Bayer

CLINICAL STUDY PROTOCOL

Title:	**O**ral **Di**rect Factor **Xa** Inhibitor BAY 59-7939 in the Prevention of VTE in Patients Undergoing Total **Hip** Replacement. **ODiXahip** - a Phase IIa Dose Escalating Proof of Principle Trial
Test Drug:	BAY 59-7939
Sponsor's Name and Address:	BAYER Vital GmbH D-51368 Leverkusen
Sponsor's Telephone Number:	
Study Number/Version/Date:	10942/Version 1.10/2002/Oct/09
Development Phase:	IIa

Study Manager

Name: PPD PPD Signature: _____

Date:

Statistician

Name: PPD PPD Signature: _____

Date:

Medical Expert

Name: PPD PPD Signature: _____

Address: BAYER Vital GmbH
PH-MED/CV, Building D162
D-51368 Leverkusen

Date:

Telephone: PPD

CONFIDENTIAL

Additional Signatures

Name: Signature: _____

Function: Date:

Address:

Name: Signature: _____

Function: Date:

Address:

The undersigned confirm that they agree to conduct the study under the conditions described in this protocol

Name: PPD PPD Signature: _____

Function: Principal Investigator Date:

Address: PPD
Sweden

Telephone: PPD

Name: Signature:

Function: Principal Investigator of the country Date:

Address:

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Glossary and Abbreviations

AC/BE	Adjudication Committee/Bleeding Event
AC/V	Adjudication Committee/Venography
AC/VTE	Adjudication Committee/Venous Thromboembolic Events
AE	Adverse Event
ALT	Alanine Transaminase (also known as SGPT, *qv)*
aPPT	Activated Partial Thromboplastin Time
ASA	Acetylsalicylic Acid
AST	Aspartate Transaminase (also known as SGOT, *qv)*
ATC	Anatomical Therapeutic Chemical Classification
BID	Bis in Die
C_{max}	Maximum Drug Concentration in Plasma after single Dose Administration
CK	Creatine Kinase
COX 2	Cyclooxygenase 2
CAC	Central Adjudication Committee
CRF/eCRF	Case Report Form either paper or electronic
CT	Computed Tomography
CVA	Cerebrovascular Attack
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
gamma GT	gamma Glutamyl Transpeptidase
GCP	Good Clinical Practice
GDS	Global Drug Safety (BAYER internal)
HDPE	High Density Polyethylene
HIT	Heparin-Induced Thrombocytopenia
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International Units
IV	Intravenous
LDH	Lactate Dehydrogenase
LDUH	Low Dose Unfractionated Heparin
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NSAID	Nonsteroidal anti-inflammatory Drug
NYHA	New York Heart Association
od	Once Daily
PE	Pulmonary Embolism
PT	Prothrombin Time (in seconds)
PTINR	Prothrombin Time expressed as International Normalised Ratio
qv	*quod vide*, which see
q8(12)hr	Every 8(12) hours
RBC	Red Blood Cell (Count)
RDE	Remote Data Entry

SAC	Safety Assessment Committee
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Steering Committee
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TID	Tris in Die
THR	Total Hip Replacement
ULN	Upper Limit of Normal
US	Ultrasound
V/Q scan	Ventilation/Perfusion Scan
VTE	Venous Thromboembolism
WBC	White Blood Cell (Count)
WHO-DD	World Health Organisation – Drug Dictionary

1. INTRODUCTION

Haemostasis is a normal physiological process following damage of the vascular system. In disease, however, the haemostasis mechanisms are inappropriately activated with pathological consequences known as thrombosis. After the German Pathologist Virchow a triad is named which states that thrombosis occurs as a result of abnormalities of blood vessel wall (e.g. vascular injury), blood flow (e.g. circulatory stasis) and/or properties of blood (hypercoagulable state).

Arterial and venous thromboembolism represents one of the most common health problems in the developed world. Cardiovascular disease (CVD) is the number one cause of death. Venous thromboembolism (VTE) including deep vein thrombosis and pulmonary embolism is also a common cause of mortality and morbidity. Patients undergoing surgery, especially hip and knee surgery, are at high risk for venous thromboembolism. The rates of DVT after hip surgeries are up to 60% without thromboprophylaxis. Prophylaxis with low-molecular-weight heparin (LMWH) is proven as efficacious therapy and is recommended as thromboprophylaxis[1]. However heparin needs to be administered subcutaneously and heparin-induced thrombocytopenia is a potential concern. Also VTE still occurs despite thromboprophylaxis. Therefore, there is still a need for new agents with better safety profile and/or higher efficacy and/or simpler route of application, especially for long-term thromboprophylaxis therapy. This year fondaparinux, a pentasaccharide with specific inhibition of Factor Xa, received marketing approval for thromboprophylaxis after orthopaedic surgery in Europe and in US. Fondaparinux showed superiority (Ephesus Study[2]) or at least non-inferiority (Pentathlon 2000 Study[3]) over enoxaparin (LMWH) in patients undergoing elective hip replacement with similar safety profile. In patients undergoing major knee surgery the postoperative treatment with 2.5 mg fondaparinux was significantly more effective in preventing deep vein thrombosis than enoxaparin 30mg twice daily (Pentamaks[4]).

BAY 59-7939 is a highly selective Factor Xa-inhibitor with oral availability. Factor Xa is at the common intersection of the extrinsic and the intrinsic pathways for thrombin formation. Selective inhibition of Factor Xa by BAY 59-7939 is expected to terminate the amplified burst of thrombin generation and may result in a better efficacy in inhibition of thrombus formation and safety profile.

The antithrombotic effect of BAY 59-7939 was demonstrated in different thrombosis models in animals at doses 0.6 - 10 mg/kg. The risk of bleeding was investigated in rats and rabbits in comparison with enoxaparin. BAY 59-7939 showed a comparable antithrombotic/bleeding risk ratio. In safety pharmacology studies a dose-dependent inhibition of blood coagulation was observed. In rats and dogs linear pharmacokinetic and a bioavailability of 60% was found. Acute toxicity was low and no induction of cytochrom P450 was seen. In rats BAY 59-7939 was mainly excreted via the biliary/faecal route.

BAY 59-7939 was tested for point mutations and for clastogenicity, all tests were negative, and BAY 59-7939 is considered as non-genotoxic.

In healthy volunteers single doses up to 30 mg were well tolerated and inhibition of factor Xa was dose-dependent. Clotting parameter (PT, aPTT, Heptest, Factor Xa inhibition) showed expected changes. For all parameters a dose dependent prolongation/increase in inhibition was observed. No effects of BAY 59-7939 on Factor II or Antithrombin III were observed. Bleeding time was not prolonged. There were no serious adverse events or deaths in the first six dose stages during single dose escalation from 5 to 30 mg. A total of 17 adverse events were reported by 15 of 51 healthy volunteers. Only 2 adverse events were considered to be possibly related to the study medication: 1. ‘taste of blood in the mouth’, which occurred approximately 3 hours after administration of 10 mg BAY 59-7939 (2x5 mg tablets); inspection of the oral cavity and washing of the mouth with water did not show any signs of bleeding and 2. headache, which resolved after treatment with analgesic. No clinically relevant changes of laboratory parameters except clotting parameters and of vital signs or of ECG-findings were observed.

