Protocol and Statistical Analysis plan

This supplement has been provided by the authors to give readers additional information about the FOXTROT (Factor XIa Inhibition for the Prevention of Venous Thromboembolism in Patients Undergoing Total Knee Arthroplasty; ClinicalTrials.gov number, NCT03276143) study.

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Cover page of the integrated protocol

A randomized, active-comparator-controlled, multicenter study to assess the safety and efficacy of different doses of BAY 1213790 for the prevention of venous thromboembolism in patients undergoing elective primary total knee arthroplasty, open-label to treatment and observer-blinded to BAY 1213790 doses

FOXTROT : FactOr XIa inhibiTion for the pRevention of venOus Thromboembolism in patients undergoing total knee arthroplasty

For this study, the protocol and subsequent protocol amendments were released as follows:

- **Original protocol,** Version 1.0, dated 27 MAR 2017
- **Amendment 1** (local amendment Germany), dated 18 JUL 2017
- **Amendment 2** (local amendment Latvia), dated 17 AUG 2017
- **Amendment 3** (local amendment Hungary), dated 26 SEP 2017
- **Amendment 4** (local amendment Canada), dated 25 OCT 2017
- **Amendment 5** (global amendment), forming integrated protocol Version 2.0, dated 13 MAR 2018

This document integrates the original protocol and the global amendment.

1. Title page

A randomized, active-comparator-controlled, multicenter study to assess the safety and efficacy of different doses of BAY 1213790 for the prevention of venous thromboembolism in patients undergoing elective primary total knee arthroplasty, open-label to treatment and observer-blinded to BAY 1213790 doses

FactOr XIa inhibiTion for the pRevention of venOus Thromboembolism in patients undergoing total knee arthroplasty

FOXTROT

Test drug:	BAY 1213790 / Anti-FXIa antibody		
Study purpose:	To assess the safety and efficacy of a range of doses of BAY 1213790 in patients undergoing total knee arthroplasty (TKA)		
Clinical study phase:	IIa	Date:	13 MAR 2018
Registration:	EudraCT: 2016-002681-31	Version no.:	2.0
Sponsor's study no.:	17664		
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany		
Sponsor's medical expert:	Cecilia Freitas, MD, PhD Study medical expert Bayer U.S. LLC Pharmaceuticals 100 Bayer Boulevard Whippany, New Jersey 07981 United States Tel: +1 862 404-3950 Mobile: + 1 862 2465194 E-mail: cecilia.freitas@bayer.com		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol amendment as presented.

Name: Carola Metzig, MD Role: Global Clinical Leader

Date: 15. March 2018 Signature:

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol amendment as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis

Title	A randomized, active-comparator-controlled, multicenter study to assess the safety and efficacy of different doses of BAY 1213790 for the prevention of venous thromboembolism in patients undergoing elective primary total knee arthroplasty, open-label to treatment and observer-blinded to BAY 1213790 doses
Short title	FactOr XIa inhibiTion for the pRevention of venOus Thromboembolism in patients undergoing total knee arthroplasty
Acronym	FOXTROT
Clinical study phase	IIa
Study objective(s)	Primary objective: • To assess the safety and efficacy of different doses of BAY 1213790 in comparison with those of enoxaparin in patients undergoing elective, primary, unilateral total knee arthroplasty (TKA) Secondary objective: • To compare the safety and efficacy of BAY 1213790 with those of apixaban Exploratory objective: • To assess the dose-response relationship of BAY 1213790 for efficacy and safety • To characterize the pharmacokinetic and the pharmacodynamic profile of BAY 1213790 and the relationship between both Other objective: • To further characterize BAY 1213790 by evaluating additional PD markers • To investigate the mechanism of thrombosis by analyzing additional PD markers

Test drug	BAY 1213790
Name of active ingredient	BAY 1213790
Doses	Post-surgery administration part (A): 3 arms (0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg) Pre-surgery administration part (B): 2 arms (0.3 mg/kg, 1.2 mg/kg; doses may be adapted according to recommendations by the IDMC and advice by the SC after evaluation of the post-surgery part (A))
Route of administration	Intravenous infusion
Duration of treatment	Post-surgery administration part (A): Single infusion the day following TKA after adequate hemostasis has been achieved, preferably in the morning, but not later than 24 hours after wound closure Pre-surgery administration part (B): Single infusion in the second half of the pre-surgery day
Reference drug 1	enoxaparin
Name of active ingredient	enoxaparin sodium
Dose	40 mg od
Route of administration	Subcutaneously
Duration of treatment	Started either in the evening before TKA or 6-8 hours after TKA (at investigator's discretion), followed by once daily subcutaneous injections for at least 10 days and until venography is performed (Day 12+3)
Reference drug 2	apixaban
Name of active ingredient	apixaban
Dose	2.5 mg bid
Route of administration	Orally
Duration of treatment	For at least 10 days post-surgery and until the day venography is performed (Day 12+3), starting within 12 to 24 hours after TKA surgery
Indication	Prevention of venous thromboembolism in patients undergoing elective, primary, unilateral TKA
Diagnosis and main criteria for inclusion /exclusion	Inclusion criteria: • Patients aged ≥18 years undergoing elective primary, unilateral TKA • Women of non-childbearing potential defined as either surgically sterile (e.g., tubal occlusion such as bilateral tubal ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal. Women are considered post-menopausal if they have had 12 months of spontaneous amenorrhea accompanied by an

appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels > 40 mIU/mL. Males must be surgically sterile, abstinent or if engaged in sexual activity of child-bearing potential, the patient must be using an acceptable contraceptive method during the treatment phase and until the end of the post-treatment observation phase.

Exclusion criteria:

- High risk for clinically significant bleeding or any of the following conditions:
  - Anemia (Hb <10 g/dL in women, < 11 g/dL in men) at Screening
  - Platelet count at Screening < 150 x 10^9/L or history of heparin-induced thrombocytopenia
  - aPTT or PT (INR or Quick) > ULN at Screening
  - Hepatic disease associated with either: coagulopathy leading to a clinically relevant bleeding risk, or alanine aminotransferase (ALT) > 3x upper level of normal (ULN) or total bilirubin (TB) > 2x ULN with direct bilirubin > 20% of the total at Screening
  - Sustained uncontrolled hypertension (diastolic blood pressure ≥ 100 mmHg and/or systolic blood pressure ≥ 180 mmHg)
  - Brain, spinal, or ophthalmologic surgery (except cataract surgery) within 3 months prior to randomization
  - Known bleeding disorders
- Prior deep vein thrombosis
- Body weight above 135 kg
- Creatinine clearance below 60 ml/min, calculated by MDRD formula at Screening
- Recent (<6 months) myocardial infarction or ischemic stroke
- Active cancer except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been curatively treated
- Contraindication listed in the local label of the comparator treatments
- Requirement for full dose anticoagulation or dual antiplatelet therapy (low dose of acetylsalicylic acid is allowed)
- Anticipated use of intermittent pneumatic compression devices or electrical/mechanical muscle stimulators
- Any severe allergy or contraindication to the use of contrast media

Post-surgery administration part (A):

- Epidural analgesia after surgery

	Pre-surgery administration part (B): • TKA under regional anesthesia, i.e. spinal or epidural anesthesia (only general anesthesia is allowed) and epidural analgesia.
Study design	This study is an open label, active-comparator-controlled, randomized study designed to investigate the safety and efficacy of BAY 1213790 in comparison with enoxaparin and apixaban in patients undergoing elective, primary, unilateral total knee arthroplasty (TKA). The study is open-label with respect to treatment assignment and observer-blinded for the different BAY 1213790 doses. The study consists of two parts: BAY 1213790 post-surgery administration, which is part (A) and BAY 1213790 pre-surgery administration, which is part (B). BAY 1213790 Post-surgery administration part (A): Patients who have met all the inclusion and none of the exclusion criteria will be randomized to receive either BAY 1213790 (single dose), enoxaparin (40 mg od, at least for 10 days post-surgery and until venography) or apixaban (2.5 mg bid, at least for 10 days post-surgery and until the day of venography). At least 300 patients will be randomized to BAY 1213790 (100 patients for each of the three arms) during this post-surgery administration part and approximately 60 patients to each of the comparator arms. BAY 1213790 Pre-surgery administration part (B): Following the post-surgery administration part, the pre-surgery administration part may be started. For the pre-surgery part, the two doses 0.3 mg/kg, 1.2 mg/kg are planned, however, the determination of the doses for the two pre-surgery arms of BAY 1213790 will be based on the independent data monitoring committee (IDMC) and steering committee (SC) evaluation of the safety and efficacy data of at least 75% of treated patients from all treatment arms of the post-surgery administration part. Patients who have met all the inclusion and none of the exclusion criteria will be randomized to receive either BAY 1213790 (single dose, pre-surgery administration), enoxaparin (40 mg od, until venography, at least for 10 days post-surgery and until venography) or apixaban (2.5 mg bid, at least for 10 days post-surgery and until the day of venography). At least 200 patients will be randomized to BAY 1213790 (100 patients for each of the two dose arms) and approximately 40 patients to each of the two comparator arms. Overall, at least 700 patients will be randomized, 500 patients to BAY 1213790 (5 different arms), or to the active comparator arms (enoxaparin, apixaban; 100 patients each). Further patients (additional to the 700 patients initially planned) may be enrolled and randomized to be treated with BAY 1213790 for the following reasons: • In case an additional BAY 1213790 arm will be opened due to low efficacy or high bleeding rate and closure of the respective dose arms in the post- and/or pre-surgery administration part • The number of adequately assessable venographies falls below 75 %, in either treatment arm, which consequently may endanger the primary efficacy outcome assessment of the study. The maximum number of patients to be enrolled will be 900.

Methodology	Randomized, open-label with respect to treatment assignment, active controlled, and observer-blinded for BAY 1213790 dose arms Safety: Safety will be assessed by monitoring/evaluation of bleeding events and adverse events (AEs). Efficacy: Efficacy will be assessed by the incidence of VTE events comprised of asymptomatic DVT as detected by mandatory bilateral venography, objectively confirmed symptomatic DVT, non-fatal PE, fatal PE, unexplained death for which PE cannot be excluded. Mandatory bilateral venography will be performed at Day 12+3. Patients will be closely followed for the occurrence of suspected study outcomes. The primary efficacy and safety outcomes will be centrally adjudicated by a blinded, central independent adjudication committee (CIAC). Investigators are instructed to report the occurrence of suspected efficacy and safety outcome events timely (within 24 hours if possible) to CIAC and record the outcomes timely (within 24 hours if possible) in the eCRF. If a suspected study outcome occurs, an adjudication package needs to be compiled and sent to the adjudication committee timely (within 24 hours if possible). The adjudication committee will perform quality check of the adjudication package, including check for completeness. Pharmacokinetic and pharmacodynamics analysis by validated analytical methods
Type of control	Active control
Data monitoring committee	The independent data monitoring committee (IDMC) will be informed regularly on the latest update of study outcomes (i.e. incidence of the composite efficacy outcome and major bleeding, tabulated separately by treatment arm) and (study drug related) adverse events. The IDMC will provide a recommendation and the steering committee (SC) will advise to continue or stop recruitment in a BAY 1213790 arm, to initiate the pre-surgery part of the study, and to open the new BAY 1213790 dose arm.
Number of patients	A total of 700 patients are planned to be randomized with the possible extension to a maximum of 900 patients, in case of opening of additional BAY 1213790 arms due to either low efficacy, high bleeding rates or high proportion of venographies of inadequate quality. The 700 patients are planned to be randomized as following: • 500 Patients to BAY 1213790 (3 observer-blinded arms with 100 patients in each arm during the post-surgery part (A) and 2 observer-blinded arms with 100 patients in each arm during the pre-surgery part (B)) • 100 Patients to the comparator arms (enoxaparin, apixaban; 100 patients in each arm)

Primary variables	• composite endpoint of asymptomatic DVT detected by bilateral venography; objectively confirmed symptomatic DVT, non-fatal PE, fatal PE, unexplained death for which PE cannot be excluded • composite of major and clinically relevant non-major bleeding
Time point/frame of measurement for primary variable(s)	Day 12+3
Plan for statistical analysis	The analysis for the primary efficacy variable will be conducted separately for each BAY 1213790 arm (defined by the dose and the time of administration (post- vs. pre-surgery)). **Primary analysis:** For the primary efficacy variable the following hypotheses will be tested: • Non-inferiority of BAY 1213790 arm compared to enoxaparin • Superiority of BAY 1213790 arm compared to enoxaparin These one-sided hypotheses will be tested for each BAY 1213790 arm to a global significance level of α=5%. In order to adjust for the multiplicity within each BAY 1213790 arm a fixed-sequence procedure in the order given above will be applied. No adjustment will be done for the multiplicity caused by the 5 arms. For the tests the two-sided 90% confidence intervals for the difference in the proportions of the BAY 1213790 arms versus enoxaparin will be calculated based on normal approximation. The hypotheses will be tested by comparing the lower limit of the two-sided 90% confidence interval with the NI margin Δ=5% (for the NI tests) or with 0 for the superiority tests. No hypothesis testing will be conducted for the comparison of the BAY 1213790 arms with apixaban but 90% confidence intervals will be provided for difference in the proportion of each of the BAY 1213790 arms and apixaban. The patients randomized in the post- and in the pre-surgery part of the study will be pooled for each of the 2 comparator groups

Protocol amendment summary of changes table

Amendment no. 5 (13 MAR 2018)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for the amendment

Overall rationale: This protocol amendment was prepared to align with HA requests from several EU countries.

Changes include clarifications of randomization scheme and prior/concomitant medication, as well as the pregnancy testing, required use of contraception, allowed forms of anesthesia and measurement of vital signs. These changes do not affect the design or the overall concept of the study.

In addition, minor changes including administrative clarifications and corrections of inconsistences and typographical errors were also made.

Section # and name	Description of change	Brief rationale
5. Study design 7.3 Treatment assignment	Description of randomization scheme was modified to allow adjustment of randomization ratio.	Flexible randomization scheme was adapted to prevent unbalanced arms in case one of the BAY 1213790 arms is prematurely closed or an additional arm is initiated.
7.4 Dosage and administration 10.5 Planned interim analyses	After evaluation of at least 75% of the patients in the post-surgery administration part (part A), a summary of the data assessment and recommendations of the IDMC and the SC will be made available to IECs/IRBs, as well as local authorities for either notification or approval according to local requirements.	This study is the first to investigate safety and efficacy of BAY 1213790.

Section # and name	Description of change	Brief rationale
8.1 Prior and concomitant therapy	The following sentence was added to the list of prior and concomitant medications not allowed during the study: “The use of monoclonal antibodies is not recommended during the study.”	The use of BAY 1213790 concomitantly with other antibodies has not been studied yet.
9.1.1 Post-surgery schedule of activities and evaluations, part A 9.1.2 Pre-surgery schedule of evaluations, part B 9.2.1 Post-surgery visit descriptions, part A (applicable subsections) 9.2.2 Pre-surgery visit descriptions, part B (applicable subsections)	IxRS activities at Visits 1 and 8 as well as PDC were added in tabular schedule of evaluations (both part A and part B). A more detailed description of IxRS activities was added in Visit description section (both part A and part B) at Visits 2 and 8.	A more detailed description of all IxRS activities was needed to ensure that they are performed at sites according to the protocol.
9.2.1.2.2 Visit 3 (Day 2), Treatment phase	A paragraph describing in more detail the forms of anesthesia that are allowed and not allowed was added.	Clearer information regarding the allowed forms of anesthesia was required.
9.6.3.1 Laboratory parameter measurement	Clarification that serum pregnancy test for women who are surgically sterile or postmenopausal who are older than 65 years is not performed was added.	To avoid unnecessary burden to patients, criteria for subjects not requiring serum pregnancy test was needed.
9.6.3.1 Laboratory parameter measurement 16. Appendices	The correct MDRD formula was provided in the appendices and referred to in the description of laboratory measurement.	To ensure that MDRD is calculated in the same manner at all sites, the MDRD formula needed to be included in the protocol.
9.6.3.4 Measurement of Vital signs	Measurement of vital signs was modified to allow blood pressure measurement after TKA at Visit 3 (Day 2) to be taken in a semi-supine position.	After TKA, it is hard to measure blood pressure at sitting position.

Section # and name	Description of change	Brief rationale
9.6.3.6 Contraception	The text was modified to clarify that if engaged in sexual activity with child-bearing potential partners, either male patients or their female partners must ensure effective contraception during the treatment phase and until the end of the post-treatment observation phase (examples of effective contraception methods provided).	A clarification that the use of spermicides is not required for the male patients if the female partner is using an effective method of contraception was needed.
10.5 Planned interim analyses	Additional potential interim analyses were added to assess both efficacy and safety.	Clarification was required at which time points potential interim analysis will be performed
2. Synopsis 5. Study design 7.4 Dosage and administration 9.1.1 Post-surgery schedule of activities and evaluations, part A 9.2.1.2.3 Visit 4 (Day 3), Treatment phase	Description of administration of BAY 1213790 was clarified by using the wording "*preferably* in the morning" instead of "in the morning".	Change was needed to allow administration of BAY 1213790 also in the afternoon.
7.5.1 Blinding measures	Wording "test drug" was changed to "study drug".	Correction of error
8.1 Prior and concomitant therapy	Stopping point of concomitant use of drugs influencing coagulation was changed to be "prior to randomization" instead of "prior to start of study treatment".	Correction of error

Section # and name	Description of change	Brief rationale
8.1 Prior and concomitant therapy	A clarification that for patients on BAY 1213790, further use of spinal or epidural anesthesia is not allowed during the study (i.e. during the treatment phase and during the post-treatment observation phase) was added. A clarification that for patients on enoxaparin and apixaban, the use of spinal and epidural anesthesia is not allowed during the treatment phase (until Day 12+3) was added.	Clarification
9.1.1 Post-surgery schedule of activities and evaluations, part A 9.1.2 Pre-surgery schedule of evaluations, part B	Explanation text of footnote “i” in tabular schedule of evaluations was modified by adding a clarification that for the apixaban arm, the explanation is only relevant for PD blood samples (section 9.1.1). Footnote “f” was added in tabular schedule of evaluations to clarify that if screening and randomization are performed on the same day, vital signs need to be assessed only at screening. Footnote “v” was added in tabular schedule of evaluations to clarify that IxRS and drug accountability activities are performed at PDC visit if premature discontinuation occurs prior to Visit 7.	Clarification

Section # and name	Description of change	Brief rationale
9.1.1 Post-surgery schedule of activities and evaluations, part A 9.1.2 Pre-surgery schedule of evaluations, part B 9.2.1.2.1 Visit 2 (Randomization; Day 1 and baseline), Treatment phase 9.2.2.2.1 Visit 2 (Randomization; Day 1 and baseline), Treatment phase 9.6.3.1 Laboratory parameter measurement	Clarification that the laboratory parameter “ristocetin cofactor activity” is also known as “von Willebrand factor activity” was added.	Clarification
9.2 Visit description	A clarification was added to define that unlike other visits, the screening visit may include procedures on several days.	Clarification
9.2.1.2.1 Visit 2 (Randomization; Day 1 and baseline), Treatment phase 9.2.1.2.3 Visit 4 (Day 3), Treatment phase 9.2.1.2.4 Visit 5 (Day 4), Treatment phase 9.2.1.2.5 Visit 6 (Day 6 ± 1), Treatment phase 9.2.1.2.6 Visit 7 (Day 12 + 3), Treatment phase 9.2.2.2.1 Visit 2 (Randomization; Day 1 and baseline), Treatment phase 9.2.2.2.2 Visit 3 (Day 2), Treatment phase 9.2.2.2.3 Visit 4 (Day 3), Treatment phase 9.2.2.2.5 Visit 6 (Day 6 ± 1), Treatment phase 9.2.2.2.6 Visit 7 (Day 12 + 3), Treatment phase	Clarifications that all blood samples are taken before administration of study drug, and for the apixaban arm before the first dose of the day, were added to visit description sections.	Clarification
9.6.3.1 Laboratory parameter measurement	The word “measured” was changed to “assessed.”	Clarification

Section # and name	Description of change	Brief rationale
2. Synopsis 5. Study design 9.4 Efficacy 9.6 Safety 10.3.1 Efficacy variables 10.3.2 Safety variables 10.3.3.3 Safety variables	Wording "*composite of* major and clinically relevant non-major bleeding/ *composite* endpoint of" was used in the description of primary and secondary efficacy and safety endpoints.	Clarification
2. Synopsis 3. Introduction 9.4 Efficacy 10.2 Analysis sets 10.3.1 Efficacy variables 10.3.3.2 Efficacy variables	Wording "symptomatic VTE" was changed to "symptomatic DVT or non-fatal PE".	Clarification
2. Synopsis 5. Study design 7.4 Dosage and administration (Part A and Part B) 9.1.1 Post-surgery schedule of activities and evaluations 9.1.2 Pre-surgery schedule of evaluations	Description of post-surgery administration of apixaban (Part A and Part B) was clarified by using the wording "until *the day* venography is performed", instead of "until venography is performed", and by adding the following sentence: "In case venography is performed on Day 12, one last dose of apixaban 2.5 mg is given in the evening of Day 12 to complete 10 days of treatment."	Clarification
9.2.1.3.2 Visit 9 (Day 90 ± 7) Post-treatment observation phase 9.2.1.3.3 Visit 10 (Day 150 ± 7) Post-treatment observation phase 9.2.2.3.2 Visit 9 (Day 90 ± 7) Post-treatment observation phase 9.2.2.3.3 Visit 10 (Day 150 ± 7) Post-treatment observation phase	The time window at Visits 9 and 10 (Part A and Part B) is ±7 days instead of ± 2 days.	Correction of inconsistency

Section # and name	Description of change	Brief rationale
9.2.1.2.3 Visit 4 (Day 3), Treatment phase 9.6.3.4 Measurement of vital signs	A clarification that in Part A, vital signs at Visit 4 (Day 3) will be assessed for the enoxaparin arm *only before*, and for the BAY 121379 and apixaban arms *both before and after* administration of the drug, was added.	Correction of inconsistency
9.4 Efficacy	The sentence “Any incidentally found asymptomatic DVT detected by an objective method after Visit 7 (Day 12+3) will also be considered” was deleted from the description of Mandatory venography.	Correction of inconsistency
9.6.3.3 Electrocardiogram	ECGs will be assessed at Visit 6 (Day 6 +/-1) instead of Visit 5 (Day 6).	Correction of inconsistency
10.4 Determination of sample size (Table 10-1)	The number of assumed evaluable patients for enoxaparin and apixaban is 80 instead of 100.	Correction of inconsistency

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List of abbreviations

AAOS	American Academy of Orthopedic Surgeons
ACCP	American College of Chest Physicians
ADA	anti-drug antibody
AE(s)	adverse event(s)
ALT	alanine aminotransferase
AP	alkaline phosphatase
aPTT	activated partial thromboplastin time
ASO	anti-sense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration vs. time curve from zero to infinity after single (first) dose
BID	bis in die = twice daily
BMI	body mass index
BP	blood pressure
BW	body weight
CCUS	complete compression ultrasound
CI	coordinating investigator
CIAC	central independent adjudication committee
CK	creatine kinase
CL	total body clearance
C_{max}	maximum observed drug concentration in measured matrix after single dose administration
CRF	case report form
CRNM bleeding	clinically relevant non-major bleeding
CRO	clinical research organization
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTPH	chronic thromboembolic pulmonary hypertension
CUS	compression ultrasound
CV	cardiovascular system
CYP3A4	cytochrome P4503A4
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme linked immunosorbent assay
ETP/TGA	endogenous thrombin potential / Thrombin generation assays
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trial (number)
FAS	full analysis set
FIX	Factor IX
FSH	follicle stimulating hormone
FVIIa	Factor VIIa
FVIII	Factor VIII
FXa	Factor Xa
FXI	Factor XI
FXIa	Factor XIa

FXI-ASO	Factor XI-antisense oligonucleotide
FXII	Factor XII
g/dL	gram/deciliter
GCP	good clinical practice
GGT	gamma glutamyl transpeptidase
GMP	good manufacturer practice
HA	health authority
Hb	hemoglobin
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonization
IDMC	independent data monitoring committee
IDMS	isotope dilution mass spectrometry
IEC	independent ethics committee
IgG1	immunoglobulin G1
INN	international non-proprietary name
INR	international normalized ratio
IRB(s)	Institutional Review Board(s)
ISTH	International society of thrombosis and haemostasis
ITT	intent-to-treat
i.v.	intravenous
IV	intravenous
IxRS	interactive voice / web response system
L	liter
LDH	lactate dehydrogenase
LDL	low density lipoprotein
L/h	liter per hour
LLOQ	lower limit of quantification
LMWH	low molecular weight heparin
LPLV	last patient last visit
LSH	life science hub
MB	major bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
mIU/mL	milli international unit / milliliter
mmHg	millimeter of mercury
MR	magnetic resonance
n.a.	not available
NI	non-inferiority
NSAIDs	nonsteroidal anti-inflammatory drugs
OD	once daily
pat	patient(s)
PD	pharmacodynamic(s)
PDC	premature discontinuation
PE	pulmonary embolism
PG	pharmacogenomics
PGt	pharmacogenetics
PK	pharmacokinetic(s)

p.o.	per os, orally
popPK	population pharmacokinetics
popPK/PD	population pharmacokinetic(s)/pharmacodynamic(s)
PPS	per protocol set
PT	prothrombin time
PTS	post-thrombotic syndrome
QA	quality assurance
QC	quality control
q.i.d	quater in die, four times a day
R	Randomization
RBC	red blood cell
ROTEM	thromboelastography
s.c.	Subcutaneously
SAE	serious adverse event
SAF	safety analysis set
SC	steering committee
sCT	spiral computed tomography
SID	subject/patient identification
SM	site manual
SUSARs	suspected, unexpected, serious adverse reactions
TAFI	thrombin-activatable fibrinolysis inhibitor
TB	total bilirubin
tbd	to be determined
TF	tissue factor
TKA	total knee arthroplasty
UK	United Kingdom
UK NICE	United Kingdom National Institute for Health and Clinical Excellence
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolism
vWF	von Willebrand factor
V_{ss}	volume of distribution at steady state
WBC	white blood cell

Definitions of terms

In this document following terminology is used:

Test drug:	BAY1 213790, sponsor's active compound
Study drug:	test drug and comparators
Study treatment:	all treatments identified in this CSP / all study drugs
Observer:	investigators and other study site staff, with the exception of specifically dedicated unblinded site personnel

3. Introduction

Background

Venous thromboembolism (VTE) is a common disorder; however the reported numbers vary widely from 250,000 to up to 900,000 cases per year in the United States (1). The estimated annual incidence rates of VTE, among people of European ancestry, range from 104 to 183

per 100,000 person-years, rates that are similar to stroke (2). VTE is one of the most frequent serious complications after total knee replacement surgery, and in the absence of thromboprophylaxis, 50-60% of these patients will develop VTE events, including deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Most of these events are asymptomatic; symptomatic VTE, i.e. DVT or non-fatal PE occurs in approximately 4% of patients within the first month after surgery (3). After elective total knee arthroplasty (TKA), DVT as assessed by venography occurs in 41-85% of patients 7-14 days after surgery (4).

