Bayer

CLINICAL STUDY PROTOCOL

Title:	Controlled, Double-Blind, Randomized, Dose-ranging Study of once-daily regimen of BAY59-7939 in the Prevention of VTE in Patients Undergoing Elective Total Hip Replacement-ODIXaHIP-OD Study
Test Drug:	BAY 59-7939
Sponsor's Name and Address:	BAYER Vital GmbH D-51368 Leverkusen
Sponsor's Telephone Number:	
Study Number/Version/Date:	11527/ version 1.6/20 Jul 2004
Development Phase:	IIb

The undersigned confirm that they agree to conduct the study under the conditions

PPD PPD **Date**

PPD PPD **Date**

PPD **Date**

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Name: PPD Signature: _____

Function: PPD Date:

Address: PPD
SWEDEN

Name: Signature: _____

Function: Date:

Address:

Name: Signature: _____

Function: PPD Date:

Address:

Telephone:

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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
Ae_{ur},	amount of drug excreted via urine
ALT	Alanine Transaminase (also known as SGPT, *qv)*
aPTT	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
$C_{max(norm)}$	(1) maximum concentration of drug in plasma, divided by dose per kg body weight (2) maximum drug concentration in plasma after single dose administration divided by dose (mg) per kg body weight
CK	Creatine Kinase
CL/f	total body clearance of drug from plasma calculated after oral administration (apparent oral clearance)
CL_R	renal clearance
CV	coefficient of variation
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
DSMB	Data Safety and Monitoring Board
DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
gamma GT	gamma Glutamyl Transpeptidase
GCP	Good Clinical Practice
GDS	Global Drug Safety (BAYER internal)
GI	Gastrointestinal
HCRU	Health Care Resource Utilisation
HDPE	High Density Polyethylene
HIT	Heparin-Induced Thrombocytopenia
HPLC	high pressure liquid chromatography
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
LOQ	limit of quantification
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
PTT	Partial Thromboplastin Time
QC	quality control
qv	*quod vide*, which see
q8(12)hr	Every 8(12) hours
RBC	Red Blood Cell (Count)
RDE	Remote Data Entry
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
$t_{½}$	(1) time of half-life (2) half-life
t_{max}	time to reach maximum drug concentration in plasma after single (first) dose
TID	Tris in Die
THR	Total Hip Replacement
ULN	Upper Limit of Normal
US	Ultrasound
V_z/f	Apparent volume of distribution during terminal phase after oral administration
V/Q scan	Ventilation/Perfusion Scan
VTE	Venous Thromboembolism
WBC	White Blood Cell (Count)
WHO-DD	World Health Organisation – Drug Dictionary

1. INTRODUCTION

In addition to the information provided below please also refer to the Investigator Brochure (version 8.0 / 09 July 2004) and any additional data supplied by the sponsor.

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. According to the German Pathologist Virchow a triad is named which states that thrombosis occurs as a result of abnormalities of blood vessel wall (eg 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 industrialised countries. 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, major hip and knee surgery, are at high risk for venous thromboembolism. The rate of Deep vein thrombosis (DVT)after hip surgery is 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. Despite thromboprophylaxis VTE may still occur. 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. Fondaparinux, a pentasaccharide with specific, indirect inhibition of Factor Xa, received marketing approval for thromboprophylaxis after orthopaedic surgery in Europe and in US in the year 2002. 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]). However, also fondaparinux needs to be administered subcutaneously.

Recently another novel anticoagulant, the direct thrombin inhibitor melagatran and its orally available prodrug, ximelagatran got regulatory approval in 14 European countries for the prevention of venous thromboembolism after major orthopedic surgery. It has been shown to be non-inferior in comparison to enoxaparin[15-17], and at least non-inferior compared to warfarin[13-14]. Ximelagatran has to be given twice daily and according to the approved regimen has to be combined with peri-operative subcutaneous melagatran. Duration of thromboprophylactic treatment with ximelagatran must not exceed 8-10 days.

BAY 59-7939 is an oral, novel direct inhibitor of Factor Xa. 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% or higher was found. In rats BAY 59-7939 was mainly excreted via the biliary/faecal route.

Acute toxicity was low and no induction of cytochrom P450 was seen. Incubation of (^{14}C)BAY 59-7939 with liver microsomes from different species, including man, showed that hydroxylation at the morpholino moiety of the drug led to the metabolites M-2 and M-3, and was the major phase I biotransformation in vitro.

CYP3A4 is the decisive enzyme for phase I transformation in humans. Drug-drug interaction between BAY 59-7939 and CYP3A4 substrates (simvastatin, nifedipine, midazolam) and CYP3A4 inhibitors (ketoconazole, erythromycin, clarithromycin) were tested in vitro. Significant effects on BAY 59-7939 turnover rate in vitro were only observed with the strong CYP3A4 inhibitor ketoconazole. Therefore the use of ketoconazole is prohibited in this study during the active treatment phase.

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 80 mg and multiple doses of 30 mg for 5 days 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 IIa or Antithrombin III were observed. Bleeding time was not prolonged to a clinical relevant extend. Apart from clotting parameter only isolated laboratory values showed minor deviation from normal however without any consistent pattern. Up to 30mg bid no accumulation of BAY 59-7939 was observed. The severity of the adverse events reported in phase I trials was mild to moderate except one adverse event with severe muscle enzyme elevation which resolved after 10 hours and was not assessed as related to study drug (excessive gym). There were no deaths reported. In the study Impact 10842 which enrolled 91 healthy volunteers five adverse events out of 38 adverse events were considered as possibly related to study drug: taste of blood in mouth (2x), headache, ecchymoses (2x). Ten subjects were enrolled in the food interaction study Impact No. 10846. In this study two adverse events were reported and both were not considered as drug related. In the Impact No.10850 study assessing the age and gender effect, five adverse events were reported by 36 volunteers. Four of these adverse events were considered as possibly related to study drug: headache (3x) and arm bruise. In Impact No.10847 64 healthy volunteers were enrolled, 87 adverse events were reported. 43 of these adverse events were considered as possibly drug related: meteorism, feeling of hyperacidity in stomach, headache (16x), heartburn

(4x), diarrhea (4x), feeling of exhaustion (8x), flatulence, exanthema, pressure on left ear, tinnitus left ear, heat sensation, salty taste, dizziness, elevated LDH and ALT. In Impact No. 10848, the enoxaparin interaction study, 11 adverse events were reported and seven were considered as possibly drug related, all headache (7x).