The pharmacokinetic profile of BAY 59-7939 was dose proportional up to 10 mg and less dose proportional above this dose.

The multiple dose application study Impact No. 10847 in healthy volunteers is still ongoing. For following doses safety, pharmacokinetic and pharmacodynamic results are available: 5 mg od (7 active and 3 placebo subjects) and 5 mg bid (7 active and 3 placebo) for five days. In these 20 volunteers 12 treatment emergent adverse events were reported. Four of the 12 adverse events were considered as possibly related to study medication: meteorism, 'feeling of hyperacidity' and headache (2x). All occurred after administration of 5 mg od. No drug related adverse event was reported after 5 mg bid administration. No clinical relevant changes of laboratory parameters (apart from clotting parameters) and vital signs were observed.

BAY 59-7939 was rapidly absorbed after oral treatment as solution (C_{max} after approximately 30 minutes) as well as tablet (C_{max} after 2-4 hours). The terminal $t_{1/2}$ was between 9 to 12 hours.

Food effect was tested in 10 subjects after a standardised American breakfast. Two subjects dropped out after the first treatment period: one subject withdrew his consent and the other showed an increase of CK. A relevant food effect of a high fat high calories standard meal was seen for all relevant clotting factors. The maximal Factor Xa inhibition was increased by 27%, this was also reflected by prolongation of PT and Heptest. PTT as the least sensitive marker remained nearly unaffected. Antithrombin III and Factor IIa were not affected. Significant food effect was also observed with AUC and C_{max} increases of 24% and 39%. The time to reach maximal plasma concentration was significantly longer when BAY 59-7939 was administered after the meal.

The effect of age and gender on the pharmacokinetics of BAY 59-7939 was investigated in male and female subjects 18-45 years and in female subjects 65-80 years. Elderly subjects exhibited higher plasma concentrations than young subjects. For more information please refer to investigator brochure (version 4, October 7th 2002).

2. STUDY OBJECTIVES

The objective of this trial is to assess the efficacy and safety in prevention of VTE of BAY 59-7939 in male patients aged 18 years or above and in postmenopausal female patients undergoing elective primary total hip replacement after repeated dosing.

3. INVESTIGATOR(S) AND OTHER STUDY PARTICIPANTS

Co-ordinating/Principal Investigator for the study

Name: PPD

Title: PPD

Address: PPD

Sweden

Telephone No: PPD

Information regarding additional key personnel involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the sponsor and on site if required according to sponsor's standards.

4. INVESTIGATIONAL PLAN

4.1 Study Design and Plan

The study will be conducted in a prospective, randomised, open-label, active comparator controlled, multi-centre and multi-national design. The clinical study described here is a proof of principle dose finding study. All primary efficacy and safety parameters will be centrally adjudicated by an Adjudication Committee blinded to treatment allocation.

Day 1 will be defined as the day before the elective total hip replacement. On day 1 the first pre-operative dose of enoxaparin will be given if the patient has been randomised to the enoxaparin treatment group.

Day 2 will be defined as the day of the elective primary total hip replacement. On day 2 the first dose of BAY 59-7939 or the second dose of enoxaparin (depending on the treatment group) will be given post-operatively.

The overall design of the study is as follows:
Active treatment period is day 1 to day 9 ± 2.
Active treatment period will be a 9 ± 2 days in-house period starting in the evening of day 1 between 17:00-21:00 with the enoxaparin dose. The patients will be randomised to either treatment group A or B (see below).

Treatment group A:
On day 1 no study drug will be administered. The surgery should be performed latest until 15:00 on day 2. Six to 8 hours after wound closure BAY 59-7939 will be administered orally every 12 hours (bid) ± 1h or every 8 hours (tid) ± 1h on

day 2. BAY 59-7939 will be given until day 9 ± 2 days. The dose regimen will refer to the dose stage of the study (see below).

Treatment group B:
40 mg enoxaparin will be administered subcutaneously in the evening prior to the total hip replacement surgery. The surgery should be performed latest until 15:00 on day 2. Enoxaparin 40 mg will be administered subcutaneously in the evening of the operation at least 6 to 8 hours after wound closure, thereafter once daily during the active treatment period between 17:00-21:00 according to the hospital routine.

For BAY 59-7939 the dose per intake and the daily dose will depend on the stage of the study (dose escalation study). Six consecutive dose stages are planned. The Steering Committee will decide based on information about all reported SAEs, bleeding events, DVTs, PEs (all based on the local assessment of the investigator) as well as on phase I data if the next dose stage can be initiated or if dose stages have to be adjusted.

Dose stage I:	5 mg BAY 59-7939 q12hr x 2 oral (bid)
	versus enoxaparin 40 mg s.c. once daily
Dose stage II	10 mg BAY 59-7939 q12hr x 2 oral (bid)
	versus enoxaparin 40 mg s.c. once daily
Dose stage III	20 mg BAY 59-7939 q12hr x 2 oral (bid)
	versus enoxaparin 40 mg s.c. once daily
Dose stage IV	20 mg BAY 59-7939 q8hr x 3 oral (tid)
	versus enoxaparin 40 mg s.c. once daily
Dose stage V	30 mg BAY 59-7939 q12hr x 2 oral (bid)
	versus enoxaparin 40 mg s.c. once daily
Dose stage VI	40 mg BAY 59-7939 q12hr x 2 oral (bid)
	versus enoxaparin 40 mg s.c. once daily

Day 7 to 11:
On day 7 to 11 or earlier if symptoms of DVT occur, a bilateral ascending venography is mandatory for all patients. No further study medication will be administered after the venography.

If symptoms of pulmonary embolism occur during the study (including 30 days of follow-up) a lung scintigraphy with chest X-Ray or a spiral CT or a pulmonary angiography should be performed.

Follow-up:
30 days (+ 30 days timeframe) after the last treatment the patient will come for a follow-up visit.

In total 100 patients are planned per dose stage, 75 patients randomised to oral BAY 59-7939 versus 25 patients randomised to enoxaparin 40 mg s.c. (3:1 randomisation scheme).

In total :
75 patients to 10 mg/day (if dose stage is not stopped prematurely)
75 patients to 20 mg/day (if dose stage is not stopped prematurely)
75 patients to 40 mg/day (if dose stage is not stopped prematurely)
150 patient to 60 mg/day (if dose stage is not stopped prematurely)
75 patients to 80 mg/day (if dose stage is not stopped prematurely)
and 150 patients to s.c. enoxaparin 40 mg/day.

Please see section 10.1 for a detailed flow-chart

4.2 Selection of Study Population

The study population will consist of male patients aged 18 years or above and postmenopausal female patients undergoing elective primary total hip replacement.

4.2.1 Inclusion Criteria

1. Male patients aged 18 years or above and postmenopausal female patients.
2. Patients scheduled for elective primary total hip replacement (cemented or non-cemented prosthesis).
3. Patients' written informed consent for participation after receiving detailed written and oral previous information to any study specific procedures.

4.2.2 Exclusion Criteria

Related to medical history

4. DVT or PE within the previous 6 months prior to study entry.
5. Myocardial infarction (MI) or cerebrovascular attack (CVA), TIA or ischaemic stroke within the last 6 months prior to study entry.
6. History of heparin-induced thrombocytopenia, allergy to heparines.
7. Intracerebral or intraocular bleeding within the last 6 months prior to study entry.
8. History of gastrointestinal disease with gastrointestinal bleeding within the last 6 months prior to the study .
9. History or presence of gastrointestinal disease which could result in an impaired absorption of the study drug.
10. Amputation of one leg.

