Steering Committee (see below).

Selected clinical sites will participate in the alternative PK&PD Sampling group. A target population of approximately 24-40 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.

Intervention Model: Parallel

Primary Purpose: Treatment

Number of Arms: 3 Dose cohorts

Blinding: Participant, Investigator, Outcomes Assessor

Number of Participants: Approximately 288 randomized

Assuming 15% screen failure rate, approximately 340 participants will be screened to achieve an estimated total of 288 randomized participants, 96 per each cohort group and an estimated 80 participants per cohort after an assumed attrition rate of approximately 15%. Additional participants may be enrolled based on recommendations from the Steering Committee and/or DMC (e.g.- based on actual retention of participants, or other scientific or safety reasons).

Intervention Groups and Duration:

Within each dose cohort, participants will be randomized in a 3:1 ratio to receive SC treatment with either BAY 2976217 or placebo. 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 BAY 2976217 or placebo SC (3:1) n~96
- Cohort B: 80 mg BAY 2976217 or placebo SC (3:1) n~96
- Cohort C: 120 mg BAY 2976217 or placebo SC (3:1) n~96

Study intervention will be administered once every 4 weeks as described in the SoA, unless there is a need for dose interruption (Section 7.1). All cohorts will consist of 1-week screening period and a 24-week main treatment period, the last 4 weeks of which are an evaluation period for certain PD and safety parameters. To collect additional long-term safety information, participants will continue to be treated as randomized in the extended treatment period, with up to 24 weeks of additional treatment with study intervention. 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, for a total of up to 65 weeks of participation.

All participants who are in the extended treatment period will need to stop treatment when the last participant enrolled into 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 move to the 16-week post-treatment follow-up period. The sponsor reserves the discretion to halt further dosing in the extended treatment period earlier in anticipation of the last participant completing the main treatment period.

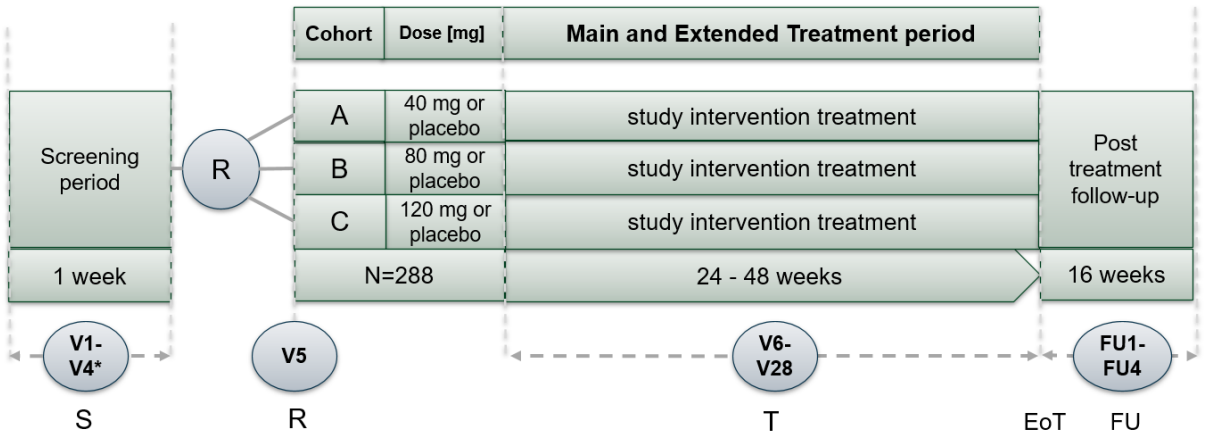
Data Monitoring Committee: Yes

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 on regular basis, as outlined in the DMC Charter. At any time, if there is an unexpected safety finding(s) in cohort C (the 120 mg dose cohort), the DMC may elect to modify the cohort to either a 100 mg dose level 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 in cohort C will have their dosing modified to 100 mg or 80 mg once monthly and all new participants in cohort C will initiate dosing at 100 mg or 80 mg once monthly.

All suspected bleeding, cardiovascular and thrombosis events will be assessed by CIAC blinded to treatment allocation.

1.2 Schema



EoT = end of treatment, N = number of subjects, S = screening, R = randomization, T = treatment, FU = follow-up, V = visit

* As per amendment 1, Visits 2, 3 and 4 are not performed (i.e. they are applicable only for patients enrolled before amendment 1).

1.3 Schedule of Activities (SoA)

- PK and PD sampling are to be performed at timepoints indicated in Section 8.5.
- In addition to the study procedures described in this section, on dialysis days HD is to be started between 15 minutes before to 15 minutes after study intervention administration.

Visit 1 procedures should preferably be done on one day; however, if not possible, some procedures can be also done over more than one day. Signing informed consent will be recorded as the V1 date, other procedures from V1 may be done on a later date, as long as all results are timely available for assessing eligibility prior to V5. It should be ensured that reports of the lab tests required for eligibility are available at randomization.

Table 1–1: Schedule of Activities, Visit V1 to Visit V13

	Screening (1 week)				Main treatment period (24 weeks)									Comments
Visit Number	**V1**	**V2****	**V3****	**V4****	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	* At sites participating in the alternative PK & PD sampling group. Study Days marked with an asterisk are as listed in the table + 1 day (e.g.- V7 is Week 2, Study Day 9). ** Not performed as of amendment 1
Week	-1				1	1	2	3	4	5	7	9	11	
Day	-7				1	2	8*	15*	22*	29*	43*	57*	71*	
Window (days)	-6				0	0	+5	+5	+5	+5	+5	+5	+5	
Informed Consent and PID	•													See Section 6.3
Inclusion/Exclusion Criteria / Eligibility Check	•				•									On V5 eligibility should be confirmed, including check of laboratory test results from the screening visits.
Medical History	•													
Height	•													
Randomization					•									See Section 6.3
Pre- & Post-HD Weight	•				•			•		•		•		See Section 8.2.2
Vital signs (post-HD BP)	•				•			•		•		•		See Section 8.2.3 for further details
ECG (12-lead)	•							•				•		See Section 8.2.4 for further details
Chemistry/Liver Panel	•	•	•	•	•			•		•	•	•	•	See Section 10.2 and Section 8.3.8 for further information
Hematology Panel	•	•	•	•	•			•		•	•	•	•	
Blood sample for genetic testing					•									Study sites in China are excluded from pharmacogenetic and BM sample collection.

Table 1–1: Schedule of Activities, Visit V1 to Visit V13

	Screening (1 week)				Main treatment period (24 weeks)									Comments
Visit Number	**V1**	**V2****	**V3****	**V4****	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	* At sites participating in the alternative PK & PD sampling group. Study Days marked with an asterisk are as listed in the table + 1 day (e.g.- V7 is Week 2, Study Day 9). ** Not performed as of amendment 1
Week	-1				1	1	2	3	4	5	7	9	11	
Day	-7				1	2	8*	15*	22*	29*	43*	57*	71*	
Window (days)	-6				0	0	+5	+5	+5	+5	+5	+5	+5	
Biomarker blood sample (FVIII, FIX, FXII, vWF antigen, vWF activity)					•									See Section 8.8
Immunogenicity blood Sampling					•			•		•				See Section 8.5 for details on sampling times
Biomarker blood sample (other BM)					•				•			•		See Section 8.8
PK blood sampling					•	•	•	•	•	•	•	•	•	See Section 8.5 for details on PK/PD sampling.
PD blood sampling	•	•	•	•	•	•	•	•	•	•	•	•	•	
Serum Pregnancy test (WOCBP only)	•	•	•	•	•					•		•		See Section 8.3.5.
Urea reduction ratio or Kt/V (local)	•				•			•		•		•		Local URR or Kt/V results obtained in the previous month to the study visit will be accepted.
Study intervention administration					•					•		•		See Section 6.1 for further details.
Dialysate effluent					•					•				See Section 8.5 for details on dialysate sampling
Clotting Score & AV access bleeding severity	•	•	•	•	•			•		•		•		See Section 8.6 for further details
Adverse events and outcome events	•	•	•	•	•	•	•	•	•	•	•	•	•	See Section 8.3; certain events will also require submission of an adjudication package to CIAC as described in Sections 8.1 and 8.2
AESI					•	•	•	•	•	•	•	•	•	See Section 8.3.8
Dialysis prescription	•				•			•		•		•		
Concomitant medications	•	•	•	•	•	•	•	•	•	•	•	•	•	

AESI = adverse events of special interest, AV = Arterio venous, BM = Biomarker, BP = Blood pressure, CIAC = Central Independent Adjudication Committee, ECG = Electrocardiogram, HD = Hemodialysis, KtV = Value used to quantify hemodialysis and peritoneal dialysis treatment adequacy, PID = participant identification code, FVIII = Coagulation Factor VIII, FIX = Coagulation factor IX, FXII = Coagulation factor XII, PK = Pharmacokinetics, PD = Pharmacodynamics(s), URR = Urea reduction ratio, vWF = Von Willebrand factor, WOCBP = Women of childbearing potential.

Table 1–2: Schedule of activities, Visit V14 to visit V22

	Main treatment period (24 weeks)									Comments
						Evaluation Period				* At sites participating in the alternative PK & PD sampling group, days marked with an asterisk are as listed in the table + 1 day (e.g.- V7 is Week 2, Study Day 9) ** these time points (Study Weeks and Study Days) are based on completion of either the main treatment period or the extended treatment period. The early termination visit will be conducted when a study participant has terminated the study (see Section 7.2)
Visit Number	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	
Week	13	15	17	19	21	22	23	24	25	
Day	85*	99*	113*	127*	141*	148*	155*	162*	169*	
Window	+5	+5	+5	+5	+5	+5	+5	+5	+5	
Pre- & Post-HD weight	●		●		●				●	See Section 8.2.2
post-HD BP	●		●		●				●	See Section 8.2.3 for further details
ECG (12-lead)					●				●	
Chemistry/liver panel	●	●	●	●	●	●	●	●	●	See Section 10.2 for further details
Hematology panel	●	●	●	●	●	●	●	●	●	See Section 10.2 for further details
Immunogenicity blood sampling	●								●	See Section 8.5 for details on immunogenicity sampling times
Biomarker blood sample (other BM)	●		●		●				●	See Section 8.8
PK blood sampling	●		●		●	●	●	●	●	See Section 8.5 for details on PK/PD sampling.
PD blood sampling	●		●		●	●	●	●	●	
Serum pregnancy test (WOCBP only)	●		●		●				●	
Urea Reduction Ratio or Kt/V (local)	●		●		●				●	
Study intervention administration	●		●		●				●***	See Section 6.1 for further details. ***Dosing of study intervention will occur at V22 in all participants except those who will not participate in the Extension Treatment Period
Clotting Score & AV access bleeding severity	●		●		●	●	●	●	●	See Section 8.6 for further details
Adverse events and outcome events	●	●	●	●	●	●	●	●	●	See Section 8.3; certain events will also require submission of an adjudication package to CIAC as described in Sections 8.1 and 8.2
AESI	●	●	●	●	●	●	●	●	●	See Section 8.3.8
Dialysis prescription	●		●		●				●	
Concomitant medications	●	●	●	●	●	●	●	●	●	

AESI = adverse events of special interest, AV = Arterio venous, BM = Biomarker, CIAC = Central Independent Adjudication Committee, ECG = Electrocardiogram, HD = Hemodialysis, PK = Pharmacokinetics, PD = pharmacodynamics(s), WOCBP = Women of childbearing potential.

Table 1–3: Schedule of Activities, extended treatment visits and Visit FU1 to FU4

	Extended treatment period (24 weeks)						Follow-up period (16 weeks)				Early Termination	Comments
Visit Number	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**FU1**	**FU2**	**FU3**	**FU4**		* At sites participating in the alternative PK & PD sampling group, days marked with an asterisk are as listed in the table +1 day (e.g.V7 is Day 9) ** these time points (Study Weeks and Study Days) are based on completion of either the main treatment period or the extended treatment period. FU1-FU4 Should take place every 4 weeks (+5 days). The early termination visit will be conducted when a study participant has terminated the study (see Section 7.2)
Week	29	33	37	41	45	49	29-53**	33-57**	37-61**	41-65**		
Day	197*	225*	253*	281*	309*	337*						
Window (days)	+5	+5	+5	+5	+5	+5					n/a	
Pre- & Post-HD weight	●	●	●	●	●	●	●	●	●	●	●	See Section 8.2.2
ECG (12-lead)						●				●	●	See Section 8.2.4
Chemistry/liver panel	●	●	●	●	●	●	●	●	●	●	●	See Section 10.2, Section 8.2.5 and Section 8.3.8. Platelet count and ALT/AST are to be measured every 2 weeks during extended treatment period, local lab monitoring, unscheduled visits can occur between the scheduled visits.
Hematology panel	●	●	●	●	●	●	●	●	●	●	●	
Immunogenicity blood sampling		●		●		●				●	●	See Section 8.5 for details on immunogenicity sampling times
PK blood sampling	●	●	●	●	●	●	●			●	●	See Section 8.5 for details on PK/PD sampling.
PD blood sampling	●	●	●	●	●	●	●			●	●	
Serum pregnancy test (WOCBP only)	●	●	●	●	●	●						
Urea reduction ratio or Kt/V(local)	●	●	●	●	●	●	●	●	●	●	●	
Study intervention administration	●	●	●	●	●							See Section 6.1 for further details.
Post-HD blood pressure	●	●	●	●	●	●	●	●	●	●	●	See Section 8.2.3 for further details
Clotting Score & AV access bleeding severity	●	●	●	●	●	●	●	●	●	●	●	See Section 8.6 for further details
Adverse Events and outcome events	●	●	●	●	●	●	●	●	●	●	●	See Section 8.3; certain events will also require submission of an adjudication package to CIAC as described in Sections 8.1 and 8.2.
AESI	●	●	●	●	●	●	●	●	●	●	●	See Section 8.3.8
Dialysis Prescription	●	●	●	●	●	●	●	●	●	●	●	
Concomitant Medications	●	●	●	●	●	●	●	●	●	●	●	

AESI = Adverse events of special interest, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, AV = Arterio venous, BM = Biomarker, CIAC = Central Independent Adjudication Committee, ECG = Electrocardiogram, FU = Follow-up, HD = Hemodialysis, PK = Pharmacokinetics, PD = pharmacodynamics(s), WOCBP = Women of childbearing potential.

2. Introduction

BAY 2976217 is a novel long-acting ligand conjugated antisense oligonucleotide (LICA) targeting the hepatic synthesis of FXI with the potential to exhibit an antithrombotic effect with lower risk of bleeding events than currently available antithrombotics.

2.1 Study Rationale

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. Pre-operative reduction of the synthesis of FXI levels by unconjugated FXI ASO in patients who had elective primary unilateral total knee arthroplasty was highly effective for prevention of venous thrombosis and was not associated with increased peri-operative or subsequent bleeding.

In ESRD patients, the reduction of the synthesis of FXI levels by the ASO was associated with less clotting of the dialysis circuit without an increase in bleeding risk. The unconjugated FXI ASO requires higher doses and a long loading phase to achieve adequate liver delivery and reduced FXI levels; therefore, the GalNAc-conjugated FXI ASO was developed, [redacted] Treatment with GalNAc-conjugated FXI ASO in patients with ESRD has a potential to prevent thromboembolic complications such as MI, stroke, peripheral arterial events, and cardiovascular death without increasing risk of clinically significant bleeding. This Phase 2 trial will assess the safety and characterize the PK/PD profile of three different doses of BAY 2976217 given SC once a month to participants with ESRD on HD.

2.2 Background

2.2.1 Unmet Need for Reducing Cardiovascular Morbidity and Mortality in ESRD

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 (2). Compared to the general population, patients receiving dialysis are at higher risk of thrombotic events including stroke (4-10x higher in dialysis patients)(3), MI (CAD prevalence in dialysis patients is 5-10x higher) (4), and amputations, limb-ischemia and chronic skin ulcers related to PAD (PAD prevalence is as high as 40%) (5). Only 40% of patients receiving HD are alive five years after onset (6), and the mortality rate for those initiating dialysis is 15x higher than in matched controls from the general population (7). This high mortality is largely driven by CV causes (7).

