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Official Title:	A randomized, double-blind, parallel group, placebo-controlled, multi-center study to assess the safety and tolerability of monthly subcutaneous administrations of a low and high dose cohort of osocimab to ESRD patients on regular hemodialysis
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Title Page

Protocol Title:

A randomized, double-blind, parallel group, placebo-controlled, multi-center study to assess the safety and tolerability of monthly subcutaneous administrations of a low and high dose cohort of osocimab to ESRD patients on regular hemodialysis

Protocol Number: 20115

Compound Number: BAY 1213790 / Osocimab

Study Phase: Phase 2b

Short Title: Osocimab in ESRD Phase 2b study

Acronym: CONVERT

Sponsor Name: Bayer AG

Legal Registered Address:

Non-US: Bayer AG, 51368 Leverkusen, Germany

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

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Sponsor Signatory

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17. March 2020

Date

Global Clinical Lead

Medical Monitor name and contact information will be provided separately.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A randomized, double-blind, parallel group, placebo-controlled, multi-center study to assess the safety and tolerability of monthly subcutaneous administrations of a low and high dose cohort of osocimab to ESRD patients on regular hemodialysis

Short Title: Osocimab in ESRD Phase 2b study

Rationale: It is well known that end-stage renal disease (ESRD) patients on dialysis are at high risk for cardiovascular diseases. By targeting FXI, osocimab has the potential to provide an efficacious treatment for the prevention of thromboembolic events like myocardial infarction (MI), stroke and cardiovascular death with a favorable risk profile for unwanted bleeding. This Phase 2b trial will assess the safety and characterize the pharmacokinetic/pharmacodynamic (PK/PD) profile of two different dose cohorts of osocimab given subcutaneously once a month to participants with ESRD.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To clinically assess the safety of different doses of osocimab administered subcutaneously once a month during main treatment period as compared to placebo	• Composite of major and clinically-relevant non-major bleeding events (in alignment with ISTH guidelines), as assessed by blinded Central Independent Adjudication Committee (CIAC) • Composite of moderate and severe AEs and SAEs
Secondary	
• To assess the change of key PD parameter from baseline	• Activated partial thromboplastin time (aPTT), FXIa activity at trough levels after 6 months

Overall Design

Disclosure Statement: This is a covariate-adaptive randomized, double-blind, parallel group, placebo controlled, multi-center study with 2 cohorts of osocimab (low and high dose) tested against placebo in ESRD patients on hemodialysis. In this protocol, the term hemodialysis includes hemodiafiltration. Sponsor, participants and investigators are being blinded with respect to active treatment versus matching placebo, but not blinded to dose cohort (low or high dose).

A Data Monitoring Committee will regularly review the safety data of the participants.

Intervention Model: Parallel

Primary Purpose: Treatment

Number of Arms: 2 dose cohorts, 3 groups, 4 arms

Blinding: Participants, Investigator, Outcome Assessor

Number of Participants: Approximately 600 randomized

Approximately 600 participants (up to 750) will be randomly assigned to study intervention such that approximately 555 participants complete the main treatment period.

For details on sample size determination see Section 9.2.

Intervention Groups and Duration:

The following study interventions will be administered in the study:

- Osocimab (BAY 1213790): sponsor's study drug under investigation
- Placebo to osocimab

Different doses will be achieved by administering a different volume.

- Low dose cohort

  105 mg single loading dose as subcutaneous abdominal injection at visit 5, followed by monthly (i.e. 30 days ± 3 days) maintenance doses of 52.5 mg starting at visit 8 until the end of the extension treatment period. Placebo will be administered subcutaneously in the same manner as osocimab.

- High dose cohort:

  210 mg single loading dose as subcutaneous abdominal injection at visit 5, followed by monthly (i.e. 30 days ± 3 days) maintenance doses of 105 mg starting at visit 8 until the end of the extension treatment period. Placebo will be administered subcutaneously in the same manner as osocimab.

The two dose cohorts (low dose and high dose) follow the same treatment schedule:

- **Screening period (visit 1)**: up to 14 days
- **Randomization (visit 2)**: 1 day
- **Pre-treatment period (from visit 2 until visit 4)**: 7 days
- **Main treatment period (from visit 5 until EOMT visit)**: 6 months
- **Extension treatment period (from visit 19 until EOET visit)**: up to 12 months
- **Follow-up period (from visit 32 until visit 35)**: 4 months after end of treatment (EOMT or EOET)

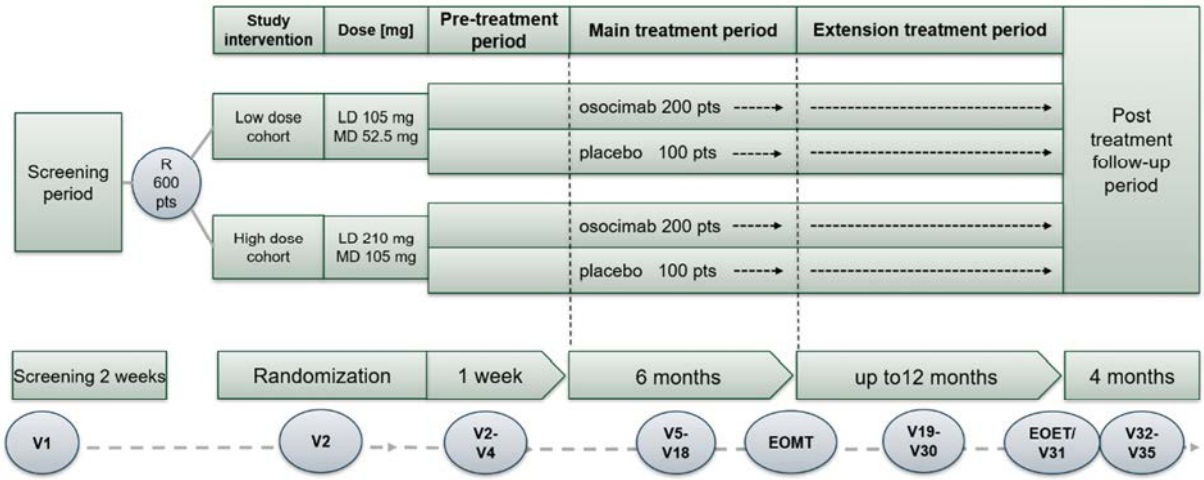
The mandatory extension treatment period is continued until the last study participant has completed its 6 months main treatment period or to a maximum of 18 months (i.e. 6 months main treatment period + 12 months extension treatment period). When the last participant has completed its 6 months main treatment period including EOMT (end of main treatment period) visit, all participants who are in extension treatment period at this time point will not receive any further dosing and will participate in an EOET (end of extension treatment period) visit at the next regular monthly extension visit and will move to the follow-up period. The last participant of the whole study will not take part in the extension treatment period.

Data Monitoring Committee: Yes

The study will be overseen by a Steering Committee (SC), a Data Monitoring Committee (DMC) and a Central Independent Adjudication Committee (CIAC).

1.2 Schema

Figure 1–1: Study Design Overview



Abbreviations: EOET = end of extension treatment period, EOMT = end of main treatment period, LD = loading dose, MD = maintenance/ monthly dose, pts = participants, R = randomization, V = visit

Further details on the randomization schema can be found in Section 6.3.
The follow-up period ends 5 months after last study intervention and 4 months after EOMT or EOET.

1.3 Schedule of Activities (SoA)

Visit procedures must be completed on a single day, except screening period.

Please note that if screening parameters are available as part of routine medical practice, these are not required to be repeated as long as they were measured within 14 days of screening and meet the thresholds defined in the in-/exclusion criteria.

It is not allowed to perform dialyses which are linked to study visits outside of the study center. Participants should come to the same dialysis center for each visit. Visits in between dialyses, i.e. not linked to a study visit, can be performed outside of the study center.

PD and biomarker sampling and analyses are mandatory for all participants except China and have to be done according to the SoA.

Please refer to Table 1–1 for the Schedule of Activities of the main treatment period and to Table 1–2 for the Schedule of Activities of the extension treatment period and the follow-up period.

Table 1–1: Schedule of Activities: Main Treatment Period

Study period (Duration)		**Pre-treatment period** (7 days)			**Main treatment period[d]** (6 months)															**Notes**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**EOMT[b] ED[a]**	
Study intervention LD or MD	**SCR[c]**	**RND**			**LD**			**MD**			**MD**		**MD**		**MD**		**MD**			
	Day					**Day since last study intervention dose**														
	-13 to 1	**1**	**3**	**6**	**8**	**2**	**4**	**30**	**2**	**4**	**30**	**4**	**30**	**4**	**30**	**4**	**30**	**4**	**30**	
Approx. month	-	1	1	1	1	1	1	2	2	2	3	3	4	4	5	5	6	6	7	
Window (days)			+3	+3	+3	+ 3	+ 3	± 3	+3	+ 3	± 3	+ 3	± 3	+ 3	± 3	+ 3	± 3	+ 3	± 3	A deviation of 2-3 days equals 1 dialysis session. Section 7.1.
Initiation procedures																				
Informed consent	●																			Signed written informed consent must be available before any study procedures are conducted.
In/ Exclusion criteria	●	●																		
Demography	●																			
Randomization via IWRS		●																		
Clinical procedures / assessments																				
Complete physical examination	●																		●	
Height, dry body weight	●																			
Vital signs	●	●			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	Pre-dialysis. See Section 8.2.4.
12-lead ECG	●	●			●			●									●			Pre-dialysis. See Section 8.2.5.
Prior and concomitant medication	---------- Continuous reporting ---------- >																			

Table 1–1: Schedule of Activities: Main Treatment Period

Study period (Duration)		**Pre-treatment period** (7 days)			**Main treatment period[d]** (6 months)															**Notes**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**EOMT[b] ED[a]**	
Study intervention LD or MD	**SCR[c]**	**RND**			**LD**			**MD**			**MD**		**MD**		**MD**		**MD**			
	Day					**Day since last study intervention dose**														
	-13 to 1	**1**	**3**	**6**	**8**	**2**	**4**	**30**	**2**	**4**	**30**	**4**	**30**	**4**	**30**	**4**	**30**	**4**	**30**	
Approx. month	-	1	1	1	1	1	1	2	2	2	3	3	4	4	5	5	6	6	7	
Window (days)			+3	+3	+3	+ 3	+ 3	± 3	+3	+ 3	± 3	+ 3	± 3	+ 3	± 3	+ 3	± 3	+ 3	± 3	A deviation of 2-3 days equals 1 dialysis session. Section 7.1.
Medical history	•																			The start of dialysis (dialysis vintage) and the start of use of the current vascular access should be documented.
AE/SAE/AESI	---------- Continuous reporting ---------- >																			
Heparin dose data collection		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Hemodialysis data collection (including pre-/post-dialysis weight, online Kt/V)		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		The term hemodialysis includes hemodiafiltration. Online Kt/V if provided by the dialysis machine.
AV access bleeding assessment		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		Not applicable for catheter dialysis access.
SQCS assessment		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Study intervention																				
Study intervention administered					•			•			•		•		•		•			Administered sc abdominally within one hour prior to dialysis.