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

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 25% and 39%. Due to the lipophilicity of the drug, food ingestion results in higher but less variable plasma concentrations. 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 male and female subjects 65-80 years. Elderly subjects exhibited higher plasma concentrations than young subjects. An interaction trial of BAY 59-7939 and enoxaparin was performed. The combination of 10mg BAY 59-7939 with 40mg enoxaparin showed an additive, but not synergetic effect. Therfore, enoxaparin can safely be used as a rescue medication in those patients who experienced a VTE despite treatment with BAY 59-7939.

The Enterium-Capsule absorption study showed still relevant absorption in the lower small intestine and colon (AUC of about 30% of total gastrointestinal tract), the main absorption occured in the upper GI.

For more information please refer to investigator brochure (version 8.0, 09 July 2004).

In the phase IIa ODIXa-HIP open label proof-of-principle study (Impact No. 10942) 641 patients undergoing elective hip replacement surgery were randomized. 625 patients were treated with study medication (162 patients in the enoxaparin group and 463 patients in the BAY 59-7939 treatment groups). In this study proof-of-principle for all BAY 59-7939 doses was demonstrated. According to the study results once daily dosing of BAY 59-7939 seems to be feasible. In this study the 30 mg once daily BAY 59-7939 dose showed an acceptable risk-benefit ratio.

For bleeding events a significant dose trend was found for BAY 59-7939. Nearly all major postoperative bleeding events were related to surgical site, except one gastric ulcer bleeding.

Please see below the tables relating to the primary efficacy endpoint (incidence of DVT, PE and death), the safety efficacy endpoint postoperative major bleedings and incidence of serious adverse events.

Primary Efficacy Results (per protocol analysis)							
BAY 59-7939 (mg)	**2.5 bid**	**5 bid**	**10 bid**	**30 qd**	**20 bid**	**30 bid**	**Enoxaparin (40 mg qd)**
Primary Efficacy Endpoint (DVT, PE, Death) (%)							
Any Event	22.2	23.8	20.0	15.1	10.2	17.4	16.8
DVT	20.6	23.8	20.0	12.3	10.2	17.4	16.8
PE	3.2	0	0	1.4	0	0	0
Death	1.6	0	0	1.4	0	0	0

Overview on Adverse Events (safety analysis)							
BAY 59-7939 (mg)	**2.5 bid**	**5 bid**	**10 bid**	**30 qd**	**20 bid**	**30 bid**	**Enoxaparin (40 mg qd)**
Serious adverse events, treatment emergent (%)							
Any Event	10.5	16.3	8.8	13.6	15.6	18.9	13.6
DR-SAE	2.6	6.3	2.9	6.8	11.7	17.6	3.1
Adverse events, treatment emergent (%)							
Any event	73.7	71.3	67.6	78.4	77.9	90.5	79.0
DR-AE	32.9	23.8	27.9	43.2	46.8	51.4	23.5

Incidence Rates of Post-Operative Major Bleeding Events (Safety Population)

Bleeding classification	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any major bleeding event	0 (0.0%)	2 (2.5%)	2 (2.9%)	4 (4.5%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retroperitoneal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraspinal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraocular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding associated with fall in HB	0 (0.0%)	2 (2.5%)	1 (1.5%)	4 (4.5%)
Clinically overt bleeding leading to blood transfusion	0 (0.0%)	2 (2.5%)	2 (2.9%)	3 (3.4%)
Bleeding leading to re-operation	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Bleeding warranting treatment cessation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Bleeding classification	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Any major bleeding event	5 (6.5%)	8 (10.8%)	0 (0.0%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retroperitoneal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraspinal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraocular	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding associated with fall in HB	3 (3.9%)	7 (9.5%)	0 (0.0%)
Clinically overt bleeding leading to blood transfusion	0 (0.0%)	6 (8.1%)	0 (0.0%)
Bleeding leading to re-operation	0 (0.0%)	1 (1.4%)	0 (0.0%)
Bleeding warranting treatment cessation	2 (2.6%)	3 (4.1%)	0 (0.0%)

For more information please refer to Investigator brochure version 8.0 dated 09 July 2004.

2. STUDY OBJECTIVES

The objective of this dose-ranging trial is to assess the efficacy and safety of BAY 59-7939 10 mg – 40 mg once daily dosing in prevention of VTE in men and in postmenopausal women aged 18 years or above undergoing elective primary total hip replacement.

Population pharmacokinetics and pharmacodynamics (Factor Xa activity, PT, PT INR, aPTT and HepTest) will also be assessed.

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 requested.

4. INVESTIGATIONAL PLAN

4.1 Study Design and Plan

The study will be conducted in a prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national design. The efficacy and safety parameter of primary interest will be centrally adjudicated by Adjudication Committees.

Day 1 will be defined as the day before the elective total hip replacement. On Day 1 the first pre-operative dose of enoxaparin or matching placebo will be given.

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 matching placebo and the second dose of enoxaparin or matching placebo will be administered post-operatively (6 to 8 hours after wound closure).

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 with the application of enoxaparin or matching placebo.

Day care (only applicable for Denmark and The Netherlands)

According to local hospital routine and if no adverse events occur the patients can be discharged at the discretion of the investigator to a closely supervised

home therapy (=Day care, for minimal requirements please refer to section 4.6.4) during the treatment phase.

The patients will be randomized to one of the following five treatment groups (see below).

I: 10 mg od of Bay 59-7939 tablets active substance (10 mg and 1 placebo tablet) plus a placebo syringe of enoxaparin

(2 tablets plus one s.c. injection in the evening)

II: 20 mg od of Bay 59-7939 tablets active substance (20 mg and 1 placebo tablet) plus a placebo syringe of enoxaparin

(two tablets plus one s.c. injection in the evening)

III: 30 mg od of Bay 59-7939 tablets active substance (30 mg and 1 placebo tablet) plus a placebo syringe of enoxaparin

(two tablets plus one s.c. injection in the evening)

IV: 40 mg od of Bay 59-7939 tablets active substance (2x 20 mg tablets) plus a placebo syringe of enoxaparin

(two tablets plus one s.c. injection in the evening)

V: 2 placebo tablets of BAY 59-7939 plus a syringe of enoxaparin active substance at a dose of 40 mg.