As patients undergoing total joint replacement are at high risk for VTE, the use of routine thromboprophylaxis is recommended in the guidelines issued by American Academy of Orthopedic Surgeons (AAOS), American College of Chest Physicians (ACCP) and the United Kingdom National Institute for Health and Clinical Excellence (UK NICE) (5). With the exception of the AAOS guideline, which does not recommend any prophylactic treatment in particular, various pharmacologic agents are recommended by ACCP and NICE for VTE prevention in patients undergoing total knee arthroplasty: vitamin K antagonists (VKA), indirect factor Xa inhibitors like enoxaparin and fondaparinux, or direct oral anticoagulants like Factor Xa or Factor IIa inhibitors (3- 6). Whilst the use of aspirin as a stand-alone prophylactic treatment in these patients is now supported by ACCP (3) and AAOS (7) (either implicitly or explicitly), the UK NICE guideline does not include aspirin among its recommended treatments. Furthermore, the U.S Surgical Care Improvement Project measures include aspirin only as an adjunct to compression devices and not as sole option for the prevention of VTE in total knee arthroplasty patients. Hence the use of aspirin alone seems still controversial and not widely accepted by orthopedic surgeons (8). Intermittent compression devices are also recommended by current ACCP guidelines but their use as a stand-alone option or as an adjunct to chemoprophylaxis is supported by a weaker evidence (1C and 2C recommendation strength respectively). VKAs (e.g. warfarin or phenprocoumon) have narrow therapeutic window and therefore are associated with an extremely variable patient-to-patient response, along with extensive food and drug interactions. Consequently, close monitoring and potential dose adjustments are required to attain an appropriate VTE prophylaxis by achieving the targeted international normalized ratio (INR). Moreover, it can take days for VKAs to exhibit their full anticoagulation potential.

Both LMWH and fondaparinux require daily subcutaneous (s.c.) injection for drug administration. This may impact on patient acceptance as well as compliance, specifically during extended prophylaxis, which in some cases may last for several weeks.

Direct oral anticoagulants targeting FXa like rivaroxaban or apixaban or FIIa like dabigatran, demonstrated equivalent or superior efficacy as compared to enoxaparin and are available in many countries for VTE prevention in orthopedic patients. In contrast to other oral anticoagulants, they do not need monitoring of coagulation parameters and have no significant food and drug interactions. Whilst all of the antithrombotic agents described above have been shown to be efficacious in the prevention of VTE after orthopedic surgery, their use is always associated with a variable bleeding risk, which is therefore considered unavoidable.

Factor XI (FXI) is a new coagulation target with the potential to reduce the incidence of more severe bleeding events in patients requiring thromboprophylaxis. The identification of FXI as a new target was supported by in vitro coagulation models, genetically modified FXI

knockout mouse models, animal models of thrombosis and hemostasis, and human physiology (9).

The formation and the stability of clots are enhanced by FXI in *in vitro* experiments (10- 11). Furthermore, FXI amplifies thrombin generation when coagulation is initiated by low levels of tissue factor (TF) or thrombin. FXI-dependent amplification of thrombin formation also leads to activation of the thrombin-activatable fibrinolysis inhibitor, which renders clots less sensitive to fibrinolysis. Therefore, a FXI inhibitor might indirectly enhance clot dissolution. Yet, the most solid evidence, which supports FXI as a potential therapeutic target comes from patients, including patients with congenital factor XI deficiency as well as results from a recent study testing an antisense oligonucleotide (ASO) targeting FXI in patients undergoing elective TKA. Observational studies analyzing FXI deficient patients suggest that these patients have a very low incidence of ischemic stroke (12) and VTE events (9- 13). More importantly, the FXI-ASO (ISIS 416858), a second generation antisense oligonucleotide that specifically reduces factor XI levels has demonstrated promising results in a first study in patients undergoing elective TKA (14).

BAY 1213790

BAY 1213790 is a fully human IgG1 antibody (anti-factor XIa antibody BAY 1213790) that binds specifically to factor XIa, close to the catalytic center, and thus modifies the factor's recognition site for binding of its natural substrates such as factor IX, leading to inhibition of enzymatic activity.

Preclinical experience

Preclinical pharmacology experiments indicated a profound antithrombotic effect, both in arterial and in venous models, in the absence of significantly prolonged bleeding times or increased blood loss. In line with the mechanism of action, the aPTT increased in a dose-dependent manner and in parallel with the antithrombotic effect. BAY 1213790 had no effect on the PT confirming that the effects of BAY 1213790 were limited to the intrinsic pathway of coagulation.

Clinical experience

Up to now, there has been one first-in-man study #17188 conducted. This was a randomized single-blind placebo-controlled dose escalation study to investigate safety, tolerability, pharmacokinetic and pharmacodynamic properties of BAY 1213790 after intravenous dosing. So far, single i.v. doses of 0.015, 0.060, 0.15, 0.3, 0.6, 1.25, 2.5, and 5.0 mg per kg individual body weight (BW) were administered and analyzed in an interim analysis. Up to 10 mg per kg BW has been administered and was well tolerated.

Treatment with BAY 1213790 at a single i.v. dose of 0.06 mg/kg BW and higher significantly increased the activated partial thromboplastin time (aPTT). aPTT further increased with increasing dose of BAY 1213790. No effect on prothrombin time (PT) and bleeding time, measured with a Surgicutt test, was seen at doses up to 5.0 mg/kg BW. Pharmacokinetics of the compound showed C_{max} and AUC increased dose dependently after i.v. administration. The overall PK variability was low to moderate for AUC (geo. CV 12-33%) and low for C_{max}

(geo. CV 11-17%) in healthy male white subjects. The mean apparent terminal half-life was in the range of 700 to 800 h, which is approx. 30 days.

The safety and tolerability showed only a few cases of treatment emergent AEs that were mostly mild in nature. No severe AE or drug related SAE have been reported. No cases of bleeding have been reported. One adverse event of special interest was reported in the dose group of 0.6 mg/kg BW of BAY 1213790, this AE included feeling of warmth, nausea and vomiting. All symptoms stopped on the same day and the subject recovered completely without any sequelae. Overall, treatment with BAY 1213790 at single i.v. doses from 0.015 to 5.0 mg administered as infusion over 60 minutes was well tolerated and considered as safe.

The dose prediction based on preclinical data (disease models), data collected in Phase 1 (population PK and PD analysis) and *in silico* modeling anticipate that 0.3, 0.6, 1.2, and 1.8 mg/kg bodyweight will provide an effective reduction of VTE events, i.e. sufficient thromboprophylaxis for patients undergoing elective TKA in the current study.

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

Rationale of the study

It is well known that patients undergoing orthopedic surgery (total knee or hip replacement) have a high risk for VTE in the absence of thromboprophylaxis. BAY 1213790 has the potential to provide an efficacious VTE prevention treatment by targeting FXI with a favorable risk profile for unwanted bleeding. This Phase IIa study will for the first time investigate the safety and efficacy of BAY 1213790 in patients undergoing TKA.

Benefit-risk assessment

Venous thromboembolism (VTE) is a common, potentially fatal disorder that affects hospitalized and non-hospitalized patients, recurs frequently, is often diagnosed late, and results in long-term complications including chronic thromboembolic pulmonary hypertension (CTPH) and the post-thrombotic syndrome (PTS). Anticoagulation is the mainstay for prevention and treatment of VTE. Although anticoagulant therapy is highly effective, it is associated with an increased risk of bleeding. An ideal anticoagulant would provide effective prevention of thrombosis without the increased bleeding risk. Based on the results of relevant animal models, known cases of human factor XI deficiency, and from compounds with similar mode of action, BAY 1213790 is a promising new drug candidate with the potential to prevent thromboembolic events without substantially increasing the bleeding risk as observed with other available anticoagulation therapies. Potential risks like bleeding or hypersensitivity reactions will be closely monitored.

Overall, the potential benefits of this new treatment are expected to outweigh potential risks.

4. Study objectives

Primary objective:

- To assess the safety and efficacy of different doses of BAY 1213790 in comparison with those of enoxaparin in patients undergoing elective, primary, unilateral total knee arthroplasty (TKA)

Secondary objective:

- To compare the safety and efficacy of BAY 1213790 with those of apixaban

Exploratory objective:

- To assess the dose-response relationship of BAY 1213790 for efficacy and safety
- To characterize the pharmacokinetic and the pharmacodynamics profile of BAY 1213790 and the relationship between both

Other objective:

- To further characterize BAY 1213790 by evaluating additional PD markers
- To investigate the mechanism of thrombosis by analyzing additional PD markers

5. Study design

Design overview

This study is an open label, active comparator-controlled, randomized, multicenter study with observer-blinding of different doses of BAY 1213790, and it is to be conducted in patients undergoing elective, primary, unilateral total knee arthroplasty. The study will assess two different BAY 1213790 administration schemes, either drug administration after surgery (post-surgery administration part, A) or drug administration before surgery (pre-surgery administration part, B). All efficacy and safety parameters will be centrally adjudicated by a central independent adjudication committee (CIAC) which is blinded to treatment allocation. See Figure 5–1, Figure 5–2, and Figure 5–3.

Informed consent must be obtained before any study related activities are performed. After providing written informed consent, patients will undergo a screening evaluation to determine their eligibility. The screening evaluation will take place between Day -13 and Day 1 (which is the day prior to TKA) (see Section 9.2) (in case screening starts on Day 1, it is recommended to obtain the informed consent prior to Day 1 in order to provide the patient ample time and the opportunity to consider participation in this study).

Following Screening, eligible patients will be randomized on the last day of the Screening phase, Day 1. A total of 700 patients are planned be randomized with the possible extension to a maximum of up to 900 patients, in case of opening of additional BAY 1213790 arms or a high proportion of venographies of inadequate quality.

The 700 patients will be randomized to BAY 1213790 arms (3 observer-blinded doses with 100 patients in each arm during the post-surgery part (A) and 2 observer-blinded doses with

100 patients in each arm during the pre-surgery part (B)), or to the comparator arms (enoxaparin, apixaban; 100 patients in each arm). Randomization ratio will thus be 5:1:1 ([pooled] BAY 1213790 arms: enoxaparin: apixaban). In case additional BAY 1213790 arms are introduced (and none are closed), the randomization will be adapted in order to obtain balanced sample sizes across all BAY 1213790 arms and thus to have similar sample sizes between each of the BAY 1213790 arms and each of the comparator arms at the end of the study. Based on recommendations from the Steering Committee, the sample size for a specific dose of FXIa might be increased while reducing the sample size for another dose so that the planned total number of a maximum of 900 patients is not exceeded.

Eligible patients will be randomized to one of the following treatment arms:

Post-surgery administration part (A):

- BAY 1213790 0.3 mg/kg administered intravenously for at least 100 patients once, the day following TKA (after adequate hemostasis has been achieved, preferably in the morning, but not later than 24 hours after wound closure)
- BAY 1213790 0.6 mg/kg administered intravenously for at least 100 patients once, the day following TKA (after adequate hemostasis has been achieved, preferably in the morning, but not later than 24 hours after wound closure)
- BAY 1213790 1.2 mg/kg administered intravenously for at least 100 patients once, the day following TKA (after adequate hemostasis has been achieved, preferably in the morning, but not later than 24 hours after wound closure)
- enoxaparin 40 mg administered subcutaneously for at least 60 patients, started either in the evening before TKA or 6-8 hours after TKA (at investigator's discretion), followed by daily subcutaneous injections for at least 10 days and until venography is performed (Day 12+3) or
- apixaban 2.5 mg administered orally for at least 60 patients twice daily starting on the day after the TKA (within 12 to 24 hours after surgery) and at least for 10 days post-surgery and until the day venography is performed (Day 12+3). In case venography is performed on Day 12, one last dose of apixaban 2.5 mg is given in the evening of Day 12 to complete 10 days of treatment.

If recommended by the SC, or if randomization to one of the BAY 1213790 arms is prematurely stopped due to an unexpectedly high rate of thrombotic events, a fourth arm (1.8 mg/kg) may be initiated with up to 100 patients.

If randomization to one of the BAY 1213790 arms is prematurely stopped due to an unexpectedly high rate of bleeding events or due to the recommendation of the SC, patients still to be randomized may be distributed between the remaining dose arms.

After the evaluation of the primary endpoint of at least 75% of patients who underwent the post-surgery administration part (A) the IDMC will make a recommendation and the SC will then advise whether or not the pre-surgery administration part (B) will be initiated. The SC will also recommend on the adaption of the doses to be investigated in the pre-surgery administration setting (details are specified in the respective SC charter).

Pre-surgery administration part (B):

- BAY 1213790 0.3 mg/kg administered intravenously for at least 100 patients once in the second half of the pre-surgery day (Day 1), the day before TKA
- BAY 1213790 1.2 mg/kg administered intravenously for at least 100 patients once in the second half of the pre-surgery day (Day 1), the day before TKA
- enoxaparin 40 mg administered subcutaneously for at least 40 patients, started either in the evening before TKA or 6-8 hours after TKA (at investigator's discretion), followed by daily subcutaneous injections for at least 10 days and until venography is performed (Day 12+3) or
- apixaban 2.5 mg administered orally for at least 40 patients twice daily starting on the day after the TKA (at the latest 24 hours from wound closure) and at least for 10 days post-surgery and until the day venography is performed (Day 12+3)

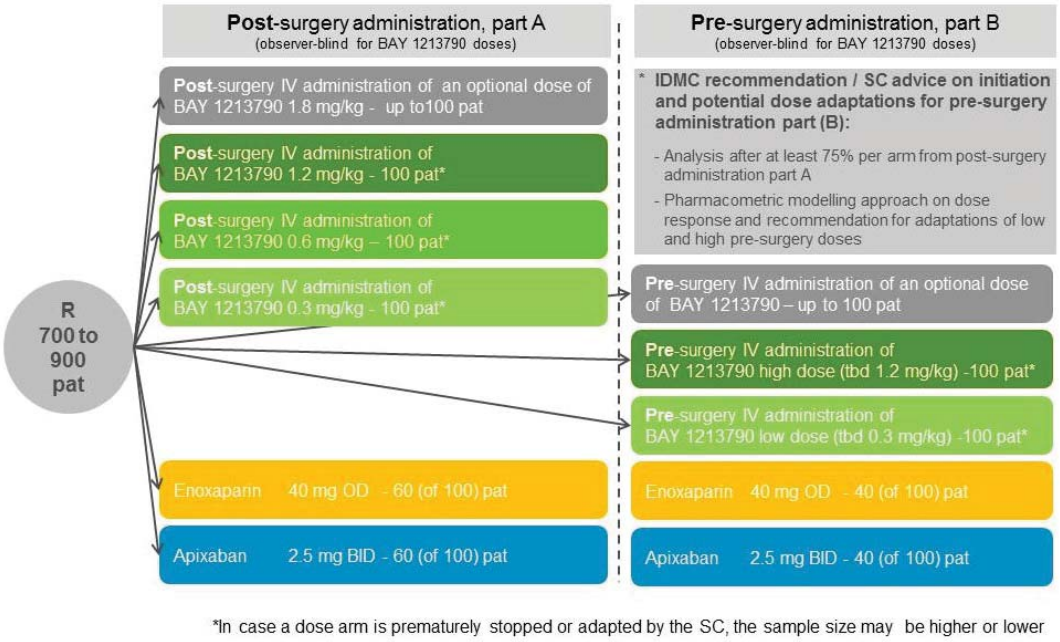
Before start of part B, the doses in the two BAY 1213790 arms might be selected differently, based on IDMC recommendation and SC advice after the evaluation of the primary endpoint of at least 75% of the patients who underwent the post-surgery administration part. The selected doses will be either 0.3, 0.6, 1.2, or 1.8 mg/kg.

If randomization to one of the BAY 1213790 arms, in the pre-surgery administration part (B), is prematurely stopped due to a high rate of thrombotic events or the recommendation of the SC, a third arm with a higher dose may be initiated with up to 100 patients. Possible doses of such dose arm depend on the IDMC recommendation/SC advice on the doses to be tested in the pre-surgery setting. Doses for this additional arm are either 0.6, 1.2, or 1.8 mg/kg.

If randomization to one of the BAY 1213790 arms is prematurely stopped due to the recommendation of the SC or due to a high rate of bleeding events, patients still to be randomized may be randomized to either the already started lower dose arm or to a newly initiated third dose arm with a lower dose than the one closed. Up to 100 patients may be randomized to this newly initiated dose arm. Possible doses of such arm depend on the IDMC recommendation/SC advice on doses to be tested in the pre-surgery setting. Doses for this additional BAY 1213790 arm are either 1.2mg/kg, 0.6 mg/kg or 0.3 mg/kg if not initially selected as starting doses for the pre-surgery administration part.

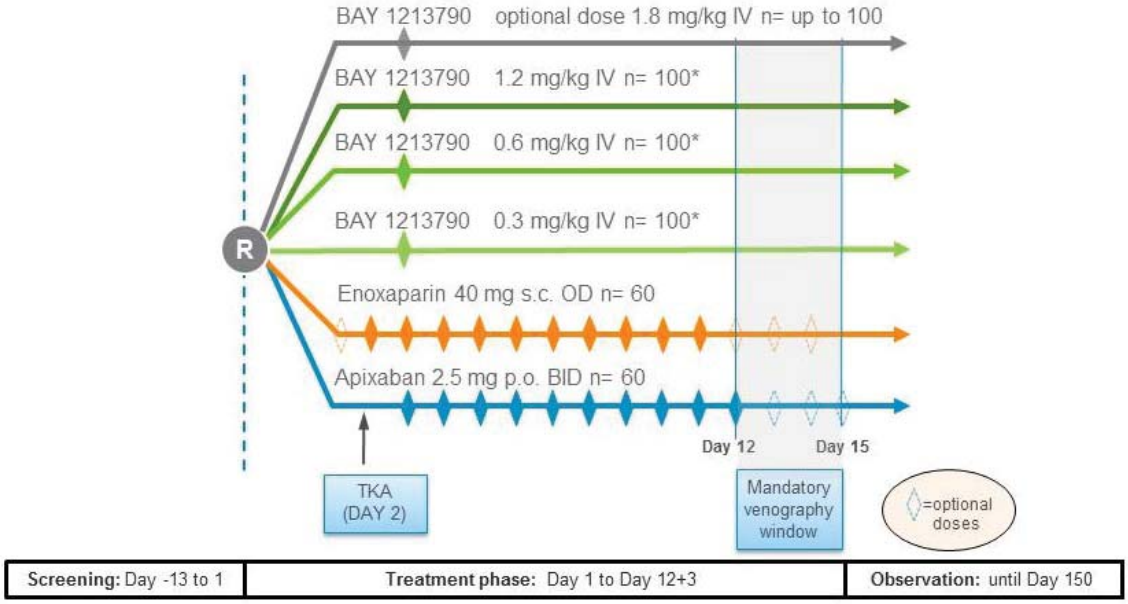
In general, the decision to stop randomization to one or more dose arms, adding a further dose arm or redistributing randomization to other dose arms is based on the recommendation by the IDMC and the advice given by the SC (details are specified in the respective IDMC and SC charters).

Figure 5–1: Planned study design post-surgery (part A) and pre-surgery (part B) administration parts



Abbreviations: BID = twice daily; IDMC = independent data monitoring committee; IV = intravenous; OD = once daily; pat = patients; R = randomization; tbd = to be determined; SC = steering committee

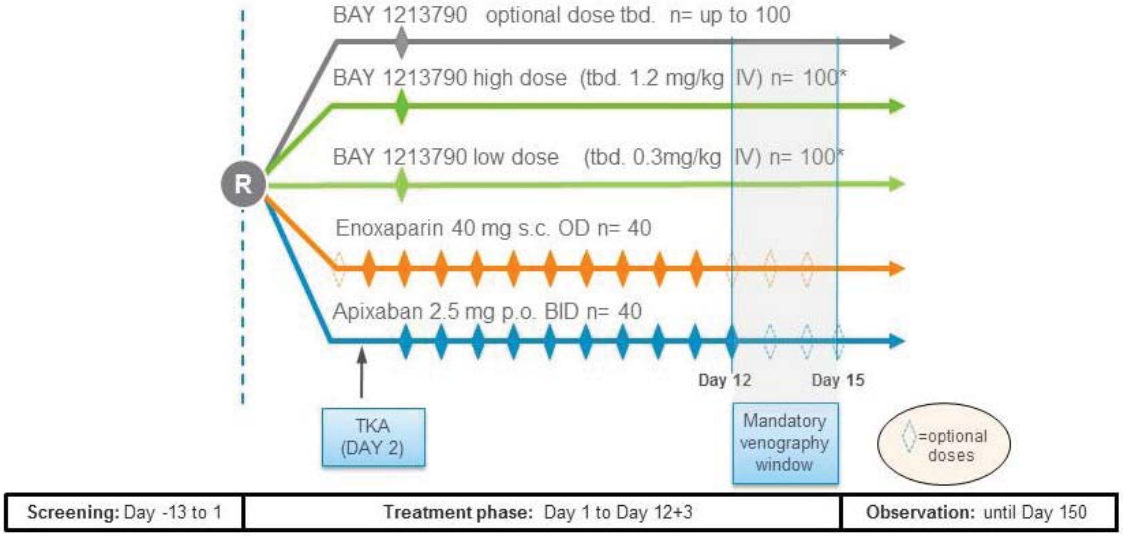
Figure 5–2: Planned study design post-surgery administration part (part A)



*In case a dose arm is prematurely stopped or adapted by the SC, the sample size may be higher or lower

Abbreviations: BID = twice daily; IV = intravenous; OD = once daily; p.o. = per os, orally; s.c. = subcutaneous; SC = steering committee; TKA = total knee arthroplasty

Figure 5–3: Planned study design pre-surgery administration part (part B)



*In case a dose arm is prematurely stopped or adapted by the SC, the sample size may be higher or lower

Abbreviations: BID = twice daily; IV = intravenous; OD = once daily; p.o. = per os, orally; tbd = to be determined; s.c. = subcutaneous; SC = steering committee; TKA = total knee arthroplasty

General aspects of the study

The results of at least 75% of patients, treated with BAY 1213790 in the post-surgery administration setting (A) and evaluated at least until the primary endpoint, will be used as the basis for the decision to initiate the pre-surgery administration part (B). The respective adjudicated venograms, safety and further efficacy data collected up to that point, will be made available to the independent data monitoring committee (IDMC) and the steering committee (SC) for evaluation. The SC will advise whether or not the pre-surgery administration part (B) may be initiated and recommend on the dose adaptations, i.e. the doses to be investigated in the pre-surgery administration setting (details are specified in the respective IDMC and SC charters). The transition from study part A to part B will be clearly defined and communicated to the study sites. The initiation of part B will only occur after randomization to part A is completed. No parallel recruitment to both parts is planned. This clear differentiation between the two study parts is important as different exclusion criteria with respect to allowed anesthesia for TKA (part A: spinal and general anesthesia allowed, part B only general anesthesia is allowed) need to be applied.