Table 1–1: Schedule of Activities: Main Treatment Period

Study period (Duration)			**Pre-treatment period** (7 days)			**Main treatment period[d]** (6 months)														**Notes**
Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**EOMT[b] ED[a]**	
Study intervention LD or MD		**SCR[c]**	**RND**			**LD**			**MD**			**MD**		**MD**		**MD**		**MD**			
		Day					**Day since last study intervention dose**														
		-13 to 1	**1**	**3**	**6**	**8**	**2**	**4**	**30**	**2**	**4**	**30**	**4**	**30**	**4**	**30**	**4**	**30**	**4**	**30**	
Approx. month		-	1	1	1	1	1	1	2	2	2	3	3	4	4	5	5	6	6	7	
Window (days)				+3	+3	+3	+ 3	+ 3	± 3	+3	+ 3	± 3	+ 3	± 3	+ 3	± 3	+ 3	± 3	+ 3	± 3	A deviation of 2-3 days equals 1 dialysis session. Section 7.1.
Laboratory assessment																					
Local laboratory	Serum pregnancy test	•			•																See Section 10.2.
	Screening tests	•																			See Section 8.2.6 and Section 10.2.
Central laboratory	Laboratory calculated URR and Kt/V								•			•		•		•		•			For BUN a post-dialysis sample needs to be taken (central lab). Local lab values of URR and Kt/V ± 7 days are accepted.
	Hematology, chemistry, coagulation and serum pregnancy		•			•			•			•		•		•		•		•	Pre-dialysis. Prior to study intervention.

Table 1–1: Schedule of Activities: Main Treatment Period

Study period (Duration)			**Pre-treatment period** (7 days)			**Main treatment period[d]** (6 months)														**Notes**
Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**EOMT[b] ED[a]**	
Study intervention LD or MD		**SCR[c]**	**RND**			**LD**			**MD**			**MD**		**MD**		**MD**		**MD**			
		Day					**Day since last study intervention dose**														
		-13 to 1	**1**	**3**	**6**	**8**	**2**	**4**	**30**	**2**	**4**	**30**	**4**	**30**	**4**	**30**	**4**	**30**	**4**	**30**	
Approx. month		-	1	1	1	1	1	1	2	2	2	3	3	4	4	5	5	6	6	7	
Window (days)				+3	+3	+3	+ 3	+ 3	± 3	+3	+ 3	± 3	+ 3	± 3	+ 3	± 3	+ 3	± 3	+ 3	± 3	A deviation of 2-3 days equals 1 dialysis session. Section 7.1.
Central laboratory	Biomarker genetics[e] (if applicable)					•															
	Biomarker[e]: FVIII, FIX, FXII, vWF antigen, vWF activity					•															
	Biomarkers[e]					•					•								•	•	Pre-dialysis. Prior to study intervention.
	Main PD[e] samples					•	•	•	•	•	•							•	•	•	
	Additional PD[e] samples					•														•	
	PK samples					•	•	•	•	•	•							•	•	•	
	ADA/NAB					•			•									•		•	

Abbreviations: ADA = anti-drug antibodies, AE = adverse event, AESI = adverse event of special interest, Approx. = approximately, AV = arteriovenous, BUN = blood urea nitrogen, ECG = electrocardiogram, ED = early discontinuation visit, EOET = end of extension treatment period visit, EOMT = end of main treatment period visit, IWRS = interactive web response system, Kt/V – K = dialyzer urea clearance, t = dialysis time, V = total volume of distribution of urea, LD = loading dose, MD = maintenance/ monthly dose, NAB = neutralizing antibodies, PD = pharmacodynamic, PK = pharmacokinetic, RND = randomization, SAE = serious adverse event, sc = subcutaneous, SCR = screening, SQCS = semi-quantitative clotting score, URR = urea reduction ratio

a. It is recommended to perform the ED visit approximately 1 month after last study intervention. After ED the participant moves directly to the follow-up period.
b. EOMT and visit 19 will be performed at the same day. Both of them are mandatory separate visits and shouldn´t be missed.

c. Screening period covers up to 14 days (From Day -13 until Day +1). No Day 0 will occur.
d. When the last participant completes his 6 months main treatment period including EOMT visit, all participants who are in the extension treatment period at this time point will not receive any further dosing and will participate in an EOET visit at the next regular monthly extension visit. They will move to the follow-up period.
e. Study participating sites in China are excluded from all PD and biomarker sampling and analyses.

Table 1–2: Schedule of Activities – Extension Treatment Period and Follow-up Period

Study period (Duration)	**Extension treatment period** (up to 12 months)													**Follow-up period** (For 4 months after EOMT or EOET)				**Notes**
Visit number	**19[b]**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31/ EOET ED[a]**	**32**	**33**	**34**	**35**	
Study intervention MD	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**						
Day since last study intervention dose	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**60**	**90**	**120**	**150**	
Approx. month	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
Window (days)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 5	± 5	± 5	± 5	A deviation of 2-3 days equals 1 dialysis session. Section 7.1.
Clinical procedures / assessments																		
Complete physical examination									•			•	•				•	
Vital signs		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Pre-dialysis. See Section 8.2.4.
12-lead ECG			•			•			•			•			•		•	Pre-dialysis. See Section 8.2.5.
Concomitant medication	---------- Continuous reporting ---------- >																	
AE/SAE/AESI	---------- Continuous reporting ---------- >																	
Heparin dose data collection	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Hemodialysis data collection (including pre-/post dialysis weight, online Kt/V)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	The term hemodialysis includes hemodiafiltration. Online Kt/V if provided by the dialysis machine.
AV access bleeding assessment	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Not applicable for catheter dialysis access.
SQCS assessment	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	

Table 1–2: Schedule of Activities – Extension Treatment Period and Follow-up Period

Study period (Duration)		**Extension treatment period** (up to 12 months)												**Follow-up period** (For 4 months after EOMT or EOET)				**Notes**
Visit number		**19[b]**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31/ EOET ED[a]**	**32**	**33**	**34**	**35**	
Study intervention MD		**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**	**MD**						
Day since last study intervention dose		**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**60**	**90**	**120**	**150**	
Approx. month		7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
Window (days)		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 5	± 5	± 5	± 5	A deviation of 2-3 days equals 1 dialysis session. Section 7.1.
Study intervention																			
Study intervention administered		•	•	•	•	•	•	•	•	•	•	•	•						Administered sc abdominally within one hour prior to dialysis.
Laboratory Assessment																			
Central laboratory	Laboratory calculated URR and Kt/V			•			•			•			•						For BUN a post-dialysis sample needs to be taken (central lab). Local lab values of URR and Kt/V ± 7 days are accepted.
	Hematology, chemistry, coagulation and serum pregnancy			•			•			•			•					•	Pre-dialysis. Prior to study intervention.
	Biomarkers[d]									•[c]				•[c]					Pre-dialysis. Prior to study intervention.
	Main PD[d] samples									•[c]				•[c]	•[e]	•	•[e]	•	
	PK samples									•[c]				•[c]	•[e]	•	•[e]	•	
	ADA/NAB									•[c]				•[c]	•[e]	•	•[e]	•	

Abbreviations: ADA = anti-drug antibodies, AE = adverse event, AESI = adverse event of special interest, Approx. = approximately, AV = arteriovenous, BUN = blood urea nitrogen, ECG = electrocardiogram, ED = early discontinuation visit, EOET = end of extension treatment period visit, EOMT = end of main treatment period visit, IWRS = interactive web response system, Kt/V – K = dialyzer urea clearance, t = dialysis time, V = total volume of distribution of urea, MD = maintenance/ monthly dose,

NAB = neutralizing antibodies, PD = pharmacodynamic, PK = pharmacokinetic, sc = subcutaneous, SQCS = semi-quantitative clotting score, URR = urea reduction ratio

a. It is recommended to perform the ED visit approximately 1 month after last study intervention. After ED the participant moves directly to the follow-up period.
b. EOMT and visit 19 will be at the same day. Both of them are mandatory separate visits and shouldn´t be missed.
c. Samples are taken prior to study intervention at visit 27 or EOET/ED, whichever comes first.
d. Study participating sites in China are excluded from all PD and biomarker sampling and analyses.
e. Samples need to be taken only if no sampling was done approximately 30 days before at a prior visit.

2. Introduction

Osocimab is a novel long-acting anticoagulant targeting the activated form of FXI with the potential to exhibit lower risk of bleeding events than currently available anticoagulants.

2.1 Study Rationale

It is well known that ESRD patients on dialysis are at high risk for cardiovascular diseases. By targeting FXI, osocimab has the potential to provide an efficacious treatment for the prevention of thromboembolic events like MI, stroke and cardiovascular death with a favorable risk profile for unwanted bleeding. This Phase 2b trial will assess the safety and characterize the PK/PD profile of two different dose cohorts of osocimab given subcutaneously once a month to participants with ESRD.

2.2 Background

2.2.1 Cardiovascular Disease in ESRD Patients

Cardiovascular disease is the leading cause of death in adults around the world. World Health Organization (WHO) data show that an estimated 17.7 million people died from cardiovascular disease in 2015, which represents 31% of all deaths worldwide. Of these deaths, an estimated 6.7 million were due to stroke and 7.4 million were due to coronary heart disease (1).

It is well known that patients with ESRD have very high cardiovascular morbidity and mortality rates. Cardiovascular disease (e.g., coronary artery disease [CAD] and acute coronary syndrome, arrhythmia, chronic heart failure, cerebrovascular events [i.e., stroke]) is the leading cause of death in ESRD patients and accounts for 53% of all deaths with a known cause in patients on hemodialysis (2). In a large prospective United States–based study, the 5-year survival rate for hemodialysis patients was only 40%, with 40% of the deaths being cardiac (3). The annual cardiovascular mortality in the general population increases with age, rising from 0.01% in 30-year-old patients to 0.1% in 80-year-old patients (4). In contrast, there is only a modest age-related increase in cardiovascular mortality in hemodialysis patients, and the annual cardiovascular mortality in a 40-year-old hemodialysis patient is comparable with the mortality observed in an 80-year-old individual in the general population.

CAD incidence among patients initiating hemodialysis is up to 38%, with a relative risk that is 5 to 20 fold higher than that in the general population. The uremic environment due to the underlying renal disease may accelerate the progression of atherosclerosis and may influence the prevalence of CAD (5). Similarly, ESRD itself is seen as a risk factor for peripheral artery disease (PAD) as an additional expression of the underlying atherothrombosis/atherosclerosis, which often leads to complications such as non-healing ulcers and lower limb amputation (6- 7).

High levels of C reactive protein and pro-inflammatory cytokines have been reported in patients with ESRD, as well as endothelial dysfunction and increased oxidative stress, which are exacerbated in the setting of ESRD. Atherosclerosis and subsequent atherothrombosis are the drivers of CAD and PAD. These are inflammatory processes and the pro-inflammatory environment in patients with ESRD predisposes them to accelerated plaque formation and rupture, which contributes to thromboembolic events such as acute coronary syndrome/MI, stroke and cardiovascular death.

2.2.2 Cardiovascular Treatment Options for ESRD Patients

Treating patients with ESRD is challenging owing to competing mortality risks. Patients with chronic kidney disease (CKD) and ESRD are at an increased risk for both thromboembolic events and bleeding (8) and treatment options need to be carefully evaluated against their benefits and risks. Furthermore, the relative benefit-risk profile of anticoagulation in ESRD patients is different from that in patients with normal kidney function. In the non-ESRD population, current anticoagulation therapies have been shown to be efficacious for prevention of thromboembolic events (9-11). However, their use is associated with a variable bleeding risk and ESRD patients have a much higher risk for severe bleeding events than the non-ESRD population (12).

Although there are numerous high-quality randomized clinical trials (RCTs) supporting therapeutic cardiovascular interventions in the general population (13), the vast majority of these studies specifically excluded patients with severe renal impairment. In contrast, very few RCTs have evaluated cardiovascular therapies in hemodialysis. Because of the paucity of RCTs in hemodialysis patients, most cardiovascular therapies in this population are based on observational studies or results extrapolated from studies that excluded hemodialysis patients. Hence, due to the much higher bleeding risk of ESRD patients and the unproven benefits of anticoagulation therapy in these patients, most hemodialysis patients are not treated with respect to the prevention of thromboembolic events.