(two tablets plus one s.c. injection in the evening)

Day 2 to Day 9±2

Day 2 will be defined as the day of the elective primary total hip replacement. Six to eight hours after wound closure BAY 59-7939 or matching placebo tablets will be administered orally. Thereafter, BAY 59-7939 or matching placebo tablets will be given once daily every 24 ± 2 hours with the evening meal until day of venography (day 10 ± 2 days). Last dose of BAY 59-7939 or matching placebo will be administered in the evening prior to venography.

Enoxaparin 40 mg or matching placebo will be administered subcutaneously in the evening of the operation at least 6 to 8 hours after wound closure, thereafter once daily in the evening according to the hospital routine.

Day 8 to 12:

On day 8 to 12 a bilateral ascending venography is mandatory for all patients. If symptoms of DVT occur earlier, an ultrasound may be allowed. If the DVT is confirmed by ultrasound, 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 follow-up) a lung scintigraphy with chest X-Ray or a spiral CT or a pulmonary angiography should be performed. Symptoms of DVT occuring during follow-up should be verified by ultrasound or venography.

Follow-up:

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

In total 670 patients are planned to be enrolled in the study, 134 patients per treatment arm.

Sparse PK/COAGULATION blood samples will be taken from all randomized patients to describe drug exposure and exposure/response relationships using BAY 59-7939 plasma concentrations and Factor Xa activity, Heptest, activated partial thromboplastin time (aPTT), International Normalized Ratio (PTINR) and prothrombin time (PT), respectively. For further details please refer to section 10.7.

4.2 Selection of Study Population

The study population will consist of men and postmenopausal women patients aged 18 years or above 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. Any VTE prior to randomization.

5. Myocardial infarction (MI) or TIA or ischaemic stroke within the last 6 months prior to randomisation.

6. History of heparin-induced thrombocytopenia, allergy to heparins.

7. Intracerebral or intraocular bleeding within the last 6 months prior to randomisation.

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 (e.g. severe active inflammatory bowel disease, short gut syndrome).

10. Amputation of one leg.

Related to current symptoms or findings

11. Heart insufficiency NYHA class III-IV.

12. Congenital or acquired haemorrhagic diathesis (PT INR/aPTT not within normal limits) including patients with acquired or congenital thrombopathy.

13. Thrombocytopenia (platelets < 100.000/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 or creatinine clearance < 30 ml/min).

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. Patients who cannot stop therapy (in the opinion of the investigator/physician) with anticoagulants (eg phenprocoumon, warfarin-sodium, heparins and factor Xa inhibitors other than study medication) should be excluded from the study.

24. Fibrinolytic therapy.

25. Therapy with acetylic salicylic acid or other platelet aggregation inhibitors (e.g. clopidogrel, dipyridamole and ticlopidine) should be stopped one week before enrolment. Patients not able to stop ASA therapy will be excluded.

26. All other drugs influencing coagulation, (exception: NSAIDs with half life < 17 hrs) will be not allowed during the study treatment period.

27. Systemic and topical treatment with azole compounds (e.g. ketoconazol, fluconazol, itraconazol) and otherstrong CYP3A4-inhibitors eg HIV-protease inhibitors. Azole compounds and other strong CYP3A4-inhibitors eg HIV-protease should be stopped at least four days before enrolment.

28. Therapy with another investigational product within 30 days prior start of study.

Miscellaneous

29. Planned intermittent pneumatic compression during active treatment period.

30. Planned epidural anaesthesia with indwelling epidural catheter (spinal or epidural anaesthesia without indwelling catheter are allowed).

31. If traumatic or repeated epidural and spinal puncture occur the patient should be excluded from study.

32. Concomitant participation in another trial or study.

4.3 Removal of Subjects from Study

A subject who withdraws is one who discontinued in a clinical study for any reason.

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 prematurely for the following reasons:

- If pulmonary embolism occurs.
- If a DVT has been confirmed by venography before day 7.

- Excluded concomitant medication.

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 Center

The sponsor has the right to close this study, and the investigator/sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The EC/IRB must be informed. Should the study/center be closed prematurely, 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 given by the sponsor for destruction.

4.5 Treatments

4.5.1 Treatments to be Administered

At Day 1, all patients who complete all screening procedures and who meet the eligibility criteria to enter the study are to be randomized into one of the following five treatment groups:

I: 10 mg od of Bay 59-7939 tablets active substance (10 mg and 1 placebo tablet) plus a placebo syringe of enoxaparin

(2 tablets plus one s.c. injection in the evening)

II: 20 mg od of Bay 59-7939 tablets active substance (20 mg and 1 placebo tablet) plus a placebo syringe of enoxaparin

(two tablets plus one s.c. injection in the evening)

III: 30 mg od of Bay 59-7939 tablets active substance (30 mg and 1 placebo tablet) plus a placebo syringe of enoxaparin

(two tablets plus one s.c. injection in the evening)

IV: 40 mg od of Bay 59-7939 tablets active substance (2x 20 mg tablets) plus a placebo syringe of enoxaparin

(two tablets plus one s.c. injection in the evening)

V: 2 placebo tablets of BAY 59-7939 plus a syringe of enoxaparin active substance at a dose of 40 mg.

(two tablets plus one s.c. injection in the evening)

4.5.2 Identity of Investigational Product(s)

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

BAY 59-7939

BAY 59-7939 will be provided by BAYER Clinical Drug Supplies as tablets at a dose of 10 mg, 20 mg, 30 mg. BAY 59-7939 tablets will be packed in HDPE bottles.

BAY 59-7939 placebo are matching tablets to the active BAY 59-7939 tablets.

40 mg Enoxaparin

Enoxaparin will be provided as Clexane 0.4 ml prefilled syringes (Aventis Pharma, Frankfurt am Main, Germany) containing 40 mg enoxaparin sodium (corresponding to 4000 I.U. anti-Xa).

Enoxaparin placebo will be provided as 0.4 ml prefilled syringe.

Route of administration:

Enoxaparin 40 mg or matching placebo 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.

BAY 59-73939 or matching placebo tablets, the route of administration will be oral with water and food.

Storage:

The medication for 9±2-days treatment course will be prepared by Clinical Supplies Department at Bayer AG, Leverkusen, Germany. Enoxaparin should not be frozen and stored at a temperature not exceeding 25°C. The study drug is to be kept in a secure area (e.g. locked cabinet).