Based on recommendations from the steering committee, the sample size for a specific arm of FXIa might be increased or reduced so that the planned total number of a maximum of 900 patients is not exceeded.

On Day 2 all randomized patients will undergo total knee arthroplasty. Further study visits will be performed at Day 3, Day 4, Day 6±1 and Day 12+3. All patients will stay in the hospital until at least Visit 6 (Day 6±1). At Day 12+3, all asymptomatic patients will undergo bilateral X-ray contrast venography. If symptoms or signs of DVT or PE occur earlier and these events are objectively confirmed (by compression ultrasound (CUS), CT/MR venography or X-ray contrast venography for DVT; by ventilation/perfusion lung scintigraphy, spiral CT, or pulmonary angiography for PE), it is not mandatory to perform the bilateral contrast venography scheduled at Day 12+3.

After the end of treatment phase, all patients will enter a post-treatment observation phase that will last until Day 150±7. During this observation phase, no study medication will be administered. Post-treatment follow-up visits will be performed at Day 30±5, Day 90±7, and at Day 150±7.

Signs and symptoms of VTE will be closely monitored during the study. If detected, an objective confirmation will be required (X-ray contrast venography for DVT (preferred), or CUS, CT/MR venography and ventilation/perfusion lung scintigraphy, spiral computed tomography (sCT), or pulmonary angiography for PE).

Primary variables

- incidence of composite endpoint consisting of asymptomatic DVT; detected by mandatory bilateral venography; objectively confirmed symptomatic DVT, non-fatal PE, fatal PE, unexplained death for which PE cannot be excluded up to Visit 7 (Day 12+3)
- incidence of composite of major and clinically relevant non-major bleeding up to Visit 7 (Day 12+3)

Justification of the design

Patients undergoing orthopedic surgery (total knee arthroplasty or hip replacement) are at high risk of VTE in the absence of thromboprophylaxis (3). All current medications approved for VTE prevention during orthopedic surgery have an increased intrinsic bleeding risk. The selective inhibition of Factor XIa achieved by BAY 1213790 has the potential to prevent VTE with a very low risk for bleeding. It could therefore be a major advantage in this and other patient populations, specifically for those who are at high risk for bleeding events and in need of thromboprophylaxis.

In the first part of this study, BAY 1213790 will be administered once intravenously the day after surgery (post-surgery administration part, A), preferably in the morning. The three different doses of BAY 1213790 will be administered in a blinded manner for both study parts (post- and pre-surgery administration part) in order to reduce a potential assessment bias of primary efficacy and safety parameters with respect to doses of BAY 1213790. The post-surgery administration will provide initial assessment of the efficacy and safety of this new compound in an administration scheme, which minimizes the risk for peri-operative bleeding events as well as a potential biased assessment for such events. After at least 75% of patients have received their respective treatment, and safety and efficacy data up to at least the

primary endpoint assessment at day 12+3, has been evaluated by the IDMC/SC, these committees will provided guidance on the initiation of the pre-surgery administration part with infusion of BAY 1213790 the day before surgery. Starting treatment with BAY 1213790 the day before surgery during part B of the trial is acceptable considering the low risk of intraoperative bleeding expected with this new approach of anticoagulation and specifically as the risk for bleeding events has already been assessed during the post-surgery administration part (part A) of this study. Moreover, the inhibition of Factor XI for VTE prevention in patients undergoing TKA has already been shown to be safe when started prior to surgery in a recent trial using an antisense oligonucleotide (ISIS 416858) to inhibit the synthesis of Factor XI. In such trial a low incidence of bleeding was observed in patients undergoing TKA (14). The factor XI activity was on average 83% lower than the baseline value at the time of the surgery. It has also been shown that in low fibrinolytic activity tissues such as knee joint, severe reduction of factor XI activity, like the one observed in patients with severe factor XI deficiency, does not increase the incidence of bleeding (15). It is therefore anticipated that the administration of BAY 1213790 prior to the surgery will not significantly increase the bleeding risk. On the other hand, the thrombotic process is known to already start during surgery and therefore a preoperative initiation of anticoagulation may also be an advantage for the prevention of postoperative thromboembolism if the bleeding risk is acceptable (16).

The BAY 1213790 dose range, which will be tested in this study, is derived from preclinical data, experience gathered in healthy volunteers as well as from a systems pharmacology approach. Preclinical pharmacology experiments indicate a major antithrombotic effect, both in arterial and in venous thrombosis models, without significantly prolonged bleeding times or increased blood loss (17) (section 4.1.2.2 Investigator Brochure ver. 3.0). As exposure – response analyses of in-vitro coagulation markers showed comparable effects in rabbits and humans, disease model relevant plasma concentrations (showing thrombus weight reduction by approx. 20-50%) were translated into human doses by using observed human plasma concentrations over time. The dose prediction based on preclinical data (disease models), data collected in Phase 1 (population PK and PD analysis) and in-silico modeling anticipate that 0.3, 0.6, 1.2, and 1.8 mg/kg bodyweight will provide an effective reduction of VTE events, i.e. sufficient thromboprophylaxis for patients undergoing elective TKA in the current study. In addition, systems pharmacology has been used to verify preclinical translations. An established systems pharmacology model of the coagulation system that represents the biochemical coagulation cascade, platelets, tissue interaction and hemodynamics has been used to establish pharmacoequivalence between FXI reduction and FXIa inhibition (18). Reference ranges for FXI/FXIa inhibition levels to clinical effects were translated from the recently finished Phase 2 trial in the same population and surgery setting (14). The proposed doses are expected to deliver at least equivalent effects to 200 mg and 300 mg ISIS 416858 as observed in the respective trial. Several drugs are now approved for VTE prevention in patients undergoing total knee arthroplasty. Whilst LMWHs remain widely used, Factor Xa inhibitors are increasingly used for this indication. In order to compare BAY 1213790 with the current standard of care, two comparators were chosen for this study: one LMWH (enoxaparin) and one Factor Xa inhibitor (apixaban).

In this study, the treatment with enoxaparin will follow the recommendations included in the 2012 CHEST guidelines (3). The treatment will be started either before or after surgery (at

investigator's discretion) and continued for 10 to 14 days (i.e. until the venography is performed). The dose chosen is 40 mg once daily, a standard dose regimen approved for thromboprophylaxis in orthopedic surgery.

The second comparator, apixaban will be started on the day after the surgery (i.e. 12-24 hours after surgery) and continued at least for 10 days post-surgery and until the day venography is performed (Day 12+3), which is in line with most local labels.

Considering the different administration methods of the three drugs used in this study (i.v. for BAY 1213790, s.c. for enoxaparin and oral for apixaban), a blinded study was not deemed feasible. In order to reduce the potential bias linked to the open-label design, neither the investigator nor the patient will know which doses of BAY 1213790 are administered. Moreover, the study outcomes will be assessed by a blinded and central independent adjudication committee (CIAC).

End of study

The end of the study as a whole will be reached as soon as the last visit of the last patient has been reached in all centers in all participating countries (EU and non-EU).

Primary completion

The primary completion event for this study is achieved when all patients underwent full assessment at Visit 7 (primary endpoint assessment).

6. Study population

6.1 Inclusion criteria

1. Written informed consent signed prior any study specific procedures
2. Patients aged ≥18 years undergoing elective primary unilateral TKA
3. Women of non-childbearing potential defined as either surgically sterile (e.g., tubal occlusion such as bilateral tubal ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal. Women are considered post-menopausal if they have had 12 months of spontaneous amenorrhea accompanied by an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels > 40 mIU/mL. Males must be surgically sterile, abstinent or if engaged in sexual activity of child-bearing potential, the patient must be using an acceptable contraceptive method during the treatment phase and until the end of the post-treatment observation phase (for further information see Section 9.6.3.6).
4. Ability to understand and follow study related instructions

6.2 Exclusion criteria

1. High risk for clinically significant bleeding or any of the following conditions:
    - Anemia (Hb <10 g/dL in women, < 11 g/dL in men) at Screening
    - Platelet count at Screening < 150 x 10^9/L or history of heparin-induced thrombocytopenia
    - aPTT or PT (INR or Quick) > ULN at Screening
    - Hepatic disease associated with either: coagulopathy leading to a clinically relevant bleeding risk, or alanine aminotransferase (ALT) > 3x upper level of normal (ULN) or total bilirubin (TB) > 2x ULN with direct bilirubin > 20% of the total at Screening
    - Sustained uncontrolled hypertension (diastolic blood pressure ≥ 100 mmHg and/or systolic blood pressure ≥ 180 mmHg)
    - Brain, spinal, or ophthalmologic surgery (except cataract surgery) within 3 months prior to randomization
    - Known bleeding disorders
2. Prior deep vein thrombosis
3. Body weight above 135 kg
4. Creatinine clearance below 60 ml/min, calculated by MDRD formula at Screening
5. Recent (<6 months) myocardial infarction or ischemic stroke
6. Active cancer except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been curatively treated
7. Contraindication listed in the local label of the comparator treatments
8. Requirement for full dose anticoagulation or dual antiplatelet therapy (low dose of acetylsalicylic acid is allowed)
9. Anticipated use of intermittent pneumatic compression devices or electrical/mechanical muscle stimulators
10. Any severe allergy or contraindication to the use of contrast media
11. Previous assignment to the treatment during this study
12. Participation in another clinical study with an investigational medicinal products within 30 days prior to randomization or concomitant participation in another clinical study with investigational medicinal product(s)
13. Close affiliation with the study site: e.g. a close relative of the investigator, dependent person (e.g. employee or student of the study site)

Exclusion criteria for patients in the post-surgery part (A):

14. Epidural analgesia after surgery

Exclusion criteria for patients in the pre-surgery part (B):

15. TKA under regional anesthesia, i.e. spinal or epidural anesthesia (only general anesthesia is allowed) and epidural analgesia.

The selection criteria were chosen to exclude (from the study) the patients who may potentially be exposed to specific risks after administration of the test drug or the comparators, along with all patients with conditions that may have an impact on the objectives of the study.

6.3 Withdrawal of patients from study

6.3.1 Withdrawal

Withdrawal criteria

In this study all efforts must be taken to engage patients to comply with all study procedures and to continue to be followed until the end of the study.

Patients *must be* withdrawn from **treatment** if the following occurs:

- If, in the investigator's opinion, continuation would be harmful to the patient's well-being

In addition, patients treated ***with enoxaparin*** must be withdrawn from treatment if the following occurs:

- Confirmed decrease of the platelet count to a value below 50% of the baseline value (see section 9.7.4).

Patients *may* be withdrawn from **treatment** if any of the following occurs:

- Any investigational drug other than the study drug is used
- Any suspected drug-related AE or SAE
- If any exclusion criterion applies during treatment

In general, patients who permanently discontinue study treatment are expected to continue to attend all protocol-specified study visits, and should be encouraged to perform all assessments described in the visit schedule (see Section 9.1) and provide information about their health status.

If a patient permanently discontinues study medication 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 patient.

Patients *must* be withdrawn from the **study** if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.

Patients *may* be withdrawn from the **study** if any of the following occurs:

- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well-being
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

Depending on the time point of withdrawal, a withdrawn patient is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A patient who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure".

Re-starting the defined set of screening procedures to enable the "screening failure" patient's participation at a later time point is not allowed – with the following exceptions:

- The patient had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).

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

Dropout

A patient who, for any reason, terminates the study before randomization is regarded a "screening failure".

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already been randomized.

General procedures

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Any patient removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Details for the premature discontinuation visit are provided in Section 9.2.1.3.4. Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12 (Premature termination of the study).

6.3.2 Replacement

No patients will be replaced.

6.4 Patient identification

After a patient has signed an informed consent form (ICF), the unique patient identification number (SID) for each patient will be provided to the investigators via IxRS (interactive voice response system/ interactive web response system). If a patient is re-screened, a new SID will be assigned. The patient number is a 9-digit number consisting of:

Digits 1 to 5 = Unique site number

Digits 6 to 9 = Unique patient number (Current patient number within the study site)

7. Treatments

7.1 Treatments to be administered

BAY 1213790 is a monoclonal antibody targeting the activated factor XI (XIa). It will be provided as a lyophilisate which will be reconstituted on study site for an infusion. Each vial will contain 110 mg of BAY 1213790 and the extractable amount of BAY 1213790 is 100 mg. The reconstituted BAY 1213790 solution will be diluted with 0.9% sterile NaCl and will be administered as a single dose intravenous infusion by infusion pump over approximately 60 min.

Further details on test drug preparation, reconstitution, and administration as well as procedures to ensure the observer-blinding with regards to BAY 1213790 doses will be provided in the site instructions (e.g. Site Manual, Pharmacy manual).

Enoxaparin 40 mg is a low molecular weight heparin that comes in pre-filled syringes containing enoxaparin sodium 40 mg in 0.4 mL of water. These syringes are for single use and should be administered subcutaneously once daily.

Apixaban 2.5 mg film-coated tablets, i.e. ELIQUIS® 2.5 mg film-coated tablets, contain 2.5 mg of the Factor Xa inhibitor apixaban and should be administered orally twice daily.

7.2 Identity of study treatment

The details of BAY 1213790 and comparators are given in Table 7–1, Table 7–2, and Table 7–3.

Table 7–1: Identity of test drug (BAY 1213790 lyophilisate)

Generic name / brand name / INN	BAY 1213790
Sponsor's substance code	BAY 1213790
Galenical form/ formulation / vehicle and reconstitution, if applicable	Lyophilisate for reconstitution / water for injection / IV solution
Strength (amount of drug per unit) or concentration	25 mg/ml
Composition (excipients of the formulation)	Active ingredient: BAY 1213790 Other ingredients: glycine, L-histidine, trehalose dihydrate, polysorbate 80, hydrochloric acid 10%, water
Type of packaging and content	10 ml glass vial for injection containing 110 mg BAY 1213790 solution as lyophilisate; extractable amount of BAY 1213790 solution as lyophilisate is 100 mg

Table 7–2: Identity of enoxaparin

Generic name / brand name / INN	Enoxaparin sodium
Sponsor's substance code	n.a.
Galenical form/ formulation / vehicle and reconstitution, if applicable	Solution for injection
Strength (amount of drug per unit) or concentration	40 mg / 0.4 ml
Composition (excipients of the formulation)	Please refer to Product information
Type of packaging and content	Prefilled syringes containing enoxaparin sodium 40 mg/0.4 ml, solution for injection

Table 7–3: Identity of apixaban

Generic name / brand name / INN	Apixaban / Eliquis
Sponsor's substance code	n.a.
Galenical form/ formulation / vehicle and reconstitution, if applicable	Tablet
Strength (amount of drug per unit) or concentration	2.5 mg
Composition (excipients of the formulation)	Please refer to Product Information
Type of packaging and content	Blisters containing Eliquis tablets 2.5 mg

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies QA group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

7.3 Treatment assignment

Patients will be randomized in a ratio of 5:1:1 to BAY 1213790, enoxaparin, and apixaban by an IxRS system. If one of the arms is prematurely stopped and/or an additional BAY 1213790 arm is opened, the randomization ratio will be adjusted to reflect this accordingly. Patients randomized to BAY 1213790 will be randomized by the IxRS in a second step to the different dose arms.

Post-surgery administration part (A): Patients randomized to BAY 1213790 will be randomized in a 1:1:1 ratio to one of the three arms. If one of the arms is prematurely stopped and/or an additional BAY 1213790 arm is opened, the randomization ratio will be adjusted to reflect this.

Pre-surgery administration part (B): Patients randomized to BAY 1213790 will be randomized in a 1:1 ratio to one of the two arms. If one of the arms is prematurely stopped and/or an additional BAY 1213790 arm is opened, the randomization ratio will be adjusted to reflect this.

7.4 Dosage and administration

Following a Screening visit, eligible patients will be randomized within 14 days.

Post-surgery administration part (A):

- BAY 1213790 0.3 mg/kg administered intravenously once, the day following the TKA, (after adequate hemostasis has been achieved, preferably in the morning, but not later than 24 hours after wound closure) or
- BAY 1213790 0.6 mg/kg administered intravenously once, the day following the TKA, (after adequate hemostasis has been achieved, preferably in the morning, but not later than 24 hours after wound closure) or
- BAY 1213790 1.2 mg/kg administered intravenously once, the day following the TKA, (after adequate hemostasis has been achieved, preferably in the morning but not later than 24 hours after wound closure) or enoxaparin 40 mg administered subcutaneously, started either in the evening before TKA or 6-8 hours after TKA (at investigator's discretion), followed by daily subcutaneous injections for at least 10 days and until venography is performed (Day 12+3) or
- apixaban 2.5 mg administered orally twice daily starting on the day after the TKA (at the latest 24 hours from wound closure) and for at least 10 days post-surgery and until the day venography is performed (Day 12+3). In case venography is performed on

Day 12, one last dose of apixaban 2.5 mg is given in the evening of Day 12 to complete 10 days of treatment.

If recommended by the SC, a fourth BAY 1213790 arm may be introduced into the study (see Section 5).

BAY 1213790 1.8 mg/kg administered intravenously once the day following the TKA, (after adequate hemostasis has been achieved, preferably in the morning, but not later than 24 hours after wound closure). All BAY 1213790 doses will be administered intravenously on Day 1 by means of an infusion pump (details can be found in the Site Manual). Given the long half-life of BAY 1213790, no further doses will be administered in patients randomized to BAY 1213790 arms.

Pre-surgery administration part (B):

Following the assessment of the primary endpoint of at least 75% of all patients, and provision of a summary to IECs/IRBs as well as local authorities for either notification or approval, the pre-surgery administration part of the study may be initiated and will be guided by the recommendation of the IDMC and advice of the SC. Randomization to the pre-surgery administration part (B) will only start after randomization to the post-surgery administration part (A) has been completed.

- BAY 1213790 0.3mg/kg administered intravenously once in the second half of the pre-surgery day (Day 1), the day before TKA
- BAY 1213790 1.2 mg/kg administered intravenously once in the second half of the pre-surgery day (Day 1), the day before TKA
- enoxaparin 40 mg administered subcutaneously, started either in the evening before TKA or 6-8 hours after TKA (at investigator's discretion), followed by daily subcutaneous injections for at least 10 days and until venography is performed (Day 12+3) or
- apixaban 2.5 mg administered orally twice daily starting on the day after the TKA (at the latest 24 hours from wound closure) and at least for 10 days post-surgery and until the day venography is performed (Day 12+3). In case venography is performed on Day 12, one last dose of apixaban 2.5 mg is given in the evening of Day 12 to complete 10 days of treatment.

If recommended by the SC, a third BAY 1213790 arm may be introduced into the study (see Section 5). Doses for this additional arm are either 0.6, 1.2, or 1.8 mg/kg.

Enoxaparin will be provided as 0.4 mL syringes containing 40 mg of enoxaparin sodium (corresponding to 4000 I.U. of anti-Xa activity). Enoxaparin 40 mg will be administered through a subcutaneous injection once daily, at approximately the same time every day. Treatment will either start in the evening of the pre-surgery day (Day 1), or 6-8 hours after the TKA (at investigator's discretion), and continue with daily subcutaneous injections for at least 10 days and until venography is performed (Day 12+3). No dose modification for enoxaparin for the prevention of VTE under this protocol will be possible during the study.

If a dose of enoxaparin 40 mg is missed, the missed dose should be administered as soon as possible (unless next scheduled dose is within 12 hours). If the missed dose is identified less than 12 hours prior to the next scheduled dose, the missed dose should be skipped and the next dose should be taken as scheduled.

Apixaban 2.5 mg film-coated tablets will each contain 2.5 mg of the Factor Xa inhibitor apixaban. Apixaban 2.5 mg will be administered orally twice daily, starting on the day after surgery (Day 3) and at least 10 days post-surgery and until the day venography is performed (Day 12+3). No dose modification for apixaban for the prevention of VTE under this protocol will be possible during the study.

If a tablet of apixaban 2.5 mg is missed, the missed dose should be administered as soon as possible (unless next scheduled dose is within 6 hours). If the missed dose is identified less than 6 hours prior to the next scheduled dose, the missed dose should be skipped and the next dose should be taken as scheduled.

For a justification of the selected doses, please refer to Section 5.

7.5 Blinding

This study is open-label for assignment to treatment and observer-blinded for the different BAY 1213790 doses. The respective dose of BAY 1213790 in either study part (A or B) will not be known to the patient, the investigator and other study site staff, with the exception of specifically dedicated unblinded site personnel responsible for the handling of the test drug.

7.5.1 Blinding measures

Only patients, investigators and all other site staff will remain blinded for the administered BAY 1213790 dose with the exception of the unblinded pharmacist or specifically dedicated site personnel. The blind will last until final database lock (after LPLV) and authorization of data release according to standard operating procedures.

The unblinded pharmacist and/or other dedicated site personnel, appropriately delegated by the investigator at each study site, will be responsible for maintaining the integrity of the blind. Unblinded site personnel will be responsible for handling, of the study drug, but otherwise have no involvement in the study. Appropriate training will be given to the site personnel to avoid any unblinding.

Independent of final concentration, reconstituted BAY 1213790 solution will be identical in appearance (color, turbidity), therefore no further blinding measures are necessary after the solution for infusion has been prepared.

7.5.2 Unblinding

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction (SUSAR, see Section 9.6.1.4) related to the blinded treatment dose, the patient's treatment code will usually be unblinded before reporting to the health authorities,

ethic committees and investigators. Notifications of ethic committees and investigator will be done according to all applicable regulations (see Section 9.6.1.4).

7.5.3 Emergency unblinding by the investigator

In the event of an emergency or any finding that requires unblinding of BAY 1213790 dose, the investigator may break the blind for an individual patient via the IxRS according to the unblinding procedure outlined in the Site Manual.

The code can be broken by the investigator when knowledge of the patient's treatment dose is required for the clinical management of the patient. If it becomes necessary during the study to know the individual treatment dose, and thus to break the code for that patient, the date and reason for unblinding are to be recorded on the relevant eCRF page. The investigator must promptly document and explain to the sponsor any premature unblinding (e.g. unblinding due to an SAE) of BAY 1213790 dose.

7.6 Drug logistics and accountability

All study drugs will be stored at the study site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. The responsible site personnel will confirm receipt of study drug via IxRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

7.7 Treatment compliance

To monitor compliance, a drug accountability log will be completed for each patient.

Patients randomized to comparator arms will be instructed to take study drug as scheduled, and to return all of the study drug packaging including unused study drug and empty packaging.