Therapies directed at both traditional and non-traditional CV risk factors have not been studied in dialysis patients (8, 9), or have failed to demonstrate a benefit in clinical trials (10-14). The use of currently available antithrombotics is uncertain, and clinicians are faced with the challenging task of assessing the risk of atherothrombosis or thromboembolism against a high risk for bleeding in their patients. Lower dose (≤150mg daily) ASA use is widely accepted as the mainstay preventative therapy (1, 15). Atrial fibrillation, one important risk factor for stroke, is present in 15%–40% of hemodialysis patients (16), which is a much higher rate than the 1% prevalence in the general adult population (17). Dialysis patients with

AFib treated with oral anticoagulation experience bleeding 10x more frequently than AFib patients with normal kidney function (18). In dialysis AFib patients' risk of hemorrhagic stroke with anticoagulation is 1.4 to 2.7x higher (19-22). In non-AFib dialysis patients, bleeding risk is increased 2-20x with anticoagulation versus without (23). These unique benefit-risk considerations (unproven benefit of antithrombotics for preventing CV events versus bleeding risk) often leave patients with inadequate protection from their CV risk.

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 (24).

2.2.2 Factor XI

FXI is a new antithrombotic target with the potential for a lower risk of bleeding than currently available antithrombotics. The identification of FXI as a safer target is supported by epidemiological data in patients with congenital deficiency of FXI, studies in FXI deficient mice, studies with FXI knockdown or inhibition, and animal bleeding models (25).

The formation and stability of clots are enhanced by FXI in vitro (26). Furthermore, FXI amplifies thrombin generation when coagulation is initiated by low levels of tissue factor or thrombin. FXI-dependent amplification of thrombin generation also leads to activation of thrombin-activatable fibrinolysis inhibitor, which renders clots resistant to fibrinolysis. Therefore, FXI inhibitors might also indirectly enhance clot dissolution.

The most solid evidence in support of FXI as a therapeutic target comes from epidemiological data. Observational studies in patients with congenital FXI deficiency suggest that these patients are at a reduced risk of ischemic stroke, myocardial infarction, and venous thromboembolism compared with those with normal FXI levels (27-29). Additionally, spontaneous bleeding is rare in FXI deficiency, and a variable bleeding risk exists after surgery or trauma, with greatest bleeding risk localized to areas of high fibrinolytic activity (30); in a recent study there was no association between FXI coagulant activity level and bleeding severity (31).

2.2.3 BAY 2976217

The investigational agent, BAY 2976217 is a ligand conjugated antisense oligonucleotide (LICA) targeting FXI synthesis in the liver. BAY 2976217 is ligand-conjugated to triantennary GalNAc [redacted] Delivery is targeted to the hepatocyte, leading to [redacted] efficient inhibition of FXI synthesis, thereby reducing potential for dose-dependent effects.

BAY 2976217 is a member of a class of molecules, 2′-MOE modified ASOs, that primarily differ from each other in their antisense nucleotide sequence that determines their specificity and binding to their respective mRNA target. The sponsor's collaboration partner for BAY 2976217 (Ionis) has studied multiple 2′-MOE modified ASOs in clinical trials. At the time of this protocol finalization, approximately 6,500 subjects have been treated systemically (dosed intravenously and/or SC) with unconjugated 2′-MOE-modified ASOs at doses of 15 mg to 1200 mg, and for durations that range from short-term (e.g., single dose) to durations that

exceed 4 years. Three publications that summarize the analyses of the Ionis integrated safety database include results from >2,600 subjects treated with 16 unconjugated 2'-MOE ASOs systemically in 52 completed clinical trials (32-34). Key safety findings include the potential for renal dysfunction and thrombocytopenia with unconjugated 2'-MOE ASOs.

More recently, conjugation of GalNAc to 2'-MOE ASOs has been shown to increase productive delivery of ASOs to the liver resulting in substantial increases in potency for hepatocyte expressed target RNAs such as FXI (35). At the time of this protocol finalization, fifteen 2'-MOE ASOs conjugated with a GalNAc moiety are in development and 10 have completed at least a 4-week clinical trial in healthy volunteers. In total, >1100 subjects have been exposed to GalNAc-conjugated ASO's and ~400 subjects for at least 6 months up to 1 year. An integrated analysis of the safety database in healthy volunteers showed increased potency of up to 30-fold over their paired unconjugated ASO; no clinically relevant changes in chemistry, hematology (including in platelet counts), urinalysis, vital sign measurements, or ECG parameters; no changes in heart rate, blood pressure, ECG or respiration function were reported; and the most commonly reported TEAEs that were considered related to ASO administration were injection site reactions and headache (35). BAY 2976217 is GalNAc conjugated and the increase in potency of BAY 2976217 relative to the unconjugated ASO was compared between Phase 1 trial results (see below). CCI [redacted]

2.2.3.1 Preclinical Data with BAY 2306001 (ISIS 416858) and BAY 2976217 (ION 957943)

Proof-of-concept studies have been conducted with both GalNAc-conjugated and unconjugated mouse-specific FXI ASOs in mouse models of thrombosis. Twice weekly administration of FXI ASOs for 3 weeks reduced hepatic levels of FXI mRNA and plasma levels of FXI protein in a dose-dependent manner. The administration of FXI ASOs to date has not caused an increase in bleeding risk. FXI ASOs evaluated in vivo using the $FeCl_3$ inferior vena cava thrombosis model demonstrated an antithrombotic effect with GalNAc-conjugation increasing potency as compared to unconjugated ASO.

In an arterial model, FXI ASO treatment reduced platelet and fibrin accumulation and completely prevented occlusion of mouse mesenteric arteries after $FeCl_3$ injury. The antithrombotic effect was comparable to clopidogrel (Plavix, 12.5 mg/kg). Furthermore, FXI ASOs have been shown to be pharmacologically active in the cynomolgus monkey and decrease the hepatic FXI mRNA expression and plasma FXI protein activity levels. (36).

FXI ASOs previously demonstrated antithrombotic activities with efficacy comparable to warfarin or enoxaparin. Warfarin and enoxaparin both have exhibited bleeding issues which have not been observed by inhibiting FXI with ASO. After withdrawal of ASO treatment there was no rebound increase (above baseline) in FXI levels. The anticoagulant effect of FXI antisense therapy has been shown to be effectively and rapidly reversed by plasma-derived FXI concentrate (37).

These results support the concept that the potent inhibition of FXI through antisense therapy may serve as a new and effective strategy for the treatment and prevention of thromboembolism with improved specificity and safety as compared to currently available drugs. Details for the preclinical programs for BAY 2306001 and BAY 2976217 can be found in the Investigator's Brochure.

2.2.3.2 Clinical Data with BAY 2306001

BAY 2306001, an unconjugated 2′-MOE ASO that has the same base sequence as BAY 2976217 and can be considered to have the same mechanism of action, has been evaluated in approximately 558 subjects in two Phase 1 studies and three Phase 2 studies. The details for each study can be found in the Investigator's Brochure.

A Phase 2, open-label multi-center study (ISIS 416858-CS3) was conducted comparing BAY 2306001 at 100, 200, and 300 mg with enoxaparin for the prophylaxis of VTE in patients undergoing total knee arthroplasty. This study showed a 7-fold reduction in VTE after SC administration of BAY 2306001 compared to the standard of care treatment with enoxaparin. The reduction in VTE in ISIS 416858-CS3 was not associated with an increase in clinically significant bleeding events (38). BAY 2306001 has also been evaluated at 200 and 300 mg SC in a Phase 2, randomized, double- blind and placebo-controlled study in patients with ESRD on hemodialysis (ISIS 416858-CS4).

Plasma PK in patients with ESRD on hemodialysis was studied in the PK cohort of ISIS 416858-CS4. The mean concentration of BAY 2306001 in plasma over 24 hours following the SC dose administration on Day 1 (300 mg administered 10 minutes after completion of the 4-hour dialysis) and on Day 29 (300 mg administered immediately prior to the start of dialysis) were very similar and there were no differences between the two treatment days for either C_{max} or AUC values including the partial AUC values ($AUC_{0\text{-}3hr}$ or $AUC_{0\text{-}4hr}$), suggesting that hemodialysis had no effect on the PK of BAY 2306001 in ESRD patients.

Furthermore, dialysate samples were collected to determine concentrations of BAY 2306001 and representative metabolites in dialysate as well as dialysis clearance of BAY 2306001, if detected in the dialysate. Samples were collected prior to dialysis (baseline, C_{0min}) and at the beginning (within first 5 minutes), during (approximately 30 minutes after start of dialysis), and toward the end of dialysis (last 15 minutes of dialysis) on Day 29 from the PK cohort and Day 78 from Cohorts A and B. Concentrations of BAY 2306001 and its 10mer metabolites were below the LLOQ (< 2.50 nM) at all the time points examined. The lack of diffusion across the dialysis membrane of BAY 2306001 is consistent with the earlier observation on hemodialysis having no effect on the PK of BAY 2306001. Only the 3′-5mer metabolite was quantifiable at the beginning (within first 5 minutes) and 30 minutes after start of dialysis, suggesting that dialysis of shortmer metabolites was a rapid process.

There were sustained dose-dependent reductions in FXI. A reduction in dialysis circuit clotting was demonstrated by BAY 2306001 treatment with no increase in clinically-significant bleeding when compared to placebo (39).

A larger 213-patient Phase 2 multicenter, double-blind, randomized, stratified, placebo-controlled study was conducted in ESRD patients receiving hemodialysis (ISIS 416858-CS5).

The results of ISIS 416858-CS5 after 26 weeks of treatment with BAY 2306001 are generally consistent with the smaller 12-week study ISIS 416858-CS4 in ESRD patients of HD.

There were sustained dose-dependent decreases in FXI, as well as in reduced clotting scores of the dialysis circuit. BAY 2306001 demonstrated a good safety profile and was well-tolerated up to 26 weeks of treatment at 200 mg, 250 mg and 300 mg doses. There were dose-dependent decreases in platelet counts, 2 cases of severe thrombocytopenia were observed with BAY 2306001 treatment. Platelet function assessments indicated BAY 2306001 did not increase platelet activation and had negligible effects on platelet reactivity. There was no

increase in MB or CRNMB over placebo. Minor bleeds did not appear to be correlated with FXI levels.

The results of the BAY 2306001 clinical development program support FXI as a therapeutic target for prevention of thrombotic events in ESRD patients on hemodialysis.

2.2.3.3 Clinical Data with BAY 2976217 (ION 957943)

ION-957943-CS1 was a double-blind, placebo-controlled, dose-escalation Phase 1 study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of BAY 2976217 administered SC to healthy volunteers.

Following SC administration, BAY 2976217 was absorbed rapidly into the systemic circulation with median t_{max} values ranging from 1.5 to 3.5 hours across all evaluated cohorts. After reaching peak concentrations, mean plasma concentrations of BAY 2976217 declined in a multiphasic fashion with time with an initial, relatively fast disposition phase that dominated plasma clearance followed by a slower elimination phase. The rapid disposition-dominated phase resulted in plasma concentrations at 24 hours post dosing being lower by several magnitudes compared to C_{max} whereas the elimination phase is characterized by an apparent terminal elimination half-life of approximately 2 to 3 weeks. Overall, pharmacokinetic parameters appear to increase in proportional with dose over a dose range of 10 mg to 120 mg.

2.3 Benefit/Risk Assessment

Due to the much higher bleeding risk of ESRD patients and the unproven benefits of currently available antithrombotic therapy in these patients, most hemodialysis patients are not adequately treated for the prevention of thromboembolic events. The mainstay of thrombosis prevention is low dose ASA, and is recommended based mostly on small studies in ESRD patients on HD treated with ASA to prevent arterio-venous access thrombosis (1). Epidemiologic data in FXI deficient patients, and preclinical and clinical data generated so far with various compounds inhibiting FXI as part of the intrinsic coagulation pathway, support the hypotheses that targeting FXI may be ideal for the reduction of the thromboembolic risk without increasing the risk for bleeding in general, as well as in the ESRD patients on HD.

BAY 2976217 is ligand-conjugated to GalNAc oligonucleotide targeting FXI synthesis. This Phase 2b study will be the first study investigating BAY 2976217 in ESRD patients on HD. However, 256 ESRD patients on HD were studied with the parent unconjugated ASO (BAY 2306001) that works by the same antisense mechanism, using the same antisense ribonucleic acid sequence to inhibit hepatic production of FXI. BAY 2306001 reduced circulating FXI levels, FXI activity and dialysis circuit clotting in a dose-dependent manner without an increase in clinically significant bleeding over placebo.

Preclinical data suggest that this compound provides antithrombotic properties without increasing the risk for bleeding. BAY 2976217 may cause transient and reversible prolongations of aPTT, which is known effect due to reduction in FXI activity.

Clinical safety and efficacy are yet to be established for BAY 2976217. However, clinical data from parent unconjugated ASO (BAY 2306001) is directly relevant to the development of BAY 2976217 because the 2 compounds share the same RNA sequence as well as same overall structure, except the addition of the GalNAc sidechain and linker to BAY 2976217. BAY 2306001 has already shown a positive proof of concept in patients undergoing TKA with less VTE after surgery than with enoxaparin at higher doses of ASO, and in patients with

ESRD on hemodialysis with dose-dependent reduction in dialysis circuit clotting. In both settings, these favorable findings did not come with an increase in clinically significant bleeding over enoxaparin in TKA or placebo in ESRD patients. Clinical data of BAY 2976217 in healthy volunteers demonstrated dose dependent reduction of FXI activity and concentration after SC administration, which may lead to prevention of thromboembolic events.

Assuming that results from relevant animal models, human congenital FXI deficiency, and other compounds with similar mode of action can be translated into ESRD patients, BAY 2976217 is a promising drug candidate with the potential to prevent thromboembolic events with a low risk of bleeding. The current development program plans to enroll ESRD patients, with an anticipated pivotal trial composite exploratory efficacy endpoint of death (due to MI, stroke, PE and SE), non-fatal stroke, non-fatal MI, major amputation of vascular etiology, acute limb ischemia and symptomatic VTE. The use of BAY 2976217 aims to achieve a 25% clinically relevant risk reduction of the composite endpoint. This would translate to an absolute risk reduction of >3%.

Potential risks such as bleeding, thrombocytopenia or increase in hepatic enzymes will be closely monitored to minimize risks to participants. In addition to routine measures in the conduct of a clinical trial, carefully chosen, specific in- and exclusion criteria, dose of study medication, and additional measure have been selected to manage the key risks identified for BAY 2976217. The elimination half-life of BAY 2976217 in plasma is approximately 2 to 3 weeks, however, plasma clearance is biphasic with a rapid decrease after t_{max} in plasma concentration due to uptake in hepatocytes. Due to the prolonged pharmacodynamic effect of the compound, participants will be kept under observation for approximately 5 months after the last administration of BAY 297217 (the first 4 weeks after the last dose is considered on-treatment, and may include an evaluation period upon completing the main treatment period or upon discontinuing study intervention early during the main treatment period, and 16-weeks for a post-treatment follow-up period for safety).

In order to ensure the safety of the participants during the study conduct, an independent data monitoring committee will monitor the safety of all participants.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BAY 2976217 can be found in the Investigator’s Brochure.

2.3.1 Risk Assessment

Risk assessment for BAY 2976217 is described in Table 2–1.

Table 2–1: Risk Assessment for the study Intervention BAY 2976217

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hemorrhage	Risk factor associated with ESRD due to uremia-induced endothelial and platelet dysfunction Increased bleeding risk due to routinely administered anticoagulant and antiplatelet agents to reduce risk of thromboembolic events and for dialysis maintenance No clinically significant bleeding (MB, CRNMB) observed so far in healthy volunteers with BAY 2976217	Specific in-and exclusion criteria Reporting as primary safety outcome Regular hematological laboratory assessment (see Section 1.3) Guidance on remedial measure and surgical prophylaxis including factor replacement DMC will periodically review all bleeding events CIAC will adjudicate bleeding events
Thrombocytopenia	Like in other unconjugated ASOs, BAY 2306001 was associated with dose dependent platelet reductions in ESRD patients on HD, however, severe thrombocytopenia was a rare event; platelet reductions were not observed in healthy volunteers with BAY 2976217	Specific in-and exclusion criteria Regular safety laboratory assessment (see Section 1.3) Regular hematological laboratory assessment (see Section 1.3) Reporting as adverse event of special interest, as well as instructions on following monitoring, evaluation, stopping rules and remedial treatment (see Section 8.3.8)
Elevation of hepatic enzymes	Based on toxicology findings in mice with BAY 297217, minimal to mild individual hepatocellular necrosis was observed and correlated with increased hepatic enzymes: also increased liver weights were observed In preclinical studies with monkeys and in the Phase 1 study with healthy volunteers no clinically relevant changes in liver chemistry were seen	Specific in- and exclusion criteria Regular liver laboratory assessment (see Section 1.3 and Section10.2) Reporting as adverse event of special interest, as well as guidance on the monitoring, evaluation, and stopping rules (see Section 8.3.8)

2.3.2 Benefit Assessment

The potential benefit of receiving study intervention is a reduced risk for thromboembolic events in patients with ESRD. Furthermore, this study will contribute to develop of new therapies in an area of high medical need, specifically as patients with ESRD are often excluded from clinical trials due to their specific risk profile.