The Investigator or their designee is responsible for the proper dispensing of the study drug.

4.5.3 Method of Assigning Subjects to Treatment Groups

All patients meeting the inclusion and none of the exclusion criteria are eligible for randomization. Patients will be assigned to treatment groups in accordance with a computer-generated random code provided by Bayer Biometry. For randomization, an interactive voice response system (IVRS) will be used. The IVRS is a telephone randomization system. The investigator will dial in the telephone randomization system and will receive via the system the random number. Please refer to the IVRS procedure manual.

Patients, investigators, adjudication committees and Bayer/contract research personnel will remain blinded as to which study drug is administered. The sealed random code will be provided to the investigators. In the event of an emergency, the random code may be broken. However, whenever possible, the investigators should contact Bayer/contract research personnel prior to breaking the code. If the code is broken, Bayer/contract research personnel must be notified by telephone or facsimile within 48 hours. The date and the reason for the code break must be documented and signed by the investigators.

4.5.4 Selection of Doses in the Study

This phase IIb study is a dose ranging study assessing different doses of once daily BAY 59-7939. 10 mg od of BAY 59-7939 will be the lowest dose tested in this phase IIb study and 40 mg od dose of BAY 59-7939 the highest dose. According to the phase IIa ODIXaHIP study results once daily for BAY 59-7939 seems to be feasible. This trial tested a once-daily dose of 30 mg which was shown to be in line with the predicted dose-trend with regard to efficacy and safety and resembled the 15 mg bid point estimate. Therefore, there is evidence to support that 10 mg od may

resemble the 5 mg bid results and the 40 mg od may behave similar to the 20 mg bid dose group in this trial. Additionally, pharmacodynamics of a single dose of 10 mg BAY 59-7939 in terms of anti-factor Xa activity produced identical curves when compared with enoxaparin 40 mg. The feasibility of once daily dosing is also supported by a pharmacodynamic study[20] which clearly demonstrated that a single dose of 30 mg BAY 59-7939 resulted in a long lasting significant inhibition of thrombin generation over more than 24 hours, whereas a dose of 5 mg was not capable to produce this long-lasting effect on thrombin generation. Single dose and multiple dose escalation studies in healthy male subjects[18-19] also indicate that doses of 10, 20, 30, and 40 mg resulted in an at least 10% inhibition of factor Xa after 24 hours – a level which was shown to be correlated with significant suppression of thrombin-generation.

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 approved for thromboprophylaxis in orthopaedic surgery.

4.5.5 Selection and Timing of Dose for Each Subject

Due to the higher bleeding risks in the acute postoperative setting 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 an effective therapeutic regimen. 10 mg od will be lowest dose and 40 mg od the highest dose tested in this phase IIb study. This concept was tested in the phase IIa ODIXaHIP study 10942 and showed an acceptable risk-benefit ratio.

In Europe enoxaparin 40 mg 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 or matching placebo s.c. will be administered in the evening according to hospital routine.

Day 2 (day of surgery):

On Day 2 the patient will receive BAY 59-7939 tablets or matching placebo tablets and 40 mg enoxaparin or matching placebo.

BAY 59-7939 or matching placebo will be administered orally 6 to 8 hours after wound closure. Thereafter, BAY 59-7939 or matching placebo will be administered every 24 ± 2 hours with the evening meal.

40 mg enoxaparin will be administered according to hospital routine, but not earlier than 6-8 hours after wound closure.

Day 3 until day of venography (Day 10 ± 2 days):

BAY 59-7939 or matching placebo tablets will be administered once daily every 24 ± 2 hours with the evening meal. 40 mg enoxaparin s.c. or matching placebo will be administered once daily in the evening according to hospital routine.

The last administration of BAY 59-7939 or matching placebo and 40 mg enoxaparin or matching placebo s.c. will be in the evening before venography.No study

medication will be administered after venography. The thromboprophylaxis therapy after venography is up to the discretion of the investigator.

4.5.6 Blinding

The study is double-blind. The packaging and dosage will be such, that the different treatment groups will appear identical. Patients, investigators and sponsor/contract research personnel will remain blinded as to which study drug is administered. Analysis of drug concentrations will be performed in parallel to the conduct of this study. The Bioanalytics group will be allowed to have access to the randomization list. To prevent unblinding during the study, transfer of drug concentration data will only be conducted to Data Management at the end of study upon request.

The Steering Committee, the Venography Adjudication Committee, the VTE Adjudication Committee, the Data Safety and Monitoring Board and the Bleeding Event Adjudication Committee will perform their assessments in a blinded manner. The Data Safety and Monitoring Board will receive semi-blinded data for regular review and has the possibility to ask for unblinding (refer to section 10.2).

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.

Patients for whom therapy with anticoagulants cannot be stopped in the opinion of the investigator/ physician (e.g. phenprocoumon, warfarin-sodium, heparins and factor Xa inhibitors other than study medication) should be excluded from the study. Fibrinolytic therapy is not allowed throughout the study. Patients who cannot stop ASA treatment have to be excluded from study. 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 labeling. If no labeling is available it is recommended to stop heparins or Factor Xa inhibitors 2-3 days prior to the start of the study. Drugs influencing coagulation are not allowed during the treatment period of the study (exception: NSAIDs with a half-life < 17 hours).

Systemic or topical treatment with azole compounds (e.g. ketoconazole, itraconazole, fluconazole) and other strong CYP3A4-inhibitors eg HIV-protease inhibitors are not allowed during the study period. Azole compounds and other strong CYP3A4-inhibitors eg HIV-protease inhibitors should be stopped at least 4 days before enrollment and for restart after the treatment phase a 1-2 day time interval after the last administration of the study drug should be followed.

Subjects on digitalis preparations should be closely monitored. Plasma levels have to be monitored during the first days of study drug intake.

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.

If traumatic or repeated epidural or spinal puncture occur the patient should be excluded from study.

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 study medication will be performed. The treatment compliance should be between 80% and 120%.

4.6 Study Variables

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 6 - 10 days after surgery (or in case of symptoms indicating VTE). The analysis of the primary efficacy endpoint will be solely based on the assessments made by the Venography and the VTE Adjudication Committees.