Any discrepancies between actual and expected amount of returned study medication must be discussed with the patient at the time of the visit, and any explanation must be documented in the source records.

8. Non-study therapy

8.1 Prior and concomitant therapy

All concomitant medications administered between signing of the informed consent and the end of post-treatment observation phase (Visit 10) must be documented in the eCRF. Medications influencing coagulation or platelet aggregation even if taken before the informed consent was signed should also be recorded in the eCRF.

Prior and concomitant medications not allowed during the study are:

- Antiplatelets (e.g. clopidogrel, ticagrelor, dipyridamole, acetylsalicylic acid >100 mg/day) should be stopped at least 7 days prior to start of study treatment and are prohibited until the end of the treatment phase. Patients who cannot stop acetylsalicylic acid >100 mg/day or any other antiplatelet treatment at least 7 days prior to start of study treatment have to be excluded from the study.
- Vitamin K antagonists (e.g. phenprocoumon, warfarin-sodium) have to be stopped at least 7 days prior to start of study treatment and are prohibited until the end of the treatment phase.
- Unfractionated heparins, LMWH, direct oral anticoagulants (e.g. rivaroxaban, non-study apixaban, dabigatran) and any other drugs influencing coagulation have to be stopped prior to randomization, according to the time frame given in their respective labelling, and are prohibited until the end of the treatment phase.
- NSAIDs should be stopped at least 7 days prior to start of study treatment and recommended not to be used more than 3 consecutive days in a row until the end of the study treatment phase. When use of NSAIDs is necessary during study treatment, the concomitant use of proton-pump inhibitors is recommended.
- Strong inhibitors of both CYP3A4 and P-gp, such as azole antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir) that are given systemically should be stopped at least 7 days prior to start of study treatment and are prohibited until end of study treatment phase.
- Strong inducers of both CYP3A4 and P-gp, such (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) that are given systemically should be stopped at least 7 days prior to start of study treatment and are prohibited until end of study treatment phase.

TKA may be performed under spinal, epidural or general anaesthesia during the post-surgery administration part (A) and only under general anaesthesia during the pre-surgery administration part (B). For patients on BAY 1213790, further use of spinal or epidural anesthesia is not allowed during the study (i.e. during the treatment phase and during the post-treatment observation phase). For patients on enoxaparin and apixaban, the use of spinal and epidural anesthesia is not allowed during the treatment phase (until Day 12+3). Moreover, the local labels for the respective drugs should be followed.

The use of intermittent pneumatic compression devices and electrical/mechanical muscle stimulators is not allowed during the study (treatment phase and post-treatment observation phase). The use of compression stockings is allowed.

See also Section 6.2

During the post-treatment observation phase, if deemed necessary by the investigator, the use of antiplatelets and anticoagulants is allowed.

In cases of symptomatic DVT or PE, confirmed by objective testing at the Investigator site, anticoagulants at therapeutic doses may be started at the Investigator's discretion if deemed necessary.

However, considering the long half-life of BAY 1213790, caution and adequate monitoring should be considered in patients who were treated with the test drug.

The use of monoclonal antibodies is not recommended during the study.

8.2 Post-study therapy

No further access to study drug will be provided after end of treatment.

9. Procedures and variables

9.1 Tabular schedule of evaluations

9.1.1 Post-surgery schedule of activities and evaluations, part A

Table 9–1: Schedule of evaluations for patients in the post-surgery part (A)

Trial phases		Screening	Treatment phase								Post treatment observation phase			
	Visit number	1	2	3		4		5	6	7	8	9	10	PDC
	Visit day and window	Day - 13 to 1[a]	Day 1[a]	Day 2		Day 3		Day 4	Day 6±1[d]	Day 12+3	Day 30±5	Day 90±7	Day 150±7	
				Pre TKA	Post TKA	Pre[b] Study drug administration BAY 1213790 Apixaban Enoxaparin	Post[c] Study drug administration BAY 1213790 Apixaban							
Post-surgery administration part (A)	Informed consents specific for ***post-surgery* administration part** and for optional PG research if applicable	●[e]												
	In-/exclusion criteria	●	●											
	Demographic data	●												
	Medical history	●												
	Prior and concomitant medication	Continuous reporting												

Trial phases		Screening	Treatment phase								Post treatment observation phase			
	Visit number	1	2	3		4		5	6	7	8	9	10	PDC
	Visit day and window	Day - 13 to 1[a]	Day 1[a]	Day 2		Day 3		Day 4	Day 6±1[d]	Day 12+3	Day 30±5	Day 90±7	Day 150±7	
				Pre TKA	Post TKA	Pre[b] Study drug administration BAY 1213790 Apixaban Enoxaparin	Post[c] Study drug administration BAY 1213790 Apixaban							
Post-surgery administration part (A)	Adverse events	Continuous reporting												
	Weight and height	●												
	Physical examination	●												
	Vital signs[f]	●	●	●	●	●	●	●	●	●[k]	●	●	●	●
	12-lead ECG	●							●					
	Local laboratory: serum pregnancy test in females	●												
	Local safety laboratory: incl. aPTT, PT, creatinine, ALT, bilirubin, platelets, Hb	●[g]												
	Central laboratory: safety analysis[h]		●			●			●	●[k]	●	●	●	●
	Central laboratory: PK blood sample **(BAY 1213790 arms only)**[u]					●	●[i]	●	●	●[k]	●	●	●	●

Trial phases		Screening	Treatment phase								Post treatment observation phase			
	Visit number	1	2	3		4		5	6	7	8	9	10	PDC
	Visit day and window	Day - 13 to 1[a]	Day 1[a]	Day 2		Day 3		Day 4	Day 6±1[d]	Day 12+3	Day 30±5	Day 90±7	Day 150±7	
				Pre TKA	Post TKA	Pre[b] Study drug administration BAY 1213790 Apixaban Enoxaparin	Post[c] Study drug administration BAY 1213790 Apixaban							
Post-surgery administration part (A)	Central laboratory: anti-drug-antibody blood sample[u] **(BAY 1213790 arms only)**					●				●[k]	●	●	●	●
	Central laboratory: D-dimer blood sample[u]		●			●			●[r]	●[k]	●			●
	Central laboratory: PD blood sample for exploratory analysis[u]		●			●	●[i]	●[r]	●[r]	●[k]	●	●	●	●
	Central laboratory: PD blood sample[s,u]		●			●	●[i]	●[r]	●[r]	●[k]	●	●	●	●
	Central laboratory: blood sample for optional pharmacogenetic test		●[m]											
	Central laboratory: blood sample for FVIII/ FIX activity/ FXII activity/ vWF antigen/ ristocetin cofactor (i.e. vWF) activity		●											

Trial phases		Screening	Treatment phase								Post treatment observation phase			
	Visit number	1	2	3		4		5	6	7	8	9	10	PDC
	Visit day and window	Day - 13 to 1[a]	Day 1[a]	Day 2		Day 3		Day 4	Day 6±1[d]	Day 12+3	Day 30±5	Day 90±7	Day 150±7	
				Pre TKA	Post TKA	Pre[b] Study drug administration BAY 1213790 Apixaban Enoxaparin	Post[c] Study drug administration BAY 1213790 Apixaban							
Post-surgery administration part (A)	IxRS	●	●								●			●[v]
	Enoxaparin s.c.[n]		●		●[z]	Once daily administration until venography								
	Primary TKA surgery			●										
	BAY 1213790 (Anti-FXIa antibody) i.v.					●[p]								
	Apixaban p.o.[n]					Twice daily administration until the day of venography								
	Drug accountability		Continuous reporting[q]											●[v]
	Study outcomes		Continuous reporting											
	Bilateral venogram and adjudication package									●				

Abbreviations: ALT = alanine amonitransferase; aPTT = activated partial thromboplastin time; ECG = electrocardiogram; Hb = hemoglobin; i.v. = intravenous; IxRS = interactive voice / web response system; PD = pharmacodynamics; PDC = premature discontinuation; PG = pharmacogenomis; PK = pharmacokinetics; p.o. = per os, orally; PT = prothrombin time; TKA = total knee arthroplasty; vWF = von Willebrand factor

[a] Screening period covers up to 14 days (From Day -13 until Day +1). No Day 0 will occur
[b] Following assessments will be done for patients in BAY 1213790 arm, enoxaparin arm, and apixaban arm
[c] Following assessments will be done only for patients in BAY 1213790 arm and in apixaban arm
[d] Mandatory in hospital stay between days 1 and 6±1
[e] Informed consent for optional pharmacogenetic research can be obtained at any visit
[f] If screening (Visit 1) and randomization (Visit 2) are performed on the same day, vital signs can be assessed only at screening
[g] Obtain blood sample for local safety laboratory if there are no available results collected within 14 days prior to randomization
[h] Chemistry, hematology, urinalysis
[i] For BAY 1213790: Obtain after end of infusion (up to 2h) via new puncture and from opposite arm;
Apixaban (only relevant for PD blood samples): approximately after 2 hours of administration
[k] Before venography
[m] Possible at any other study visit, provided separate informed consent is signed prior to sampling
[n] Enoxaparin 40 mg administered s.c. started either before or after surgery and continued with daily injections until venography is performed,
Apixaban 2.5 mg administered p.o. twice daily starting on the day after the TKA (no later than 24 hours after wound closure) and for at least 10 days post-surgery and until the day venography is performed. In case venography is performed on Day 12, one last dose of apixaban 2.5 mg is given in the evening of Day 12 to complete 10 days of treatment
[p] BAY 1213790 the day following the TKA (after adequate hemostasis has been achieved, preferably in the morning, but not later than 24 hours after wound closure)
[q] If applicable
[r] Take sample before administering the next dose of enoxaparin or apixaban
[s] aPTT, PT, FXI concentration and FXI activity
[u] Take PK (if BAY 1213790) and all PD samples at the same timepoint
[v] If premature discontinuation occurs prior to Visit 7
[z] 6 to 8 hours after surgery

See further details on schedule of evaluations from Site Manual.

9.1.2 Pre-surgery schedule of evaluations, part B

Table 9–2: Schedule of evaluations for patients in the pre-surgery part (B)

	Trial phases	Screening	Treatment phase							Post treatment observation phase			
	Visit number	1	2		3		4	5	6	7	8	9	10	PDC
	Visit day and window	Day - 13 to 1[a]	Day 1[a]		Day 2		Day 3	Day 4	Day 6±1[d]	Day 12+3	Day 30±5	Day 90±7	Day 150±7	
			Pre-study[b] drug administration For all treatment arms	Post-study[c] drug administration BAY 1213790 only	Pre TKA	Post TKA								
Pre-surgery administration part (B)	Informed consents specific for ***pre-surgery* administration part** and for optional PG research if applicable	●[e]												
	In-/exclusion criteria	●	●											
	Demographic data	●												
	Weight and height	●												
	Medical history	●												
	Prior and concomitant medication	Continuous reporting												
	Adverse events	Continuous reporting												

	Trial phases	Screening	Treatment phase								Post treatment observation phase			
	Visit number	1	2		3		4	5	6	7	8	9	10	PDC
	Visit day and window	Day - 13 to 1[a]	Day 1[a]		Day 2		Day 3	Day 4	Day 6±1[d]	Day 12+3	Day 30±5	Day 90±7	Day 150±7	
			Pre-study[b] drug administration For all treatment arms	Post-study[c] drug administration BAY 1213790 only	Pre TKA	Post TKA								
Pre-surgery administration part (B)	Physical examination	●												
	Vital signs[f]	●	●	●	●	●	●	●	●	●[k]	●	●	●	●
	12-lead ECG	●							●					
	Local laboratory: serum pregnancy test in females	●												
	Local safety laboratory: incl. aPTT, PT, creatinine, ALT, bilirubin, platelets, Hb	●[g]												
	Central laboratory: safety analysis[h]		●				●		●	●[k]	●	●	●	●
	Central laboratory: PK blood sample **(BAY 1213790 arms only)**[u]		●	●[i]	●	●[o]	●		●	●[k]	●	●	●	●

	Trial phases	Screening	Treatment phase								Post treatment observation phase			
	Visit number	1	2		3		4	5	6	7	8	9	10	PDC
	Visit day and window	Day - 13 to 1[a]	Day 1[a]		Day 2		Day 3	Day 4	Day 6±1[d]	Day 12+3	Day 30±5	Day 90±7	Day 150±7	
			Pre-study[b] drug administration For all treatment arms	Post-study[c] drug administration BAY 1213790 only	Pre TKA	Post TKA								
Pre-surgery administration part (B)	Central laboratory: anti-drug-antibody blood sample **(BAY 1213790 arms only)**[u]		●							●[k]	●	●	●	●
	Central laboratory: D-dimer blood sample[u]		●			●[o,r]			●[r]	●[k]	●			●
	Central laboratory: PD blood sample for exploratory analysis[u]		●	●[i]	●	●[o,r]	●[r]		●[r]	●[k]	●	●	●	●
	Central laboratory: PD blood sample [s,u]		●	●[i]	●	●[o,r]	●[r]		●[r]	●[k]	●	●	●	●
	Central laboratory: blood sample for optional pharmacogenetic test		●[m]											

	Trial phases	Screening	Treatment phase								Post treatment observation phase			
	Visit number	1	2		3		4	5	6	7	8	9	10	PDC
	Visit day and window	Day - 13 to 1[a]	Day 1[a]		Day 2		Day 3	Day 4	Day 6±1[d]	Day 12+3	Day 30±5	Day 90±7	Day 150±7	
			Pre-study[b] drug administration For all treatment arms	Post-study[c] drug administration BAY 1213790 only	Pre TKA	Post TKA								
Pre-surgery administration part (B)	Central laboratory: blood sample for FVIII/ FIX activity/ FXII activity/ vWF antigen/ ristocetin cofactor (i.e. vWF) activity		●											
	IxRS	●	●								●			●[v]
	BAY 1213790 (Anti-FXIa antibody i.v.)		●[p]											
	Enoxaparin s.c.[n]		●			●[z]	Once daily administration until venography							
	Primary TKA surgery				●									
	Apixaban p.o.[n]						Twice daily administration until the day of venography							
	Drug accountability		Continuous reporting[q]											●[v]
	Study outcomes		Continuous reporting											
	Bilateral venogram and adjudication package									●				

Abbreviations: ALT = alanine amonitransferase; aPTT = activated partial thromboplastin time; ECG = electrocardiogram; Hb = hemoglobin; i.v. = intravenous; IxRS = interactive voice / web response system; PD = pharmacodynamics; PDC = premature discontinuation; PG = pharmacogenomis; PK = pharmacokinetics; p.o. = per os, orally; PT = prothrombin time; TKA = total knee arthroplasty; vWF = von Willebrand factor

[a] Screening period covers up to 14 days (From Day -13 until Day +1). No Day 0 will occur
[b] Following assessments will be done for patients in BAY 1213790 arm, enoxaparin arm, and apixaban arm
[c] Following assessments will be done only for patients in BAY 1213790 arm
[d] Mandatory in hospital stay between days 1 and 6±1
[e] Informed consent for optional pharmacogenetic research can be obtained at any visit
[f] If screening (Visit 1) and randomization (Visit 2) are performed on the same day, vital signs can be assessed only at screening
[g] Obtain blood sample for local safety laboratory if there are no available results collected within 14 days prior to randomization
[h] Chemistry, hematology, urinalysis
[i] For BAY 1213790: Obtain after end of infusion (up to 2h) via new puncture and from opposite arm
[k] Before venography
[m] Possible at any other study visit, provided separate informed consent is signed prior to sampling
[n] Enoxaparin 40 mg administered s.c. started either before (optional, at the discretion of the investigator) or after surgery and continued with daily injections until venography is performed,
Apixaban 2.5 mg administered p.o. twice daily starting on the day after the TKA (no later than 24 hours after wound closure) and for at least 10 days post-surgery and until the day venography is performed. In case venography is performed on Day 12, one last dose of apixaban 2.5 mg is given in the evening of Day 12 to complete 10 days of treatment.
[o] 3 to 6 hours after surgery
[p] BAY 1213790 administered in the second half of the pre-surgery day
[q] If applicable
[r] Take sample before administering study drug
[s] aPTT, PT, FXI concentration and FXI activity
[u] Take PK (if BAY 1213790) and all PD samples at the same timepoint
[v] If premature discontinuation occurs prior to Visit 7
[z] 6 to 8 hours after surgery

See further details on schedule of evaluations from Site Manual.

9.2 Visit description

Before any study-specific examination takes place, potentially eligible patients will be given a full explanation as to what the study would involve. This will be done both verbally and in writing in the form of a written subject informed consent form (ICF). Patients will be given sufficient time to consider their participation in the study and to ask any questions concerning the study. Patients who are willing to take part in the study will then be asked to sign an informed consent form. The signed informed consent form must be available before any study-specific procedure will be performed.

Although study visits should occur as close as possible to the time points specified in the protocol, a time frame of ±1 days is allowed for Visit 6, +3 days is allowed for Visit 7 and ±5 days is allowed for Visit 8, and a time frame of ±7 days is allowed for Visit 9 and Visit 10. All visit assessments should be performed on a single day, except for the screening visit which may include procedures on several days. Screening and randomization are allowed to be performed at the same day (Day 1). Screening period covers up to 14 days (From Day -13 until Day +1). No Day 0 will occur. If the patient prematurely discontinues the treatment phase, the premature discontinuation visit should be performed as soon as possible after the premature permanent discontinuation of study drug.

9.2.1 Post-surgery visit descriptions, part A

9.2.1.1 Visit 1 (Day -13 to 1), Screening

The following procedures and assessments will be performed during the Screening Visit:

- Obtain the signed and dated Informed Consent prior to any study specific procedures (enrollment in the study is defined as the signing of the Informed Consent) (see Section 13.4)
- Obtain Informed Consent to optional pharmacogenetic research (can be obtained at any visit, but in any case before the pharmacogenetic sample is drawn)
- Register the patient in IxRS to allocate unique patient identification number (see Section 6.4)
- Collect demographic information (see Section 9.3.1)
- Record the medical history (see Section 9.3.2)
- Record prior and concomitant medications (see Section 8.1)
- Record weight and height
- Perform physical examination (see Section 9.6.3.2)
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Obtain 12-lead ECG in supine position, after the patient rested for at least 5 minutes (see Section 9.6.3.3)

- Perform local serum pregnancy test in females
- Perform local safety laboratory including aPTT, PT, creatinine, ALT, bilirubin, platelets, and Hb if prior values are not available within 14 days prior to randomization
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Assess all inclusion and exclusion criteria for eligibility (see Sections 6.1 and 6.2)

9.2.1.2 Treatment phase

9.2.1.2.1 Visit 2 (Randomization; Day 1 and baseline), Treatment phase

- Assess all inclusion and exclusion criteria for eligibility (see Sections 6.1 and 6.2)
- Register the patient in IxRS for Randomization
- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1) before study drug administration
- Obtain blood sample for central laboratory for D-dimer before study drug administration
- Obtain PD blood sample for central laboratory for exploratory analysis before study drug administration
- Obtain PD blood sample for central laboratory before study drug administration: aPTT, PT, FXI concentration, and FXI activity
- Obtain blood sample for optional pharmacogenetic test: An additional sample of blood - i.e. PGt blood (research) - will be taken from those patients who signed the separate Informed Consent form for pharmacogenetic research (can be obtained at any visit)
- Obtain blood sample for FVIII, FXII activity, FIX Activity, vWF antigen, and for ristocetin cofactor (i.e. von Willebrand factor) activity for central laboratory before study drug administration
- Randomize patient using IxRS
- OPTIONAL: Administer 40 mg of enoxaparin s.c. once in the evening of the pre-surgery day (enoxaparin arm only)
- Perform drug accountability if applicable

- Check for signs and symptoms of DVT, PE, and bleeding and if applicable compile and send the adjudication package to the adjudication office as soon as possible

9.2.1.2.2 Visit 3 (Day 2), Treatment phase

Before TKA surgery

- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

Conduct primary TKA surgery under spinal, epidural or general anesthesia:

Spinal anesthesia, i.e. when an anesthetic drug is injected directly into the subarachnoid space (cerebrospinal fluid), and epidural anesthesia i.e. when an anesthetic drug is injected through a catheter placed into the epidural space, are both considered regional anesthesia. Spinal, epidural and general anesthesia is allowed (only epidural analgesia not allowed) for Part A of the study.

After TKA surgery

- Record prior and concomitant medications (see Section 8.1)
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Administer 40 mg of enoxaparin s.c. 6 to 8 hours after TKA surgery (enoxaparin arm only)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.1.2.3 Visit 4 (Day 3), Treatment phase

- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4):
    - Enoxaparin arms: before study drug administration
    - BAY 1213790 and apixaban arms: before and after study drug administration

- Perform central safety laboratory (see Section 9.6.3.1) before study drug administration (for apixaban arm before the first dose of the day)
- Obtain PK blood sample for central laboratory (BAY 1213790 arms only. Obtain sample before and - via new puncture and from opposite arm - between end of study drug infusion until up to 2h after end of study drug infusion)
- Obtain blood sample for anti-drug antibody (BAY 1213790 arms only. Obtain sample before BAY 1213790 administration)
- Obtain blood sample for central laboratory for D-dimer before study drug administration (for apixaban arm before the first dose of the day)
- Obtain PD blood sample for central laboratory for exploratory analysis:
    - BAY 1213790 arms: obtain sample before and after BAY 1213790 administration at the same time as the PK sample
    - Enoxaparin arm: obtain once during the visit, prior to administering the next dose of enoxaparin
    - Apixaban arm: obtain before and approximately after 2 hours of administration
- Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity:
    - BAY 1213790 arms: obtain sample before and after BAY 1213790 administration at the same time as the PK sample
    - Enoxaparin arm: obtain once during the visit, prior to administering the next dose of either enoxaparin
    - Apixaban arm: obtain before and approximately after 2 hours of administration
- Administer BAY 1213790 intravenously once, the day following the TKA (or after adequate hemostasis has been achieved), preferably in the morning, but not later than 24 hours after wound closure (BAY 1213790 arms only). For further details see Section 9.6.3.7.
- Administer 40 mg of enoxaparin s.c. (enoxaparin arm only)
- Administer apixaban 2.5 mg BID p.o. (apixaban arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.1.2.4 Visit 5 (Day 4) Treatment phase

- Record use of concomitant medications (see Section 8.1)

- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- BAY 1213790 arm, take all samples at the same timepoint:
    - Obtain PK blood sample for central laboratory
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Enoxaparin or apixaban arm, take all samples at the same timepoint before administering study drug (for apixaban arm before the first dose of the day):
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Administer 40 mg of enoxaparin s.c. (enoxaparin arm only)
- Administer apixaban 2.5 mg BID p.o. (apixaban arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.1.2.5 Visit 6 (Day 6 ± 1), Treatment phase

- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Obtain 12-lead ECG in supine position, after the patient rested for at least 5 minutes (see Section 9.6.3.3)
- Perform central safety laboratory (see Section 9.6.3.1) before study drug administration (for apixaban arm before the first dose of the day)
- BAY 1213790 arm, take all samples at the same timepoint:
    - Obtain PK blood sample for central laboratory
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity

- Enoxaparin or apixaban arm, take all samples at the same timepoint before administering study drug (for apixaban arm before the first dose of the day):
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Administer and/or instruct the patient how to self-inject 40 mg of enoxaparin s.c. (enoxaparin arm only)
- Administer and/or instruct the patient to take apixaban 2.5 mg BID p.o. (apixaban arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.1.2.6 Visit 7 (Day 12 +3) Treatment phase

- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs before venography (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory before study drug administration (for apixaban arm before the first dose of the day) and before venography (see Section 9.6.3.1)
- BAY 1213790 arm, take all samples at the same time point prior to venography:
    - Obtain PK blood sample for central laboratory
    - Obtain blood sample for anti-drug antibody
    - Obtain blood sample for central laboratory for D-dimer before venography
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Enoxaparin or apixaban arm, take all samples at the same timepoint before administering study drug (for apixaban arm before the first dose of the day):
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity

- Administer and/or instruct the patient how to self-inject 40 mg of enoxaparin s.c. (enoxaparin arm only)
- Administer and/or instruct the patient to take apixaban 2.5 mg BID p.o. (apixaban arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible
- Obtain bilateral venogram and send adjudication package to the adjudication office

9.2.1.3 Post-treatment observation phase

9.2.1.3.1 Visit 8, (Day 30 ± 5) Post-treatment observation phase

- Perform IxRS confirmation [a]
- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1)
- Take PK and PD samples at the same timepoint
    - Obtain PK blood sample for central laboratory (BAY 1213790 arms only)
    - Obtain blood sample for anti-drug antibody (BAY 1213790 arms only)
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

[a] Although the actual End of Treatment Period occurs at Visit 7, it should be confirmed in IxRS with Visit 8 date.