2.3.3 Overall Benefit: Risk Conclusion

Currently available preclinical and clinical data regarding the key risks do not indicate an unfavorable risk profile for BAY 2976217. Considering the measures taken to minimize risk to participants in this study, the overall risk is projected to be acceptable in the context of the anticipated benefit.

3. Objectives and Endpoints

Objectives and endpoints are listed in Table 3–1.

Table 3–1: Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary	
• To evaluate the safety of BAY 2976217as compared to placebo	Primary Endpoint • The incidence of composite 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 Estimand components for primary endpoint are defined in section 9.4.2
Secondary	
• To evaluate the safety of BAY 2976217as compared to placebo	• The incidence of 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 BAY 2976217	Pharmacokinetic Endpoints • Trough concentrations for 3 dose levels of BAY 2976217 Pharmacodynamic Endpoints • Maximum change in FXI antigen levels during the main treatment period

Table 3–1: Objectives and Endpoints

Objectives	Estimands/Endpoints
	• Maximum change in FXI activity levels during the main treatment period
Exploratory	
• To evaluate the effect of BAY 2976217 on thromboembolic events as compared to placebo	Exploratory Efficacy Endpoints • Incidence of composite and event types of death due to MI, stroke, PE and SE, and non-fatal stroke, non-fatal 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 BAY 2976217 as compared to placebo	Other pre-specified Safety Endpoints • Incidence and severity of AESIs: hepatic enzyme elevation, thrombocytopenia • Changes in blood pressure and, laboratory assessments • Incidence and severity of bleeding of the arterio-venous grafts or fistulas
• To further evaluate the pharmacodynamics of BAY 2976217 as compared to placebo	Other Pre-specified Pharmacodynamic Endpoints • 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 • TAT and F1.2
Other pre-specified	
• To further investigate BAY 2976217 (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)

AESI = Adverse event of special interest, aPTT = Activated partial thromboplastin time, CIAC = Central Independent Adjudication Committee, F1.2 = Prothrombin fragment 1 + 2, FXI = Coagulation factor XI, INR = International normalized ratio, MI = Myocardial infarction, PD = Pharmacodynamics(s), PE = Pulmonary embolism, PK = Pharmacokinetics, SE = Systemic embolism, TAT = Thrombin-antithrombin complex, TEAEs = Treatment-emergent adverse event(s); VTE = Venous thromboembolism

4. Study Design

4.1 Overall 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 BAY 2976217 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 BAY 2976217 or placebo SC (3:1) n~96
- Cohort B: 80 mg BAY 2976217 or placebo SC (3:1) n~96
- Cohort C: 120 mg BAY 2976217 or placebo SC (3:1) n~96

Participants will be stratified at randomization for use of ASA (yes/no). 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 1-week screening period and a 24-week main treatment period, the last 4 weeks of which are an evaluation period for certain PD and safety parameters. To collect additional long-term safety information, participants will continue to be treated as randomized in the extended treatment period, with up to 24 weeks of additional treatment with study intervention. 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 of the extended treatment period. Once the overall treatment period is completed, participants will have a 16-week post-treatment follow-up period.

All participants who are in the extended treatment period will need to stop further treatment no later than when the last participant enrolled into 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 move to the 16-week post-treatment follow-up period. 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.

The data and outcomes collected in the study will be analyzed by 4 groups:

- Pooled Placebo Group (from Cohorts A, B and C),
- 40 mg Dose Group (BAY 2976217 from Cohort A),
- 80 mg Dose Group (BAY 2976217 from Cohort B), and
- 120 mg Dose Group (BAY 2976217 from Cohort C).

All suspected bleeding, cardiovascular and thromboembolic events occurring after randomization will be assessed by CIAC blinded to treatment 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 on regular basis, 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 (Section 8.5.1.2).

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 to expedite Phase 3 dose selection. 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).

4.2 Scientific Rationale for Study Design

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.

Patients with congenital deficiency of FXI are at decreased risk of thrombotic events, without spontaneous bleeding. Investigational compounds used to inhibit or decrease production of FXI have also shown promise in reducing thrombotic events without increasing clinically significant bleeding, making it an attractive candidate for use in the ESRD patient on HD. An unconjugated FXI ASO (BAY 2306001) was studied in clinical trials. Pre-operative reduction of the synthesis of FXI levels by the unconjugated FXI ASO in patients who had elective primary unilateral total knee arthroplasty was highly effective for prevention of venous thrombosis and was not associated with increased peri-operative or subsequent bleeding. Two Phase 2 studies were conducted in ESRD patients, that showed that the reduction of the synthesis of FXI levels by the ASO was associated with less clotting of the dialysis circuit without an increase in clinically significant bleeding.

This previous experience with the unconjugated FXI ASO showed effective reduction in thrombotic events without increase in clinically significant bleeding. However, the unconjugated FXI ASO requires higher doses and relatively high injection volume, and a long loading phase to achieve adequate liver delivery and reduce FXI levels, and was associated with certain adverse events such as thrombocytopenia and injection site reactions. Therefore, the GalNAc-conjugated FXI ASO BAY 2976217 was developed, CCI [redacted]

Animal studies as well as Phase 1 human trials of BAY 2976217 have confirmed significant dose-dependent reduction in FXI activity with lower circulating serum levels of the drug, and no evidence of injection site reactions or platelet effects. Progression to a Phase 2 trial in ESRD patients on HD is reasonable as there is a high unmet medical need to reduce thrombotic events without increasing bleeding in this population. 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.

4.3 Justification for Dose

This study will investigate three dose levels (40 mg, 80 mg, and 120 mg BAY 2976217 given SC every 4 weeks). These doses were determined based on clinical data from the parent drug BAY 2306001 in healthy volunteers and in ESRD patients and clinical data from BAY 2976217 in healthy volunteers. A population PK/PD model has been developed in order to bridge into the current Phase 2b study. The investigation of a range of less FXI suppression (approximately 50% remaining FXI activity) is justified by real life data from congenitally deficient patients. A large observation cohort including 10,193 adults in Israel demonstrating that FXI activity of 30-50% was associated with reduced CV event rates in a population with genetically lowered FXI levels when compared to the group of patients with >50% of FXI levels (27).

The investigation of a higher range of FXI suppression is justified by two publications describing a lower incidence of ischemic stroke and DVT in patients with FXI levels below 15% (29, 40). Additionally, a Phase 2 study (ISIS 416858 -CS3) explored the role of FXI reduction in post-surgical VTE by comparing two doses of the unconjugated ASO BAY 2306001 (200mg and 300 mg) to enoxaparin (38). The mean FXI activities around the time of knee surgery were 0.38 ± 0.01 U/mL and 0.20 ± 0.01 U/mL in patients given the 200 mg and 300 mg BAY 2306001 regimens, respectively. VTE events occurred in 27% of patients receiving the 200 mg dose of FXI-ASO and in 4% of patients receiving the 300 mg dose of FXI-ASO, as compared with 30% of patients receiving enoxaparin. The authors concluded

that the 200 mg regimen was noninferior, and the 300 mg regimen of FXI-ASO was superior to enoxaparin. These data would support the investigation of a higher FXI suppression level of approximate 20% remaining FXI activity.

Spontaneous bleeding, including clinically significant bleedings, do not show dependency on lower levels of FXI in the above cited publications and other published literature. In addition, no increase in number of clinically significant bleeding under treatment with the parent compound BAY 2306001 was seen in two studies with ESRD patients.

With a view on potential clinical efficacy and considering safety, reduced FXI levels of less than 15% to approximately 50% remaining activity are justified for the current study. The three doses of 40 mg, 80 mg, and 120 mg BAY 2976217 have been selected to optimally cover for this range.

A protocol-defined option for dose step-down for the 120 mg dose level (see section 4.1) is provided to the DMC. Also, the predicted steady-state FXI levels with 120 mg once monthly dosing are expected to be similar to those achieved with the 300 mg dose level in the TKA study (ISIS 416858-CS3) in which no increased clinically significant bleeding was observed.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all protocol defined visits/contacts.

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

The primary completion date is the date when the last participant completes the main treatment period (Visit 22) and the following ”on treatment” time window (28 days from the last intake of study intervention).

5. Study Population

Subjects with ESRD on hemodialysis treatment (including hemodiafiltration) who meet all the inclusion criteria and none of the exclusion criteria will be eligible for enrollment in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be at least 18 years of age at the time of signing the ICF.

Type of Participant and Disease Characteristics

2. Participants with ESRD on HD for ≥3 months at the time of signing of the ICF, receiving dialysis at least 9 hours a week and stable in the view of the investigator.[1]

[1] See section 5.4 for information on rescreening.

Sex

3. Male or female
   Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.[2].

Informed Consent

4. Capable of giving signed ICF as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Prior/Concomitant Therapy

1. Receiving antiplatelet therapy except daily ASA ≤ 150 mg/day
2. Receiving anticoagulation in therapeutic doses, other than standard anticoagulation during the hemodialysis procedure.

Medical Conditions

3. Known inherited bleeding disorder e.g. von-Willebrand disease or Hemophilia A, B or C
4. Recent (<6 months before screening) clinically significant bleeding, or at high risk of bleeding (in the judgement of the investigator)
5. Recent (<3 months before screening) thromboembolic event, e.g. acute coronary syndrome, stroke, or VTE (except dialysis access thrombosis)
6. Recent (<3 months before screening) major surgery or scheduled major surgery during participation in the study
7. Scheduled living donor renal transplant during study participation
8. Known Hepatitis B or C
9. Known HIV with recent documented detectable viral load (<3 months before screening)
10. Persistent heart failure as classified by the New York Heart Association classification of 3 or higher
11. Life expectancy less than 6 months
12. Sustained uncontrolled hypertension (persistent measurements of diastolic blood pressure ≥ 100 mmHg, and/or systolic blood pressure ≥180 mmHg)
13. Hepatic disease associated with either: coagulopathy leading to a clinically relevant bleeding risk, or ALT > 3x ULN, or total bilirubin >2x ULN with direct bilirubin > 20% of the total

[2] See Section 10.4 for requirements on contraception

14. Hb < 9.0 g/dL at screening[3]
15. Platelet count < 120,000 / mm^3 at screening[3]
16. Known hypersensitivity to the investigational drug or to inactive constituents of the study intervention
17. Active malignancy requiring treatment during study participation (except non-melanoma skin cancer, or cervical carcinoma in situ)

Prior/Concurrent Clinical Study Experience

18. Participation in a study with an investigational medicinal product within 30 days or within 5 half-lives of the previous administered drug, whichever is longer, prior to the screening period
    Note: Participants from previous BAY 2306001/ISIS 416858 and BAY 2976217 / ION 957943 studies are eligible.

Other Exclusions

19. Any other conditions, which, in the opinion of the investigator or Sponsor would make the subject unsuitable for inclusion
20. Confirmed pregnancy

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (declared as screen failure) may be rescreened once.

The investigator should ensure that the resolution of a prior exclusionary circumstance or condition is fully resolved.

The investigator has to ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. In addition, the participant must re-sign the ICF during re-screening. Rescreened participants will be assigned a new participant number and all assessments for the study must be repeated.

[3] One re-assessment of hemoglobin and platelet levels is allowed during the screening period.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

Table 6–1: Study interventions administered

Arm Name	BAY 2976217	Placebo
Intervention Name	BAY 2976217	Placebo
Type	Drug	Placebo
Dose Formulation	solution for injection	solution for injection
Unit Dose Strength(s)	100 mg/mL	not applicable
Dosage Level(s)	40 mg, 80 mg or 120 mg (or 100 mg if dose reduction is recommended by DMC)	not applicable
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
Packaging and Labeling	Study intervention will be provided in 2 mL colorless vials. Each vial will be labelled as required per country requirement.	Study intervention will be provided in 2 mL colorless vials. Each vial will be labelled as required per country requirement.
Current/Former Name(s) or Alias(es)	ION-957943	not applicable

DMC = Data Monitoring Committee, SC = Subcutaneous

BAY 2976217 is supplied in 2 mL clear, single-use injection glass vials as a solution. BAY 2976217 is a solution with a concentration of 100 mg/mL. The total content of the glass vial is approximately 1.05 mL, corresponding to 100 mg BAY 2976217. From the total 1.05 mL, 0.8 mL (i.e. 80 mg) are extractable volume and 0.25 mL (i.e. 25 mg) are overfill.

Placebo to BAY 2976217 is supplied in 2 mL clear, single-use glass vials as a solution with a content of 1.05 mL (0.8 ml extractable volume). Further details can be found in the handling instruction provided separately.

Different doses will be achieved by administering a different volume. For dosage regimen and planned duration of intervention see Section 4.1.

Study intervention will be administered any time from 15 minutes before the start of dialysis to 15 mins after the start of dialysis, when administered on a dialysis day.

Study intervention can be administered in the following SC injection areas:

- Abdomen (upper right, upper left, lower right, lower left)
- Thigh
- Outer area of upper arm

Note: Injection is not to be given within two inches (5cm) of any of the following: the umbilicus, the active reaction area of a previous injection, or in areas of the skin that are burned, reddened, inflamed, or swollen. Injections may be administered to a location that previously was involved in an injection site response provided that any symptoms have largely resolved.

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the investigator site file.

6.3 Measures to Minimize Bias: Randomization and Blinding

After a participant has signed an ICF, the unique PID will be assigned via IWRS. If a participant is re-screened, a new PID will be assigned. The PID is a 9-digit number consisting of:
Digits 1 to 5 = Unique site number
Digits 6 to 9 = Unique participant number (current participant number within the study site). The unique participant number will start with 7 for each participant.

All participants will be centrally assigned to randomized study intervention using IWRS. Study intervention will be administered at the study visits summarized in SoA (Section 1.3). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site

Participants who meet the entry criteria will be randomized as described in Section 4.1
Participants will be stratified as described in Section 4.1

In order to be able to prepare and administer the correct volume of study intervention to be injected, sponsor, participants and investigators will be aware of dose cohort assignment, but blinded with respect to active treatment versus matching placebo. The CIAC will be blinded to cohort allocation and treatment assignment. DMC will have access to unblinded data as outlined in the DMC charter.

In order to maintain the blind, BAY 2976217 and matching placebo will be packaged in identical vials and each vial will be labeled with a unique, pre-printed number.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's intervention assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the emergency medical advice 24 hours/7-day service. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is

unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

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

Bioanalytics and pharmacometrics staff will be unblinded according to Bayer SOPs. Bioanalysis and popPK evaluation might be started prior to database lock: if this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g., data will be stored separately, and members of the study team will not have access to the unblinded data.

6.4 Study Intervention Compliance

Participants are dosed at the site, and they will receive study intervention directly from the investigator or other qualified and trained staff. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The vial number(s) and study participant identification will be confirmed at the time of dosing. To monitor compliance, drug accountability information will be documented for each participant.

6.5 Concomitant Therapy

Prior medications that should be stopped at least 5 days prior to the first study intervention (if clinically appropriate) and are not allowed concomitantly with the study intervention are:

- Antiplatelets except ASA ≤ 150 mg/day (e.g., clopidogrel, ticagrelor, prasugrel, dipyridamole, ASA >150 mg/day).
    - If a participant is taking low dose ASA (≤150mg/day) at randomization, the dosage should not be changed during the study, unless clinically indicated; if the dose is permanently increased >150 mg/day the participant should discontinue study intervention.
    - All efforts should be made during the treatment period to avoid change in ASA use, unless clinically indicated
- Anticoagulant agents (e.g., VKAs such as phenprocoumon, warfarin-sodium, or DOAC oral anticoagulants such as rivaroxaban, apixaban, dabigatran, UFH, LMWH, etc.).
- UFH or LMWH other than used during the hemodialysis session to prevent clotting of dialysis circuit or to maintain patency of hemodialysis access.

If a prohibited concomitant medication is indicated, study intervention will be temporarily interrupted.

In case study intervention is interrupted for >56 days, the participant will be discontinued from study intervention as described in Section 7.2.

