Bayer

CLINICAL STUDY PROTOCOL AMENDMENT

Title	**O**ral **Di**rect Factor **Xa** Inhibitor BAY 59-7939 in the Prevention of VTE in Patients Undergoing total **Hip** Replacement. **OdiXahip** – a Phase IIa Dose Escalating Proof of Principle Trial
Test Drug:	BAY 59-7939
Sponsor's Name and Address:	BAYER Vital GmbH D - 51368 Leverkusen
Sponsor's Telephone Number:	PPD
Study Number/Version/Date:	10942/ Version 1.10/ 2002/Oct/09
Previous Amendments (Numbers/Version/Date):	Amendment 1 / Version 1.2/ 2003/Feb/06
Development Phase:	**Phase IIa**
Amendment Number/Version/Date:	Amendment 2 / Version 1.3/ 2003/Mar/17
Applicable to:	Selected centres

Study Manager

Name: PPD PPD Signature: _____

Date:

Statistician

Name: PPD PPD Signature: _____

Date:

Medical Expert

Name: PPD PPD Signature: _____

Date:

CONFIDENTIAL

Additional Signatures

Name: Signature: _____

Function: Date:

Address:

Name: Signature: _____

Function: Date:

Address:

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

Name: PPD PPD Signature: _____

Function: **Principal Investigator** Date: _____

Address: PPD
Sweden

Telephone: PPD

Name: Signature: _____

Function: Principal Investigator of the country Date: _____

Address:

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Description of the Amendment

Pharmacokinetic evaluation will be performed in selected centres.

Glossary

These abbreviations will be added

Ae_{ur},	amount of drug excreted via urine
AUC	(1) area under the curve (2) area under the [concentration*time] curve (3) area under the plasma concentration vs. time curve from zero to infinity after single (first) dose
$AUC(0\text{-}t_n)$	AUC from time 0 to the last data point
$AUC(t_n\text{-}\infty)$	AUC from the last data point to infinity
$AUC_{0\text{-}12}$	area under concentration versus time the curve from time 0 to 12 hours
$AUC_{0\text{-}12(norm)}$	area under concentration versus time curve from time 0 to 12 hours, divided by dose per kg body weight
$AUC(0\text{-}t_n)_{norm,}$	AUC from time 0 to the last data point, divided by dose per kg body weight
$C_{max(norm)}$	(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
CL/f	total body clearance of drug from plasma calculated after oral administration (apparent oral clearance)
CL_R	renal clearance
CV	coefficient of variation
HPLC	high pressure liquid chromatography
LOQ	limit of quantification
QC	quality control
$t_{½}$	(1) time of half-life (2) half-life
t_{max}	time to reach maximum drug concentration in plasma after single (first) dose
V_z/f	Apparent volume of distribution during terminal phase after oral administration

4.1 Study design and plan

The following section will be added

In selected centres additional blood samples and urine samples will be taken from patients willing to participate in the pharmacokinetic and pharmacodynamic part of the study and randomised to treatment with BAY 59-7939.

For further details please refer to section 10.8.

4.6.5 Drug Concentration Measurements

No drug concentration measurements planned

Will be changed to

Selected centres will take additional blood samples and urine samples for pharmacokinetic and pharmacodynamic measurements from patients randomised to BAY 59-7939 treatment.

For the investigation of pharmacokinetics the concentrations of BAY 59-7939 in plasma and urine will be determined and calculated. For the investigation of pharmacodynamics the Factor Xa activity will be determined and calculated (see section 6.1.6 and 10.8).

The time points of sampling are outlined in section 10.8.

The following section will be added

6.1.6 Pharmacokinetic Data

For investigation of pharmacokinetics, the plasma and urine concentrations of BAY 59-7939 will be determined at the times given in Section 10.8.

Pharmacokinetic parameters will be calculated according to BAYER Guidelines [11]. Based on the plasma and urine concentration time data the following pharmacokinetic parameters are to be calculated for both profile days:

AUC(0-12h), $AUC(0\text{-}12h)_{norm}$, $AUC(t_n\text{-}\infty)$, C_{max}, $C_{max,norm}$, t_{max}, CL/f, V_z/f, Ae_{ur}, CLR(0-12h), points terminal and, if applicable, $t_{1/2}$, $AUC(0\text{-}t_n)$, $AUC(0\text{-}t_n)_{norm}$.

The data processing and statistical analysis will be performed in accordance with BAYER Guidelines [11].

The following statistics will be calculated for each of the sampling points for both pharmacokinetics and pharmacodynamics:

arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and CV, minimum, median, maximum value and the number of measurements.

Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the limit of quantification (LOQ). For the calculation of

the mean value a data point below LOQ will be substituted by one half of this limit. In tables showing mean values, where values below LOQ are included in the calculation of mean values, these means will be marked. Individual and mean concentration versus time profiles will be plotted by dose using both linear and semilogarithmic scale.

Pharmacokinetic characteristics (t_{max} excluded) will be summarised by the statistics mentioned above. t_{max} will be described utilising minimum, maximum as well as frequency counts.

The pharmacokinetic characteristics $AUC(0\text{-}12h)_{norm}$ and $C_{max,norm}$ will be analyzed assuming log-normally distributed data. To compare pharmacokinetics between both profile days, the logarithms of these pharmacokinetic characteristics will be analyzed using paired t-tests. Based on these analyses, point estimates and exploratory 90% confidence intervals for the ratios will be calculated by re-transformation of the logarithmic results given by the t-tests.