9.2.1.3.2 Visit 9, (Day 90 ± 7) Post-treatment observation phase

- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1)
- Take PK and PD samples at the same timepoint:
    - Obtain PK blood sample for central laboratory (BAY 1213790 arms only)
    - Obtain PD blood sample for anti-drug antibody (BAY 1213790 arms only)
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.1.3.3 Visit 10 (Day 150 ± 7) end of study visit, Post-treatment observation phase

- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1)
- Take PK and PD samples at the same timepoint
    - Obtain PK blood sample for central laboratory (BAY 1213790 arms only)
    - Obtain blood sample for anti-drug antibody (BAY 1213790 arms only)
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.1.3.4 Premature discontinuation visit (PDC)

If a patient prematurely discontinues the study during the treatment phase, this visit will take place as soon as possible. The investigator should make every possible effort to ensure that the following procedures are performed during this visit:

- Record use of concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1)
- Take PK and PD samples at the same timepoint
    - Obtain PK blood sample for central laboratory (BAY 1213790 arms only)
    - Obtain blood sample for anti-drug antibody (BAY 1213790 arms only)
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.2 Pre-surgery visit descriptions, part B

9.2.2.1 Visit 1 (Day -13 to 1), Screening

- Obtain the signed and dated Informed Consent prior to any study specific procedures (enrollment in the study is defined as the signing of the informed consent) (see Section 13.4)
- Obtain Informed Consent to optional pharmacogenetic research (can be obtained at any visit, but in any case before the pharmacogenetic sample is drawn)
- Collect demographic information (see Section 9.3.1)
- Register the patient in IxRS to allocate unique patient identification number (see Section 6.4)
- Record weight and height
- Record the medical history (see Section 9.3.2)
- Record prior and concomitant medications (see Section 8.1)

- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Perform physical examination (see Section 9.6.3.2)
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Obtain 12-lead ECG in supine position, after the patient rested for at least 5 minutes (see Section 9.6.3.3)
- Perform local serum pregnancy test in females
- Perform local safety laboratory including aPTT, PT, creatinine, ALT, bilirubin, platelets, and Hb if prior values are not available within 14 days prior to randomization
- Assess all inclusion and exclusion criteria for eligibility (see Sections 6.1 and 6.2)

9.2.2.2 Treatment phase

9.2.2.2.1 Visit 2 (Randomization; Day 1 and baseline), Treatment phase

- Assess all inclusion and exclusion criteria for eligibility (see Sections 6.1 and 6.2)
- Register the patient in IxRS for Randomization
- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4). For BAY 1213790 arms only: record vital signs at the beginning and at the end of BAY 1213790 infusion
- Perform central safety laboratory (see Section 9.6.3.1) before study drug administration
- Obtain PK blood sample (BAY 1213790 arms only)
    - before test drug administration
    - between end of infusion until up to 2 h after end of infusion via new puncture and from opposite arm
- Obtain blood sample for anti-drug-antibody before test drug administration (BAY 1213790 arms only)
- Obtain blood sample for central laboratory for D-dimer before study drug administration
- Obtain PD blood sample for central laboratory for exploratory analysis:

- BAY 1213790 arms: obtain sample before and between end of infusion until up to 2 hours end of infusion of BAY 1213790 administration, obtain PD blood sample via new puncture and from opposite arm
- Enoxaparin arm: obtain sample before study drug administration

- Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity.
  - BAY 1213790 arms: obtain sample before and between end of infusion until up to 2 hours end of infusion of BAY 1213790 administration, obtain PD blood sample via new puncture and from opposite arm
  - Enoxaparin arm: obtain sample before study drug administration
- Obtain blood sample for optional pharmacogenetic test: An additional sample of blood - i.e. PGt blood (research) - will be taken from those patients who signed the separate Informed Consent form for pharmacogenetic research (can be obtained at any visit)
- Obtain blood sample for FVIII, FXII activity, FIX Activity, vWF antigen, and for ristocetin cofactor (i.e. von Willebrand factor) activity for central laboratory before study drug administration
- Randomize patient using IxRS
- Administer BAY 1213790 intravenously once in the second half of the pre-surgery day (BAY 1213790 arms only). For further details see Section 9.6.3.7
- OPTIONAL: Administer 40 mg of enoxaparin s.c. once in the evening of the pre-surgery day (enoxaparin arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.2.2.2 Visit 3 (Day 2), Treatment phase

Before TKA surgery

- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Obtain PK blood sample for central laboratory before TKA surgery (BAY 1213790 arms only)
- Obtain PD blood sample for central laboratory for exploratory analysis
- Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity

- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

Conduct primary TKA surgery under general anesthesia

After TKA surgery

- Record prior and concomitant medications (see Section 8.1)
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Obtain PK blood sample for central laboratory 3 to 6 hours after TKA surgery (BAY 1213790 arms only)
- Obtain blood sample for central laboratory for D-dimer 3 to 6 hours after TKA surgery
- Obtain PD blood sample for central laboratory for exploratory analysis 3 to 6 hours after TKA surgery
- Obtain PD blood sample for central laboratory at 3 to 6 hours after TKA surgery: aPTT, PT, FXI concentration, and FXI activity
- Administer 40 mg of enoxaparin s.c. 6 to 8 hours after TKA surgery (enoxaparin arm only)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.2.2.3 Visit 4 (Day 3), Treatment phase

- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1) before study drug administration
- BAY 1213790 arm: take all samples at the same timepoint:
    - Obtain PK blood sample for central laboratory
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity

- Enoxaparin or apixaban arm, take all samples at the same timepoint before administering study drug (for apixaban arm before the first study dose of the day):
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Administer 40 mg of enoxaparin s.c. (enoxaparin arm only)
- Administer apixaban 2.5 mg BID p.o. (apixaban arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.2.2.4 Visit 5 (Day 4), Treatment phase

- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Administer 40 mg of enoxaparin s.c. (enoxaparin arm only)
- Administer apixaban 2.5 mg BID p.o. (apixaban arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.2.2.5 Visit 6 (Day 6 ± 1), Treatment phase

- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Obtain 12-lead ECG in supine position, after the patient rested for at least 5 minutes (see Section 9.6.3.3)
- Perform central safety laboratory (see Section 9.6.3.1)
- BAY 1213790 arm: take all samples at the same timepoint:
    - Obtain PK blood sample for central laboratory
    - Obtain blood sample for central laboratory for D-dimer

- Obtain PD blood sample for central laboratory for exploratory analysis
- Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity

- Enoxaparin or apixaban arm, take all samples at the same timepoint before administering study drug (for apixaban arm before the first study dose of the day):
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Administer and/or instruct the patient how to self-inject 40 mg of enoxaparin s.c. (enoxaparin arm only)
- Administer and/or instruct the patient to take apixaban 2.5 mg BID p.o. (apixaban arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.2.2.6 Visit 7 (Day 12 +3) Treatment phase

- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs before venography (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory before venography (see Section 9.6.3.1)
- BAY 1213790 arm: take all samples at the same timepoint:
    - Obtain PK blood sample for central laboratory before venography
    - Obtain blood sample for anti-drug antibody before venography
    - Obtain blood sample for central laboratory before venography for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis before venography
    - Obtain PD blood sample for central laboratory before venography: aPTT, PT, FXI concentration, and FXI activity
- Enoxaparin or apixaban arm, take all samples at the same timepoint before administering study drug (for apixaban arm before the first study dose of the day):
    - Obtain blood sample for central laboratory for D-dimer

- Obtain PD blood sample for central laboratory for exploratory analysis
- Obtain PD blood sample for central laboratory: aPTT, PT (seconds and INR), FXI concentration, and FXI activity

- Administer and/or instruct the patient how to self-inject 40 mg of enoxaparin s.c. (enoxaparin arm only)
- Administer and/or instruct the patient to take apixaban 2.5 mg BID p.o. (apixaban arm only)
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible
- Obtain bilateral venogram and send adjudication package

9.2.2.3 Post-treatment observation phase

9.2.2.3.1 Visit 8, (Day 30 ± 5) Post-treatment observation phase

- Perform IxRS confirmation [b]
- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1)
- Take all samples at the same timepoint
    - Obtain PK blood sample for central laboratory (BAY 1213790 arms only)
    - Obtain blood sample for anti-drug antibody (BAY 1213790 arms only)
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

[b] Although the actual End of Treatment Period occurs at Visit 7, it should be confirmed in IxRS with Visit 8 date.

9.2.2.3.2 Visit 9, (Day 90 ± 7) Post-treatment observation phase

- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1)
- Take all samples at the same timepoint
    - Obtain PK blood sample for central laboratory (BAY 1213790 arms only)
    - Obtain blood sample for anti-drug-antibody (BAY 1213790 arms only)
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.2.3.3 Visit 10 (Day 150 ± 7) end of study visit, Post-treatment observation phase

- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1)
- Take all samples at the same timepoint
    - Obtain PK blood sample for central laboratory (BAY 1213790 arms only)
    - Obtain blood sample for anti-drug-antibody (BAY 1213790 arms only)
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.2.2.3.4 Premature discontinuation visit (PDC)

If a patient prematurely discontinues the study during the treatment phase, this visit will take place as soon as possible. The investigator should make every possible effort to ensure that the following procedures are performed during this visit:

- Record prior and concomitant medications (see Section 8.1)
- Assess adverse events / serious adverse events (see Section 9.6.1), and report as appropriate
- Record vital signs (blood pressure, pulse; see Section 9.6.3.4)
- Perform central safety laboratory (see Section 9.6.3.1)
- Take all samples at the same timepoint
    - Obtain PK blood sample for central laboratory (BAY 1213790 arms only)
    - Obtain blood sample for anti-drug-antibody (BAY 1213790 arms only)
    - Obtain blood sample for central laboratory for D-dimer
    - Obtain PD blood sample for central laboratory for exploratory analysis
    - Obtain PD blood sample for central laboratory: aPTT, PT, FXI concentration, and FXI activity
- Perform drug accountability if applicable
- Check for signs and symptoms of DVT, PE, and bleeding and if applicable, compile and send the adjudication package to the adjudication office as soon as possible

9.3 Population characteristics

9.3.1 Demographic

The following demographic data will be collected in the eCRF during Screening:

- year of birth and age at Screening
- sex
- race/ethnicity
- body weight
- body height
- calculated BMI
- Smoking history and alcohol consumption

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the patient's study eligibility

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.4 Efficacy

Primary variable:

- incidence of composite endpoint, consisting of asymptomatic DVT; detected by mandatory bilateral venography; objectively confirmed symptomatic DVT, non-fatal PE, fatal PE, unexplained death for which PE cannot be excluded up to Visit 7 (Day 12+3)

Secondary variable:

- incidence of composite endpoint of symptomatic DVT or non-fatal PE, fatal PE, unexplained death for which PE cannot be excluded up to Visit 10 (Day 150±7), objectively confirmed asymptomatic DVT up to Visit 7 (Day 12+3)

The analysis of the primary and secondary efficacy variables will be solely based on the assessments made by the central independent adjudication committee. The adjudication of these events will be blinded to treatment assignment and will be conducted according to definitions included in the adjudication committee charter.

The secondary efficacy variable needs to be interpreted with care as it is a composite endpoint of asymptomatic DVTs until study Visit 7 (Day 12+3) and symptomatic DVT or non-fatal PE up to Visit 10 (Day 150±7).

Mandatory venography:

The X-ray contrast venography should be performed according to the method of Rabinov and Paulin (19). The technique will be standardized aiming at high quality examinations where all the deep veins are visualized including posterior tibial, peroneal, fibular, popliteal, femoral–common and iliac veins. An adequate examination is defined as a bilateral venography where all deep veins listed above are evaluable

The venogram should be obtained first from the operated leg. Multiple views of each venous segment should be obtained, preferably from different positions. A copy of the venogram should be sent for adjudication (further details can be found in the Site Manual).

Bilateral X-ray contrast venography at Visit 7 (Day 12+3) is not required, if a symptomatic DVT or non-fatal PE is objectively confirmed by an appropriate measure, i.e. CUS, X-ray contrast venography or MR/CT venography for DVT, or ventilation/perfusion lung scintigraphy, pulmonary CT angiography or pulmonary angiography for PE prior to the

scheduled time of this examination. If a suspected VTE is not confirmed using one of the above techniques, the patient must undergo bilateral venography as scheduled.

Any suspected symptomatic DVT or non-fatal PE should be objectively confirmed by one of the above mentioned measures.

All suspected symptomatic or asymptomatic VTE (i.e. DVT or PE) including the respective images will be adjudicated by the central independent adjudication committee.

9.5 Pharmacokinetics / pharmacodynamics

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

9.5.1 Pharmacokinetics

It is essential that the exact date and time of blood sampling and exact date and time of dose administration of study medication are documented accurately in the eCRF.

For investigation of exposure, plasma concentrations of BAY 1213790 will be determined at the times given below using a sparse sampling approach in all participating patients. If the investigator decides to take additional PK samples, those may be used for PK analysis as well.

For details regarding the timing of PK sampling, and flow charts detailing the order of procedures at these visits, please refer to Table 9–1 (part A) and Table 9–2 (part B).

The pharmacokinetic calculations will be based on the actual sampling and dosing times. Therefore, it is crucial to have this data thoroughly documented in the CRF.

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. Since this is an open-label study, this evaluation might be started prior to database lock.

Exploratory analysis of unbound BAY 1213790 or of the complex of BAY 1213790 bound to FXI(a) might be done if applicable.

PK samples will be analyzed, using validated analytical methods. The bioanalyst will be unblinded and have access to the randomization list. 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 CSR for this study.

Any residual PK samples will be destroyed at end of study.

9.5.2 Pharmacodynamics

Blood samples will be taken for PD measurements from all patients. For details regarding the timing of PD sampling, and flow charts detailing the order of procedures at these visits, please

refer to Table 9–1 (part A) and Table 9–2 (part B). The exact dates and times of blood sampling and time of dose administration of study drug must be recorded in the CRF.

The following parameters will be analyzed (see details in Sections 9.1 and 9.2):

- aPTT
- PT (seconds and INR)
- FXI concentration (antigen)
- FXI activity
- D-dimer

The aPTT measurement will be performed via the kaolin-trigger method. PT will be measured using a standard coagulation assay. Results will be provided in seconds and as INR value.

Factor XI activity will be assessed by an aPTT-based coagulation test using FXI-deficient plasma. Factor XI concentration will be analyzed using an enzyme-linked immunosorbent assay (ELISA).

Furthermore, exploratory assessments of coagulation and related processes by other means are planned, e.g. FXII activity/concentration, TAFI (thrombin-activatable fibrinolysis inhibitor), ETP/TGA, ROTEM, chromogenic/fluorogenic FXI activity measurements or the analysis of complexes of FXIa with endogenous inhibitors (C1 inhibitor, alpha-1-antitrypsin) using ELISA.

In addition to the PD markers listed above, other PD markers deemed relevant to gain further knowledge about the mechanism of the disease or about the drug (i.e. mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and / or literature data. Details on the collection, processing, storage and shipment of PD marker samples will be provided in separate documents (e.g. sample handling sheets or lab manual).

9.6 Safety

Primary safety variable

- incidence of composite of major and clinically relevant non-major bleeding up to Visit 7 (Day 12+3)

Secondary variable:

- incidence of composite of major and clinically relevant non-major bleeding up to Visit 10 (Day 150±7)

Other safety variables are:

- treatment-emergent adverse events
- treatment-emergent serious adverse events
- laboratory parameters

The analysis of the primary and secondary safety variables will be solely based on the assessments made by the central independent adjudication committee (CIAC). The adjudication of these events will be blinded to study drug assignment and will be conducted according to definitions included in the CIAC charter.

Bleeding

All suspected bleeding events occurring after randomization will be reviewed by the Central Independent Adjudication Committee in a blinded fashion. The procedures followed by the CIAC and definitions to classify bleeding are detailed in the CIAC charter. Detailed instructions regarding documentation, reporting and shipment of bleeding dossiers will be provided in the Site Manual (SM).

Bleeding will be evaluated by the IDMC on an ongoing basis.

Definitions (Please refer to the adjudication charter for details):

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

- Bleeding that contributed to death
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intramuscular with compartment syndrome or intraarticular (operated joint excluded)
- Extra surgical site 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, with temporal association within 24-48 h to the bleeding.
- Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular), or causing a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or wound healing, resulting in prolonged hospitalization or deep wound infection.
- Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability. There should be an associate fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.

A clinically relevant non-major (CRNM) bleeding is an acute or sub-acute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

- A hospital admission for bleeding, or
- A physician guided medical or surgical treatment for bleeding, or
- A change in antithrombotic therapy (including interruption or discontinuation of study drug).

The definitions for major and clinically relevant non-major bleeding are based on ISTH criteria.

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the patient 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

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
- The admission is not associated with an AE
  (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild – A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living
- Moderate – A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant
- Severe – A type of AE that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects clinical status. The event possesses a significant risk of harm to the research participant and hospitalization may be required

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF.

Causality should be assessed separately for each study treatment as detailed in the CRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event

- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.
- The assessment is not possible

Causal relationship to protocol-required procedures

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the CRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

The investigator has to record on the respective CRF pages all adverse events occurring in the period between the signing of the informed consent and the end of the post-treatment observation phase; after the end of the post-treatment observation phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

“Death” should not be recorded as an AE on the AE page. Instead, “death” is the outcome of underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.6.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator’s notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator’s reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator’s awareness) all SAEs occurring during the observation phase defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF as well as the RAVE complementary AE pages must be completed for each SAE.

SAEs occurring after the protocol-defined observation phase will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the study sites

The sponsor will inform all study sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this study, for test drug, the applicable reference document is the most current version of the investigator's brochure (IB) / summary of product characteristics.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

For comparators the applicable reference document is the most current version of the local label or Summary of Product Characteristics.

9.6.1.6 Adverse events of special safety interest

Adverse events of special interest have to be reported to the sponsor along the timelines set for serious adverse events (even though they may not be classified as serious), i.e. within 24 hours of the investigator's awareness, as described in section 9.6.1.4.

Adverse events of special interest are:

- Decrease in platelets below the lower limit of the normal range
- Hypersensitivity and infusion related reactions

Hypersensitivity or infusion related reactions

Hypersensitivity or infusion related reactions will be assessed according the common terminology criteria for adverse events of the National Cancer Institute (CTCAE v4.0), see Table 9–3.

Table 9–3: Common terminology for adverse events related to immune system disorders (CTCAE v-4.0)

Immune system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for <=24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	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 nonessential 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 resulting from 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.					

Immune system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					
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: A 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. Abbreviations: IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs					

Depending on the observed grade of reaction, respective measures like temporary or permanent interruption of the infusion, general and specific drug treatment (e.g. anti-histamines) will be applied. In case of a mild (grade 1 according to CTCAE v4.0) infusion reaction with an apparent symptoms relief within 30 min after a premature stop of infusion, the investigator may decide to cautiously re-start infusion with half of the initial infusion rate. If any hypersensitivity symptom re-occurs, infusion will be stopped immediately and definitely.

Anaphylaxis is strongly suspected when respiratory symptoms or hypotension occurs within 10 minutes of infusion. All measures at site will be performed according the S2 Guideline for acute therapy and management of anaphylaxis (20).

9.6.2 Pregnancies

Females of childbearing potential are excluded from the study. However, the investigator must report to the sponsor any pregnancy occurring in a female study patient during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported to Sponsor.

The child's health should be evaluated at birth.

For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE to Sponsor.

9.6.3 Further safety

The following points will be described further in detail:

- Blood sample for laboratory parameter measurements (see Section 9.6.3.1)
- Physical examination
- 12-lead ECG
- Vital signs
- Data regarding adverse events (collected at all visits after signing of the informed consent)
- Anti-drug antibodies
- Data about surgical procedure
- Contraception
- Patient monitoring during BAY 1213790 infusion

9.6.3.1 Laboratory parameter measurement

Central laboratory

Only centrally analyzed blood samples will be considered for analysis.

The name and address for the central lab service provider can be found in the documentation supplied by the vendor. The following laboratory tests will be performed centrally:

Hematology: white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and platelets.

Clinical chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), total bilirubin and direct bilirubin if total bilirubin is elevated, cholesterol [high density lipoprotein (HDL), low density lipoprotein (LDL), total],

triglycerides, creatinine, eGFR (MDRD formula, see Section 16), blood urea nitrogen, uric acid, sodium, potassium, calcium, chloride, bicarbonate, magnesium, glucose, total protein, albumin, and high-sensitivity C-reactive protein (hs-CRP)

Urinalysis: color, appearance, specific gravity, pH, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocyte esterase. Microscopic examination (casts, crystals, bacteria, epithelial cells, RBC, WBC, yeast)

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

If the blood sample for the central laboratory taken at any visit is missing or not evaluable, sampling and measurement has to be repeated as soon as possible.

Local laboratory

During Screening visit, only local laboratory samples will be assessed to check the eligibility of the patient. At least the following parameters must be assessed at the Screening visit and entered in the eCRF to check the patient's eligibility for the study:

- aPTT
- PT
- Hemoglobin
- Platelet count
- Creatinine and creatinine clearance calculated with the MDRD formula (see Section 16).
- ALT
- Total bilirubin and direct bilirubin if total bilirubin is elevated,

and in women only:

- Serum pregnancy test except in women who are surgically sterile (hysterectomy or bilateral ovariectomy) or postmenopausal who are older than 65

In addition to the parameters given above, any other laboratory parameter, which will be measured locally, should be carefully assessed by the investigator to check the patient's eligibility for the study.

9.6.3.2 Physical examination

A comprehensive physical examination should be performed by the investigator at Screening. Any abnormal findings are to be recorded (see Section 9.6.1.1).

After randomization, patients should be evaluated for signs and symptoms of DVT and PE (i.e., unexplained shortness of breath, chest pain that gets worse with a deep breath, or coughing up blood) during the post-surgery in hospital phase and at all follow-up contacts after discharge.

9.6.3.3 Electrocardiogram

ECGs in supine position will be assessed locally as safety measures: standard electrocardiograms (12-lead ECG) according to Goldberger / Einthoven and Wilson will be recorded after resting for at least 5 min at the Screening visit and at Visit 6 (Day 6 +/- 1).

All ECG print-outs will be identified with the SID as well as date and time of recording and will be attached to the patient's file.

ECG printouts will be examined locally by the investigator on the day of recording for safety and quality. All ECG findings will be reported in the eCRF and any clinically relevant abnormality will be documented as an AE.

9.6.3.4 Measurement of Vital signs

Vital signs will be assessed at the Screening visit, Visit 2 (Day 1: Part B vital signs will be assessed before and after study drug administration for BAY 1213790 arms), Visit 3 (Day 2:before and after surgery), Visit 4 (Day 3: Part A vital signs will be assessed before and after study drug administration for BAY 1213790 and apixaban arms, and only before study drug administration for enoxaparin arm. Part B: Vital signs will be assessed for all treatment arms, and twice for the apixaban arm), Visit 5 (Day 4), Visit 6 (Day 6±1), Visit 7 (Day 12+3) Visit 8 (Day 30±5), Visit 9 (Day 90±7), Visit 10 (Day 150±7) as well as during premature discontinuation visit. This will include blood pressure (BP) and heart rate (HR) measurements. BP will be measured by using a standard sphygmomanometer with an appropriate size cuff in the sitting position after 5 minutes of rest, at Visit 3 (Dav 2) a semi-supine position is also accepted.