2.2.3 Factor XI

Factor XI (FXI) is a new target for anticoagulants that have the potential to be associated with a lower risk of bleeding events than currently available anticoagulants. The identification of FXI as a safer target is supported by epidemiological data, studies in FXI deficient mice, studies with FXI knockdown or inhibition, and animal bleeding models (14).

The formation and the stability of clots are enhanced by FXI in in-vitro experiments (15- 16). Furthermore, FXI amplifies thrombin generation when coagulation is initiated by low levels of tissue factor (TF) 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 potential therapeutic target came from epidemiological data. Observational studies in patients with congenital factor XI deficiency suggested that these patients are at reduced risk of ischemic stroke, myocardial infarction, and venous thromboembolism (VTE) compared with those with normal factor XI levels (14-19). Furthermore, a second-generation antisense oligonucleotide (ASO) that specifically reduces FXI levels (ISIS 416858) yielded promising results when compared with enoxaparin for thromboprophylaxis in patients undergoing elective total knee arthroplasty (TKA) (20).

2.2.4 Osocimab (BAY 1213790)

Osocimab is a fully human monoclonal immunoglobulin G1 (IgG1) antibody that binds specifically to activated factor XIa (FXIa) (21) and exhibits a terminal half-life in plasma ranging from approximately 30 to 44 days after intravenous administration.

2.2.4.1 Preclinical Data

Preclinical pharmacology experiments indicated a profound antithrombotic effect, both in arterial and in venous thrombosis models, in the absence of significantly prolonged bleeding times or increased blood loss. In line with the mechanism of action, the activated partial

thromboplastin time (aPTT) increased in a dose-dependent manner and in parallel with the antithrombotic effect. Osocimab had no effect on the prothrombin time (PT), confirming that the effects of Osocimab were limited to the intrinsic pathway of coagulation.

As with any protein product, Osocimab may induce immune responses affecting safety and product efficacy. However, the compound is a fully human monoclonal IgG1 antibody that has been optimized for affinity and low immunogenicity. The immunogenic potential of Osocimab was tested in silico and showed a favorable overall score, similar to other marketed monoclonal antibodies. Furthermore, toxicological studies have not identified relevant hypersensitivity effects in Cynomolgus monkeys after intravenous (iv) or subcutaneous (sc) injections. Nevertheless, injection and hypersensitivity reactions may occur and the possibility of hitherto unforeseen side effects and allergic reactions to interventions, which can result in severe damage and even death, must always be considered.

2.2.4.2 Human Experience

So far osocimab has been tested in 4 Phase 1 studies (Studies #17188, 17956, 17780, 19513) with either iv or sc administration in healthy volunteers (175 participants received osocimab up to 10 mg/kg iv), as well as in a study in patients undergoing total knee arthroplasty for the prevention of VTE (#17664 FOXTROT study, 587 participants received osocimab up to 1.8 mg/kg).

In the single dose Phase 1 studies #17188 (study report available) and #17780 and #17956 (clinically completed, reporting ongoing), osocimab administrations were safe and well tolerated. No drug related serious adverse events (SAEs) were reported. Further details can be found in Section 5.2.3 of the Investigator's Brochure (IB).

There were no clinically relevant bleeding events, no relevant bleeding time prolongations and no signs or symptoms for hidden bleedings in the single dose Phase 1 studies.

In the multiple dose study #19513, which investigated two dose steps, two bleeding events of a moderate severity were reported in the dose step 1 (loading dose 100 mg sc; maintenance dose 35 mg sc) of the study: bleeding hemorrhoids and rupture of tympanic membrane of the right ear. These hematomas were also assessed as not related to the study intervention. In dose step 2 (loading dose 210 mg sc; maintenance dose 105 mg sc), an intra-cranial hemorrhage was observed. The sponsor together with external experts performed a thorough evaluation of the case including follow-up Magnetic Resonance Imaging (MRI). In conclusion, and although the contribution of osocimab cannot be excluded, the overall benefit risk assessment for osocimab has not changed according to the data generated so far, specifically as from the image interpretation there is a greater than 50% likelihood for an underlying arteriovenous (AV)-malformation/cavernoma as the underlying cause for the bleeding event.

In summary, bleeding events in the single dose studies and in the multiple dose study in healthy volunteers did not indicate any increased risk of bleeding.

In a Phase 2a study (#17664, FOXTROT), osocimab was administered in patients undergoing elective TKA. This was a randomized, active comparator controlled, multicenter study to assess the safety and efficacy of different doses of osocimab for the prevention of VTE in comparison to enoxaparin and apixaban (22).

In the FOXTROT study, 2 different administration schemes of osocimab were assessed: post-surgery administration (part A) and pre-surgery administration (part B). A total of 813 patients were randomized in the overall study.

Part A investigated osocimab at single iv doses of 0.3, 0.6, 1.2, and 1.8 mg/kg. Part B investigated osocimab at single iv doses of 0.3 and 1.8 mg/kg.

Overall, FOXTROT showed that FXIa inhibition is effective for the prevention of VTE in patients undergoing TKA whether administered post- or pre-operatively. Osocimab demonstrated good hemorrhagic as well as non-hemorrhagic safety and good tolerability (22).

Further details can be found in the latest available version of the Investigator's Brochure, which contains comprehensive information on the test drug.

Furthermore, a small Phase 1, observer-blind, multicenter, placebo-controlled study is ongoing in patients with ESRD to assess the safety and tolerability and to characterize the PK and the PD of different doses of osocimab (sc and iv) in this patient population (Study #20046). So far 13 patients with ESRD received a single iv dose of osocimab (0.3 mg/kg or 1.2 mg/kg). No clinically significant bleeding events (i.e. major or clinically relevant non-major bleeding) occurred after study drug administration nor were any treatment-emergent SAEs reported, so far.

2.2.4.3 Rationale for the Development of Osocimab in ESRD Patients

The aim for the development of osocimab in patients with ESRD is to prevent thromboembolic events without increasing the risk for bleeding events, as it is known from currently available anticoagulation therapies, which could provide a favorable benefit risk profile in patients with ESRD on hemodialysis. Due to the characteristics of osocimab as a monoclonal antibody targeting FXIa additional benefits suit very well to the ESRD patient population:

- Low dosing frequency of once a month subcutaneous injection, which does not add to the already high pill-burden in this patient population.
- Low risk for drug-drug interaction via Cytochrome P450 (CYP) enzymes in the liver. Generally, monoclonal antibodies are metabolized to peptides and amino acids in several tissues, by circulating phagocytic cells or by their target antigen-containing cells (23). In contrast to many other drugs that are taken by ESRD patients, osocimab will not interfere with other drugs that are metabolized in the CYP system of the liver as it is metabolized via other pathways.
- No influence of plasma concentrations is expected with impaired kidney function as the drug is not excreted via this pathway. Furthermore, due to the large size of osocimab it not expected to be dialyzable.

2.3 Benefit/Risk Assessment

Due to the higher bleeding risk of ESRD patients and the unproven benefits of currently available anticoagulation therapy in these patients, most hemodialysis patients are not treated for the prevention of thromboembolic events.

Targeting factor XI may attenuate thrombosis without increasing the risk for bleeding. The separation of bleeding and efficacy might be explained by the fact that inhibition of FXIa affects the intrinsic and propagation pathways, but keeps the extrinsic pathway unaffected, which is activated in case of vessel injury.

Based on the results of relevant animal models, known cases of human FXI deficiency, clinical experience with compounds with a similar mode of action (second-generation antisense oligonucleotide), initial clinical testing in healthy volunteers, and most importantly

patients undergoing TKA and receiving osocimab post- and pre-surgery, osocimab is a promising new drug candidate with the potential to prevent thromboembolic events with a low risk for bleeding. Potential risks such as bleeding, thrombocytopenia, hypersensitivity/ injection-related reactions will be closely monitored during this trial. Strict inclusion and exclusion criteria are applied to exclude ESRD patients who are at higher risk for bleeding events. Due to the long half-life of the compound in plasma, participants will be kept under observation for approximately 5 months after the last administration of osocimab.

A DMC will frequently review safety data to ensure the safety of the participants in the ongoing study. Further details can be found in the DMC charter.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of osocimab may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Risk assessment for osocimab is described in Table 2–1.

Table 2–1: Risk Assessment for Osocimab

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hemorrhage (Bleeding)	• Risk factor associated with ESRD due to uremia-induced endothelial dysfunction • Increased bleeding risk due to routinely administered anticoagulant and antiplatelet agents to reduce risk of thromboembolic events and for dialysis maintenance • So far, no increased risk of bleeding across studies and doses for osocimab was identified	• Specific in-and exclusion criteria to be applied • Reporting as primary safety outcome • Regular hematological laboratory assessment (see Section 1.3) • DMC will frequently review all safety events including bleeding events • CIAC will adjudicate all suspected bleeding events
Thrombocytopenia	• Osocimab reduces dose and concentration-dependently FXI activity and prolongs aPTT (expected mode of action)	• Specific in- and exclusion criteria to be applied • Regular safety laboratory assessment (see Section 1.3) • Reporting as adverse event of special interest and stopping rule for drug administration (see Section 8.3.8) • DMC will frequently review all safety events laboratory results
Hypersensitivity	• Observed cases of infusion or hypersensitivity reactions were rare and of mild degree in healthy volunteers • In participants undergoing TKA, frequency of hypersensitivity and infusion-related reactions were low and comparable across treatment groups including comparators (enoxaparin and apixaban)	• Reporting as adverse event of special interest (see Section 8.3.8) • DMC will frequently review all safety events

Table 2–1: Risk Assessment for Osocimab

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Development of anti-drug antibodies (ADA) and neutralizing antibodies (NAB)	• In two Phase 1 studies (#17188 and #17780) the majority of participants did not develop anti-osocimab antibodies; participants with ADA- or NAB-positive samples had low titers and did not show altered plasma concentrations of osocimab or unexpected PD or safety findings. In participants undergoing TKA, a small number of anti-osocimab antibodies (ADAs) and NABs were detected	• Measurements of ADA/NAB formation over the course of the study (see Section 8.9)

Abbreviations: ADA = anti-drug antibodies, aPTT = activated partial thromboplastin time, CIAC = Central Independent Adjudication Committee, DMC = Data Monitoring Committee, ESRD = end-stage renal disease, NAB = neutralizing antibodies, PD = pharmacodynamic(s), TKA = total knee arthroplasty

Currently available preclinical and clinical data regarding the important potential risks including the assessment of the safety from the clinical studies do not indicate an unfavorable risk profile for osocimab.

2.3.2 Benefit Assessment

The potential benefit of receiving study intervention during study duration may already be a reduced risk for thromboembolic events in participants with ESRD, although this has not yet been proven clinically. Furthermore, this study will contribute to develop 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

Taking into account the potential benefits of this new compound, the potential risks identified in association with osocimab are justified by the anticipated benefits that may be afforded to participants with ESRD. Currently available preclinical and clinical data do not indicate an unfavorable risk profile for osocimab.

3. Objectives and Endpoints

Objectives and endpoints are listed in Table 3–1.