Related to current symptoms or findings

11. Heart insufficiency NYHA III-IV.
12. Congenital or acquired haemorrhagic diathesis (PT INR/aPTT not within normal limits).
13. Thrombocytopenia (platelets < 50.000/µl).
14. Macroscopic haematuria.
15. Allergy to contrast media.
16. Severe hypertension (SBP > 200mmHg, DBP > 100 mmHg).
17. Impaired liver function (transaminases > 2 x ULN).
18. Impaired renal function (serum creatinine > 1.5 x ULN).
19. Active malignant disease.
20. Presence of active peptic ulcer or gastrointestinal disease with increased risk of gastrointestinal bleeding.
21. Body weight < 45 kg.
22. Drug- or alcohol abuse.

Related to current treatment

23. Therapy with oral anticoagulants (e.g. phenprocoumon, warfarin-sodium).
24. Therapy with acetylic salicylic acid or other thrombocyte aggregation inhibitors (e.g. clopidogrel, dipyridamole and ticlopidine) should be stopped one week before enrolment
25. Treatment with heparines or Factor Xa Inhibitors other than study medication.
26. All other drugs influencing coagulation, (exception: NSAIDs with half life < 17 hrs will be allowed).

Miscellaneous

27. Planned intermittent pneumatic compression during active treatment period.
28. Planned epidural anaesthesia with indwelling epidural catheter (spinal and epidural anaesthesia without indwelling catheter is allowed).

29. Concomitant participation in another trial or study.
30. Therapy with another investigational product within 30 days prior start of study.

4.3 Removal of Subjects from Study

Subjects may be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative.
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
- At the specific request of the sponsor.

Premature stop of study treatment

Subjects must stop medication for the following reasons:

- If major bleeding or clinically relevant bleeding (for definition please refer to appendix 10.5 and to the bleeding event manual) occur during active treatment.
- If pulmonary embolism occurs.
- If a DVT has been confirmed by venography before day 7.

In all cases, the reason for withdrawal must be recorded in the electronic case report form and in the subject's medical records.

4.4 Premature Termination of Study/Closure of Centre

The sponsor has the right to close this study, and the investigator/sponsor has the right to close a centre, at any time, although this should occur only after consultation between involved parties. The IEC/IRB must be informed. Should the study/centre be closed prematurely, all study materials (laptops (electronic

case report forms), equipment, study medication, etc.) must be returned to the sponsor.

Safety data (including VTE and bleeding event data) will be monitored on-line by an independent Steering Committee to assess each dose stage before start of the next dose-escalation stage. If the Steering Committee will come to a negative risk/benefit ratio while a dose stage is ongoing this dose stage will be discontinued prematurely.

The specific criteria for the risk/benefit ratio are defined as follows:

Go criteria:

- Phase I results available which allow next dose stage.
- No AEs/SAEs possibly related to study medication reported which may change the overall risk assessment (especially bleeding rate or VTE rate).
- The risk/benefit ratio is positive.

No go criteria:

- AEs/SAEs possibly related to study medication reported which may change the overall risk assessment.
- Occurrence of multiple sources bleeding
- The number of major bleeding or VTE events is unacceptably high (for details see section 6.1.5.)

The go and no go decisions will be made by the steering committee.

4.5 Treatments

4.5.1 Treatments to be Administered

BAY 59-7939

BAY 59-7939 will be provided by BAYER Clinical Drug Supplies as tablets at a dose of 5 mg or 20 mg. BAY 59-7939 tablets will be packed in HDPE bottles. The content will depend on the treatment and dosage group.

The route of administration will be oral with water.

40 mg Enoxaparin

Enoxaparin will be provided as Clexane 0.4 ml syringes (Aventis) containing 40 mg enoxaparin sodium (corresponding to 4000 I.U. anti-Xa) by BAYER Clinical Drug Supplies.

Route of administration:

Enoxaparin 40 mg will be administered subcutaneously. The patient should preferably be in a lying position. To prevent haematoma or allergic reactions drops attached to the needle should be removed before injection.

The injection must be given into a skin fold lifted with 2 fingers. The injection should be given slowly without aspiration and without loosen up the fold. Intramuscular administration should be avoided.

Storage:

Storage of BAY 59-7939: Temperature below 25 °C.

Storage of enoxaparin: Temperature below 25 °C. Enoxaparin should not be frozen.

The study medication should be stored in an area with limited access (e.g. locked cabinet).

4.5.2 Identity of Investigational Product(s)

BAY 59-7939 and enoxaparin will be labelled by Clinical Drug Supplies. Medication will be labelled according to the requirements of local law and legislation. Label text will be approved according to agreed procedures, and the master labels will be available in the study file(s).

4.5.3 Method of Assigning Subjects to Treatment Groups

The department of Biometry at BAYER will generate the random list for the study.

Patients who fulfil the inclusion criteria and do not fulfil the exclusion criteria will be assigned on day 1 to either oral BAY 59-7939 (treatment group A) or 40 mg enoxaparin s.c. (treatment group B) treatment following randomisation. The patients will be allocated to the random number in ascending order. To reveal the treatment group of a patient the investigator will open the random code envelope on day 1 after the inclusion. Afterwards he has to sign and date the opening of the envelope.

The patients randomised to oral BAY 59-7939 will start the intake of study medication on day 2 (day of surgery) as described in section 4.5.5. The patients randomised to 40 mg enoxaparin s.c. will receive their first study medication on day 1 (day prior surgery).

The random number will reflect the dose stages.

4.5.4 Selection of Doses in the Study

This phase IIa study is a Proof-of-Principle and dose finding study assessing different doses and dose regimens of BAY 59-7939. During the study an ongoing risk/benefit assessment on the basis of the rate of VTE, bleeding events and serious adverse events will be performed (for detail see section 6.1.5).

5 mg bid of BAY 59-7939 was chosen as dose for the 1st dose stage as minimal effective therapeutic dose according to phase I and pharmacokinetic data. The 40 mg bid dose of BAY 59-7939 is considered as the highest effective tolerable dose.

In Europe enoxaparin is approved for thrombosis prophylaxis in patients at risk for VTE. It is widely used in the area of venous and arterial thrombosis. The administration of 40 mg s.c. once daily is the standard dose regimen for thromboprophylaxis in orthopaedic surgery.

4.5.5 Selection and Timing of Dose for Each Subject

Due to the unknown bleeding risks in patients BAY 59-7939 will be started 6 to 8 hours after wound closure to avoid bleeding during surgery and not to increase the risk of postoperative wound haematoma. This just-in-time concept is considered as effective therapeutic regimen. 5 mg bid is considered as the minimal therapeutic effective dose and 40 mg bid as the highest effective tolerable dose. To assess different doses and dose regimens several in-between dose stages will be studied (see below).

In Europe enoxaparin 40mg starting in the evening prior to surgery followed by enoxaparin once daily is the standard regimen of thromboprophylaxis in orthopaedic surgery.

Timing of administration

Day 1 (day prior to surgery):

40 mg enoxaparin s.c. will be administered between 17:00-21:00 according to hospital routine for patients randomised to the enoxaparin treatment group.