9.6.3.5 Development of anti-drug antibodies (ADAs)

The development of ADAs will be investigated in blood samples taken at the time points given in the study flow chart (See Section 9.1.1 for part A, and Section 9.1.2 for part B). Measurement of ADAs will be done batch-wise only as there is no expected direct impact on patients´ safety in this respective study setting. In case of any hypersensitivity adverse event of life-threatening consequences or in case of unexpected drop of PK levels the ADA measurement will be carried out at short notice.

Sample collection, processing and storage

Further details on collection, labeling, storage, and shipping of samples are provided in a separate laboratory manual. Anti-drug antibody samples will be analyzed using validated analytical methods. The bioanalyst will be unblinded and have access to the randomization list. Positive control 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.

Any residual anti-drug antibody samples will be destroyed at end of this study.

9.6.3.6 Contraception

If engaged in sexual activity with child-bearing potential partner, male patients with their female partner must use effective contraception during the treatment phase and until the end of the post-treatment observation phase.

Effective contraception methods are for example:

- History of surgical sterilization (male patient or female partner)
- Female partner uses hormonal contraception or intrauterine contraception/device
- The use of barrier methods together with spermicidal foam/gel/film/cream/suppository. Barrier methods are male or female condom*, diaphragm, sponge, cervical cap.

Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the study drug.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing

9.6.3.7 Patient monitoring during BAY 1213790 infusion

Although not necessarily expected for BAY 1213790, patients should be monitored closely for infusion related reactions or signs of hypersensitivity during and immediately after infusion with BAY 1213790. Vital signs may be checked before, during, and after the infusion. Hypersensitivity reactions in general are not predictable and may also occur with delay. In addition to careful monitoring, patients should be strongly encouraged to notify a clinician immediately, if they notice any discomfort during the infusion. Appropriate medical resources should be available to sustain a patient who experiences a severe infusion related reaction.

9.7 Other procedures and variables

9.7.1 Biomarker investigations

See Section 9.5.2.

9.7.2 Pharmacogenetic research investigations

Genetic variants of the factor XI pathway explain a considerable proportion of variability of markers of the coagulation cascade (21), and are related to thrombotic clinical endpoints (22). Specifically, common genetic variants of the factor XI gene influence FXI activity in patients already receiving thromboprophylaxis (23), and have been demonstrated to be related to occurrence of first and recurrent thrombotic events (24). It has hence been suggested that these variants could be useful for identifying *i)* individuals at high risk of thrombotic events in a clinical trial setting, and *ii)* patients who respond better to FXI inhibition. Relevant genetic variants will include the currently known variants of the FXI pathway, or variants which have been linked to a thrombotic clinical endpoint, as well as additional variants which may be

described in the future. We aim to correlate genetic variants individually, as well as in combinations ("genetic scores") with *i)* measurements of markers of the coagulation system (e.g. activated partial thromboplastin time, FXI activity) and *ii)* occurrence of clinical endpoints (e.g. occurrence of venous thromboembolism). The impact of genetic variants (individually or in combinations) on the treatment response (FXI inhibition) will be assessed, measured as changes markers of the coagulation system and occurrence of clinical endpoints (i.e. statistical test for an interaction between genetic variant and treatment). Furthermore, we will evaluate the utility of genetic variants in predicting clinical events in combination with, as well as in comparison to, clinical and demographic risk factors (e.g. age, sex) and marker of the coagulation system.

A whole blood sample will be obtained from those patients who have signed a separate informed consent form for this pharmacogenetic research. The sample may be used as source of germline DNA. The participation in this part of the study is voluntary and has no influence on the participation in this study. Results will be reported under separate cover, if the evaluations are performed.

9.7.3 Recommendations to manage bleeding in a patient

In general, the management of bleeding is under the discretion of the treating physician and may be directed by the Guidelines from the European Society of Anaesthesiology for severe perioperative bleeding (25).

In patients who received BAY 1213790, the management of bleeding may 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 these patients when undergoing surgery (26). In patients undergoing tooth extractions, i.e. an invasive procedure in tissue with high fibrinolytic activity in the oropharynx, Berliner at 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 an 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 1g 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).

In addition, in vitro data showed that the prolongation of aPTT and ROTEM CT induced by BAY 1213790 can be fully reversed by recombinant FVIIa (NovoSeven®) or factor eight inhibitor bypass activity (FEIBA®) (further details can be found in the current version of the investigator's brochure) (17).

If a patient treated with enoxaparin or apixaban has a severe bleed, the recommendations included in the respective labels should be followed to control the bleeding.

9.7.4 Stopping Rule for Platelet Count Results

In the event of a confirmed decrease of the platelet count to a value below 50% of the baseline value, the dosing of a patient with enoxaparin must be stopped immediately and permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor's medical expert. In case of the above event the Investigator should contact the study medical expert immediately. See also Section 6.3.1.

9.8 Appropriateness of procedures / measurements

In this study all asymptomatic patients will undergo bilateral ascending venography at Visit 7 (Day 12+3). Venography is an invasive method, which can sometimes be painful for the patient. Additionally, the radiation burden and exposure to contrast agents pose a certain risks to the patient. However, this diagnostic procedure was chosen because it is the diagnostic gold standard for assessing the presence or absence of deep vein thrombosis (DVT) and has provided plausible and useful results in many clinical studies. Nevertheless, the inter-observer agreement in interpreting venograms is variable (31), (32- 33), (34). Therefore, the venograms will be assessed by a central adjudication committee, which will reduce the inter-observer variability.

Venous ultrasound is a non-invasive and easily repeatable technique with almost no contraindications (35- 36). The extended and standardized version of this diagnostic examination, the complete compression ultrasound (CCUS), proved to be safe for the exclusion of both proximal and distal DVT (37- 38) in symptomatic patients. In addition, an excellent inter-observer agreement for the presence or absence of DVT in both proximal and distal veins (39) was documented when using CCUS in symptomatic patients. For this reason venous ultrasound has become the most widely accepted test for the diagnosis of clinically suspected DVT but it has failed to demonstrate sufficient accuracy for the detection of asymptomatic DVT (36) (40).

The VENUS study in particular compared the results of centrally adjudicated CCUS with those of centrally adjudicated venography in a large population of patients that had recently undergone elective major hip or knee replacement surgery (41). In the 1104 matching pairs evaluated, the sensitivity of CCUS compared to venography was 31% for any DVT when both types of surgery were combined. In addition, none of the proximal DVTs identified by venography in patients who had undergone TKA were identified by CCUS. The peculiar characteristics of the thrombi identified by venography after hip or knee replacement surgery (all small, non-occluding, or distal) were suggested by the authors as an explanation for the poor sensitivity of CCUS. Finally, the same trial showed that using a standardized venography technique and the same venography adjudicators allows achieving a high inter-observer agreement (0.95) with this technique.

Based on these results, CCUS seems unable to replace venography for the detection of asymptomatic DVT early after major orthopaedic surgery and therefore this study will use what is still considered the gold standard for the detection of asymptomatic DVT, i.e. contrast venography.

10. Statistical methods and determination of sample size

10.1 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 will be summarized by treatment arm and by providing frequency tables for categorical variables and summary statistics for continuous variables. Where appropriate, results for BAY 1213790 will be displayed by dose and pooled.

10.2 Analysis sets

Safety Set (SAF): The safety set will include all patients that received at least one dose of study drug.

Per Protocol Set (PPS): All patients that received at least one dose of study drug, had a valid venography at Day 12+3 (or an objectively confirmed symptomatic DVT or non-fatal PE before Day 12), and did not have an important deviation from the protocol or validity finding having an impact on the primary efficacy variable.

The primary analysis set for the efficacy evaluation will be the PPS with sensitivity analyses performed on the SAF. The primary analysis set for safety analysis will be the SAF.

Efficacy analyses on the PPS will be conducted using the treatment arms that the patients actually received (as treated), while efficacy analyses on the SAF will be conducted using the treatment arms as randomized (following the ITT principle).

Safety analyses on the SAF will be conducted using the treatment arms as treated.

PK analysis sets: All patients with at least 1 valid BAY 1213790 plasma concentration in accordance with the PK sampling strategy (see Section 9.5.1) and without deviation from the protocol that would interfere with the evaluation of the PK data will be included in the PK analysis (PK analysis set).

PD analysis set: All patients with at least 1 blood sample for PD marker in accordance with the PD sampling strategy (see Section 9.5.2) and without deviation from the protocol that would interfere with the evaluation of the PD data will be included in the PD analysis (PD analysis set).

10.3 Variables and planned statistical analyses

10.3.1 Efficacy variables

Primary efficacy variable: The incidence of composite endpoint consisting of asymptomatic DVT; detected by mandatory bilateral venography; objectively confirmed symptomatic DVT, non-fatal PE, fatal PE, unexplained death for which PE cannot be excluded up to Visit 7 (Day 12+3)

Secondary efficacy variable: The incidence of composite endpoint of symptomatic DVT, non-fatal PE, fatal PE, unexplained death for which PE cannot be excluded up to Visit 10 (Day 150±7), objectively confirmed asymptomatic DVT up to Visit 7 (Day 12+3)

When interpreting the results for the secondary efficacy endpoint it should be noted that this is a composite endpoint of asymptomatic DVTs as identified by mandatory venography at Visit 7, objectively confirmed asymptomatic DVTs detected until Visit 7 (Day 12+3) and objectively confirmed symptomatic DVT or non-fatal PE detected at any time up to Visit 10 (Day 150±7).

Other efficacy variable: Other efficacy variables might be defined in the statistical analysis plan.

Only positively adjudicated events will be considered for primary and secondary endpoints.

10.3.2 Safety variables

Primary safety variable: incidence of composite of major and clinically relevant non-major bleeding up to Visit 7 (Day 12+3)

Secondary safety variable: incidence of composite of major and clinically relevant non-major bleeding up to Visit 10 (Day 150±7)

Only positively adjudicated events will be considered for the primary and secondary safety variables.

10.3.3 Statistical and analytical plans

10.3.3.1 Demography and baseline characteristics

Demography and baseline characteristics will be presented descriptively.

10.3.3.2 Efficacy variables

Primary efficacy variable

The analysis for the primary efficacy variable will be conducted separately for each arms of BAY 1213790.

Let p_{XI} and p_E be the true probabilities for a primary endpoint event in the considered BAY 1213790 arm and the enoxaparin arm. Let Δ=5% denote the non-inferiority margin. This chosen NI margin of 5% is assumed to provide sufficient information for conclusions regarding the similarity between two of the treatment arms in this Phase 2 setting.

For the primary efficacy variable the following hypothesis will be tested:

1. Non-inferiority of BAY 1213790 arm compared to enoxaparin
   $H_0: p_{XI} \geq p_E + \Delta \quad vs. \quad H_1: p_{XI} < p_E + \Delta$
2. Superiority of BAY 1213790 arm compared to enoxaparin
   $H_0: p_{XI} \geq p_E \quad vs. \quad H_1: p_{XI} < p_E$

These one-sided hypotheses will be tested for each BAY 1213790 arm (dose level, time of administration (pre- vs. post-surgery)) to a global significance level of α=5%. In order to

adjust for the multiplicity within arm a fixed-sequence procedure will be applied: Each of the single tests will be performed at the full alpha level of α=5% in the order given above up to the first null hypothesis in this sequence that cannot be rejected. All further hypotheses later in this sequence cannot be rejected. No adjustment will be done for the multiplicity caused by the five arms.

For the tests the two-sided 90% confidence intervals for the difference in the proportions of BAY 1213790 dose arm versus enoxaparin or apixaban will be calculated based on normal approximation. The hypotheses will be tested by comparing the lower limit of the two-sided 90% confidence interval with the NI margin Δ=5% (for the NI tests) or with 0 for the superiority tests.

The comparison between the BAY 1213790 arms and apixaban will be descriptively only. No hypothesis testing will be applied. 90% Confidence intervals for the difference in proportions between each of the BAY 1213790 arms and apixaban will be provided based on normal approximation.

As an adequate venogram is necessary for the determination of the primary endpoint, the primary analysis will be conducted on the PPS, thus no imputation of missing data is necessary for the primary analysis.

Analyses on the SAF will be provided as sensitivity analyses. As the SAF includes all patients that were treated regardless of whether data for the primary variable is available, missing data needs to be accounted for. Given the short duration of the study, the drop-out pattern can be considered to be unrelated to the primary outcome variable. Furthermore, the readability of venographies is considered to be independent of the (missing) results of the read. Missing data for the primary variable can therefore be considered to be missing at random. The analysis on the SAF will therefore be conducted using a multiple imputation method: A logistic regression model will be fitted to the data of patients without missing data for the primary variable using the treatment arm and baseline characteristics as factors/covariates. For a patient with missing primary endpoint data, the probability for an event will be predicted from this model based on his baseline characteristics and treatment arm and the missing outcome will be imputed multiple times from a Bernoulli distribution using this predicted probability. Each imputed complete dataset will be analyzed separately and the results will be combined.

Secondary efficacy variable

The analysis of the secondary efficacy variable (the incidence of symptomatic DVT, non-fatal PE, fatal PE and unexplained death for which PE cannot be excluded up to Visit 10 (Day 150±7) or objectively confirmed asymptomatic DVT up to Visit 7 (Day 12+3)) will be done descriptively by providing the proportion of patients with the respective event. Furthermore, 90% confidence intervals for the difference in proportions between each of the BAY 1213790 dose arms and the enoxaparin and apixaban arm respectively will be provided based on normal approximation.

The analysis will be provided on the PPS as well as on the SAF.

Furthermore, this variable will be analyzed as time to event variable. Kaplan-Meier estimates for the time to the first event will be provided.

Other efficacy analyses

Exploratory analyses of the dose-response relationship of BAY 1213790 will be conducted by applying a logistic regression model to the occurrence of the primary outcome variable with the dose arm as explanatory variable.

10.3.3.3 Safety variables

Primary safety variable

The analysis of the primary safety variable (incidence of composite of major and clinically relevant non-major bleeding up to Visit 7 (Day 12+3)) will be done descriptively by providing the proportion of patients with the respective event. Furthermore 90% confidence intervals for the difference in proportions between each of the BAY 1213790 dose arms and the enoxaparin and apixaban arm respectively will be provided based on normal approximation. In addition, the analysis will be provided for the comparison of the pooled BAY 1213790 dose arms versus the enoxaparin and apixaban arm respectively. For the analysis of the primary safety variable all events between randomization and Visit 7 will be included regardless of their start relative to study drug administration.

Secondary safety variable

The secondary safety variable will be analyzed in the same way as described for the primary safety variable.

Other safety variables

All other safety variables will be analyzed descriptively.

10.3.3.4 Pharmacokinetic and Pharmacodynamic variables

PK variables

For the investigation of PK, the plasma concentrations of BAY 1213790 will be determined at the times given in Section 9.5.1 using a sparse sampling approach.

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

BAY 1213790 concentrations will be summarized by visit, separated according to actual dose.

Descriptive statistics of plasma concentrations [geometric mean and percent coefficient of variation (%CV), arithmetic mean and %CV, median and range] will be presented by dose 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 pharmacodynamics data will be displayed utilizing appropriate summary statistics and figures. aPTT, PT (seconds and INR), D-dimer, factor XI activity, factor XI concentration, and exploratory PD markers will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by BAY 1213790 dose for the original data as well as for the absolute and relative changes from baseline (aPTT, PT (seconds and INR), D-dimer, factor XI activity, factor XI concentration). In addition, for each patient 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.

10.4 Determination of sample size

It is targeted to randomize 100 patients to each of the BAY 1213790 arms and 100 patients to the enoxaparin arm and the apixaban arm respectively.

Assuming that approximately 80 patients in each of treatment arm will be evaluable for the primary analysis, leads to the characteristics summarized in Table 10–1 for the primary endpoint analyses.

If, e.g., a true probability of 10% for a primary endpoint event is assumed for the BAY 1213790 arm and 25% for the enoxaparin arm, this would result in a power of 97% for showing non-inferiority and 81% for showing superiority.

Similarly if a probability for an event of 4% is assumed for the BAY 1213790 arm and 10% for apixaban, this leads to a probability of 90% that the upper limit of the 88% confidence interval for the difference between the BAY 1213790 arm and apixaban is below 5% (non-inferiority) and probability of 43% that it is below 0 (superiority).

Table 10–1: Sample size characteristics assuming 80 evaluable patients for BAY 1213790 and 80 patients for enoxaparin and apixaban

Comparison	Assumed true probability for event in BAY 1213790 arm	Assumed true probability for event in reference arm	Power for one-sided test (α=5%) for superiority	Power for one-sided test (α=5%) for non-inferiority Δ=5%
BAY 1213790 – enoxaparin	10%	25%	81%	97%
BAY 1213790 – enoxaparin	4%	25%	99%	99%
BAY 1213790 – apixaban	10%	10%	0%	29%
BAY 1213790 – apixaban	4%	10%	43%	88%

The sample size calculation assumes that for approximately 20% of the patients no evaluable venographies (due to quality or drop-out) will be available. After approximately 75% patients have completed Visit 7 (venography visit), this assumption will be assessed on the pooled data of all treatment arms in the post-surgery administration part (part A). If the estimated rate of unavailable venography results exceeds 30% the power for testing superiority of BAY 1213790 over enoxaparin (assuming a probability for an event of 10% for BAY 1213790 and 25% for enoxaparin) will drop below 75%. In this case the sample size may be increased to reach a power of 80%.

10.5 Planned interim analyses

The IDMC will continuously monitor the safety of the patients. Furthermore, together with the SC the IDMC will review the available data after 75% of the patients in the post-surgery part have completed Visit 7. These data will be provided to the IDMC as part of the regular IDMC review and to the SC for evaluation (no formal interim analysis will be performed) to give their recommendation/advice regarding the start of the pre-surgery part and the doses to be used therein. A summary of the data assessment, including the IDMC and SC recommendations plus the decision taken, along with a justification, will be made available to IECs /IRBs, as well as local authorities for either notification or approval in depending on and in conformity with local law, regulations, and requirements.

In addition, interim analyses may be performed to assess both efficacy and safety in support of the future clinical development of BAY 1213790 after finalization of the post-surgery administration and after finalization of the post-treatment observation phase of part (A) of the study, which means all patients randomized for the post-surgery administration part have completed Visit 7 and Visit 10, respectively. An additional interim analysis is considered after all patients from both parts (A and B) have completed Visit 7. Details will be provided in the Statistical Analysis Plan. No formal report will be written.

Note that these are not interim analyses in the sense of a group-sequential or adaptive design, and no early stopping for efficacy is planned based on the results. Therefore, no adjustment for multiplicity is required.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (LSH).

Data required according to this protocol will be recorded by study site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator’s site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all patients enrolled in this study.

Source documentation

The site must implement processes to ensure availability of all required source documentation (e.g. patient file, local laboratory report, etc.). A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site.

Race and ethnic group may be entered directly into the CRF, without availability of corresponding source documentation. Thus, these CRF data will be the source and no additional source documentation will be available. For all other data, source documentation must be available at the site.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE such as:
  - The SAE itself
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary pages

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol
  (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. IxRS, laboratory, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for biometrical analysis, additional data release for analysis is possible, to include, for example, the following data: pharmacokinetic data, pharmacodynamic data, anti-drug antibody data etc.

11.4 Missing data

All efforts will be made to collect complete data for all patients randomized in this study. Patients will be followed up to the study end and all required data will be collected, regardless of patients' compliance with study drug use or the visit schedule.

Data from patients who prematurely terminate the study will be used to the maximum extent possible. All missing or partial data will be presented in the patient data listing as they are recorded in the eCRF. Data are collected primarily through an EDC system, which allows ongoing data entry and monitoring.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study site.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority (ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing patients, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.3.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

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L8L 2X2
Canada

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the study site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.1.1 External data evaluation bodies

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

13.1.1.1 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. In addition, the SC will advise to continue or stop recruitment in the BAY 1213790 arms as well as provide guidance on initiating the pre-surgery administration part (B), including recommendation on the doses to be used in this part of the trial. The Steering Committee may advise to modify enrollment in specific BAY 1213790 arms and/or open additional arms as well as recommends to make sample size adjustments for the study. For these purposes the SC will receive unblinded data. The Steering committee will consist of: External key experts in the field of thrombosis and sponsor representatives. Further details can be found in the SC charter.

13.1.1.2 Independent Data monitoring committee (IDMC):

The primary role of the IDMC is to periodically review the safety data and ensure the safety of the patients in the ongoing study including unblinded data if deemed necessary. In addition, the IDMC will provide a recommendation to the Steering Committee to continue or stop recruitment in the BAY 1213790 arms as well as whether the pre-surgery administration part may be started. The IDMC will consist of a chair, and members who have recognized expertise in clinical trials, anti-coagulation, and 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 IDMC charter.

13.1.1.3 Central Independent Adjudication committee (CIAC):

The central independent adjudication committee is blinded for treatment allocation and will objectively assess the safety and efficacy outcomes of the study and convene on an ad-hoc basis for timely assessment. Further details will be found in the CIAC charter.

13.1.2 Central laboratories

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).

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

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 patients 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.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Patient information and consent

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the sponsor or the study center. A sample patient information and informed consent form is provided as a document separate to this protocol. A separate informed consent form will be provided for patients willing to participate to the optional pharmacogenetic research.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient / legal representative or proxy consenter (if the patient is under legal protection), prior to his/her entry into the study / optional pharmacogenetic

research (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each patient will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers end-of-study examinations as specified in the visit description described in Sections 9.1, 9.2.1.3.4 and 9.2.2.3.4 to be conducted after withdrawal of consent.
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The patient has the right to object to the generation and processing of this post-withdrawal data. The patient's oral objection may be documented in the patient's source data.

Each patient / legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the patient / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The patient / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient´s clinical record must clearly show that informed consent was obtained prior to these procedures.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.
2. For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The informed consent form and any other written information provided to patients / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to

the protocol that necessitates a change to the content of the patient information and / or the written informed consent form. The investigator will inform the patient / legal representative or proxy consenter of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

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.

13.6 Compensation for health damage of patients / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the CRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient’s identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

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15. Protocol amendments

15.1 Amendment 5

Amendment 5 is presented using an updated approach. The rationale for changes in this amendment and all affected sections are provided right before the Table of Contents in this document. The detailed description of changes compared to the last global CSP version is replaced by a track change protocol separate from this document.

16. Appendices

16.1 Estimation of glomerular filtration rate (eGFR) using modification of diet in renal disease

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the eGFR, calculated using the abbreviated MDRD Study equation.

This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older. The formula is as follows:

GFR (mL/min/1.73 $m^{2)}$ = k × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American),

where

k=175 if serum creatinine was measured by methods calibrated to an IDMS reference method.

For the purpose of the study, it is recommended to use Bayer-verified calculator (preferred) or online MDRD GFR calculator at http://mdrd.com/

A randomized, active-comparator-controlled, multicenter study to assess the safety and efficacy of different doses of BAY 1213790 for the prevention of venous thromboembolism in patients undergoing elective primary total knee arthroplasty, open-label to treatment and observer-blinded to BAY 1213790 doses

FactOr XIa inhibiTion for the pRevention of venOus Thromboembolism in patients undergoing total knee arthroplasty

Bayer study drug	BAY 1213790 / Anti-FXIa antibody		
[Study purpose:]	To assess the safety and efficacy of a range of doses of BAY 1213790 in patients undergoing total knee arthroplasty (TKA)		
Clinical study phase:	IIa	**Date:**	28 NOV 2018
Study No.:	17664	**Version:**	3.0
Author:	Bastian Becker Thomas Schmelter		

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

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

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List of Abbreviations

AAOS	American Academy of Orthopedic Surgeons
ACCP	American College of Chest Physicians
ADA	anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AP	Asia Pacific
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CSR	Clinical Study Report
DVT	deep vein thrombosis
eCRF	electronic case report form
FAS	full analysis set
FFP	fresh frozen plasma
FIX	Factor IX
FSH	follicle stimulating hormone
FVIIa	Factor FVIIa
FVIII	Factor VIII
FXa	Factor Xa
FXI	Factor XI
FXIa	Factor Xia
FXI-ASO	Factor XI-antisense oligonucleotide
FXII	Factor XII
GCP	Good Clinical Practice
HEOR	Health Economics, Outcomes & Reimbursement
ICH	International Committee on Harmonization
ITT	Intent-to-treat
IDMC	independent data monitoring committee
IEC	independent ethics committee
LOS	Listing only set
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat Set
N/A	Not applicable
PD	pharmacodynamic(s)
PDC	premature discontinuation
PE	pulmonary embolism
PG	pharmacogenomics
PGt	pharmacogenetics
PK	pharmacokinetic(s)
popPK	population pharmacokinetics
popPK/PD	population pharmacokinetic(s)/pharmacodynamic(s)

PPS	Per-protocol set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class
TKA	total knee arthroplasty
VKA	vitamin K antagonist
VTE	venous thromboembolism

1. Introduction

This SAP is based on Study Protocol version 1.0 (dated 27 MAR 2017).

