Bayer

CLINICAL STUDY PROTOCOL AMENDMENT

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-ODIXa-OD.HIP 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
Previous Amendments /Version/Date:	Amendment 01, version 1.1, 29-Nov-2004
Development Phase:	**Phase II**
Amendment /Version/Date:	Amendment 02, version 1.3, 21-Jan-2005
Applicable to:	All countries

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

PPD

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Date

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Confidentiality statement:

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Additional Signatures

Name: PPD

Function: PPD

Address: PPD

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1. Description of the Amendment

Following the strong recommendation of the Steering Committee and after reviewing the recent data of the ODIXa-HIP IIb trial (10944) and the ODIXa-KNEE trial (10945), it became obvious that the lower dose of 5 mg/d was more effective than anticipated, and in line with the standard of care, enoxaparin. Furthermore, Regulatory Authorities asked to determine the lowest effective dose. Only 2.5 mg bid provided the same level of bleeding events as enoxaparin. In addition the 2.5 mg bid dose (5mg /d) provided a favourable safety profile with regard to major and non-major clinical relevant bleeding events and therefore it is recommendable to assess a lower dose. Thus it makes perfect sense to assess whether a lower dose would be safer without compromising on efficacy.

Change to section 1. Introduction

Original Text

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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.

Will be added

New Text

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In the phase IIb study ODIXa-HIP2 dose –ranging study (Impact 10944) 722 patients undergoing elective hip replacement surgery were randomized. 706 patients were treated with study medication (133 patients in the enoxaparin group and 573 patients in the BAY 59-7939 treatment groups). This study supports evidence for efficacy of BAY 59-7939 in preventing DVT, PE and death (primary composite endpoint) in subjects undergoing elective hip replacement. The net clinical benefit (major bleeding events plus major VTE) of doses ranging from 2.5 to 10 mg bid was comparable to enoxaparin. If also clinically relevant bleeding events are taking into consideration, the BAY 59-7939 dose of 2.5 mg bid seems to be the recommendable dose.

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 adverse events.

Incidence rates of efficacy endpoints (PP population)- 10944

Endpoint	BAY 59-7939 2.5 mg bid (N=104) n (%)	BAY 59-7939 5 mg bid (N=109) n (%)	BAY 59-7939 10 mg bid (N=101) n (%)
Primary efficacy endpoint	16 (15.4%)	15 (13.8%)	12 (11.9%)
Deep vein thrombosis	16 (15.4%)	15 (13.8%)	12 (11.9%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Endpoint	BAY 59-7939 20 mg bid (N=99)	BAY 59-7939 30 mg bid (N=29)	Enoxaparin 40 mg od (N=106)
Primary efficacy endpoint	18 (18.2%)	2 (6.9%)	18 (17.0%)
Deep vein thrombosis	18 (18.2%)	2 (6.9%)	18 (17.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Incidence rates of post-operative major bleeding events (safety population)- 10944

Bleeding Event	BAY 59-7939 2.5 mg bid (N=132) n (%)	BAY 59-7939 5 mg bid (N=136) n (%)	BAY 59-7939 10 mg bid (N=133) n (%)
Any major bleeding	1 (0.8%)	3 (2.2%)	3 (2.3%)
Clin. overt bleeding associated with fall in Hb +	0 (0.0%)	1 (0.7%)	1 (0.8%)
Clin. overt bleeding leading to blood transfusion ++	1 (0.8%)	1 (0.7%)	1 (0.8%)
Bleeding leading to re-operation	0 (0.0%)	2 (1.5%)	2 (1.5%)
Clin. overt bleeding warranting treatment cessation	0 (0.0%)	0 (0.0%)	0 (0.0%)

Bleeding Event	BAY 59-7939 20 mg bid (N=134) n (%)	BAY 59-7939 30 mg bid (N=37) n (%)	Enoxaparin 40 mg od (N=132) n (%)
Any major bleeding	6 (4.5%)	2 (5.4%)	2 (1.5%)
Clin. overt bleeding associated with fall in Hb +	3 (2.2%)	1 (2.7%)	2 (1.5%)
Clin. overt bleeding leading to blood transfusion ++	4 (3.0%)	2 (5.4%)	2 (1.5%)
Bleeding leading to re-operation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clin. overt bleeding warranting treatment cessation	1 (0.7%)	1 (2.7%)	1 (0.8%)

Note: + Associated with a fall in Hb of 2g/dl or more within 24 hours from first post-operative day.
Note: ++ Leading to transfusion of 2 or more units blood.
Note: Bleeding events that had occurred more than two days after last intake of study drug are not considered here.