In case study intervention is interrupted for ≤56 days, study intervention may be restarted as per SoA after the concomitant medication is no longer used.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of signing of the ICF or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Specifically, anticoagulants and antiplatelet agents taken within 30 days prior to Visit 1 even if taken before the ICF was signed should also be recorded in the eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6 Dose Modification

See Section 4.1 for information on dose modification. No dose modifications are allowed except for the one described in section 4.1 (Cohort C), if recommended by the DMC.

6.7 Intervention after the End of the Study

No further intervention is planned after the end of the study. No long-term effects are expected that would need any additional care or intervention. Participants who completed or prematurely discontinued the study will discontinue study intervention and will switch to the most appropriate available treatment at the physician's discretion.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for key outcome events, as described in Section 7.1.1, unless the participant withdraws from the study. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up, and for any further evaluations that need to be completed.

Abnormal liver function

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Section 8.3.8.2 or if the investigator believes that it is in best interest of the participant.

Cardiac changes

If a clinically significant finding is identified in ECG (including, but not limited to changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Events Requiring Definitive Discontinuation of Study Intervention

A participant must permanently discontinue study intervention for any of the following:

- The participant becomes pregnant. The pregnancy will be reported per reporting procedures in Section 8.3.5.
- The participant is unwilling to continue study intervention.
- The participant experiences an AE (including clinically significant bleeding [Sections 8.2.1 and 8.3]) that in the judgment of the investigator necessitates permanent discontinuation of study intervention.
- Requires surgery that in the judgment of the investigator necessitates permanent discontinuation of study intervention.
- The participant develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.3.8.1.2 and 8.3.8.2.2.
- The participant is no longer on maintenance hemodialysis (including hemodiafiltration) for a minimum of 9 hours per week, including a change in dialysis modality (e.g. peritoneal dialysis) or renal transplantation.
- The participant moves their dialysis care to a different hemodialysis facility where the study team cannot continue to follow the participant.
- The participant begins treatment with a disallowed concomitant medication and the study intervention is interrupted for >56 days, as described in Section 6.5.

When a study participant discontinues the study intervention early:

- During the main treatment period, the participant should conduct Visit 22 four weeks after the last dose of study intervention
- During the extended treatment period, the participant will conduct Visit 28 four weeks after the last dose of study intervention
- In both cases, the participant will then enter the 16-week follow-up period, giving a total of 20 weeks of follow-up from the last dose of study intervention.

If the participant moves their dialysis care to a different hemodialysis facility where the study team cannot follow the participant, all efforts should be made to conduct the evaluation and post-treatment follow-up visits in person to complete all study procedures. If in-person visits by the participant are impossible, limited remote contact visits (e.g. phone) may be conducted recording as much information as possible for eCRF entry. The reason for discontinuation of study intervention must be recorded in the eCRF and source documentation.

7.1.2 Temporary Discontinuation

The investigator may temporarily discontinue study intervention for an AE, bleeding event, temporary use of prohibited concomitant medication, for a surgery or other invasive procedure, or any other reason not listed as reasons for definitive discontinuation of study intervention (Section 7.1.1) or withdrawal from the study (Section 7.2). Examples of these are

(but not limited to): if any exclusion criterion applies during treatment, if a significant violation of the protocol occurs, as defined by the sponsor.

If the discontinuation remains necessary > 56 days from the last dose, the participant will be permanently discontinued from study intervention.

7.1.3 Rechallenge

Participants who permanently discontinue the study intervention must not be re-challenged (i.e., must not restart study intervention). Participants who temporarily discontinue study intervention (for less than 57 days) (Section 7.1.2) may be rechallenged after careful assessment by the investigator of the potential risks.

7.2 Participant Discontinuation/Withdrawal from the Study

- 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. This is expected to be uncommon. If the participant withdraws consent, or the investigator withdraws the participant, the reason for withdrawal should be recorded on the eCRF.
- Additional reasons for withdrawal from the study:
  - Death of participant, in which case only relevant eCRF pages will be completed (e.g.- AEs [including the cause of death] and concomitant medications up to death, vital status, etc).
  - The participant signs-off dialysis without expected return of life-sustaining kidney function or without transferring to an alternative form of renal-replacement therapy, the reason for withdrawal of renal replacement therapy should be recorded on the eCRF.
  - If a stopping rule is met (see Sections 8.3.8.1.2, 8.2.1.1 and 8.3.8.2.2) during the screening period, the participant should be screen-failed.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant is permanently discontinued/withdrawn from the study, the Early Termination Visit in the SoA will be conducted immediately. All study outcomes will be censored at Early Termination.

7.3 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 following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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). The survival status will be recorded in the eCRF. If no survival status is known, the contact attempt will be recorded.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- If deemed necessary for an individual participant, the investigator or designee, at his/her discretion, may arrange visits in addition to the scheduled study visits. Unscheduled study visits will be documented in the eCRF.

8.1 Efficacy Assessments

The following efficacy outcomes will be assessed by the blinded CIAC in accordance with the pre-specified endpoint criteria in the adjudication charter:

- Death due to MI, stroke, PE or SE
- Non-fatal MI
- Non-fatal stroke

- Major amputation of vascular etiology
- Acute limb ischemia (new onset ischemia or worsening or pre-existing ischemia)
- Venous thromboembolism
- Thrombosis of the arterio-venous grafts or fistulas

All deaths and events suspected to be related to cardiovascular disease, or other arterial or venous thrombosis events (including arterio-venous access thrombosis), but not limited to these, will be reported as an AE or SAE as per adverse event reporting procedure in Section 8.3. Additionally, the event will be triggered, within the eCRF, for adjudication by the CIAC. Details for the adjudication process are described in the adjudication charter.

8.2 Safety Assessments

- Bleeding events, including minor bleeding such as injection site-related bleeding
- AEs, including AEs of Special Interest, AEs leading to discontinuation of study intervention
- Vascular access bleeding: Assessment of the severity of bleeding at the dialysis access following the hemodialysis procedure (see Section 8.2.1.4 for details)
- Injection site events (see section 8.3.9 for details)
- Signs of hypersensitivity during and immediately after the administration of BAY 2976217 or placebo
- Clinical laboratory data including (but not limited to):
    - CBC with differential count and platelets
    - Liver enzymes
- Post HD blood pressure and ECG
- Evaluation of concomitant medication
- Changes in dialysis prescription and missed dialysis sessions

Laboratory assessments for safety will occur every 2 weeks during main treatment period. During extended treatment period, platelet count and ALT/AST should be measured every 2 weeks, local lab monitoring at unscheduled visits can occur between the scheduled visits. Clinically significant changes in platelet count, ALT/AST are to be reported (as laboratory parameters as well as adverse events). All other laboratory assessments for safety will occur every 4 weeks at the scheduled visits, as described in the SoA.

If the platelet value or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a local or central laboratory repeat blood specimen may be re-drawn as soon as possible (preferably at the next dialysis session).

Incidence, severity and seriousness of AEs, and SAEs as well as the causal relationship between an AE/SAE and the administration of the study intervention and a causal relationship with ESRD and/or dialysis will be assessed throughout the study.

Planned time points for all safety assessments are provided in the SoA. Clinically significant abnormal findings will be reported as AEs in the eCRF.

8.2.1 Bleeding events

The composite of MB and CRNMB as assessed by CIAC, is the primary endpoint in this study.

Participants will be evaluated for occurrence of bleeding events continuously after signing consent up to end of the post-treatment follow-up for all cohorts. All bleeding events (other than the normal bleeding from arterio-venous graft or fistula post-dialysis) will be reported as AE or SAE per Section 8.3. Additionally, CIAC will have continuous access to data necessary for adjudication.

Bleeding events that are clinically significant will need to be monitored and treated immediately. Monitoring will include post HD blood pressure, labs (local CBC as needed), additional outpatient visits, overnight stays and laboratory tests may be needed for as long as necessary. Coagulation parameters are potentially unblinding, and local measurement should be avoided unless clinically indicated.

Bleeding after dialysis from arterio-venous graft or fistulas is expected and will only be reported as an AE or SAE and submitted to CIAC if there is a change in the pattern or intensity of bleeding in a participant, or if exceptional measures are taken for hemostasis beyond normal, relative to post-dialysis bleeding that was observed in that participant over the prior week.

The CIAC will classify bleeding events primarily based upon the ISTH definitions (41):

Major bleeding is defined as symptomatic bleeding and:

- Fatal bleeding, and/or
- Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (2.0 g/dL) (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

Clinically relevant non-major bleeding is defined as any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:

- Requiring medical intervention by a healthcare professional
- Leading to hospitalization or increased level of care
- Prompting a face-to-face (i.e., not just a telephone or electronic communication) evaluation

Bleeding after dialysis from arterio-venous graft or fistulas is frequent, often requiring medical intervention. Medical interventions and face-to-face evaluations taken for post-dialysis hemostasis of arterio-venous graft or fistula may be considered expected bleeding for the clinical circumstance by the investigator, and not reported as an AE/SAE and an adjudication package does not need to be sent to the CIAC. If events of post-dialysis bleeding are submitted to the CIAC that do not represent a change over the prior week for those participants, the events will be considered as expected bleeding for the clinical circumstance by the CIAC, and not adjudicated as CRNMB.

All other symptomatic bleeding episodes not meeting the criteria for CRNMB will be classified as minor bleeding.

8.2.1.1 Stopping Rules for Bleeding Events

If clinically significant bleeding occurs, careful assessment of the suitability of the participant for continuation of dosing by the investigator will be made prior to resuming study intervention. In case the study intervention should be discontinued permanently, the participant should complete study visits as described in Section 7.1.1 including evaluation period and the post-treatment follow-up period.

8.2.1.2 Remedial Treatment for Bleeding

In general, the management of bleeding is at the discretion of the treating physician and should follow standard of care or applicable local guidelines, and should be tailored to the patient and their condition. Local prescribing information should be consulted for usage in ESRD for any drug administered. The following suggested approach is preliminary, based on currently available information and advice from external experts. As clinical experience accrues, these suggestions may be refined.

If a participant has clinically significant bleeding event during the study, the following basic measures should be considered by the investigators to control bleeding:

- Local measures for hemostasis - mechanical compression, interventional radiology, surgical intervention.
- Hemodynamic resuscitation and volume management: fluid replacement & hemodynamic support, replacement blood products as appropriate, with careful volume management- packed red blood cells, platelet concentrate, FFP, cryoprecipitate or fibrinogen concentrate
- If knowledge of treatment assignment will influence the choice of intervention during a bleeding event, the investigator may immediately obtain the participant's treatment assignment by contacting IWRS; if unblinding is planned, aPTT, FXI levels and other standard coagulation tests may be measured locally.
- Delay of the next injection of study intervention, or permanent discontinuation (Section 7.1).
- Discontinue antiplatelet drugs and discontinue other concomitant medications that could exacerbate bleeding

Antifibrinolytics are often the first line therapy administered to congenital FXI deficient patients with bleeding (42). These agents are also used in patients without FXI deficiency (e.g.- bleeding after trauma (43), post-partum bleeding (44)), and can be administered without unblinding the patient.

- Tranexamic acid (consult prescribing information for use in reduced kidney function (45))
- Epsilon aminocaproic acid

If bleeding cannot be controlled by applying basic measures and antifibrinolytic therapy (if available), the investigator may consider administration of one of the following FXI replacement therapies, if available and used as part of local practice (according to the dosages advised in the package insert of the respective compound):

- Fresh-frozen plasma (FFP)
- Factor XI concentrate (Hemoleven®)

The dose of FFP or factor concentrate given should aim to increase Factor XI activity above 0.3 U/mL. In a study of congenital FXI deficient patients, those with FXI > 0.2 U/mL had 1/4 to 1/5th of the bleeding risk of those with FXI < 0.2 U/mL (42). Careful assessment of the participant's volume status should be made when infusing factor replacement.

The investigator should recognize that the half-life of circulating Factor XI is approximately 50 hours when considering the potential need for re-administration, particularly of FFP or FXI concentrate. Additionally, the time necessary to obtain a Factor XI concentration locally and to infuse FFP should be taken into consideration.

If uremic coagulopathy/platelet dysfunction is suspected, adjuvant measures may be considered (e.g.- desmopressin, conjugated estrogens, etc) (46).

If bleeding cannot be controlled by these measures, administration of one of the following medications may be considered, if available and used as part of local practice (according to the dosages advised in the package insert of the respective compound). Due to risk of thrombosis, careful attention to dosing these procoagulants is needed.

- Recombinant Factor VIIa (NovoSeven®)
- 4-factor concentrate (prothrombin complex concentrate)

If a participant is unblinded, they may resume study treatment at the discretion of the investigator, but may be excluded from certain analyses.

8.2.1.3 Recommendations for Surgeries Including Kidney Transplant

Regarding management of bleeding risk in the surgical setting with FXI deficiency, there is clinical trial experience with BAY2306001. Patients undergoing total knee replacement in ISIS 416858-CS3 with the unconjugated FXI ASO (BAY 2306001), treated prior to surgery with 300 mg of the ASO, underwent their surgery with mean FXI levels of less than or equal to 0.2 U/mL (severe deficiency is < 0.3 U/mL) and a mean aPTT ratio of 1.4. Despite this, patients treated with ASO before their surgery had a rate of clinically significant bleeding of 3%, less than half the rate observed in patients treated with enoxaparin (40 mg initiated the day of surgery and administered for 9 consecutive days), however, these differences were not statistically significant (38).

BAY 2306001 was also studied in 213 ESRD patients on HD in ISIS 416858-CS5. Three kidney transplants occurred without prophylactic measures taken after dosing with BAY 2306001, without bleeding or other complications. Values for FXI activity collected prior to surgery ranged from 0.42 to 0.74 U/mL (reference range 0.73 to 1.45 U/mL), and the aPTT 28.5 to 39.4 sec (reference range 22.4 to 30.0 sec).

Spinal/epidural anesthesia should only be considered if the FXI levels are known, and within normal limits. Otherwise, only general or local anesthesia should be used.

In the event a participant requires an elective surgical or other invasive procedure and a delay in the procedure until 20 weeks after the last dose of study intervention is not possible, the investigator should consider scheduling the surgery at the time of the next scheduled dose of study intervention (the end of a 28-day dose cycle) and the dose will be held until after surgery. In case of a surgery or other invasive procedure, participants may be temporarily or

permanently discontinued from further dosing of study intervention as outlined in Sections 7.1.1 and 7.1.2.

In the setting of an elective procedure that cannot be postponed until 20 weeks from the last dose of study intervention, or for an emergent procedure that is:

- A major surgery (surgical procedure involving an organ within the cranium, chest, abdomen, or pelvic cavity) including kidney transplant
- An extensive procedure in tissue with high fibrinolytic activity (e.g. gynecologic, urologic, or surgeries of the nasal and oral cavities)
- or otherwise at high risk of perioperative bleeding,
- and if knowledge of treatment assignment will influence the choice of intervention to manage bleeding risk prior to or during the surgery

the investigator may immediately obtain the participant's treatment assignment by contacting IWRS. In this setting, it is appropriate to monitor coagulation parameters locally and the investigator may also monitor FXI levels locally.

Careful post-operative assessment of the participant and his/her ongoing bleeding risk should be made by the investigator, before restarting study intervention. The investigator may consider restarting study intervention for minor procedures or surgeries at sites with low fibrinolytic activity (e.g. knee arthroplasty). Caution should be used when restarting study intervention after a major surgery or a surgery in an area of high fibrinolytic activity (e.g., gynecologic, urologic, or surgeries of the nasal and oral cavities). Participants who discontinue study intervention early due to a surgery will continue in the study as described in Section 7.1.1.

If a participant is unblinded, he/she may resume treatment at the discretion of the investigator but may be excluded from certain analyses.

There is an accepted approach to managing bleeding risk in surgical patients with congenital FXI deficiency that is likely relevant to acquired FXI deficiency with BAY 2976217 treatment (42). Firstly use of ASA should be discontinued 1 week before surgery; sites of surgery that include tissues with increased fibrinolytic activity are expected to bleed more than sites with low fibrinolytic activity; and assessment of the cardiovascular status of the participant when using factor replacement therapy is essential for two reasons: (i) when use of fresh-frozen plasma (FFP) is planned, volume overload might be a problem if cardiovascular function is compromised, and (ii) compromised cardiovascular function confers a risk of thrombosis when FXI concentrate is used.