Background

Venous thromboembolism (VTE) is a common disorder; however the reported numbers vary widely from 250,000 to up to 900,000 cases per year in the United States. The estimated annual incidence rates of VTE, among people of European ancestry, range from 104 to 183 per 100,000 person-years, rates that are similar to stroke. VTE is one of the most frequent serious complications after total knee replacement surgery, and in the absence of thromboprophylaxis, 50-60% of these patients will develop VTE events, including deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Most of these events are asymptomatic; symptomatic VTE occurs in approximately 4% of patients within the first month after surgery. After elective total knee arthroplasty (TKA), DVT as assessed by venography occurs in 41-85% of patients 7-14 days after surgery.

As patients undergoing total joint replacement are at high risk for VTE, the use of routine thromboprophylaxis is recommended in the guidelines issued by American Academy of Orthopedic Surgeons (AAOS), American College of Chest Physicians (ACCP) and the United Kingdom National Institute for Health and Clinical Excellence (UK NICE). With the exception of the AAOS guideline, which does not recommend any prophylactic treatment in particular, various pharmacologic agents are recommended by ACCP and NICE for VTE prevention in patients undergoing total knee arthroplasty: vitamin K antagonists (VKA), indirect factor Xa inhibitors like enoxaparin and fondaparinux, or direct oral anticoagulants like Factor Xa or Factor IIa inhibitors. Whilst the use of aspirin as a stand-alone prophylactic treatment in these patients is now supported by ACCP and AAOS (either implicitly or explicitly), the UK NICE guideline does not include aspirin among its recommended treatments. Furthermore, the U.S Surgical Care Improvement Project measures include aspirin only as an adjunct to compression devices and not as sole option for the prevention of VTE in total knee arthroplasty patients. Hence the use of aspirin alone seems still controversial and not widely accepted by orthopedic surgeons. Intermittent compression devices are also recommended by current ACCP guidelines but their use as a stand-alone option or as an adjunct to chemoprophylaxis is supported by a weaker evidence (1C and 2C recommendation strength respectively). VKAs (e.g. warfarin or phenprocoumon) have narrow therapeutic window and therefore are associated with an extremely variable patient-to-patient response, along with extensive food and drug interactions. Consequently, close monitoring and potential dose adjustments are required to attain an appropriate VTE prophylaxis by achieving the targeted international normalized ratio (INR). Moreover, it can take days for VKAs to exhibit their full anticoagulation potential.

Both LMWH and fondaparinux require daily subcutaneous (SC) injection for drug administration. This may impact on patient acceptance as well as compliance, specifically during extended prophylaxis, which in some cases may last for several weeks.

Direct oral anticoagulants targeting FXa like rivaroxaban or apixaban or FIIa like dabigatran, demonstrated equivalent or superior efficacy as compared to enoxaparin and are available in many countries for VTE prevention in orthopedic patients. In contrast to other oral anticoagulants, they do not need monitoring of coagulation parameters and have no significant

food and drug interactions. Whilst all of the antithrombotic agents described above have been shown to be efficacious in the prevention of VTE after orthopedic surgery, their use is always associated with a variable bleeding risk, which is therefore considered unavoidable.

Factor XI (FXI) is a new coagulation target with the potential to reduce the incidence of more severe bleeding events in patients requiring thromboprophylaxis. The identification of FXI as a new target was supported by in vitro coagulation models, genetically modified FXI knockout mouse models, animal models of thrombosis and hemostasis, and human physiology.

The formation and the stability of clots are enhanced by FXI in in vitro experiments. Furthermore, FXI amplifies thrombin generation when coagulation is initiated by low levels of tissue factor (TF) or thrombin. FXI-dependent amplification of thrombin formation also leads to activation of the thrombin-activable fibrinolysis inhibitor, which renders clots less sensitive to fibrinolysis. Therefore, a FXI inhibitor might indirectly enhance clot dissolution. Yet, the most solid evidence, which supports FXI as a potential therapeutic target comes from patients, including patients with congenital factor XI deficiency as well as results from a recent study testing an antisense oligonucleotide (ASO) targeting FXI in patients undergoing elective TKA. Observational studies analyzing FXI deficient patients suggest that these patients have a very low incidence of ischemic stroke and VTE events. More importantly, the FXI-ASO (ISIS 416858), a second generation antisense oligonucleotide that specifically reduces factor XI levels has demonstrated promising results in a first study in patients undergoing elective TKA.

BAY 1213790

BAY 1213790 is a fully human IgG1 antibody (anti-factor XIa antibody BAY 1213790) that binds specifically to factor XIa, close to the catalytic center, and thus modifies the factor's recognition site for binding of its natural substrates such as factor IX, leading to inhibition of enzymatic activity.

Clinical experience

Up to now, there was one first-in-man study #17188 conducted. This was a randomized single-blind placebo-controlled dose escalation study to investigate safety, tolerability, pharmacokinetic and pharmacodynamic properties of BAY 1213790 after intravenous dosing. So far, single i.v. doses of 0.015, 0.060, 0.15, 0.3, 0.6, 1.25, 2.5, and 5.0 mg per kg individual body weight (BW) were administered and analyzed in an interim analysis. Up to 10 mg per kg BW has been administered and was well tolerated.

Treatment with BAY 1213790 at a single i.v. dose of 0.06 mg/kg BW and higher significantly increased the activated partial thromboplastin time (aPTT). aPTT further increased with increasing dose of BAY 1213790. No effect on prothrombin time (PT) and bleeding time, measured with a Surgicutt test, was seen at doses up to 5.0 mg/kg BW. Pharmacokinetics of the compound showed C_{max} and AUC increased dose dependently after i.v. administration. The overall PK variability was low to moderate for AUC (geo. CV 12-33%) and low for C_{max} (geo. CV 11-17%) in healthy male white subjects. The mean apparent terminal half-life was in the range of 700 to 800 h, which is approx. 30 days.

The safety and tolerability showed only a few cases of treatment emergent AEs that were mostly mild in nature. No severe AE or drug related SAE have been reported. No cases of bleeding have been reported. One adverse event of special interest was reported in the dose

group of 0.6 mg/kg BW of BAY 1213790, this AE included feeling of warmth, nausea and vomiting. All symptoms stopped on the same day and the subject recovered completely without any sequelae. Overall, treatment with BAY 1213790 at single i.v. doses from 0.015 to 5.0 mg administered as infusion over 60 minutes was well tolerated and considered as safe.

The dose prediction based on preclinical data (disease models), data collected in Phase 1 (population PK and PD analysis) and in-silico modeling anticipate that 0.3, 0.6, 1.2, and 1.8 mg/kg bodyweight will provide an effective reduction of VTE events, i.e. sufficient thromboprophylaxis for patients undergoing elective TKA in the current study.

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

Rationale of the study

It is well known that patients undergoing orthopedic surgery (total knee or hip replacement) have a high risk for VTE in the absence of thromboprophylaxis. BAY 1213790 has the potential to provide an efficacious VTE prevention treatment by targeting FXI with a favorable risk profile for unwanted bleeding. This Phase IIa study will for the first time investigate the safety and efficacy of BAY1213790 in patients undergoing TKA.

2. Study Objectives

Primary objective:

- To assess the safety and efficacy of different doses of BAY 1213790 in comparison with those of enoxaparin in patients undergoing elective, primary, unilateral total knee arthroplasty (TKA)

Secondary objective:

- To compare the safety and efficacy of BAY 1213790 with those of apixaban

Exploratory objective:

- To assess the dose-response relationship of BAY 1213790 for efficacy and safety
- To characterize the pharmacokinetic and the pharmacodynamics profile of BAY 1213790 and the relationship between both

Other objective:

- To further characterize BAY 1213790 by evaluating additional PD markers
- To investigate the mechanism of thrombosis by analyzing additional PD markers

3. Study Design

This study is an open label, active comparator-controlled, randomized, multicenter study with observer-blinding of different doses of BAY 1213790, and it is to be conducted in patients undergoing elective, primary, unilateral total knee arthroplasty. The study will assess two different BAY 1213790 administration schemes, either drug administration after surgery (post-surgery administration part, A) or drug administration before surgery (pre-surgery administration part, B). All efficacy and safety parameters will be centrally adjudicated by a central independent adjudication committee (CIAC) which is blinded to treatment allocation.

See Figure 3–1, Figure 3–2 and Figure 3–3.

Following Screening, eligible patients will be randomized on the last day of the Screening phase, Day 1. A total of 700 patients are planned be randomized with the possible extension to a maximum of 900 patients, in case of opening of additional BAY 1213790 arms or a high proportion of venographies of inadequate quality.

The 700 patients will be randomized to BAY 1213790 arms (3 observer-blinded doses with 100 patients in each arm during the post-surgery part (A) and 2 observer-blinded doses with 100 patients in each arm during the pre-surgery part (B)), or to the comparator arms (enoxaparin, apixaban; 100 patients in each arm). Randomization ratio will thus be 5:1:1 ([pooled] BAY 1213790 arms: enoxaparin: apixaban). In case additional BAY 1213790 arms are introduced (and none are closed), the randomization will be adapted in order to obtain balanced sample sizes across all BAY 1213790 arms, and a randomization ratio of 5:1:1 between each BAY 1213790 arms and each of the comparator treatment arms at the end of the study. Based on recommendations from the Steering Committee, the sample size for a specific dose of FXIa might be increased while reducing the sample size for the other dose so that the planned total number of a maximum of 900 patients is not exceeded.

Eligible patients will be randomized to one of the following treatment arms:

Post-surgery administration part (A):

- BAY 1213790 0.3 mg/kg administered intravenously for at least 100 patients once in the morning of the day following TKA
- BAY 1213790 0.6 mg/kg administered intravenously for at least 100 patients once in the morning of the day following TKA
- BAY 1213790 1.2 mg/kg administered intravenously for at least 100 patients once in the morning of the day following TKA
- enoxaparin 40 mg administered subcutaneously for at least 60 patients, started either in the evening before TKA or 6-8 hours after TKA (at investigator's discretion), followed by daily subcutaneous injections for at least 10 days and until venography is performed (Day 12+3) or
- apixaban 2.5 mg administered orally for at least 60 patients twice daily starting on the day after the TKA (within 12 to 24 hours after surgery) and at least for 10 days post-surgery and until venography is performed (Day 12+3)

If randomization to the lowest BAY 1213790 arm is prematurely stopped due to an unexpectedly high rate of thrombotic events, a fourth arm (1.8 mg/kg) may be initiated with up to 100 patients.

If randomization to the highest BAY 1213790 arm (1.2 mg/kg) is prematurely stopped due to an unexpectedly high rate of bleeding events, patients still to be randomized may be distributed between the two lower arms (0.3 mg/kg and 0.6 mg/kg).

After the evaluation of the primary endpoint of at least 75% of patients who underwent the post-surgery administration part (A) the IDMC will make a recommendation and the SC will then advise whether or not the pre-surgery administration part (B) will be initiated. The SC will also recommend on the adaption of the doses to be investigated in the pre-

surgery administration setting (details are specified in the respective IDMC and SC charters).

Pre-surgery administration part (B):

- BAY 1213790 0.3 mg/kg administered intravenously for at least 100 patients once in the second half of the pre-surgery day (Day 1), the day before TKA
- BAY 1213790 1.2 mg/kg administered intravenously for at least 100 patients once in the second half of the pre-surgery day (Day 1), the day before TKA
- enoxaparin 40 mg administered subcutaneously for at least 40 patients, started either in the evening before TKA or 6-8 hours after TKA (at investigator's discretion), followed by daily subcutaneous injections for at least 10 days and until venography is performed (Day 12+3) or
- apixaban 2.5 mg administered orally for at least 40 patients twice daily starting on the day after the TKA (at the latest 24 hours from wound closure) and at least for 10 days post-surgery and until venography is performed (Day 12+3)

Before start of the part B, the doses in the two BAY 1213790 arms might be selected differently, based on IDMC recommendation and SC advice after the evaluation of the primary endpoint of at least 75% of the patients who underwent the post-surgery administration part. The selected doses will be either 0.3, 0.6, 1.2, or 1.8 mg/kg.

If randomization to the lowest BAY 1213790 arm, in the pre-surgery administration part, is prematurely stopped due to an unexpectedly high rate of thrombotic events, a third arm with a higher dose, may be initiated with up to 100 patients. Possible doses of such dose arm depend on the IDMC recommendation/SC advice on the doses to be tested in the pre-surgery setting. Doses for this additional arm are either 0.6, 1.2, or 1.8 mg/kg if not initially selected as starting doses for the pre-surgery administration part.

If randomization to the highest BAY 1213790 arm is prematurely stopped due to an unexpectedly high rate of bleeding events, patients still to be randomized may be randomized to either the already started lower dose arm or to a newly initiated third dose arm with a lower dose than the one closed. Up to 100 patients may be randomized to this newly initiated dose arm. Possible doses of such arm depend on the IDMC recommendation/SC advice on doses to be tested in the pre-surgery setting. Doses for this additional BAY 1213790 arm are either 1.2mg/kg, 0.6 mg/kg or 0.3 mg/kg if not initially selected as starting doses for the pre-surgery administration part.

Figure 3–1: Study overview post-surgery (part A) and pre-surgery (part B) administration parts

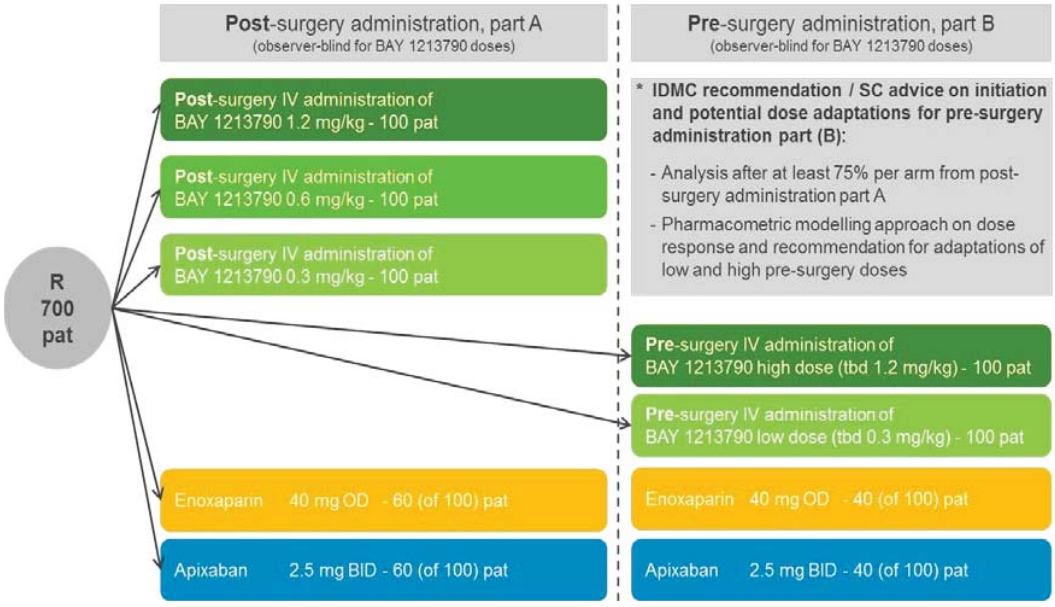


Figure 3–2: Study overview post-surgery administration part (part A)

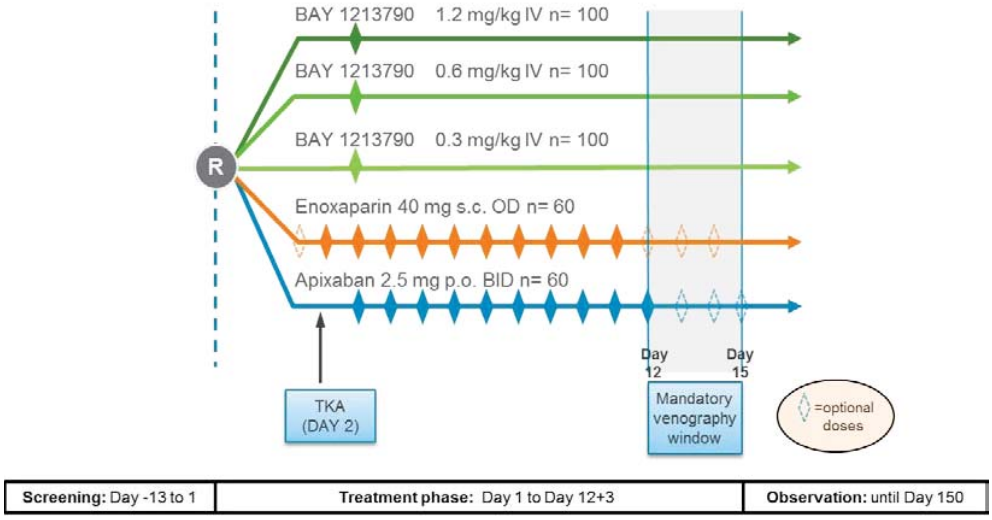
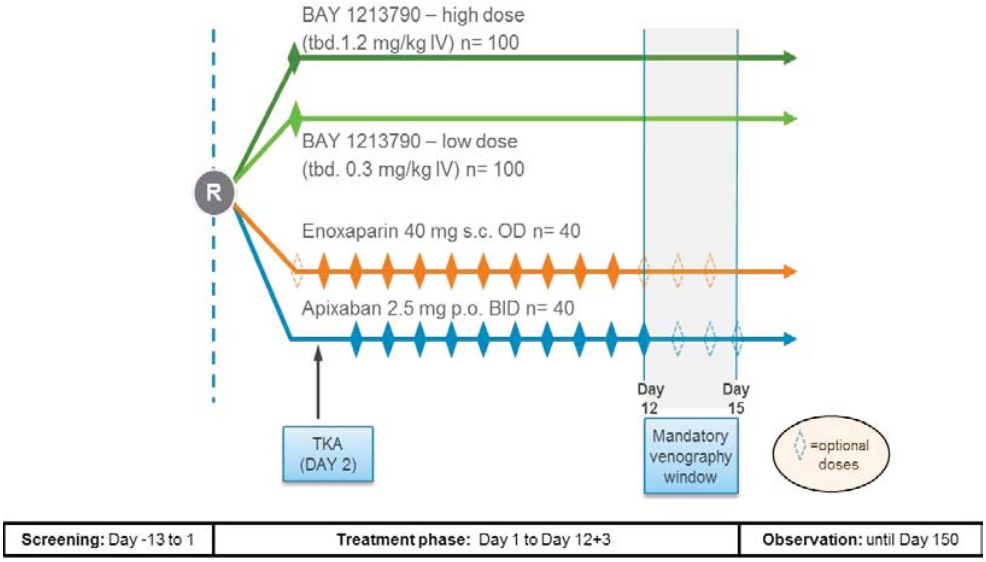


Figure 3–3: Study overview pre-surgery administration part (part B)



3.1 Efficacy variables

- Primary efficacy variable: The incidence of composite endpoint consisting of asymptomatic DVT, detected by mandatory bilateral venography, and objectively confirmed symptomatic DVT or non-fatal PE, fatal PE and unexplained death for which PE cannot be excluded up to Visit 7 (Day 12+3)
- Secondary efficacy variable: The incidence of symptomatic DVT or non-fatal PE, fatal PE and unexplained death for which PE cannot be excluded up to Visit 10 (Day 150±7) or objectively confirmed asymptomatic DVT up to Visit 7 (Day 12+3)

When interpreting the results for the secondary efficacy endpoint it should be noted that this is a composite endpoint of composites with different time window.

- Other efficacy variables: Incidence of DVT (total, proximal, distal), Incidence of bilateral DVT (total, proximal, distal), Incidence of symptomatic VTE (total, DVT, PE), Incidence of asymptomatic VTE (total, DVT, PE), Incidence of death (total, fatal PE, unexplained death for which PE cannot be excluded, non-PE death)

Only positively adjudicated events will be considered for primary and secondary endpoints.

3.2 Safety variables

- Primary safety variable: The incidence of major and clinically relevant non-major bleeding up to Visit 7 (Day 12+3)
- Secondary safety variable: The incidence of major and clinically relevant non-major bleeding up to Visit 10 (Day 150±7)
- Other safety variables: Incidence of (any, non-major, major) post-operative bleeding (the post-operative period starts 6 hours after end of surgery and ends at the end of visit 7 (Day 12+3))

Only positively adjudicated events will be considered for the primary and secondary safety variables.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

4.2 Handling of Dropouts

In this study all efforts must be taken to engage patients to comply with all study procedures and to continue to be followed until the end of the study.

In general, patients who permanently discontinue study treatment are expected to continue to attend all protocol-specified study visits, and should be encouraged to perform all assessments described in the visit schedule and provide information about their health status.Depending on the time point of withdrawal, a withdrawn patient is referred to as either “screening failure” or “dropout”. A patient who, for any reason, terminates the study before randomization is regarded a “screening failure”. A patient who discontinues study participation prematurely for any reason is defined as a “dropout” if the patient has already been randomized. A patient who is randomized but did not take the study medication is not a Screen Failure the patient is a Drop Out.

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records.

If a patient prematurely discontinues the study during the treatment phase, the Premature discontinuation visit (PDC) will take place as soon as possible.

The number of subjects who prematurely discontinue the study during the treatment phase or during the post-treatment observation phase for any reason, as well as the reasons for premature discontinuation of study, will be displayed by treatment arm. Baseline characteristics will be displayed by premature discontinuation (yes/no) from study.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

General rules

When appropriate, the following rules will be implemented for the analyses so as not to exclude subjects from statistical analyses due to missing or incomplete data:

- **Efficacy and Safety clinical variables, adverse events**
  For cases where start month and year are reported but day is missing, impute the maximum of (date of randomization, first date of study medication, 01.month.year).
  For cases where only start year is reported, impute the maximum of (date of randomization, first date of study medication, 01.01.year), but not later than death date if the patient died.
- **Study medication start date**
  If the start date and time is missing it will be imputed with the randomization date and time. If start date and time is recorded as earlier than randomization and cannot be clarified, date and time of randomization will be used for the statistical analysis.
- **Study medication stop date**
  If the stop date of BAY 1213790 study medication is missing, it will be imputed as identical to the start date. If the stop day of Enoxaparin or Apixaban is missing, but the stop month and stop year are available then the stop date will be imputed as minimum of (15.month.year and last study visit date and death date).
  If the stop day and month are missing then the stop date will be imputed as minimum of (the last study visit date before the observational visit and death date).

4.4 Interim Analyses and Data Monitoring

The IDMC will continuously monitor the safety of the patients. Furthermore, together with the SC the IDMC will review the available data after 75% of the patients in the post-surgery part have completed Visit 7. These data will be provided to the IDMC as part of the regular IDMC review and to the SC for evaluation (no formal interim analysis will be performed) to give their recommendation/advice regarding the start of the pre-surgery part and the doses to be used therein. A summary of such data assessment, including the IDMC and SC recommendations plus the decision taken, along with a justification, will be made available to IECs /IRBs, as well as local authorities for either notification or approval in conformity with local law, regulations, and requirements.

In addition, interim analyses may be performed to assess both efficacy and safety in support of the future clinical development of BAY 1213790 after finalization of the post-surgery administration and after finalization of the post-treatment observation phase of part (A) of the study, which means all patients randomized for the post-surgery administration part have completed Visit 7 respectively have completed Visit 10. An additional interim analysis is considered after all patients from both parts have completed Visit 7. No formal report will be written.

