INVESTIGATOR'S BROCHURE

Title Page

Sponsor's Name:	Bayer Pharma
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Summary of Changes to Investigator Brochure

The following sections have been changed in this version of the Investigator's Brochure.

Section	Summary of Change
3.2 Relevant physical, chemical and pharmaceutical properties	Numbers and statements have been changed
4.1.9 Effects on hERG mediated potassium channel (in-vitro)	Information added
4.2.5.1 Metabolism In Vitro	Additional in vitro results for CYP interaction included
5.3 Clinical Pharmacology	Additional information included on: Single dose application Multiple dose application Interaction with Enoxaparin
5.4 Efficacy and Safety	Adverse event listings are completed based on additional phase I studies
6. Summary of Data and Guidance for the Investigator	Further information added reflecting the new data from phase I and preclinical in vitro studies
All section	Formatting changes were made where appropriate

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Glossary of Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
ALAT/SGPT	Alanine Transaminase/Serum glutamate pyruvate transaminase
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APC	Activated protein C
APTT	activated Partial Thromboplastin Time
ASAT/SGOT	Aspartate Transaminase/Serum glutamic-oxaloacetic transaminase
ATIII	Antithrombin III
BP	Blood pressure
BL	Baseline
CI	Confidence Interval
CMC	Chemistry, Manufacturing and Controlling
d-b	Double-blind
DVT	Deep Venous Thrombosis
EACA	Epsilon-aminocaproic acid
ECG	Electrocardiogram
EEG	Electroencephalogram
e.g.	exempli gratia
EPI	Extrinsic pathway inhibitor
i.e.	id est
FBC	Full Blood Count
FDA	Food and Drug Administration
GGT	Gamma-glutamyltransferase
Hb	Hemoglobin
IA	Interim analysis
Iv	Intravenous
HIT	Heparin-induced thrombocytopenia
HMWK	High molecular weight kininogen
INR	International Normalized Ratio (=PT patient/PT normal)
IP	Intraperitoneal
LMWH	Low-molecular-weight heparin
LOQ	Limit of Quantification
Multi	Multicenter
NA	Not Applicable
NOEL	No Observed Effect Level
NS	difference not statistically significant ($p > 0.05$)
o.d.	omni die (once daily)
ULN	Upper Limit of Normal
P	Page

pl-c	Placebo-controlled
PAI-I	Plasminogen activator inhibitor
PD	Pharmacodynamic
PE	Pulmonary Embolism
PK	Pharmacokinetics
PMH	Past Medical History
PT	Doubling concentration of prothrombin time
PT_2	Percutaneous transluminal angioplasty
PTA	Percutaneous transluminal angioplasty
R	Randomized
RBC	Red Blood Cell
SAE	Serious Adverse Event
Sig	Difference statistically significant (p # 0.05)
sc	Subcutaneous
SD	Standard Deviation
SK	Streptokinase
susp.	Suspension
TAT	AntithrombinIII/thrombin-complex
THR	Total Hip Replacement
TK	Toxicokinetics
TKR	Total Knee Replacement
Tab	Tablet
Tox	Toxicology
TFPI	Tissue factor pathway inhibitor
t-PA	Tissue plasminogen activator
UK	Urokinase
UH	Unfractionated heparin
uPA	Urinary plasminogen activator
US	Ultrasonography
VTE	Venous Thromboembolism
WBC	White Blood Cell

1. Summary

Key Points:

- BAY 59-7939 is a potent and selective orally available Factor Xa inhibitor Antithrombotic effects have consistently been demonstrated in different thrombosis models over several species at doses of 0.6-10 mg/kg
- Safety pharmacology showed only a mechanistically driven inhibition of blood coagulation
- Antithrombotic effect of Enoxaparin and Heparin is not diminished by concomitant application of BAY 59-7939
- Acute toxicity was low and under subacute conditions (4 weeks) the compound was well tolerated
- Linear pharmacokinetics in rats and dogs, bioavailability of 60 % in rats and 60-86% in dogs
- Excretion in rats is predominantly through the biliary/fecal route, in dogs renal excretion contributed considerably
- No induction or inhibition of cytochrome P450 isoforms was found
- BAY 59-7939 was well-tolerated up to 80 mg after single dose application in healthy volunteers
- Multiple dosing with up to 30 mg BID (total daily dose 60 mg) for 5 days was well tolerated in healthy subjects
- No drug related serious adverse events were reported in phase I
- BAY 59-7939 is rapidly absorbed after oral treatment as solution (C_{max} after approx. 30 min) as well as tablet (C_{max} after 2-4 hours)
- Elimination of BAY 59-7939 from plasma occurred with terminal half-lives of 4.77 to 5.88 hrs (day 1) and 5.75 to 8.94 hrs (day 8) with no relevant accumulation
- Steady state after multiple dose application of 30 mg BID was reached approx. after the 2-3 days
- Administration of BAY 59-7939 with food (high calorie/high fat meal) resulted in an increase of AUC by 25 %, a delayed absorption by about 1.5

hours and a 40% increase in C_{max}

- Elderly subjects exhibited higher plasma concentrations than young subjects, with mean AUC values being approximately 52 % greater in elderly males, and 39 % higher in elderly females, compared to the young subjects of the same gender.
- Clotting parameters (PT, PTT, Heptest) were effected in a dose dependent way
- No influence on bleeding time was observed neither after single dose nor multiple dose application
- Co-medication of Enoxaparin showed an additive effect on pharmaco-dynamic parameters. Bleeding time was not affected to a clinically relevant degree
- Factor Xa was inhibited in a dose dependent way

Arterial and venous thromboembolism represent one of the most relevant health problems associated with a high rate of morbidity and mortality. Standards of care – anticoagulants and antiplatelets – are available in these indications. However, treatment and prevention in these conditions still exhibit substantial failure rates. Improvement of therapy, in particular by oral treatments alternatives, is highly desirable.

BAY 59-7939 is a highly selective Factor Xa inhibitor with oral availability. Activation of factor Xa plays a central role in the cascade of blood coagulation. Therefore, its selective inhibition by BAY 59-7939 should terminate the amplified burst of thrombin generation and should result in a better efficacy/ safety profile than available anticoagulants.

In preclinical studies BAY 59-7939 showed a consistent and potent anticoagulation and antithrombotic effect. The endogenously generated FXa in human plasma was inhibited with an IC_{50} of 21+/- 1 nM. PT and aPTT was increased about two fold at concentrations in the sub- µM-range. The

antithrombotic effect was demonstrated in different thrombosis models at 0.6-10 mg/kg depending on model and species.

The risk for bleeding was investigated in rats and rabbits. BAY 59-7939 increased bleeding time dose dependently, but these doses were beyond the antithrombotic dose. In comparison with enoxaparin, a standard LMWH, Bay 59-7939 showed a comparable antithrombotic/bleeding risk ratio.

The concomitant use of BAY 59-7939 with enoxaparin or heparin did not diminish their antithrombotic effect in the arterio-venous shunt model in rats.

In safety pharmacology studies only a dose dependent inhibition of blood coagulation was observed.

The pharmacokinetics in rats and dogs was linear after oral and i.v. administration, with a bioavailability of 60% in rats and 60-86% in dogs. Elimination from plasma was rapid and excretion is predominantly via biliary/fecal route in rats; renal rout of excretion contributed considerably in dogs. The inhibitory potency of BAY 59-7939 on cytochrome P450 isoforms was investigated with recombinant CYPs and no relevant effects were seen. Likewise no induction potential, investigated in cultured human hepatocytes, was observed.

Bay 59-7939 has a low acute toxicity in rats and mice. After subacute administration (4-weeks) in dogs and rats BAY 59-7939 was well tolerated. The changes seen in Quick values, as well as the increases in PT an aPPT are related to the underlying pharmacological principle. There was no evidence for a genotoxic potential based on two in vitro and one in vivo test.

BAY 59-7939 was well tolerated up to 80 mg after single dose in healthy volunteers. Multiple dosing with 30mg BID for 5 days was well-tolerated and the pharmacokinetics after multiple dosing were as expected from single dose application. Steady state was reached after 2-3 days. Clotting parameters (PT,

PTT, Heptest) and Factor Xa activity were affected in a dose dependent way. No influence on bleeding time was observed with any dose or dosing regimen tested.

2. Introduction

Key Points:

- Thromboembolic disorders are the single largest cause of disease and death in the Western world
- Standard treatment for thrombotic events are antiplatelets and anticoagulants
- High medical need for oral antithrombotic drugs with an improved risk/benefit ratio

2.1 Medical Need

Thrombosis is a pathological process in which both a platelet aggregate and fibrin clot occludes a blood vessel. Arterial flow conditions produce platelet- rich ("white") thrombi. Static venous flow yields fibrin and red cell-rich ("red") thrombi with a variable platelet and leukocyte component. Arterial thrombosis may result in ischemic necrosis of the tissue supplied by the artery e.g., myocardial infarction (MI) due to thrombosis of a coronary artery. Venous thrombosis may cause tissues drained by the vein to become edematous and inflamed. Thrombosis of a deep vein may be complicated by pulmonary embolism.

Thromboembolic disorders are the single largest cause of disease and death in the Western world, causing or contributing to acute coronary syndromes (unstable angina, non-Q wave myocardial infarction, acute myocardial infarction), embolic and thrombotic stroke and peripheral arterial occlusion.

The clinical manifestation of venous thromboembolism is deep vein thrombosis (DVT) and its most important complication, pulmonary embolism (PE). It is the most common cause of preventable death among hospitalized patients.

2.2 Therapeutic Standard

At present standard therapy for treatment and prevention of thrombotic events are antiplatelet drugs (Aspirin, the thienopyridine derivatives Ticlopidin and Clopidogrel, the GPIIb/IIIa-receptor antagonists Abciximab, Tirofiban and Integrelin) and anticoagulants (anti-thrombins, Unfractionated Heparin, Low Molecular Weight Heparin and Hirudin and the non-specific coumarin-type anticoagulant Warfarin). Nonetheless, while their use has been associated with improved clinical outcomes in patients with thrombosis-related disorders, problems still remain. The orally active Warfarin needs close monitoring to reduce bleeding complications. The heparins and the GPIIb/IIIa- receptor antagonists can only be administered parenterally and used for short term treatment only. Antiplatelet drugs such as Aspirin are effective in secondary prevention of arterial thromboembolism, clearly reducing the vascular mortality.

Consequently, there is a high medical need for improved orally available antithrombotic drugs, especially for anticoagulants with a better risk/benefit ratio than the currently used drugs. BAY 59-7939 offers a new opportunity for oral treatment without need for body weight adjustment and monitoring.

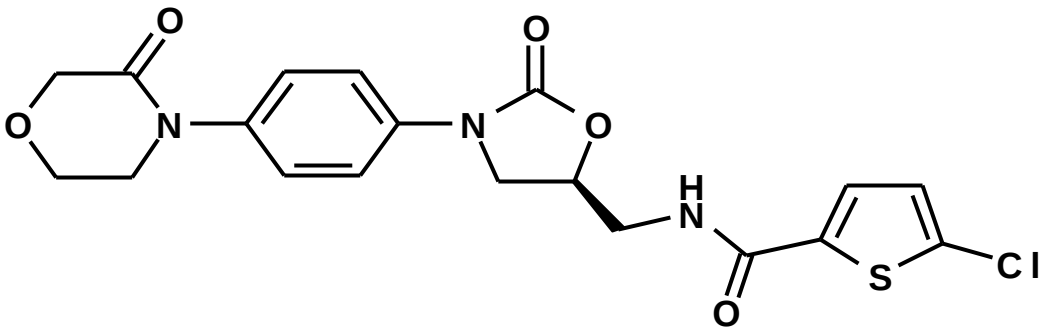
3. Physical, Chemical and Pharmaceutical Properties and Formulation

Key Points:

- An oral solution (0.1 %) and immediate release tablets (1.25, 5 + 20mg) have been developed.
- Storage temperature should not exceed 25 °C.

3.1 Investigational product's substance(s) including the chemical and structural formula

Structural Formula



Chemical name	:	5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide
BAY-No.	:	BAY 59-7939
Empirical Formula	:	$C_{19}H_{18}ClN_3O_5S$

3.2 Relevant physical, chemical and pharmaceutical properties

Molecular Weight	:	435.89
Structure	:	CCI [redacted] verified by x-ray
Appearance	:	CCI [redacted]
Odor	:	CCI [redacted]
^{1}H NMR	:	NMR data support the BAY 59-7939 structure
pK-Value(s)	:	CCI [redacted]
		CCI [redacted]
UV/VIS Spectrum	:	CCI [redacted]
Specific Rotation	:	CCI [redacted]
Hygroscopy	:	CCI [redacted]
Solubilities		
Water	:	CCI [redacted]

0.1 N HCl	:	CCI
Ethanol	:	CCI
PEG 400	:	CCI
Membrane affinity	:	CCI
HSA-binding	:	CCI

3.3 Description of the formulations to be used

Oral Solution 0.1 %

A BAY 59-7939 oral solution with 1 mg drug per g solution has been developed. The solution is filled in brown glass bottles; each bottle contains 10 g solution.

The solution is composed of macrogol, polysorbate and peppermint oil.

A corresponding placebo formulation containing the same excipients is available.

Composition:

BAY 59-7939 micronized	CCI
Macrogol 400 (PEG 400)	CCI
Polysorbate 20 (Tween 20)	CCI
Peppermint oil	CCI

Tablets 1.25, 5, 20 mg

BAY 59-7939 tablets are available in dose strengths 5 and 20 mg. They are round white tablets and 6 mm in diameter. The tablets are immediate release dosage forms with rapid dissolution characteristics under in-vitro test conditions.

Each tablet contains the active ingredient BAY 59-7939 and the excipients croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, hypromellose and sodium lauryl sulfate.

The tablets are film-coated with hypromellose, macrogol and titanium dioxide.

A corresponding placebo formulation is available. The placebo tablets contain lactose, microcrystalline cellulose, magnesium stearate and a film-coat of hypromellose, macrogol and titanium dioxide.

3.4 Instructions for storage and handling

Oral Solution

The storage temperature for BAY 59-7939 solution should not exceed 25 °C and the solution should be protected from light.

Doses up to 10 mg, according to 10 g solution (equivalent to 8.9 ml) can be dispensed in total. Before administration, the solution has to be diluted with about 100 ml water and has to be taken directly after dilution. The dispensed amount of solution should be checkweighed (density of solution: CCI .

Tablets 1.25 /5 / 20 mg

BAY 59-7939 tablets are packaged in glass-bottles, HDPE-bottles or PP-blister. They should only be stored in the pack provided and should be swallowed immediately after they have been taken out of the packaging.

The storage temperature should not exceed 25 °C.

3.5 Known similar compounds

No similar compounds known.

4. Nonclinical Studies

Key Points:

Primary Pharmacology

- Selective, potent and competitive inhibition of human Factor Xa
- Anticoagulant activity in vitro without impairment of platelet function
- Oral antithrombotic activity in vivo in different thrombosis models in rats

and rabbits

- Antithrombotic activity without prolongation of bleeding time in rats and rabbits

- No influence on the antithrombotic effect of Enoxaparin or Heparin after concomitant application

Safety Pharmacology

- Dose dependent inhibition of blood coagulation was observed, as expected by the underlying pharmacological mechanism
- Other Safety Pharmacology produced no clinically relevant effects
- No objections to initiate clinical studies

Pharmacokinetics and Drug Metabolism in Animals

- In rats limited absorption of radioactivity from the gastrointestinal tract (66.8 %); bioavailability of 60 % (in rats and dogs)
- Linear pharmacokinetics in rats and dogs after intravenous and oral administration
- No major metabolites in rat plasma
- Rapid elimination from plasma in rats and dogs
- High and species-dependent protein binding
- Morpholino moiety as main target of metabolic degradation
- No drug-drug interaction potential due to neither inhibition nor induction of major CYP isoforms
- 80 % of the dose in the excreta attributed to known structures
- Excretion of radioactivity in rats predominantly via biliary/fecal route
- Low radioactive residues, no evidence of irreversible binding or retention of radioactivity in organs and tissues of rats

Toxicology:

- Low acute toxicity in rats and mice

- Well tolerated in rats and dogs after subacute administration
- Findings in the subacute studies in rats and dogs can be explained by the pharmacological activity of the drug candidate
- No evidence for genotoxicity

4.1 Nonclinical Pharmacology

Key Points:

- Selective, potent and competitive inhibition of human Factor Xa
- Anticoagulant activity in vitro without impairment of platelet function
- Oral antithrombotic activity in vivo in different thrombosis models in rats and rabbits
- Antithrombotic activity without prolongation of bleeding time in rats and rabbits
- No influence on the antithrombotic effect of Enoxaparin or Heparin after concomitant application
- Safety Pharmacology: no prohibitive findings

4.1.1 Summary

Activation of factor Xa (FXa) plays a central role in the cascade of blood coagulation. Its selective inhibition by BAY 59-7939 should terminate the amplified burst of thrombin generation and should result in a potent antithrombotic activity. It is well accepted that the inhibition of FXa represents an attractive approach for intervention in various thrombotic disorders. BAY 59-7939 could become an orally available alternative to the “gold-standard” enoxaparin, a low molecular weight heparin.

BAY 59-7939 is a selective, highly potent, and competitive FXa-inhibitor (Ki = 0.4 $\pm$ 0.02 nM). It does not affect other trypsin-like serine proteases (selectivity > 10,000). It can block thrombin generation by inhibiting the prothrombinase-bound FXa (IC_{50} = 2.1 $\pm$ 0.4 nM). In human plasma BAY 59-7939 inhibited the endogenously generated FXa with an IC_{50} value of 21 $\pm$ 1 nM. BAY 59-7939

prolonged prothrombin time (PT: 2 fold increase at 0.23 ± 0.02 µM) and activated partial thromboplastin time (aPTT: 2 fold increase at 0.69 ± 0.09 µM) concentration-dependently, the effect on PT being more pronounced than on aPTT.

BAY 59-7939 does not impair platelet function. Only thrombin mediated platelet aggregation was slightly inhibited at high concentrations (IC_{50} = 81 µM). Similarly thrombin time (TT) was prolonged at high concentrations (2 fold increase at 26 ± 1µM) indicating a high specificity against thrombin.

The antithrombotic effect of BAY 59-7939 could be demonstrated in different thrombosis models in rats and rabbits. After oral administration to rats ED_{50} values of 5.0 mg/kg (arteriovenous shunt), 2.0 mg/kg (mechanical damage of the V.jugularis), 10 mg/kg (mechanical damage of the A.carotis) were obtained. In rabbits (arteriovenous shunt) intravenous injection of BAY 59-7939 resulted in an ED_{50} value of 0.6 mg/kg. Enoxaparin, which we used as reference compound, reduced thrombus weight in these models after intravenous injection between 1.0-3.0 mg/kg.

In the arteriovenous shunt models clotting times increased dose dependently. In the rat PT values were prolonged 2.4 – 3.7 fold and APTT 1.4 fold at doses close to the ED_{50}. The clotting times correlated well with the measured plasma concentrations. A comparable effect on clotting times was observed in the rabbit model. PT values were prolonged 2.2 – 3.5 fold and APTT 1.3 –2.3 fold at doses close to the ED_{50} value. In the rat the endogenous FXa activity and the thrombin/ antithrombin concentration were dose-dependently reduced. At doses (3.0 and 6.0 mg/kg) near the ED_{50} value (5.0 mg/kg) FXa activity was reduced by 61-78% and thrombin/antithrombin concentration by 75-78%. These data suggest, that an antithrombotic effect may be observed at doses leading to an anti-FXa inhibition of about 70% in humans.

In in-vitro experiments with rat plasma 10 fold higher concentrations were needed to inhibit FXa (IC_{50}= 21 nM in human vs. 290 nM in rat plasma). Similarly, higher concentrations were needed to increase clotting times in rat plasma (2XPT = 0.2 µM vs. 0.3 µM; 2XAPTT = 0.7 µM vs. 2.1 µM) suggesting

that in humans the expected effective plasma concentration could be 10 times lower than in rats.

In the arteriovenous shunt model in rats subcutaneous treatment with enoxaparin reduced thrombus formation dose dependently (ED_{50} = 21 mg/kg) in the arteriovenous shunt model. An equieffective antithrombotic effect (about 40 % thrombus weight reduction) was observed after 10 mg/kg enoxaparin and 3 mg/kg BAY 59-7939. In humans the therapeutic dose of enoxaparin is about 10-20 fold lower than observed in the rat shunt model (30 or 40 mg).

Taken into consideration the higher dosages of enoxaparin necessary for an antithrombotic effect in rats compared to the treatment dose in humans, the lower IC_{50} value for anti-FXa activity and the lower concentrations needed to effect coagulation in human plasma it is assumed, that the therapeutic dose of BAY 59-7939 may be 0.3 mg/kg in humans.

To estimate bleeding risk the tail bleeding time in rats and the ear bleeding time in rabbits were measured. In both models BAY 59-7939 increased dose-dependently bleeding time at doses above an antithrombotic dose (arteriovenous shunt model, rat and rabbit). With enoxaparin, bleeding time was prolonged at the lowest antithrombotic dose in rats, but enoxaparin did not increase bleeding time at the lowest antithrombotic dose in rabbits. In rabbits, higher doses of BAY 59-7939 caused longer bleeding times than enoxaparin. These results suggest an antithrombotic activity / bleeding risk ratio for BAY 59-7939 comparable to enoxaparin.

To test the possible influence of BAY 59-7939 on the concomitant use with Enoxaparin or Heparin the antithrombotic effect of these compounds was investigated in the arterio-venous shunt model in rats after simultaneous treatment with BAY 59-7939. The effect of Enoxaparin and Heparin in this model was not diminished by BAY 59-7939.

4.1.2 Primary Pharmacology

Over the past 20 years, significant advances in antithrombotic therapy have yielded a number of drugs that are now used as standard therapy. Although

efficacious, these drugs have limitations that stimulated the development of new antithrombotic agents, which act selectively on single targets in the coagulation cascade such as factor Xa (FXa). It is now well admitted that the inhibition of FXa represents an attractive approach for clinical intervention in various thrombotic disorders [1].

The activated serine protease FXa plays a central role in blood coagulation. It is activated by both the intrinsic and extrinsic coagulation pathways. FXa directly converts prothrombin to thrombin through the prothrombinase complex, which consists of prothrombin, FXa, factor Va, Ca^{2+} and a phospholipid surface, and ultimately this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000 fold compared to that of free FXa and causes an explosive burst of thrombin generation. Selective inhibitors of FXa can terminate the amplified burst of thrombin generation.

In the past many attempts to achieve orally active FXa inhibitors have failed. BAY 59-7939 is a new orally available competitive and selective FXa inhibitor showing antithrombotic properties in animal models.

4.1.2.1 In vitro

(for reference see Perzborn E. (2002) PH 32009)

BAY 59-7939 is a potent, competitive and selective inhibitor of FXa (Fig. 1, 2) (PH-32009). It inhibited concentration-dependently human FXa (Ki = 0.4 ± 0.02 nM), but did not affect other serine proteases as thrombin, factor XI, plasmin, urokinase, activated protein C even at the highest concentration (69 µM) investigated (selectivity for FXa is > 10,000-fold). The only other serine protease which was found sensitive to BAY 59-7939 was trypsin which was inhibited only 25% at 69 µM. Lineweaver-Burk analysis demonstrated that BAY 59-7939 is a competitive inhibitor (Fig. 2).

The inhibitory activity of BAY 59-7939 has also been demonstrated by measuring the inhibition of prothrombinase-bound FXa in a reconstituted prothrombinase complex using prothrombin as substrate and measuring thrombin activity. In the prothrombinase complex BAY 59-7939 inhibited thrombin generation with an IC_{50} value of 2.1 ± 0.4 nM (Fig. 1).

To measure inhibition of endogenous FXa activity in plasma the zymogen FX was converted to FXa by an enzyme in Russell's Viper Venom (RVV). BAY 59-7939 inhibited concentration-dependently the endogenous human FXa activity with an IC_{50} value of 21 ± 1 nM. In rat plasma 10 fold higher concentrations are needed to inhibit FXa (IC_{50}= 290 ± 18 nM). In rabbit plasma the IC_{50} value (21 ± 2 nM) was similar compared to that measured in human plasma.

Fig. 1: Inhibitory effect of BAY 59-7939 on unbound human Factor Xa (FXa) and on prothrombinase–bound human FXa. Each value represents the mean ± SEM.

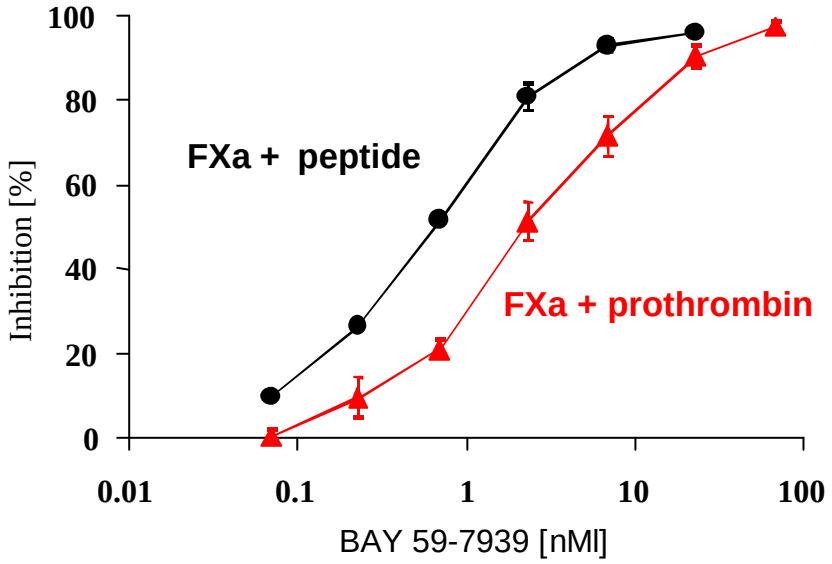
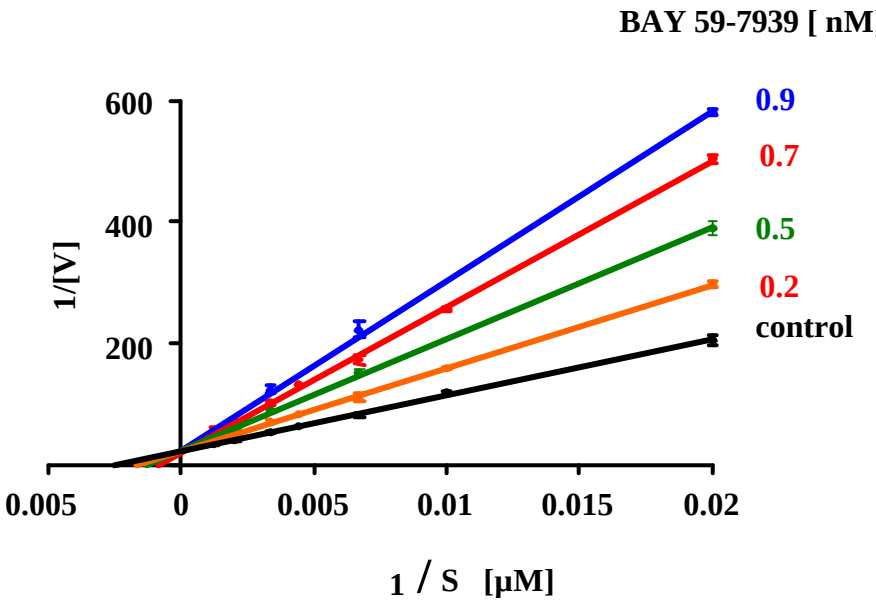


Fig. 2: Kinetic analysis of the inhibitory effects of BAY 59-7939 on human Factor Xa; Lineweaver Burk Plots.



Activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin time (TT) were measured with commercial available kits in plasma. BAY 59-7939 prolonged concentration-dependently PT and APTT in human plasma (Fig. 3). A 2 fold prolongation of PT or APTT was measured at 0.23 ± 0.02 µM or 0.69 ± 0.09 µM, respectively. BAY 59-7939 increased TT at much higher concentrations, the doubling concentration being 26 ± 1 µM.

In rat plasma higher concentrations are necessary to increase clotting times (Fig. 4, 5). A 2 fold prolongation of PT or APTT was achieved at 0.3 ± 0.02 µM and 2.09 ±0.19 µM, respectively. In rabbit plasma a 2 fold increase of PT or APTT was measured at 0.12 ± 0.02 µM or 1.97 ± 0.49 µM (Fig. 4, 5).

Fig. 3: Prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT) in human plasma. Each value represents the mean ± SEM.

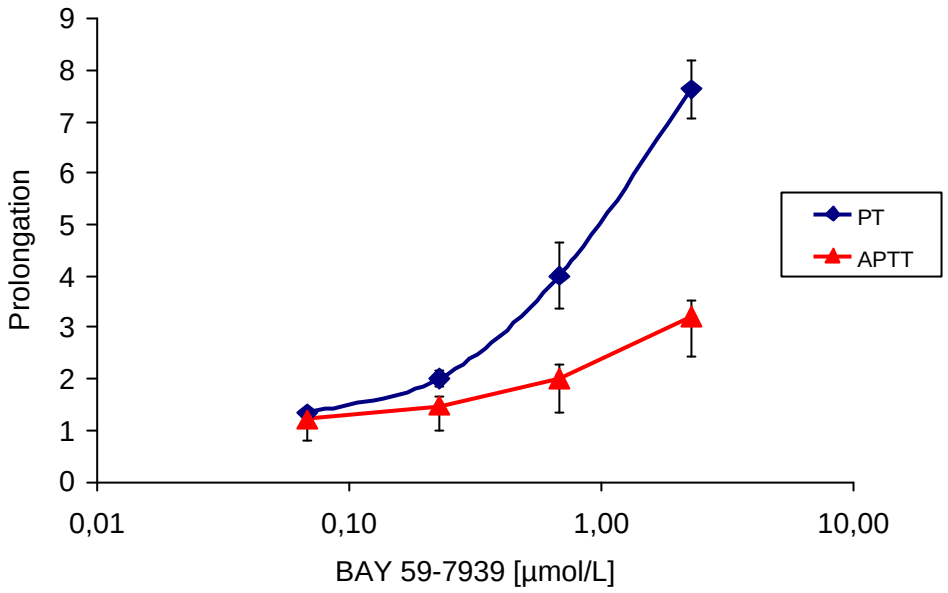


Fig. 4: Prolongation of prothrombin time (PT) in human, rat and rabbit plasma. Each value represents the mean ± SEM.

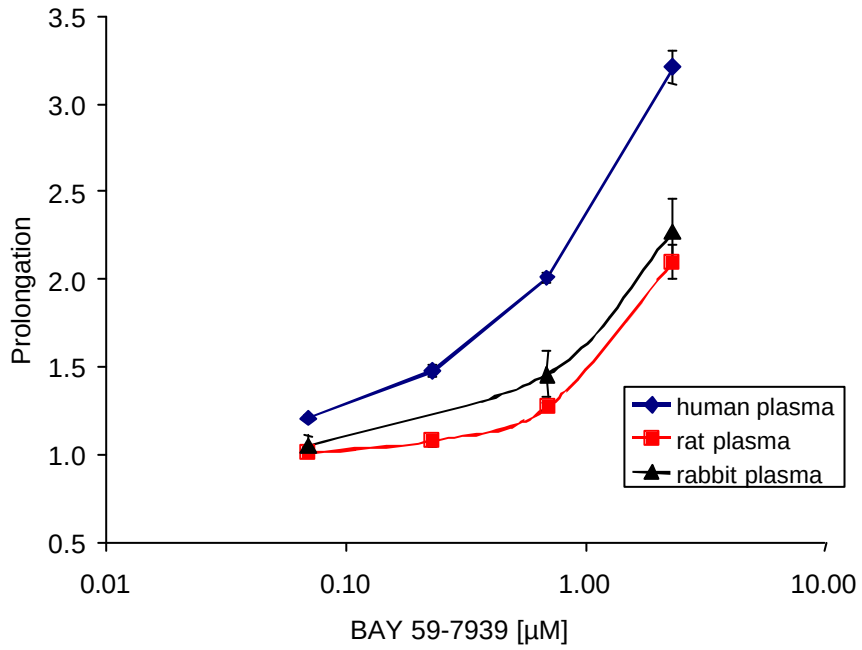
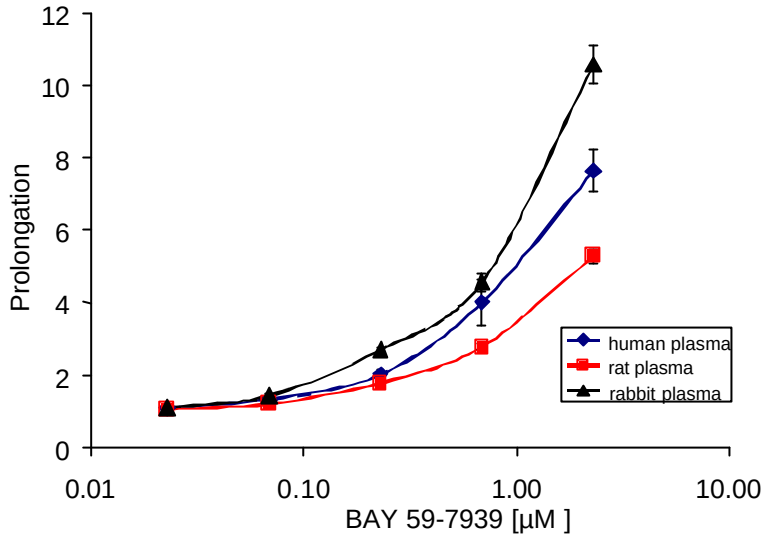


Fig. 5: Prolongation of activated partial thromboplastin time (APTT) in human, rat and rabbit plasma. Each value represents the mean ± SEM.



Platelet aggregation was investigated in human platelet rich plasma in an aggregometer. BAY 59-7939 inhibited neither collagen, U46619, ADP nor TRAP-6 (thrombin receptor activated peptide) induced platelet aggregation up to 200 µM. Gamma thrombin mediated platelet aggregation was inhibited slightly with an IC_{50} value of 81 µM.

4.1.2.2 In vivo

The antithrombotic activity of BAY 59-7939 was investigated in an arteriovenous shunt model in rats (report Perzborn E. 2001, PH-31612). The right common carotid artery and the left jugular vein were connected by polyethylene catheters containing a rough thrombogenic nylon thread. The extracorporal circulation was opened for 15 min and afterwards the thrombus wet weight was determined. In addition, anti-FXa activity, thrombin/antithrombin III (TAT)-concentrations, activated partial thromboplastin time (APTT) and prothrombin time (PT) were measured at the end of the experiment. BAY 59-7939 was given orally 90 min

before anesthesia, and enoxaparin, a low molecular heparin used as reference compound, was administered subcutaneously 60 min before anaesthesia.

Oral treatment with BAY 59-7939 resulted in a dose-dependent reduction of thrombus mass showing an ED_{50} value of 5.0 mg/kg p.o.. BAY 59-7939 inhibited significantly thrombus formation by 41 ± 7% at 3.0 mg/kg, by 51 ± 6% at 6 mg/kg and by 73 ± 2% at 10.0 mg/kg (Fig. 6).

After 1.0 mg/kg, an antithrombotic ineffective dose, a low inhibition of FXa activity and TAT by 38% and 26% was obtained (Table 1). PT was slightly increased by 1.7 fold. At doses near the ED_{50} value (3 and 6 mg/kg) FXa-activity and TAT concentration were reduced by 61 or 78% and 75 or 78%. PT values were prolonged by 2.4 and 3.7 fold, respectively. A slight prolongation of APTT of 1.4 fold was measured after 6 mg/kg (Table 1).

Subcutaneous treatment with the reference compound enoxaparin reduced thrombus formation showing an ED_{50} value of 21 mg/kg s.c. (Fig. 7). At 50% thrombus mass reduction TAT was inhibited by 61% (Table 2). This effect is comparable to the results obtained with BAY 59-7939. APTT was increased by 2.6 fold (Table 2).

Fig. 6: Effect of BAY 59-7939 on thrombus development in an arteriovenous shunt model in rats. BAY 59-7939 was given orally 90 min before opening the shunt. Each value represents the mean ± SEM.

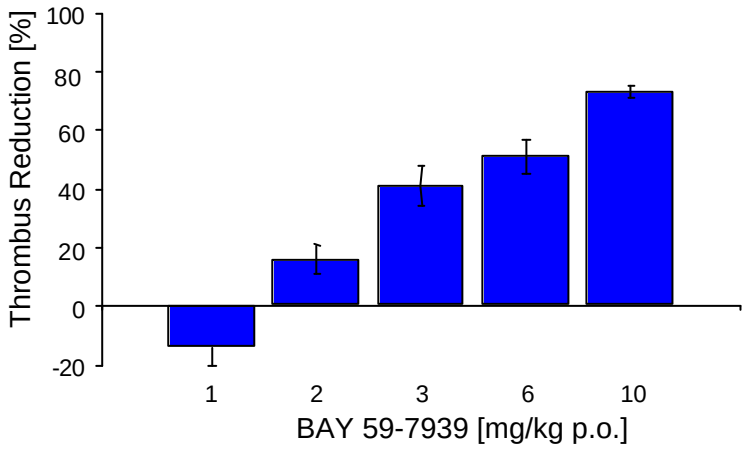


Table 1: Ex vivo effect of BAY 59-7939 on PT, APTT, anti FXa-activity, TAT in an arteriovenous shunt model in rats

Dose [mg/kg] p.o.	**PT Prolongation mean ± SEM**	**APTT Prolongation mean ± SEM**	**Anti FXa-Activity Inhibition [%] mean ± SEM**	**TAT Inhibition [%] mean ± SEM**
1.0	1.71 ±.0.16**	N.D.	38 ± 5	26 ±.9
2.0	1.80 ±.0.09***	1.12 ±.0.05*	46 ± 3***	51 ±.10**
3.0	2.38 ±.0.20***	N.D.	61 ±.2***	75 ±.14**
6.0	3.66 ±.0.36***	1.40 ±.0.02***	78 ±.2***	78 ± 4*
10.0	5.06 ±.0.14***	1.77 ±.0.07***	89 ±.2***	105 ±.4*

$p < 0.05$ = * N.D. = not determined
$p < 0.02$ = **
$p < 0.001$ = ***

Fig. 7: Effect of enoxaparin on thrombus development in an arteriovenous shunt model in rats. enoxaparin was given subcutaneously 60 min before opening the shunt. Each value represents the mean ± SEM.

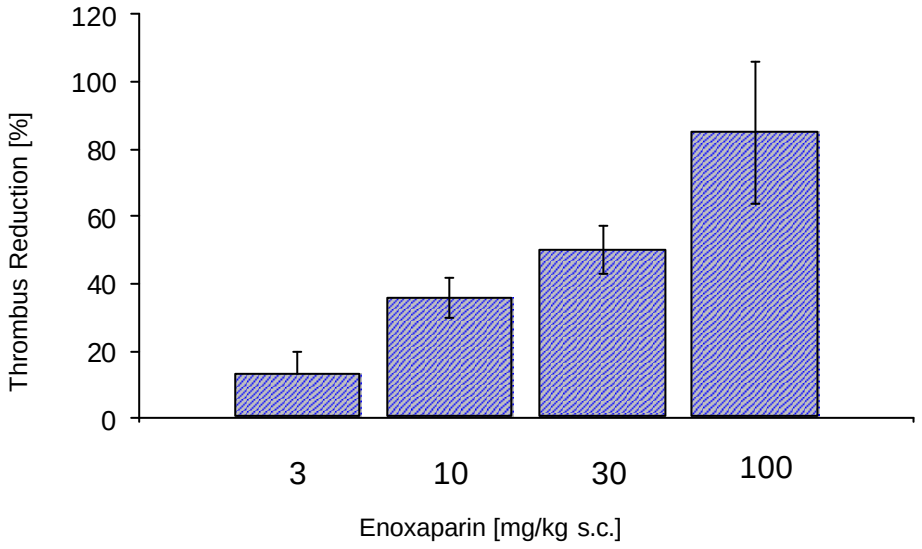


Table 2: Ex vivo effect of enoxaparin on APTT and TAT in an arteriovenous shunt model in rats

Dose [mg/kg] s.c.	**APTT Prolongation mean ± SEM**		**TAT Inhibition [%] mean ± SEM**
3.0	1.00 ±.0.02	n.s.	56 ±.8 (p < 0.05)
10	1.75 ±.0.12	p < 0.001	57 ±.8 (p < 0.002)
	2.58 ±.0.08	p < 0.001	61 ±.7 (p < 0.02)
100	8.43 ±.0.68	p < 0.001	87 ±.2 (p < 0.002)

n.s. = not significant

The antithrombotic activity of BAY 59-7939 was determined after mechanical damage of both the A.carotis and V.jugularis in rats (report Perzborn E. 2001, PH-31613). Thrombus development was induced by chilling the vessels. After 4 hours the thrombi were removed and weighted. enoxaparin was used as reference compound. BAY 59-7939 or the solvent were given orally 90 min before damage. enoxaparin or the solvent were administered intravenously 15 min before damage.

On the venous site oral treatment with BAY 59-7939 resulted in a dose-dependent reduction of thrombus mass showing an ED_{50} value of 2.0 mg/kg (Fig. 8). On the arterial site 10.0 mg/kg BAY 59-7939 significantly reduced thrombus weight by 51 ± 8% (Fig. 9). After treatment with 3.0 mg/kg a thrombus mass reduction of 34 ± 16% was achieved, but this effect did not reach statistical significance. Enoxaparin, was nearly equi-effective on the arterial and venous sides with an ED_{50} between 1 and 3 mg/kg i.v. (Fig. 10,11).

Fig. 8: Effects of BAY 59-7939 on thrombus development in the V.jugularis in rats. BAY 59-7939 was given orally 90 min before damage of the vessel. Each value represents the mean ± SEM.

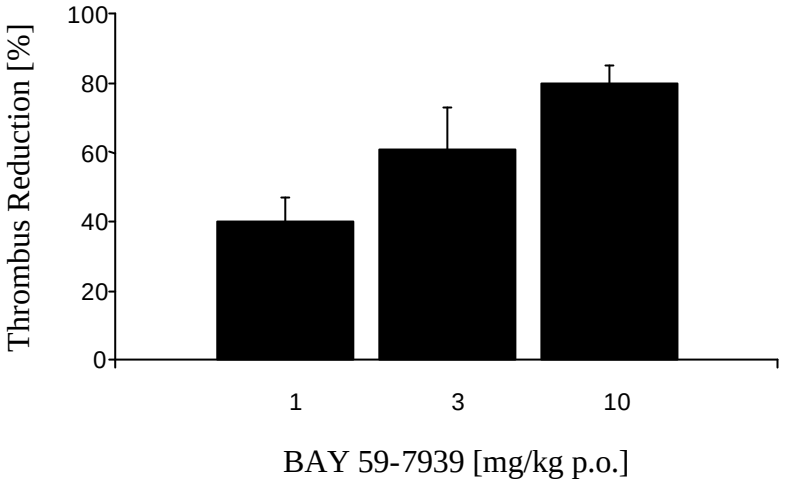


Fig. 9: Effects of BAY 59-7939 on thrombus development in the A.carotis in rats. BAY 59-7939 was given orally 90 min before damage of the vessel. Each value represents the mean ± SEM.

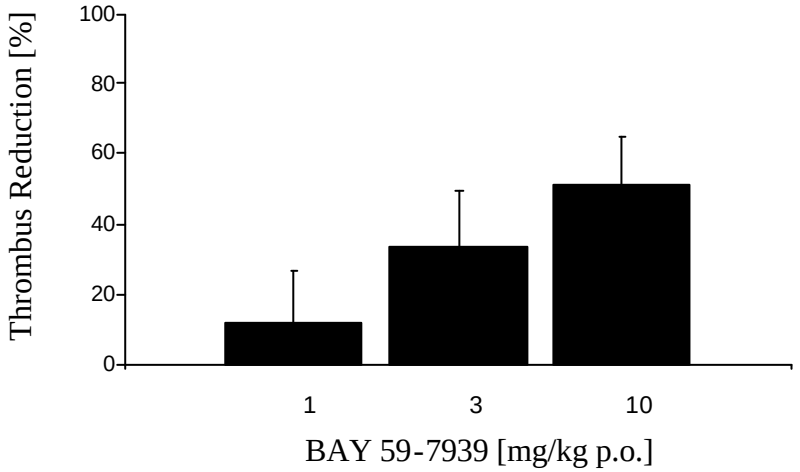


Fig. 10: Effects of enoxaparin on thrombus development in the V.jugularis in rats. enoxaparin was given by intravenous injection 15 before damage of the vessel. Each value represents the mean ± SEM.

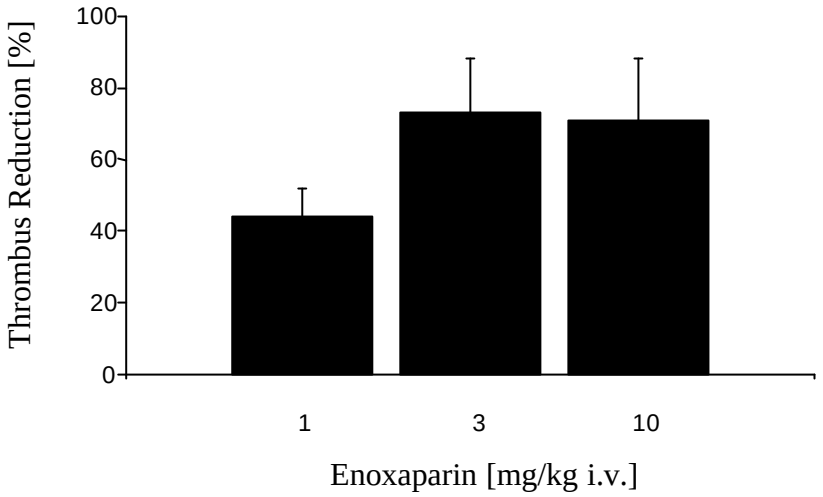
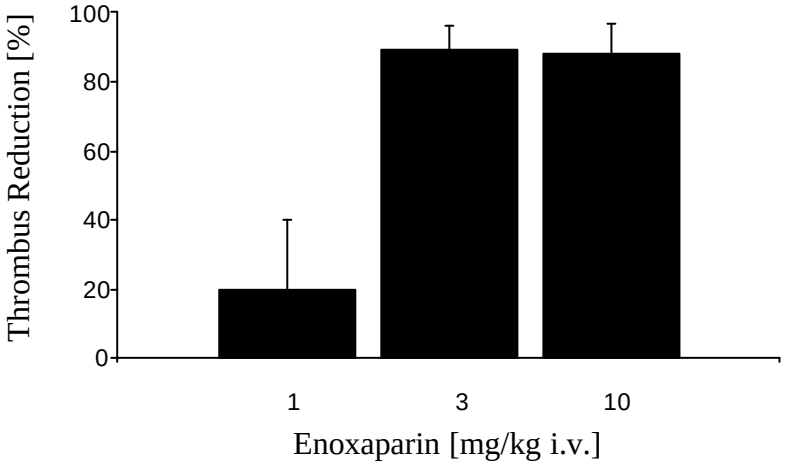


Fig. 11: Effects of enoxaparin on thrombus development in the A.carotis in rats. Enoxaparin was given by intravenous injection 15 before damage of the vessel. Each value represents the mean ± SEM.



The antithrombotic activity of BAY 59-7939 was evaluated in an arteriovenous shunt model in rabbits according to Berry et al (report Perzborn E. 2001, PH-31614). The right common carotid artery and the left jugular vein were connected by polyethylene catheters containing a rough thrombogenic nylon thread. The extracorporal circulation was opened 10-20 min after i.v. administration of BAY 59-7939, enoxaparin or the appropriate control. The extracorporal circulation was opened for 15 min and afterwards the thrombus wet weight was determined. In addition, clotting times were measured at the end of the experiments.

Intravenous injection of BAY 59-7939 resulted in a dose-dependent reduction of thrombus mass showing an ED_{50} value of 0.6 mg/kg (Fig. 12). At a dose of 0.3 mg/kg BAY 59-7939 inhibited thrombus formation by 40 ± 10%, at 1.0 mg/kg by 58 ± 5% and at 3.0 mg/kg by 83 ± 7%.

Doubling of APTT (2.3 ± 0.11 fold) was observed after 1.0 mg/kg of BAY 59-7939, but was not significantly increased at the lowest antithrombotic dose of 0.3 mg/kg (Table 3). The effect on PT was more pronounced showing a dose-dependent increase from 0.1 mg/kg up (Table 4). Doubling of PT (2.19 ± 0.13 fold) was observed after 0.3 mg/kg.

In comparison intravenous injection of enoxaparin inhibited thrombus formation in a dose-dependent manner with an ED_{50} value of 1.8 mg/kg (Fig. 13).

Fig. 12: Effect of BAY 59-7939 on thrombus formation in the arteriovenous-shunt model in rabbits. BAY 59-7939 was given intravenously 10-20 min before opening the shunt. Each value represents the mean ± SEM.

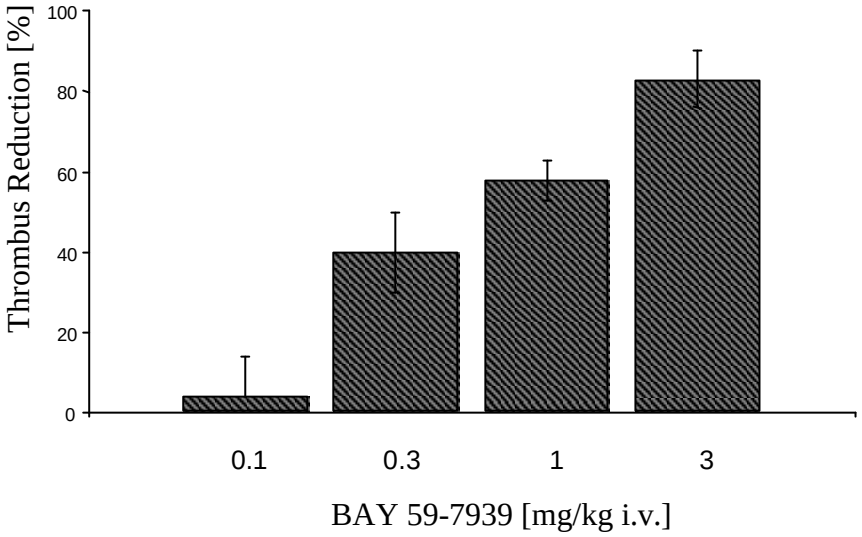


Table 3: Ex vivo effects of BAY 59-7939 on APTT in an arteriovenous shunt model in rabbits

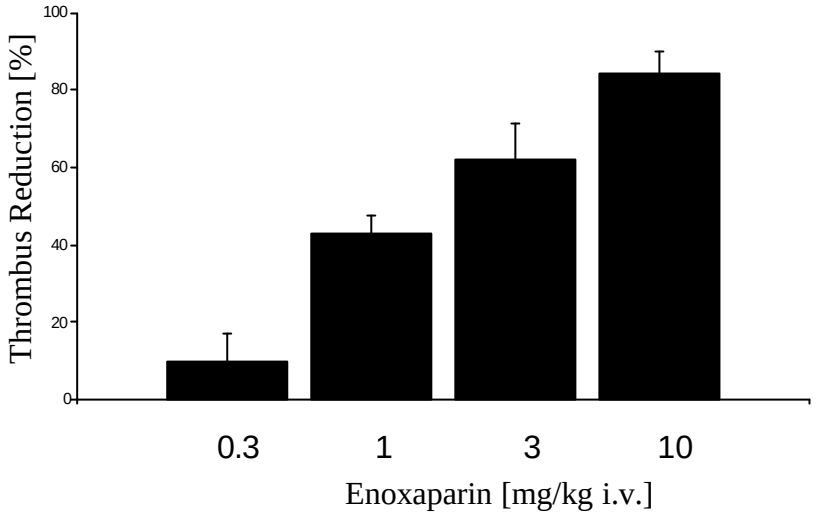
Doses [mg/kg] i.v.	**Prolongation mean ± SEM**	**n**	**P**
0.1	1.05 ± 0.07	6	n.s.
0.3	1.25 ± 0.11	6	n.s.
1.0	2.27 ± 0.11	5	P < 0.001

n.s. = not significant

Table 4: Ex vivo effect of BAY 59-7939 on PT in an arteriovenous shunt model in rabbits

Dose [mg/kg] i.v.	**Prolongation mean ± SEM**	**n**	**p**
0.1	1.25 ±.0.02	6	p < 0.001
0.3	2.19 ±.0.13	6	p < 0.001
1.0	3.48 ±.0.24	11	p < 0.001
3.0	8.60 ±.0.58	5	p < 0.001

Fig. 13: Effect of enoxaparin on thrombus formation in the arteriovenous-shunt model in rabbits. Enoxaparin was given intravenously 10-20 min before opening the shunt. Each value represents the mean ± SEM.



Effect on Bleeding Time

The aim of these in vivo studies was to investigate the effect of BAY 59-7939 on hemostasis measuring tail bleeding time after oral treatment in rats (report Perzborn E. 2002, PH-31659). The bleeding time was determined by measuring the time from cutting the tip of the tail until continuous blood flow ceased for longer than 30 sec. The maximal observation time was 10 min. BAY 59-7939 was given orally 90 min and enoxaparin subcutaneously 60 min before bleeding time measurement.