Further data-driven statistical analyses may be performed in a descriptive and hypothesis generating manner. The applied statistical analyses and results will be described in detail in the final report.

In addition, PK/PD modelling using population approaches (e.g. NONMEM [12]) to describe BAY 59-7939 pharmacokinetics including potential influence of relevant patient co-variables (eg. age, gender, etc.) and to relate pharmacodynamic parameters with BAY 59-7939 plasma concentrations will be investigated under a separate detailed PK/PD analysis plan.

9. References

The following will be added

11, BAYER Guideline 'Harmonisation of Data Evaluation in Pharmacokinetics – A Task Force Report-' (1992 Report No. R 5747 (P) 1992 & 5747A (P) 2000)

12, Beal, S.L. and Sheiner L.B. NONMEM User Guides, NONMEM Project Group, UCSF, San Francisco, CA

Following section will be added as appendix 10.8

10.8 PK/PD Part of the study

In order to describe the pharmacokinetic and pharmacodynamic profile of BAY 59-7939 on the first post-operative day (day 3) and on day 6 or 7 during steady state condition a day profile consisting of eight plasma samples with separate tubes for PK and PD analysis and four urine samples will be taken.

In addition on two days between the profile days one plasma sample should be taken at trough prior (up to 1 hour) to the next intake of BAY 59-7939.

The number of samples taken for the assessment of pharmacokinetics and pharmacodynamics parameters have been optimised to take the minimum amount of blood (in total 120.6 ml, or up to 156.6 ml if an indwelling catheter is used during the days of assessment) needed for adequate analysis.

PK/PD samples will be analysed at BAYER AG, Institute of Clinical Pharmacology, Wuppertal, Germany.

Sampling Times

Plasma samples for PK and PD

On day 3:

Pre-dose (up to 1 hour before first administration of BAY 59-7939 on profile day)

1 h, 2 h, 3 h, 4 h, 6 h, 9h and 12 h after first administration of BAY 59-7939

In between the profile days

On two days in between the profile days one blood sample should be taken at trough prior to the intake of BAY 59-7939. The time window is up to one hour before administration of BAY 59-7939.

On day 6 or 7:

Pre-dose (up to 1 hour before first administration of BAY 59-7939 on profile day)

1 h, 2 h, 3 h, 4 h, 6 h, 9 h and 12 h after first administration of BAY 59-7939

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

Urine samples for PK

Urine samples will be taken on the day when the day profile will be taken.

Please see below the time points of urine sampling:

- Pre-dose (up to 1 hour before first administration of BAY 59-7939 on the profile day)
- 0 - 4 h, 4 - 9 h, 9 - 12 h after first administration of BAY 59-7939 on the profile day

Sample handling instructions for plasma and urine samples

Plasma sampling

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

Plasma samples for PK

4 ml blood are to be taken in NH_4 heparine tubes (alternatively Li-heparinate may be used). The blood has to be centrifuged within 2 hours (centrifugation at room temperature for10 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 PD

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 labelled 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 laboratory in Wuppertal.

Urine samples

After each collection period, the total volume of urine has to be determined and noted in the CRF. After thorough mixing of the urine an aliquot of ~ 10 ml has to be transferred into labeled polypropylene tubes and kept frozen at –20 °C until shipment to the laboratory in Wuppertal.

It is essential that the dates and exact time points of sampling are recorded in the provided paper Case Report Form. Furthermore, the timing of meals and the type of meal (Breakfast, lunch, dinner, snack) should be tracked.

General Instructions

Labelling of the samples

The labelling of the samples will be as follows:

Substance No/Study No:	BAY 59-7939/10942
Subject No	Sitebase No
Dose Stage	e.g. I, II, ...
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:

Please inform the laboratory of PPD PPD BAYER AG in due time on sample shipment (delivery on Tuesday to Thursday) by fax or phone.

Please contact the courier immediately after the second day profile and request the collection of samples and the delivery of the samples to the laboratory in Leverkusen. Always the whole batch of samples of one patient should be collected.

The samples should be shipped frozen covered with dry ice (sufficient for 2 days transport) and well protected using appropriate containers.

Shipment address:

PPD PPD
BAYER AG
Pharma Research Center
Institute of Clinical Pharmacology
Clinical Pharmacokinetics, 405V
42096 Wuppertal
Germany
Tel: PPD
Fax: PPD

Methods and Measurements

Bioanalytics and Pharmacokinetics

BAY 59-7939 concentrations in plasma will be measured by a validated HPLC method. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of QC samples will be reported together with concentrations in unknown samples in the Medical Research Report of this study. Concentrations are calculated from the chromatographic raw data in accordance with the guidelines given in report No. PH-30516 on the harmonization of analytical methods in pharmacokinetic investigations. The data are evaluated using CCW software in its most recently released version.
Only values above the limit of quantification are used to determine pharmacokinetic parameters. Non-compartmental evaluation of pharmacokinetic parameters will be conducted using KINCALC software in its most recently released version.

Biochemical Analysis

Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of QC samples will be reported together with analyte concentrations in the Medical Research Report of this study.
Concentrations of the analyte are calculated according the method description.