No BAY 59-7939 will be administered for patients randomised to the BAY 59-7939 treatment group.

Day 2 (day of surgery):

BAY 59-7939 will be administered orally 6 to 8 hours after wound closure for patients randomised to treatment group A. Thereafter, BAY 59-7939 will be administered every 8 hours ± 1 hour or every 12 hours ± 1 hour (depending on the dose stage, see below).

40 mg Enoxaparin will be administered according to hospital routine for patients randomised to treatment group B, but not earlier than 6-8 hours after wound closure.

Day 3 and 4:

After 24 hours of the first administration of BAY 59-7939 the study dosing schedule should be adapted to the hospital's dispensing schedule. This will be done by allowing to dispense BAY 59-7939 medication within a time frame of 6-10 hours for tid dose stages and within a time frame of 10-14 hours for bid dose stages . The resulting time schedule should be kept during the study.

40 mg enoxaparin s.c. will be administered between 17:00-21:00 according to hospital routine.

Day 5 until day of venography (Day 9 ± 2 days):

BAY 59-7939 will be administered every 8 hours ± 1 hour or 12 hours ± 1 hour (depending on dose stage, see below) following the schedule given by adapting on day 3 to 4 for patients randomised to treatment group A.

40 mg enoxaparin s.c. will be administered between 17:00-21:00 according to hospital routine for patients randomised to treatment group B.

Treatment will be stopped before the venography will be performed. No study medication will be administered after venography.

The thromboprophylaxis therapy after the venography is up to the discretion of the investigator.

Doses of oral BAY 59-7939:

Stage I (5 mg q12hr x 2):	2 doses à 5 mg (in total 2 tablets daily)
Stage II (10mg q12hr x 2)	2 doses à 2 x 5 mg (in total 4 tablets daily)
Stage III (20mg q12hr x 2)	2 doses à 20 mg (in total 2 tablets daily)
Stage IV (20 mg q8hr x 3)	3 doses à 20 mg (in total 3 tablets daily)
Stage V (30mg q12hr x 2)	2 doses à 2 x 5 mg + 20 mg (in total 6 tablets daily)
Stage VI (40mg q12hr x 2)	2 doses à 2 x 20 mg (in total 4 tablets daily)

4.5.6 Blinding

This study is an open label study, therefore investigators and patients will not be blinded.

However, there will be a blinded treatment allocation (please refer to section 4.5.3)

The Venography Adjudication Committee, the VTE Adjudication Committee and the Bleeding Event Adjudication Committee will perform their assessments in a blinded manner. The Safety Committee has the possibility of unblinding.

4.5.7 Prior and Concomitant Therapy

All medication taken by the patient in addition to the study medication are termed concomitant medication. All concomitant medication taken during the study must be documented on the electronic case report form (trade name, start and stop date and daily dose). Medication influencing coagulation or platelet aggregation taken within a time frame of 2 weeks before start of the study has to be documented as well. Concomitant medication must also be recorded in the patient's records.

Therapy with oral anticoagulans (e.g. phenprocoumon, warfarin-sodium), with acetylic salicylic acid or other platelet aggregation inhibitors (e.g. clopidogrel, dipyridamole, ticlopidine) has to be stopped minimum one week prior to enrolment. Also heparins or Factor Xa inhibitors other than study medication and all drugs influencing coagulation have to be stopped prior to enrolment according to the time frame given in their respective labelling. Drugs influencing coagulation are not allowed during the treatment period of the study (exception: NSAIDs with a half-life < 17 hrs).

For patients receiving Metformin this treatment should be stopped 2 days prior to venography and restarted earliest 2 days after venography.

After the end of the study treatment period thromboprophylaxis therapy is at the discretion of the investigator.

The use of indwelling epidural catheters is not allowed during surgery and during the study treatment period.

Thromboprophylaxis with pneumatic compression is not allowed during the study.

4.5.8 Treatment Compliance

Study medication will be administered under the supervision of the trial personnel. Administration will be documented (date, time, dose and signature of dispensing person). The study personnel at the study site will supervise the intake of the study medication to control the compliance. Drug account of the unused BAY 59-7939 medication will be performed.

4.6 Study Variables[5]

4.6.1 Efficacy Variable

The primary efficacy endpoint is a composite endpoint of:

- Any DVT (proximal and/or distal) and
- Non fatal PE and
- Death from all causes.

The primary endpoint will be evaluated 5 - 9 days after surgery. The analysis of the primary efficacy endpoint will be solely based on the assessments made by the adjudication committee.

Secondary efficacy endpoints are:

- Incidence of DVTs (total, proximal, distal)
- Incidence of symptomatic VTEs
- The composite endpoint that results from the primary endpoint by using alternative definition of deaths (i.e. VTE related death)
- Incidence of symptomatic VTEs (total, PE, DVT) within 30 days after stop of treatment with the study drug.

The analysis of the secondary efficacy endpoint will be solely based on the assessments made by the adjudication committees.

4.6.2 Safety Variables

The main safety endpoint is the incidence of major bleeding observed after the first intake of study drug and not later than 2 days after last intake of study drug. Major bleeding observed after this period will be considered separately.
The analysis of the primary safety endpoint will be solely be based on the classification made by the Safety Committee and Bleeding Committee.

Other safety variables are:

- Incidence of non-major bleeding (clinically significant and minor bleeding)
- Treatment-emergent adverse events
- Treatment-emergent serious adverse events
- Deaths
- Adverse events starting more than 7 days after stop of treatment
- Incidence of prolonged hospitalisation
- Transfusion requirements (heterologous and autologous transfusions)
- Amount of blood loss (intraoperative blood loss)
- Post-operative volume in drainage
- Laboratory parameter.

4.6.3 Assessment Periods

This trial will consist of six dose stages (please refer to chapter 4.1).
The assessment period per patient includes a 7 to 11 days treatment period followed by a 30 days follow-up period which can be extended up to 60 days.

In house period

Day 1 will be defined as the day before the elective total hip surgery. Day 2 will be defined as the day of the surgery. On day 1 the patient will be informed about the study and will sign the Informed Consent, thereafter he will be randomised to

either treatment of oral BAY 59-7939 or 40 mg enoxaparin s.c.. Treatment with enoxaparin will start on day 1, treatment with BAY 59-7939 will start on day 2 six to 8 hours after wound closure. Study medication will be given until day 7 to 11 depending on the day of bilateral venography.

Follow up

30 days (+30 days time frame) after the last intake of study medication an out-patient follow up visit will be performed.

4.6.4 Observations and Measurements

Day 1 to day 9 ± 2 (day of venography) and follow-up visit

Every day a physical examination with assessment of vital signs will be performed.

After randomisation a daily assessment of signs of DVT, signs of PE, bleeding events and adverse events will be performed until the day of venography.

Day 2 to day 9 ± 2 (day of venography) and follow up visit

Post-operatively on day 2 and afterwards daily a clinical assessment will be performed.

Additionally:

Day 1:

On day 1 before administration of any study drug the eligibility check will be performed, and Patient Information and Informed Consent have to be obtained. Medical history (incl. alcohol consumption and nicotine abuse) and demographic data will be recorded. Risk factors for VTE will be assessed and blood samplings for clinical chemistry, haematology and coagulation parameter will be done, urinalysis will be performed (see below). Additionally, an electronic ECG will be derived.