BAY 59-7939 dose-dependently increased bleeding time at doses above the antithrombotic dose of 3.0 mg/kg (arteriovenous shunt model, rat). At 3.0 mg/kg bleeding time was not prolonged (Fig. 14, Table 5). Bleeding time was significantly increased 2 fold at 6 mg/kg and 2.7 fold at 10 mg/kg. With the

exception of 2 animals in both of these groups bleeding stopped within the observation time.

After subcutaneous injection of the reference compound, enoxaparin, bleeding time was significantly prolonged above 3.0 mg/kg (Fig.15, Table 6). A 2 fold prolongation was measured at the lowest antithrombotic dose of 10 mg/kg (arteriovenous shunt model, rat). After 30 mg/kg of enoxaparin, which is comparable to 6.0 mg/kg of BAY 59-7939 concerning its antithrombotic efficacy, bleeding did not stop in 9 of 10 animals within the observation time.

These results demonstrate a favorable antithrombotic activity / bleeding risk ratio for BAY 59-7939. Bleeding risk of BAY 59-7939 is similar or even reduced in comparison to enoxaparin in the rat tail model.

Prothrombin time (PT) was significantly prolonged by BAY 59-7939 from 3.0 mg/kg and above in a dose-dependent manner (Table 5). Doubling of PT was measured after 3.0 mg/kg.

Activated partial thromboplastin time (APTT) was slightly increased (1.4 fold) at 10 mg/kg.

Fig. 14: Effect of BAY 59-7939 on rat tail bleeding time after oral treatment. Each value represents the mean ± SEM of n=10 animals. At 6.0 and 10 mg/kg bleeding did not stop within the observation time of 10 min in 2 animals. These times were given a 10 min value. The animals were orally pre-treated for 90 min. For each treated group a separate control group was performed.

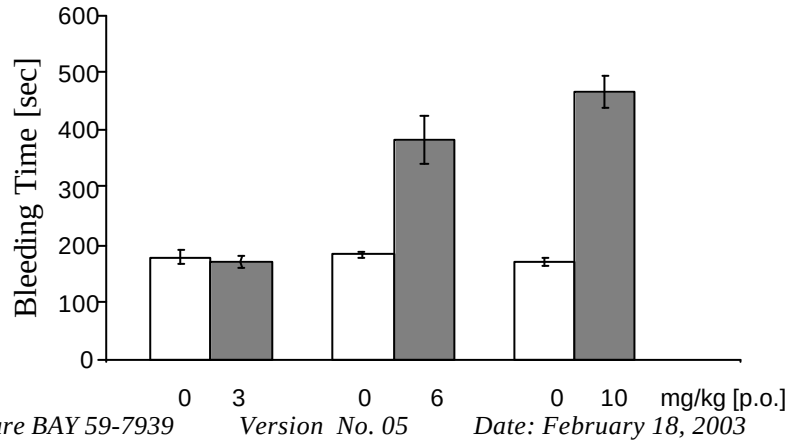


Table 5: Effect of BAY 59-7939 on Bleeding Time, APTT and PT in rats

Group [mg/kg] p.o.	**Bleeding Time [sec.] Mean ± SEM**	**p**	**APTT Prolongation Mean ± SEM**	**p**	**PT Prolongation Mean ± SEM**	**p**	**n**
control	179 ± 13						9
3.0	172 ± 11	n.s.	1.14 ± 0.02	< 0.001	1.99 ± 0.12	< 0.001	9
control	185 ± 5.0						10
6.0	381 ± 42*	<0.002	1.04 ± 0.02	n.s.	4.35 ± 0.73	< 0.002	10
control	171 ± 7.0						10
10	466 ± 29*	< 0.001	1. 39 ± 0.06	< 0.001	3.59 ± 0.34	< 0.001	10

n.s. = not significant

Bleeding Time > 600 sec in n = 2 animals.

Fig. 15: Effect of enoxaparin on rat tail bleeding time after subcutaneous treatment. Each value represents the mean ± SEM of n=10 animals. At 10 mg/kg 1 animal showed a bleeding time above 10 min. At 30 mg/kg 9 animals showed bleeding times above 10 min. These times were given a 10 min value. The animals were subcutaneously pretreated for 60 min. For each treated group a separate control group (n=10 animals) was performed.

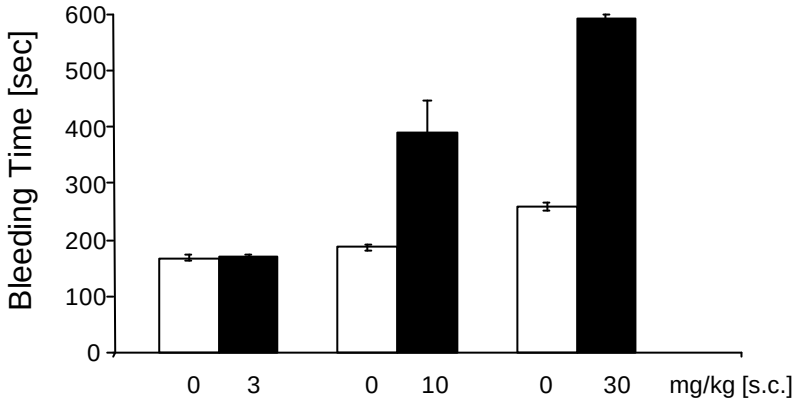


Table 6: Effect of enoxaparin on Bleeding Time and APTT in rats

Group [mg/kg]s.c.	**Bleeding Time [sec.] Mean ± SEM**	**p**	**APTT Prolongation Mean ± SEM**	**p**	**n**
control	168 ± 5.0				10
3.0	170 ± 5.0	n.s.	1.97 ± 0.12	< 0.001	10
control	187 ± 5.0				10
10	365 ± 37*	<0.001	3.27 ± 0.18	< 0.001	10
control	258 ± 13				10
30	592 ± 8.0**	< 0.001	3.90 ± 0.19	< 0.001	10

n.s. = not significant

* Bleeding Time > 600 sec in n = 1 animals.

** Bleeding Time > 600 sec in n = 9 animals.

The effects of BAY 59-7939 on ear bleeding time (EBT) was determined in rabbits after intravenous treatment (report Perzborn E. 2001, PH-31611). EBT was determined after setting a standardized incision parallel to the long axis of the ear. The incision sites were blotted at 30 sec intervals with filter paper. The bleeding time was determined by measuring the time from incision until blood no longer stained the filter paper. Bleeding times were measured 5 and 15 min after intravenous injection of BAY 59-7939 or enoxaparin.

BAY 59-7939 increased bleeding time dose-dependently at doses above the antithrombotic dose of 0.3 mg/kg (arteriovenous shunt model, rabbit). Bleeding time was significantly increased 4.0 fold at 1.0 mg/kg and 4.7 fold at 3.0 mg/kg (Fig. 16).

After intravenous injection of enoxaparin bleeding time was not prolonged at the lowest antithrombotic effective dose of 1.0 mg/kg (Fig. 17). A significant 1.5 fold and 2.7 fold increase in bleeding time was measured at 3.0 and 10 mg/kg, respectively.

In the rabbit ear model with both compounds a differentiation between an thrombotic effect and increase in bleeding time was observed. However higher doses of BAY 59-7939 caused longer bleeding times than enoxaparin.

Fig. 16: Effect of BAY 59-7939 on rabbit ear bleeding time. Bleeding times were measured 5 and 15 min after intravenous injection of the compound or the solvent. Each value represents the mean ± SEM.

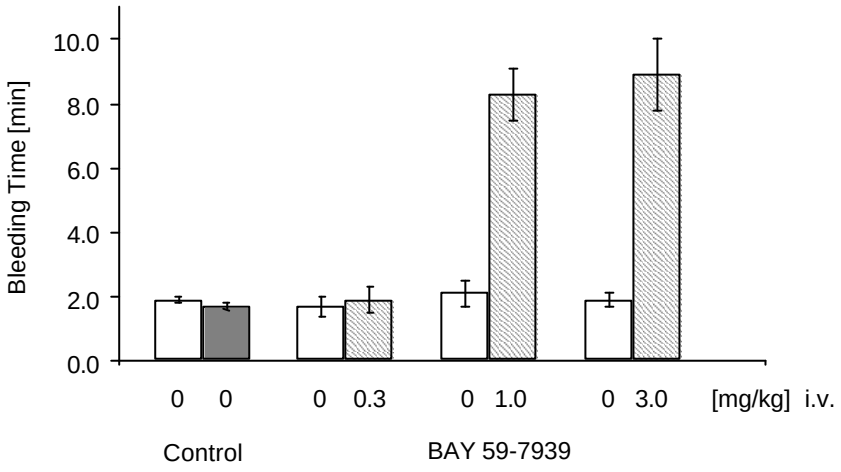
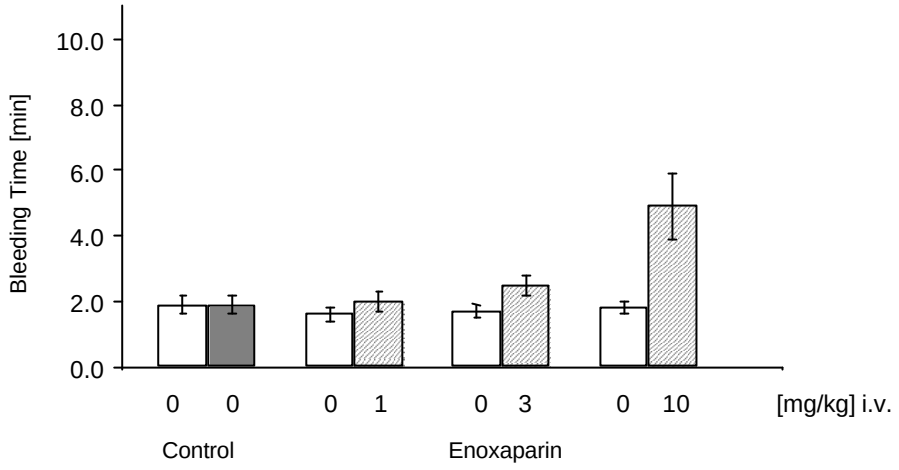


Fig. 17: Effect of enoxaparin on rabbit ear bleeding time. Bleeding times were measured 5 and 15 min after intravenous injection of the compound or the solvent. Each value represents the mean ± SEM.



Effect on the antithrombotic activity of Enoxaparin or Heparin in the arterio-venous shunt model in rats

In order to estimate the potential of BAY 59-7939 to interact with the antithrombotic activity of a low molecular weight heparin (Enoxaparin) or unfractionated Heparin (UFH) the antithrombotic activity of the single compounds was compared to the effects after simultaneous treatment with BAY 59-7939 and Enoxaparin or Heparin in the arterio-venous shunt model in rats. BAY 59-7939 or its vehicle were given orally 90 minutes before anaesthesia. 10 or 30 mg/kg Enoxaparin or its vehicle were administered subcutaneously 60 minutes before anaesthesia. 15 IE/kg Heparin or its vehicle were given intravenously 10 minutes after anaesthesia. In the combination groups the animals were orally treated with BAY 59-7939 (3.0 mg/kg) 90 minutes before anaesthesia and Enoxaparin sodium (10 or 30 mg/kg) given subcutaneously 60 minutes before anaesthesia or 15 IE/kg

Heparin given intravenously 10 minutes after anaesthesia. The control groups received the solvent of BAY 59-7939 90 minutes before anaesthesia and saline given intravenously 10 minutes after anaesthesia or given subcutaneously 60 minutes before anaesthesia.

Oral treatment with 3 mg/kg BAY 59-7939 significantly reduced thrombus formation by 25 ± 4% or 32 ± 9% (Tables 7,8). Single treatment with 10 or 30 mg/kg Enoxaparin given subcutaneously reduced thrombus weights significantly by 43 ± 9% or 57 ± 4%. After treatment with 3 mg/kg BAY 59-7939 and 30 mg/kg Enoxaparin thrombus weight was reduced by 62 ± 5% which was not significantly different from the value obtained after single treatment with Enoxaparin (Table 7). Furthermore, after simultaneous treatment with 3 mg/kg BAY 59-7939 and 10 mg/kg Enoxaparin the antithrombotic effect was increased significantly leading to a thrombus weight reduction of 65 ± 3% indicating an additive effect of both drugs (Table 8).

15 IE/kg Heparin reduced thrombus development by 27 ± 3% (Table 9). After treatment with both 3 mg/kg BAY 59-7939 and 15 IE/kg Heparin the antithrombotic effect was increased significantly leading to 49 ± 7% reduction of thrombus development indicating an additive effect.

In addition, the maximal values of PT, APTT and anti-FXa activity observed after single treatment with BAY 59-7939, Enoxaparin or Heparin were achieved or even surpassed in the corresponding combinations of BAY 59-7939 and Enoxaparin or Heparin, respectively.

Therefore, it can be concluded that BAY 59-7939 does not reduce the antithrombotic activity of Enoxaparin and UFH in rats.

Table 7: Effect of BAY 59-7939 and Enoxaparin (30 mg/kg s.c.) and their combination on clotting times and FXa activity in the arterio-venous shunt model in rats. Each value represents the mean ± SEM.

	BAY 59-7939 3 mg/kg p.o.	**Enoxaparin 30 mg/kg s.c.**	**BAY 59-7939 plus Enoxaparin**
Thrombus weight reduction [%]	25 ± 4 ***	57 ± 4 ***	62 ± 5 ***
PT (fold prolongation)	2.4 ± 0.2 ***	1.2 ± 0.1	2.8 ± 0.2 ***
APTT (fold prolongation)	1.2 ± 0.1	4.3 ± 0.5 ***	7.4 ± 1.4 **
Inhibition of FXa [%]	62 ± 3 ***	96 ± 1 ***	97 ± 1 ***

** $p < 0.005$ and *** $p < 0.001$ versus control

Table 8: Effect of BAY 59-7939 and Enoxaparin (10 mg/kg s.c.) and their combination on aPTT and FXa activity in the arterio-venous shunt model in rats. Each value represents the mean ± SEM.

	BAY 59-7939 3 mg/kg p.o.	**Enoxaparin 10 mg/kg s.c.**	**BAY 59-7939 plus Enoxaparin**
Thrombus weight reduction [%]	32 ± 9 *	43 ± 9 **	65 ± 3 ***
APTT (fold prolongation)	1.13 ± 0.03 *	1.9 ± 0.2 **	2.9 ± 0.3 **
Inhibition of FXa [%]	68 ± 2 ***	89 ± 1***	93 ± 1***

* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ versus control

Table 9: Effect of BAY 59-7939 and Heparin and their combinations on clotting times and FXa activity in the arterio-venous shunt model in rats. Each value represents the mean ± SEM.

	BAY 59-7939 3 mg/kg p.o.	**Heparin 15 IE/kg i.v.**	**BAY 59-7939 plus Heparin**
Thrombus weight reduction [%]	25 ± 4 ***	27 ± 3 ***	49 ± 7 ***
PT (fold prolongation)	2.4 ± 0.2 ***	1.1 ± 0.1	2.5 ± 0.5 *
APTT (fold prolongation)	1.2 ± 0.1	> 13 ***	> 14 ***
Inhibition of FXa [%]	62 ± 3 ***	96 ± 1***	98 ± 1***

$p < 0.05$, *** $p < 0.001$ versus control

4.1.3 Safety Pharmacology

4.1.3.1 Cardiovascular System and Respiratory System

BAY 59-7939 showed no effects on cardiovascular function, ECG, respiration, acid/base-status, hematocrit and electrolytes. The plasma levels rose dose-dependently up to a mean C_{max} of 3924 µg/l after 30 mg/kg. [Report PH31616]. Key study data and results of kinetics are shown in the tables below.

Table 1: Key study data of Cardiovascular/Respiration study in anesthetized dogs

Study Type	Safety GLP: yes
Bayer Reference	Hoffmann M. (2001), study no. T 1064731, Report 31616
Batch No.	507047, co-precipitate 010507
Animals	beagle dogs, 3 animals/group
Dose	0 – 3 - 10 – 30 mg/kg
Administration	Intraduodenal Vehicle: melt-coprecipitate in demineralized water, supplemented with PEG6000
NOAEL	= 30 mg/kg i.d.

Table 2: Summary on exposure in the Cardiovascular/Respiration study in anesthetized dogs.

Parameter	**Unit**	**3 mg/kg**		**10 mg/kg**		**30 mg/kg**	
		Mean	**S.D.***	**Mean**	**S.D.***	**Mean**	**S.D.***
AUC(0-4)	[µg·h/L]	2231	1.97	3661	2.58	11414	2.62
$AUC(0-4)_{norm}$	[kg·h/L]	0.744	1.97	0.366	2.58	0.380	2.62
C_{max}	[mg/L]	724	2.05	1206	2.59	3924	2.84
$C_{max, norm}$	[kg/L]	0.241	2.05	0.121	2.59	0.131	2.84

4.1.4 Central Nervous System

Treatment with BAY 59-7939 did not elicit any symptoms of adverse effects. In the dose-range tested, BAY 59-7939 did not affect open-field behavior or body temperature of rats. [Report PH 31412]

BAY 59-7939 did not alter the convulsive threshold dose of pentylenetetrazole or the duration of hexobarbital-induced anesthesia indicating that BAY 59-7939 is devoid of pro- and anticonvulsive as well as of sedative and stimulatory effects. However, at doses above 3 mg/kg, nocifensive reactions were dose-dependently delayed indicating a weak analgesic effect. [Report PH 31413]

Table 3: Key study data of CNS study in rats

Study Type	Safety GLP: es
Bayer Reference	Himmel H., Breier P. (2001), study no. T 2064732, Pharma report 31412 Himmel H., Breier P. (2001), study no. T 3064733, report PH 31413
Batch No.	507047, co-precipitate 010507
Animals	Male rats (HsdCpb: WU, about 6 weeks old), 6-8 animals/group
Dose	0 – 3 - 10 – 30 mg/kg
Administration	oral (gavage) Vehicle: melt-coprecipitate in demineralized water, supplemented with PEG6000
NOAEL	Analgesic effect: 3 mg/kg, otherwise = 30 mg/kg

4.1.5 Renal Function, Lipid Metabolism, Hematology

A single oral administration of BAY 59-7939 to rats did not affect any of the parameters tested, i.e., urine volume, renal electrolyte excretion (except a minor natriuretic effect at 10 mg/kg), blood cell counts, hematocrit, blood hemoglobin and plasma concentrations of triglycerides or cholesterol, in a dose-dependent and physiologically relevant manner. Coagulation was dose-dependently inhibited; thromboplastin time rose from 16.5 s to 73.2 s, while thrombin time was only little

increased (from 18.3 s to 20.9 s) as expected from the mechanism of action of the factor Xa inhibitor BAY 59-7939. [Report PH 31411]

Table 4: Key study data of Renal Function, Lipid Metabolism, Hematology study in rats

Study Type	Safety GLP: yes
Bayer Reference	Himmel H., Breier P. (2001), study no. T 1070969, report PH 31411
Batch No.	507047, co-precipitate 010507
Animals	Male rats (HsdCpb: WU, about 6 weeks old), 10 animals/group
Dose	0 – 3 - 10 – 30 mg/kg
Administration	Oral (gavage)
	Vehicle: melt-coprecipitate in demineralized water, supplemented with PEG6000
NOAEL	= 30 mg/kg

Table 5: Results of Hematology study in rats

Group	**Dose (mg/kg) p.o.**	**Number of animals**	**Thrombin time (sec)**	**Thromboplastin time (sec)**
			(Mean ± S.D.)	
1 (Control)	0 (Vehicle)	9[a]	18.3 ± 0.33	16.5 ± 1.16
2	3	9[b]	19.5 ± 0.69[*]	33.8 ± 3.65[*]
3	10	10	20.6 ± 1.45[*]	53.1 ± 11.17[*]
4	30	8[a]	20.9 ± 1.33[*]	73.2 ± 11.61[*]

[*] $p < 0.05$ compared to vehicle-treated controls, Kruskal-Wallis test followed by an adjusted U test

[a] $n < 10$ because animals (1 in control group, 2 at 30 mg/kg) died in urethane anesthesia before completion of blood sampling

[b] one sample excluded because of strong coagulation

4.1.6 Blood Glucose Concentration

Treatment with BAY 59-7939 did not change the blood glucose concentration of fed or fasted rats. [Report PH 31410]

Table 6: Key study data of Blood Glucose study in rats

Study Type	Safety	GLP: yes
Bayer Reference	Himmel H., Breier P. (2001), study no. T 0070968, report PH 31410	
Batch No.	507047, co-precipitate 010507	
Animals	Male rats (HsdCpb: WU, about 6 weeks old), 6 fasted animals/group and 6 fed animals/group	
Dose	0 – 3 - 10 – 30 mg/kg	
Administration	oral (gavage)	
	Vehicle: melt-coprecipitate in demineralized water, supplemented with PEG6000	
NOAEL	= 30 mg/kg	

4.1.7 Gastrointestinal Tract

Treatment with BAY 59-7939 had no effect on the intestinal barium sulfate transport in rats and is therefore considered to be without effect on gastrointestinal motility in the dose-range tested. [Report PH 31414]

Table 7: Key study data of Gastrointestinal Tract study in rats

Study Type	Safety	GLP: yes
Bayer Reference	Himmel H., Breier P. (2001), study no. T 4064734, report PH 31414	
Batch No.	507047, co-precipitate 010507	
Animals	Male rats (HsdCpb: WU, about 6 weeks old), 5 animals/group	
Dose	0 – 3 - 10 – 30 mg/kg	
Administration	oral (gavage)	
	Vehicle: melt-coprecipitate in demineralized water, supplemented with PEG6000	
NOAEL	= 30 mg/kg	

4.1.8 Effects on Smooth Muscle (in vitro)

Incubation with BAY 59-7939 did not induce contractions or relaxation of the ileal segments, nor did the test substance exert any clinically or physiologically relevant effects on ileal contractions elicited by acetylcholine, histamine, serotonin, or barium chloride.[Report PH 31503].

Table 8: Key study data of smooth muscle in vitro – study

Study Type	Safety	GLP: yes
Bayer Reference	Himmel H., Breier P. (2001), study no. T 5064735, report PH 31503	
Batch No.	507047	
Test system	isolated guinea pig ileum	
Concentration	10^{-7} – 10^{-6} g/ml Vehicle: DMSO	
Effects on ileal contractions induced by:	acetylcholine 2.3 x 10^{-7} mol/lbarium chloride 3 x 10^{-3} mol/l serotonin 5 x 10^{-6} mol/l histamine 10^{-6} mol/l	
NOAEL	= 10^{-6} g/ml	

4.1.9 Effects on hERG mediated potassium channel (in-vitro)

BAY 59-7939 did not show any effect on the current amplitude of hERG transfected CHO cells at concentrations of 0.1 – 10 µM.

Table : Key study data of hERG Channel in vitro - study

Study Type	**Safety**	GLP: no
Bayer Reference	Evotec OAI AG, Hamburg, Draft report	
Batch No.	BX005AJ	
Test system	CHO cells, stably expressing humanERG potassium channel	
Concentration	0.1 – 10 µM Vehicle: DMSO	
Effects on current amplitude:	no effects	
NOAEL	= 10 µM	

4.2 Pharmacokinetics and Drug Metabolism in Animals

Key Points:

- Limited absorption of radioactivity from the gastrointestinal tract in rats (66.8 %) and almost complete absorption in dogs (approx. 94.9 %); bioavailability of 60 % in rats and 60 – 86 % in dogs
- Linear pharmacokinetics in rats and dogs after intravenous and oral administration
- No major circulating metabolites in rat and dog plasma
- Rapid elimination from plasma in rats and dogs
- High and species-dependent protein binding
- Morpholino moiety as main target of metabolic degradation
- CYP3A4 decisive enzyme for biotransformation *in vitro*
- No inhibition or induction of major CYP isoforms
- 87 % of the dose in the excreta of rats attributed to known structures
- Excretion of radioactivity in rats predominantly via biliary/fecal route; renal route contributed also considerably in dogs
- binding to melanin-containing tissues (pigmented skin areas and eyes) to minor extent
- Low radioactive residues, no evidence of irreversible binding or retention of radioactivity in organs and tissues of rats

4.2.1 Summary

Pharmacokinetics of BAY 59-7939 was investigated *in vivo* in Wistar rats and in Beagle dogs. Additionally, *in vitro* studies were performed to investigate plasma

protein binding, blood cell/plasma partitioning and drug metabolism in several species including man.

After oral administration of [^{14}C]BAY 59-7939 the absorption of radioactivity (unchanged compound and radioactive metabolites) from the gastrointestinal tract was limited in rats (approx. 66.8 %) and almost complete in dogs (approx. 94.9 %). The absolute bioavailability was moderate to high amounting to 60 % in rats and to 60 – 86 % in dogs.

The pharmacokinetics of BAY 59-7939 was linear within the investigated dose range in rats and dogs after intravenous and oral administration.

Plasma clearance in rats (0.4 L/(kg·h)) and dogs (0.3 L/(kg·h)) was low. V_{ss} was moderate, amounting to 0.3 L/kg for the rat and to 0.4 L/kg for the dog.

The plasma elimination half-lives of unchanged substance were about 0.9 h after i.v. (interval: 4 – 8 h) and between 1.2 to 2.3 h after oral (interval: up to 8 h) administration in rats. In dogs the half-life of elimination of BAY 59-7939 was about 0.9 h in the time interval up to 9 and 10 h after both routes of administration.

The protein binding of BAY 59-7939 was high and species dependent. The fraction unbound to plasma proteins (f_u) was about 0.86 % in rats, and about 6.6 % in dogs, and about 2.8 % in humans at the BAY 59-7939 concentration of 1 mg/L. Albumin was identified as important binding component in human plasma. Acidic α_1-glycoprotein contributed only marginally. At plasma concentrations below 25 mg/L, the protein binding of BAY 59-7939 was linear in dogs, mice, rats, rabbits, and human. Saturation of protein binding was observed when the plasma concentration of BAY 59-7939 was increased from 25 to 100 mg/L. Relevant effective therapeutic plasma concentrations in man are expected in the range of 0.07 to 1 mg/L.

The radioactivity was rather heterogeneously distributed to organs and tissues. The distribution patterns after intravenous and oral administration were similar. There

was binding to melanin-containing tissues (pigmented skin areas and eyes) to minor extent in the pigmented rat. There was no evidence of irreversible binding or retention of radioactivity in organs and tissues of rats after oral administration of [^{14}C]BAY 59-7939.

Incubations with microsomes of different species revealed Rhesus monkey and Wistar rat as the most human like animals. Additionally, Beagle dog and NMRI mouse were attributed as human like, too. The morpholino moiety is the main target of oxidative metabolism. Hydroxylation lead to metabolites **M-2** and **M-3**, further oxidation and ring opening to **M-1** was observed to a minor degree.

In human and rat hepatocytes in sandwich culture, metabolite **M-1** was detected as major metabolite. The metabolic pattern in rat hepatocyte sandwich cultures represented the situation in rats *in vivo,* indicating that this is the most valuable *in vitro* model to predict metabolism *in vivo* in man.