Table 3–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To clinically assess the safety and tolerability of different doses of osocimab administered subcutaneously once a month during main treatment period as compared to placebo	• Composite of major and clinically-relevant non-major bleeding events (in alignment with ISTH guidelines) as assessed by blinded CIAC • Composite of moderate and severe AEs and SAEs
Secondary	
• To assess the change of key PD parameter from baseline	• aPTT, FXIa activity at trough levels after 6 months
Tertiary/Exploratory	
• To clinically assess the efficacy of osocimab during main treatment period	• Composite endpoint consisting of: vascular 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 as assessed by blinded CIAC • Incidence of thrombosis of the arteriovenous fistulas or grafts
• To evaluate the anticoagulant effect of osocimab on the extracorporeal blood circuit by the assessment of a semi-quantitative clotting score (SQCS)	• SQCS
• To evaluate the impact of osocimab on the AV access for participants with fistulas or grafts	• AV access bleeding score
• To assess key PK parameter	• Osocimab trough levels
• To explore additional PK/PD parameters, biomarkers and biomarker genetics • To further investigate the study intervention (i.e. mode-of-action-related effects and / or safety) and to further investigate pathomechanisms deemed relevant to cardiovascular and renal diseases and associated health problems	• Various biomarkers and biomarker genetics may be explored (e.g., diagnostic, safety, population PK, PD, monitoring, or potentially predictive biomarkers)

Abbreviations: AE = adverse event, aPTT = activated partial thromboplastin time, AV = arteriovenous, CIAC = Central Independent Adjudication Committee, ISTH = International Society on Thrombosis and Hemostasis, MI = myocardial infarction, PD = pharmacodynamic(s), PE = pulmonary embolism, PK = pharmacokinetic(s), SAEs = serious adverse events, SE = systemic embolism, SQCS = semi-quantitative clotting score, VTE = venous thromboembolism

The primary objective is to assess the safety under an osocimab concentration which is expected to be maintained during a chronic treatment. Thus the attributes constituting the primary estimand are the following:

Population: The population consists of ESRD patients, further defined by the in- and exclusion criteria, who received study intervention at least once.

Variable:

a. Time from first dose of intervention to treatment emergent major and clinically-relevant non-major bleeding events (in alignment with ISTH guidelines) up until 30 days after last study intervention

b. Time from first dose of intervention to moderate or severe AEs and SAEs up until 30 days after last study intervention

Treatment: Low/high-dose osocimab or matching placebo on top of standard of care

Intercurrent events: Of interest is the response to treatment while the participant is

- alive (intercurrent event "death") and
- exposed to study intervention (intercurrent event "premature discontinuation of treatment"),

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

Population-level summary: Hazard ratios comparing each of the osocimab dose groups with the placebo group as estimated from Cox proportional hazards models.

Please refer to Section 9.4 for further details.

4. Study Design

4.1 Overall Design

Study 20115 is a covariate-adaptive randomization, double-blind, parallel group, placebo-controlled, multi-center study to assess the safety and tolerability of monthly administrations of a low and high dose cohort of osocimab given subcutaneously in ESRD patients on hemodialysis. In this protocol, the term hemodialysis includes hemodiafiltration. The overall study design is depicted in Figure 1–1.

Approximately 600 participants (up to 750) from approximately 150 sites are planned to be randomized and will receive either osocimab (200 participants on each dose arm), or placebo (200 participants, i.e. 100 participants receiving low dose volume placebo and 100 participants receiving high dose volume placebo).

The following regions are planned to be included: North America, Europe, Asia Pacific.

The planned study will consist of:

- **Screening period (visit 1):** up to 14 days
- **Randomization (visit 2):** 1 day
- **Pre-treatment period (from visit 2 until visit 4):** 7 days
- **Main treatment period (from visit 5 until EOMT visit):** 6 months
- **Extension treatment period (from visit 19 until EOET visit):** up to 12 months
- **Follow-up period (from visit 32 until visit 35):** 4 months after end of treatment (EOMT or EOET)

Informed consent form will be obtained at the beginning of the screening period. During the screening period, participant's eligibility evaluations will be performed. Participants will be randomized either to osocimab or to placebo using a covariate-adaptive randomization technique (minimization methods) (for details see Section 6.3).

During the pre-treatment period, which will serve as a baseline period, a series of 3 hemodialysis sessions will be performed. Unfractionated or low molecular weight heparin (UFH/LMWH) is allowed as anticoagulation for maintenance of hemodialysis treatment during the whole study duration.

The study intervention will be administered subcutaneously abdominal with one single loading dose at visit 5 and monthly maintenance doses from visit 8 onwards until the end of the extension treatment period with an overall maximum of 18 months of treatment. The main treatment period consists of 6 months of treatment as this time frame is deemed to be the minimum clinically relevant treatment time to assess osocimab as chronic life-time treatment in an appropriate manner and in preparation for Phase 3.

Study intervention will be administered during the extension treatment period for up to a maximum of 12 months or until the last participant randomized to the study has performed the EOMT visit (whichever comes first).

The treatment period (main or extension) will end with the study assessments performed 30 days after the last study intervention administration.

The follow-up period is an observational period of 4 months, i.e. ends approximately 5 months after the administration of the last dose of osocimab.

All suspected bleeding and cardiovascular (CV) or thromboembolic (TE) events occurring after signing informed consent (randomized participants only) will be adjudicated by the CIAC in a blinded fashion; blinded to treatment allocation and dose cohort (details are described in the CIAC charter).

The procedures followed by the CIAC are detailed in the CIAC charter. Detailed instructions regarding documentation, reporting and transferal of adjudication dossiers will be provided in a study specific guidance document.

A DMC will frequently review safety data to ensure the safety of the participants in the ongoing study. Further details can be found in the DMC charter.

Details of study procedures and their timing are summarized in the SoA (see Section 1.3).

4.2 Scientific Rationale for Study Design

This is the first multiple dose study of osocimab in ESRD patients with the aim to investigate the safety, tolerability and PK/PD after chronic monthly treatment with subcutaneous administrations in comparison to placebo. No established treatment exists for the prevention of thromboembolic events in patients with ESRD.

The selection criteria were chosen to exclude patients from the study, who may potentially be exposed to specific risks after administration of osocimab, as well as all patients with conditions that may have an impact on the objectives of the study.

A main treatment period of 6 months until the primary endpoint assessment is deemed to be appropriate to assess the safety, tolerability and efficacy of osocimab for an envisaged chronic treatment regimen. However, participants will receive osocimab for a maximum of 18 months

which will generate additional long-term safety data and allow participants to potentially benefit from long-term treatment.

The study procedures were planned to be as close as possible aligned with the usual dialysis procedures in order to limit the extra burden for participants.

The envisaged indication for osocimab is prevention of thromboembolic events in male and female patients with ESRD undergoing hemodialysis.

4.3 Justification for Dose

The medium doses (0.6 and 1.2 mg/kg iv single dose administration) tested in the FOXTROT study were identified as the most promising doses to be tested in further studies, as they showed efficacy numerically comparable to that with enoxaparin and apixaban and were not associated with any primary safety event, i.e. clinical significant bleeding event (22) (further details on FOXTROT can be found in the current version of the IB). The doses tested in FOXTROT were substantially lower than the doses that were administered during the first Phase 1 study (up to 10 mg/kg iv). It is currently assumed that the dose levels which were efficacious and safe in the FOXTROT trial will be safe and efficacious for the prevention of thromboembolic events in ESRD patients as well. The selected single iv doses from FOXTROT were translated into comparable sc doses independent from body weight (i.e. fixed dosing) taking into account the bioavailability of sc administration. It was the aim to achieve with monthly fixed sc doses similar trough levels (plasma concentration approximately one month after dosing) as in FOXTROT at the primary endpoint assessment (approx. 10-14 days after dosing). Therefore, osocimab doses needed to be adapted to achieve the FOXTROT exposure level after that longer period of one month. Furthermore, therapeutic drug level should be reached as soon as possible after initiation of treatment to allow for an immediate treatment effect. Therefore, a loading dose concept was developed and tested in a multiple dose Phase 1 study (#19513). This loading dose concept provides with a single (higher) loading dose (compared to the maintenance doses) a rapid achievement of a therapeutic drug concentration and ensures steady state exposure already from study drug initiation.

As already tested in multiple dose study #19513, in this study the sc dose administration will be independent from the body weight (BW) (fixed dose concept). This is supported by preliminary population PK analyses of Phase 1 data indicating that BW-adjusted dosing and flat dosing provide similar exposure distributions, with no clear advantage to both dosing approaches with respect to reducing variability in pharmacokinetics.

When the fixed doses of the high dose cohort of 210 mg (LD) and 105 mg (MD) and are back-converted to BW-adjusted dosing, the corresponding sc doses for a participant of 80 kg will be 2.625 mg/kg and 1.3125 mg/kg BW, respectively. This is below 6 mg/kg BW sc, a dose already shown to be safe in a Phase 1 study (#17780).

In an alternative scenario of administering fixed doses to a light weight participant of 50 kg, the calculated BW-adjusted sc doses would be 4.2 mg/kg BW for a flat dose of 210 mg and 2.1 mg/kg BW for 105 mg. For both, the low and high dose cohort, and both BWs the loading and maintenance doses are below 6 mg/kg BW sc that were tested in the Phase 1 study (#17780). Additionally, the sc doses of the high dose cohort of 105 mg (MD) and 210 mg (LD) have already been tested in multiple dose study #19513 (administration on study days 1, 29, 57 and 85). Importantly, all doses intended for the current study are considerably lower

than the highest tested iv dose of 10 mg/kg BW, which was has been shown to be safe and well tolerated in healthy volunteers (#17188).

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed at least the main treatment period of the study including the last visit (EOMT).

The primary completion of the study is defined as the date of the last visit of the last participant in the main treatment period.

The end of the study is defined as the date of the last visit of the last participant in the study globally.

5. Study Population

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

The study population will consist of stable end-stage-renal disease patients requiring hemodialysis (including hemodiafiltration) sessions for approx. 3 times per week at least 9 hours a week with no restriction to vascular access (e.g., catheter, AV fistulas and graft are allowed).

5.1 Inclusion Criteria

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

Age

1. Participants must be at least 18 years of age

Type of Participant and Disease Characteristics

2. Patients with end-stage renal disease on hemodialysis (including hemodiafiltration) for ≥3 months, receiving dialysis at least 9 hours a week and stable in the view of the investigator

Weight

3. Body weight of at least 50 kg

Sex

4. Male and/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. For details see Section 10.4.

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2 Exclusion Criteria

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

Medical Conditions

1. Recent (<6 months before screening) clinically significant bleeding
2. Hemoglobin (Hb) < 9.0 g/dL
3. Platelet count < 100 x 10^9/L
4. aPTT or PT > ULN (upper limit of normal)
5. Hepatic disease associated with ALT > 3x ULN, or total bilirubin >2x ULN with direct bilirubin > 20% of the total
6. Sustained uncontrolled hypertension (diastolic blood pressure ≥100 mmHg and/or systolic blood pressure ≥ 180 mmHg)
7. Known intracranial neoplasm, arteriovenous malformation or aneurysm
8. Known bleeding disorders e.g., von-Willebrand disease or Hemophilia A, B or C
9. Recent (<3 months before screening) thromboembolic event, e.g., acute coronary syndrome, stroke or VTE (except dialysis access thrombosis)
10. Recent (<3 months before screening) major surgery or scheduled major surgery during study participation
11. Scheduled living donor renal transplant during study participation
12. Persistent heart failure as classified by the New York Heart Association (NYHA) classification of 3 or higher
13. Receiving antiplatelet therapy except daily ASA (acetylsalicylic acid) ≤ 150 mg/day
14. Receiving anticoagulation in therapeutic doses, other than standard anticoagulation during the hemodialysis procedure
15. Life expectancy less than 6 months
16. Active malignancy requiring treatment during study participation (except non-melanoma skin cancer, or cervical carcinoma in situ)
17. Known hypersensitivity to the investigational drug or to inactive constituents of the study drug

Prior/Concurrent Clinical Study Experience

18. Participation in another clinical study with an investigational medicinal product within 30 days or within 5 half-lives of such, whichever is longer, prior to randomization and during the study

Other Exclusions

19. Any other conditions, which, in the opinion of the investigator or sponsor would make the subject unsuitable for inclusion

5.3 Lifestyle Considerations

No restrictions during any of the study periods pertaining to lifestyle and/or diet apply.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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 (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant identification code (PID) and sign a new informed consent form.

