Bayer

CLINICAL STUDY PROTOCOL AMENDMENT

Title	**Oral Direct Factor Xa** Inhibitor BAY 59-7939 in the Prevention of VTE in Patients Undergoing total **Hip** Replacement. **OdiXahip** – a Phase IIa Dose Escalating Proof of Principle Trial
Test Drug:	BAY 59-7939
Sponsor's Name and Address:	BAYER Vital GmbH D - 51368 Leverkusen
Sponsor's Telephone Number:	PPD
Study Number/Version/Date:	10942/ Version 1.10/ 2002/Oct/09
Previous Amendments:	none
Numbers/Version/Date:	
Development Phase:	**Phase IIa**
Amendment Number/Version/Date:	1 / 1.2/ 2003/Feb/06
Applicable to:	Applicable to all participating countries

Study Manager

Name: PPD PPD

Signature PPD

Date: PPD

Statistician

Name: PPD PPD

Signature: PPD

Date: PPD

Medical Expert

Name: PPD PPD

Signature: PPD

Date: PPD

CONFIDENTIAL

Additional Signatures

Name: Signature: _____

Function: Date:

Address:

Name: Signature: _____

Function: Date:

Address:

PPD

The undersigned confirm that they agree to conduct the s
described in this protocol

Name: PPD PPD Signature: PPD

Function: **Principal Investigator** Date: PPD

Address: PPD

Sweden

Telephone: PPD

Name: Signature: _____

Function: Principal Investigator of the country Date:

_____

Address:

1. Table of Contents

2. Description of the Amendment

There are some inconsistencies in the protocol which needed clarification.

For follow up after the surgery additional RBC, Hb and Hct, serum albumin and creatinine measurements have been introduced on visit 2.

Exclusion criteria have been specified.

Platelet count and serum albumin measurements have been introduced for visit 1, 3, 5, 9 ± 2.

Time frame of at least 6 hours between last administration of study drug and planned venography has been introduced.

Drug Concentration Measurements at BAYER Wuppertal for patients with symptomatic DVTs, PEs deaths or major bleeding during treatment have been introduced.

4.1 Study Design and Plan

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The overall design of the study is as follows:

Active treatment period is day 1 to day 9 ± 2.

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

Treatment group A:

On day 1 no study drug will be administered. The surgery should be performed latest until 15:00 on day 2.

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BAY 59-7939 will be given until day 9 ± 2 days.

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Treatment group B:

40 mg enoxaparin will be administered subcutaneously in the evening prior to the total hip replacement surgery. The surgery should be performed latest until 15:00 on day 2.

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will be changed to

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The overall design of the study is as follows:

Active treatment period is day 1 to ***day 6 - 11***.

Active treatment period will be a 9 ± 2 days in-house period starting in the evening of day 1 between 17:00-21:00 with the enoxaparin dose. ***Depending on the time of the venography on day 9 ± 2 the treatment may be stopped the day before the venography***. The patients will be randomised to either treatment group A or B (see below).

Treatment group A:

On day 1 no study drug will be administered. The surgery should be performed ***the*** latest until 15:00 on day 2. ***If the time of wound closure is after 15:00 care should be taken that the study medication will be administered on day 2 before 24:00.***

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BAY 59-7939 will be given until day 9 ± 2 days. ***BAY 59-7939 has to be stopped at least 6 hours before the venography. (In case that the venography will be performed on day 7 the last intake of BAY 59-7939 may be on day 6 depending on the time of the venography.)***

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Treatment group B:

40 mg enoxaparin will be administered subcutaneously in the evening prior to the total hip replacement surgery. The surgery should be performed ***the*** latest until 15:00 on day 2. ***If the time of wound closure is after 15:00 care should be taken that the study medication will be administered on day 2 before 24:00.***

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4.2.2. Exclusion Criteria

Related to medical history

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5. Myocardial infarction (MI) or cerebrovascular attack (CVA), TIA or ischaemic stroke within the last 6 months prior to study entry.

Will be changed to

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

4.2.2 Exclusion Criteria

Related to current symptoms or findings

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12. Congenital or acquired haemorrhagic diathesis (PTINR/aPPT not within normal limits)

Will be changed to

12. Congenital or acquired haemorrhagic diathesis (PTINR/aPPT not within normal limits) ***including patients with acquired or congenital thrombopathy.***

4.2.2 Exclusion Criteria

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Related to current treatment

24. Therapy with acetylic salicylic acid or other thrombocyte aggregation inhibitors (e.g. clopidogrel, dipyridamol and ticlopidine) should be stopped one week before enrolment.