BAY 59-7939 exhibited no inhibitory or inductive potential on major CYP isoforms. CYP3A4 is the decisive enzyme for biotransformation of BAY 59-7939 in humans. The high K_m-values for formation of metabolites **M-2** and **M-3** indicate a low affinity of BAY 59-7939 towards P450 enzyme preparations.

The potential for drug-drug CYP3A4 interactions between BAY 59-7939 and a number of drugs (CYP3A4 substrates and inhibitors) that maybe co-administered clinically was explored in CYP interaction studies *in vitro*. Out of the possible potentially interacting compounds, only the strong CYP3A4 inhibitor ketoconazole showed a notable effect on the human microsomal metabolism of BAY 59-7939 at therapeutically relevant concentrations , when co-incubated with BAY 59-7939.

In vivo in rat metabolite **M-1** was detected as major metabolite in urine, bile, and fecal fractions. Approximately 87 % of the dose found in the excreta could be attributed to known structures. The unchanged drug was the main compound in plasma at all investigated time-points. In total, 88 – 97 % of the radioactivity in plasma could be attributed to known structures.

In vivo in dog metabolite **M-1** was detected as major metabolite in feces fractions and as an important metabolite, besides major metabolite **M-4**, in urine fractions. The unchanged drug was the main compound in plasma at all investigated time-points.

The radioactivity in the rat was excreted mainly via the biliary/fecal route. In dogs contributed also the renal route considerably to elimination. The residues remaining in the body of rats seven days after administration were low (approx. 0.2 % of the dose).

4.2.2 Pharmacokinetics after a Single Dose

4.2.2.1 Rat

4.2.2.1.1 Studies with Radiolabeled Compound

[Schwarz TH et al., 2002]

The pharmacokinetics of [^{14}C]BAY 59-7939-radioactivity was studied after intravenous bolus administration and after oral administration to male Wistar rats at doses of 3 mg/kg body weight (b.w.). Additional studies were performed in bile duct-cannulated rats with intraduodenal and intravenous administration of the radiolabeled test compound. The compound was dissolved in a formulation containing PEG 400 and aqua dest.

The extent of absorption of radioactivity was 66.8 % as derived from the studies in BDC-rats with intraduodenal and intravenous administration of [^{14}C]BAY 59-7939. This points at limited oral absorption of BAY 59-7939-radioactivity in rats.

The following pharmacokinetic parameters were derived from the radioactivity (unchanged substance and radioactive metabolites) concentration time data in plasma of intact Wistar rats after administration of [^{14}C]BAY 59-7939 (Table 1).

Table 1: Pharmacokinetics of radioactivity in male Wistar rats after single administration of [14C]BAY 59-7939. Pharmacokinetic parameters calculated from geometric means of 3 male animals per time point.

Dose	[mg/kg]	3	3
Route		i.v.	p.o.
AUC	[mg-eq·h/L]	8.78	4.20
AUC_{norm}	[kg·h/L]	2.82	1.35
CEQ_{max}	[mg-eq/L]	n.c.	2.04
$CEQ_{max,norm}$	[kg/L]	n.c.	0.657
T_{max}	[h]	n.c.	0.25
$T_{1/2app}$	[h]	1.81	1.46
Interval*	[h]	4 – 8	4 - 8
$T_{1/2}$	[h]	18.8	42.1
Interval*	[h]	8 – 48	24 – 72

* = used for regression to determine terminal $t_{1/2}$
n.c. = not calculated

4.2.2.1.2 Studies with Non-labeled Compound

[Bütehorn U, Schwarz TH, 2002

The pharmacokinetics of the unchanged substance was investigated in male Wistar rats after single intravenous bolus injection of 1 and 3 mg/kg and after oral administration of 1, 3 and 10 mg/kg b.w., respectively. The following pharmacokinetic parameters were determined for the unchanged substance (see Table 2 and Table 3, respectively).

Table 2: Pharmacokinetics of BAY 59-7939 after intravenous administration to male Wistar rats. Pharmacokinetic parameters calculated from geometric means of 3 animals per time point.

Dose	[mg/kg]	1	3
AUC	[mg·h/L]	2.27	8.51
AUC_{norm}	[kg·h/L]	2.27	2.84
CL	[L/(h·kg)]	0.440	0.352
V_{ss}	[L/kg]	0.323	0.277
$t_{1/2}$	[h]	0.830	0.935
Interval*	[h]	1-4	4-8

* = used for regression to determine terminal half life

After single intravenous administration of 1 and 3 mg/kg of unlabeled BAY 59-7939, the unchanged compound showed dose-proportional pharmacokinetics. Plasma concentrations decreased to about 1 % of C_{max} after 4 h at both doses. The mean plasma clearance amounted to 0.4 L/(h·kg). Taking the *in*

vitro plasma to blood ratio of 1.68 into account [Kohlsdorfer C], the whole blood clearance is low with 0.7 L/(h·kg).

The volume of distribution (V_{ss}) was moderate, amounting to about 0.3 L/kg.

After single oral administration of 1, 3 and 10 mg BAY 59-7939 per kg b.w. to male Wistar rats, maximum plasma concentrations were rapidly reached at 0.5 h. Thereafter the concentrations decreased with half-lives between 1.2 and 2.3 h in the period up to 8 h post-administration.

Table 3: Pharmacokinetics of BAY 59-7939 after single oral administration to male Wistar rats. Pharmacokinetic parameters calculated from geometric means of 3 animals per time point.

Dose	**[mg/kg]**	**1**	**3**	**10**
Route		p.o.	p.o.	p.o.
AUC	[mg·h/L]	1.49	5.04	14.7
AUC_{norm}	[kg·h/L]	1.49	1.68	1.47
C_{max}	[mg/L]	0.926	3.11	6.01
$C_{max,norm}$	[kg/L]	0.926	1.04	0.601
T_{max}	[h]	0.5	0.5	0.5
$T_{1/2}$	[h]	2.29	1.41	1.19
Interval*	[h]	4-8	4-8	2-8
F	[%]	58.2**	65.6**	57.4**

* = used for regression to determine $t_{1/2}$

** = calculated with the mean AUC_{norm} of 2.56 kg·h/L after 1 and 3 mg/kg i.v.

This half-life roughly approximated that observed after intravenous administration. AUC values increased dose-proportionally. The maximum plasma concentrations increased dose-proportionally from the low to the medium dose group and less than dose-proportionally from the medium to the high dose-group. The absolute bioavailability in fasted male rats was moderate to high (60 %).

The studies with [^{14}C]BAY 59-7939 and non-labeled BAY 59-7939 were performed in different groups of Wistar rats. Somewhat lower AUC_{norm} and $C_{max,norm}$-values for radioactivity in comparison with unchanged substance after oral administration of [^{14}C]BAY 59-7939 or BAY 59-7939 are assumed to be the result of slight differences in the feeding conditions (feed composition; residual feed content in the stomach during administration). Additional studies with intraindividual comparison

of radioactivity and unchanged substance concentration showed, that the AUC of unchanged compound covered approx. 70 % of the radioactivity AUC after oral administration of 3 mg/kg [^{14}C]BAY 59-7939.

4.2.2.2 Dog

4.2.2.2.1. Studies with Labeled Compound

[Schwarz TH et al 2003a]

The pharmacokinetics of radioactivity was studied in female Beagle dogs after a single intravenous short-term infusion (T=0.25 h) of 1.0 mg/kg, and after oral administration of 1.0 mg/kg [^{14}C]BAY 59-7939. The following pharmacokinetic parameters (geometric means and deviations) were determined for radioactivity (unchanged substance and metabolites) (see Table 4).

Table Fehler! Unbekanntes Schalterargument.**: Pharmacokinetics of radioactivity after single administration of [^{14}C]BAY 59-7939 to female Beagle dogs (n=3).**

Dose	**[mg/kg]**	**1**		**1**	
Route		**i.v. inf (T = 0.25 h)**		**p.o.**	
Param.		**Mean Geom.**	**S.D.§ Geom.**	**Mean Geom.**	**S.D.§ Geom.**
AUC	[mg-eq·h/L]	5.38	1.16	5.10	1.10
AUC_{norm}	[kg·h/L]	5.38	1.16	5.10	1.10
CEQ_{max}	[mg-eq/L]	2.71	1.07	1.67	1.27
$CEQ_{max,norm}$	[kg/L]	2.71	1.07	1.67	1.27
t_{max}	[h]	0.25	1	0.572	1.26
$t_{1/2}$	[h]	111	1.56	128	1.14
Interval*	[h]	48 – 168		48 – 168	
f_{abs}**	[%]	n.c.		94.9	1.19

* = used for regression to determine terminal half life
** = fraction absorbed
§ = 1-s interval ranges from mean / S.D. to mean * S.D.

The absorption of radioactivity was high after oral administration of [^{14}C]BAY 59-7939 and amounted to 94.9 % of the dose (estimated from a comparison of the AUC_{norm} for the total radioactivity in plasma after oral and intravenous administration).

4.2.2.2.2. Studies with Non-labeled Compound

[Bütehorn U, Schwarz TH, 2002, Schwarz TH et al 2003a]

The pharmacokinetics of the unchanged substance was investigated in female Beagle dogs after a single intravenous short-term infusion (T = 0.25 h) of 0.3 and 1.0 mg/kg, as well as after oral administration of 0.3, 1.0 and 3.0 mg/kg BAY 59-7939 by gavage in an intra-individual comparison. The following pharmacokinetic parameters (geometric means and standard deviations) were determined for the unchanged substance (Table 5 and Table 6).

After the end of infusion, plasma concentrations decreased within 8 h to about 0.3 % of the C_{max}. In the terminal phase up to 9 h, half-lives of about 1 h were determined. The mean plasma clearance amounted to 0.3 L/(h·kg) corresponding to a low blood clearance of 0.4 L/(h·kg) in the dog, taking an *in vitro* plasma to blood ratio of 1.22 into account [Kohlsdorfer C]. The mean volume of distribution (V_{ss}) was moderate, amounting to 0.4 L/kg.

Table 5: Pharmacokinetics of BAY 59-7939 after intravenous infusion (T > 0.25 h) to female Beagle Dogs (n=3).

Dose	**[mg/kg]**	**0.3**		**1.0**	
Parameters		**Mean Geom.**	**S.D. Geom.**	**Mean Geom.**	**S.D. Geom.**
AUC	[mg·h/L]	1.00	1.35	3.18	1.39
AUC_{norm}	[kg·h/L]	3.34	1.35	3.18	1.39
C_{max}	[mg/L]	0.762	1.26	2.36	1.34
$C_{max,norm}$	[kg/L]	2.54	1.26	2.36	1.34
t_{max}	[h]	n. c.	n. c.		
$t_{1/2}$	[h]	0.952	1.27	0.972	1.03
Interval*	[h]	0.25 - 6		4 - 9	
V_{ss}	[L/kg]	0.402	1.33	0.398	1.31
CL	[L/(h·kg)]	0.300	1.35	0.314	1.39

* = used for regression to determine terminal half life
n.c. = not calculated

After single oral administration of 0.3, 1.0 and 3 mg/kg the maximum plasma concentrations were reached early (between 0.25 and 1 h). C_{max} values increased almost dose-proportionally from 0.3 to 3 mg/kg. The plasma elimination half-lives calculated in the period up to 10 h resulted in values of about 0.9 h and were thus

similar to that found after intravenous administration. Generally, the AUC rose also dose-proportionally in the examined dose range.

However, the AUC after oral administration of radio-labeled [^{14}C] BAY 59-7939 at 1.0 mg/kg was somewhat higher than in the 0.3 and 3.0 mg/kg dose groups. The same observation was made with regard to C_{max}. This was obviously the result of reduced water intake and decreased renal clearance of the animals in the balance studies.

The absolute bioavailability in the dog was moderate to high (60.2 – 86 %, see Table 6).

Table 6: Pharmacokinetics of BAY 59-7939 after oral administration to female Beagle dogs (n=3).

Dose	[mg/kg]	0.3		1.0		3	
Parameters		Mean Geom.	S.D. Geom.	Mean Geom.	S.D. Geom.	Mean Geom.	S.D. Geom.
AUC	[mg·h/L]	0.605	2.04	2.72	1.24	6.03	1.39
AUC_{norm}	[kg·h/L]	2.02	2.04	2.72	1.24	2.01	1.39
C_{max}	[mg/L]	0.254	1.35	1.28	1.22	2.72	1.23
$C_{max,norm}$	[kg/L]	0.848	1.35	1.28	1.22	0.906	1.23
T_{max}	[h]	0.454	1.74	0.572	1.26	0.500	2.00
$T_{1/2}$	[h]	0.876	1.12	0.915	1.42	0.924	1.09
Interval*	[h]	2 – 8		1.5 - 10		3 – 8	
F	[%]	60.4**		86***		60.2**	

* = used for regression to determine terminal half life
** = related to 0.3 mg/kg i.v. infusion
*** = related to 1.0 mg/kg i.v. infusion

The AUC of unchanged BAY 59-7939 covered 59 % of the radioactivity AUC after intravenous infusion of [^{14}C] BAY 59-7939 to Beagle dogs. The corresponding percentage was 53 % after oral administration. The difference is the result of progressive biotransformation of [^{14}C] BAY 59-7939.

4.2.3 Pharmacokinetics after Repeated Administration

No separate studies on pharmacokinetics after repeated administration of BAY 59-7939 were performed. Limited data on pK after repeated administration

can be derived from the exposure determination performed under GLP as part of the toxicity studies. These measurements revealed a slightly higher AUC after repeated administration to rats [Bütehorn U, Renhof M, 2002] and dogs [Bütehorn U, Ruf J, 2002]. This is possibly due to differences in absorption between Day 1 and Week 4 and/or a long lasting absorption of the higher doses used in the studies. Furthermore, it has to been taken into account, that the AUC calculation is based on a limited number of time-points.

Accumulation due to a decreased elimination is less likely (short-half-life and low residual concentrations at 24 h in the therapeutic dose range). Comprehensive data on the exposure achieved in toxicity studies are given in the expert opinion from toxicology.

4.2.4 Tissue Distribution

4.2.4.1 Whole Body Autoradiography

[Steinke W, Kockerols C, 2002]

The qualitative distribution patterns of radioactivity were investigated in rats using whole-body autoradiography.

[^{14}C]BAY 59-7939 was administered at a single oral dose of 3 mg/kg and an intravenous dose of 1 mg/kg body weight to male albino rats (Wistar). Additionally, [^{14}C]BAY 59-7939 was administered orally at a dose of 3 mg/kg to female albino rats (Wistar) and one male pigmented rat (Long Evans). The rats were sacrificed at selected times up to seven days after oral administration.

The qualitative distribution patterns were quite similar by either route of administration and in both sexes. Radioactivity was rather heterogeneously distributed to organs and tissues and also inside of most organs. No penetration across the blood/brain barrier was observed, except a slight uptake of radioactivity in the brain which was found only 5 minutes after intravenous injection. There was no clear evidence for specific affinity of radioactivity for melanin-containing tissues

in the pigmented rat. Compared to the albino rat, only slight enrichments were seen in some (not all) melanin-bearing tissues (eye wall, Harderian gland).

During the period of absorption and main elimination, the distribution of radioactivity was as follows:

Table 7: Tissue distribution of radioactivity in male Wistar rats between 2 - 8 h after oral administration of [14C]BAY 59-7939 as determined qualitatively by whole body autoradiography (selected organs after oral administration of [14C]BAY 59-7939).

Highest exposure	Moderate exposure	Low exposure
Gastrointestinal contents, contents of bile-ducts and urinary bladder	Liver, kidneys, skin, intestinal mucosa, coagulation gland.	Most organs and tissues: e.g. blood, heart, lungs, skeletal muscles, testes, seminal vesicles, salivary and lachrymal glands, lymphatic system, pancreas, thyroid, adrenals, adipose tissues, eye wall > (LOD) brain, spinal cord, bone, eye-lens.

Twenty-four hours after oral administration, highest radioactivity was located in intestinal contents, moderate concentrations in liver and urinary bladder contents. After 7 days, elimination was virtually complete. Moderate to low residual concentrations were still detectable in liver, kidneys, skin, hair follicles, and the gastro-intestinal contents. The radioactivity concentration in all other organs and tissues was below the autoradiographic detection limit.

In conclusion, there was no evidence of irreversible binding or retention of radioactivity in organs and tissues of rats after oral administration of [^{14}C]BAY 59-7939.

4.2.4.2 Quantitative Tissue Distribution Study

[Schwarz et al, 2003b]

The quantitative organ and tissue distribution study was conducted in Wistar rats (=albino rats) and Long Evans rats (=pigmented rats) with dissection method and determination of the radioactivity concentrations with LSC. [^{14}C]BAY 59-7939 was administered at a single oral dose of 3 mg/kg body weight.

In Wistar rats, the maximum radioactivity concentrations were reached between 0.5 and 1 hour post-administration in almost all organs and tissues.

The highest exposure of radioactivity in terms of AUC was obtained for liver (factor 16.3 higher than blood-AUC of 2.0 mg-eq·h/L), urinary bladder (factor 14.6), kidneys (factor 8.1), and pancreas (factor 2.9). The AUC in plasma (AUC: 3.99 mg-eq·h/L) was twice the blood AUC indicating low affinity of radioactivity to blood cells. The prostate gland, seminal vesicle, skin, renal fat, aorta and v. cava showed radioactivity AUC´s in the range between blood and plasma. Lower AUC´s (< 2.0 mg-eq·h/L) were calculated for carcass, compact bone, bone marrow, cartilage, heart, lungs, skeletal muscle, spleen, thyroid gland, parotid gland, submandibular gland, testes and epididymis. By far the lowest exposures were observed for eyes (0.262 mg-eq·h/L), brain (0.149 mg-eq·h/L) and spinal cord (0.167 mg-eq·h/L).

Up to 24 h after administration the radioactivity concentrations had already decreased very close to or below the LOQ in the majority of the investigated organs and tissues. The corresponding half-lives were between 0.9 (renal fat) – 6.5 h (pancreas, submandibular gland). The elimination half-life amounted to 4.6 h in blood. Besides the gastro-intestinal tract with contents, the radioactivity elimination could be observed beyond 24 h post dose only in liver ($t_{1/2}$: 70 h), kidneys ($t_{1/2}$: 155 h), skin ($t_{1/2}$: 102 h), plasma ($t_{1/2}$: 18 h) and the body excl. git ($t_{1/2}$: 59 h). However, terminal elimination took place at very low concentration levels.

The tissue distribution of total radioactivity following single oral administration of [^{14}C]BAY 59-7939 to Long Evans rats was essentially the same for the tissues

measured as was seen in Wistar rats (blood, plasma, liver, kidneys, non-pigmented areas of the skin).

Between 7 and 35 days after administration the radioactivity concentration in eyes and pigmented skin scattered around the detection limit (0.01 – 0.001 mg-eq/L) showing that there was binding to melanin to a minor extent.

4.2.4.3 Protein Binding and Blood Cell/Plasma Distribution

[Kohlsdorfer C and Bütehorn U, Report in preparation, Trial no. 54-56]

The binding of BAY 59-7939 to proteins was determined by the ultrafiltration method *in vitro* in plasma of various animal species and man using radiolabeled [^{14}C]BAY 59-7939 (Table 8).

The extent of protein binding was high and clear species-related differences were evident. The fraction of BAY 59-7939 unbound to plasma proteins (f_u) amounted to 2.8 % in humans (m) at plasma concentrations of approx. 1 mg/L. The f_u was 3.9 % in mouse and thus, very similar to humans. At the same concentration level the f_u was lower in rat with only 0.86 %. In dog (f) the f_u was about twice as much as in humans amounting to 6.6 %. The highest f_u was measured in rabbit with 18.2 %.

Albumin was identified as important binding component in human plasma. Acidic α1-glycoprotein contributed only marginally to the binding of BAY 59-7939 in human plasma.

Table 8: In vitro plasma protein binding of [^{14}C]BAY 59-7939 in different species.

Species	Conc. [mg/L]	f_u* [%]
Human (m)	1.08	2.85
Wistar rat (m)	0.842	0.859
Dog (f)	0.911	6.59
Rabbit (f)	1.12	18.2
CD-1 mouse (m)	1.01	3.9

*fu = fraction unbound

Saturation of protein binding was observed in all species when the plasma concentration of BAY 59-7939 was increased from 25 to 100 mg/L. At plasma concentrations below 25 mg/L the protein binding of BAY 59-7939 was linear in dogs, mice, rats, rabbits, and human. Relevant effective therapeutic plasma concentrations in man are expected in the range of 0.07 to 1 mg/L.

The protein binding was completely reversible.

The ratio C_{plasma}/C_{blood} was between 1.06 and 1.68 for [^{14}C]BAY 59-7939 in the investigated species incl. rat, dog, and man.

4.2.5 Metabolism

4.2.5.1 Metabolism In Vitro

4.2.5.1.1 Species Comparison

[Schmeer K, Weinz C, 2001]

[Weinz C, Löffler T, 2002]

[Weinz C, Report in preparation, 2003]

Incubations of [^{14}C]BAY 59-7939 with liver microsomes from man (mix), Rhesus monkey, Beagle dog, New Zealand rabbit, Wistar rat, CD-1 mouse, and NMRI mouse revealed Rhesus monkey and Wistar rat as the most human like animals. Additionally, Beagle dog and NMRI mouse were attributed as human like, too. Hydroxylation at the morpholino moiety, leading to metabolites **M-2** and **M-3**, was distinguished as major primary phase I biotransformation reaction. Further oxidative opening of the morpholino ring leading to metabolite **M-1** was found to a minor extent.

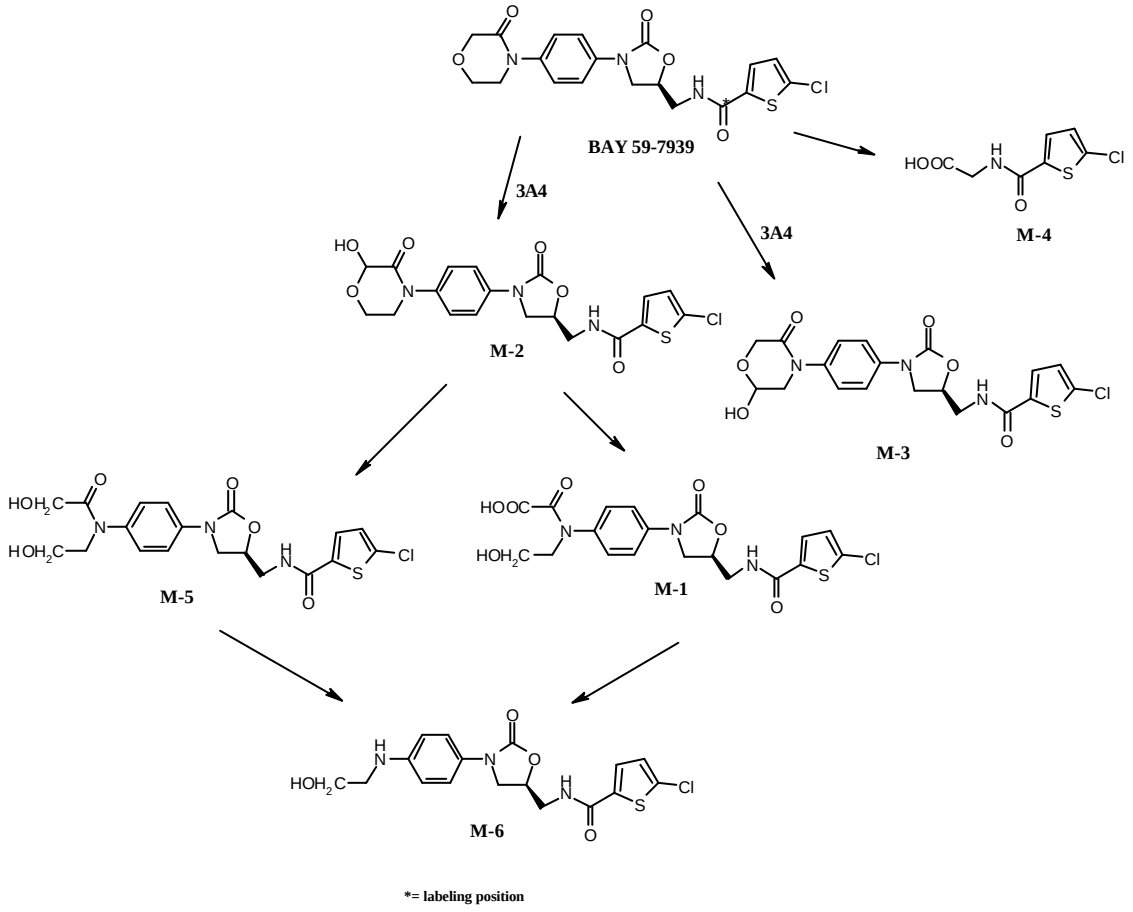
Upon incubation of [^{14}C]BAY 59-7939 with rat and human hepatocytes in sandwich culture **M-1** was detected as major metabolite (65 % and 29 – 49 % of drug turnover in rat and human hepatocytes, respectively, after 48 h in culture), whereas **M-2** and **M-3** were only minor metabolites. Metabolite **M-4** accounted for 13 % and

5 - 9 % of drug turnover in rat and human hepatocytes, respectively, after 48 h in culture.

The *in vitro* metabolic pattern in hepatocytes well resembled the urine, bile, and feces profiles after administration of [^{14}C]BAY 59-7939 to rats and dogs.

Thus, the metabolic pattern in hepatocyte sandwich cultures represented the situation *in vivo,* indicating that this is the most valuable *in vitro* model to predict metabolism *in vivo* in man.

Figure 1: Proposed metabolic pathways observed *in vitro* and *in vivo* (rat, dog)



4.2.5.1.2. CYP Enzyme Involved in Metabolism

[Radtke M, Report in preparation, 2003]

Incubations of [^{14}C]BAY 59-7939 (11 µM) with microsomes of cell lines expressing single human CYPs revealed CYP3A4 capable of forming **M-2** and **M-3** in almost equal amounts. These hydroxylation reactions were also catalyzed by CYP2C8, but to a much lower extent compared with CYP3A4. Determination of kinetic parameters was performed with recombinant CYP3A4 and human liver microsomes. K_m-values of 236.6 µM (recombinant CYP3A4) and 138.6 µM (human liver microsomes) were calculated for **M-3** formation, respectively. The K_m -value for **M-2** formation catalyzed by recombinant CYP3A4 was highly similar (215.5 µM).

These considerably high K_m-values indicate a low affinity of BAY 59-7939 towards P450 enzyme preparations. This finding might be advantageous with respect to the drug-drug interaction potential with inhibitors of CYP3A4.

In conclusion, CYP3A4 is the decisive enzyme for phase I biotransformation in humans.

4.2.5.1.3. CYP Enzyme Inhibitory Potential

[Radtke M, 2001.]