Secondary efficacy endpoints are:

- Incidence of DVTs (total, proximal, distal)
- Incidence of symptomatic VTEs
- Incidence of major VTE (ie. Proximal DVT, PE or VTE-related death)
- The composite endpoint that results from the primary endpoint by substituting VTE related death for all 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 endpoints related to VTE will be solely based on the assessments made by the venography and VTE Adjudication committees.

4.6.2 Safety Variables

The main safety endpoint is the incidence of major bleeding observed after the first post-operative intake of study drug and not later than 2 days after last intake of study drug. Major bleeding observed before or after this period will be considered separately.

The analysis of the primary safety endpoint will solely be based on the classification made by the Bleeding Adjudication 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 parameters.

4.6.3 Assessment Periods

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 randomized to one of the treatment arms. Treatment with enoxaparin or matching placebo will start on day 1 and treatment with BAY 59-7939 or matching placebo tablets will start on Day 2 six to eight hours after wound closure. Study medication will be given until Day 7 to 11 depending on the day of bilateral venography .

Day care (only applicable for Denmark and The Netherlands)

According to local hospital routine and if no adverse events occur, patients can be discharged at the discretion of the investigator to a closely supervised home therapy (= day care, minimal requirements please refer to section 4.6.4) during the treatment phase.

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 10 ± 2 (day of venography) and follow-up visit

Every day a physical examination with assessment of vital signs (heart rate and blood pressure measurement in supine position after five minutes rest) will be performed.

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

Day care (only applicable for Denmark and The Netherlands)

For day care (only valid for the treatment period, not for the follow-up period) the following requirements must be ensured: a close geographical proximity to hospital, access to an emergency facility, home visits of a trained nurse at least once a day and access to a day care facility for PK/COAGULATION blood

sampling (if the patient was discharged before the planned PK/COAGULATION days).

Every day until discharge or during day care period an assessment of vital signs (heart rate and blood pressure measurement in supine position after five minutes rest) and patients health conditions will be performed. After randomization during the treatment period a daily assessment of VTE signs, bleeding events and adverse events 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, one electronic ECG reading will be derived. In case it is not possible to perform all the assessments on Day 1 due to hospital routine (e.g. weekend) it is allowed to perform the assessments for Day 1 up to 7 days before the scheduled date of surgery.

Thereafter, the patient will be randomized if eligible for the study (central telephon randomisation).

40 mg enoxaparin or matching placebo injections will be administered subcutaneously in the evening.

Day 2:

6-8 hours after wound closure:

Oral BAY 59-7939 or matching placebo will be administered. Oral medication must start 6 to 8 hours after wound closure. To avoid postoperative hemorrhage no oral medication should be administered earlier than 6 hours after wound closure.

Additionally, enoxaparin or matching placebo will be administered subcutaneously in the evening.

Blood samples (haematology, clinical chemistry parameter) will be taken 2-4 hours after administration of the first dose of BAY 59-7939. Furthermore there will be 1 PK/Coagulation sample taken after taken after 2-4- hours after the first administration of BAY 59-7939.

All assessments will be done post-operatively.

Day 3 or Day 4:

On Day 3/Day 4 blood sampling for clinical chemistry and haematology parameter will be done for all patients 2 to 4 hours after administration of BAY 59-7939 or matching placebo in the evening. Additionally, for all patients there will be in total 4 blood samples taken for PK/Coagulation sampling. The first sample will be taken in the time interval of 4 to 0,5 hours before the administration of BAY 59-7939 in the evening. The other three samples will be drawn at 1h (± 30 min), 3h (± 1h), 12h (± 2h) after the intake of oral study medication.

Day 5 or Day 6/Day 7:

An electronic ECG should be derived.

For all patients blood sampling for clinical chemistry and haematology parameter will be performed 2 to 4 hours after administration of BAY 59-7939 or matching placebo in the evening.

For all patients there will be in total 2 blood samples taken for PK/Coagulation sampling. The first sample will be taken in the time interval of 4 to 0,5 hours before administration of BAY 59-7939. The second sample will be drawn 3h (± 1h) after the oral intake of BAY 59-7939 (details see section 10.7).

The day of PK/COAGULATION measurement should not be the day of venography!

Day 10 ± 2:

Blood samples for clinical chemistry, haematology and PK/Coagulation parameter will be taken 12 h (± 2h) after the last intake of BAY 59-7939 or matching placebo before the planned venography. If this is not possible the blood samples can be taken directly before BAY 59-7939 or matching placebo intake between Day 6 to the day of venography.

For all patients an electronic ECG will be derived 12 h (± 1h) after the last dose of BAY 59-7939 or matching placebo before venography . If this is not possible the electronic ECG can be derived 12 h (± 1h) after the intake of BAY 59-7939 between Day 6 to the day of venography .

Urinalysis will be performed in the morning before venography.

Bilateral venography will be performed the day after the last intake of study medication (Day 10 ± 2).

Follow up on Day 40 (to Day 70)

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, serum albumin, urea, uric acid, SGOT/AST, SGPT/ALT, GGT, LDH, bilirubin, alkaline phosphatase, amylase, triglyceride, total cholesterol, lipase and blood glucose.

Haematology: haemoglobin, haematocrit, RBC, WBC, neutrophils (total), lymphocytes, monocytes, eosinophils, basophils, platelets.

Coagulation parameter: prothrombin time (PT in seconds), activated partial thromboplastin time (aPTT), prothrombin ratio (PTINR), Heptest and Factor-Xa activity.

All laboratory parameter except for haematology and urinalysis (dip-stick) will be determined in a central laboratory. For monitoring the postoperative course of the patient the investigator should stick to the blood samples routinely taken in the hospital.

To ensure the blindness of the study the investigator should not measure coagulation parameters locally. He will not receive regularly the results of the coagulation parameters of the central laboratory.

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

In case of symptomatic DVT, PE, major or clinically relevant bleeding or any other adverse event which may be related to study drug additional blood samples should be taken for the assessment of haematology, clinical chemistry and coagulation parameters.

Urinalysis:

pH, protein, glucose and blood. Urinalysis will be performed by dip-stick analysis (dip sticks from local stock).

Electrocardiography

For deriving the ECG the patient should always be in supine position. The ECG should be derived after five minutes rest. 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. In case of any cardiac adverse event an additional ECG should be derived.

Bilateral Venography:

The bilateral venograms for this study will be assessed centrally. Please refer to the Committees Manual of Operation 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, e.g. for AE reporting.