Note that these are not interim analyses in the sense of a group-sequential or adaptive design, and no early stopping for efficacy is planned based on the results. Furthermore all data for the respective endpoints will be available at te time of the interim analysis. Therefore, no adjustment for multiplicity is required.

4.5 Data Rules

Only the values took on scheduled visits will be used for all visit based analyses. Data collected on unscheduled visits will be listed.

4.5.1 Data scopes

The primary analysis will be based on all respectice events that occurred during the treatment phase, i.e. in the time-window between randomization (Visit 2) and the mandatory venography visit (Visit 7).

The secondary analysis will be based on all respectice events that occurred during the study, i.e. in the time-window between randomization (Visit 2) and the end of study visit (Visit 10).

The analysis of the adverse events will be based on treatment emergent events, i.e. all respecitive events that occurred between start of treatment and not later than five month afterwards.

In addition, further analyses will be based on:

- All events occuring after the mandatory venography visit and up until the end of study visit (Observation phase)
- All events occuring after or at Randomization and until TKA surgery (Pre-TKA phase)
- All events occuring after or at Randomization and until end of TKA surgery
- All events occuring 6 hours after TKA surgery until venography visit
- All events occuring before Randomization

4.5.2 Baseline values

Baseline values for vital sign measures are planned to be taken at randomization. If values are not available up to randomization, values taken before TKA will be considered. In case of more than one available lab value the non-missing value closest to randomization will be taken.

4.6 Blind Review

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see section 4.6).

Per Protocol Set (PPS)

All patients that received at least one dose of study drug, had a valid venography at Day 12+3 (or an objectively confirmed symptomatic VTE before Day 12+3), and did not have an important deviation from the protocol or validity finding having an impact on the primary efficacy variable. This includes the following:

- The exclusion criteria "Prior deep vein thrombosis" or "Body weight above 135 kg" were fulfilled
- A dose of study drug was administered which deviates significantly from the protocol guidance
- Prohibited Concomitant medications were taken during study, namely anticoagulation or dual antiplatelet therapy during the treatment phase (low dose of acetylsalicylic acid is allowed, and in cases of symptomatic DVT or PE, confirmed by objective testing at the Investigator site, anticoagulants at therapeutic doses may be started at the Investigator's discretion if deemed necessary)

Further details will be specified in the Protocol Deviation Document.

Modified Intention-to-Treat Set (mITT)

All patients that received at least one dose of study drug, had a valid venography at Day 12+3 (or an objectively confirmed symptomatic VTE before Day 12+3).

Safety Set (SAF)

The safety set will include all patients that received at least one dose of study drug.

The primary analysis set for the efficacy evaluation will be the PPS with sensitivity analyses performed on the mITT and SAF. The primary analysis set for safety analysis will be the SAF.

Efficacy analyses on the PPS will be conducted using the treatment arms that the patients actually received (as treated), while efficacy analyses on the SAF will be conducted using the treatment arms as randomized (following the ITT principle).

Safety analyses on the SAF will be conducted using the treatment arms as treated.

PK analysis sets

All patients that received BAY 1213790 and with at least 1 valid BAY 1213790 plasma concentration in accordance with the PK sampling strategy and without deviation from the protocol that would interfere with the evaluation of the PK data. This includes the following:

- A dose of BAY 1213790 was administered which deviates significantly from the protocol guidance

PD analysis set

All patients that received at least one dose of study drug with at least 1 blood sample for PD marker in accordance with the PD sampling strategy and without deviation from the protocol that would interfere with the evaluation of the PD data. This includes the following:

- A dose of study drug was administered which deviates significantly from the protocol guidance

6. Statistical Methodology

The evaluations will be conducted on each BAY 1213790 arm (dose level, time of administration (pre- vs. post-surgery)), the Enoxaparin and Apixaban arm (no separation between part A and B).

In addition, the primary and secondary efficacy and safety analyses will be conducted on

- each post-surgery BAY 1213790 arm, part A Enoxaparin arm (first 60 subjects), part A Apixaban arm (first 60 subjects)
- each pre-surgery BAY 1213790 arm, part B Enoxaparin arm (last 40 subjects), part B Apixaban arm (last 40 subjects)
- pooled post-surgery BAY 1213790 arm (i.e. all dose levels), Enoxaparin arm (part A and part B), Apixaban arm (part A and part B)
- pooled pre-surgery BAY 1213790 arm (i.e. all dose levels), Enoxaparin arm (part A and part B), Apixaban arm (part A and part B)
- pooled post-surgery BAY 1213790 arm, pooled pre-surgery BAY 1213790 arm
- post-surgery BAY 1213790 arm(s), dose corresponding pre-surgery BAY 1213790 arm(s)

6.1 Population characteristics

6.1.1 Demography and baseline characteristics

Demographic and baseline data will be evaluated descriptively for the SAF as well as for the PPS, by treatment groups and overall. No statistical tests will be performed to compare these characteristics across treatment groups.
Descriptive statistics (such as mean, standard deviation, median, quartiles (inter quartile range), minimum and maximum) will be provided for continuous variables such as

- age at Screening
- body weight
- body height
- calculated BMI

Counts and (appropriate) percentages will be provided for categorical variables such as

- year of birthsex
- race/ethnicity
- Smoking history and alcohol consumption
- Creatinine clearance

Reasons for exclusion from analysis populations will be summarized.

6.1.2 Medical history

Medical history data will be evaluated by frequency tables, showing the number and percentage of subjects with medical history findings ((i.e. previous diagnoses, diseases or surgeries) that started before signing of the informed consent and that are considered relevant to the study using MedDRA Primary System Organ Class / Prefered Term.

6.1.3 Prior and Concomitant Medication

The dictionary used for coding concomitant medications is the World Health Organization Drug Registration and Listing. Frequency tables displaying frequency of subjects for each drug category summarized by Anatomical Therapeutic Chemical (ATC) and coded terms will be used to summarize the number and percentage of subjects with prior medications where administration stopped prior to the date of informed consent,, concomitant medications administered between signing of the informed consent and the end of post-treatment observation phase (Visit 10) and new concomitant medications administered between start of study medication and end of post-treatment observation phase (Visit 10). Frequency tables of subjects taking prohibited concomitant medications.

6.2 Efficacy

6.2.1 Primary efficacy analysis

The primary efficacy variable is the incidence of composite endpoint consisting of asymptomatic DVT, detected by mandatory bilateral venography, and objectively confirmed symptomatic DVT or non-fatal PE, fatal PE and unexplained death for which PE cannot be excluded up to Visit 7 (Day 12+3). For the analysis of the primary efficacy variable only positively adjudicated events will be considered.

The analysis for the primary efficacy variable will be conducted separately for each arms of BAY 1213790.

Let p_{XI} and $p_E$be the true probabilities for a primary endpoint event in the considered BAY 1213790 arm and the enoxaparin arm. Let Δ=5% denote the non-inferiority margin. This chosen NI margin of 5% is assumed to provide sufficient information for conclusions regarding the similarity between two of the treatment arms in this Phase 2 setting.

For the primary efficacy variable the following hypotheses will be tested:

1. Non-inferiority of BAY 1213790 arm compared to enoxaparin
$$H_0: p_{XI} \geq p_E + \Delta \quad vs. \quad H_1: p_{XI} < p_E + \Delta$$
2. Superiority of BAY 1213790 arm compared to enoxaparin
$$H_0: p_{XI} \geq p_E \quad vs. \quad H_1: p_{XI} < p_E$$

These one-sided hypotheses will be tested for each BAY 1213790 arm (dose level, time of administration (pre- vs. post-surgery)) to a global significance level of α=5%. In order to adjust for the multiplicity within arm a fixed-sequence procedure will be applied: Each of the single tests will be performed at the full alpha level of α=5% in the order given above up to the first null hypothesis in this sequence that cannot be rejected. The hypotheses later in this

sequence cannot be rejected. No adjustment will be done for the multiplicity caused by the five arms.

For the tests the two-sided 90% confidence intervals for the difference in the proportions of BAY 1213790 dose arm versus enoxaparin will be calculated based on normal approximation. The hypotheses will be tested by comparing the lower limit of the two-sided 90% confidence interval with the NI margin Δ=5% (for the NI tests) or with 0 for the superiority tests. Aditonally the proportions of patients with the respective event will be provided.

The comparison between the BAY 1213790 arms and apixaban will be descriptively only by providing the proportion of patients with the respective event. No hypothesis testing will be applied. 90% Confidence intervals for the difference in proportions between each of the BAY 1213790 arms and apixaban will be provided based on normal approximation.

The following exemplary SAS code will be:

```
proc freq data=<data> order=data;
   tables <treat>*<event> / riskdiff (cl=wald alpha=0.10);
   exact riskdiff;
run;
```

As an adequate venogram is necessary for the determination of the primary endpoint, the primary analysis will be conducted on the PPS, thus no imputation of missing data is necessary for the primary analysis.

Additional a descriptive analysis will be provided on the mITT similar to the comparison between the BAY 1213790 arms and apixaban as descripted above.

6.2.2 Secondary efficacy analysis

The secondary efficacy variable is the incidence of symptomatic DVT or non-fatal PE, fatal PE and unexplained death for which PE cannot be excluded up to Visit 10 (Day 150±7) or objectively confirmed asymptomatic DVT up to Visit 7 (Day 12+3).

The analysis of the secondary efficacy variable will be done descriptively by providing the proportion of patients with the respective event. Furthermore, 90% confidence intervals for the difference in proportions between each of the BAY 1213790 dose arms and the enoxaparin and apixaban arm respectively will be provided based on normal approximation.

The analysis will be provided on the PPS and additional on the mITT.

Other efficacy variables are the incidence of DVT (total, proximal, distal,), the incidence of bilateral DVT (total, proximal, distal), the incidence of symptomatic VTE (total, DVT, PE), the incidence of asymptomatic VTE (total, DVT, PE) and the incidence of death (total, fatal PE, unexplained death for which PE cannot be excluded, non-PE death).

The analysis of the other efficacy variables will be done analogues to the analysis of the secondary efficacy variable as described above taking into account events occurring between randomization (Visit 2) (visit Visit 1) and the mandatory venography visit (visit Visit 7) and events occurring between randomization (Visit 2) (visit Visit 1) and the end of study visit (visit Visit 10)..

6.2.3 Additional analyses

The secondary efficacy variable will be additionally analyzed as time to event variable on the PPS ,SAF and mITT.

Time to event is defined as the time from randomization to the first outcome contributing to the secondary efficacy outcome until end of study.

Patients who have no secondary efficacy outcome during the intended 150±7 days period, or patients lost to follow-up, or patients who die because of other reasons than DVT/PE, or patients who withdraw informed consent before the end of the predefined treatment duration, or administrative censoring at the end of the study and who do not have a secondary efficacy outcome will be censored at the last contact date assuming that these types of censoring are independent of the outcome.

As this is a liberal censoring approach for the SAF, we will additionally apply a conservative approach for the SAF. Here patients who have no secondary efficacy outcome during the intended 150±7 days period, or patients lost to follow-up, or patients who die because of other reasons than DVT/PE, or patients who withdraw informed consent before the end of the predefined treatment duration, or administrative censoring at the end of the study and who do not have a secondary efficacy outcome will be censored at a minimum until the last contact date and day 12+3 (planned day for the venography visit).

For each treatment arm (BAY 1213790 dose arms and the enoxaparin and apixaban arm) the following parameters and analyses will be provided:
Kaplan-Meier product-limit estimates of the survival distribution functions, total number of subjects, total failed, total censored, survival time (median and its 90% confidence interval, 25th and 75th percentile, range), survival rates at 2, 4, 6, 8, etc. days and Kaplan-Meier curves. The following exemplary SAS code will be used:

```
PROC LIFETEST;
TIME  time * censor(0);
STRATA = treat;
```

The hazard ratio of each of the BAY 1213790 dose arms over enoxaparin and apixaban arm respectively and its 90% confidence interval will be generated from the Cox proportional hazard model, including treatment group as categorical explanatory variable using the following exemplary SAS code*:*

```
PROC PHREG;
MODEL  time * censor (0) = treatment;
```

An additional time to event analysis will analyse the primary efficacy variable. In this context time to event is defined as the time from randomization to the first outcome contributing to the primary efficacy outcome until day 12+3 (planned day for the venography visit). Thus the introduced liberal censoring approach as defined above will be applied.

The time to event analysis will be additionally performed for the following treatment arms:

- pooled post-surgery BAY 1213790 arm, Enoxaparin arm, Apixaban arm
- pooled pre-surgery BAY 1213790 arm, Enoxaparin arm, Apixaban arm
- pooled post-surgery BAY 1213790 arm, pooled pre-surgery BAY 1213790 arm

- post-surgery BAY 1213790 arm(s), dose corresponding pre-surgery BAY 1213790 arm(s)

Exploratory analyses of the dose-response relationship of BAY 1213790 will be conducted by applying a logistic regression model to the occurrence of the primary outcome variable with the dose arm as explanatory variable. Pearson goodness-of-fit analysis, an analysis of the effect of the dose and a plot of the regression curve will be presented.

The following exemplary SAS code will be used:

```
ods graphics on;
proc logistic data=Data1 plots(only)= effect;
     model <sumevent>/<n>=<dose> / scale=none clparm=wald clodds=pl
     alpha=0.1;
```

6.2.4 Subgroup analysis

Incidence of the primary efficacy variable and secondary efficacy variable, 90% confidence intervals for the difference in proportions between each of the BAY 1213790 dose arms and the enoxaparin and apixaban arm respectively based on normal approximation will be presented by the following subgroups:

- age group (<60 years, >=60 years)
- sex (male, female)
- race (white, black, Asian, other incl. not reported/unknown)
- Ethnicity (not Hispanic or Latino; Hispanic or Latino; Not reported)
- weight (<90kg, >=90kg)
- BMI (< 30 kg/m², >= 30 kg/m²)
- Country
- Type of anesthesia received (general, spinal) for part A
- History of thrombophilia (Yes/No)
- Use of prophylactic tranexamic acid prior to TKA surgery (Yes/No)

Forest plot will be provided.

6.2.5 Sensitivity analysis

Analyses of the primary and secondary efficacy variables on the SAF will be provided as sensitivity analyses. As the SAF includes all patients that were treated regardless of whether data for the primary variable is available, missing data needs to be accounted for.

Given the short duration of the study, the drop-out pattern can be considered to be unrelated to the primary outcome variable. Furthermore, the readability of venographies is considered to

be independent of the (missing) results of the read. Missing data for the primary variable can therefore be considered to be missing at random.

The analysis on the SAF will therefore be conducted using a multiple imputation method: A logistic regression model will be fitted to the data of patients without missing data for the primary variable using the treatment arm and baseline characteristics as factors/covariates. For a patient with missing primary endpoint data, the probability for an event will be predicted from this model based on his baseline characteristics and treatment arm and the missing outcome will be imputed multiple times from a Bernoulli distribution using this predicted probability.

The following exemplary SAS code will be used to achive this :

```
proc mi data=<data> nimpute=<n> seed=17664 out=<out>;
      class <event>,<class baseline>;
      monotone logistic( <event>= <baseline>/ details);
      var <event> <baseline>;
run;
```

Each imputed complete dataset will be analyzed separately using the following exemplary SAS code:

```
proc surveyfreq data=<out> order=data;
   tables <treat>*<event> / riskdiff (cl=wald alpha=0.10);
   var <event>
   domain _imputation_;
   ods output domain=<out2>
run;
```

The results will be combined using the following exemplary SAS code:

```
proc mianalyze data=<out2>;
       modeleffects <riskdiff> ;
       stderr <stderr> ;
run ;
```

Additionally, an analysis of the secondary efficacy variables restricted to the observation phase will be provided as sensitivity analyses. These analyses will be based on the PPS.

6.3 Pharmacokinetics/pharmacodynamics

PK variables

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

BAY 1213790 concentrations will be summarized by visit, separated according to actual dose.

Descriptive statistics of plasma concentrations [geometric mean and percent coefficient of variation (%CV), arithmetic mean and %CV, median and range] will be presented by dose 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.

The following plots will be provided:

- Geometric mean concentration vs. time curves of BAY 1213790 (using the planned sampling times for mean plots) will be plotted by active treatment using both linear and semilogarithmic scale.
- Plots will be prepared by treatment by pooling all individual plasma concentrations (naive pooling) vs actual relative study times (time of sample collection after time of study drug administration) using both linear and semi-logarithmic scale.

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 pharmacodynamics data will be displayed utilizing appropriate summary statistics and figures. aPTT, PT (seconds and INR), D-dimer, factor XI activity, factor XI concentration, and exploratory PD markers will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by BAY 1213790 dose for the original data as well as for the absolute and relative changes from baseline (aPTT, PT (seconds and INR), D-dimer, factor XI activity, factor XI concentration). In addition, for each patient 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.

6.4 Safety

6.4.1 Primary safety variable

The primary safety variable is the incidence of major and clinically relevant non-major bleedings up to Visit 7 (Day 12+3). For the analysis of the primary safety variable only positively adjudicated events will be considered.

The analysis will be done descriptively by providing the proportion of patients with the respective event. 90% confidence intervals (based on normal approximation) will be provided for the difference in proportions between each of the BAY 1213790 dose arms (separately for the post-surgery and the pre-surgery groups) and the enoxaparin arm (and the apixaban arm, respectively). In addition this analysis will be done for the pooled post-surgery BAY 1213790 groups and the pre-surgery BAY 1213790 groups.

To allow a fair comparison between the treatment groups, the primary analysis will include all events that occurred after randomization (i.e., events might be included that occurred before start of study drug treatment).

Additionally, the analysis described above will be repeated restricted to treatment emergent events (see section 4.5.1) as well as separately for each of the components (major bleedings and clinically relevant non-major bleedings)

6.4.2 Secondary safety variables

The secondary safety variable is the incidence of major and clinically relevant non-major bleeding up to Visit 10 (Day 150±7). Only positively adjudicated events will be considered

The same analyses as described for the primary safety endpoint will be conducted.

Other safety variables are the incidence of (any, non-major, major) post-operative bleeding (the post-operative period starts 6 hours after end of surgery and ends at the end of visit 7 (Day 12+3)).

The analysis of the other safety variables will be done analogues to the analysis of the secondary safety variable as described above. The analysis of the latter variable will take events into account that occurred between randomization (Visit 2) and the mandatory venography visit (visit Visit 7) and events occurring between randomization (Visit 2) and the end of study visit (visit Visit 10).

In addition the secondary safety variable will be analysed as a time-to-event endpoint analogous to section 6.2.3. Kaplan-Meier curves will be provided as well as pairwise hazard ratios based on a proportional-hazards model.

6.4.3 Adverse events

The investigator has to record on the respective CRF pages all adverse events (AEs) occurring in the period between the signing of the informed consent and the end of the post-treatment observation phase; after the end of the post-treatment observation phase there is no requirement to actively collect AEs including deaths.

The original terms used by investigators to report AEs via the CRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events during the study, i.e. after randomization will be summarized by means of AE tables based on the treatment-emergent data scope (see section 4.5.1).

For each AE, the number and percentage of subjects who experienced at least 1 occurrence of the given event will be tabulated according to the affected primary system organ class (SOC) and preferred term (PT) by treatment arm. A total column will be included in all safety summaries.

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

- if AE (/ SAE/AESI) occurred with causal relationship to study drug ,
- if AE (/SAE/AESI) occurred with casual relationship to study procdedures (venography or TKA)
- maximum intensity for any AE / any study-drug related AE,
- AE related deaths.
- AE resulting in permanent discontinuation of study drug

A similar table showing overall summary information of AEs during screening will be given.

In addition, frequency tables will summarize the number of subjects with

- any event occurring during pre-TKA phase (see section 4.5.1)
- any event occurring during treatment phase
- any event occurring during observation phase.

6.4.4 Vital signs

Vital signs (blood pressure and heart rate) obtained at Screening visit, Visit 2 (Day 1), Visit 3 (Day 2, before and after surgery), Visit 4 (Day 3 before study drug administration), Visit 5 (Day 4), Visit 6 (Day 6±1), Visit 7 (Day 12+3) Visit 8 (Day 30±5), Visit 9 (Day 90±7), Visit 10 (Day 150±7) as well as during premature discontinuation visit will be displayed by means of descriptive statistics and change from baseline.

6.4.5 Laboratory parameter

Only centrally analyzed blood samples will be considered for analysis.

Central laboratory parameters at Visit 2 (Day 1), Visit 4 (Day 3 before study drug administration), Visit 6 (Day 6±1), Visit 7 (Day 12+3) Visit 8 (Day 30±5), Visit 9 (Day 90±7), Visit 10 (Day 150±7) as well as during premature discontinuation visit will be displayed by means of descriptive statistics and change from baseline. High/low abnormalities by laboratory parameter will be presented. This includes various hematology (white blood cell count (WBC), red blood cell count (RBC), …), clinical chemistry (aspartate aminotransferase (AST), alanine aminotransferase (ALT), …) and urinalysis (color, appearance, specific gravity, …) parameters.

6.4.6 Pregnancies

Any pregnancy occurring in a study subject (or in partners of study subjects) during the subject's participation in this study will be displayed.

7. Document history and changes in the planned statistical analysis

- SAP finalized on 30 AUG 2017
- A further Interim Analysis were added to section 4.4 on 08 SEP 2017
- A further Subgroup Analysis were added to section 6.2.4 on 27 SEP 2017
- The definitions of the Per Protocol Set, PK analysis set and PD analysis set were refined, including an elaboration of the validity findings which have an impact on the primary efficacy variable , the PK or PD analyses on 21 NOV 2018.
- The definition of the other efficacy variable DVT (total, proximal, distal), were corrected by excluding the level "bilateral" and introduced the other efficacy variable bilateral DVT (total, proximal, distal) due to medical reasons on 21 NOV 2018
- Section 6.2.3 and 6.2.5 were corrected by acknowledging the fact that the secondary efficacy variable restricted on treatment phase is identical to the primary efficacy variable on the 21 NOV 2018
- The other safety variable incidence of surgical site bleedings associated with ≥ 2 g/dL fall in hemoglobin or leading to infusion of equal or more than 2 units of whole blood or packed cells were deleted from the SAP as this information is captured in the analysis of the components of ISTH major bleedings on 21 NOV 2018.

8. References

9. Appendix

9.1 Determination of sample size

It is targeted to randomize 100 patients to each of the 3 BAY 1213790 arms and 100 patients to the enoxaparin arm and the apixaban arm respectively.

Assuming that approximately 80 patients in each of treatment arm will be evaluable for the primary analysis, leads to the characteristics summarized in Table 10–1 for the primary endpoint analyses.

If, e.g., a true probability of 10% for a primary endpoint event is assumed for the BAY 1213790 arm and 25% for the enoxaparin arm, this would result in a power of 97% for showing non-inferiority and 81% for showing superiority.

Similarly if a probability for an event of 4% is assumed for the BAY 1213790 arm and 10% for apixaban, this leads to a probability of 90% that the upper limit of the 88% confidence interval for the difference between the BAY 1213790 arm and apixaban is below 5% (non-inferiority) and probability of 43% that it is below 0 (superiority).

Table 10–1: Sample size characteristics assuming 80 evaluable patients for BAY 1213790 and 100 patients for enoxaparin and apixaban

Comparison	Assumed true probability for event in BAY 1213790 arm	Assumed true probability for event in reference arm	Power for one-sided test (α=5%) for superiority	Power for one-sided test (α=5%) for non-inferiority Δ=5%
BAY 1213790 – enoxaparin	10%	25%	81%	97%
BAY 1213790 – enoxaparin	4%	25%	99%	99%
BAY 1213790 – apixaban	10%	10%	0%	29%
BAY 1213790 – apixaban	4%	10%	43%	88%

The sample size calculation assumes that for approximately 20% of the patients no evaluable venographies (due to quality or drop-out) will be available. After approximately 75% patients have completed Visit 7 (venography visit), this assumption will be assessed on the pooled data of all treatment arms in the post-surgery administration part (part A). If the estimated rate of unavailable venography results exceeds 30% the power for testing superiority of BAY 1213790 over enoxaparin (assuming a probability for an event of 10% for BAY 1213790 and 25% for enoxaparin) will drop below 75%. In this case the sample size may be increased to reach a power of 80%.