In order to estimate the inhibitory potency of BAY 59-7939 towards eight human cytochrome P450 enzymes, incubations of standard probes with recombinant CYPs were performed in the absence and presence of the compound. No relevant effects on CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4-catalyzed biotransformation were observed as indicated by Ki-estimates higher than 100 µM.

Therefore, clinical drug-drug interactions through inhibition of CYP isoforms by BAY 59-7939 appear to be unlikely.

4.2.5.1.4. CYP Enzyme Induction Potential

[Kern A, Data on file.]

The potential of BAY 59-7939 to induce major human P450 isoforms (CYP1A2, 3A4, 2B6, and 2C19) was investigated in one batch of cultured human hepatocytes. No inductive effects were observed after treatment of human hepatocytes with 0.003 – 3 µg/mL BAY 59-7939.

4.2.5.1.5. CYP3A4 Drug-Drug Interaction Potential with Comedications

[Radtke M, Data on File]

The potential for drug-drug CYP3A4 interactions between BAY 59-7939 and a number of drugs that maybe co-administered clinically was explored in CYP interaction studies *in vitro*. The influence of several CYP3A4 substrates and inhibitors on turnover rates of BAY 59-7939 was tested in incubations with human liver microsomes and compared to turnover rates in control incubations. The CYP3A4 substrates Simvastatin (1, 10, 100 µM), nifedipine (10, 100 µM), and midazolam (10, 100 µM) exhibited no significant impact on BAY 59-7939 turnover at low substrate concentrations, only at the highest tested concentration of 100 µM an influence on turnover was shown. Therapeutic C_{max} for these drugs are in a lower concentration range, e.g. nifedipine 0.09 µM (60 mg p.o.) or midazolam 0.07 µM (7.5 mg p.o.); therefore, drug-drug CYP3A4 interactions *in vivo* at therapeutic levels of these drugs are unlikely.

Influence on BAY 59-7939 turnover rates was investigated for the mechanism-based CYP3A4 inhibitors erythromycin (10, 100 µM) and clarithromycin (10, 50 µM). Without pre-incubation no inhibitory effects and with pre-incubation only slight inhibitory effects on BAY 59-7939 turnover rates were found.

Significant effects on BAY 59-7939 turnover rates *in vitro* were only observed with the strong CYP3A4 inhibitor ketoconazole (0.1, 0.5, 1, 2.5, 5 µM). The IC_{50}-value for ketoconazole on BAY 59-7939 was 0.55 µM. Therapeutic C_{max} for ketoconazole

is 9.5 µM (200 mg p.o.). Ketoconazole exhibited the highest inhibitory effects on BAY 59-7939 drug turnover *in vitro* of all tested drugs.

In summary, only ketoconazole, out of the possible potentially interacting compounds, showed a notable effect on the human microsomal metabolism of BAY 59-7939 at therapeutically relevant concentrations, when co-incubated with BAY 59-7939. The effects of ketoconazole co-administration on BAY 59-7939 pharmacokinetics *in vivo*, meaning influence on exposure and half-life, will be investigated in a clinical interaction study with ketoconazole in man.

4.2.5.2 Metabolism In Vivo

4.2.5.2.1. Rat

[Weinz C, Loeffler T, Gondol D, 2002]

[Weinz C, Loeffler, T, Gondol D, Report in preparation, 2003]

Metabolite profiles in rat plasma were investigated 1, 2, 4, and 8 h following oral administration of 3 mg/kg [^{14}C]BAY 59-7939. The metabolic pattern is shown in Table 9.

Table 9 Metabolic pattern [%] of radioactivity in rat plasma (p.o., arithmetic means, n=3, selected metabolites).

Time [h]	BAY 59-7939	M-1	M-2	M-3
1	87.9	5.3	0.3	1.3
2	83.5	6.0	2.4	2.8
4	69.0	11.1	4.8	5.4
8	78.1	7.7	3.3	3.0

In total, 1, 2, 4, and 8 h after administration approx. 88 – 97 % of the radioactivity in plasma could be attributed to known structures.

Metabolite profiles were investigated in rat urine after different routes of administration. The metabolic pattern is shown in Table 10.

Table 10: Metabolic pattern [%] of radioactivity in urine of rats (arithmetic means, n=5, selected metabolites)

Time [h]	Route	% of dose In sample	% of compound (of dose) in sample				
			BAY 59-7939	M-1	M-2	M-3	M-4
0-48	p.o.	23.6	5.2	9.1	0.7	4.1	3.2
0-48	i.v.	27.7	8.5	9.0	0.9	4.3	3.6
0-24	i.d. (BDC)	17.1	3.1	6.9	0.7	2.9	2.6
0-24	i.v. (BDC)	30.3	8.1	11.9	1.0	3.4	5.4

Independent of the route of administration the metabolic pattern in rat urine was qualitatively similar. After intraduodenal administration to BDC rats lower amounts of the dose were recovered in urine and bile fractions (see below) compared to intravenous administration, reflecting incomplete absorption from the duodenum.

In total, approx. 95 % of radioactivity in the 0 – 48 h urine fractions, corresponding to 22 – 26 % of the dose, could be attributed to known structures after oral and intravenous administration.

The metabolite pattern in rat bile fractions was investigated after intraduodenal and intravenous administration of 3 mg/kg [^{14}C]BAY 59-7939 to BDC rats. The metabolic pattern is shown in Table 11.

Table 11: Metabolic pattern [%] of radioactivity in bile of BDC rats (arithmetic means, n= 5, selected metabolites).

Time [h]	Route	% of dose In sample	% of compound (of dose) in sample			
			BAY 59-7939	M-1	M-2	M-3
0-24	i.d.	34.7	0.6	30.7	0.4	0.3
0-24	i.v.	48.4	0.0	44.4	0.0	0.0

In total, approx. 92 % of the radioactivity in 0 – 24 h bile fractions, corresponding to approx. 44 % of the dose could be attributed to known structures after intravenous administration.

The metabolite pattern in fecal extracts was investigated after intraduodenal and intravenous administration of 3 mg/kg [^{14}C]BAY 59-7939. The metabolic pattern is shown in Table 12.

Table 12: Metabolic pattern [%] of radioactivity in feces of BDC rats (arithmetic means, n= 5, selected metabolites).

Time [days]	Route	% of dose in sample	% of compound (of dose) in sample				
			BAY 59-7939	M-1	M-2	M-3	M-5
1	i.d.	46.4	20.8	6.8	0.2	12.5	5.6
1	i.v.	12.9	2.9	5.5	0.0	2.5	1.9

After intraduodenal administration to BDC rats higher amounts of the dose were recovered in fecal extracts compared to intravenous administration, reflecting incomplete absorption from the duodenum (mainly) in addition to the extrabiliary excretion. About 13 % of the dose were recovered in fecal extracts after intravenous administration, resulting from extrabiliary excretion of BAY 59-7939 related radioactivity. In total, approximately 100 % of the radioactivity in the 0 - 24 h feces extracts, corresponding to approx. 13 % of the dose, could be attributed to known structures after intravenous administration.

In total, approximately 87 % of the dose could be attributed to known structures in the excreta after intravenous administration to BDC rats.

4.2.5.2.2. Dog

[Weinz C, Report in preparation, 2003]

The biotransformation of BAY 59-7939 was investigated in Beagle dogs following oral and intravenous administration of 1 mg/kg [^{14}C]BAY 59-7939.
The metabolic pattern in dog plasma is shown in Table 13.

Table 13: Metabolic pattern [%] of radioactivity in dog plasma (p.o., arithmetic means, n=3, selected metabolites).

Time [h]	BAY 59-7939	M-1	M-2	M-3
0.25	86.7	0.7	0.8	3.6
0.5	85.1	1.5	1.0	3.7
1	78.2	3.1	1.4	4.2
2	72.3	6.2	1.6	3.0
4	69.7	6.5	1.6	3.0
8	52.4	8.5	2.6	3.9
10	47.0	9.5	1.7	5.0

In total, approx. 63 – 92 % of the radioactivity in plasma could be attributed to known structures until 10 h following oral administration.

Approximately 38 - 71 % of the dose was excreted in urine fractions until 7 days following oral administration. Unchanged drug accounted for 6 - 8 % of dose in 0 - 5 day urine fractions. Three major metabolites, **M-1**, **M-3**, **M-4,** accounted for 5 - 12 %, 5 - 9 %, and 12 - 25 % of dose in 0 – 5 day urine fractions.
In total, 81 - 84 % of radioactivity in the 0 - 5 day urine fractions, corresponding to 31 - 57 % of the dose, could be attributed to known structures following oral administration.
Approximately 27 - 59 % of the dose was excreted in feces until 7 days following oral administration. Unchanged drug was only present in traces. Metabolite **M-1**, as main metabolite, accounted for 17 - 32 % of the dose in 0 - 5 day feces extracts. Metabolites **M-2**, **M-3**, **M-5**, and **M-6** figured as minor metabolites.
In total, 82 – 83 % of the radioactivity in 0 - 5 day feces extracts, corresponding to 21 - 48 % of the dose, could be attributed to known structures following oral administration.

Independent of the route of administration the metabolic pattern in dog plasma, urine fractions, and feces extracts were qualitatively similar.

4.2.6 Excretion

[Schwarz TH et al., 2002; Schwarz TH et al. 2003a]

[^{14}C]BAY 59-7939-radioactivity was excreted via the biliary/fecal route as well as via the renal route after intravenous and oral administration to Wistar rats and Beagle dogs (Tables 14 and 15).

In ***intact rats***, 65.5 % of the radioactivity were found in feces and 28.1 % were excreted via urine until Day 7 after intravenous administration. The corresponding values were 66.9 % for feces and 24.7 % for urine after oral administration. Excretion occurred rapidly since >95 % of the dose were excreted within the first day after administration. The recovery amounted to 93.9 % (intravenous) and 91.8 % (oral), respectively of the administered radioactive dose.

Bile duct-cannulated rats excreted fairly the whole radioactive dose within 24 h after intravenous and intraduodenal administration. After intraduodenal administration, 17.1 % of dose were excreted with urine, 34.7 % with bile and 46.4 % of the administered radioactivity were recovered in feces. The fecal excretion of radioactivity reflected incomplete absorption of [^{14}C]BAY 59-7939 and extrabiliary radioactivity excretion as well. In the study with intravenous administration of [^{14}C]BAY 59-7939 to bile duct-cannulated rats, 30.3 % of administered radioactivity were found in urine, 48.4 % in bile and 12.9 % in feces. In BDC rats with intravenous substance administration, the radioactivity in feces reflects the extrabiliary radioactivity excretion. The recovery of radioactivity in the BDC rats was 98.8 % (intraduodenal) and 92.7 % (intravenous) in relation to the administered dose.

The radioactive residues in the animals were low. 24 h after administration, the residues in the animal excl. gastro intestinal tract were 0.421 % (intraduodenal) and 0.755 % (intravenous) of dose in BDC rats. On Day 7 after administration of [^{14}C]BAY 59-7939 there was a further drop to about 0.2 % of dose.

Table 14: Excretion of radioactivity in male Wistar rats [% of dose] after single administration of [^{14}C]BAY 59-7939.

Route / Time		Dose [mg/kg]	Urine	Bile	Feces	Residues**	Recovery
i.v.	7 days	3	28.1	n.a.	65.5	0.224	93.9
p.o.	7 days	3	24.7	n.a.	66.9	0.147	91.8
i.d.*	1 day	3	17.1	34.7	46.4	0.421	98.8
i.v.*	1 day	3	30.3	48.4	12.9	0.755	92.7

*bile duct-cannulated rats (BDC)
**animal excl. gastro intestinal tract
n.a. = not applicable

In *female Beagle dogs*, 40.4 % of the radioactivity were found in feces and 50.7 % were excreted via urine until Day 7 after intravenous administration. The corresponding values were 42.8 % for feces and 52.2 % for urine after oral administration. The recovery amounted to 93.0 % (intravenous) and 97 % (oral), respectively of the administered radioactive dose.

Table 15: Excretion of radioactivity in female Beagle dogs [% of dose] after single administration of [^{14}C]BAY 59-7939.

Route / Time		Dose [mg/kg]	Urine	Feces	Urine Rinse	Balance
i.v.	7 days	1	50.7	40.4	1.83	93.0
p.o.	7 days	1	52.2	42.8	2.03	97.0

n.a. = not applicable

The radiolabel was shown to be very stable against metabolic degradation. Only 0.0248 % of the radioactive dose were expired as $^{14}CO_2$ within 24 h after oral administration of [^{14}C]BAY 59-7939 to male Wistar rats.

4.2.7 Discussion Including Interspecies Comparison

The two species used in pharmacokinetic investigations, rat and dog, showed similar pharmacokinetics. In rats and also in dogs a moderate to high absolute bioavailability (60 % in the rat and 60-86 % in the dog) and relatively short plasma elimination half-life (in rats 0.8 - 0.9 h after i.v. and 1.2 to 2.3 h after p.o., in dogs 0.9 h after i.v. and p.o. administration) was found.

The binding of the substance to plasma proteins was high and species dependent. At plasma concentrations below 25 mg/L the protein binding of BAY 59-7939 was linear. In the concentration range from 25 to 100 mg/L BAY 59-7939 saturation of plasma protein binding was observed. Relevant effective therapeutic plasma concentrations in man are expected in the range of 0.07 to 1 mg/L.

The radioactivity of [^{14}C]BAY 59-7939 was rather heterogeneously distributed to organs and tissues of rat. There was no penetration of the blood-brain barrier and no affinity to melanin-containing tissues was only observed to a minor extend.

Elimination of unchanged substance and excretion of radioactivity occurred rapidly and completely in rats. On Day 7 after intravenous or oral administration the radioactive residues were less than 0.2 % of dose. There was no evidence for any irreversible binding or retention of radioactivity in organs and tissues of rats.

Incubations with liver microsomes from different species revealed Rhesus monkey and Wistar rat as the most human-like animals. Beagle dog and NMRI mouse were attributed as human like, too. In human and rat hepatocytes in sandwich culture, metabolite **M-1** was detected as major metabolite. The metabolic pattern in rat hepatocyte sandwich cultures represented the situation in rats *in vivo,* indicating that this is the most valuable *in vitro* model to predict metabolism *in vivo* in man.

4.3 Toxicology

Key Points:

- Low acute toxicity in rats and mice
- Well tolerated in rats and dogs after subacute administration
- Findings in the subacute studies in rats and dogs can be explained by the pharmacological activity of the drug candidate
- No evidence for genotoxicity
- No objections to initiate clinical studies in man by oral application

4.3.1 Summary

BAY 59-7939 is intended for the prevention of deep venous and arterial thrombosis. Mode of action is a potent inhibition of coagulation factor Xa, preventing the activation of prothrombin to thrombin and thus inhibiting the intrinsic and extrinsic coagulation pathway. The first clinical trials in humans are performed with orally administered BAY 59-7939. In order to justify clinical studies in man, subacute (4-week) toxicity studies were performed in a rodent (rat) and a non-rodent (dog) species. In addition, the toxicologic program included single dose toxicity studies in rats and mice. To investigate a genotoxic potential of BAY 59-7939, two in vitro and one in vivo test for point mutations and clastogenicity were performed.

BAY 59-7939 has a low acute toxicity in rats and mice, i.e. the highest dose which could be technically applied (500 mg/kg per os, 25 mg/kg i.v.) did not cause any mortality.

After repeated administration (4-week studies) BAY 59-7939 was generally well tolerated in rats and dogs. In rats, the only finding probably indicating unspecific toxicity was a slight and transient decrease in body weights (males 200 mg/kg). The changes in the Hquick values which were seen at oral doses = 12.5 mg/kg had to be expected and can be explained by the pharmacological activity of the drug candidate.

The same holds true for the increase of PTT and PT in dogs at 50 mg/kg and above which was seen in the blood samples taken approx. 24 h after administration. This prolongation of the clotting time resulted in an increased bleeding time after invasive blood pressure measurement and subsequently in an increased incidence of hematomas. The slight increase in reticulocytes as well as the increase in spleen weights and in splenic extramedullary hematopoesis are considered as a sequel of these hematomas and blood loss respectively. In the absence of decreases in the number of erythrocytes, hematocrit and hemoglobin they are indicative of a complete compensation of the blood loss. Thus, all findings reported in the 4 week study in dogs can be explained as a consequence of the anti-coagulative effect of the compound and hence secondary to an enhanced pharmocodynamic effect of BAY 59-7939 under the conditions of the toxicological experiment. Since coagulation parameters can be easily monitored in humans, there is no risk for the first administration in human volunteers.

The genotoxic/mutagenic potential of BAY 59-7939 was assessed in two in vitro and one in vivo assays. There was no evidence for a genotoxic potential of BAY 59-7939.

In summary and from a toxicological point of view, there are no objections to initiate clinical studies in man by oral application.

4.3.2 Single dose toxicity

BAY 59-7939 was tested in acute single dose toxicity studies in rats and mice as non-toxic after oral administration and moderately to non-toxic after i.v. administration . Key study data and results are summarized in the tables below.

Table 1: Key study data of the acute toxicity studies in rats and mice

Study Type	Acute Toxicity	GLP: Yes
Guidelines	OECD Guidelines for testing of Chemicals No 401, adopted July 21, 1997	
Bayer Reference	Renhof M (2002), Pharma Report No. 31843	
Batch No.	010507	
Test system	Rats, 5 animals/sex/group, strain Hsd Cpb:WU, oral (gavage)	
	Mice, 5 animals/sex/group, strain Hsd WIN:NMRI oral (gavage) and iv. administration	
Vehicle/s	Oral administration:	Melt coprecipitate in Solutol/water 20/80 , 25 ml/kg
	i.v. administration:	Melt coprecipitate in PEG 400, 5 ml/kg

Table 2: Results of the acute toxicity studies in rats and mice

Species	Route of Administr.	Sex	LD50 [mg/kg bw]	Symptoms
Mouse	p.o.	?	> 500*	-
		?	> 500*	-
	i.v.	?	> 25*	Decreased motility Abdominal position
		?	> 25*	Labored breathing Narrowed palpebral fissure Piloerection
Rat	p.o.	?	> 500*	-
		?	> 500*	-

* due to technical reasons, higher doses could not be administered Repeated dose toxicity

4.3.3 Repeated dose toxicity

BAY 59-7939 was tested in a 4-week oral toxicity study in rats. Key study data, results and toxicokinetic data of the individual study are summarized in the tables below. With the exception of a slight and transient decrease in body weights of high dose males (200 mg/kg) BAY 59-7939 was well tolerated without any treatment-related clinical signs. As expected and as a consequence of its pharmacological activity the drug candidate had an influence on clotting parameters (increase in Hquick at doses of = 12.5 mg/kg). Under the conditions of this study an oral dose of 50 mg/kg was tolerated by rats without toxicity.

Table 3: Key study data of the subacute oral toxicity study in rats

Study Type	Subacute (4-week) oral toxicity study	GLP: Yes
Guidelines	OECD Guidelines for testing of Chemicals No 407, adopted July 27, 1995	
Bayer References	Renhof M, Millar PM (2002) Pharma Report 32303 Bütehorn U, Renhof M (2002) Pharma Report 32333	
Batch No.	010507	
Animals	Rats, strain Hsd Cpb:WU, 10 animals/sex/group	
Dose	0 – 12.5 – 50 – 200 mg/kg/d)	
Administration	Oral (gavage), Vehicle: Solutol/water (v/v 20/80)	
NOAEL	50 mg/kg/d	

Table 4: Noteworthy findings in the subacute oral toxicity study in rats

Endpoint	Findings	Sex	Dose [mg/kg]
Mortality	None		
Clinical signs	None		
Feed consumption	None		
Water consumption	None		
Body weights	Transient decrease in males of 200 mg in 2^{nd} and 3^{rd} week	M	200
Hematology	Increase of Hquick,	M,F	= 12.5
Clinical chemistry	None		
Urinalysis	None		
Liver Tissue	Increase of Glutathion Transferase, Epoxide Hydrolase	M	= 50
Organs weight	Decrease of heart weights	F	200
Gross pathology	None		
Histopathology	None		

Table 5: Summary on exposure in the subacute oral toxicity study in rats at steady state (Week 4)

Sex		Male			Female		
Dose	[mg/kg/d]	12.5	50	200	12.5	50	200
AUC(0-24)	[mg·h/L]	17.7	83.3	156	22.3	99.5	227
$AUC(0\text{-}24)_{norm}$	[kg·h/L]	1.42	1.67	0.779	1.79	1.99	1.14
C_{max}	[mg/L]	6.11	16.6	26.0	6.01	24.6	42.0
$C_{max,norm}$	[kg/L]	0.489	0.332	0.130	0.481	0.493	0.210
$C(24)/C_{max}$	[%]	0.0524	0.223	2.89	0.175	0.426	6.04
R_{A1}	[%]	139	238	152	80.2	146	137
R_{A3}	[%]	140	185	116	98.1	143	137

R_{A1}/R_{A3}: Ratio of accumulation for C_{max} / AUC(0-24). Day 1 = 100 %.

4.3.3.1 Subacute toxicity study in dogs

Table 6: Key study data of the subacute oral toxicity study in dogs

Study Type	Subacute (4-week) oral toxicity study	GLP: Yes
Guidelines	OECD Guidelines for testing of Chemicals No 409, adopted Sept. 21, 1998	
Bayer References	Ruf J (2001), Pharma Report 31548, Buetehorn U, Ruf J (2002), Pharma Report 32348	
Batch No.	010505	
Animals	Dogs, Beagle, Marshall, USA, 3 animals/sex/group	
Dose	0* – 0** – 15 – 50 – 150 mg/kg * tap water control, ** PEG 6000 in tap water	
Administration	PVP coprecipitate of BAY 59-7939 suspended in tap water Oral (gavage)	

Table 7: Noteworthy findings in the subacute oral toxicity study in dogs

Endpoint	Findings	Sex	Dose [mg/kg]
Mortality	None		
Clinical signs	Increased incidence of hematoma after invasive blood pressure measurement	M,F	= 15
	Vomitus	M,F	= 50
	Discolored feces	M, F	150
Feed consumption	None		
Water consumption	None		
Body weights	None		
Hematology	Reticulocytes increased (~ 2-fold)	M, F	≥ 15
Clinical chemistry	Partial thromboplastin time, incr. (2-3-fold)	M F	= 50 = 50
		M	= 50
	Prothrombin time, incr. (2-5fold) (up to 2-fold)	F	= 50
Urinalysis	None		
Organs weight	Spleen, increased	M	= 50
Gross pathology	Increased incidence of subcutaneous hematomas in the inguinal region at the site of blood pressure measurements	M, F	≥ 15
Histopathology	Hematomas described at necropsy were confirmed	M, F	=15
	Spleen: Slight hematopoiesis	M, F	=15

With the exception of occasional vomitus BAY 59-7939 was generally well tolerated in dogs. The increased incidence of subcutaneous hematomas in the inguinal region at the site of blood pressure measurements is a consequence of the prolongation of the clotting time and an increase in bleeding time. These effects can easily be explained by the anti-coagulative activity of the drug. The same is true for the increase of reticulocytes, the increase in spleen weights and the extramedullary hematopoiesis, all of which can be regarded as consequences of the enhanced

pharmocodynamic effect of BAY 59-7939 at the high doses used in the toxicological study.

Table 8: Summary on exposure in the subacute oral toxicity study in dogs at steady state (Week 4), Bütehorn U, Ruf (2002)

Dose [mg/kg]	15	50	150
AUC(0-24) [mg·h/L]	8.91	27.1	37.0
$AUC(0\text{-}24)_{norm}$ [kg·h/L]	0.594	0.542	0.247
C_{max} [mg/L]	2.14	5.33	6.71
$C_{max,norm}$ [kg/L]	0.142	0.107	0.0447
$C(24)/C_{max}$ [%]	0.581	1.79	2.28
R_{A1} [%]	82.4	101	93.4
R_{A3} [%]	92.7	127	136

R_{A1} / R_{A3}: Ratio of accumulation for C_{max} / AUC(0-24). Day 1 = 100

4.3.3.2 Comparison of Exposure in Animals

Data on the systemic exposure to BAY 59-7939 in different animal species at steady state are taken from 4 week toxicological studies (see also corresponding tables for each toxicological study) and summarized in the table below.

Table 9: Overview on systemic exposure at steady state in toxicological studies

Species	**Dose [mg]**	**NOAEL [mg/kg]**	**Total C_{max} [mg/L]**	**Unbound C_{max} [mg/L]**	**Total AUC_{0-24} [mg·h/L]**	**Unbound AUC_{0-24} [mg·h/L]**
Human	30 (tablet)		0.226	0.00644	1.994	0.0568
Rat		50	16.6	0.143	83.3	0.716
Safety ratio to human			**73***	**22***	**42**	**13**
Dog		15**	2.14	0.141	8.91	0.587
Safety ratio to human			**9***	**22***	**4.5**	**10**

Protein binding (free fraction f_u): human: 2.85 %, rat: 0.859 %, dog: 6.59 % (refer to Section A.2.3.2).

* The highest C_{max} in the single dose escalation studies in human volunteers was achieved after administration of 10 mg in solution.
The calculated safety ratios for C_{max}/unbound C_{max} after administration of 10 mg in solution were slightly lower: 62/19 compared to rat, <8/<19 compared to dog.

** due to the inguinal hematomas a sequel of the pharmacological mode of action, a NOAEL could not be defined. Excluding these findings the NOAEL was 15 mg/kg

Differences in the extent of protein binding of BAY 59-7939 between the animal species used in the toxicological studies and man have to be considered in the safety evaluation.

The toxicological relevant fraction of BAY 59-7939 unbound to plasma proteins (f_u) was between 2.9 and 3.4 % in humans at plasma concentrations of 1 mg/L BAY 59-7939. The corresponding fu was lower in rats amounting to 0.7 - 0.9 %

only. Thus, the exposure in terms of C_{max} and AUC obtained in the rat toxicity studies has to be multiplied with the ratio f_u rat vs. humans of 0.2 for the calculation of safety margins.

In dog plasma, the f_u of BAY 59-7939 was 6.6 % at concentrations of 1 mg/L. This would provide an additional safety margin of about 2 for the exposure evaluation with regard to man.

4.3.4 Genotoxicity

BAY 59-7939 was tested in a Salmonella Microsome Test for point mutations and in a Cytogenetics *in vitro* Assay as well as in a Micronucleus Test for clastogenicity. All tests revealed a negative result. Thus BAY 59-7939 is considered as non-genotoxic. The key study data are summarized in the Tables below.