Thereafter, the patient will be randomised if eligible for the study.

40 mg enoxaparin injections will be administered if the patient has been randomised to the respective treatment group.

Day 2:

6-8 hours after wound closure:

Oral BAY 59-7939 will be administered if the patient has been randomised to the corresponding treatment group. Oral medication must start 6 to 8 hours after wound closure to avoid postoperative wound haematoma.

All assessments will be done post-operatively.

Day 3:

For patients randomised to BAY 59-7939 treatment 2 to 4 hours after first administration of BAY 59-7939 on day 3 an electronic ECG will be derived and blood sampling for clinical chemistry, haematology and coagulation parameters (including central laboratory) will be done.

For patients randomised to enoxaparin treatment an electronic ECG will be derived and blood sampling will be done on day 3 during the day according to hospital schedule.

Day 5:

For patients randomised to BAY 59-7939 treatment blood sampling for clinical chemistry, haematology and coagulation parameters will be performed 2 to 4 hours after administration of BAY 59-7939.

For patients randomised to enoxaparin treatment these blood samples will be taken during the day according to hospital schedule.

Day 9 ± 2:

Blood samples for clinical chemistry, haematology and coagulation parameter will be taken directly before the last intake of BAY 59-7939 or the last enoxaparin s.c. treatment before the planned venography. If this is not possible the blood samples

can be taken directly before a dose application between day 7 to the day of venography.

For patients receiving BAY 59-7939 treatment an electronic ECG will be derived 2-4 hours after the last morning dose of BAY 59-7939 before the venography. For patients randomised to enoxaparin treatment the ECG will be derived during the day.

Urinalysis will be performed in the morning before venography.

Bilateral venography will be performed.

Follow up on day 39 (to day 69)

Adverse events, signs and diagnosis of VTE and bleeding events during the 30 days after stop of treatment will be recorded. No ECG or laboratory assessments will be done.

Methods of Measurements

Laboratory:

Clinical Chemistry: sodium, potassium, calcium, creatinine, urea, uric acid, SGOT/AST, SGPT/ALT, gamma GT, LDH, alkaline phosphatase and blood glucose.

Haematology: haemoglobin, haematocrit, RBC, WBC, neutrophils (total), lymphocytes, monocytes, eosinophils, basophils.
Coagulation parameters: prothrombin time (PT and PT INR), activated partial thrombin time (aPTT), anti-Xa activity.

Clinical Chemistry parameters, haematology parameters, PT INR and aPTT will be assessed in the local laboratory. PT and anti Xa activity will be determined in a central laboratory.

Urinalysis: pH, protein, glucose and blood.

For blood sample handling instructions for the central laboratory please refer to the laboratory manual.

Urinalysis will be performed by dip-stick analysis (dip sticks from local stock).

Electrocardiography

The ECGs for the study will be transferred electronically and assessed centrally. The investigator will print-out the ECG locally and will receive later an assessed print-out of the central ECG-assessment sent to the site.
For ECG procedures please refer to the ECG manual.

Bilateral Venography[6,7,8]:

The bilateral venograms for this study will be assessed centrally. Please refer to the operational manual for the requirements of the bilateral venography. The bilateral venograms will be first assessed by the hospital radiologist and the investigator will refer to this assessment.

The venography film has to be sent to the central assessment unit for further assessment. If only US videotape will be available, this should also be sent to the central assessment unit.

Diagnosis of PE:

If symptoms of PE occur pulmonary angiography or a lung scintigraphy with X-ray thorax or spiral CT should be performed and the pictures will be sent to the Adjudication Committee (AC/VTE) (see appendix). In case the patient died an autopsy should be performed, if possible, and the autopsy report has to be sent to the AC/VTE. Additionally, all available information, e.g. laboratory results, hospital letters have to be collected and sent to the central adjunction committee. Care must be taken that the identity of the patient will be blinded (i.e. just initials, random number, patient number and centre number given).

4.6.5 Drug Concentration Measurements

No drug concentration measurements planned.

4.7 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with GCP guidelines. Each centre will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the case report forms (CRF) for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

4.8 Documentation

Entries made in the EDC system must be either verifiable against source documents, or have been directly entered into the EDC system, in which case the entry in the EDC system will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained until notified by the sponsor.

5. ETHICAL AND LEGAL ASPECTS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Documented approval from appropriate Ethics Committee(s)/IRBs will be obtained for all participating centres/countries prior to study start, according to ICH GCP, local laws, regulations and organisation. When necessary, an extension, amendment or renewal of the Ethics Committee approval must be obtained and also forwarded to the sponsor. The Ethics Committees must supply to the sponsor, upon request, a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organised and operates according to GCP and applicable laws and regulations.

5.2 Ethical 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 Guidelines and under the guiding principals detailed in the Declaration of Helsinki[9,10]. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or Regulatory Authority

representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties.

5.3 Regulatory Authority Approvals/Authorisations

Regulatory Authority approvals/authorisations/ notifications, where required, will be in place and fully documented prior to study start.

5.4 Subject Information and Consent

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the IRB/IECs written approval/favourable opinion of the written Informed Consent Form and any other written information to be provided to subjects. The written approval of the IRB/IEC together with the approved subject information/Informed Consent Forms must be filed in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

5.5 Insurance

All subjects participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

5.6 Confidentiality

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

Subject names will not be supplied to the sponsor or to the different committees. Only the subject number and subject initials will be recorded in the case report form, and if the subject 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 or to the different study committees. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects 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 subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical and Analytical Plans

6.1.1 General

All statistical tests will be performed two sided with a type I error rate of α=5%. An adjustment for country effects is planned for the analysis of efficacy as well as for the analysis of treatment group comparability. In case of countries with too few patients, appropriate pooling based on geographical criteria should be done.

Demographic variables and baseline characteristics will be summarised by treatment group for all three analysis populations (i.e. valid for safety analysis, valid for intent to treat analysis, and valid for per protocol analysis). Medical history findings and adverse events will be coded by MedDRA codes and medications by ATC codes (WHO-DD).

The treatment group comparability will be checked for each of the analysis populations mentioned before. This comparison will be done with respect to age and body mass index by a two-way analysis of variance main effects model including treatment group and country as fixed effects. Categorical variables sex and race will be compared by a Cochran-Mantel-Haenszel test adjusted for country. Furthermore, treatment groups will be compared with respect to smoking status, alcohol consumption and thromboembolic risk factors.

6.1.2 Patients' Validity

A randomised patient is valid for safety analysis, if

- at least one dose of study medication was administered
- data allowing an assessment of safety are available

A patient is valid for intent to treat analysis, if the patient

- is valid for safety analysis
- has undergone the appropriate surgery
- has an adequate assessment of thromboembolism

An adequate assessment of thromboembolism is present if at least one of the following conditions is fulfilled:

- an adequate bilateral ascending venography was performed between 5 - 9 days after surgery
- confirmed symptomatic deep venous thrombosis up to 9 days after surgery
- confirmed symptomatic pulmonary embolism up to 9 days after surgery

The definition of an adequate bilateral ascending venography will be given in the adjudication committee manual of operation. In case that a symptomatic pulmonary embolism is diagnosed 10 days after surgery, it will still be considered in the evaluation as long as study medication was not stopped more that one day prior to diagnosis of pulmonary embolism.