Re-screening is allowed only if any of the following applies:

- The participant had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The in- / exclusion criteria preventing the participant's initial attempt to participate have been changed (via protocol amendment).
- The participant suffered from a temporary and not clinical relevant disease, e.g., a common cold.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. Also, for re-screening, the participant has to re-sign the informed consent form, even if it was not changed after the participant's previous screening.

Suspected events of screen failures will not be submitted to the CIAC.

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 Interventions Administered

The following study interventions will be administered in the study:

- Osocimab (BAY 1213790): sponsor's study drug under investigation
- Placebo to osocimab

Different doses will be achieved by administering a different volume:

- Low dose cohort

  105 mg single loading dose as subcutaneous abdominal injection at visit 5, followed by monthly (i.e. 30 days ± 3 days) maintenance doses of 52.5 mg starting at visit 8 until the end of the extension treatment period. Placebo will be administered subcutaneously in the same manner as osocimab.

- High dose cohort:

  210 mg single loading dose as subcutaneous abdominal injection at visit 5, followed by monthly (i.e. 30 days ± 3 days) maintenance doses of 105 mg starting at visit 8 until the end of the extension treatment period. Placebo will be administered subcutaneously in the same manner as osocimab.

Participants will be treated up to 18 months.

Osocimab/ placebo is administered within one hour (60 minutes) prior to start of dialysis session by site personnel at site.

Further details for study interventions are described in Table 6–1.

Table 6–1: Study Interventions

Study Intervention	Osocimab low dose	Osocimab high dose	Placebo to osocimab
Intervention Name	osocimab	osocimab	placebo to osocimab
Type	drug	drug	placebo
Dose Formulation	solution	solution	solution
Unit Dose Strength(s)	150 mg/mL	150 mg/mL	NA
Dosage Level(s)	105 mg (LD) once, 52.5 mg (MD) monthly	210 mg (LD) once, 105 mg (MD) monthly	NA
Route of Administration	sc injection	sc injection	sc injection
Use	experimental	experimental	Placebo
Packaging and Labeling	Study intervention will be provided in 6 mL glass vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in 6 mL glass vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in 6 mL glass vials. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	BAY 1213790	BAY 1213790	NA

Abbreviations: LD = loading dose, MD = maintenance/ monthly dose, NA = not applicable

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.

Osocimab is supplied in 6 mL clear, single-use injection glass vials as a solution. Osocimab is a solution with a concentration of 150 mg/mL at pH 5.0. The total content of the glass vial is 2.3 mL, corresponding to 345 mg of osocimab. From the total 2.3 mL, 2.0 mL (i.e. 300 mg) are the extractable volume and 0.3 mL (i.e. 45 mg) are overfill. Placebo to osocimab is supplied in 6 mL clear, single-use glass vials as a solution. Further details can be found in the handling instruction provided separately.

6.3 Measures to Minimize Bias: Randomization and Blinding

After a participant has signed an informed consent form, the unique participant identification number (PID) will be assigned via Interactive Web Response System (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 *5* for each participant.

All participants will be centrally assigned to randomized study intervention using an 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 IWRS will be provided to each site.

Covariate-adaptive randomization techniques (minimization methods) will be utilized taking into account the following baseline covariates (weights of the baseline covariates for the calculation of imbalance in brackets):

- Region (categorical) (17.0%)
- Age (17.0%)
- Prior major adverse cardiovascular event (MACE) (17.0%)
- Dialysis access via catheter (17.0%)
- Low-dose ASA use (Yes/No) (17.0%)
- Diabetes (Yes/No) (7.5%)

- Atrial fibrillation (Yes/No) (7.5%)

Sponsor, participants and investigators are being blinded with respect to active treatment versus placebo, but not blinded to dose cohort (low or high dose). The CIAC will be blinded to the participant's treatment allocation and dose cohort. The DMC will review blinded data and will have access to unblinded data as outlined in the DMC charter.

In order to maintain the blind, osocimab 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.

Bioanalytics and pharmacometrics staff will be unblinded according to Bayer SOPs. Bioanalysis and population PK (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 unblinded data.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving between signing of the ICF and the end of 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, medications influencing coagulation or platelet aggregation even if taken before the informed consent was signed should also be recorded in the eCRF (up to 6 months prior to randomization).

Prior and concomitant medications that should be stopped at least 10 days prior to start of study intervention, i.e. 3 days prior to randomization and not allowed during the study are:

1. Antiplatelets (e.g., clopidogrel, ticagrelor, dipyridamole, acetylsalicylic acid >150 mg/day)
2. Vitamin K antagonists (e.g., phenprocoumon, warfarin-sodium)
3. Unfractionated heparins and LMWH other than for dialysis maintenance
4. Direct oral anticoagulants (e.g., rivaroxaban, apixaban, dabigatran, edoxaban). Participants who cannot stop the respective treatment have to be excluded from the study.
5. Thrombolytic drugs for systemic use (e.g., streptokinase, alteplase, tenecteplase, etc.)

For participants, who are receiving ASA ≤ 150 mg/day, any dose adaptation should be avoided if possible. Especially, during the main treatment period any adaptation of the current ASA dose or any initiation of ASA should be avoided and should only be done if medically necessary.

Surgery, which is deemed necessary should be performed under general anesthesia only. Spinal or epidural anesthesia is not allowed during the study.

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

6.6 Dose Modification

This protocol does not allow any pre-planned alteration from the currently outlined dosing schedule (Section 6.1).

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.

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 until the end of the follow-up period. See the SoA 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.

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 8.2.2 and 8.3]) or requires surgery (Section 8.2.2.2) that in the judgment of the investigator necessitates permanent discontinuation of study intervention.
- The participant develops laboratory test abnormalities that meet the stopping rule outlined in Section 8.3.8.1.
- The participant moves their dialysis care to a different hemodialysis facility where the study team cannot regularly follow the participant. All efforts should be made to conduct the 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.
- At the discretion of the investigator due to participant non-compliance, or major protocol deviation(s)
- The sponsor has the right to withdraw a participant from the study due to non-compliance, major protocol deviations or for safety reasons

A participant may permanently discontinue study intervention for any of the following at the discretion of the investigator:

- The participant begins treatment with a disallowed concomitant medication as described in Section 6.5.
- The participant is no longer on regular maintenance hemodialysis of at least 3-times per week for a minimum of 9 hours per week, including a change in dialysis modality.

If a participant permanently discontinues study intervention and is unwilling or unable to attend regular study visits at the study site, all possible efforts should be made to obtain information on the health status of the participant.

A participant may be withdrawn from study intervention at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The reason for discontinuation of study intervention must be recorded in the eCRF and source documentation.

7.1.1 Temporary Discontinuation

This protocol does not allow any pre-planned alteration from the currently outlined dosing schedule. However, there may be rare circumstances due to which the investigator may need to temporarily discontinue study intervention for an adverse event (Section 8.3), bleeding event (Section 8.2.2), or surgery (Section 8.2.2.2) and any other reason not listed as reasons for discontinuation of study intervention (Section 7.1) or withdrawal from the study (Section 7.2).

The following guidance should be observed in case maintenance dosing cannot be administered according to dosing schedule.

Delayed maintenance dosing:
A dose is delayed if it is given up to 4-7 days from the original schedule. The dose should be administered at the next possible time point, but not later than 7 days than originally scheduled.

Missed maintenance dosing:
Any dose which is delayed for more than 7 days will be considered as missed dose. The dose should be administered at the next possible time point, but not later than 60 (+3) days after the last given dose. There should be also minimum 30 days ± 3 days between the doses. If the dose is delayed more than 60 (+3) days after the last given dose, the participant will need to move into the follow-up period. Only one maintenance dose can be missed (i.e. given > 7 days after the originally scheduled dosing and not later than 60 (+3) days after the last actually administered dose) per main treatment or per extension treatment period. Between missed doses at least 5 regular maintenance doses should have been administered according to protocol, otherwise the participant will also need to move into the follow-up period. Obtain blood samples for PK/PD analysis 30 (±3) days after the date of the delayed dose, if not already scheduled according to the study protocol.

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.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) 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 permanently discontinues/withdraws from the study and is unwilling or unable to attend regular study visits at the study site, all possible efforts should be made to obtain information on the health status of the participant.

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.

Data that have been collected until the time the participant is considered to be lost to follow up may be retained and continued to be used.

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., platelet 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. Relevant unscheduled visits will be documented in the eCRF.

8.1 Efficacy Assessments

The efficacy will be assessed by analyzing exploratively the incidence of the following components

- Death due to MI, stroke, pulmonary embolism (PE) and systemic embolism (SE)
- Non-fatal stroke
- Non-fatal MI
- Major amputation of vascular etiology
- Acute limb ischemia
- Symptomatic VTE
- Thrombosis of AV fistulas or grafts

Furthermore, the effect of osocimab on the clotting in the dialysis circuit will be assessed by the SQCS. At the end of the hemodialysis procedure, the filter and line (including drip chamber/air trap) will be examined by the hemodialysis nurse (or respective appropriate personnel) after rinsing the circuit. If possible the same rinsing volume should be used within one participant throughout the course of the study. 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”.

Additional details for assessment of SQCS can be found in a study specific guidance document .

8.2 Safety Assessments

During all contacts with the participant from signing the informed consent form, investigators will check for and record the following in the eCRF:

- Bleeding events
- Adverse events, including adverse events of special interest
- Concomitant medication changes
- Changes in dialysis prescription

Planned time points for all safety assessments are provided in the SoA in Section 1.3.. Abnormal safety findings which have started after signing of informed consent should be reported as an AE/SAE. Clinically significant abnormal findings will be reported as AEs in the eCRF.

AEs requiring submission to the CIAC are listed in Section 8.3.9.

8.2.1 Main Safety Assessment

Incidence, severity and seriousness of AE, and SAE, including bleeding events, as well as the causal relationship between an AE/SAE and the administration of the study intervention will be assessed throughout the study.

In order to evaluate the safety and tolerability of osocimab, AEs will be assessed as the main safety endpoint. See Section 8.3 for further information.

8.2.2 Bleeding Events

Major bleeding (MB) and clinically-relevant non-major bleeding (CRNMB) events, as assessed by CIAC, will be the primary safety endpoint in this study.

Randomized participants will be evaluated for occurrence of bleeding events continuously after signing informed consent up to the end of the post-treatment follow-up for all cohorts. All bleeding events (other than the normal bleeding from AV graft or fistula post-dialysis) will be reported as AE or SAE per Section 8.3 and submitted to the CIAC.

However, bleeding after dialysis from AV graft or fistulas is expected and will only be reported as an AE/SAE and submitted to CIAC if there is a change in the pattern, duration 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 (approximately) the prior 4 weeks.

Bleeding after dialysis from the AV fistula have also to be assessed by the AV bleeding score (Section 8.2.2.1).