Congenital FXI deficiency patients requiring minor procedures such as tooth extraction or skin biopsy have been safely treated with local antifibrinolytic agents alone (mouthwash (47), topical), however, care in use and dosing is needed for systemic dosing in ESRD patients (e.g., aminocaproic acid, tranexamic acid). Uneventful tooth extractions were reported in patients with severe FXI deficiency treated with systemic tranexamic acid alone (48).

For major surgery (defined as a surgical procedure involving an organ within the cranium, chest, abdomen, or pelvic cavity) including kidney transplant, prophylaxis with an antifibrinolytic such as aminocaproic acid or tranexamic acid could be considered with careful consideration of appropriate use and dose in ESRD (consult the prescribing information). Prophylaxis with antifibrinolytics have been used in both congenital FXI deficiency (42) and those without FXI deficiency (49). The administration of low-dose recombinant FVIIa along

with tranexamic acid was also reported as a prophylaxis option in patients with severe FXI deficiency undergoing surgery (50, 51).

Factor replacement therapy may also be considered prophylactically, and in any case should be on stand-by during surgery. Factor replacement is typically with FFP, as FXI concentrate replacement is not universally available. Careful attention to and management of ESRD participant's volume status when infusing blood product is essential. If uremic platelet dysfunction is suspected, adjunctive therapy could also be considered (e.g., desmopressin, conjugated estrogens).

Based on recommendations in congenital FXI deficiency (42), replacement therapy with FFP (or FXI concentrate infusions, if available) should be targeted to reach a trough FXI level of 0.45 U/mL (or higher) for approximately 7 days after surgery. The investigator should recognize that the half-life of circulating Factor XI is approximately 50 hours when considering the potential need for re-administration, particularly of FFP or FXI concentrate. Additionally, the time necessary to obtain a Factor XI concentration locally (if the investigator chooses to unblind the participant) and to infuse FFP should be taken into consideration.

8.2.1.4 AV access bleeding

Severity of bleeding at the dialysis access will be assessed approximately 15 minutes after removal of the dialysis needle(s) from the vascular access at the end of the dialysis session on the visit day (or from a dialysis session within the visit window if the visit is not conducted on a dialysis day) according to the following categories (exploratory bleeding score):

- "0" no access bleeding
- "1" slow oozing
- "2" overt bleeding

In the case the bleeding stops before the end of the 15-minute period after removal of the dialysis needle(s) from the vascular access (score 0), the assessment may be done prior to the end of the 15-minute period.

In case a catheter is used, the AV access bleeding is not applicable.

8.2.2 Physical Examinations

Physical examinations will be conducted in a response to new or changes in symptoms. Any clinically meaningful change in physical examination will be reported as an AE/SAE. Height will only be measured at screening visit. Weight will be measured pre- and post-hemodialysis (wet-weight and dry-weight, respectively).

8.2.3 Vital Signs

- The investigator will assess blood pressure eligibility (Section 5.2) using the most appropriate method of blood pressure measurement available for the participant to determine the presence/absence of sustained uncontrolled hypertension.
- For subsequent study visits, blood pressure measurement will be assessed post-HD on the visits indicated in the SoA (Section 1.3), either in a supine or sitting position (preferably in the same position for all visits), on the same arm at each visit, and using the appropriate size cuff.

- The AV graft or fistula arm cannot be used to measure blood pressure.

8.2.4 Electrocardiograms

- Single 12-lead ECG will be obtained locally as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- Any clinically meaningful change in the ECG tracings as assessed by the investigator relative to baseline (tracings from the Screening Period) will be reported as an AE/SAE.
- All events of potential myocardial ischemia or infarction will be submitted to the CIAC for evaluation.

8.2.5 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and refer to the SoA for the timing and frequency.
- Where possible, pediatric-sized blood volumes (as opposed to adult-sized blood volumes) are to be taken and blood collections should be combined to minimize the number of needle punctures.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with abnormal values considered clinically significant during participation in the study after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the Medical Monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.6 Dialysis information

8.2.6.1 Renal Replacement Therapy Baseline Information

Information on the participant’s history of ESRD and RRT, as well as current dialysis prescription with be collected at screening (Visit 1) on the appropriate eCRF.

Note: anticoagulation use during hemodialysis must be reported in the Concomitant Medication page in the eCRF (separate log lines for bolus applications, continuous application, dose changes).

8.2.6.2 Dialysis Prescription Changes

Changes to the dialysis prescription and compliance with dialysis will be recorded on the appropriate eCRF at visits specified in the SoA (Section 1.3).

Note: changes in anticoagulation use during hemodialysis must be reported on the appropriate eCRF page.

8.2.7 Medical History

Medical history findings (i.e., previous diagnoses, diseases or surgeries) meeting all criteria listed below (but not limited to) will be collected as available to the investigator:

- Start before signing of ICF
- Considered relevant for the participant's study eligibility
- Pertaining to the study indication or considered relevant to the study (e.g. thromboembolism, major adverse cardiac events and related chronic conditions/diseases, major adverse limb events and related chronic conditions/diseases, metabolic diseases, and ESRD related diseases)
- Medical history related to concomitant medication.

A targeted medical history regarding cardiovascular and thromboembolic disease history will be collected in the eCRF on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

8.3 Adverse Events and Serious Adverse Events

In order to evaluate the safety and tolerability of BAY 2976217, adverse events will be assessed as a secondary safety endpoint.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AE/SAEs will be collected from the signing of the ICF until the final follow-up visit at the time points specified in the SoA (Section 1.3). Adverse events of special interest (AESI) have to be reported at any time after randomization (treatment, and post-treatment follow-up periods).

All SAEs/AESI will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Reporting of Disease-Related Events

Overall, in compliance with applicable regulations, in the event of a SUSAR related to the blinded treatment, the participant's treatment code will usually be unblinded before reporting to the health authorities. Notifications of IECs / IRBs and investigators will be done according to all applicable regulations with the restrictions described below.

During the study there will be instances where AEs are also potential efficacy or safety endpoints. The following efficacy and pre-defined disease-related outcome events are expected in patients with ESRD.

i. Bleeding

ii. Vascular Death (due to MI, stroke, PE, and SE)

iii. Non-fatal stroke, non-fatal MI

iv. Major amputation of vascular etiology

v. Acute Limb ischemia

vi. Symptomatic VTE

vii. Thrombosis of arterio-venous grafts or fistulas

These will be recorded on the corresponding eCRF page in the participant's eCRF.

If any of the above listed outcome events fulfil the definition of SAEs as given in Section 10.3.2, the investigator must report them immediately (within 24 hours of the investigator's awareness) to the sponsor's pharmacovigilance department as described in Section 10.3.4. However, SUSARs that derive from these efficacy outcome events (as specify above ii – vii: vascular death, non-fatal stroke/MI, major amputation, acute limb ischemia, symptomatic VTE, thrombosis of arterio-venous graft or fistulas), including events indicative of those outcome events (details will be described in the adjudication charter and additional study specific guidance documents) will be waived from unblinding and are not subject to expedited reporting to health authorities. In case of unblinding, SUSARs may be submitted blinded, either expedited or aggregated, to investigators and IEC/IRB. Unblinded SUSAR reports are submitted only when required by local legislation.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after signing of the ICF and during the participant's participation in this study.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

As serum βHCG levels are high in pregnancy and may be elevated in non-pregnant women with ESRD undergoing hemodialysis, one measurement of high βHCG will not be sufficient to establish pregnancy. Several serum βHCG will be collected during the study (SoA) for this reason and only sequential increasing levels of βHCG will be considered for further investigation. If deemed necessary, a follow-up ultrasound can be performed to confirm pregnancy.

If a female participant becomes pregnant, she must permanently discontinue study intervention.

8.3.6 Cardiovascular and Death Events

Death will be reported with the known cause of death as a SAE. Additionally, an electronic adjudication package will be submitted to the CIAC. If the cause of death is unknown, then a cause of death will be assigned by the CIAC. In order not to delay reporting within the required timeframe, when the cause of death is not known, the event should be reported as "Death not otherwise specified." If follow-up reports are received with the actual cause of death, the report will be updated.

For cardiovascular events see Section 9.4.6.1

8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Bleeding after dialysis from arterio-venous graft or fistulas is expected and will only be reported as an AE or SAE if there is a change in the pattern or intensity of bleeding in a participant, or if exceptional measures are taken for hemostasis beyond normal.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest have to be reported to the sponsor along the timelines set for SAEs, i.e. within 24 hours of the investigator's awareness, as described in Section 8.3.1.

Declaration of an event as serious should only occur if one or more of the serious criteria is applicable. Non-serious adverse events of special interest should not automatically be upgraded to serious by the reporting investigator.

Adverse events of special interest are:

- Decrease in platelets below 75,000/mm^3, or > 50% decrease in platelet from baseline
- Elevation of Hepatic Enzymes (> 3 x ULN, or 3 x baseline value, if the baseline value was > ULN)

8.3.8.1 Thrombocytopenia

8.3.8.1.1 Criteria for Reporting Thrombocytopenia as an Adverse Event of Special Interest

In the event of a platelet count that is <75,000/mm^3, or >50% decrease in platelet count from baseline, at any time after randomization (treatment, and post-treatment follow-up periods), the event will be reported as an AESI within 24 hours of the investigator's awareness. Non-serious AESI should not automatically be upgraded to serious on the AE page in the eCRF by the reporting investigator.

8.3.8.1.2 Stopping Rule for Thrombocytopenia

If a participant's platelet count is <75,000/mm^3, the initial measurement should be confirmed by drawing a repeat measurement at the next dialysis session (by local lab), and no more than 7 days after the initial value was obtained. The repeat measurement must occur before further dosing of study intervention. In the event of confirmed <75,000/mm^3 and the event is without an alternative explanation, dosing of a participant with study intervention will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed.

If the stopping rule criteria is met during the screening period, the participant should not be randomized and will discontinue from the study.

8.3.8.1.3 Monitoring and Evaluation of Thrombocytopenia

If a participant's platelet count is 100,000/mm^3 or less, or there is > 50% decrease in platelet count from baseline, then the platelet count should be monitored weekly by local lab. Additional assessments can be done locally, as deemed necessary, at the investigator's discretion. The following list is only a suggestion and is not limited to the lab tests outlined below. Only relevant local laboratory values need to be recorded in the eCRF.

- Von Willebrand factor
- Total globulins, total IgA, IgG and IgM
- Serology for:
    - Hepatitis B, Hepatitis C, HIV
    - Rubella
    - Cytomegalovirus
    - Epstein–Barr virus
    - Parvo B19
    - Helicobacter pylori (IgG serum test)
- Auto-antibody screen:
    - Antiphospholipid
    - Rheumatoid factor
    - Anti-dsDNA
    - Anti-thyroid

Central labs to be performed if platelet count < 75,000/mm^3:

- Complement: total C3, total C4, Bb, C5a

To be performed at specialty lab(s)

- Antiplatelet antibodies and Anti-PF4 assay
- Anti-ASO antibody

In the event of a platelet count < 50,000/mm^3, platelets are to be monitored daily (local lab) until 2 successive values show improvement, then monitored every 2-3 days until the platelet count is stable.

A stable platelet count is considered when at least 2 consecutive values measured are > 100,000/mm^3 with no downward trend.

8.3.8.1.4 Remedial Treatment for Thrombocytopenia

It is recommended that the participant receive glucocorticoid therapy to accelerate the recovery in the platelet decline (strongly recommended if platelet count < 25,000/mm^3). Treatment guidelines for immune thrombocytopenia recommend dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; prednisolone 0.5-2 mg/kg/day for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral corticosteroids after methylprednisolone) (54).

All additional platelet values, results of evaluations, and remedial treatments will be reported to the Sponsor as unscheduled laboratory visits and by updating the AESI report with all additional information, within the required timelines for follow-up information.

8.3.8.2 Elevation of Hepatic Enzymes

In the event of an ALT or AST measurement that is > 3 x ULN, or 3 x baseline value (if the baseline value was > ULN), at any time after randomization (treatment, and post-treatment follow-up periods), the event will be reported as an AESI and the following monitoring, evaluation, and stopping rules will apply. The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009 (55).

8.3.8.2.1 Criteria for Reporting Elevation of Hepatic Enzymes as an Adverse Event of Special Interest

In the event of an ALT or AST measurement that is > 3 x ULN, or 3 x baseline value (if the baseline value was > ULN), at any time after randomization (treatment, and post-treatment follow-up periods), the event will be reported as an AESI.

8.3.8.2.2 Stopping Rule for Elevation of Hepatic Enzymes

The initial measurement(s) should be confirmed by drawing a repeat measurement at the next dialysis session (local lab- unscheduled visit), and no more than 7 days after the initial value was obtained. The repeat measurement must occur before further dosing of study intervention. Hepatic enzyme values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed. In the event of confirmed laboratory results meeting the following criteria, and the event is without an alternative explanation, dosing of a participant with study intervention will be stopped permanently.

Liver Chemistry:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN or 5 x baseline value (if the baseline value was >ULN), which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN or 3 x baseline value (if the baseline value was >ULN), which is confirmed and total bilirubin > 2 x ULN or 2 x baseline value (if the baseline value was >ULN),
4. ALT or AST > 3 x ULN, which is confirmed (or 3 x baseline value if the baseline value was > ULN) with the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

In the event that the stopping rule criteria are met during the screening period, the participant should not be randomized and will discontinue from the study.

8.3.8.2.3 Monitoring and Evaluation of Elevation of Hepatic Enzymes

If the participant has confirmed post-baseline ALT or AST levels > 3 x ULN, or 3 x baseline value (if the baseline value was > ULN) that are continuing to rise, they should have their liver chemistry tests (ALT, AST, INR and total bilirubin) retested at least once-weekly by

local lab until ALT and AST levels become ≤ 1.2 x ULN or ≤ 1.2 x baseline (if the baseline value was > ULN).

If the participant has discontinued treatment due to achieving stopping rule (see Section 8.3.8.2.2) they will still be monitored until ALT and AST levels become ≤ 1.2 x ULN or ≤ 1.2 x baseline (if the baseline value was > ULN).

Additionally, for participants with confirmed ALT or AST levels > 3 x ULN (if baseline values ≤ ULN) or > 3 x baseline (if baseline value was > ULN) during the treatment and post-treatment follow-up periods, the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography or magnetic resonance imaging scans, may be performed at the discretion of the investigator. Repetition of the above evaluations should be considered if a participant's ALT and/or AST levels further increase and reach > 5 x ULN (or 5 x baseline value, if baseline value was > ULN).

All additional hepatic enzyme values and results of evaluations will be reported to the Sponsor as unscheduled laboratory visits and by updating the AESI report with all additional information, within the required timelines for follow-up information.

8.3.9 Injection-related events

An injection site event is defined as:

(a) any AE at the injection site presenting as Injection site erythema, Injection site swelling, Injection site pruritus, or Injection site pain that started on the day of injection

(b) any AE at the injection site, regardless of severity, that led to discontinuation of Study Drug, where the AE at the injection site was the principal reason for discontinuation.

8.3.10 AEs requiring submission of an adjudication package to the CIAC

All deaths, and events suspected to be related to cardiovascular disease, or other arterial or venous thrombosis (including arterio-venous access thrombosis) occurring after randomization, but not limited to these, will be submitted to the CIAC for adjudication. Additionally, all bleeding events (except a participant's normal/expected post-dialysis bleeding from arterio-venous access) will be submitted to the CIAC for adjudication. Details for the adjudication process are described in the adjudication charter and additional study specific guidance documents.

8.4 Treatment of Overdose

For this study, any dose of study intervention given in addition to the pre-defined regular monthly administration of BAY 2976217 will be considered an overdose. The Sponsor does not have a general recommendation for treatment of an overdose especially in the absence of any signs or symptoms.

In the event of an overdose, the investigators should:

1. Contact the Sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until BAY 2976217 can no longer be detected systemically (at least 20 weeks).
3. Obtain a plasma sample for PK analysis within 21 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

- Plasma and dialysate samples will be collected for measurement of plasma and dialysate concentrations of BAY 2976217 and its metabolites (e.g. in plasma as total full-length oligonucleotide, including fully conjugated, partially conjugated, and unconjugated BAY 2976217) as specified in the SoA. 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 (Section 8.5.1.2).
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The exact actual date and time (24-hour clock time) of each sample will be recorded. In addition, the actual date and time of study intervention intake on the visit day will be documented in the eCRF.
- Non-compartmental PK parameters will not be evaluated in this study. However, plasma concentration data will be used to evaluate the PK of BAY 2976217 (as total full-length oligonucleotide, including fully conjugated, partially conjugated, and unconjugated BAY 2976217) using population PK. PK and PD data obtained from this study will be subject to PK and/or PK/PD modeling and simulation. Details of the model development and evaluation will be described in a separate evaluation plan and the results will be reported in a separate evaluation report. Optionally, BAY 2976217 metabolites (e.g. unconjugated BAY 2976217) may be analyzed in an exploratory fashion. If measured, results will be reported separately.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. sample handling sheets or laboratory manual).