A patient is valid for per protocol analysis, if the patient

- is valid for intent to treat analysis
- has an adequate assessment of thromboembolism that was done not later than one day after stop of study drug
- shows no major protocol deviations

Major protocol deviations are given by:

- intake of prohibited anticoagulant concomitant medication
- overall compliance of less than 80%
- administration of study medication not according to protocol

6.1.3 Efficacy Analysis

The primary efficacy analysis will be performed in patients valid for per protocol analysis. The intent to treat analysis will be performed as supportive analysis.
The dose-response relationship of BAY 59-7939 will be investigated by a trend test. For this purpose, the primary efficacy endpoint (see section 4.6.1) will be evaluated by a logistic regression model including the total daily dosage of BAY 59-7939 as a covariate and country as a fixed effect. Only patients treated with BAY 59-7939 will be included in this analysis. In order to check for a trend in the dose-response relationship, the hypothesis that the regression parameter of the covariate equals zero will be tested in the logistic regression model by the Likelihood Ratio Test.

In a secondary analysis the existence of a treatment by country interaction will be checked by a logistic regression model additionally including the interaction of country and total daily dosage of BAY 59-7939. Furthermore, the influence of age, gender, body mass index and history of thromboembolism on the primary efficacy endpoint will be investigated.

Subsequent to the trend test, each of the individual BAY 59-7939 treatment groups will be compared with enoxaparin. If the hypothesis of no trend is rejected, these pairwise comparisons will be done confirmatively applying a hierarchical multiple testing procedure. In this procedure the six pairwise comparisons have to be performed in a fixed sequence defined by the total daily dosage of BAY 59-7939 and starting with the comparison of the highest dose of BAY 59-7939 with enoxaparin. In case that bid administration and tid administration result in the same total daily dosage, the bid administration will be compared with enoxaparin first. Any of the individual hypotheses can only be rejected in case that all preceding hypotheses have already been rejected. Thus, the multiple testing procedure has to be stopped (i.e. no further confirmative comparisons are permissible), once one of the six hypotheses cannot be rejected.

The individual pairwise comparisons will be done by Fisher's exact test. Exact two sided 95% confidence intervals for the event rates of the primary composite endpoint will be derived stratified by treatment group. Each of the BAY 59-7939 groups will be compared to the enoxaparin group by calculating an asymptotic two sided 95% confidence interval for the difference between the corresponding event rates.

The incidence rates for the secondary efficacy parameter will be tabulated stratified by treatment group.

6.1.4 Safety Analysis

The safety analysis will be performed in the population of patients valid for safety analysis.

The incidence of major bleeding will be tabulated and further analysed by the logistic regression model already specified for the primary efficacy analysis. Furthermore, the individual comparisons of each BAY 59-7939 treatment group with enoxaparin will be performed based on Fisher's exact test.

The incidence of clinically significant non-major bleeding and minor bleeding will be tabulated stratified by treatment group.

The incidence of treatment-emergent adverse events will be tabulated stratified by treatment group. Adverse events are considered to be treatment-emergent if they have occurred after first application of study medication up to 7 days after end of treatment with study medication. Further tables will be prepared for serious and/or drug-related treatment-emergent adverse events as well as for deaths (if applicable). The incidence of adverse events during follow-up (i.e. adverse events occurring more than 7 days after end of treatment with study medication) will be tabulated separately.

Treatment groups will be compared regarding the incidence of premature termination with special focus on premature termination due to adverse events.

The safety evaluation of lab data will include

- listing of lab data out of normal range
- descriptive analysis of continuous lab parameters and their changes from baseline by visit and treatment group
- cross-tabulation of baseline vs. post-baseline status by visit and treatment group
- incidence rates of treatment emergent lab abnormalities by treatment group

All other safety endpoints (see section 4.6.2) will be analysed by appropriate descriptive methods (i.e. sample statistics or frequency tables) stratified by treatment group.

6.1.5 Interim Analysis

During the study a continuous safety monitoring for major bleeding will be performed by the Steering Committee in an unblinded manner for each of the six dose stages. It is recommended to terminate a dose stage prematurely either in case that the lower limit of the two sided 95% confidence interval for the event rate of major bleeding exceeds 5% or if 6 or more major bleedings have been observed in the corresponding dose stage. The resulting decision recommendation is given in the following table.
However, the final decision will be made by the Steering Committee.

Table 6.1.5/1: Decision recommendation for premature termination due to major bleeding

No. of Major Bleeding Events	Recommendation for Premature Termination
1	no termination
2	premature termination if N ≤ 5
3	premature termination if N ≤ 13
4	premature termination if N ≤ 22
5	premature termination if N ≤ 33
6	premature termination

N denotes the number of patients currently treated in the respective dose stage

Furthermore, a continuous efficacy monitoring will be performed by Bayer Global Drug Safety for each dose stage based on the SAE reports on VTE sent by the investigators. If the lower limit of the two sided 95% confidence interval for the VTE rate in the BAY 59-7939 group exceeds 35% in one dose stage, Bayer Global Drug Safety will inform the Safety Committee and the Steering Committee accordingly. The decision to stop one dose stage will be made by the Steering Committee only.

6.2 Determination of Sample Size

For sample size determination it is assumed that the event rate of the primary efficacy criterion is 30% (or more) in the lowest dose group and 10% (or less) in the highest dose group of BAY 59-7939. Furthermore, it is assumed that the event rate only depends on the total daily dosage of BAY 59-7939.

In order to determine an appropriate sample size for the phase IIa study, several scenarios regarding the event rates of the primary efficacy criterion were considered for a two sided trend test with a type I error rate of $\alpha = 0.05$ and a type II error rate of $\beta = 0.2$. Sample sizes were calculated using nQuery Advisor, Version 4, Module PGT1-1.

Table 6.2/1: Scenarios (Event Rates) for Sample Size Calculation

Dose Group / Scenario	I	II	III	IV	V	VI	Sample Size per Group
1	30.0%	20.0%	15.0%	12.5%	12.5%	10.0%	50
2	30.0%	15.0%	12.5%	10.0%	10.0%	10.0%	52
3	30.0%	12.5%	10.0%	10.0%	10.0%	10.0%	59
4	29.0%	20.0%	15.0%	12.5%	12.5%	11.0%	59
5	28.5%	20.0%	15.0%	12.5%	12.5%	11.5%	65
6	30.0%	30.0%	30.0%	30.0%	30.0%	10.0%	103
7	30.0%	10.0%	10.0%	10.0%	10.0%	10.0%	67

From the results presented above it can be seen that a sample size of 60 patients per group is sufficient to provide a reasonable power not only for scenarios assumed to be likely (see scenarios 1 and 2), but even in less ideal scenarios (see scenarios 3 and 4) as long as the deviations are not too extreme (see scenarios 5, 6 and 7). In the latter case, a power of at least 80% can of course not be guaranteed.

Assuming an invalidity rate of 20%, a sample size of 75 patients treated with BAY 59-7939 is required for each of the 6 dose groups. Taking further into account the planned 3:1 randomisation of BAY 59-7939 and enoxaparin, a number of 100 patients has to be randomised for each dose stage resulting in a total number of 600 patients to be randomised.