The CIAC will classify bleeding events primarily in alignment with the ISTH definitions (24):

Definitions in alignment with ISTH (Please refer to the adjudication charter for details):

Major bleeding (MB) is defined as symptomatic bleeding with one of the following:

- Bleeding that contributed to death
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of 2 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 (CRNM) bleeding is 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 evaluation (i.e. not a telephone or electronic communication)

8.2.2.1 Assessment of AV Access Bleeding

Severity of bleeding at the dialysis access will be assessed approx. 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

In case the AV access exhibits overt bleeding 15 minutes after removal of the dialysis needle(s) (AV access bleeding score of 2), the investigator may consider the reduction of heparin (i.e. UFH, LMWH) for the subsequent dialysis sessions during the treatment and follow-up period. For such decision, the investigator should take all available participant information into account (e.g., laboratory values, concomitant medication, details of hemodialysis session, adverse events etc.).

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

8.2.2.2 Recommendations for Bleeding and Surgery Management

Bleeding

In general, the management of bleeding is at the discretion of the treating physician and local prescribing information should be consulted for usage in ESRD for any drug administered. Evidenced-based treatment recommendations for uremic bleeding in patients with ESRD are summarized in Hedges et al, 2007 (25).

In case a participant experiences a severe bleeding event (e.g., bleeding that leads to surgical procedures or transfusion of blood components or to prolonged hospitalization or bleeding into a critical organ or in close space) and further treatment of the participant is harmful in the view of the investigator, treatment should be discontinued and participants should be treated as medically indicated. So far no data for management of bleeding and surgery under osocimab have been gathered.

The following measures may be considered by the investigators to control bleeding and are at the discretion of the treating physician:

- Mechanical compression or surgical intervention
- Delay of the next injection or discontinuation of treatment
- Review and discontinue concomitant medications that could exacerbate bleeding
- General volume management: fluid replacement & hemodynamic support.
- Transfusion (e.g., whole blood/packed cells/fresh frozen plasma [FFP]/platelets) with careful volume management
- Antifibrinolytics (e.g., aminocaproic acid or tranexamic acid, consult local prescribing information for guidance on usage in patients with severe renal impairment/ESRD)
- Desmopressin
- Conjugated estrogens

If bleeding cannot be controlled by these measures, administration of the following may be considered, if used as part of local practice (consult local prescribing information for guidance on usage in patients with severe renal impairment/ESRD) and are under discretion of the treating physician:

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

In vitro data with osocimib showed that the prolongation of aPTT and ROTEM CT induced by osocimab can be fully reversed by recombinant FVIIa (NovoSeven) or factor eight inhibitor bypass activity (FEIBA). In in vitro experiments PCC (prothrombin complex concentrate) was not able to normalize aPTT and ROTEM CT. However, this may be due to the inability to show effects on the coagulation tests by these measures (further details may be found in the current version of the IB).

As coagulation parameters are potentially unblinding these should only be reviewed if medically indicated.

Surgery

Major surgery (e.g., surgical procedure involving an organ within the cranium, chest, abdomen, or pelvic cavity) or major procedures in tissue with high fibrinolytic activity (e.g., gynecologic, urologic, or surgeries of the nasal and oral cavities) or surgeries with high risk for perioperative bleeding, should not be performed during the trial. However, if deemed medically necessary and surgery cannot be postponed until the end of the follow-up period, the surgery is only allowed to be performed under general anesthesia. Spinal or epidural anesthesia/analgesia is not allowed during the study. Investigators are encouraged to postpone surgeries whenever possible until the end of the study including the 4 months follow-up period or at least as long as possible after the last study intervention. Hence, study intervention should be immediately discontinued if a participant is scheduled for the above mentioned surgeries. Participants who permanently discontinue study intervention due to a surgery will enter the post-treatment follow-up period (Section 7.1).

Minor surgeries or surgeries with low bleeding potential (e.g., knee replacement surgery) may be performed during the trial if deemed necessary and can't be postponed. Of note, during the FOXTROT trial participants have been operated for total knee replacement under full anti-coagulation with osocimab (doses up to 1.8 mg/kg). Study interventions may be further administered after such surgery if deemed appropriate by the investigator and after careful post-operative assessment. Before restarting study intervention administration of prohibited concomitant medication needs to be taken into account (Section 6.5).

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.

Management of bleeding and surgery of study participants may further be guided by published data regarding patients with inherited FXI deficiency. There have been reports in the literature about the successful use of tranexamic acid or ε-amino caproic acid in the management of non-ESRD, hemophilia C patients when undergoing surgery (26). The local package insert need to be consulted for usage in patients with ESRD on dialysis. In patients

undergoing tooth extractions, i.e. an invasive procedure in tissue with high fibrinolytic activity in the oropharynx, Berliner et al. reported uneventful extractions in 19 patients with severe FXI deficiency treated with tranexamic acid alone (1 g q.i.d.) started 12 h prior to surgery and continued for 7 days after surgery (27). The administration of recombinant FVIIa in addition to tranexamic acid was also reported as a therapeutic option in patients with severe FXI deficiency undergoing surgery (28- 29). O'Connell et al. reported effective hemostasis when a dose of 90 µg/kg of recombinant FVIIa given every two hours in the first 24 hours and every 4 hours in the second 24 hours, followed by postoperative tranexamic acid for 7 days, was used in patients undergoing major surgery. Subsequently, Livnat et al. showed that even a single dose of recombinant FVIIa at a dose of 15-30 µg/kg, along with 1 g of tranexamic acid given before surgery and then every 6 hours post-surgery for 7-14 days achieved satisfactory hemostasis in patients with FXI inhibitors undergoing major surgery (30).

Please consider that for severe renal impairment/ESRD specific limitation or even contraindications for use of certain agents may apply. This may differ between countries.

8.2.3 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems and will follow standard practice of the site. Height will only be measured at screening visit. Weight will be measured pre- and post-hemodialysis (dry-weight).

8.2.4 Vital Signs

- Vital signs will consist of 1 pulse and 1 blood pressure measurements. Vital signs will be measured after 5 minutes rest.
- Blood pressure and pulse measurements will be assessed pre-dialysis (with the exception of the screening visit), 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. These measurements will be performed at the time points specified in the SoA (see Section 1.3).

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

8.2.5 Electrocardiograms

- Single standard electrocardiograms (12 lead ECG) according to Goldberger / Einthoven and Wilson will be recorded pre-dialysis after resting for at least 5 min at the time points specified in the SoA (see Section 1.3).
- All ECG print-outs will be identified with the PID as well as date and time of recording and will be attached to the participant's file.
- ECG printouts will be examined locally by the investigator on the day of recording for safety and quality. Any clinically relevant abnormality will be documented as an AE.
- All suspected acute coronary syndrome events need to be submitted to the CIAC for evaluation.

8.2.6 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for timing and frequency.
- 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 values considered clinically significantly abnormal during participation in the study or until the end of study 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.
- Appropriate blood draws from the dialysis access for any type of blood sampling, collected from the hemodialysis line (not directly from the fistula, nor from any vein on the fistula arm), or tunneled catheters are permitted. Whenever possible, the blood should be drawn under the same conditions (details are depicted in the laboratory manual).
- Where possible for safety laboratory, 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.
- During the screening visit, only local laboratory samples will be assessed to check the eligibility of the patient. For details see Section 10.2.

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

8.2.7 Dialysis Information

8.2.7.1 Renal Replacement Therapy (RRT) Baseline Information (General Dialysis Information)

Current dialysis prescription will be collected on the appropriate eCRF.

Note: anticoagulation use during hemodialysis must be reported in the Concomitant Medication page in the eCRF.

8.2.7.2 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.

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

8.3 Adverse Events and Serious Adverse Events

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 study (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from signing of informed consent until the last follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs 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 AESIs (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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) 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 IEC/IRB and investigators will be done according to all applicable regulations (see Section 8.3.4) 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. Death due to MI, stroke, PE and SE
iii. Non-fatal stroke
iv. Non-fatal MI
v. Major amputation of vascular etiology
vi. Acute limb ischemia
vii. Symptomatic VTE
viii. Thrombosis of AV fistulas or grafts

These will be recorded on the corresponding CRF 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, 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. However, SUSARs that derive from these efficacy outcome events (as specified above ii – viii: Death due to MI, stroke, PE and SE, non-fatal stroke, non-fatal MI, major amputation of vascular etiology, acute limb ischemia, symptomatic VTE, thrombosis of AV fistulas or grafts), 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, if indicated, female partners of male participants will be collected after signing of informed consent and until the last follow-up visit (visit 35).
- 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 beta human chorionic gonadotropin (βhCG) levels are high in pregnant and may be elevated in non-pregnant women with ESRD undergoing hemodialysis, one measurement of high βhCG may not be sufficient to establish pregnancy. Only sequential increasing levels of βhCG may be considered for further investigation on pregnancy. If deemed necessary, a follow-up ultrasound may be performed to confirm pregnancy. If a female participant becomes pregnant, she must permanently discontinue study intervention.

8.3.6 Cardiovascular and Death Events

Not applicable.

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

Bleeding after dialysis from AV 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

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 x 10^9/L or > 50 % decrease in platelet count from baseline
- Hypersensitivity (i.e. any allergic reactions of ≥ CTCAE criteria 2 [Common Terminology Criteria for Adverse Events] or anaphylaxis)

8.3.8.1 Stopping Rule for Study Drug Administration in Case of Thrombocytopenia

In the event of a platelet count that is < 75,000mm^3, or > 50% decrease in platelet count from baseline the initial measurement should be confirmed by drawing repeat measurement(s) within 2 weeks. The repeat measurement(s) must occur before further study intervention (i.e. study drug administration). In the event that the platelet count has not recovered to > 100,000 mm^3 within 2 weeks , dosing of the participant will be postponed until the platelet has increased at least above 100,000 mm^3. In the event that after resumed dosing thrombocytopenia (< 75,000 mm^3) occurs again, study drug administration will be stopped permanently. A participant may be withdrawn from study intervention at any time at the discretion of the investigator for safety reasons (Section 7.1).

8.3.8.2 Hypersensitivity Reactions

Hypersensitivity reactions will be assessed according the Common Terminology Criteria for Adverse Events of the National Cancer Institute (CTCAE v5.0), see Table 8–1.

Table 8–1: Common Terminology for Adverse Events Related to Immune System Disorders (CTCAE v-5.0)

Immune system disorders					
Adverse Event	**Grade**				
	1	**2**	**3**	**4**	**5**
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/ angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ⩾ 40% O2	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or iv fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					

CTCAE= common terminology criteria for adverse events; iv= intravenous

Depending on the observed grade of reaction, respective measures like general and specific drug treatment (e.g., anti-histamines) as well as temporary or permanent stop of study drug administration in the affected participant will be applied. In case of a mild (grade 1-2 according to CTCAE v5.0) hypersensitivity reaction and an apparent symptoms relief, the

investigator may decide to cautiously continue further dosing. If any hypersensitivity symptom re-occurs dosing will be stopped permanently.

In case of hypersensitivity reactions of ≥ 3 dosing will be directly stopped permanently.

Anaphylaxis is strongly suspected when respiratory symptoms or hypotension occurs within 10 minutes of injection. All measures at site will be performed according the S2 Guideline for acute therapy and management of anaphylaxis (31).

8.3.9 AEs Requiring Submission to the CIAC

All deaths, and events suspected to be related to cardiovascular disease, or other arterial or venous thrombosis (including AV access thrombosis), but not limited to these and starting after signing informed consent (randomized participants only), will be submitted to the CIAC for adjudication. Similarly, all bleeding events in randomized participants (except a participant's normal/expected post-dialysis bleeding from AV access) will be submitted to the CIAC for adjudication. Details of the adjudication process will be described in the adjudication charter and additional study specific guidance documents.