4.3.4.1 Salmonella microsome test

Table 10: Salmonella/Microsome Test

Study Type	Salmonella / Microsome test (Ames Test)	GLP: yes
Guidelines	OECD Guidelines for testing of Chem. No 471, adopt. July 21, 1997	
Bayer Reference	Herbold B (2002), Pharma Report 31770	
Endpoint	Point mutation	
Batch No.	010621	
Test System	Salmonella strains: TA 1535, TA 100, TA 1537, TA 98, TA 102 Incubation: 17 h at 37°C, with and without metabolic activation (S9 Mix)	
Results	Negative	

4.3.4.2 Cytogenetics in vitro assay

Table 11: Cytogenetics in vitro Assay

Study Type	Cytogenetics in vitro	GLP: Yes
Guidelines	OECD Guidelines for testing of Chem. No 473, adopt. July 21, 1997	
Bayer Reference	Herbold B (2001a), study ID T2070546, PH 31537	
Endpoint	Chromosomal aberration	
Batch No.	010621	
Test System	Chinese hamster V79 cells, in vitro	
	Incubation: - 4 h with S9 mix up to 120 µg/ml - 4 h without S9 mix up to 120 µg/ml - 18 h without S9 mix up to 90 µg/ml	
Results	Negative	

4.3.4.3 Micronucleus Test

Table 12: Micronucleus Test

Study Type	Micronucleus Test	GLP: Yes
Guidelines	OECD Guidelines for testing of Chem. No 474, adopt. July 21, 1997	
Bayer Reference	Herbold B (2001b), Pharma Report 31536	
Endpoint	Chromosomal aberration	
Batch No.	010621	
Test System	Male mice, strain Hsd/Win: NMRI, in vivo	
	Administration. i.p., twice, in Cremophor® up to 140 mg/kg	
Results	Negative	

4.3.5 Reproductive toxicity

No data available

4.3.6 Carcinogenicity

No data available

4.3.7 Special Studies

No data available

5. Effects in Humans

Key Points:

- BAY 59-7939 was well-tolerated up to 80 mg after single dose application in healthy volunteers
- Multiple dosing up to 30mg BID (total daily dose 60 mg) for 5 days was well tolerated in healthy subjects
- No drug related serious adverse events were reported
- BAY 59-7939 is rapidly absorbed after oral treatment as solution (C_{max} after approx. 30 min) as well as tablet (C_{max} after 2-4 hours)
- Elimination of BAY 59-7939 from plasma occurred with terminal half-lives of 4.77 to 5.88 hours (day 1) and 5.75 to 9.15 hours (day 8) with no relevant accumulation.
- After multiple doses administered with food, dose proportional increases in AUC and C_{max} were seen up to the highest dose tested (i.e. 30 mg bid).
- Administration of BAY 59-7939 with food (high calorie/high fat meal) resulted in an increase of AUC by 25 %, a delayed absorption by about 1.5 hours and a 40% increase in C_{max}
- Elderly subjects exhibited higher plasma concentrations than young subjects, with mean AUC values being approximately 52 % greater in elderly males, and 39 % higher in elderly females, compared to the young subjects of the same gender.
- Clotting parameters (PT, PTT, Heptest) were effected as mechanistically expected
- No relevant influence on bleeding time was observed neither after single dose nor multiple dose application
- Factor Xa was inhibited in a dose dependent way
- Co-medication with Enoxaparin showed an additive effect on pharmacodynamic parameters. Bleeding time was not affected to a clinically relevant degree.

5.1 Summary

BAY 59-7939 was investigated after single and multiple dose application. The highest dose applied was 80 mg as single dose and 30 mg (BID) as multiple dose for 5 days. The effect of food and the influence of age and gender on the pharmacokinetic and pharmacodynamic profile was investigated after single dose application of 10 mg. Additionally, the influence of enoxaparin on the pharmacodynamic and pharmacokinetic parameters was assessed.

In total 216 healthy volunteers were enrolled in phase I trials with BAY 59-7939. 132 healthy volunteers received BAY 59-7939 as single dose up to 80 mg, while 46 subjects received multiple dose treatments with doses up to 30 mg BID.

No drug related serious adverse events or death were reported in any of the trials and BAY 59-7939 was well-tolerated at all doses tested. In particular no bleeding events were reported at all.

In the single dose escalation trial 96 healthy male subjects were enrolled and 91 completed the study. Of the 5 participants discontinuing, one withdraw consent and 4 were excluded because of protocol violations.

Thirty-eight treatment emergent adverse events were reported by 28 of 91 healthy volunteers. Only 5 of the 38 adverse events were considered to be possibly related to the study medication: two cases of “taste of blood” which occurred after administration of 10 and 80 mg BAY 59-7939. Inspection of the oral cavity and washing out the mouth with clear water did not show any signs or symptoms of bleeding. Additionally both subjects had no unusual prolongation of the clotting parameters or inhibition of Factor Xa. Both events resolved without any actions taken after about 45 and 105 minutes. One additional subject complained of headache. The event resolved after treatment with pain relieve medication. Furthermore two episodes of ecchymosis were observed.

Furthermore no clinically relevant changes of vital signs or ECG were observed within these dose steps. Laboratory tests did not show any clinically relevant changes, there

was especially no increase in bleeding time noted. Both the clotting tests (PT, PTT, Heptest) and Factor Xa inhibition were influenced in a dose dependent way. The pharmacokinetic profile of BAY 59-7939 was as well dose dependent but not dose proportional above 10 mg tablet. Other than this no unexpected findings were observed in this study.

The effect of food on the absorption of BAY 59-7939 was investigated in a cross-over design trial. Ten subjects were enrolled in this study, two dropped out after the first treatment period: one subject withdrew his consent, the other subject was excluded because of an increase in CK.

No drug related adverse events were observed in this study. Only the above mentioned laboratory value (CK) was increased which was considered to be related to non-compliance of the volunteer who was subsequently excluded from the study. Other than this only relevant changes of the clotting parameters were observed which is to be expected in this pharmacologically active compound. Bleeding time was not affected. Likewise, no signs or symptoms of bleeding were observed. Vital signs and ECGs were not affected to a clinically meaningful extend.

A relevant food effect of a high fat high calorie standard meal was seen for all relevant clotting factors. The maximal Factor Xa inhibition as the most important pharmacodynamic marker was increased by 27%. The changes in Factor Xa inhibition were also reflected by prolongation of PT and HepTest. PTT as the least sensitive marker remained nearly unaffected. ATIII and Factor IIa activities were not changed.

With regard to pharmacokinetics, a significant food effect was observed with AUC and C_{max} both showing relevant increases of 24% and 39%, respectively, after administration in the fed state. Time to reach maximal plasma concentration was significantly longer when BAY 59-7939 was administered after the meal.

BAY 59-7939 was well tolerated when administered as an oral tablet with and without a high calorie, high fat breakfast. A considerable food effect was observed on pharmacodynamic and pharmacokinetic parameters.

The effect of age and gender on the pharmacokinetics of BAY 59-7939 was investigated in male and female subjects aged 18-45 years versus male and female subjects age 65-80 years. Pharmacokinetics were similar between males and females. Slight differences in AUC between young males and young females could be attributed to differences in body weight. Elderly subjects exhibited higher plasma concentrations than young subjects, with mean AUC values being approximately 50% greater in elderly males, and 40% higher in elderly females, compared to the young subjects of the same gender.

Factor Xa inhibition appeared to be slightly greater in the elderly, consistent with the observation made with respect to pharmacokinetics. The average inhibition was greater in females than in males . Bleeding times were also assessed in this study. The upper limit of the normal range for this test is 8 minutes. Only 2 subjects had values which exceeded 8 minutes – 1 young male with a bleeding time of 12.7 minutes at 2 hours after dosing, and 1 elderly male with bleeding times of 11 and 14 minutes at 2 and 4 hours after dosing, respectively. There were no consistent age or gender effects observed with regard to bleeding time.

Multiple dose application was investigated at doses up to 30 mg BID for 5 days. The data presented are based on an interim analysis and can not be considered as final. Sixty-eight healthy male subjects aged 18 to 45 years were enrolled. Four of these subjects were enrolled into the study but not treated with the study drug. They were excluded from the analyses. Three subjects discontinued participation in the study prematurely: one subject was withdrawn because of non-compliance on day 8 of treatment, one subject was withdrawn because of pronounced pharmacokinetic response to the drug, and one other subject was withdrawn due to invalid essential data. Therefore sixty-four subjects were included in the safety analysis. There were no serious adverse events or deaths in this study.

Eighty-seven treatment emergent adverse events were reported by 44 of 64 healthy volunteers. Forty-three of these adverse events were considered to be possibly related to the study medication. The majority of the events were considered to be of mild intensity. One subject was found to have relevant increases in liver enzyme tests (GLDH, AST, ALT) after administration of 30 mg BAY 59-7939 BID which may have had a causal relationship to the study drug. However, other than this laboratory tests did not show any clinically relevant changes, there was especially no clinically relevant increase in bleeding time noted. Both clotting tests (PT, PTT, Heptest) and Factor Xa inhibition were influenced by the study medication as expected. No effect of BAY 59-7939 on AT III was observed.

The pharmacokinetic behaviour of the drug after multiple dosing was comparable to the results obtained after single dosing with no change of absorption or elimination kinetics. There was no relevant accumulation seen after once daily dosing as well as after bid and tid dosing. Dose proportional increases in AUC and C_{max} were seen up to the highest dose tested (i.e. 30 mg bid), demonstrating that the decreased bioavailability seen with higher doses in fasted state can be overcome by administration of the drug with food.

Twelve healthy male subjects were enrolled in an interaction study with enoxaparin, two dropped out (one prior to start of the study, one after the first study period). Therefore, ten subjects completed the study.

One serious adverse event was reported which occurred prior to administration of the study drug and was consequently considered to be not related to the study medication. Overall only six treatment emergent adverse events were observed in four subjects. Only four of them were judged to be possibly related to the study drug. All but one adverse event (rhinitis which improved) resolved. No clinically relevant changes of laboratory parameters other than the clotting parameters were observed. Bleeding time was not affected in any of the treatment periods to a clinically relevant extend. Likewise no relevant changes of vital signs or ECG occurred.

After concomitant administration of BAY 59-7939 and enoxaparin an additive effect was observed on anti-Xa. Factor Xa, Heptest, PT, and PTT did not demonstrate an additive effect – these tests showed changes which were comparable to those observed after administration of BAY 59-7939 alone.

In conclusion, BAY 59-7939 was well tolerated when administered as single and multiple oral doses. Intake with food increases the absorption of the compound. Furthermore, the exposure is higher in elderly and in females. The pharmacodynamic parameters show dose dependent increases over the whole dose range tested. No hints for clinically relevant prolonged bleeding exist from the doses tested so far. The half-life is short and steady state is reached after 2-3 days. The information available so far demonstrates that BAY 59-7939 is a well tolerated compound after single and multiple dose (30 mg BID) application. The interaction study with enxoaparin showed a moderate increase of the clotting parameters. (All information on phase I are based on preliminary analysis with data on file)

5.2 Introduction

BAY 59-7939 was investigated in healthy volunteers in basic phase I single and multiple dose escalation trials.

5.3 Clinical Pharmacology

Key Points:
See 5. Effect in humans

5.3.1 Summary

See 5.1 Summary Effect in Humans

5.3.2 Pharmacokinetics (ADME)#

Impact No. 10842

Randomized, single-blind, placebo-controlled, group-comparison (with one cross-over dose step) dose-escalation study in healthy male subjects to investigate the safety, tolerability and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after single oral doses starting with 10 mg of BAY 59-7939 as oral solution or tablet.

After administration of the solution, the plasma concentration time profiles were characterised by a rapid absorption reaching maximal plasma concentrations after about 0.5 h followed by a fairly rapid decline leading to a terminal half-life of 3-4 h. In contrast, after administration of the tablet, a flatter profile was obtained with peak concentrations observed after 2 hours. Whilst the dose normalized C_{max} was reduced by approximately 50 % after administration of the tablet when compared to the solution, the two formulations were comparable in terms of AUC. BAY 59-7939 concentrations increased dose proportionally after administration of the solution and this was also observed in the tablets up to a dose of 10 mg. With the higher tablet doses, less than dose proportional increases in C_{max} and AUC were observed, which were probably due to the low solubility of the drug. The slightly longer terminal half-life is not due to a decreased elimination but is most probably induced by a slow absorption rate (flip-flop kinetics). Further pharmacokinetic parameters are provided in table 1. With the higher dose steps, in addition to plasma kinetics the urinary excretion of unchanged drug has been investigated. In general, about 10-20% of the administered dose have been detected as unchanged BAY 59-7939 in urine. However, based on the reduced bioavailability seen with the higher doses, a fraction of about 40% of the absorbed dose is estimated to be renally excreted in unchanged form.

Table 1: Pharmacokinetic parameter of BAY 59-7939 after administration of a single oral dose [geo. Mean (geo. SD)]

		Step 1		**Step 2**				**Step 3**	
		10 mg solution		**5 mg solution**		**5 mg tablet**		**10 mg tablet**	
		(n=8)		(n=6)		(n=6)		(n=8)	
AUC	[ug*h/l]	997	(1.28)	461	(1.19)	446	(1.26)	1020	(1.16)
AUC_{norm}	[g*h/L]	8366	(1.41)	7734	(1.21)	7479	(1.24)	8766	(1.20)
AUC/D	[h/L]	0.100	(1.28)	0.092	(1.19)	0.089	(1.26)	0.102	(1.16)
C_{max}	[ug/l]	266	(1.28)	119	(1.20)	72.0	(1.22)	141	(1.17)
$C_{max,}$	[g/L]	2231	(1.36)	1991	(1.32)	1208	(1.22)	1211	(1.23)

norm									
C_{max}/D	[1/L]	0.027	(1.28)	0.024	(1.20)	0.014	(1.22)	0.014	(1.17)
t_{max}*	[h]	0.500	(0.25-1.00)	0.625	(0.50-0.75)	1.88	(0.50-4.00)	2.00	(0.50-2.50)
$t_{1/2}$	[h]	4.16	(1.23)	3.25	(1.09)	4.27	(1.28)	9.07	(1.77)
MRT	[h]	5.06	(1.19)	4.62	(1.08)	6.84	(1.26)	11.3	(1.55)
V_z/f	[l/kg]	0.717	(1.21)	0.605	(1.20)	0.823	(1.35)	1.49	(1.83)

		Step 4		**Step 5**		**Step 6**	
		15 mg tablet		**20 mg tablet**		**30 mg tablet**	
		(n=7)		(n=7)		(n=6)	
AUC	[ug*h/l]	1408	(1.32)	1612	(1.42)	1994	(1.19)
AUC_{norm}	[g*h/L]	7446	(1.40)	6369	(1.36)	5578	(1.22)
AUC/D	[h/L]	0.094	(1.32)	0.081	(1.42)	0.066	(1.19)
C_{max}	[ug/l]	176	(1.45)	173	(1.41)	226	(1.21)
$C_{max,norm}$	[g/L]	930	(1.59)	684	(1.38)	632	(1.32)
C_{max}/D	[1/L]	0.012	(1.45)	0.009	(1.41)	0.008	(1.21)
t_{max}*	[h]	1.25	(0.75-4.00)	1.50	(0.50-4.00)	1.25	(0.75-4.00)
$t_{1/2}$	[h]	11.45	(1.51)	7.60	(1.41)	10.8	(2.14)
MRT	[h]	12.9	(1.54)	11.2	(1.29)	14.1	(2.00)
V_z/f	[L/kg]	2.22	(1.74)	1.72	(1.58)	2.79	(2.30)

		Step 7		**Step 8**		**Step 9**	
		40 mg tablet		**60 mg tablet**		**80 mg tablet**	
		(n=8)		(n=7)		(n=7)	
AUC	[ug*h/l]	2412	*(1.22)*	3767	*(1.61)*	3250	*(1.37)*
AUC_{norm}	[g*h/L]	5128	*(1.20)*	4328	*(1.51)*	3238	*(1.31)*
AUC/D	[h/L]	0.060	*(1.22)*	0.063	*(1.61)*	0.041	*(1.37)*
C_{max}	[ug/l]	234	*(1.43)*	350	*(1.10)*	316	*(1.48)*
$C_{max,norm}$	[g/L]	499	*(1.38)*	403	*(1.24)*	315	*(1.36)*
C_{max}/D	[1/L]	0.006	*(1.43)*	0.006	*(1.10)*	0.004	*(1.48)*
t_{max}*	[h]	1.50	*(1.00-*	2.00	*(1.00-*	2.00	*(0.50-*

			4.00)		*4.00)*		*4.00)*
$t_{1/2}$	[h]	8.88	*(1.63)*	15.5	*(2.51)*	16.9	*(1.74)*
MRT	[h]	12.9	*(1.36)*	18.9	*(2.60)*	19.6	*(1.65)*
V_z/f	[L/kg]	2.50	*(1.53)*	5.16	*(1.81)*	7.55	*(1.60)*
Ae_{ur}**	[%]	19.8	*(5.66)*	12.6	*(2.98)*	10.8	*(1.56)*

*t_{max} given as median (min-max)

**arith. Mean (SD)

Impact No. 10846

Randomized, open-label, two-fold cross-over study to investigate the effect of a high fat, high calorie meal on safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 given orally as 2 x 5 mg tablets in 12 healthy male subjects.

A clinically relevant food-effect on the pharmacokinetics of BAY 59-7939 was shown after administration of a high fat, high calorie meal. With t_{max} being delayed by about 1.5h, AUC was increased by about 25% and maximal concentrations were about 40% higher after the meal. Further pharmacokinetic parameters are given in table 2.

From a more detailed investigation of the absorption kinetics it can be concluded, that absorption after administration with food shows a delay of about 1.5h, however is more complete leading to a higher bioavailability after a meal.

Table 2: Pharmacokinetic parameter of BAY 59-7939 after administration of a single oral dose of 10 mg with or without administration of a high fat, high calorie meal [geo. Mean (geo. SD)]

		Fasted (n=9)		**fed** (n=9)	
AUC	[ug*h/l]	895	(1.25)	1115	(1.28)
AUC_{norm}	[g*h/L]	7557	(1.26)	9364	(1.28)
AUC/D	[h/L]	0.090	(1.25)	0.112	(1.28)
C_{max}	[ug/l]	117	(1.30)	164	(1.27)
$C_{max, norm}$	[g/L]	984	(1.33)	1378	(1.27)
C_{max}/D	[1/L]	0.012	(1.30)	0.016	(1.27)
t_{max}*	[h]	2.50	(0.75-4.00)	4.00	(3.00-4.00)
$t_{1/2}$	[h]	6.92	(1.29)	6.06	(1.41)
MRT	[h]	9.38	(1.19)	8.40	(1.08)

Impact No. 10850

Randomized, double-blind, placebo-controlled, group comparison study in healthy young and elderly subjects of both genders to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of BAY 59-7939 after a single 10 mg dose (as 2 x 5 mg tablets).

Initial estimates of the principal pharmacokinetic parameters for each of the 4 subgroups included in this study are presented in table 3. Pharmacokinetics were similar between males and females. Slight differences in AUC between young males and young females could be attributed to differences in body weight. Elderly subjects exhibited higher plasma concentrations than young subjects, with mean AUC values being approximately 52% greater in elderly males, and 39% higher in elderly females, compared to the young subjects of the same gender. The respective changes in C_{max} were 35% for both males and females. No changes in terminal half-life due to age and/or gender were apparent. Statistical evaluation of these data has not been completed at this time.

Table 3: Pharmacokinetic parameter of BAY 59-7939 after administration of a single oral dose of 10 mg in young and elderly females and males [geometric mean]

		Young	Elderly	Young	Elderly
		PPD			
AUC	[µg*h/l]	1220	1852	1338	1859
AUC_{norm}	[kg*h/L]	9.947	13.686	9.090	12.98
AUC/D	(h/L)	0.122	0.185	0.134	0.186
AUC_{0-tn}	[µg*h/l]	1189	1808	1304	1817
C_{max}	[µg/l]	158.1	213.7	224.5	303.6
$C_{max, norm}$	(kg/L)	1.289	1.580	1.524	2.169
$C_{max/D}$	(1/L)	0.0158	0.0214	.0.224	.0.304
T_{max} *	[h]	1.5 (0.5 - 4)	2.5 (1 – 2.5)	2.0 (0.5 – 4)	2.5 (1 – 2.5)
$T_{1/2}$	[h]	9.9	9.4	10.0	8.4

t_{max} given as median (min-max)

Impact No. 10847

Single-centre, randomised, placebo-controlled, single-blind, parallel-group investigation of the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 after multiple dose application of BAY 59-7939 as conventional BAY 59-7939 tablet.

The pharmacokinetic behavior of the drug after multiple dosing was comparable to the results obtained after single dosing. BAY 59-7939 was moderately fast absorbed and no change of absorption kinetics of BAY 59-7939 depending on multiple dose administration was observed within inter-individual variability. Elimination of BAY 59-7939 from plasma occurred with terminal half-lives of 4.77 to 5.88 hours (day 1) and 5.75 to 9.15 hours (day 8) and was not changed after multiple dose administration within inter-individual variability. There was no relevant accumulation seen after once daily dosing as well as after bid and tid dosing, which is in line with the expectations from animal work. In this study, dose proportional increases in AUC and Cmax were seen up to the highest dose tested (i.e. 30 mg bid), demonstrating

that the decreased bioavailability seen with higher doses in fasted state can be overcome by administration of the drug with food. Detailed pharmacokinetic parameter are provided in table 4.

Table 4: Pharmacokinetic parameter of BAY 59-7939 after administration of multiple oral doses at day 1 and day 8 [geo. Mean (geo. SD)]
Dose step 1: 5 mg tablet od

		Day 1 (n=7)		**Day 8** (n=7)	
AUC	[ug*h/l]	512	(1.25)	--	--
AUC_{norm}	[g*h/L]	8032	(1.29)	--	--
AUC/D	[h/L]	0.102	(1.25)	--	--
AUC_{tau}	[µg*h/L]	487	(1.25)	506	(1.22)
$AUC_{tau.norm}$	[g*h/L]	7643	(1.29)	7932	(1.24)
AUC_{tau}/D	[h/l]	0.097	(1.25)	0.101	(1.22)
C_{max}	[ug/l]	74.3	(1.23)	76.4	(1.20)
$C_{max. norm}$	[g/L]	1166	(1.31)	1199	(1.30)
C_{max}/D	[1/L]	0.015	(1.23)	0.015	(1.20)
t_{max}*	[h]	4.00	(2.50-6.00)	3.00	(0.75-6.00)
$t_{1/2}$	[h]	5.36	(1.19)	8.43	(1.37)
MRT	[h]	8.33	(1.21)	8.77	(1.26)
Ra1	[%]	--	--	103	(1.21)
Ra3	[%]	--	--	104	(1.12)
Ra4	[%]	--	--	98.8	(1.11)

* tmax given as median (min-max)

Dose step 2: 5 mg tablet bid

		Day 1, first dose (n=7)		Day 8 (n=7)	
AUC	[ug*h/l]	537	(1.17)		
AUC_{norm}	[g*h/L]	8685	(1.16)		
AUC/D	[h/L]	0.108	(1.17)		
AUC_{tau}	[ug*h/L]	431	(1.19)	459	(1.14)
$AUC_{tau,no}$	[g*h/L]	6959	(1.12)	7411	(1.21)
AUC_{tau}/D	[h/l]	0.086	(1.19)	0.092	(1.14)
C_{max}	[ug/l]	74.6	(1.28)	85.3	(1.19)
$C_{max, norm}$	[g/L]	1205	(1.25)	1379	(1.12)
C_{max}/D	[1/L]	0.015	(1.28)	0.017	(1.19)
t_{max}*	[h]	2.50	(1.00-4.00)	3.00	(1.50-4.00)
$t_{1/2}$**	[h]	4.91	(1.17)	7.02	(1.31)
MRT	[h]	7.88	(1.26)	7.60	(1.23)
Ra1	[%]	--	--	114	(1.27)
Ra3	[%]	--	--	107	(1.23)
Ra4	[%]	--	--	85.3	(1.19)

* tmax given as median (min-max)

** $t_{1/2}$ dose 1 taken from dose 2

Dose step 3: 5 mg tablet tid

		Day 1, first dose (n=7)		**Day 8** (n=6)	
AUC	[ug*h/l]	504	(1.17)	--	--
AUC_{norm}	[g*h/L]	8518	(1.28)	--	--
AUC/D	[h/L]	0.101	(1.17)	--	--
AUC_{tau}	[µg*h/L]	337	(1.20)	557	(1.22)
$AUC_{tau,norm}$	[g*h/L]	5699	(1.18)	9206	(1.32)
AUC_{tau}/D	[h/l]	0.067	(1.20)	0.112	(1.22)
C_{max}	[ug/l]	81.4	(1.16)	124	(1.22)
$C_{max, norm}$	[g/L]	1375	(1.13)	2045	(1.22)
C_{max}/D	[1/L]	0.016	(1.16)	0.025	(1.22)
T_{max}*	[h]	3.00	(0.50-4.00)	2.00	(0.50-4.02)
$t_{1/2}$**	[h]	4.83	(1.37)	5.75	(1.41)
MRT	[h]	7.49	(1.30)	6.27	(1.30)
Ra1	[%]	--	--	146	(1.19)
Ra3	[%]	--	--	160	(1.18)
Ra4	[%]	--	--	114	(1.09)

* t_{max} given as median (min-max)

** $t_{1/2}$ dose 1 taken from dose 3

Dose step 4: 10 mg tablet bid

		Day 1, first dose (n=7)	**Day 8** (n=7)
AUC	[ug*h/l]	816 (1.24)	-- --
AUC_{norm}	[g*h/L]	6400 (1.33)	-- --
AUC/D	[h/L]	0.082 (1.24)	-- --
AUC_{tau}	[µg*h/L]	640 (1.15)	864 (1.20)
$AUC_{tau,norm}$	[g*h/L]	5013 (1.20)	6771 (1.27)
AUC_{tau}/D	[h/l]	0.064 (1.15)	0.086 (1.20)
C_{max}	[ug/l]	114 (1.17)	158 (1.21)
$C_{max, norm}$	[g/L]	892 (1.18)	1239 (1.26)
C_{max}/D	[1/L]	0.011 (1.17)	0.016 (1.21)
T_{max}*	[h]	4.00 (1.00-4.00)	2.98 (1.50-4.00)
$t_{1/2}$**	[h]	5.84 (1.14)	7.63 (1.30)
MRT	[h]	7.86 (1.35)	7.10 (1.16)
Ra1	[%]	-- --	139 (1.23)
Ra3	[%]	-- --	135 (1.15)
Ra4	[%]	-- --	106 (1.16)

* t_{max} given as median (min-max)

** $t_{1/2}$ dose 1 taken from dose 2

Dose step 5: 20 mg tablet bid

		Day 1, first dose (n=7)	**Day 8** (n=7)
AUC	[ug*h/l]	2014 (1.28)	-- --
AUC_{norm}	[g*h/L]	8240 (1.22)	-- --
AUC/D	[h/L]	0.101 (1.28)	-- --
AUC_{tau}	[µg*h/L]	1608 (1.29)	1899 (1.27)
$AUC_{tau,norm}$	[g*h/L]	6578 (1.22)	7767 (1.20)
AUC_{tau}/D	[h/l]	0.080 (1.29)	0.095 (1.27)
C_{max}	[ug/l]	278 (1.28)	318 (1.20)
$C_{max, norm}$	[g/L]	1136 (1.20)	1301 (1.17)
C_{max}/D	[1/L]	0.014 (1.28)	0.016 (1.20)
T_{max}*	[h]	3.00 (2.50-4.00)	2.50 (0.50-4.00)
$t_{1/2}$**	[h]	5.88 (1.15)	8.15 (1.52)
MRT	[h]	8.10 (1.13)	8.50 (1.23)
Ra1	[%]	-- --	115 (1.12)
Ra3	[%]	-- --	118 (1.13)
Ra4	[%]	-- --	94.3 (1.15)

* t_{max} given as median (min-max)

** $t_{1/2}$ dose 1 taken from dose 2

Dose step 7: 30 mg tablet bid

		Day 1, first dose (n=8)	**Day 8** (n=7)
AUC	[ug*h/l]	2565 (1.20)	-- --
AUC_{norm}	[g*h/L]	6911 (1.25)	-- --
AUC/D	[h/L]	0.086 (1.20)	-- --
AUC_{tau}	[µg*h/L]	2024 (1.16)	2728 (1.16)
$AUC_{tau,norm}$	[g*h/L]	5453 (1.19)	7239 (1.20)
AUC_{tau}/D	[h/l]	0.067 (1.16)	0.091 (1.16)
C_{max}	[ug/l]	383 (1.19)	452 (1.11)
$C_{max, norm}$	[g/L]	1032 (1.20)	1199 (1.13)
C_{max}/D	[1/L]	0.013 (1.19)	0.015 (1.11)
t_{max}*	[h]	3.00 (2.50-4.00)	3.02 (1.50-4.00)
$t_{1/2}$**	[h]	5.75 (1.21)	9.15 (1.80)
MRT	[h]	8.10 (1.19)	8.94 (1.26)
Ra1	[%]	-- --	123 (1.11)
Ra3	[%]	-- --	139 (1.21)
Ra4	[%]	-- --	110 (1.24)

* t_{max} given as median (min-max)

** $t_{1/2}$ dose 1 taken from dose 2

Impact No. 10848

Single dose, non-blinded, randomized, non-placebo-controlled crossover study to investigate the potential influence of 40 mg of Enoxaparin on the safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 and vice versa in healthy, male subjects

Plasma concentration time profiles for BAY 59-7939 after oral application of 10 mg BAY 59-7939 either alone or together with 40 mg Enoxaparin s.c. were proven to be virtually identical. Accordingly, no changes in the resulting PK parameter for BAY 59-7939 were detected (ref to table 5). AUC, C_{max} and $t_{1/2}$ were not changed at all, the marginal difference in t_{max} (2.75 vs 4 h) is judged to

be not clinically relevant. Thus, no influence of Enoxaparin co-administration on pharmacokinetics of BAY 59-7939 was detectable.