The venography film has to be sent to the central assessment unit for further assessment.

In case of a suspected symptomatic DVT before day 10 ± 2 an ultrasound has to be performed first. If the DVT is confirmed by ultrasound, a venography have to be performed, too. If a DVT is not proven, the study can go on and the planned bilateral venography on day 10 ± 2 will be performed. If the venography is positive for DVT the treatment with study medication will be stopped.

Diagnosis of PE:

If symptoms of PE occur, pulmonary angiography or a perfusion/ventilation lung scintigraphy combined with chest radiography or spiral CT should be performed and the images or films will be sent to the VTE 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 random number, patient number and center number given).

Diagnosis of bleeding events:

If bleedings events occur all available information, e.g. anaesthesia and surgery report, laboratory results, number of transfusions, hospital letters, short narrative, radiology or ultrasound findings etc. have to be collected and sent to the central Bleeding Adjudication Committee. Care must be taken that the identity of the patient will be blinded (i.e. just random number, patient number and center number given).

4.6.5 Drug Concentration Measurements

Blood samples will be taken for pharmacokinetic and pharmacodynamic measurements from all patients.

For the investigation of pharmacokinetics the concentrations of BAY 59-7939 in plasma will be determined. For the investigation of pharmacodynamics the Factor Xa activity, prothrombin time (PT), International Normalized Ratio (PT INR), Heptest and aPTT will be determined (see Section 6.3 and 10.7).

The time points of PK/COAGULATION sampling for the sparse PK/COAGULATION sampling are outlined in Section 10.7.

The blood samples taken in connection with DVT, PE or major bleeding events will be transferred from the central lab to the Pharmacokinetic Department of Bayer AG, Wuppertal, Germany for drug concentration measurements.

4.7 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with GCP guidelines. Each center 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 CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF 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 notification given by the sponsor for destruction.

5. ETHICAL AND LEGAL ASPECTS

5.1 Ethics Committee (EC) or Institutional Review Board (IRB)

Documented approval from appropriate Ethics Committee(s)/IRBs will be obtained for all participating centers/countries prior to study start, according to GCP, local laws, regulations and organizations. 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 organized 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 principles detailed in the Declaration of Helsinki. 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. However, the investigator may implement a deviation form, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior EC/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 EC/IRB/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

5.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/ notifications, where required, must 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 ECs/IRB written approval/favorable opinion of the written Informed Consent Form and any other written information to be provided to subjects. The written approval of the EC/IRB

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. 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. 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, EC/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 variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum).

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 prior to breaking the blind.

Demographic variables and baseline characteristics will be summarized 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 randomized 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 6 - 10 days after surgery
- confirmed symptomatic deep venous thrombosis up to 10 days after surgery
- confirmed symptomatic pulmonary embolism up to 10 days after surgery
- Death up to 10 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 or VTE-related death is diagnosed 11 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.

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, in case of a positive finding, was done not later than 36 hours after stop of study drug
- shows no major protocol deviations.

Major protocol deviations e.g. are given by:

- intake of prohibited anticoagulant concomitant medication
- overall compliance of less than 80%
- administration of study medication not according to protocol (e.g. initiation of BAY 59-7939 not within 12 hours of wound closure, more than 36 hours between two subsequent administrations of study medication).

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 VTE risk factors 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 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. 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 a hypothesis 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 VTE-related efficacy endpoints 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 post-operative major bleeding will be tabulated and further analysed by the logistic regression model already specified for the primary efficacy analysis. However, no country effect will be considered in the logistic regression analysis due to the small number of major bleeding events that is to be expected. 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 specific 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

No formal interim analysis is planned in this study for specific time points. However, there will be an ongoing safety and efficacy monitoring to be performed by the Data Safety and Monitoring Board (DSMB) in a semi-blinded manner. In case of an unacceptable efficacy and/or safety profile seen in a treatment arm, the DSMB can recommend to the SC to prematurely stop this treatment arm. If deemed necessary, the DSMB will even have the opportunity of complete unblinding (see Section 10.2 Study committees).

6.2 Determination of Sample Size

For sample size determination it is assumed that the event rates of the primary efficacy criterion range from 25% (or more) in the lowest dose group to 10% (or less) in the highest dose group of BAY 59-7939.

Table 6.2/1: Event Rates used for Sample Size Calculation

Dose Group	10 mg od	20 mg od	30 mg od	40 mg od	Sample Size per Group
	25.0%	20.0%	15.0%	10.0%	103

Assuming a linear trend in the dose-response relationship (see Table 6.2/1), a sample size of 103 patients per treatment group is sufficient in order to perform a two sided trend test with a type I error rate of $\alpha = 0.05$ and a type II error rate of $\beta = 0.15$ (ie. a power of 85%). Sample size was calculated using nQuery Advisor, Version 5, Module PGT 1-1.

In order to cope with an invalidity rate of approximately 23%, a sample size of 134 patients is required for each of the four BAY 59-7939 dose groups. The enoxaparin treatment group is planned to have the same size as the individual BAY 59-7939 treatment groups, so that in total 670 patients have to be randomized.

6.3 Population Pharmacokinetic/Coagulation Data

For investigation of pharmacokinetics and coagulation, the plasma concentrations of BAY 59-7939, Factor Xa activity, heptest, activated partial thromboplastin time (aPTT), PT INR and prothrombin time (PT) will be determined at the times given in Section 10.7. using a sparse sampling approach.

PK/Coagulation modelling using population approaches (e.g. NONMEM [12] see reference no. 12) to describe BAY 59-7939 pharmacokinetics including potential influence of relevant patient co-variables (eg age, gender, serum creatinine, etc.) and to relate pharmacodynamic parameters with BAY 59-7939 plasma concentrations will be investigated under a separate detailed PK/Coagulation evaluation plan.

7. ADVERSE EVENTS

7.1 Warnings/Precautions

For BAY 59-7039 phase I and phase IIa data are available (for more information please refer to chapter 1 introduction). In healthy volunteers single doses up to 80 mg of BAY 59-7939 and multiple dosing of 30 mg for five days were well tolerated and inhibition of Factor Xa was dose-dependent. Clotting parameter (PT, PT INR, aPTT, Heptest) showed expected changes. Bleeding time was not affected to a clinically relevant extend. There were no drug-related deaths. For more details please refer to the Investigator brochure, version 8.0, 09 July 2004.