7. ADVERSE EVENTS

7.1 Warnings/Precautions

For BAY 59-7039 up to now only phase I data are available. In healthy volunteers single doses up to 30 mg of BAY 59-7939 and multiple dosing with 5mg od and 5 mg bid were well tolerated and inhibition of Factor Xa was dose-dependent. Clotting parameter (PT, PTT, Heptest) showed expected changes. Bleeding time was not affected. There were no serious adverse events or deaths. For more details please refer to section 1, introduction, and to the Investigator brochure, version 4 October 7th 2002.

BAY 59-7939 is a Factor Xa inhibitor which affects the coagulation. Therefore bleeding adverse events as described below for enoxaparin could be expected. Also thrombocytopenia and other changes of laboratory parameter are possible adverse events. In addition, the possibility of hitherto unforeseen side effects and allergic reaction to the drug, which can result in severe damage and even death must always be considered. Any new relevant information about side effects of BAY 59-7039 will be given to the patient and investigator.

See also Investigator's Brochure, Version 4, October 7th, 2002.

Enoxaparin: Intramuscular application of enoxaparin should be avoided. The following side effects may occur after application of enoxaparin: allergic reactions (e.g. pruritus, erythema, urticaria), in rare cases anaphylactoid reactions, injection site haematoma, injection site reactions (e.g. pain), purpura with skin necrosis, open and occult bleeding complications (especially skin, mucosa, wound, gastrointestinal and urogenital) and increased bleeding during surgery. Severe bleedings (retroperitoneal and intracranial) were reported. In some cases at start of treatment mild transient thrombocytopenia (HIT I) and in rare cases thrombocytopenia with thrombocytes below 100 000/µl or rapid decrease of thrombocytes which starts normally 6 to 14 days after begin of therapy (HIT II)

may occur. The last severe form of thrombocytopenia (HIT II) could be combined with thromboses/thromboembolisms, consumption coagulopathy, skin necrosis at injection site, petechia, purpura and melaena. Additionally, in some cases organ infarction or peripheral ischaemia occured. In such cases enoxaparin has to be stopped immediately.

After spinal or epidural anaesthesia or postoperative indwelling epidural catheter spinal or epidural haematoma were seen, which could cause paralysis.

Increase of liver enzymes is possible, which resolved after stop of therapy. Rarely thrombocytemia, leucopenia and increase of serum potassium were found. Following adverse events known with unfractioned heparines are possible: alopecia, osteoporosis, priapism, hypotension, bradycardia and hypoaldosteronism.

Please see also product characteristic information.

7.2 Adverse Event Monitoring

Subjects must be carefully monitored for adverse events. This monitoring includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug.

7.3 Adverse Event Definitions

7.3.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. The adverse event does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical (investigational) product, whether or not considered related to the medicinal product.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from an overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

7.3.2 Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose results in:

Death

Life-threatening drug experience

Inpatient hospitalisation or prolongation of existing hospitalisation (an exception is planned for rehabilitation measures)

Persistent or significant disability/incapacity

Congenital anomaly/birth defect.

Some important medical events, although they may not result in death, be life-threatening, or require hospitalisation may still be considered serious adverse drug events when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This does not include an adverse event that, if more severe, might have caused death.

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

7.3.3 Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator Brochure (or Package Insert for marketed products). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. For example, an event more specific or more severe than described in the Investigator Brochure would be considered “unexpected”. Specific examples would be; (a) acute renal failure as a labelled adverse event with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

7.3.4 Relationship of Adverse Event to Investigational Product

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of ‘No’ would include:

1. The existence of a clear alternative explanation (e.g., mechanical bleeding at surgical site); or
2. Non-Plausibility (e.g., the subject 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 drug administration).

An assessment of ‘Yes’ indicates that the adverse event is reasonably associated with the use of the drug.

Factors to be considered in assessing the relationship of the adverse event to study drug 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 discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.

Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be recognised to cause 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 test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

7.3.5 Intensity (Severity) of the Adverse Event

The following classification should be used:
The intensity or severity of adverse events should be graded as follows:

Mild – usually transient in nature and generally not interfering with normal activities

Moderate – sufficiently discomforting to interfere with normal activities

Severe – prevents normal activities.

7.3.6 Adverse Event Documentation

All adverse events occurring during the study period must be fully recorded in the subject's case record.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to drop out of the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, intensity, relationship to investigational product, action taken and outcome.

7.4 Reporting of Serious Adverse Events

Serious adverse events, including laboratory test abnormalities fulfilling the definition of serious, occurring during the study and follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person detailed in the study file. A Serious Adverse Event Form must also be completed within 24 hours of the investigator awareness and forwarded to the designated person as detailed in the study file.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

Elective rehabilitations referring to the total hip replacement on day 2 of this study must not be reported an a serious adverse event.

SAEs have to be reported starting from signing the Informed Consent until to day of the follow-up visit.

8. USE OF DATA AND PUBLICATION

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 utilise the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, whilst free to utilise data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognises the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

9. REFERENCES

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10.APPENDICES

10.1 Study Flow Chart and/or Schedule Procedure

	DAY OF TREATMENT									Follow up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**39**
Allowed time frame		**Day of THR**							**± 2 days**	**+30 days**
Eligibility	X									
Informed Consent	X									
Demographic Data	X									
Medical History	X									
Physical Examination	X	X	X	X	X	X	X	X	X	X
Randomisation	X									
Start of Enoxaparin	X[1]									
Surgery		X[2]								
Start of BAY 59-7939		X[3]								
Laboratory	X		X[4]		X[5]				X[6]	
Clotting Parameter	X		X[4]		X[5]				X[6]	
Central Laboratory	X		X[4]		X[5]				X[6]	
Urinalysis	X								X[7]	
ECG	X		X[4]						X[8]	
Venography									X	
Vital signs	X	X[9]	X	X	X	X	X	X	X	X
Clinical signs of DVT/PE	X	X[9]	X	X	X	X	X	X	X	X
Clinical Assessment		X[9]	X	X	X	X	X	X	X	
Adverse Events	X	X[9]	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Study Medication	X	X	X	X	X	X	X	X	X[10]	
RDE Entry and Data Transmission	X	X	X	X	X	X	X	X	X	X
In-house	X	X	X	X	X	X	X	X	X	
Out-patient										X

1: First administration of enoxaparin between 17:00 and 21:00 according to hospital schedule (if randomised to enoxaparin treatment group).
2: Last possible end of wound closure 15:00.
3: Start of BAY 59-7939 6-8 hours after wound closure.
4: Blood samples to be taken and ECG to be performed 2-4 hours after first administration of BAY 59-7939 on day 3. For patients randomised to enoxaparin these tests should be performed on day 3 during the day according to hospital schedule.
5: Blood samples to be taken 2-4 hours after administration of BAY 59-7939. For patients randomised to enoxaparin blood samples can be taken during the day.
6: Blood samples to be taken before administration of study medication.
7: Urinalysis to be performed in the morning before venography.
8: ECG to be derived 2-4 hours after last morning dose of BAY 59-7939 before venography. For patients randomised to enoxaparin the ECG will be derived during the day according to hospital schedule.
9: To be performed post-operatively.
10: Study medication will be stopped before venography.
In case that the hospital stay will be prolonged to day 10 (or 11) for day 9 (and day 10) the schedule of day 8 will be followed.