Table 5: Pharmacokinetic parameter for BAY 59-7939 after oral application of 10 mg either alone or together with 40 mg Enoxaparin s.c. [geo. mean (geo. SD)]

		BAY 59-7939 alone		**BAY 59-7939 + Enoxaparin**	
		(n = 11)		**(n = 10)**	
		geo.mean	**geo.SD**	**geo.mean**	**geo.SD**
AUC	**[ug*h/l]**	956	(1.33)	957	(1.31)
AUC_{norm}	**[kg*h/L]-3**	7420	(1.32)	7422	(1.30)
AUC/D	**[h/L]**	0.096	(1.33)	0.096	(1.31)
C_{max}	**[ug/l]**	123	(1.22)	119	(1.38)
$C_{max, norm}$	**[kg/L]-3**	953	(1.22)	923	(1.37)
$C_{max/D}$	**[1/L]**	0.012	(1.22)	0.012	(1.38)
t_{max*}	**[h]**	4.00	(1.25-4.02)	2.75	(0.75-4.08)
$t_{1/2}$	**[h]**	11.3	(1.32)	11.7	(1.59)

* t_{max} given as Median (min-max)

5.3.3. Pharmacodynamic effects

Impact No. 10842

Randomized, single-blind, placebo-controlled, group-comparison (with one cross-over dose step) dose-escalation study in healthy male subjects to investigate the safety, tolerability and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after single oral doses starting with 10 mg of BAY 59-7939 as oral solution or tablet.

In accordance with the pharmacological profile of BAY 59-7939 clotting parameters PT, PTT, Heptest, and Factor Xa inhibition were assessed as

pharmacodynamic surrogate parameters. As expected PT, PTT and Heptest showed a prolongation, for PT up to a factor of 2.8. Inhibition of Factor Xa activity was observed up to 75% in individual volunteers. For all parameters a dose dependent prolongation/increase in inhibition was observed. Selected results on individual clotting parameters and Factor Xa inhibition are given in table 1-4.

Impact No. 10846

Randomized, open-label, two-fold cross-over study to investigate the effect of a high fat, high calorie meal on safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 given oral as 2 x 5 mg tablets in 12 healthy male subjects.

A relevant food effect of a high fat high calorie standard meal was seen for the clotting tests PT, Heptest, and Factor Xa inhibition. The maximal Factor Xa inhibition as the major pharmacodynamic marker was increased by 27% (see table 1-4). The changes in Factor Xa inhibition were also reflected by the prolongation increases of PT and HepTest (both around 10%; see table). PTT which is the least sensitive marker remained unaffected.

Impact No. 10850

Randomized, double-blind, placebo-controlled, group comparison study in healthy young and elderly subjects of both genders to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of BAY 59-7939 after a single 10 mg dose (as 2 x 5 mg tablets).

Changes in the pharmacodynamic parameters, Factor Xa inhibition, PT, PTT, and Heptest consistent with the mechanism of action of BAY 59-7939 were seen, and are presented in Tables 1 – 4. There appeared to be a slightly greater degree of Factor Xa inhibition in the elderly, consistent with the observations made with respect to pharmacokinetics. Also, within each age group the average inhibition was greater in females than in males. The mean maximal changes seen with the

other parameters were an approximate 2-fold increase in PT and Heptest values, and about a 40% increase in mean PTT.

Impact No. 10847

Single-centre, randomised, placebo-controlled, single-blind, parallel-group investigation of the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 after multiple dose application of BAY 59-7939 as conventional BAY 59-7939 tablet

In accordance with the pharmacological profile of BAY 59-7939 clotting parameters PT, PTT, Heptest, and Factor Xa inhibition were assessed as pharmacodynamic surrogate parameters. As expected PT, PTT and Heptests were prolonged. Selected results on individual clotting parameters and Factor Xa inhibition are given in table 1-4.

Table 1 Factor Xa inhibition [%]: Maximal mean changes from

Dose/ Formulation	N	Mean change from baseline/SD	Range
Results from study Impact 10842, "single dose escalation" parallel group dose steps			
Placebo solution	3	-5.1 / 6.5	-12 to 1.1
Placebo tablet	12	-4.3 / 3.2	-9 to 0
10 mg solution	8	53 / 7	46 to 65
10 mg (2x5 mg tablet)	8	33 / 7	24 to 43
15 mg (3x5 mg tablet)	7	41 / 9	25 to 53
15 mg (3x5 mg tablet)	7	35 / 10	23 to 48
30 mg (6x5 mg tablet)	6	38 / 9	27 to 50
40 mg (6x5 mg tablet)	8	46 / 13	22 to 60
60 mg (6x5 mg tablet)	7	58 / 6	45 to 63

80 mg (6x5 mg tablet)	6	60 / 11	43 to 75
Results from study Impact 10842, "single dose escalation" crossover dose step			
Placebo solution	4	-4.3 / 2.7	-8.3 to –2.0
Placebo tablet	4	-1.1 / 4.7	-8.1 to 2.2
5 mg solution	6	30 / 5	23 to 37
5 mg tablet	6	20 / 5	14 to 29
Results from study Impact 10846, "food effect"			
10 mg (2x5 mg tablet) fasted	9	33	18 to 41
10 mg (2x5 mg tablet) fed	9	42	34.to 51
Results from study Impact 10850, "age and gender"			
10 mg (2x5 mg tablet) young male	9	40	(29 to 52)
10 mg (2x5 mg tablet) elderly male	9	50	(28 to 63)
10 mg (2x5 mg tablet) young female	9	47	(35 to 60)
10 mg (2x5 mg tablet) elderly female	9	58	(48 to 63)
Results from study Impact 10847 "multiple dose escalation"			
5 mg OD day 0	7	20	7 to 25
5 mg OD day 5	7	16	4 to 25
5 mg BID day 0	7	20	8 to 32
5 mg BID day 5	7	22	5 to 32
5 mg TID day 0	7	20	13 to 28

5 mg TID day 5	6	25	13 to 36
10 mg BID day 0	7	32	28 to 42
10 mg BID day 5	7	39	29 to 46
20 mg BID day 0	7	54	45 to 66
20mg BID day 5	7	51	35 to 62
30 mg BID day 0	8	68	60 to 74
30 mg BID day 5	7	66	47 to 76

Table 2 PT (times of individual baseline): Mean changes from baseline

Dose/ Formulation	N	Mean change from baseline/SD	Range
Results from study Impact 10842, "single dose escalation" parallel group dose steps			
Placebo solution	3	1.0 / 0.02	1.0 to 1.0
Placebo tablet	12	1.02/ 0.05	0.9 to 1.1
10 mg solution	8	1.9 / 0.3	1.3 to 2.5
10 mg (2x5 mg tablet)	8	1.3 / 0.1	1.1 to 1.5
15 mg (3x5 mg tablet)	7	1.5 / 0.17	1.3. to 1.7
20 mg (4x5 mg tablet)	7	1.5 / 0.2	1.3 to 2.0
30 mg (6x5 mg tablet)	6	1.7 / 0.1	1.6 to 2.01
40 mg (6x5 mg tablet)	8	1.7 / 0.2	1.7 to 2.0
60 mg (6x5 mg tablet)	7	2.05 / 0.3	1.5 to 2.4

80 mg (6x5 mg tablet)	6	2.08 / 0.4	1.6 to 2.8
Results from study Impact 10842, "single dose escalation" crossover dose steps			
Placebo solution	4	1.0 / 0.01	1.0 to 1.0
Placebo tablet	4	1.01 / 0.03	1.0 to 1.0
5 mg solution	6	1.5 / 0.11	1.3 to 1.6
5 mg tablet	6	1.2 / 0.09	1.1 to 1.3
Results from study Impact 10846, "food effect"			
10 mg (2x5 mg tablet) fasted	9	1.44	(1.30 to 1.52)
10 mg (2x5 mg tablet) fed	9	1.53	(1.37 to 1.72)
Results from study Impact 10850, "age and gender"			
10 mg (2x5 mg tablet) young male	9	1.69	1.41 – 1.99
10 mg (2x5 mg tablet) elderly male	9	1.95	1.51 – 2.48
10 mg (2x5 mg tablet) young female	9	1.90	1.59 – 2.38
10 mg (2x5 mg tablet) elderly female	9	2.37	1.79 – 3.00
Results from study Impact 10847 "multiple dose escalation"			
Placebo	6	1.03 / 0.04	0.99 to 1.08
Placebo	6	1.01 / 0.04	0.96 to 1.06
5 mg OD day 0	7	1.18 / 0.08	1.05 to 1.28
5 mg OD day 5	7	1.22 / 0.06	1.10 to 1.26
5 mg BID day 0	7	1.21 / 0.05	1.12 to 1.27

5 mg BID day 5	7	1.21 / 0.09	1.09 to 1.31
5 mg TID day 0	7	1.24 / 0.06	1.2 to 1.3
5 mg TID day 5	6	1.37 / 0.11	1.2 to 1.5
10 mg BID day 0	7	1.38 / 0.09	1.2 to 1.5
10 mg BID day 5	7	1.55 / 0.07	1.5 to 1.7
20 mg BID day 0	7	1.97 / 0.29	1.7 to 2.6
20 mg BID day 5	7	2.08 / 0.33	1.6 to 2.7
30 mg BID day 0	8	2.37 / 0.27	2.0 to 2.7
30 mg BID day 5	7	2.62 / 0.27	2.4 to 3.1

Table 3: PTT [times of individual baseline]: Mean changes from baseline

Dose/ Formulation	N	Mean change from baseline/SD	Range
Results from study Impact 10842, "single dose escalation" in parallel group dose steps			
Placebo solution	3	1.0 / 0.0	1.0 to 1.0
Placebo tablet	12	1.0/ 0.05	0.9 to 1.1
10 mg solution	8	1.5 / 0.1	1.2 to 1.7
10 mg (2x5 mg tablet)	8	1.3 / 0.05	1.2 to 1.4
15 mg (3x5 mg tablet)	7	1.3 / 0.06	1.3 to 1.4
20 mg (4x5 mg tablet)	7	1.3 / 0.09	1.3 to 1.5
30 mg (6x5 mg tablet)	6	1.74/ 0.05	1.3 to 1.5
40 mg (6x5 mg tablet)	8	1.4 / 0.1	1.2 to 1.5
60 mg (6x5 mg tablet)	7	1.5 / 0.08	1.4 to 1.7

80 mg (6x5 mg tablet)	6	1.5 / 0.1	1.4 to 1.7
Results from study Impact 10842, "single dose escalation" in crossover dose steps			
Placebo solution	4	0.99 / 0.02	1.0 to 1.0
Placebo tablet	4	1.03 / 0.02	1.0 to 1.0
5 mg solution	6	1.3 / 0.04	1.2 to 1.3
5 mg tablet	6	1.2 / 0.04	1.1 to 1.2
Results from study Impact 10846, "food effect"			
10 mg (2x5 mg tablet) fasted	9	1.31	(1.21 to 1.38)
10 mg (2x5 mg tablet) fed	10	1.31	(1.10 to 1.36)
Results from study Impact 10850, "age and gender"			
10 mg (2x5 mg tablet) young male	9	1.39	1.16 – 1.68
10 mg (2x5 mg tablet) elderly male	9	1.44	1.02 – 1.57
10 mg (2x5 mg tablet) young female	9	1.40	1.19 – 1.56
10 mg (2x5 mg tablet) elderly female	9	1.47	1.27 – 1.63
Results from study Impact 10847 "multiple dose escalation"			
Placebo Day 0	6	1.02 / 0.02	0.99 to 1.04
Placebo Day 5	6	1.00 / 0.04	0.91 to 1.05
5 mg OD day 0	7	1.21 / 0.06	1.13 to 1.29
5 mg OD day 5	7	1.19 / 0.05	1.10 to 1.29
5 mg BID day 0	7	1.15 / 0.06	1.03 to 1.2
5 mg BID day 5	7	1.18 / 0.04	1.11 to 1.24

5 mg TID day 0	7	1.18 / 0.05	1.10 to 1.20
5 mg TID day 5	6	1.22 / 0.08	1.10 to 1.30
10 mg BID day 0	7	1.29 / 0.05	1.20 to 1.40
10 mg BID day 5	7	1.37 / 0.07	1.30 to 1.50
20 mg BID day 0	7	1.67 / 0.43	1.40 to 2.60
20 mg BID day 5	7	1.55 / 0.10	1.40 to 1.70
30 mg BID day 0	8	1.65 / 0.08	1.5 to 1.80
30 mg BID day 5	7	1.70 / 0.13	1.50 to 1.90

Table 4: Heptest [times of change from baseline]: Mean changes from baseline

Dose/ Formulation	N	Mean change from baseline/SD	Range
Results from study Impact 10842, "single dose escalation" in parallel group dose steps			
Placebo solution	3	1.0 / 0.0	1.0 to 1.0
Placebo tablet	12	1.0/ 0.05	0.9 to 1.1
10 mg solution	8	1.5 / 0.1	1.2 to 1.7
10 mg (2x5 mg tablet)	8	1.3 / 0.05	1.2 to 1.4
15 mg (3x5 mg tablet)	7	1.3 / 0.06	1.3 to 1.4
20 mg (4x5 mg tablet)	7	1.3 / 0.09	1.3 to 1.5
30 mg (6x5 mg tablet)	6	1.7/ 0.05	1.3 to 1.5
40 mg (6x5 mg tablet)	**8**	1.8 / 0.23	1.6 to 2.2
60 mg (6x5 mg tablet)	7	2.3 / 0.3	1.9 to 2.7

80 mg (6x5 mg tablet)	6	2.4 / 0.58	1.9 to 3.4
Results from study Impact 10842, "single dose escalation" in crossover dose steps			
Placebo solution	4	0.99 / 0.02	1.0 to 1.0
Placebo tablet	4	1.03 / 0.02	1.0 to 1.0
5 mg solution	6	1.3 / 0.04	1.2 to 1.3
5 mg tablet	6	1.2 / 0.04	1.1 to 1.2
Results from study Impact 10846, "food effect"			
10 mg (2x5 mg tablet) fasted	9	1.31	(1.21 to 1.38)
10 mg (2x5 mg tablet) fed	10	1.31	(1.10 to 1.36)
Results from study Impact 10850, "age and gender"			
10 mg (2x5 mg tablet) young male	9	1.80	1.60 – 2.07
10 mg (2x5 mg tablet) elderly male	9	2.08	1.76 – 2.62
10 mg (2x5 mg tablet) young female	9	1.84	1.61 – 2.07
10 mg (2x5 mg tablet) elderly female	9	2.10	1.87 – 2.38
Results from study Impact 10847 "multiple dose escalation"			
Placebo Day 0	6	1.02 / 0.02	0.99 to 1.04
Placebo Day 5	6	1.00 / 0.04	0.91 to 1.05
5 mg OD day 0	7	1.21 / 0.06	1.13 to 1.29
5 mg OD day 5	7	1.19 / 0.05	1.10 to 1.29
5 mg BID day 0	7	1.15 / 0.06	1.03 to 1.2
5 mg BID day 5	7	1.18 / 0.04	1.11 to 1.24

5 mg TID day 0	7	1.5 / 0.1	1.3 to 1.8
5 mg TID day 5	6	1.7 / 0.1	1.5 to 1.8
10 mg BID day 0	7	1.5 / 0.1	1.3 to 1.7
10 mg BID day 5	7	1.7 / 0.1	1.6 to 1.9
20 mg BID day 0	7	2.2 / 0.3	1.9 to 2.7
20 mg BID day 5	7	2.2 / 0.3	1.8 to 2.8
30 mg BID day 0	8	2.6 / 0.1	2.4 to 3.0
30 mg BID day 5	7	2.7 / 0.1	2.3 to 2.9

5.3.4. Safety/Tolerability

Impact No. 10842

Randomized, single-blind, placebo-controlled, group-comparison (with one cross-over dose step) dose-escalation study in healthy male subjects to investigate the safety, tolerability and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after single oral doses starting with 10 mg of BAY 59-7939 as oral solution or tablet.

Ninety-six healthy male subjects aged 18 to 45 years were enrolled who were at least 10 hours fasting prior to drug administration. Five of them discontinued participation in the study prematurely: one subject withdrew his consent, four subjects were excluded because of protocol violations. Therefore ninety-one subjects completed the study.

Thirty-eight treatment emergent adverse events were reported by 28 of 91 healthy volunteers. Only 5 of the 38 adverse events were considered to be possibly related to the study medication: two cases of “taste of blood” which occurred after administration of 10 and 80 mg BAY 59-7939. Inspection of the oral cavity and washing out the mouth with clear water did not show any signs or symptoms

of bleeding. Additionally both subjects had no unusual prolongation of the clotting parameters or inhibition of Factor Xa. Both events resolved without any actions taken after about 45 and 105 minutes. One additional subject complained of headache. The event resolved after treatment with pain relieve medication.

Impact No. 10846

Randomized, open-label, two-fold cross-over study to investigate the effect of a high fat, high calorie meal on safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 given oral as 2 x 5 mg tablets in 12 healthy male subjects.

Ten subjects were enrolled in this study, two subjects dropped out. The reasons for drop out was withdrawal of consent and exclusion from the trial due to high CK values after the wash-out period.

Impact No. 10850

Randomized, double-blind, placebo-controlled, group comparison study in healthy young and elderly subjects of both genders to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of BAY 59-7939 after a single 10 mg dose (as 2 x 5 mg tablets).

Five subjects (14%) on active drug and one subject (8%) on placebo reported an adverse event. The most common event in the drug treatment groups was headache, which was reported by 2 elderly females, and 1 young female. None of the males on active drug reported an adverse event. There were no serious adverse events.

Mean bleeding time values in the BAY 59-7939-treated subjects were slightly higher than in the placebo-treated subjects, but still within the normal range. Only two subjects had bleeding times that exceeded 8 minutes (the upper limit of normal for this methodology) – a young male had a bleeding time of 12.2 minutes at 2 hours post-dose; and an elderly male had bleeding times of 11 and 14 minutes at 2 and 4 hours post-dose, respectively. Mean bleeding times in the drug-treated groups at 4 hours post-dose (approximate peak effect) compared to pre-dose values are shown in Table 1. Elderly males had the most prolonged

mean bleeding times relative to baseline, with a 60% increase. However, the mean value was still well within the normal range.

Impact No. 10847

Single-centre, randomised, placebo-controlled, single-blind, parallel-group investigation of the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 after multiple dose application of BAY 59-7939 as conventional BAY 59-7939 tablet

Sixty-eight healthy male subjects aged 18 to 45 years were enrolled. Four of these subjects were enrolled into the study but not treated with the study drug. They were excluded from the analyses. Three subjects discontinued participation in the study prematurely: one subject was withdrawn because of non-compliance on day 8 of treatment, one subject was withdrawn because of pronounced pharmacokinetic response to the drug, and one other subject was withdrawn due to invalid essential data. Therefore sixty-four subjects were included in the safety analysis. There were no serious adverse events or deaths in this study.

Eighty-seven treatment emergent adverse events were reported by 44 of 64 healthy volunteers. Forty-three of these adverse events were considered to be possibly related to the study medication. The majority of the events were considered to be of mild intensity. One subject was found to have relevant increases in liver enzyme tests (GLDH, AST, ALT) after administration of 30 mg BAY 59-7939 BID which may have a causal relationship to the study drug. However other than this laboratory tests did not show any clinically relevant changes, there was especially no clinically relevant increase in bleeding time noted. Both Clotting tests (PT, PTT, Heptest) and Factor Xa inhibition were influenced by the study medication as expected. No effect of BAY 59-7939 on AT III was observed.

Impact 10848

Single dose, non-blinded, randomized, non-placebo-controlled crossover study to investigate the potential influence of 40 mg of Enoxaparin on the safety,

tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 and vice versa in healthy, male subjects

Twelve subjects were enrolled in this study, however only 10 of them completed the trial. One subject was withdrawn after the second study period because of non-compliance, the other subject experienced an myocardial infarction after the screening procedure but prior to start of the study and was consequently withdrawn from the study. This event was judged to be serious without relation to the study medication.

Table 1 Bleeding time (seconds)

Dose/ Formulation	N	Mean bleeding time/SD	Range
Results from study Impact 10842, "single dose escalation"			
Placebo solution Predose Post 1st dose at 4h	3	 80.0 / 16.1 70.7 / 3.1	 65 to 97 68 to 74
Placebo tablet Predose Post 1st dose at 4h	12	 88.9 / 16.3 66.7 / 13.1	 64 to 114 42 to 88
10 mg solution Predose Post 1st dose at 4h	8	 86.1 / 22.7 70.5 / 10.5	 52 to 120 54 to 85
10 mg (2x5 mg tablet) Predose Post 1st dose at 4h	8	 121.8/ 40.6 78.0 / 14.4	 55 to 173 58 to 96
15 mg (3x5 mg tablet) Predose Post 1st dose at 4h	7	 57.3 / 15.4 72.6 / 12.9	 45 to 85 52 to 85
20 mg (4x5 mg tablet) Predose Post 1st dose at 4h	7	 80.1 / 10.2 84.7 / 14.4	 67 to 97 67 to 111
30 mg (6x5 mg tablet) Predose Post 1st dose at 4h	6	 57.0 / 22.1 44.8 / 8.1	 33 to 85 35 to 55

40 mg (8x5 mg tablet) Predose Post 1st dose at 4h	8	 65.5 / 11.9 113.1 / 41.4	 47 to 86 52 to 167
60 mg (12x5 mg tablet) Predose Post 1st dose at 4h	7	 61.1 / 6.1 77.0 / 15.3	 52 to 68 63 to 109
80 mg (16x5 mg tablet) Predose Post 1st dose at 4h	6	 81.2 / 12.1 82.2 / 10.2	 74 to 105 73 to 96
Results from study Impact 10846, "food effect"			
10 mg (2x5 mg tablet) fasted Predose Post 1st dose at 4h	 9	 65 / 15.7 77.9 / 9.5	 50 to 99 69 to 94
10 mg (2x5 mg tablet) fed Predose Post 1st dose at 4h	 10 9	 67.8 / 13.3 80.9 / 15.9	 52 to 97 60 to 109

Results from study Impact 10850, "age and gender"			
10 mg (2x5 mg tablet) young male Predose Post 1st dose at 4h	12	 175/71 206/72	 75 to 300 * 120 to 313
10 mg (2x5 mg tablet) elderly male Predose Post 1st dose at 4h	12	 205/102 328/235	 68 to 360 54 to 840
10 mg (2x5 mg tablet) young female Predose Post 1st dose at 4h	12	 205/62 253/100	 100 to 300 60 to 480
10 mg (2x5 mg tablet) elderly female Predose Post 1st dose at 4h	12	 196/56 253/85	 104 to 270 150 to 360
Results from study Impact 10847 "multiple dose escalation"			

5 mg OD day 0 Predose Post 1st dose at 4h Post last dose at 4h	7	 78 / 34 67 / 10 100 / 22	 33 to 137 54 to 79 72 to 141
5 mg BID day 5 Predose Post 1st dose at 4h Post last dose at 4h	7	 67 / 32 61 / 13 84 / 6	 42 to 138 48 to 89 75 to 92
5 mg TID day 5 Predose Post 1st dose at 4h Post last dose at 4h	7	 50 / 12 70 / 20 79 / 21	 38 to 70 52 to 112 56 to 113
10 mg BID day 5 Predose Post 1st dose at 4h Post last dose at 4h	7	 67 / 19 72 / 13 67 / 5.1	 55 to 109 57 to 92 61 to 76
20 mg BID day 5 Predose Post 1st dose at 4h Post last dose at 4h	7	 76 / 14 59 / 16 73 / 10	 51 to 91 35 to 84 63 to 93
30 mg BID day 5 Predose Post 1st dose at 4h Post last dose at 4h	8	 62 / 5 64 / 6 70 / 9	 54 to 72 55 to 76 57 to 84
Results from study Impact 10848 “Interaction with Enoxaparin”			
10 mg BAY 59-7939 Preddose Post 1st dose at 4h	11	 67.4 / 8.9 78.5 / 23.9	 52 to 80 56 to 132
10 mg BAY 59-7939 and 40 mg Enoxaparin Preddose Post 1st dose at 4h	10	 71.6 / 15.0 90.3 / 24.7	 46 to 93 53 to 126

40 mg Enoxaparin Preddose Post 1st dose at 4h	10	 78.8 / 13.4 97.8 / 32.4	 64 to 104 34 to 107

* different methodology used for determination o0f bleeding time

Vital signs, ECG

There were no clinically relevant changes in blood pressure, heart rate and ECG parameters with the doses tested so far.