8.4 Treatment of Overdose

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (approx. 5 months).
3. Obtain blood samples for PK/PD analysis within 4 to 10 days and an additional one around 30 days from the date of the last dose of study intervention if not already scheduled according to the study protocol.
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

For the investigation of systemic exposure of osocimab and its relationship with treatment effects, the plasma concentrations of osocimab will be determined at different time points using a sparse sampling approach in all participating subjects. Details about the collection, processing, storage and shipment of samples will be provided separately (e.g., in the laboratory manual). Analysis of samples from participants not treated with osocimab is optional.

Blood samples will be collected at the time points indicated in the SoA (Section 1.3). PK samples obtained at additional time points based on the investigator's discretion will not qualify as a protocol deviation and will be used for PK analysis as well. Deviations from the specified time points will be documented and taken into account for the PK analysis. Date and time of the PK sample collection and date and time of most recent study drug administration must be documented accurately in the eCRF.

PK samples will be analyzed, using validated analytical methods. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of

calibration samples and QC samples will be reported in the Bioanalytical Report which will be included in the clinical study report (CSR) for this study.

Pharmacokinetic and exposure-response analysis might be performed using population approaches (popPK and popPK/PD, e.g., by non-linear mixed effect modeling). Analysis and report will be done under separate cover (see Section 6.3).

Exploratory analysis of unbound osocimab or of the complex of osocimab bound to FXI(a) might be done if applicable.

8.6 Pharmacodynamics

For the investigation of the pharmacodynamic response to osocimab and its relationship with treatment effects, pharmacodynamic parameters detailed below will be determined at different time points using a sparse sampling approach in all participating subjects. Details about the collection, processing, storage and shipment of samples will be provided separately (e.g., in the laboratory manual). Samples from participants not treated with osocimab will also be analyzed.

Blood samples will be collected at the time points indicated in the SoA (Section 1.3). Blood samples obtained at additional time points based on the investigator's discretion will not qualify as a protocol deviation and will be used for the PD analysis as well. Deviations from the specified time points will be documented and taken into account for the PD analysis. Date and time of the PD sample collection and date and time of most recent study drug administration must be documented accurately in the eCRF.

For PD evaluation of osocimab the last sample taken prior to first drug administration will be defined as reference time point (i.e., will be assigned to a relative time of 00d00h00m).

The actual date and time of blood sampling will be collected 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 parameters, results of QC samples will be reported together with analyte concentrations in the Clinical Study Report (CSR) for this study. Concentrations of the analyte are calculated according to the method description. Detailed method descriptions of all PD methods will be filed with the CSR for this study.

The following parameters will be used to assess the PD effects after administration of the investigational drug:

Main pharmacodynamic parameters:

- aPTT will be measured via the kaolin-trigger method (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 osocimab.
- 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 osocimab.

Other pharmacodynamic parameters:

- Activated Factor XIa activity (AXIA) will be analyzed using a kaolin-trigger and a fluorogenic substrate readout.

- Factor XI concentration will be analyzed using an enzyme-linked immunosorbent assay (ELISA).
- D-dimer will be analyzed using a particle-enhanced immunoturbidimetric method.
- TAT (thrombin-antithrombin complex) will be analyzed using ELISA.
- F1.2 will be analyzed using ELISA.

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 may be part of the biomarker investigations in this study. Genetic investigations may be of any kind, except for whole genome sequencing. See Section 8.8 for details.

8.8 Biomarkers

Genetic as well as non-genetic biomarkers will be investigated. Biomarker analyses might be performed optionally and/or only in a subset of participants.

Exploratory biomarkers: FVIII activity, FIX activity, FXII activity, von Willebrand factor antigen level, ristocetin cofactor (i.e. von Willebrand factor) activity.

Furthermore, some PD markers listed under Section 8.6 might also be analyzed using alternative reagent/analyzer manufacturers in order to assess potential systematic influences of the analysis technology.

In addition to the biomarkers described above, further biomarkers related to, e.g., the mode of action or the safety of the study intervention and similar drugs may be investigated. 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, pharmacodynamic, monitoring, or potentially predictive biomarkers.

Timing

See SoA (Section 1.3) for planned time points of sample collection.

Sample handling and storage

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (e.g., sample handling sheets or laboratory 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.

Reporting

Some of the results of biomarker investigations may be reported separately (e.g., in a biomarker evaluation report).

8.9 Immunogenicity Assessments

The development of anti-drug antibodies (ADAs) to osocimab will be investigated in plasma samples from all participants taken at the time points indicated in the SoA (Section 1.3). Measurement of ADAs will be done batch-wise only as there is no expected direct impact on

participants´ safety in this respective study setting. In case of any hypersensitive AE of life-threatening consequences the ADA measurement will be carried out at short notice.

Plasma samples will be screened for ADAs to osocimab and the result as well as the titer of confirmed positive ADA samples will be reported. ADA positive samples will be further characterized for their ability to neutralize the activity of osocimab (i.e. Neutralizing antibody (NAB) analysis). Other analyses may be performed to further characterize the immunogenicity of osocimab. Analysis of samples from participants not treated with osocimab is optional.

Further details on collection, labeling, storage, and shipping of samples are provided in a separate laboratory manual. Immunogenicity samples will be analyzed using validated analytical methods. Positive controls will be analyzed concurrently with study samples. The results of samples and positive control samples will be reported in the Bioanalytical Report which will be included in the CSR for this study.

8.10 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses

The primary objective of this study is a qualitative assessment of safety. All analyses are performed in a descriptive manner and thus no formal hypothesis is defined.

9.2 Sample Size Determination

Assuming 25% screen failure proportion as based on historic operational experience, approximately 800 participants will be screened to achieve an estimated total of approximately 600 participants randomly assigned to study intervention. Of those, 555 participants are expected to complete the main treatment period assuming a true incidence rate of 15 participants with LTFU (lost to follow-up) (including e.g., withdrawal of consent) per 100 participant-years across all groups.

As a participant will be evaluated once he was randomized and received at least one dose of study intervention, the number of evaluable and randomized participants can be assumed to be similar.

In case that the observed overall incidence rate of participants with LTFU after the 400th participant is significantly higher than expected, the number of randomized participants may be increased (max. of 750 participants) to ensure a sufficient number of participants completing the main treatment period.

As all analyses will be performed in a descriptive manner, no statistically driven sample size calculation was performed.

The expected 90% confidence interval for the hazard ratio of the primary safety outcome is given by [0.57; 2.28], assuming

1. a true incidence rate of 10 participants with a major or clinically-relevant non-major bleeding event (in alignment with ISTH guidelines) per 100 participant-years in the placebo group (see below for definition)
2. a true hazard ratio of 1.0 (i.e. no change in relative risk) in both osocimab groups as compared to placebo
3. 6 months of treatment with a true incidence rate of 15 participants with LTFU per 100 participant-years across all groups.

The corresponding expected 90% confidence interval for the hazard ratio of the primary efficacy outcome is given by [0.44; 1.53]. while additionally assuming

1. a true incidence rate of 13 participants with a primary efficacy outcome per 100 participant-years in the placebo group.
2. a true hazard ratio of 0.75 in both osocimab groups as compared to placebo

For details on screen failures see Section 5.4.

9.3 Populations for Analyses

The populations are defined in Table 9–1.

Table 9–1: Populations for Analyses

Population	Description
Enrolled	All participants who sign the ICF
Full analysis set	All participants randomly assigned to study intervention.
Safety	All participants randomly assigned to study intervention who received at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic analysis set	All osocimab-treated participants with at least 1 PK sample in accordance with the PK sampling schedule (Section 1.3 and 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 analysis 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.

Abbreviations: ICF = Informed consent form, PD = pharmacodynamic(s), PK = pharmacokinetic(s)

9.4 Statistical Analyses

The statistical analysis plan will be finalized prior to FPFV (first patient first visit) 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.

9.4.1 General Considerations

The statistical analysis will be performed using SAS; the version used will be specified in the statistical analysis plan. In general, all variables including demography and baseline characteristics will be summarized by treatment group and by providing frequency tables for categorical variables and summary statistics for continuous variables.

For the primary analysis, only the main treatment period will be considered. The partial data of a participant's extended treatment period up until primary completion may be presented in separate tables. Furthermore, the primary analysis will be performed on the safety analysis set in accordance with the "population" attribute of the primary estimand.

In general, participants receiving placebo in either the low-dose or the high-dose cohort will be analyzed in a pooled manner. This group will be referred to as placebo group. The group of participants receiving osocimab in the high dose cohort (or low dose cohort) will be referred to as high dose (or low dose osocimab) group.

Where appropriate, the osocimab groups will be additionally displayed in a pooled manner.

9.4.2 Primary Endpoints

The primary safety analysis is a descriptive time to first primary safety event (for both endpoints: composite of major and clinically-relevant non-major bleeding events [in alignment with ISTH guidelines] and moderate and severe AEs and SAEs).

The primary objective is to assess the safety under an osocimab concentration which is expected to be maintained during a chronic treatment. Thus the aim it to assess the response to treatment while the participant is

- alive (intercurrent event "death") and
- exposed to study intervention (intercurrent event "premature discontinuation of treatment").

Therefore, the time to the first primary safety event is defined as time from first dose of study intervention to the first event of the endpoint of interest up until 30 days after last study intervention in the main treatment period. The time under risk for a participant without a primary safety event will be censored at the date of the EOMT visit, or 30 days after study intervention discontinuation, or at the last date data was collected for a participant (e.g., for participants lost to follow-up) in the main treatment period, whatever occurs first.

The cumulative incidence risk for the primary safety event together with its confidence interval will be estimated. Each of the osocimab groups will be compared to the placebo group using two-sided log-rank tests at a type I error rate of α=10%. Due to the explorative nature of these analyses, no multiplicity adjustment will be done.

Hazard ratios comparing each of the osocimab groups with the placebo group and corresponding 90% (and 95%) confidence intervals will be estimated, as appropriate, from Cox proportional hazards models.

Hazard ratio, relative risk reduction (RRR; RRR = 100 × [1 – hazard ratio]%), and corresponding 2-sided 90% and 95% confidence intervals comparing each of the osocimab groups with the placebo group will be estimated based on two separate Cox proportional hazards models. Censoring will be assumed independent of the randomized group assignment.

For the analysis of the primary endpoint in this study, the hazard function h(t) is the chance that an individual experiences an event of the primary safety outcome in the next instant in time, given that the individual has not had such an event up to time t. For example, for the comparison of the osocimab high dose group with the placebo group, the corresponding Cox proportional hazards model can be described by the following equation:

$$h(t,x_i) = h_0(t) \exp(\beta x_i),$$

where

h(.) hazard function for primary safety outcome, as a function of time and participant's covariates

$h_0(.)$ unspecified underlying baseline hazard function for primary safety outcome; hazard of an individual with $x_i = 0$

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

x_i treatment group of participant i
(0 corresponds to "placebo group" and
1 corresponds to "osocimab high dose group")

β unknown parameter (to be estimated); hazard ratio = exp(β)

Only events that started after the first dose of study treatment and during the main treatment period are considered for the primary analysis. Events that occurred during the pre-treatment period will be displayed in an exploratory manner.

9.4.3 Secondary Endpoints

The activated partial thromboplastin time (aPTT) and FXIa activity at trough levels after 6 months will be analyzed as ratio to baseline by providing the mean and median, together with the standard deviation and quantiles, respectively.

The exploratory composite efficacy endpoint will be analyzed using a time to event analysis similarly to the primary safety endpoints. Thus, the descriptive analysis focuses on estimating the efficacy under an osocimab concentration which is expected to be maintained during a chronic treatment.

Only events that started after the first dose of study treatment and during the main treatment period are considered for the primary analysis. Events that occurred during the pre-treatment period will be displayed in an exploratory manner.