10.2 Study Committees

Steering Committee (SC):

The Steering Committee will guide the trial in all aspects of safety and efficacy and has to assure that all relevant information coming from investigators, from the Global Drug Safety and from the different committees will thoroughly be reviewed and all relevant decisions with regard to the conduct will be taken in due time.

The Steering Committee has to decide based on information about reported SAEs, in particular bleeding events, DVTs, PE (all based on the local assessment of the investigator) on an ongoing basis

-if a particular dose stage can be continued as planned

-if a particular dose stage has to be stopped (stopping rules to be applied, see section 4.4).

The Steering Committee has to decide based on information about reported SAEs, DVTs, PE and bleeding events (all based on the local assessment of the investigator) towards the end of a particular dose stage

-if the next dose stage in the escalation can be started as planned per protocol

-if the next dose stage in the dose escalation needs to be adapted.

Adjudication Committee/Venography (AC/V):

The AC/V will assess all scheduled and unscheduled venographies performed during the study in a blinded manner. The assessment of the AC/V is the basis for the final DVT based efficacy analysis according to the protocol. The assessment of the AC/V will not influence the acute decision taken by the Steering Committee.

Adjudication Committee/Venous Thromboembolic Event (AC/VTE):

The AC/VTE will adjudicate symptomatic DVTs during active treatment, all DVTs during the follow-up, all PE events and all deaths in a blinded manner.
The assessment of the AC/VTE is the basis for the final VTE based efficacy analysis for the intent-to-treat analysis. The assessment of the AC/VTE will not influence the acute decision taken by the Steering Committee.

Adjudication Committee/Bleeding Event (AC/BE):

The AC/BE will adjudicate all bleeding events reported during the trial in a blinded manner.
The assessment of the AC/BE is the basis for the final analysis of all bleeding events for the intent to treat analysis. The assessment of the AC/BE generally should not influence the decision taken by the Steering Committee, however the AC/BE and SC are encouraged to closely interact in the discussion and assessment of particular cases and give advise to the Steering Committee.

Safety Assessment Committee (SAC):

During the course of the trial the SAC and the SC should closely interact and alert each other in order to assess all safety relevant information. The SAC should also closely interact with the sponsor's GDS in reviewing and assessing SAEs and it should be involved in contacts with IRB's and Ethics Committees.
At the end of the trial, the SAC will assist the sponsor in the assessment of the overall safety of BAY 59-7939 after the completion of all dose stages and will advise the sponsor in the characterisation of the risk-benefit profile of BAY 59-7939.

10.3 Venography

DVT will be diagnosed by mandatory bilateral venography on day 7 to 11.
Each venogram will be initially read by the local radiologist of the centre and the result will be recorded in the RDE-system. Thereafter the venograms will be send by courier to the central assessment unit.

Address of Central Assessment Unit:

PPD

Department of Radiology
Östra Hospital
Göteborg University
S-41685 Göteborg
Sweden

Diagnostic criterion of DVT for central assessment**:**
A constant intraluminal filling defect of the same shape on two different images (direct signs). Indirect signs, only fluoroscopic report or results from a non-invasive test, e.g. compression ultrasonography will not be used for assessment during treatment period. A bilateral venography at day 7-11 or if symptoms occur is mandatory.
The veins will be scored as: 1: normal
2: constant intraluminal filling defect (DVT)
3: inadequate.

Examination:

The venographic technique should be standardised using the modified technique of Rabinov & Paulin[6,7,8]:

A non-ionic, low osmolar contrast medium, 200-300 mg I/ml should be used.

Start with the newly operated leg, were the chance of a positive finding is highest.

Adequate volume of contrast media, preferably 100 ml per leg, must be used to ensure complete filling of the deep stems and, as far as possible, filling of the muscular veins.

Generally, tourniquets should be avoided and should only be used as an adjunct if the first examination has failed to visualise the deep veins.

The examined leg should be non-weight bearing, completely relaxed and without external compression of the calf.

The examination should be performed in a semi-upright position without tourniquets, preferably 60° elevation from the horizontal plane, to accomplish an adequate mixing of contrast media and to allow filling of the veins.

Utilise 70-80 kV at exposures.

A minimum of 9 images per leg must be taken: frontal, internal oblique and external oblique views of the calf, at least two views of the popliteal, two of the femoral and two of the iliac veins up to the cava inferior confluence. At least three different calf views and duplicate exposures of each of the proximal veins are mandatory to make it possible to assess a constant intraluminal filling defect or to recognize flow artefacts (see table below). The examination must be bilateral.

The following veins will be assessed: muscular veins, the anterior and posterior tibial veins, the fibular veins, the popliteal veins, the superficial femoral veins, deep and common femoral veins and the iliac vein.

In patients with obscuring radiopaque material, e.g. previous metallic prosthesis or internal fixing devices, appropriate views should be added in order to visualise the veins free from such dense metallic material.

The diagnosis of postoperative thrombosis will be based on direct signs and the diagnosis finding must be able by reading the hard copy film. A fluoroscopic diagnosis will not be sufficient.
Only original films should be sent to the central assessment unit.
A check-list has to be filled out, signed and sent together with the adequately marked films (patient initials, patient's random number, right/left leg, date of venography, centre name). The local reading results should not be sent to the central assessors.

Documentation:

The venograms must be performed using long films, preferably conventional analog film, split in 2 or 3 images, i.e. 35 x 43 cm or if not possible 35 x 35 cm or 30 x 40 cm. Smaller film size is not adequate. Computed radiographic film (CR) is accepted. If digital films are used, the images on the film have to be large enough to allow adequate reading, generally not more than 4 images on one laser film. The contrast medium must appear white on the black film, not vice versa.

Minimum mandatory venogram

Calf	1. Frontal view
	2. Internal oblique view
	3. External oblique view
Knee	4. External oblique view
	5. Frontal view
Thigh	6. Frontal view
	7. Frontal view
Pelvis	8. Frontal view
	9. Frontal view

10.4 Assessment of Pulmonary Embolism

For diagnosis of pulmonary embolism the participating centres will use different methods to verify PE.

The methods to be used for an objective diagnosis of PE by the VTE- Adjunction Committee are:

Autopsy report

Pulmonary angiography

Spiral CT

Lung scintigraphy plus X-ray thorax.

The adjunction committee must have as much information as possible regarding each case including original images from the examinations, written reports and excerpts from patient records (e.g. ECG, laboratory data) and hospital discharge letter.

Images and patient records should be send to:

PPD

Department of Radiology

Östra Hospital

Göteborg University

S-41685 Göteborg

Sweden

10.5 Preparation of Frozen Blood Samples

The preparation of frozen blood samples will be described in the laboratory manual.

10.6 Bleeding Assessment

All bleedings will be assessed by the Safety Committee using following predefined criteria:

All bleeding events will be classified into 3 categories:

major bleeding event

clinically relevant non major bleeding event

minor bleeding event.

Major bleedings are:

fatal bleeding

clinically overt bleeding associated with 2 g/dl fall in haemoglobin

clinically overt bleeding leading to infusion > 2 units blood

retroperitoneal, intracranial, intraocular or intraspinal bleeding

bleeding warranting treatment cessation

bleeding leading to re-operation.

Clinically relevant non major bleeding and minor bleeding will be defined in the manual of the Bleeding Event Committee.