8.5.1 Sampling time for PK, PD and immunogenicity

Table 8–1: Overview PK/PD and immunogenicity, sampling

Main treatment period																					
Sampling	**Type**	**V1**	**V2[a]**	**V3[a]**	**V4[a]**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V16**	**V18**	**V19**	**V20**	**V21**	**V22**
Plasma PD	At any time	●	●	●	●																
Plasma PK/PD	pre-dose (trough)					●					●		●		●	●	●				●[b]
	3-4 h post administration [c]					●					●										
	5-6 h post administration [d]					●					●										
	22-32 h post administration						●														
	At any time during the visit							●	●	●		●		●				●	●	●	●[b]
Dialysate PK	15 min to 30 min after the start of dialysis					●	(●)[e]				●										
	30 min to 0 min prior to the end of dialysis					●	(●)[e]				●										
Immunogenicity	Pre-dose					●[f]					●				●						●[b]
	At any time								●												
Extension treatment and Follow-up period																					
		V23	**V24**	**V25**	**V26**	**V27**	**V28**	**FU1**	**FU4**	**ET**											
Plasma PK/PD	pre-dose (trough)	●	●	●	●	●															
PK/PD	Any time during the visit						●	●	●	●											
Immunogenicity	Pre-dose		●		●																
	At any time						●		●	●											

ET = early termination visit, min = minute(s), h = hour(s), PD = Pharmacodynamic(s), PK = Pharmacokinetic(s)
a Visits 2, 3 and 4 are only applicable before implementation of amendment 1, for patients enrolled as of amendment 1 these visits are not performed.
b At Visit 22, plasma PK and PD, and immunogenicity sampling will be done before dosing (trough sample) if the participant receives study intervention. In cases when the participant does not receive study intervention at Visit 22, sampling can occur at any time during the visit.
c 3-4 hour PK sample should be taken very close to the 3 hour timepoint if possible.
d If routine care procedures are incompatible with the 5-6 hour time window, the sample may be taken earlier but not before 4 1/2 hours after study drug administration.
e Samples will be collected on V6 for patients in alternative PK&PD sampling group, as they will have dialysis on V6.
f At V5 Immunogenicity sample will be drawn pre-hemodialysis, before the first dose of study intervention.

8.5.1.1 PK, PD and immunogenicity sampling (all participants)

- Visit 5 will be conducted on a dialysis day. The first dose of study intervention will be administered on Visit 5, prior to the start of the dialysis session. Visit 5 plasma PK/PD samples will be drawn at timepoints described in Table 8–1. Dialysate effluent will be collected 15 minutes to 30 minutes after the start of dialysis, and during the final 30 minutes of dialysis. Visit 5 immunogenicity sample will be drawn pre-HD, before the first dose of study intervention.
- Visit 6 will be conducted the day after Visit 5, on a non-dialysis day. The Visit 6 plasma PK/PD sample will be drawn 22-32 hours after the first dose of Study intervention administration on Visit 5.
- Visit 10 will be conducted on a dialysis day. Dosing on Visit 10 will occur prior to the start of the dialysis session. Visit 10 plasma PK/PD samples will be drawn at timepoints described in Table 8–1. Dialysate effluent will be collected at 15 min to 30 min after the start of dialysis and during the final 30 minutes of dialysis. The total dialysis volume should be recorded.
- At Visit 12, Visit 14, Visit 16, Visit 18 (main treatment period) and Visits 23-27 (extended treatment period) plasma PK and PD, and immunogenicity (when applicable) sampling will be done before dosing (trough sample), at other visits sampling can occur at any time during the visit.
- At Visit 22, plasma PK and PD, and immunogenicity sampling will be done before dosing (trough sample) if the participant receives study intervention. In cases when the participant does not receive study intervention at Visit 22, sampling can occur at any time during the visit.

8.5.1.2 PK, PD and immunogenicity sampling, participants from the alternative PK&PD sampling group starting on a non-dialysis day

- For these participants, study intervention will be administered on a non-dialysis day preceding a scheduled dialysis day.
- Visit 5 will be conducted on a non-dialysis day preceding a scheduled dialysis day. The first dose of study intervention will be administered on Visit 5. Visit 5 plasma PK/PD samples will be drawn at timepoints described in Table 8–1. Immunogenicity samples will be drawn before the first dose of study intervention on Visit 5.
- Visit 6 will be conducted the day after Visit 5, on a dialysis day. The Visit 6 plasma PK/PD sample will be drawn 22-32 hours after the first study intervention administration on Visit 5, and whether the sample was taken before, during or after dialysis will be recorded. Dialysate effluent will be collected at 15 min to 30 min after the start of dialysis and during the final 30 minutes of dialysis. The total dialysis volume should be recorded.
- Visit 10 will be conducted on a dialysis day. Dosing on Visit 10 will occur prior to the start of the dialysis session. Visit 10 plasma PK/PD samples will be at timepoints described in Table 8–1. Dialysate effluent will be collected at 15 min to 30 min after the start of dialysis and during the final 30 minutes of dialysis. Visit 10 immunogenicity sample will be drawn pre-HD, before dosing.

- At Visit 12, Visit 14, Visit 16, Visit 18 (main treatment period) and Visits 23-27 (extended treatment period) plasma PK, PD, and immunogenicity (when applicable) sampling will be done before dosing (trough sample), at other visits sampling can occur at any time during the visit.
- At Visit 22, plasma PK and PD, and immunogenicity sampling will be done before dosing (trough sample) if the participant receives study intervention. In cases when the participant does not receive study intervention at Visit 22, sampling can occur at any time during the visit.

8.6 Pharmacodynamics

Blood sampling for PD parameters is scheduled for the time points as given in Section 8.5.1. The actual date and time of blood sampling will be documented in the eCRF. All PD parameters will be measured using validated methods.

Quality control and calibration samples will be analyzed concurrently with study samples. For selected PD parameters, the results of quality control samples will be reported together with analyte concentrations in the Clinical Study Report of this study.

Analyte results are calculated according to the method description. Detailed method descriptions of all PD methods will be filed with the study report.

8.6.1 Secondary pharmacodynamic parameters:

The following parameters will be used to assess the PD effects after administration of the investigational drug, but may be performed optionally and/or only in a subset of participants:

- Factor XI activity will be assessed with an aPTT-based coagulation test using FXI deficient plasma. Furthermore, the assay will be conducted after in vitro - neutralization of heparin in order to separate potential heparin effects from the PD effect of BAY 297621
- FXI antigen concentration will be measured via enzyme-linked immunosorbent assay using polyclonal antibodies

8.6.2 Other Pharmacodynamic parameters:

The following parameters will be used to assess the PD effects after administration of the investigational drug, but may be performed optionally and/or only in a subset of participants:

- aPTT will be measured using a standard clotting assay. Furthermore, the aPTT assay will be conducted after in vitro -neutralization of heparin in order to separate potential heparin effects from the PD effect of BAY 297621
- AXIA will be analyzed using a kaolin-trigger and a fluorogenic substrate readout
- PT (seconds and INR) will be determined using standard methods
- D-Dimer will be measured using an immunoturbidometric method
- TAT and F1.2, will be analyzed using immunoassays
- SQCS will be analyzed as described below

Semi-quantitative Clotting Score: Extent and frequency of clotting on the dialysis filters & circuit

The rate/frequency of clotting on the dialysis filters and circuit will be measured as an exploratory PD analysis. The effect of BAY 2976317 on the clotting in the dialysis circuit will be assessed by the SQCS. The clotting assessment is a quantitative scale by descriptive category that is performed by trained personnel.

At the end of the hemodialysis procedure, at specified time points, the filter and line (including drip chamber/air trap) will be examined by the hemodialysis nurse (or respective appropriate personnel) after rinsing the circuit. Clotting scores will be assigned as follows:

- "0" clean filter and no visible clots in the drip chamber/air trap
- "1" traces of coagulation in the filter and/or in the drip chamber/air trap
- "2" intermediate state between "1" and "3"
- "3" fully clotted extracorporeal system resulting in an interruption of the hemodialysis session

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

Overall score is the highest of the individual component scores:

Inspection Site	Category 0	Category 1	Category 2	Category 3
Drip chamber (also referred to as air trap)	No visible clots in the drip chamber	Trace (e.g.- fibrinous ring with no clot formation on venous chamber)	Intermediate (e.g.- clot formation on venous chamber, more than "1" but not fully clotted)	Fully clotted system (treatment cannot continue without new setup)
Dialyzer	Clean dialyzer	Trace (e.g.- blood stripes affecting less than approximately 5% of the fibers seen at the surface of the dialyzer)	Intermediate (e.g.- blood stripes affecting approximately 5% or more of the fibers seen at the surface of the dialyzer, but not fully clotted)	Fully clotted filter

Only one (highest) score will be documented in the eCRF.

The clotting score will be recorded as specified in the SoA. The dialyzer and drip chamber/air trap will be assessed for clotting score at the end of the dialysis session on the visit day (or from a dialysis session within the visit window if the visit is not conducted on a dialysis day).

For information on PD sampling see Section 8.5.

The study sponsors reserve the right not to conduct all or part of the above-mentioned analysis.

8.7 Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study. Genetic investigations may be of any kind, except for whole genome sequencing.

8.8 Biomarkers

Exploratory biomarker analyses (scheduled for the time points as given in Section 1.3), that might be performed optionally and/or only in a subset of participants are:

- FVIII, FIX and FXII activity using clotting assay (V5 only)
- vWF antigen and vWF risocetin cofactor activity (V5 only)
- TAFI and C1 inhibitor activity, measured using chromogenic substrate assays

In addition to the biomarkers described above, further biomarkers related to the mode of action or the safety of BAY 2976217 and similar drugs may be examined. The same applies to further biomarkers deemed relevant to cardiovascular and renal diseases and associated health problems. These investigations may include e.g. diagnostic, safety, PD, monitoring, or potentially predictive biomarkers.

Furthermore, some PD markers listed under Section 8.6 may also be analyzed using alternative reagent/analyzer manufacturers in order to assess potential systematic influences of the analysis technology. The additional analyses may include genetic as well as non-genetic biomarkers. Results will be reported under separate cover, if the evaluations are performed.

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (e.g., sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

8.9 Immunogenicity Assessments

Antibodies to BAY 2976217 will be evaluated in samples collected from all participants according to the SoA (Section 1.3). Additionally, samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Samples will be screened for antibodies binding to BAY 2976217 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to BAY 2976217 and/or further characterize the immunogenicity of BAY 2976217.

The detection and characterization of antibodies to BAY 2976217 will be performed using a validated assay method by or under the supervision of the sponsor. Samples collected for detection of antibodies to study intervention may also be evaluated for BAY 2976217 concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant’s last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to BAY 2976217.

For information on immunogenicity sampling see Section 8.5.1.

8.10 Health Economics

Not applicable

9. Statistical Considerations

9.1 Statistical Hypotheses

There is no plan for statistical hypothesis testing for this study.

9.2 Sample Size Determination

No formal statistical samples 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. 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 participant is assumed to be similar. 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. 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 BAY 2976217 or placebo.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

Table 9–1 summarizes 95% expected range for the true population proportion of participants with the composite of MB and CRNMB bleeding. For example, with 60 participants, if 5% had the 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 9–1: Confidence Interval for proportion of participants with 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 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)

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Full analysis set	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	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.
Pharmacokinetic set	All LICA-treated participants with at least 1 PK sample in accordance with the PK sampling schedule (Section 8.5) 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	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.

9.4 Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

For the primary analysis: an 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. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection while maintaining sufficient blinding in the study. The partial data of a participant's extended treatment period up until primary completion may be presented in separate tables. More details on the primary analysis are provided in the SAP. No formal interim report will be written.

The investigator, study staff, participants, monitors, members of the Sponsor's clinical operations team and CIAC will remain blinded until the end of the study.

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 appropriately.

9.4.1 General considerations

9.4.1.1 Planned Methods of Analysis

Descriptive statistics will be provided by treatment group for all demographic variables, safety endpoints, and exploratory endpoints. The placebo groups from each cohort will be combined, so that there are four treatment groups to be included for analysis– 40 mg, 80 mg, 120 mg, and placebo, all equal in size.

- The safety analysis set will be used for all safety endpoints, including the primary endpoint.
- The full analysis set will be used for the exploratory endpoints or otherwise specified.
- The PK analysis set will be used for the pharmacokinetic endpoints, and
- The PD analysis set will be used for the pharmacodynamics endpoints.

For categorical variables, frequencies and proportions will be provided by treatment group. For continuous variables, means, medians, standard deviations, standard error of mean, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) will be provided by treatment group. For continuous variables collected at multiple time points, the descriptive statistics will be provided at each time point.

All analyses and tabulations will be performed using SAS@ Version 9.2 or higher or if applicable, other software.

9.4.1.2 Incomplete or Missing Data

In general, missing data values will not be imputed. Incomplete data handling rules will be described in the specified section in the SAP if needed.

9.4.1.3 Inter-current event

The list of possible inter-current events identified in this study are:

- Unblinding to study intervention: the study allows unblinding of the treatment assignment if the investigator deemed it necessary related to a bleeding event or AE.
- Premature treatment discontinuation or kidney transplant or death
- Lowering high dose study intervention from 120 mg to either 100 mg or 80 mg based on DMC recommendation.

Other inter-current events will be described in the specified section where appropriate.

9.4.1.4 Demographic and Baseline characteristics

Demographic and baseline characteristics including dialysis and ESRD disease characteristics obtained before the first study intervention administration, e.g.;

- age, gender, ethnicity, race, weight, height, BMI,
- current hemodialysis characteristics,
- medical condition that most likely led to RRT,
- time since the start date for renal replacement therapy,

will be summarized using descriptive statistics by treatment group and all participants for full analysis set population and safety population.

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.

The study sample sizes will be summarized by the trial unit (site) for enrolled participants. All participants with signed ICF will be included in the enrolled participants.

9.4.1.5 Definition of Baseline

Generally, measurements taken before first dose will be considered baseline values unless otherwise specified. For further details see the SAP.

9.4.1.6 On treatment

The "on-treatment" period is defined as the period between first administration of study intervention up to 28 days after the last administration of study intervention.

9.4.2 Primary endpoint(s)

The primary endpoint is the incidence of the composite of major bleeding and clinically-relevant non-major bleeding, as assessed by blinded CIAC.

Estimand for the primary safety endpoint:

The five attributes of the estimand are as follows:

- **Population:** ESRD patients as described by the inclusion/exclusion criteria given in Section 5.
- **Variable:** The incidence of composite of MB and CRNMB during the main treatment period, as assessed by CIAC.
- **Treatment:** Three dose groups of BAY 2976217 or placebo
- **Intercurrent events:**
    - Unblinding to study intervention: the study allows unblinding of the intervention code: regardless of whether such an event occurs (treatment-policy strategy)
    - Early definitive discontinuation of study treatment 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:** Proportion of subjects with a bleeding event by study intervention groups.

The primary objective is to assess the safety of the three different doses of BAY 2976217 given once a month which is expected to be maintained during a chronic treatment. The primary safety analysis is based on a descriptive proportion of subjects with bleeding events based on the Safety analysis population. (see Section 9.3).

- All suspected events of bleeding will be reported as an AE or SAE as per adverse event reporting procedure in Section 8.3. Additionally, an adjudication package will be sent to the CIAC. The CIAC will classify bleeding as defined in Section 8.2.1.
- Proportion of subjects with bleeding events including the following categories will be tabulated by treatment as assessed by the CIAC:
    - Composite of MB and CRNMB
    - MB
    - CRNMB
    - Minor bleeding
- For the primary safety analysis, primary safety outcomes will be considered during the main treatment period and while on-treatment. Incidences of MB, CRNMB, minor bleeding will be analyzed similarly.

The frequency and percentage of participants with bleeding will be reported where the denominator will be total number of participants in each treatment group in the safety analysis set. The corresponding exact binomial 95% confidence interval will be provided.

In addition, exposure adjusted bleeding rate analysis will be performed for the primary endpoint (for example, 100 person-years bleeding rate) and for the MB, CRNMB, minor bleeding, separately.