The endpoint of thrombosis of the arterio-venous grafts or fistulas will be handled similar.

9.4.4 Other Analyses

The difference in the median of SQCSs during main treatment period between each of the osocimab groups and the placebo group will be displayed together with the corresponding 90% (and 95%) confidence intervals based on a T-test.

Furthermore, the difference of the proportion of hemodialysis sessions with adequate anticoagulation during main treatment period between each of the osocimab groups and the placebo group will be summarized with the corresponding 90% (and 95%) confidence intervals based on a proportion test.

The difference in the median of AV access bleeding score during main treatment period between each of the osocimab groups and the placebo group will be displayed with the corresponding 90% (and 95%) confidence intervals based on a T-test.

Furthermore, the difference of the proportion of hemodialysis sessions with no AV access bleeding during main treatment period between each of the osocimab groups and the placebo group will be summarized with the corresponding 90% (and 95%) confidence intervals based on a proportion test.

Both the safety and efficacy analyses will be repeated based on the full data to also include events that occurred during the extension treatment period and during the follow-up period.

PK variables

For the investigation of PK, the plasma concentrations of osocimab will be determined at the times given in Section 1.3 using a sparse sampling approach.

The data processing and the statistical analysis will be performed in accordance with the sponsor's current guidelines.

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

Further details will be specified in the statistical analysis plan.

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

PD variables

Results of the additional pharmacodynamics parameter will be displayed utilizing appropriate summary statistics and figures. The parameters will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by actual dose group for the original data as well as for the absolute and relative changes from baseline as ratio to baseline. In addition, for each participant the maximum and minimum relative change from baseline will be determined and presented by appropriate summary statistics and figure.

The exploratory PD marker results may be reported separately.

9.5 Interim Analyses

No formal interim analysis is planned.

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 follow-up of 4 months (study completion).

Furthermore, the DMC will frequently review safety data to ensure the safety of the participants in the ongoing study. The required tables and listings will be created by an independent Statistical Analysis Center (SAC).

9.6 Data Monitoring Committee (DMC)

A DMC will frequently review safety data to ensure the safety of the participants in the ongoing study.

For details on DMC refer to Section 10.1.5.

10. Supporting Documentation and Operational Considerations

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

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol. Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to the trial participants without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

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 (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (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:
    1. 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
    2. Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    3. Providing oversight of the conduct of the study at the site and adherence to requirements of 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 (Code of Federal Regulations), local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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.

The signed informed consent is to remain in the Investigator Site File or, if locally required, in the participant's note/file of the medical institution.

Participants who are re-screened are required to sign a new ICF.

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

Three independent committees will be established in order to ensure a high-standard study conduct according to GCP, aiming to achieve ultimate integrity, consistency, and high quality data, and most importantly ensure the safety of the participants enrolled in the study. The committees are:

Steering Committee (SC):

The SC will advise on all scientific aspects of the study and it will ensure that study execution and management of the study are of the highest quality. The Steering committee will consist of: External key experts in the field of nephrology, cardiology and hematology and sponsor representatives. Further details can be found in the SC charter.

Data Monitoring Committee (DMC):

The primary role of the DMC is to frequently review the safety data and ensure the safety of the participants in the ongoing study including unblinded data if deemed necessary. The DMC will consist of members who have recognized clinical expertise or expertise in biostatistics and who are not members of the steering committee, or involved as investigators or otherwise in the trial. Further details can be found in the DMC charter.

Central Independent Adjudication Committee (CIAC):

The central independent adjudication committee is blinded to treatment allocation and dose cohort and will objectively assess the safety and efficacy outcomes of the study and may convene on an ad-hoc basis for timely assessment. Further details will be found 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 European Union (EU) Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-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 EU on or after January 01, 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 CRF 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 the source data location list.

10.1.9 Study and Site Start and Closure

The study start date is the date on which the first clinical study site is opened for recruitment of participants.

The first act of recruitment is the First Patient First Visit for whole study.

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.
- In addition the sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

10.2 Appendix 2: Clinical Laboratory Tests

For details on the sampling scheme, please refer to Section 1.3 Schedule of Activities (SoA).

- The tests detailed in Table 10–1 will be mostly performed by the central laboratory.
- Central laboratory results may not be available in time for necessary medical decisions. Therefore, local laboratory tests are performed according to usual patient care schemes at the site, per decision of the investigator/treating physicians. If SAEs are triggered by local laboratory results the respective findings must be documented in the eCRF.
- 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
- Biomarkers (for details see Section 8.8)

Pharmacodynamic and pharmacokinetic parameters as well as safety laboratory parameters will be analyzed by central laboratories. The names and the addresses of the central laboratory service providers can be found in the documentation supplied by the vendor (laboratory manual).

During the screening visit, only local laboratory samples will be assessed to check the eligibility of the patient.
At least all parameters listed in Table 10–1 under screening tests at local laboratory must be assessed at the screening visit and entered in the eCRF to check the patient's eligibility for the study.

Table 10–1: Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
Central laboratory	
Hematology	Hemoglobin Hematocrit Red blood cell (RBC) count (MCV, MCH, MCHC, %reticulocytes) Platelet count White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Clinical chemistry	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Amylase Aspartate aminotransferase (AST) Bicarbonate Bilirubin, total and direct Blood urea nitrogen (BUN) Calcium Chloride Cholesterol [high density lipoprotein (HDL), low density lipoprotein (LDL), total] Creatinine Creatine kinase (CK) Glucose Gamma glutamyl transpeptidase (GGT) high-sensitivity C-reactive protein (hs-CRP) Highly sensitive serum beta human chorionic gonadotropin (βhCG) Iron saturation and ferritin Lactate dehydrogenase (LDH) Lipase Magnesium Parathyroid hormone (PTH) Phosphorus Potassium Serum glutamic-oxaloacetic transaminase (SGOT) Serum glutamic-pyruvic transaminase (SGPT) Sodium Total protein Triglycerides Troponin Uric acid
Coagulation parameters should not be reviewed by blinded staff.	
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (PT), seconds and INR (International normalized ratio) D-Dimer

Laboratory Assessments	Parameters
Local laboratory	
Screening Tests	Highly sensitive serum beta human chorionic gonadotropin (βhCG) pregnancy test (as needed for women of childbearing potential) All study-required laboratory assessments for eligibility will be performed by a local laboratory: Activated partial thromboplastin time (aPTT) Prothrombin time (PT) Bilirubin (direct, total) Alanine aminotransferase (ALT) Hemoglobin Platelet count The results of each test must be entered into the electronic case report form.
NOTES: Please note that if screening parameters are available as part of routine medical practice, these are not required to be repeated as long as they were measured within 14 days of screening and meet the thresholds defined in the in-/exclusion criteria.	

Abbreviations: MCH = mean corpuscular/cellular hemoglobin, MCHC = mean corpuscular/cellular hemoglobin concentration, MCV = mean corpuscular/cell volume

Investigators must document their review of each laboratory safety report.

Coagulation parameters that could unblind the study will not be reported to investigative sites or other blinded personnel if not medically required.

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 in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug 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 sponsor and CIAC. 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 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.
- 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 (IB) 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's PV. 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 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 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 CIAC with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor's PV 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 sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (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 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

Definitions:

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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (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:

Women of childbearing potential with their partner must agree to use a highly effective contraception method from signing informed consent until approx. 150 days (due to long half-life with only monthly administration) after last study intervention.

If engaged in sexual activity with child-bearing potential partner, male participants with their female partner must use highly effective contraception from signing informed consent until approx. 150 days (due to long half-life with only monthly administration) after last study intervention.

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 does not get in contact with sperm fluid in case it may contain osocimab. Also male participants with female partners who are breast feeding must use condoms.

Collection of Pregnancy Information:

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 up to the last follow-up visit (5 months after the last intervention is given).
- After obtaining the necessary signed informed consent 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: Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study. See Section 8.8 for details.

Details on sample handling will be provided separately.

10.6 Appendix 6: Country-specific Requirements

China:

- Study participating sites in China are excluded from all PD and biomarker sampling and analyses.

Germany:

- The exclusion of participants, who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

10.7 Appendix 7: Abbreviations and Definitions

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
AV	Arteriovenous
AXIA	Activated Factor XIa activity
BUN	Blood urea nitrogen
BW	Body weight
βhCG	Beta human chorionic gonadotropin
CAD	Coronary artery disease
CFR	Code of Federal Regulations
CIAC	Central Independent Adjudication Committee
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CKD	Chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRNMB	Clinically relevant non-major bleeding
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CYP	Cytochrome P450
DMC	Data Monitoring Committee
e.g.	*exempli gratia,* for example
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Early discontinuation
ELISA	Enzyme-linked immunosorbent assay
EOET	End of extension treatment period
EOMT	End of main treatment period
ESRD	End-stage renal disease
EU	European Union
EudraCT	European Clinical Trials Database
FEIBA	Factor eight inhibitor bypass activity
FFP	Fresh frozen plasma
FPFV	First patient first visit
FSH	Follicle stimulating hormone
FVIIa	Factor VIIa
FVIII	Factor VIII
FXI	Factor XI
FXIa	Factor XIa

FXII	Factor XII
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
Hb	Hemoglobin
HDL	High density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormonal replacement therapy
hs-CRP	high-sensitivity C-reactive protein
i.e.	*id est,* that is
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IMP	Investigational medical product
IND	Investigational new drug
INN	International non-proprietary name
INR	International normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
iv	Intravenous(ly)
IWRS	Interactive web response system
LD	Loading dose
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
LMWH	Low molecular weight heparin
LTFU	Lost to follow-up
MACE	Major adverse cardiovascular event
MB	Major bleeding
MCH	Mean corpuscular/cellular hemoglobin
MCHC	Mean corpuscular/cellular hemoglobin concentration
MCV	Mean corpuscular/cell volume
MD	Maintenance/ monthly dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NA	Not applicable
NAB	Neutralizing antibodies
NYHA	New York Heart Association
PAD	Peripheral artery disease
PCC	Prothrombin complex concentrate
PD	Pharmacodynamic(s)
PE	Pulmonary embolism
PID	Participant identification code
PK	Pharmacokinetic(s)
popPK	Population PK

PRIND	Prolonged reversible ischemic neurological deficit
PT	Prothrombin time
PTH	Parathyroid hormone
pts	Participants
PV	Pharmacovigilance
QC	Quality control
q.i.d	*Quater in die,* four times a day
R	Randomization
RBC	Red blood cell
RCTs	Randomized clinical trials
RND	Randomization
RRR	Relative risk reduction
RRT	Renal replacement therapy
SAC	Statistical Analysis Center
SAE	Serious adverse event
SAS	Statistical Analysis Software
sc	Subcutaneous(ly)
SC	Steering Committee
SE	Systemic embolism
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	Schedule of activities
SOP	Standard operating procedure
SQCS	Semi-quantitative clotting score
SUSAR	Suspected unexpected serious adverse reactions
TAT	Thrombin-antithrombin complex
TE	Thromboembolic
TF	Tissue factor
TKA	Total knee arthroplasty
UFH	Unfractionated heparin
ULN	Upper limit of normal
URR	Urea reduction ratio
V	Visit
VTE	Venous thromboembolism
vWF	Von Willebrand factor
WBC	White blood cell (count)
WHO	World Health Organization
WOCBP	Woman of childbearing potential
%CV	Percent coefficient of variation

Month	equals 30 days ± 3 days when referring to monthly dosing
Hemodialysis	the term hemodialysis includes hemodiafiltration
Outcome Assessor	the term Outcome Assessor includes CIAC and DMC

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