25. Treatment with heparines or Factor Xa Inhibitors other than study medication.

26. All other drugs influencing coagulation, (exception: NSAIDs with half life < 17 hrs will be allowed).

Miscellaneous

27. Planned intermittent pneumatic compression during active treatment period.

28. Planned epidural anaesthesia with indwelling epidural catheter (spinal and epidural anaesthesia without indwelling catheter is allowed).

29. Concomitant participation in another trial or study.

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

will be changed to

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

25. ***Any t***reatment with heparines or Factor Xa Inhibitors other than study medication.

26. All other drugs influencing coagulation, (exception: NSAIDs with half life < 17 hrs will be allowed).

27. Therapy with ketoconazol.

Miscellaneous

28. Planned intermittent pneumatic compression during active treatment period.

29. Planned epidural anaesthesia with indwelling epidural catheter (spinal and epidural anaesthesia without indwelling catheter is allowed).

30. Concomitant participation in another trial or study.

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

4.3 Removals of subjects from the study

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Premature stop of study treatment

Subjects must stop study medication for the following reasons:

- If major bleeding or clinically relevant bleeding (for definition please refer to appendix 10.5 and to the bleeding event manual) occur during active treatment.

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will be changed to

Subjects must stop study medication for the following reasons:

- ***If major bleeding (for definition please refer to appendix 10.6 and to the Committees' Manual of Operation) occur during active treatment.***

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4.4 Premature Termination of Study/Closure of Centre

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Go criteria

...

The risk/benefit ratio is positive.

will be deleted

4.5 Treatments

4.5.1 Treatments to be Administered

BAY 59-7939

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The route of administration will be oral with water.

will be changed to

The route of administration will be oral with water.

For this study it is recommended to administer the study medication with food.

4.5.5 Selection and Timing of Dose for Each Subject

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

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

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will be changed to

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

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Treatment will be stopped before the venography will be performed. No study medication will be administered after venography. ***On the day of the venography no enoxaparin will be administered. The last administration of 40 mg enoxaparin s.c. will be in the evening before the venography.***

For BAY 59-7939 the time mimimum to the venography should be 6 hours. Depending on the time of the venography the last administration of BAY 59-7939 may be the day before the venography.

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4.5.7 Prior and Concomitant Therapy

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

Will be changed to

Therapy with oral anticoagulans (e.g. phenprocoumon, warfarin-sodium), with acetylic salicylic acid or other platelet aggregation inhibitors (e.g. clopidogrel, dipyridamole, ticlopidine) has to be stopped minimum one week prior to enrolment. ***Patient who cannot stop ASA treatment have to be excluded from the study.*** Also ***any*** 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. Drugs influencing coagulation are not allowed during the treatment period of the study (exception: NSAIDs with a half-life < 17 hrs). ***Treatment with ketoconazol is not allowed during the study period.***

4.6.1 Efficacy Variable

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

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- The composite endpoint that results from the primary endpoint by using alternative definition of deaths (i.e. VTE related death)

will be changed to

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The primary endpoint will be evaluated 5 - 9 days after surgery (***or earlier in case of symptoms indicating VTE)***. The analysis of the primary efficacy endpoint will be solely based on the assessments made by the adjudication committee.

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- The composite endpoint that results from the primary endpoint by using VTE related death.

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4.6.2 Safety Variables

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The analysis of the primary safety endpoint will be solely be based on the classification made by the Safety Committee and Bleeding Committee.

will be changed to

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The analysis of the primary safety endpoint will solely be based on the classification made ***by the Adjudication Committee/Bleeding Event.***

4.6.3 Assessment Periods

This trial will consist of six dose stages (please refer to chapter 4.1).

The assessment period per patient includes a 7 to 11 days treatment period followed by a 30 days follow-up period which can be extended up to 60 days.

will be changed to

This trial will consist of six dose stages (please refer to chapter 4.1).

The assessment period per patient includes a ***5*** to 11 days treatment period followed by a 30 days follow-up period which can be extended up to 60 days.

4.6.4 Observation and Measurements

Day 2

6-8 hours after wound closure:

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

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Day 9 ± 2:

Blood samples for clinical chemistry, haematology and coagulation parameter will be taken directly before the last intake of BAY 59-7939 or the last enoxaparin s.c. treatment before the planned venography. If this is not possible the blood samples can be taken directly before a dose application between day 7 to the day of venography.

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

Urinalysis will be performed in the morning before venography.