9.4.3 Secondary endpoints

- The incidence of composite of major bleeding and clinically-relevant non-major bleeding during the main and extended treatment periods and within the on-treatment time window. Similar additional analyses will also be done for MB, CRNMB, minor bleeding, separately.
- TEAE are defined as AEs that occurred or worsened after first dosing until 20 weeks after the last study intervention dose. For the primary analysis, TEAEs will be analyzed during the on-treatment time window within the main treatment period in the safety analysis set. In addition, TEAEs will be analyzed during the main and extended treatment periods and within the on-treatment time window. Results will be presented as incidence tables. All TEAEs, all TEAEs potentially related to study intervention, all TEAEs potentially related to ESRD, all TESAEs, and all TESAEs potentially related to study intervention (BAY 2976217 or placebo), TEAEs leading to early withdrawal of study intervention will be summarized by treatment group and by MedDRA preferred term and system organ class. Listings will be also provided.

9.4.4 Pharmacokinetic endpoints

Trough (pre-dose) concentrations (C_{trough}) for 3 dose levels of BAY 2976217 will be summarized descriptively by dose level and visit (i.e. V12, V14, V16, V18). Details will be specified in SAP.

9.4.5 Pharmacodynamic endpoints

The PD profile will be assessed as described in Section 8.6.

- **Changes in FXI antigen levels and FXI activity levels:**

  Maximum change in FXI activity and antigen levels during the main treatment period will be summarized by treatment groups.

9.4.6 Tertiary/exploratory endpoints

Further details on exploratory endpoints (e.g. biomarker and immunogenicity analyses) are described in the SAP.

9.4.6.1 Exploratory efficacy endpoints

The exploratory efficacy endpoints, as assessed by the CIAC, are:

- Incidence of composite and event types of death due to MI, stroke, PE and SE, and non-fatal stroke, non-fatal MI, VTE, major amputation of vascular etiology, and acute limb ischemia
- Incidence of thrombosis of the arterio-venous grafts or fistulas.

9.4.6.2 Other pre-specified safety endpoints

All safety analyses will be made on the Safety Population.

- **Incidence and severity of AESIs:**

  Hepatic enzyme elevation, thrombocytopenia

- **Changes in blood pressure, laboratory assessments**:

  Laboratory tests (see Section 8.2.4) to ensure subject safety including chemistry/liver panel, coagulation panel, hematology panel etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after study intervention (BAY 2976217 or placebo) administration, as appropriate. In addition, the number of subjects who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

- **Incidence and severity of bleeding of the arterio-venous grafts or fistulas:**

  All events of arterio-venous graft or fistula bleeding, in excess of expected post-dialysis bleeding or requiring additional hemostatic measures than usual, will be reported as an AE or SAE as per adverse event reporting procedure in Section 8.3. The incidence and severity of the events will be summarized by treatment group.

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 after removal of the dialysis needle(s) from the AV access according to the following categories (exploratory bleeding score):

"0" no access bleeding

"1" slow oozing

"2" overt bleeding

The 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 3 bleeding score categories.

9.4.6.3 Pre-specified PD endpoints

- **Changes in PT, INR, and aPTT:**

  Maximum change in PT, INR, and aPTT levels during the main treatment period will be summarized by treatment group.

- Extent and frequency of clotting on the dialysis filters & circuit:

  The extent and occurrence of clotting on the dialysis filters and circuit will be summarized descriptively by category scoring (SQCS) as described in Section 8.6. For a change from baseline to evaluation period analysis, the baseline for liver enzymes, platelets, PD biomarkers including the clotting score, AV access bleeding score will be the mean of measurements taken during the 1-week screening period. The final 4 weeks (Visits 19-22) would be the evaluation period from which a mean value can be determined from measurements taken during this period.

- Changes in d-dimers:

  Change and percent change in d-dimers will be tabulated by treatment group by study visit.
- TAT
- F1.2

9.4.7 Other analyses

Analysis of COVID-19 Patients

Analysis to evaluate the COVID-19 impact on the study primary safety and exploratory efficacy endpoints will be performed by comparing the descriptive statistics among confirmed COVID-19 versus non-COVID-19 patient population. Additional COVID-19 analysis considerations will be described in the SAP.

9.5 Interim Analyses

No formal interim analysis is planned.

9.6 Data Monitoring Committee (DMC)

An independent data monitoring committee will monitor the safety of the participants. For details on DMC, see Section 10.1.5.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements, ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- The following ICFs are available for the study:
  - Regular ICF for study entry;
  - Regular ICF for study entry for alternative PK&PD sampling group;
  - Pregnancy ICF for female participants for follow-up data;
  - Pregnancy ICF for male participants for follow-up data.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

The primary role of the DMC is to periodically review the safety data and ensure the safety of the participants in the ongoing study including unblinded data. The full description of the DMC structure and tasks is provided in the DMC charter.

A Study Steering Committee will be established to provide medical consultancy. The full description of the Steering Committee structure and tasks is provided in the Steering Committee charter.

CIAC is blinded for treatment allocation and will objectively assess the incidence of major bleeding and clinically relevant non-major bleeding as well as all suspected bleeding and thrombosis events. The full description of the CIAC structure and tasks is provided in the CIAC charter.

10.1.6 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases. In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers participant-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after 01 JAN 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in a source document check list.

10.1.9 Study and Site Start and Closure

First Participant First Visit is considered the first act of recruitment and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory.
- Local laboratory results are required if central laboratory kits are not available, or central laboratory results are not available. If a local sample is required, if possible a sample for central analysis should be obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF. Local laboratory results should not be used for eligibility check.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing, See Section 5.1 for screening pregnancy criteria.

Table 10–1: Protocol-Required Safety and Routine Laboratory Assessments

Laboratory assessments	Parameters
Hematology	Hemoglobin, Hematocrit, Red blood cell count (MCV MCH, MCHC, %Reticulocytes), Platelets, white blood cell count with differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)
Blood Chemistry[1]	Sodium, Potassium, Phosphorus, Magnesium, calcium, chloride, bicarbonate, Creatinine, BUN, Total protein, Albumin Amylase, lipase Creatine kinase, high-sensitivity C-reactive protein, troponin T, NT-pro BNP Lactate dehydrogenase
Liver enzymes	AST (=ASAT / GOT), ALT (=ALAT/GPT), alkaline phosphatase (ALP), γ-GT, GLDH, TBL, Direct bilirubin, Indirect bilirubin
Carbohydrate metabolism	HbA1c
Lipids	Total cholesterol, Triglyceride, HDL-cholesterol, LDL-cholesterol
Dialysate effluent	BAY 2976217 concentrations, 3‘- and 5‘- 10-mers, and 3‘- and 5‘- 5-mers
PK / PD / immunogenicity sampling / biomarkers	FXI antigen, FXI activity, AXIA, FXI concentration, plasma concentrations of BAY 2976217 (as total full-length oligonucleotide, including fully conjugated, partially conjugated, and unconjugated BAY 2976217), Antibodies to BAY 2976217, TAFI and C1 inhibitor activity, TAT and F1.2, Prothrombin time (Quick), aPTT, Fibrinogen, INR, d-dimer.
Other Screening Tests	• Highly sensitive serum human chorionic gonadotropin (HCG) pregnancy test (as needed for WOCBP) • Genetic analysis

1: Details of liver chemistry assessment and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.3.8.2.
ALAT = alanine aminotransferase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; ASAT = Aspartate-aminotransferase; AST = aspartate aminotransferase; AXIA = Activated Factor XIa activity, BUN = Blood urea nitrogen; FXI = Coagulation factor XI, GLDH = Glutamate dehydrogenase; GOT = serum glutamic oxaloacetic transaminase; GPT = Garment package test; γ-GT = glutamyltransferase, HbA1c = Hemoglobin A1c; HDL = high-density lipoprotein; INR= international normalized ratio, LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, NT-pro BNP = NT-proB-type Natriuretic Peptide, TAFI = Thrombin-activatable fibrinolysis inhibitor; TAT = Thrombin-antithrombin complex; TBL = total bilirubin, WOCBP = Women of childbearing potential

If the platelet value or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat blood specimen should be re-drawn as soon as

possible (ideally at the next dialysis session) and reviewed prior to dosing. Valid platelet counts and liver enzymes must be obtained at least every 2 weeks and reviewed prior to dosing.

Investigators must document their review of each laboratory safety report.

PD results including coagulation parameters that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) whether or not associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:	
a.	**Results in death**
b.	**Is life-threatening** • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c.	**Requires inpatient hospitalization or prolongation of existing hospitalization** • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- The investigator will also assess the relationship between each occurrence of each AE/SAE to the presence of ESRD or the hemodialysis procedure.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health

care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor´s Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the investigator site file.

SAE Reporting to Sponsor via Paper CRF

- Email transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator site file.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

WOCBP with their partner must agree to use a highly effective contraception method from the time signing of ICF until 20 weeks after the participant's last dose of study treatment (due to long terminal half-life and once monthly dosing).

If engaged in sexual activity with childbearing potential partner, male participants with their female partner must use highly effective contraception from the time of signing the ICF until 20 weeks after the participant's last dose of study treatment.

Highly effective contraception methods are for example:

- History of surgical sterilization (male participant or female partner)
- Female partner uses hormonal contraception or intrauterine contraception/device
- Sexual abstinence

Male participants with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the study intervention. Also, male participants with female partners who are breast feeding must use condoms.

Collection of Pregnancy Information:

The investigator must report to the sponsor any pregnancy occurring in a study participant, or in the study participant's partner, during the participant's participation in this study using the pregnancy reporting form. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother or child should be reported. For the pregnancy of a study participant's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
    - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
    - A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Country-specific Requirements

China:

- Study sites in China are excluded from exploratory biomarker analyses and pharmacogenetic sample collection

10.6 Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.6.1 Amendment 1: (29 SEP 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This amendment was prepared to address the change in the new contraception guidance as requested by Health Authorities. Additionally, the number of procedures and visits was decreased to reduce the burden on the participants. This reduction does not impact the participants' safety nor affect the benefit-risk assessment.

Key changes

Section # and Name	Description of Change	Brief Rationale
10.4 Contraceptive Guidance and Collection of Pregnancy Information	Contraception was changed into highly effective (removing the barrier method as example for contraception)	Request from Health Authorities
1.3. Schedule of Activities (SoA) + throughout the protocol	Visits 2, 3 and 4 removed; screening period shortened to 7 (+6) days with provision that some procedures can be done on more than one day	To reduce the burden on the participants. The visits are reduced during screening before randomization therefore there is no safety concern.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	ECG assessments removed on Visits 5, 10, 14, 15, 16, 23, 24, 25, 26, 27, FU1	To reduce the burden on the participants. Frequent ECGs was initially deemed necessary for the documentation of efficacy outcomes. However, since the efficacy outcomes are mainly based on symptomatic events, the use of pre-planned ECGs is not expected to contribute to an adequate assessments of suspected outcomes. For unsuspected changes on the ECGs related to the study drug, the protocol requires 4 routine ECGs to be done during the main treatment phase.
1.3 Schedule of Activities (SoA), 8.2.3 Vital Signs	Post HD BP measurements changed from average of 3 blood pressure readings to one post HD BP measurement; temperature, pulse and heart rate measurements removed => vital signs comprise only post HD BP measurements.	To reduce the burden on the participants. The patients are seen at the center at least 3 times a week (9 hours/week) and post-HD blood pressure will be collected on a regular basis. Therefore, collection of vital signs is redundant.
5.2 Exclusion Criteria	Pregnancy added as an exclusion criterion	Ensure safety as there is no information about the effect of the study intervention on pregnant women
6.5 Concomitant Therapy	Prohibited medications should be stopped 5 days before the study drug administration, not 28 days	5 days is sufficient for the drugs listed as prohibited during the study.
6.5 Concomitant Therapy	Thrombolytic drugs for systemic use (e.g., streptokinase, alteplase, tenecteplase, etc.) removed from the list of prohibited drugs	Thrombolytic therapy is not a routine therapy but an emergency therapy provided for acute care of myocardial infarction/stroke. These patients will not be eligible at that time. The protocol cannot prohibit a life-saving treatment in the event of emergency.
7.1 Discontinuation of Study Intervention	If a patient discontinues study intervention, he/she should continue with the scheduled visits	To collect efficacy and safety data according to intent-to-treat principle
8.2.1.1 Stopping Rules for Bleeding Events	In the event of clinically significant bleeding, dosing of study intervention does not necessarily have to be suspended. Instead, the investigator should carefully assess whether a participant can continue with the study intervention.	Many clinically relevant non-major bleeds occur at home and are resolved at the time of reporting. Study treatment should only be stopped if the patient is considered to be at high risk for continued / deterioration of bleeding.
8.3.8.1.3 Monitoring and Evaluation of Thrombocytopenia, 8.3.8.2.3 Monitoring and Evaluation of Elevation of Hepatic Enzymes	Several lab tests done at central lab in the event of thrombocytopenia or elevation of hepatic enzymes removed; they can be performed at local lab if needed, at the investigator's discretion	To reduce the burden on the participants. In the event of thrombocytopenia or elevation of hepatic enzymes a patient will be individually followed to ascertain appropriate documentation.
9.4.1.4 Demographic and Baseline characteristics	Disease characteristics to be collected at baseline updated.	According to SAP version 1.0.
10.2 Clinical laboratory tests	Mean platelet volume (MPV) and platelet distribution width (PDW) measurements removed	Sensitivity and specificity of these tests are poor and most of the time it is difficult to interpret the results. It does not impact safety.
10.2 Clinical laboratory tests	Follicle stimulating hormone and estradiol (in women of non-childbearing potential) removed	Action to evaluate the potential for pregnancy is at the discretion of the investigator.

AV = arterio-venous, BP =blood pressure, ECG = electrocardiogram, HD = hemodialysis, PD = pharmacodynamic(s), PK = pharmacokinetic(s), SPA = statistical analysis plan

Clarifications to the protocol

Section # and Name	Description of Change
1.3 Schedule of Activities (SoA), Table 1-3	A note added to the table („Day“ row) that at sites participating in the PK&PD sampling group, days marked with an asterisk are as listed in the table +1 day.
1.3 Schedule of Activities (SoA), 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Clarification added that AESIs have to be reported after randomization until the end of follow-up period.
1.3 Schedule of Activities (SoA), Table 1-3, 8.2 Safety Assessments, 8.2.5 Clinical Safety Laboratory Assessments	Frequency of measuring platelet count and ALT/AST during follow-up period is 4 weeks; 2-week frequency is during extended treatment period, with local lab monitoring at unscheduled visits.
8.5.1 Sampling time for PK, PD and immunogenicity	Sampling clarified for: • Plasma PK/PD and immunogenicity at V22 time points (whether to be collected pre-dose or at any time) • Immunogenicity time points (whether to be collected pre-dose or at any time) • Dialysate PK (for patients in alternative PK&PD group collected on V6)

AE = adverse event, AESI = adverse events of special interest, PD = pharmacodynamic(s), PK = pharmacokinetic(s), SAE = serious adverse event, ULN = upper limit of normal, V = visit

Corrections of inconsistencies and minor corrections (editorial corrections not detailed):

Section # and Name	Description of Change
1.3 Schedule of Activities (SoA)	“URR and KtV” changed to “URR or KtV” in comments field.
1.3 Schedule of Activities (SoA), Table 1-3, 8.2 Safety Assessments, 8.2.5 Clinical Safety Laboratory Assessments	Platelet count and ALT/AST are to be measured every 2 weeks, local lab monitoring ~~or central lab~~ at unscheduled visits can occur between the scheduled visits~~ that are scheduled every 4 weeks~~ .
1.3 Schedule of Activities (SoA)	Vital status line removed from the table
2.3.1 Risk Assessment	No clinically significant bleeding (MB, CRNMB) observed so far in healthy volunteers with BAY 2976217, ~~or in multiple populations with BAY 2306001~~
6.5 Concomitant Therapy	If ~~initiation of~~ prohibited medication is medically necessary during the treatment period, the participant will be discontinued from study intervention…
2.2.3 BAY 2976217	„Co-development partner“ changed to „collaboration partner“
5.1 Inclusion Criteria	„Male and/or female“ changed to „Male or female“
Section 6.1 Study Intervention(s) Administered	Volume of the vial changed from 1.0 mL to 1.05 mL, and consequently the volume of overfill from 0.2 mL to 0.25 mL for consistency with IMPD.
7.1.1 Events Requiring Definitive Discontinuation of Study Intervention, 8.2.1 Bleeding events, 9.4.1.3 Inter-current event, 9.4.2 Primary endpoint(s)	Major surgery removed as an event requiring definite discontinuation of the study intervention. The participant will be discontinued in the event of surgery that in the judgement of the investigator necessitates permanent discontinuation of the study intervention.
7.2 Participant Discontinuation /Withdrawal from the Study	... "Death of participant, in which case only relevant eCRF pages will be completed ~~for the Early Termination Visit~~..“
8.1 Efficacy Assessments	Wording corrections without change in content
8.2.1 Bleeding Events	Major bleeding is defined as symptomatic ~~overt~~ bleeding and: ....
8.2.1.4 AV access bleeding	A paragraph deleted, which stated that the bleeding severity will be recorded for all dialysis sessions during screening, observation and at the end of the main treatment periods. Bleeding severity is recorded at the planned study visits only.
8.2.4 Electrocardiogram	Third bullet point (“Atypical symptomatic presentation…”) deleted
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	All AE/SAEs will be collected from the signing of the ICF until the final follow-up visit… (added “final”). All SAEs/AESI will be recorded and reported to the sponsor or designee immediately... (added “AESI”)