Summary of adverse events (safety population)-10944

Adverse event type	BAY 59-7939 2.5 mg bid (N = 132) n (%)	BAY 59-7939 5 mg bid (N = 136) n (%)	BAY 59-7939 10 mg bid (N = 133) n (%)
Treatment-emergent AEs	98 (74.2%)	99 (72.8%)	98 (73.7%)
Drug-related treatment-emergent AEs	30 (22.7%)	36 (26.5%)	36 (27.1%)
Treatment-emergent SAEs	10 (7.6%)	12 (8.8%)	14 (10.5%)
Drug-related treatment-emergent SAEs	5 (3.8%)	7 (5.1%)	4 (3.0%)

Adverse event type	BAY 59-7939 20 mg bid (N = 134) n (%)	BAY 59-7939 30 mg bid (N = 37) n (%)	Enoxaparin 40 mg od (N = 132) n (%)
Treatment-emergent AEs	110 (82.1%)	29 (78.4%)	95 (72.0%)
Drug-related treatment-emergent AEs	36 (26.9%)	10 (27.0%)	31 (23.5%)
Treatment-emergent SAEs	20 (14.9%)	6 (16.2%)	15 (11.4%)
Drug-related treatment-emergent SAEs	8 (6.0%)	2 (5.4%)	3 (2.3%)

Change to section 2 Study Objectives

Original Text

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.

Change to

New Text

The objective of this dose-ranging trial is to assess the efficacy and safety of BAY 59-7939 **5** 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.

Change to section 4.1 Study Design and Plan

Original Text

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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)

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

Change to

New Text

The patients will be randomized to one of the following 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)

VI: 5 mg od of Bay 59-7939 tablets active substance (5 mg and 1 placebo tablet) plus a placebo syringe of enoxaparin.

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

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In total **810** patients are planned to be enrolled in study, **135** patients per treatment arm.

Change to section 4.5.1 Treatments to be Administered

Original Text

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)

Change to

New Text

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 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)

VI: 5 mg od of Bay 59-7939 tablets active substance (5 mg and 1 placebo tablet) plus a placebo syringe of enoxaparin.

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

Change to section 4.5.2 Identity of Investigational Product(s)

Original Text

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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.

Change to

New Text

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BAY 59-7939

BAY 59-7939 will be provided by BAYER Clinical Drug Supplies as tablets at a dose of **5 mg,** 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.

Change to section 5.4.5 Selection of Doses in the Study

Original text

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.

Change to

New Text

This phase IIb study is a dose ranging study assessing different doses of once daily BAY 59-7939. **5** 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. **Despite this evidence in healthy subjects the recently completed 10944 study revealed that a total daily dose of 5 mg (2.5 mg bid) was effective and safe in preventing VTE after total hip replacement surgery. With total DVT incidence in the range of enoxaparin and an even lower incidence of proximal deep vein thrombosis of 2.9% compared to 4.7% with enoxaparin there is a good justification for this dose. Even if one assumes that the efficacy of 5 mg od might be worse compared to 2.5 mg bid, it seems to be unlikely that the efficacy drops below the incidence rates assumed sample size calculation.**

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.

Change to section 4.5.5 Selection and timing of Dose for Each Subject

Original Text

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.

Change to

New Text

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. **5 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.

Change to section 4.5.6 Blinding

Original Text

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.

Change to

New Text

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. **The BAY 59-7939 5 mg dose will be packed separately but for blinding purposes all doses will be labeled on the BAY 59-7939 5 mg od study medication packs. The BAY 59-7939 5 mg od dose will be allocated in a blinded manner.** 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.

Change to section 6.2 Determination of Sample Size

Original Text

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.

Change to

New Text

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	5 mg od	10 mg od	20 mg od	30 mg od	40 mg od	Sample Size per Group
	25.0%	**21.0%**	**17.0%**	**13.0%**	**10.0%**	**104**

Assuming the event rates given in Table 6.2/1, a sample size of **104** 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 $\beta = \mathbf{0.1}$ (ie. a power of **90%**). 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 **135** patients is required for each of the individual 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 **810** patients have to be randomized.

As the BAY 59-7939 5 mg od group can only be initiated after implementation of this amendment, a randomization ratio of 2:1:1:1:1 will be applied in order to ensure that a sufficient number of patients will be randomized to the 5 mg od group. Furthermore, depending on the actual time of implementation, the overall sample size might be slightly increased so that the expected numbers of patients for each group are not below the planned number.