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Will be changed to:

Day 2

4-6 hours after wound closure:

Hb, Hct, RBC, creatinine and serum albumin measurement will be taken before administration of the study medication.

6-8 hours after wound closure:

Oral BAY 59-7939 will be administered if the patient has been randomised to the corresponding treatment group. Oral medication must start 6 to 8 hours after wound closure. ***T***o avoid postoperative wound haematoma ***no oral medication should be administered earlier than 6 hours after wound closure.***

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Day 9 ± 2:

Blood samples for clinical chemistry, haematology and coagulation parameter will be taken directly before the last intake of BAY 59-7939 or the last enoxaparin s.c. treatment before the planned venography. ***(Depending on the time of the venography the day of the last study medication intake may be on the day before the venography.)*** If this is not possible the blood samples can be taken directly before a dose application between day ***6*** to the day of venography.

For patients receiving BAY 59-7939 treatment an electronic ECG will be derived 2-4 hours after the last dose of BAY 59-7939 before the venography. For patients randomised to enoxaparin treatment the ECG ***should be derived 2 – 4 hours after the last administration of enoxaparin if possible. If deriving an ECG for patients randomised to enoxaparin is not possible during this time frame, an ECG should***

be derived during the day of the venography before the venography will be performed.

Urinalysis will be performed in the morning before ***the*** venography.

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4.6.4 Observations and Measurements

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Methods of Measurements

Laboratory:

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

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

Coagulation parameters: prothrombin time (PT and PT INR), activated partial thrombin time (aPTT), anti-Xa activity.

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

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Electrocardiography

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

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Bilateral Venography[6,7,8]:

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

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

Diagnosis of PE:

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

will be changed to

Laboratory:

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

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

Coagulation parameters: prothrombin time (PT and PT INR), activated partial thrombin time (aPTT), ***Factor*** Xa activity.

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

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

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Electrocardiography

For deriving the ECG the patient should always be in supine position.

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.

In case of any cardiac adverse event an additional ECG should be derived.

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Bilateral Venography[6,7,8]:

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.

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

In case of a suspected symptomatic DVT before day 9 ± 2 a compression ultrasound may be allowed. If the DVT is confirmed by ultrasound, a venography has to be performed. If a DVT is not proven, the study can go on and the planned bilateral venography on day 9 ± 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 Adjudication Committee (AC/VTE) (see appendix). In case the patient died an autopsy should be performed, if possible, and the autopsy report has to be sent to the AC/VTE. Additionally, all available information, e.g. laboratory results, hospital letters have to be collected and sent to the central adjunction committee. Care must be taken that the identity of the patient will be blinded (i.e. just initials, random number, patient number and centre number given).

4.6.5 Drug Concentration Measurements

No drug concentration measurements planned.

Will be changed to

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

10.1 Study Flow Chart and/or Schedule Procedure

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

1: First administration of enoxaparin between 17:00 and 21:00 according to hospital schedule (if randomised to enoxaparin treatment group).

2: Last possible end of wound closure 15:00.

3: Start of BAY 59-7939 6-8 hours after wound closure.

4: Blood samples to be taken and ECG to be performed 2-4 hours after first administration of BAY 59-7939 on day 3. For patients randomised to enoxaparin these tests should be performed on day 3 during the day according to hospital schedule.

5: Blood samples to be taken 2-4 hours after administration of BAY 59-7939. For patients randomised to enoxaparin blood samples can be taken during the day.

6: Blood samples to be taken before administration of study medication.

7: Urinalysis to be performed in the morning before venography.

8: ECG to be derived 2-4 hours after last morning dose of BAY 59-7939 before venography. For patients randomised to enoxaparin the ECG will be derived during the day according to hospital schedule.

9: To be performed post-operatively.

10: Study medication will be stopped before venography.
In case that the hospital stay will be prolonged to day 10 (or 11) for day 9 (and day 10) the schedule of day 8 will be followed.