Section # and Name	Description of Change
8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Bleeding after dialysis from arterio-venous graft or fistulas is expected and will only be reported as an AE or SAE if there is a change in the pattern or intensity of bleeding in a participant, or if exceptional measures are taken for hemostasis beyond normal ~~relative to post-dialysis bleeding that was observed in that participant over the prior 4 weeks.~~
8.3.8 Adverse Events of Special Interest	• Elevation of Hepatic Enzymes (> 3 x ULN, or 3 x baseline value, if the baseline value was > ULN) ("if the baseline value was >ULN" added)
8.3.8.2.2 Stopping Rule for Elevation of Hepatic Enzymes	2. ALT or AST > 5 x ULN or 5 x baseline value (if the baseline value was >ULN), which is confirmed and persists for ≥ 2 weeks 3. ALT or AST > 3 x ULN or 3 x baseline value (if the baseline value was >ULN), which is confirmed and total bilirubin > 2 x ULN or 2 x baseline value (if the baseline value was >ULN) 4. ALT or AST > 3 x ULN, which is confirmed (or ~~the greater of 2~~ 3 x baseline value if the baseline value was > ULN) with the new appearance
8.3.8.2 Elevation of Hepatic Enzymes	"In the event of an ALT or AST measurement that is > 3 x ULN, or 3 x baseline value (if the baseline value was > ULN), at any time after randomization ~~during the study~~ (treatment, and post-treatment follow-up periods), the event will be reported as an AESI..."
8.5.1.2 PK, PD and immunogenicity sampling from the alternative PK&PD sampling group starting on a non-dialysis day	In alternative PK&PD sampling group, at Visit 10 dialysate effluent to be collected as for all participants, i.e. at 15 to 30 minutes after the start of dialysis and during the final 30 minutes of dialysis.
8.6.2 Other Pharmacodynamic parameters	Clotting score documentation corrected to be as in the SoA. Clarification added that only the highest score will be documented.
9.4.1.3 Inter-current event	Unblinding to study intervention: the study will allow unblinding of the treatment assignment if the investigator deemed necessary after a bleeding event or ~~major surgery~~ AE („major surgery" replaced by „AE")
9.4.2 Primary endpoint(s)	~~Minor bleeding will be further categorized as injection site and non-injection site bleeding events.~~
9.4.3 Secondary endpoint(s)	TEAE definition changed to AEs that occurred or worsened post-dose until 20 weeks after the last study intervention dose (i.e. 4 weeks after the last dose plus 16-week post-treatment follow-up period) A paragraph added describing the primary analysis of TEAEs.
9.4.6.1 Exploratory efficacy endpoints, 9.4.6.2 Other pre-specified safety endpoints	Sections re-worded, in particular, sentences specifying that endpoints will be summarized by treatment group removed.
9.4.7 Other analyses	Analysis to evaluate COVID-19 impact added
10.4 Contraceptive Guidance and Collection of Pregnancy Information	The first 2 paragraphs removed from the contraceptive guidance.

AE = adverse event, AESI = adverse event of special interest, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CIAC = central independent adjudication committee, CRNMB = clinically relevant non-major bleeding, eCRF = electronic case report form, HIV = human immunodeficiency virus, ICF = informed consent form, IMPD = investigational medicinal product dossier, KtV = value used to quantify hemodialysis and peritoneal dialysis treatment adequacy, MB = major bleeding, PD = pharmacodynamic(s), PK = pharmacokinetic(s), SAE = serious adverse event, ULN = upper limit of normal, URR = urea reduction ratio

Administrative changes

Section # and Name	Description of Change
Title page	Investigational New Drug (IND) number added
Title page	Sponsor's responsible person changed
Title page	Wet ink signature replaced with electronic signature on a content approval form (filed separately)

10.7 Appendix 7: Abbreviations

2'-MOE	2'-O-methoxy-ethyl
AE	Adverse event
AESI	Adverse event of special interest
AFib	Atrial fibrillation
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
ASO	Anti-sense oligonucleotide
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Arterio-venous
AXIA	Activated Factor XIa activity
BMI	Body mass index: weight [kg] / (height [m])²
C	Concentration
CAD	Coronary artery disease
CBC	Complete blood count
CI	Confidence interval
CIAC	Central Independent Adjudication Committee
CFR	Code if Federal Regulations
CHF	Congestive heart failure
C_{max}	Maximum concentration
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CRNMB	Clinically relevant non-major bleeding
CV	Cardiovascular
DM	Diabetes mellitus
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOAC	Direct oral anticoagulant
dsDNA	Double stranded DNA
DVT	Deep vein thrombosis
e.g.	Exempli gratia (for example)
ECG	Electrocardiogram
eCRF	Electronic case report form
ESRD	End stage renal disease
EudraCT	EU data repository for clinical trials
F1.2	Prothrombin fragment 1 + 2
FFP	Fresh frozen plasma
FSH	Follicle stimulating hormone
FU	Follow-up
FVII	Coagulation factor VII
FVIII	Coagulation factor VIII
FIX	Coagulation factor IX
FXI	Coagulation factor XI
FXIa	Coagulation factor XIa
FXI-D	FXI deficiency
GalNAc	N-acetyl galactosamine
GCP	Good clinical practice
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HD	Hemodialysis
HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C-reactive protein
HRT	Hormonal replacement therapy
ICF(s)	Informed consent form(s)
ICH	International Council on Harmonization

IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional review board
ISTH	International Society on Thrombosis and Haemostasis
IWRS	Interactive web response system
LICA	Ligand conjugated antisense oligonucleotide
LLOQ	Lowest level of quantification
LMWH	Low molecular weight heparin
MB	Major bleeding
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MOE	Methoxyethyl
mRNA	Messenger RNA (Ribonucleic acid)
PAD	Peripheral arterial disease
PD	Pharmacodynamics(s)
PE	Pulmonary embolism
PF4	Platelet factor 4
PID	Participant identification code
PK	Pharmacokinetics
popPK	Population pharmacokinetics
PT	Prothrombin time
RNAi	RNA interference
RRT	Renal replacement therapy
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SE	Systemic embolism
SoA	Schedule of activities
SOP	Standard operating procedure
SQCS	Semi-quantitative clotting score
SUSAR	Suspected unexpected serious adverse reaction
TAFI	Thrombin-activatable fibrinolysis inhibitor
TAT	Thrombin-antithrombin complex
TEAE(s)	Treatment-emergent adverse event(s)
TESAE(s)	Treatment-emergent serious adverse event(s)
TIA	Transient ischemic attack
TKA	Total knee arthroplasty
t_{max}	Time to reach C_{max}
UFH	Unfractionated heparin
ULN	Upper limit of norm (upper limit of normal laboratory values)
VKA	Vitamin K antagonists
VTE	Venous thromboembolism
vWF	Von Willebrand factor
WOCBP	Women of childbearing potential

11. References

1. Basra SS, Tsai P, Lakkis NM. Safety and efficacy of antiplatelet and antithrombotic therapy in acute coronary syndrome patients with chronic kidney disease. J Am Coll Cardiol. 2011;58(22):2263-9.
2. Zoccali C, Mallamaci F, Tripepi G. Inflammation and atherosclerosis in end-stage renal disease. Blood Purif. 2003;21(1):29-36.
3. Seliger SL, Gillen DL, Longstreth WT, Jr., Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. Kidney Int. 2003;64(2):603-9.
4. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32(5 Suppl 3):S112-9.
5. United States Renal Data System. 2019 USRDS annual data report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. Available online: https://www.usrds.org/2019/view/USRDS_2019_ES_final.pdf. 2019.
6. de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA. 2009;302(16):1782-9.
7. Mann JF, Anderson C, Gao P, Gerstein HC, Boehm M, Ryden L, et al. Dual inhibition of the renin-angiotensin system in high-risk diabetes and risk for stroke and other outcomes: results of the ONTARGET trial. J Hypertens. 2013;31(2):414-21.
8. Palmer SC, Sciancalepore M, Strippoli GF. Trial quality in nephrology: how are we measuring up? Am J Kidney Dis. 2011;58(3):335-7.
9. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. Kidney Int. 2006;70(11):2021-30.
10. Marrs JC, Saseen JJ. Effects of lipid-lowering therapy on reduction of cardiovascular events in patients with end-stage renal disease requiring hemodialysis. Pharmacotherapy. 2010;30(8):823-9.
11. St Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. Am J Kidney Dis. 2008;51(3):445-54.
12. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347(25):2010-9.
13. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339(9):584-90.
14. Evolve Trial Investigators, Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012;367(26):2482-94.
15. Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011;80(6):572-86.
16. Turakhia MP, Blankestijn PJ, Carrero JJ, Clase CM, Deo R, Herzog CA, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving

Global Outcomes (KDIGO) Controversies Conference. Eur Heart J. 2018;39(24):2314-25.
17. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-5.
18. Jun M, James MT, Manns BJ, Quinn RR, Ravani P, Tonelli M, et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. BMJ. 2015;350:h246.
19. Shen JI, Montez-Rath ME, Lenihan CR, Turakhia MP, Chang TI, Winkelmayer WC. Outcomes After Warfarin Initiation in a Cohort of Hemodialysis Patients With Newly Diagnosed Atrial Fibrillation. Am J Kidney Dis. 2015;66(4):677-88.
20. Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation. 2014;129(11):1196-203.
21. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol. 2011;6(11):2662-8.
22. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol. 2009;20(10):2223-33.
23. Elliott MJ, Zimmerman D, Holden RM. Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates. Am J Kidney Dis. 2007;50(3):433-40.
24. Von dem Borne PA, Bajzar L, Meijers JC, Nesheim ME, Bouma BN. Thrombin-mediated activation of factor XI results in a thrombin-activatable fibrinolysis inhibitor-dependent inhibition of fibrinolysis. J Clin Invest. 1997;99(10):2323-7.
25. Schumacher WA, Luettgen JM, Quan ML, Seiffert DA. Inhibition of factor XIa as a new approach to anticoagulation. Arterioscler Thromb Vasc Biol. 2010;30(3):388-92.
26. Bouma BN, Meijers JC. Role of blood coagulation factor XI in downregulation of fibrinolysis. Curr Opin Hematol. 2000;7(5):266-72.
27. Preis M, Hirsch J, Kotler A, Zoabi A, Stein N, Rennert G, et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. Blood. 2017;129(9):1210-5.
28. Cushman M, O'Meara ES, Folsom AR, Heckbert SR. Coagulation factors IX through XIII and the risk of future venous thrombosis: the Longitudinal Investigation of Thromboembolism Etiology. Blood. 2009;114(14):2878-83.
29. Salomon O, Steinberg DM, Koren-Morag N, Tanne D, Seligsohn U. Reduced incidence of ischemic stroke in patients with severe factor XI deficiency. Blood. 2008;111(8):4113-7.
30. Asakai R, Chung DW, Davie EW, Seligsohn U. Factor XI deficiency in Ashkenazi Jews in Israel. N Engl J Med. 1991;325(3):153-8.
31. Peyvandi F, Palla R, Menegatti M, Siboni SM, Halimeh S, Faeser B, et al. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders. J Thromb Haemost. 2012;10(4):615-21.
32. Crooke ST, Baker BF, Kwoh TJ, Cheng W, Schulz DJ, Xia S, et al. Integrated Safety Assessment of 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides in

NonHuman Primates and Healthy Human Volunteers. Mol Ther. 2016;24(10):1771-82.
33. Crooke ST, Baker BF, Pham NC, Hughes SG, Kwoh TJ, Cai D, et al. The Effects of 2'-O-Methoxyethyl Oligonucleotides on Renal Function in Humans. Nucleic Acid Ther. 2018;28(1):10-22.
34. Crooke ST, Baker BF, Witztum JL, Kwoh TJ, Pham NC, Salgado N, et al. The Effects of 2'-O-Methoxyethyl Containing Antisense Oligonucleotides on Platelets in Human Clinical Trials. Nucleic Acid Ther. 2017;27(3):121-9.
35. Crooke ST, Baker BF, Xia S, Yu RZ, Viney NJ, Wang Y, et al. Integrated Assessment of the Clinical Performance of GalNAc3-Conjugated 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides: I. Human Volunteer Experience. Nucleic Acid Ther. 2019;29(1):16-32.
36. Younis HS, Crosby J, Huh JI, Lee HS, Rime S, Monia B, et al. Antisense inhibition of coagulation factor XI prolongs APTT without increased bleeding risk in cynomolgus monkeys. Blood. 2012;119(10):2401-8.
37. Zhang H, Lowenberg EC, Crosby JR, MacLeod AR, Zhao C, Gao D, et al. Inhibition of the intrinsic coagulation pathway factor XI by antisense oligonucleotides: a novel antithrombotic strategy with lowered bleeding risk. Blood. 2010;116(22):4684-92.
38. Büller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, et al. Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis. N Engl J Med. 2014;372(3):232-40.
39. Bethune C, Walsh M, Jung B. Pharmacokinetics and Pharmacodynamics of Ionis-FXIRx, an antisense inhibitor of factor XI, in patients with end-stage renal disease on hemodialysis. Poster No.1116. ASH 2017 - 59th Annual Meeting and Exposition, Atlanta, December 2017.
40. Salomon O, Steinberg DM, Zucker M, Varon D, Zivelin A, Seligsohn U. Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis. Thromb Haemost. 2011;105(2):269-73.
41. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(11):2119-26.
42. Seligsohn U. Factor XI deficiency in humans. J Thromb Haemost. 2009;7 Suppl 1:84-7.
43. Crash-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23-32.
44. Novikova N, Hofmeyr GJ. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2010(7):CD007872.
45. Downey P, Tagle R, Pereira J, Mezzano D. Tranexamic acid and uremic bleeding: evidence-based treatment recommendations. Nat Clin Pract Nephrol. 2007;3(6):E2; author reply E3.
46. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ. Evidence-based treatment recommendations for uremic bleeding. Nat Clin Pract Nephrol. 2007;3(3):138-53.

47. Sindet-Pedersen S, Stenbjerg S. Effect of local antifibrinolytic treatment with tranexamic acid in hemophiliacs undergoing oral surgery. J Oral Maxillofac Surg. 1986;44(9):703-7.
48. Berliner S, Horowitz I, Martinowitz U, Brenner B, Seligsohn U. Dental surgery in patients with severe factor XI deficiency without plasma replacement. Blood Coagul Fibrinolysis. 1992;3(4):465-8.
49. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2007(4):CD001886.
50. Livnat T, Tamarin I, Mor Y, Winckler H, Horowitz Z, Korianski Y, et al. Recombinant activated factor VII and tranexamic acid are haemostatically effective during major surgery in factor XI-deficient patients with inhibitor antibodies. Thromb Haemost. 2009;102(3):487-92.
51. Riddell A, Abdul-Kadir R, Pollard D, Tuddenham E, Gomez K. Monitoring low dose recombinant factor VIIa therapy in patients with severe factor XI deficiency undergoing surgery. Thromb Haemost. 2011;106(3):521-7.
52. Herzog CA, Littrell K, Arko C, Frederick PD, Blaney M. Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. Circulation. 2007;116(13):1465-72.
53. Nacb Writing Group, Wu AH, Jaffe AS, Apple FS, Jesse RL, Francis GL, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. Clin Chem. 2007;53(12):2086-96.
54. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-86.
55. FDA. Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), July 2009.