BAY 59-7939 is a factor Xa inhibitor which affects the coagulation. Due to the pharmacological action of BAY 59-7939 prolongation of coagulation parameters (eg bleeding time, PT, aPTT, HepTest) occurs regularly. A therapeutic INR range for BAY 59-7939 has not yet been determined and therefore the known therapeutic INR range for wafarin cannot automatically be translated. There is an increased dose-dependent risk for haemorrhage for the same reason. This may include overt or occult bleeding resulting in eg haematoma or anaemia. 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.

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.

IF traumatic or repeated epidural and spinal puncture occur, the patient should be excluded from study.

Increase of liver enzymes is possible, which resolved after stop of therapy. Rarely thrombocytaemia, 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. Adverse events should be assessed in terms of their seriousness, severity, 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 with 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an 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.
- An adverse events where there is a reasonable possibility that the event occurred purely as a result of the subjects participation in the study (eg adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an adverse event even if it is not related to the investigational product.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an adverse event if it is already reflected as a data point captured in the CRF. If, however, the event fulfills any of the criteria for a "serious" adverse event, it must be recorded and reported as such.

Both venous thromboembolism and bleeding events are characteristic for the underlying disease and its natural history. Surgical bleeding occurs also without anticoagulation. All anticoagulants may increase the bleeding risk. Patients undergoing major orthopedic surgery have a very high inherent risk for VTE, which can be minimized, yet not abounded by anticoagulation. Moreover, both bleeding events and VTE are pre-specified endpoints of this trial. Therefore, these cases will not be considered as unexpected and thus there is no need to unblind them during the course of the trial.

7.3.2 Serious Adverse Event

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

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met :

- The admission results in a hospital stay of less than 12 hours.

OR

- The admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study).

OR

- The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfil the criteria of 'medically important' and as such may be reportable as a serious adverse event dependant on clinical judgement. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

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

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "WHO Adverse Reaction Terminology – Critical Terms List. These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

Asymptomatic DVT events are study efficacy endpoints will be recorded as Adverse Events and only be expedited as Serious Adverse Events if required by authorities. However, any clinical symptomatic event (symptomatic DVT or symptomatic PE) are clinically relevant, medical important events and therefore will be reported expedited as Serious Adverse Event.

All overt bleeding events considered as serious by the investigator will be reported as SAE. However bleeding events not considered as serious by the investigator but later adjudicated as major by the the Bleeding Event Committee will not be reported as SAE. During the study a regular safety monitoring will be performed by an independent DMSB.

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 labeled adverse event with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Both surgical site bleedings and venous thromboembolic events are expected due to the natural history of the disease and the surgical procedure itself.

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 eg, mechanical bleeding at surgical site.

OR

2. Non-Plausibility eg, 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 the first drug administration.

An assessment of 'Yes' indicates that there is a reasonable suspicion that the adverse event is associated with the use of the investigational 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 suspected to cause the event in question.
- 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 Severity of the Adverse Event

The following classification should be used:

The 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 after the subject has signed the informed consent must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, eg, causing the subject to withdraw from 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, severity, relationship to investigational product, action taken and outcome.

7.4 Reporting of Serious Adverse Events/Pregnancy

Serious adverse events (SAEs), including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent and during 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. Each serious adverse event must be

followed up until resolution or stabilization by submission of updated reports to the designated person.

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

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to Bayer within the same timelines as a serious adverse event on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

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 utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, whilst free to utilize 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 recognizes 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.

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10.APPENDICES

10.1 Study Flow Chart and/or Schedule Procedure

	DAY OF TREATMENT									Follow up
Visit	1	2[A]	3	4	5	6	7	8-11[E]	10	40
Allowed time frame									± 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 study medication	X									
Surgery		X								
Haematology (local)	X	X	X		X				X	
Clotting parameters[B]	X	X							X	
Clinical Chemistry[B]	X	X	X		X				X	
Urinalysis	X								X	
PK/Coagulation sparse		X	X[C]		X[D]				X	
ECG	X				X[D]				X	
Venography									X	
Vital signs	X	X	X	X	X	X	X	X	X	X
Clinical signs of DVT/PE	X	X	X	X	X	X	X	X	X	X
Clinical Assessment		X	X	X	X	X	X	X	X	
Adverse Events	X	X	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		
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

[A] THR is performed on Day 2
[B] will be assessed in Central laboratory
[C] Should be performed either on Day 3 or Day 4
[D] Should be performed either on Day5 or DAY6 or DAY 7
[E] Depending on day of venography

10.2 Study Committees

Steering Committee :

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.

Adjudication Committee/Venography (AC/V):

The AC/V will assess all scheduled and unscheduled venographies performed during the treatment period in a blinded manner. The assessment of the AC/V is the basis for the final DVT based efficacy analysis.

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

The AC/VTE will adjudicate all DVTs during the follow-up, all PE events during treatment and follow-up and all deaths during treatment and follow-up in a blinded manner.

The assessment of the AC/VTE is the basis for the final VTE based efficacy analysis.

Bleeding Event Adjudication Committee:

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.

Data Safety and Monitoring Adjudication Board (DSMB):

During the course of the trial the DSMB and the SC should closely interact and alert each other in order to assess all safety relevant information. The DSMB should also closely interact with the sponsor´s GDS in reviewing and assessing SAEs.

During the trial the DSMB will do an ongoing safety monitoring in a semi-blinded manner, ie. will be provided with tables presenting frequencies of adverse events stratified by treatment group with blinded treatment group labels. These tables will be prepared by an independent statistician. In case of unacceptable safety profile, for example, due to a high bleeding risk or in case of insufficient therapeutic effect, the DSMB can recommend to stop a specific treatment arm. However, the final decision will be made by the SC.

At the end of the trial, the DSMB will assist the sponsor in the assessment of all overall safety of BAY 59-7939 and will advise the sponsor in the characterization of the risk-benefit profile of BAY 59-7939.

10.3 Venography

DVT will be diagnosed by mandatory bilateral venography on day 8 to 12.

Each venogram will be initially read by the local radiologist of the center 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

PPD

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 8-12 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 /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, center 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

DVTs during Follow-up

Symptomatic DVTs during follow-up must be verified by venography and compression ultrasonography (CUS). The venographic diagnosis will be based on direct signs. The CUS diagnosis of DVTs will be based on non-compressibility of vessels with doppler as an adjunct.