10.1 Study Flow Chart and/or Schedule Procedure

	DAY OF TREATMENT									Follow up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**39**
Allowed time frame		**Day of THR**							**± 2 days**	**+30 days**
Eligibility	X									
Informed Consent	X									
Demographic Data	X									
Medical History	X									
Physical Examination	X	X	X	X	X	X	X	X	X	X
Randomisation	X									
Start of Enoxaparin	X[1]									
Surgery		X[2]								
Start of BAY 59-7939		X[3]								
Laboratory	X		X[4]		X[5]				X[6]	
Clotting Parameter	X		X[4]		X[5]				X[6]	
Central Laboratory	X		X[4]		X[5]				X[6]	
Laboratory day 2		X[7]								
Urinalysis	X								X[8]	
ECG	X		X[4]						X[9]	
Venography									X	
Vital signs	X	X[10]	X	X	X	X	X	X	X	X
Clinical signs of DVT/PE	X	X[10]	X	X	X	X	X	X	X	X
Clinical Assessment		X[10]	X	X	X	X	X	X	X	
Adverse Events	X	X[10]	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Study Medication	X	X	X	X	X	X	X	X	X[11]	
RDE Entry and Data Transmission	X	X	X	X	X	X	X	X	X	X
In-house	X	X	X	X	X	X	X	X	X	
Out-patient										X

1: **First administration of enoxaparin between 17:00 and 21:00 according to hospital schedule (if randomised to enoxaparin treatment group).**

2: **Last possible end of wound closure 15:00.**

3: **Start of BAY 59-7939 6-8 hours after wound closure.**

4: **Blood samples to be taken and ECG to be performed 2-4 hours after first administration of BAY 59-7939 on day 3. For patients randomised to enoxaparin these tests should be performed on day 3 during the day according to hospital schedule.**

5: **Blood samples to be taken 2-4 hours after administration of BAY 59-7939. For patients randomised to enoxaparin blood samples can be taken during the day.**

6: **Blood samples to be taken before administration of study medication.**

7: ***Blood samples are taken 4-6 hours after wound closure before administration of the study drug.***

8: **Urinalysis to be performed in the morning before venography.**

9: **ECG to be derived 2-4 hours after last dose of BAY 59-7939 *or enoxaparin* before venography.**

10: **To be performed post-operatively.**

11: **Study medication will be stopped *at least 6 hours before the venography.***

In case that the hospital stay will be prolonged to day 10 (or 11) for day 9 (and day 10) the schedule of day 8 will be followed.

10.2 Study Committees

Adjudication Committee/Venography (AC/V):

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

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

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

The assessment of the AC/VTE is the basis for the final VTE based efficacy analysis for the intent-to-treat analysis. The assessment of the AC/VTE will not influence the acute decision taken by the Steering Committee.

Adjudication Committee/Bleeding Event (AC/BE):

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The assessment of the AC/BE is the basis for the final analysis of all bleeding events for the intent to treat analysis.

will be changed to

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. The assessment of the AC/V will not influence the acute decision taken by the Steering Committee.

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

The AC/VTE will adjudicate ***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. The assessment of the AC/VTE will not influence the acute decision taken by the Steering Committee.

Adjudication Committee/Bleeding Event (AC/BE):

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The assessment of the AC/BE is the basis for the final analysis of all bleeding events.

10.4 Assessment of Pulmonary Embolism

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

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

Autopsy report

Pulmonary angiography

Spiral CT

Lung scintigraphy plus X-ray thorax.

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

Images and patient records should be send to:

PPD

Department of Radiology

Östra Hospital

Göteborg University

S-41685 Göteborg

Sweden

will be changed to

10.4 Assessment of the AC/VTE

DVTs during Follow-up

Symptomatic DVTs during follow-up must be verified by either venography or 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 centres will use different methods to verify PE.

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

Autopsy report

Pulmonary angiography

Spiral CT

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

Fibrinolyslab

Östra Hospital, Central Clinic

S-41685 Göteborg

Sweden

10.6 Bleeding Assessment

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clinically overt bleeding leading to transfusion > 2 units blood

will be changed to

clinically overt bleeding leading to transfusion **≥2** units blood

10.7 not available yet

will be changed to

10.7 Blood Sample Summary

Value	Day 1	Day 2	Day 3	Day 5	Day 9 ± 2
Clinical Chemistry					
Sodium	X		X	X	X
Potassium	X		X	X	X
Calcium	X		X	X	X
Creatinine	X	X	X	X	X
Albumin	X	X	X	X	X
Urea	X		X	X	X
Uric Acid	X		X	X	X
SGOT/AST	X		X	X	X
SGPT/ALT	X		X	X	X
Gamma GT	X		X	X	X
LDH	X		X	X	X
Alkaline Phosphatase	X		X	X	X
Blood glucose	X		X	X	X
Haematology					
Haemoglobin	X	X	X	X	X
Haematocrit	X	X	X	X	X
RBC	X	X	X	X	X
WBC	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
Coagulation Parameter (local)					
PT	X		X	X	X
PT INR	X		X	X	X
Coagulation Parameter (Central)					
aPTT	X		X	X	X
Factor Xa	X		X	X	X