The local radiology report, images and possible videotapes of CUS together have to be sent to the AC/VTE.

Assessment of Pulmonary Embolism

For diagnosis of pulmonary embolism the participating centers 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

Perfusion/Ventilation lung scintigraphy plus chest radiography.

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.

The images of PE and follow-up DVTs and death reports including patient records should be send to:

PPD

PPD

Östra Hospital, Central Clinic

S-41685 Göteborg

Sweden

10.5 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 of whole blood or packed cells
- retroperitoneal, intracranial, intraocular or intraspinal bleeding
- clinically overt 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.

10.6 Preparation of Blood samples for central laboratory

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

Blood Sample Summary

Value	Day 1	Day 2	Day 3/Day4	Day 5/Day6/7	Day 10 ± 2
Clinical Chemistry (central)					
Sodium	X	X	X	X	X
Potassium	X	X	X	X	X
Calcium	X	X	X	X	X
Creatinine	X	X	X	X	X
Albumin	X	X	X	X	X
Urea	X	X	X	X	X
Uric Acid	X	X	X	X	X
SGOT/AST	X	X	X	X	X
SGPT/ALT	X	X	X	X	X
Gamma GT	X	X	X	X	X
LDH	X	X	X	X	X
Bilirubin	X	X	X	X	X
Alkaline Phosphatase	X	X	X	X	X
Amylase	X	X	X	X	X
Triglycerides	X	X	X	X	X
Cholesterol	X	X	X	X	X
Lipase	X	X	X	X	X
Blood glucose	X	X	X	X	X
Haematology (local)					
Haemoglobin	X	X	X	X	X
Haematocrit	X	X	X	X	X
RBC	X	X	X	X	X
WBC	X	X	X	X	X
Neutrophils (total)	X		X	X	X
Lymphocytes	X		X	X	X
Monocytes	X		X	X	X
Eosinophils	X		X	X	X
Basophils	X		X	X	X
Platelets	X	X	X	X	X
Coagulation Parameter (central)					
PT (in sec.)	X	X	X	X	X
PT INR	X	X	X	X	X
APTT	X	X	X	X	X
Heptest	X	X	X	X	X
Factor Xa activity	X	X	X	X	X
PK Sampling					
Sparse PK		X	X	X	X

10.7 PK/Coagulation Part of the study

Population PK/Coagulation

In order to describe the pharmacokinetic and coagulation characteristics of BAY 59-7939 in all participating patients both shortly after surgery (on the first post-operative day (study Day 3 or Day 4) and during steady-state condition of BAY 59-7939 treatment (on study days 5,6 or 7), a sparse PK/Coagulation sampling approach, consisting of eight blood samples with separate tubes for PK and coagulation analysis, will be used.

The number of samples taken for the assessment of pharmacokinetics and coagulation parameters have been optimised to take the minimum amount of blood (in total 72 ml, or up to 108 ml if an indwelling catheter is used during the days of assessment) needed for adequate analysis.

PK samples will be analysed under the responsibility of the Institute of Clinical Pharmacology, BAYER AG, Wuppertal, Germany, while PD samples will be analysed in the selected central laboratory.

Sparse Population PK/Coagulation Sampling Times

On Day 2:

On Day 2 a blood sample should be taken 2-4 hours after the supervised administration of the first dose of BAY 59-7939 after the surgery.

On Day 3/Day 4:

Clear-cut recommendations on time points when to draw the blood samples are intentionally not been given; the purpose is to include a variety of time intervals from the last dosage in this analysis of population pharmacokinetics/ pharmacodynamics (PopPK/Coagulation):

On Day 3/Day 4 the first blood sample should drawn in the time interval of 4 to 0,5 hours before the supervised evening administration of BAY 59-7939. After supervised evening administration of BAY 59-7939The other tree samples should betaken: at 1 h (+/- 0.5 h), 3 h (+/- 1 h), at 12 h (+/- 2 h) post-dosing.

Day 5/Day 6/Day 7:

On Day 5/day 6/Day 7 the first blood sample should drawn in the time interval of 4 to 0,5 hours before the supervised evening administration of BAY 59-7939. The second blood sample should be taken 3 h (+/- 1 h) after evening administration of BAY 59-7939.

Cave: The day of PK/Coagulation measurement should not be the day of the venography.

Day 10 ± 2:

On Day 10 ± 2 a blood sample should be taken 12 ± 2 hours after the supervised administration of the last dose of BAY 59-7939 and before venography.

Sample handling instructions for all PK/Coagulation blood samples

Cave: When using an indwelling catheter, 2 ml of blood have to be discarded before the PK and coagulation samples are taken.

Plasma samples for PK

4 ml blood are to be taken in ammonium(NH_4)-heparinate tubes (alternatively lithium(Li)-heparinate may be used). The blood has to be centrifuged within 2 hours (centrifugation at room temperature for 10 min, approx. 1600g).

The resulting plasma sample has to be transferred to labelled polypropylene tubes and to be frozen at -20 °C as soon as possible. The samples have to be stored at -20 °C or lower until dry-ice shipment to the laboratory in Wuppertal.

Plasma samples for Coagulation

2.7 ml blood are to be taken in citrate tubes. The blood is to be centrifuged within 2 hours (centrifugation at 15 °C for 15 min, approx. 2500g). The resulting plasma sample has to be divided into 2 labeled propylene tubes a 600 µl and to be shock-frozen (covered with dry ice if available) at -20 °C as soon as possible. The samples have to be stored at -20 °C or lower until dry-ice shipment to the central laboratory.

It is essential that the precise timing of previous medication (plus of the two preceding doses) and of the blood sampling are accurately documented in the

provided Case Report Form (CRF). Furthermore, the timing of meals and the type of meal (breakfast, lunch, dinner, snack) should be tracked as indicated on the CRF.

General Instructions

Labelling of the samples

The labelling of the samples will be as follows:

Substance No/Study No:	BAY 59-7939/10944
Subject No	Sitebase No
Time of sampling	hh:mm (for plasma samples)
Timeframe of sampling	hh:mm-hh:mm (for urine samples)
Date of sampling	dd/mmm/yyyy

All labels have to adhere to the tubes and have to be readable at all storage conditions.

Shipment:

The PK/Coagulation samples will be collected together with the other blood samples by the central laboratory and then forwarded to Bayer Wuppertal.