5.3.5. Drug Interaction Studies

Impact No 10848

Single dose, non-blinded, randomized, non-placebo-controlled crossover study to investigate the potential influence of 40 mg of Enoxaparin on the safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 and vice versa in healthy, male subjects

Analysis of the potential interaction between BAY 59-7939 and enoxaparin was performed for the maximum values of the pharmacodynamic characteristics anti-Xa activity, PT, PTT, HepTest and bleeding time and the minimum values of the Factor Xa activity assuming log-normally distributed data. To compare treatment effects, the logarithms of these characteristics were analyzed using analysis of variance (ANOVA) including sequence, subject(sequence), period and treatment effects. Based on these analyses point estimates (LS-Means) and exploratory 90% confidence intervals for the treatment ratios were calculated by re-transformation of the logarithmic results given by the ANOVA.

No interaction effects between BAY 59-7939 and enoxaparin were found regarding factor Xa activity. Factor Xa-antigen revealed slightly higher values with enoxaparin compared to BAY 59-7939 alone and an additive effect when both drugs were given together. PT changes were comparable between BAY 59-7939 and Enoxaparin. Combining the drugs did not show any alterations of PT.

PTT showed to be longer in the BAY 59-7939 treatment group when compared to enoxaparin. The drug combination here resulted in slightly prolonged PTT values. Compared to the BAY 59-7939 treatment group, the Heptest values were considerably longer when subjects were treated with enoxaparin. However, this effect with Enoxaparin vanished when both drugs were given together. No obvious effects were observed for the bleeding time.

Table 1 Treatment effects in different test systems based on maximum (*minimum) observations [ratio (90% confidence interval)].

Test System	Treatment	Enoxaparin	Both
Factor Xa*	BAY59-7939	1.43 (1.31-1.56)	0.98 (0.90-1.07)
	Enoxaparin	1	0.69 (0.63-0.75)
Factor Xa-antigen	BAY59-7939	1.04 (0.91-1.18)	1.48 (1.30-1.69)
	Enoxaparin	1	1.43 (1.25-1.63)
PT	BAY59-7939	0.73 (0.70-0.76)	1.01 (0.97-1.05)
	Enoxaparin	1	1.38 (1.33-1.44)
PTT	BAY59-7939	0.83 (0.71-0.96)	0.97 (0.84-1.13)
	Enoxaparin	1	1.18 (1.01-1.37)
Heptest	BAY59-7939	2.54 (2.05-3.16)	1.18 (0.95-1.47)
	Enoxaparin	1	0.46 (0.37-0.58)
Bleeding Time	BAY59-7939	1.23 (1.07-1.43)	1.18 (1.02-1.37)
	Enoxaparin	1	0.96 (0.83-1.11)

The ODIXaHip trial is planned to be the first proof-of-principle, dose-ranging trial with BAY 59-7939 covering a 10-fold range of doses from a low-effective dose up to a highest dose which probably has to be prematurely terminated due to bleeding events.

The most important medical concern is the effective treatment of patients diagnosed with deep vein thrombosis in the course of this trial. Therefore, we investigated the interaction of BAY 59-7939 with enoxaparin, a low-molecular-weight heparin, which will be given as a rescue treatment to those patients. Animal studies addressed the question whether the concomitant use of both anticoagulants will result in a lower or in a lack of efficacy of enoxaparin (due to sterical hindrance).

5.3.6. Special Studies

No data available.

5.4. Efficacy and Safety

Key Points:
See information on Clinical Pharmacology 5.3

5.4.1. Efficacy

No information on efficacy from clinical trials in patients available so far.
Efficacy data based on surrogate parameters from phase I trials are included in section 5.3.3 Pharmacodynamic Effects.

5.4.2. Safety

5.4.2.1. Dosage and Administration

Dose per administration	Formulation	Number of subjects	Design
Study Impact 10842			
10 mg	Oral solution	8 (active)+ 4-3 (placebo)	Parallel-group

5 mg	Oral solution, Tablet	6 (active) + 4 (placebo) 6 (active) + 4 (placebo)	Cross-over
10 mg (2x5mg)	Tablet	8 (active) + 4 (placebo)	Parallel-group
15 mg (3x5mg)	Tablet	7 (active) + 3 (placebo)	Parallel-group
15 mg (3x5mg)	Tablet	7 (active) + 3 (placebo)	Parallel-group
20 mg (4x5 mg)	Tablet	7 (active) + 3 (placebo)	Parallel-group
30 mg (6x5 mg)	Tablet	6 (active) + 2 (placebo)	Parallel-group
40 mg (6x5mg)	Tablet	8 (active) + 2 (placebo)	Parallel-group
60 mg (6x5mg)	Tablet	7 (active) + 3 (placebo)	Parallel-group
80 mg (6x5mg)	Tablet	6 (active) + 4 (placebo)	Parallel-group
Study Impact 10846			
10 mg (2x5mg)	Tablet fasted Tablet fed	9 9	Cross-over
Study Impact 10850			
10 mg (2x5mg)	Tablet	36 (active) + 12 (placebo)	Parallel-group
Study Impact 10847			
5 mg OD	Tablet	7 (active) + 3 (placebo)	Parallel-group
5 mg BID	Tablet	7 (active) + 3 (placebo)	Parallel-group
5 mg TID	Tablet	8 (active) + 4 (placebo)	Parallel-group
10 mg BID	Tablet	8 (active) + 4 (placebo)	Parallel-group
20 mg BID	Tablet	8 (active) + 4 (placebo)	Parallel-group
30 mg BID	Tablet	8 (active) + 4 (placebo)	Parallel-group

5.4.2.2 Adverse Events

Impact No. 10842

Randomized, double-blind, placebo-controlled, group-comparison (with one cross-over dose step) dose-escalation study in healthy male subjects to investigate the safety, tolerability and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after single oral doses starting with 10 mg of BAY 59-7939 as oral solution or tablet.

Thirty-eight treatment emergent adverse events were reported by 28 of 91 healthy volunteers. Only 5 of the 38 adverse events were considered to be possibly related to the study medication: two cases of "taste of blood" which occurred after administration of 10 and 80 mg BAY 59-7939. Inspection of the oral cavity and washing out the mouth with clear water did not show any signs or symptoms of bleeding. Additionally both subjects had no unusual prolongation of the clotting parameters or inhibition of Factor Xa. Both events resolved without any actions taken after about 45 and 105 minutes. One additional subject complained of headache. The event resolved after treatment with pain relieve medication. Furthermore two episodes of ecchymosis were observed.

Impact No. 10846

Randomized, open-label, two-fold cross-over study to investigate the effect of a high fat, high calorie meal on safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 given oral as 2 x 5 mg tablets in 12 healthy male subjects.

Ten subjects were enrolled in this study, two subjects dropped out: one withdrew his consent for further participation, one was excluded due to high CK values after the wash-out period of the first treatment period. The single oral doses of 10 mg as tablets alone or together with a standard high calorie, high fat breakfast were safe and well tolerated. No adverse events were observed when BAY 59-7939 was given with the breakfast. Only two adverse events were observed in the fasted state after drug administration which were moderate in intensity and considered to be not related to the study drug.

Impact No. 10850

Randomized, double-blind, placebo-controlled, group comparison study in healthy young and elderly subjects of both genders to investigate the safety,

tolerability, pharmacokinetics, and pharmacodynamics of BAY 59-7939 after a single 10 mg dose (as 2 x 5 mg tablets).

Adverse events were reported by 5 of 36 volunteers who took BAY 59-7939, and by 1 of 12 volunteers who took placebo. The events were all rated as mild, and consisted of headache (reported by 2 elderly and 1 young female), arm bruise (reported by 1 young female), and pain while urinating (reported by 1 young female).

Impact No. 10847

Single-centre, randomised, placebo-controlled, single-blind, parallel-group investigation of the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 after multiple dose application of BAY 59-7939 as conventional BAY 59-7939 tablet

Eighty-seven treatment emergent adverse events were reported by 44 of 64 healthy volunteers. Forty-three of these adverse events were considered to be possibly related to the study medication. The majority of the events were considered to be of mild intensity. One subject was found to have relevant increases in liver enzyme tests (GLDH, AST, ALT) after administration of 30 mg BAY 59-7939 BID which may have had a causal relationship to the study drug

5.4.2.2.1. Adverse Events (Tabular summaries for all clinical trials)

Impact No. 10842

Randomized, double-blind, placebo-controlled, group-comparison (with one cross-over dose step) dose-escalation study in healthy male subjects to investigate the safety, tolerability and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after single oral doses starting with 10 mg of BAY 59-7939 as oral solution or tablet.

Vol. No.	Dose	AE	Onset DD:HH:MM	Duration DD:HH:MM	Severity	Rel. to Study Drug	Out-come
09	10mg Verum	flushing eyes	4:11	19:49	mild	no	resolved
13	5mg Verum	headache	5:30	17:45	mild	no	resolved
14	5mg Verum	febrile illness	3:07:57	10:15:00	moderate	no	resolved
25	10mg Verum	backpain	6:02:00	not calc.	mild	no	unchanged
		hay fever	2:04:00	8:17:45	mild	no	resolved
26	10mg Verum	bloody taste in mouth	2:57	45	mild	yes	resolved
27	10mg Verum	headache	7:00:54	21:00	mild	no	resolved
28	10mg Verum	nausea	4:06	3:30	mild	no	resolved
29	10mg Verum.	distortion of the right ankle-joint	-4:20:42	4:19:30	mild	no	resolved
30	10mg Plac.	common cold	-6:02:15	10:02:00	mild	no	resolved
31	10mg Plac.	nausea	-19:18	8:10	mild	no	resolved
		vomiting	-11:08	5	moderate	no	resolved
		contusion of the left knee	7:07:12	3:20:30	mild	no	resolved
34	10mg Plac.	hay fever	2:23:33	7:02:00	mild	no	resolved
38	15mg Plac.	pain in the renal area left and right	2:06:57	4:16:00	mild	no	resolved
		shooting pain in the left hypogastric region	2:06:57	2:17:00	mild	no	resolved
45	15mg Verum	common cold	5:23:39	5:04:00	mild	no	resolved
46	15mg Verum	headache	7:46	5:50	mild	yes	resolved

Vol. No.	Dose	AE	Onset DD:HH:MM	Duration DD:HH:MM	Severity	Rel. to Study Drug	Out-come
54	20mg Verum	common cold	-2:09	9:01:00	mild	no	resolved
55	20mg Verum	thrombophlebitis right arm	2:03:48	15	mild	no	resolved
		thrombophlebitis right arm	3:23:48	10:00:00	moderate	no	resolved
56	20mg Verum	headache	1:00	7:15	mild	no	resolved
58	20mg Plac.	common cold	-1:51	9:23:45	mild	no	resolved
		headache	4:00:39	4:00	mild	no	resolved
59	20mg Plac	headache	-2:24	14:00	mild	no	resolved
		nausea	4:06	3:30	mild	no	resolved
60	20mg Verum	common cold	-1:19:27	1:10:00	mild	no	resolved
62	30mg Verum	headache	-1:12:03	13:45	mild	no	resolved
65	30mg Plac.	sore throat	5:48	9:20:00	mild	no	resolved
74	40mg Verum	common cold	-4:01:03	na:na:na	mild	no	resolved
78	40mg Verum	headache	12:45	22:45	mild	no	resolved
	40mg Verum	headache	4:08:45	4:09:45	mild	no	resolved
82	40mg Verum	common cold	-9:01:27	12:21:33	mild	no	resolved
	40mg Verum	headache	-1:42	2:03	mild	no	resolved
87	60mg Verum	tender on pressure at needle insertion site ri. cubitus	6:13	6:37	mild	no	resolved
	60mg Verum	hypotension	6:13	6:37	moderate	no	resolved

Vol. No.	Dose	AE	Onset DD:HH:MM	Duration DD:HH:MM	Severity	Rel. to Study Drug	Out-come
	60mg Verum	sore throat	11:23:54	12:21:54	mild	no	resolved
89	60mg Plac.	headache	2:58	11:18	mild	no	resolved
90	60mg Verum	headache	13:00:15	13:08:45	mild	no	resolved
	60mg Verum	sore throat	13:00:15	13:08:45	mild	no	resolved
93	60mg Verum	muscle enzyme elevation	12:23:36	22:23:36	severe	no	resolved
97	80mg Verum	taste of blood in the mouth	6:30	8:15	mild	yes	resolved
98	80mg Plac.	common cold	-3:00:03	3:22:57	mild	no	resolved
	80mg Plac.	pain in the stomach	11:27	12:27	mild	no	resolved
	80mg Plac.	nasal bleeding	23:27	23:30	mild	no	resolved
101	80mg Verum	common cold	3:10:48	12:21:03	mild	no	resolved
103	80mg Plac.	pain in the right shoulder	13:20:57	16:00:42	moderate	no	improved
	80mg Plac.	ache right lower jaw	13:20:57	16:00:57	mild	no	resolved
	80mg Plac.	pain in the right ear	13:20:57	16:00:57	mild	no	resolved
	80mg Plac.	pain in the right shoulder	16:00:42	19:20:57	mild	no	improved
	80mg Plac.	pain in the stomach	17:10:42	17:20:57	mild	no	resolved
104	80mg Verum	ecchymoses	23:39	3:22:39	mild	yes	resolved
	80mg Verum	common cold	9:06:39	18:06:39	mild	no	resolved
105	80mg Verum	ecchymoses	4:06	1:22:36	mild	yes	resolved

0 d = day of dosing

Impact No. 10846

Randomized, open-label, two-fold cross-over study to investigate the effect of a high fat, high calorie meal on safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 given oral as 2 x 5 mg tablets in 12 healthy male subjects.

Vol. No.	Dose	AE	Onset DD:HH:MM	Duration DD:HH:MM	Severity	Rel. to Study Drug	Out-come
2	Fasted	Common cold	-11d00h03	21d22h	mild	no	resolved
3	fasted	Inflammation of the root of tooth	3d23h54	7d	moderate	no	resolved
4	fasted	Muscle enzyme elevation	NA	11d16h50m	moderate	yes	resolved

0 d = day of dosing, NA=exact starting time is not available, the relative day to start of medication is given

Impact 10850

Randomized, double-blind, placebo-controlled, group comparison study in healthy young and elderly subjects of both genders to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of BAY 59-7939 after a single 10 mg dose (as 2 x 5 mg tablets).

Vol. No.	Dose	AE	Onset DD:HH:MM	Duration DD:HH:MM	Severity	Rel. to Study Drug	Out-come
22	10 mg OD	Headache	0d 14h	9h 30‘	mild	yes	resolved
23	10 mg OD	Burning when urinating	0d 5h54’	20 days	mild	no	resolved
25	10 mg OD	Arm bruise	0d3h	5 days	mild	yes	resolved
50	10 mg OD	headache	0d2h52’	18 hours	Mild	Yes	resolved
53	10 mg OD	Headache	0d4h3’	6h45’	Mild	Yes	resolved

0 d = day of dosing

Impact 10847

Single-centre, randomised, placebo-controlled, single-blind, parallel-group investigation of the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 after multiple dose application of BAY 59-7939 as conventional BAY 59-7939 tablet

Vol. No.	Dose	AE	Onset DD:HH:MM	Duration DD:HH:MM	Severity	Rel. to Study Drug	Out-come
1	5mg OD	meteorism	8:00	1:15:00	mild	yes	resolved
		feeling of hyperacidity in stomach	8:30	1:14:30	mild	yes	resolved
		pain in left lower arm (canula)	2:22:30	2:00:30	moderate	no	improved
		pain in left lower arm	5:00:00	3:23:00	mild	no	improved
		common cold	9:23:00	1:12:00	mild	no	resolved
2	5mg OD	headache	9:56	13:00	mild	no	resolved
		abdominal pain	2:21:56	14:00	mild	no	resolved
4	5mg Plac.	obstipation	9:00:33	8:30	moderate	no	resolved
5	5mg Plac.	prurims both legs	1:11:44	4:00:00	mild	no	resolved
		isolated papulas both legs	1:11:44	4:00:00	mild	no	resolved
6	5mg OD	phlebitis right forearm	12:00	7:11:40	mild	no	resolved
		sore throat	4:22:30	1:20	mild	no	resolved
		erythema (at chest)	6:02:00	8:20:40	mild	no	resolved
		headache	7:05:40	5:00	moderate	yes	resolved
8	5mg OD	headache	7:00:17	8:30	mild	yes	resolved
9	5mg OD	erythema	4:22:18	10:14:10	mild	no	resolved
13	5mg BID	common cold	3:10:30	12:45	mild	no	resolved
16	5mg BID	erythema at chest	7:14:28	9:08:06	mild	no	resolved
17	5mg Plac.	insomnia	12:15:44	4:12:00	moderate	no	resolved

		dizziness	13:06:44	3:21:00	moderate	no	resolved
21	5mg BID	common cold	4:22:18	5:40	mild	no	resolved
22	5mg Plac.	hematoma right arm	8:na:na*	not calc	mild	no	resolved
25	5mg TID	hematoma left fore-arm	4:23:30	8:00:00	moderate	no	resolved
26	5mg TID	heartburn	4:13:26	4:23:01	mild	yes	resolved
	5mg TID	heartburn	5:10:29	5:13:56	mild	yes	resolved
	5mg TID	erythema at chest due to ECG electrodes	5:23:11	na:na:na	mild	no	resolved
	5mg TID	heartburn	7:01:51	7:04:51	mild	yes	resolved
	5mg TID	swallowing disorder	9:04:06	9:14:26	mild	no	resolved
27	5mg TID	diarrhea	-19:38	23:52	mild	no	resolved
	5mg TID	headache	3:08:07	3:15:52	mild	yes	resolved
	5mg TID	feeling of exhaustion	3:08:07	3:23:52	mild	yes	resolved
	5mg TID	sore throat	3:10:52	3:23:52	mild	no	resolved
	5mg TID	rhinitis	3:10:52	14:00:52	mild	no	resolved
28	5mg TID	diarrhea	4:18	5:21:48	mild	yes	resolved
	5mg TID	headache	3:00:48	3:15:48	mild	yes	worsened
	5mg TID	feeling of exhaustion	3:00:48	4:12:48	mild	yes	resolved
	5mg TID	headache	3:15:48	3:22:48	moderate	yes	resolved
	5mg TID	two small hematoma left forearm	5:12:48	16:23:48	mild	no	resolved
29	5mg Plac.	feeling of exhaustion	3:04:14	3:22:44	mild	yes	resolved

	5mg Plac.	excoriation D iv left hand	3:13:44	12:22:44	mild	no	resolved
	5mg Plac.	diarrhea	4:04:44	4:12:44	mild	yes	resolved
	5mg Plac.	flatulence	4:04:44	4:15:44	mild	yes	resolved
	5mg Plac.	feeling of exhaustion	4:22:44	5:22:44	moderate	yes	resolved
	5mg Plac.	exanthema left cubital fossa	4:22:44	14:22:44	mild	yes	resolved
	5mg Plac.	feeling of exhaustion	6:00:44	6:15:58	mild	yes	resolved
	5mg Plac.	feeling of exhaustion	7:01:44	7:23:44	moderate	yes	resolved
30	5mg Plac.	hematoma left cubital fossa	3:08:55	7:03:40	mild	no	resolved
	5mg Plac.	hematoma right cubital fossa	4:05:10	8:03:40	mild	no	resolved
	5mg Plac.	diarrhea	5:08:40	6:01:15	moderate	yes	resolved
	5mg Plac.	headache	7:11:40	7:14:40	mild	yes	resolved
31	5mg TID	pressure on left ear	4:46	8:54	moderate	yes	resolved
	5mg TID	tinnitus left ear	8:54	10:01	mild	yes	resolved
34	5mg Plac.	erythema at chest due to ECG electrodes	24	13:07:24	mild	no	resolved
	5mg Plac.	feeling of exhaustion	4:02:54	4:11:54	mild	yes	resolved
	5mg Plac.	feeling of exhaustion	4:17:24	5:02:24	mild	yes	resolved
38	10mg BID	pain in flank	3:05:00	3:17:00	mild	no	resolved
41	10mg BID	headache	7:04:48	7:11:18	mild	no	resolved
42	10mg BID	erythema	1:12:14	13:22:44	mild	no	resolved

	10mg BID	phlebitis	9:00:04	17:02:14	mild	no	resolved
43	10mg BID	erythema	7:04:10	11:22:40	mild	no	resolved
44	10mg Plac.	phlebitis	9:00:01	17:02:36	mild	no	resolved
45	10mg BID	conjuncti-vitis	9:06:32	13:23:32	mild	no	resolved
46	10mg BID	mandibular pain	2:06:28	14:21:58	mild	no	resolved
	10mg BID	gingiva ulcer in mandibula	9:00:28	14:21:58	moderate	no	improved
	10mg BID	gingiva ulcer in mandibula	14:21:58	21:23:28	mild	no	resolved
48	10mg BID	hematoma	3:23:53	4:03:35	moderate	no	improved
	10mg BID	hematoma	4:03:35	14:22:20	mild	no	improved
51	20mg BID	conjunc-tivitis	2:12:37	4:23:52	mild	no	resolved
52	20mg BID	fatigue	20:21:18	28:23:48	mild	no	resolved
	20mg BID	pain right flank	20:23:48	24:23:48	mild	no	resolved
53	20mg BID	headache	2:09:44	2:11:14	moderate	yes	resolved
54	20mg Plac.	headache	5:23:40	6:20:40	mild	yes	resolved
55	20mg BID	nasal congestion	3:20:36	3:22:36	moderate	no	resolved
	20mg BID	nasal congestion	5:22:36	5:22:56	mild	no	resolved
	20mg BID	headache	6:08:16	6:10:20	mild	no	resolved
56	20mg Plac.	pain right arm	12:32	22:32	moderate	no	resolved
	20mg Plac.	hematoma right arm	22:32	1:02:32	mild	no	resolved
	20mg Plac.	headache	10:11:32	10:22:32	moderate	no	resolved
	20mg Plac.	tumescence left lid	10:23:02	11:23:00	moderate	no	resolved
58	20mg BID	folliculitis	3:23:28	na:na:na	mild	no	Insuff. follow-up
	20mg BID	headache	1:28	08:00	mild	yes	resolved

	20mg BID	laceration 4th finger	5:03:58	18:07:28	mild	no	resolved
59	20mg BID	headache	13:32	2:14:24	mild	yes	resolved
74	30mg BID	reddening of skin after ECG electrodes	1:00:11	1:23:56	mild	no	resolved
76	Plac.	headache	7:04:48	7:11:48	mild	yes	resolved
77	30mg BID	heat sensation	14:43	15:42	mild	yes	resolved
	30mg BID	haematoma left fore-arm	3:01:43	22:09:43	mild	no	resolved
	30mg BID	haematoma right fore-arm	4:01:43	14:03:43	mild	no	resolved
78	30mg Plac.	rhinitis	2:23:40	8:04:40	mild	no	resolved
79	30mg BID	salty taste	1:16	4:36	mild	yes	resolved
	30mg BID	dizziness	2:11	2:46	mild	yes	resolved
	30mg BID	headache	10:36	11:51	mild	yes	resolved
	30mg BID	diarrhea	1:05:36	1:08:06	mild	yes	resolved
	30mg BID	heartburn	3:04:06	3:07:36	moderate	yes	resolved
	30mg BID	reddening of skin after ECG electrodes	3:13:36	3:20:36	mild	no	resolved
	30mg BID	constipation	4:06:06	5:00:06	mild	no	resolved
	30mg BID	headache	7:03:06	7:13:36	mild	yes	resolved
	30mg BID	headache	8:00:06	8:21:06	mild	yes	resolved
	30mg BID	constipation	10:00:36	10:05:06	mild	no	resolved
80	30mg BID	headache	7:07:02	7:08:02	mild	yes	resolved
81	30mg Plac.	headache	7:22:43	7:23:43	mild	yes	resolved
84	30mg BID	elevated GLDH	3:23:29	26:22:26	moderate	yes	resolved
	30mg BID	elevated ALT	5:23:27	26:22:26	moderate	yes	resolved

*if the exact start/Stop time is not available (na) the relative day to start of medication is given

0 d = day of dosing

Impact 10848

Single dose, non-blinded, randomized, non-placebo-controlled crossover study to investigate the potential influence of 40 mg of Enoxaparin on the safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 and vice versa in healthy, male subjects

Vol. No.	Dose	AE	Onset DD:HH:MM	Duration DD:HH:MM	Severity	Rel. to Study Drug	Out-come
1	BAY 59-7939	exanthema on back at shoulders	6:13:00	8:03:20	mild	no	resolved
2	BAY 59-7939	headache	11:05	14:50	mild	yes	resolved
6	BAY 59-7939	headache	1:40	5:07	mild	yes	resolved
7	ENOXA-PARIN	loss of inlay tooth 14	-1:na:na*	-22:09	mild	no	resolved
	BAY 59-7939	headache	8:36	11:36	mild	yes	resolved
	BAY 59-7939	headache	11:36	20:36	moderate	yes	resolved
	BAY 59-7939 + ENOXA-PARIN	headache	5:11	11:31	moderate	yes	resolved
	BAY 59-7939 + ENOXA-PARIN	headache	14:31	20:31	mild	yes	resolved
	ENOXA-PARIN	headache	11:06	20:36	moderate	yes	resolved
	ENOXA-PARIN	rhinitis	2:22:21	5:00:26	moderate	no	resolved
	ENOXA-PARIN	rhinitis	5:00:26	14:07:36	mild	no	resolved

0 d = day of dosing

*if the exact start/Stop time is not available (na) the relative day to start of medication is given

5.4.2.2.2. Adverse Event Discontinuations

No discontinuations due to adverse events.

5.4.2.2.3. Serious Adverse Events

In the Enoxaparin Interaction study (Impact 10848) one subject experienced an myocardial infarction after screening but prior to admission to the first study period. This event was judged to be serious but without relation to the study drug.

5.4.2.2.4. Deaths

No death reported.

5.4.2.2.5. Laboratory Abnormalities

Apart from changes of clotting parameters that are detailed in section 5.2.3 and data of one subject detailed below, only isolated laboratory values showed minor deviations from normal. However there was no consistent pattern of onset or duration that would have given a well-founded suspicion of drug induced changes.

In study Impact 10846 one subject presented with an increase in CK after wash-out phase of the first period. This subject was withdrawn from the study subsequently. The CK values normalized until follow-up visit. Complete course of CK of volunteer no PPD is shown in table 1.

Table 1:

Time		**CK [U/L] [times of upper limit of normal]**
Period 1	Screening -1d00 00 0d00 00	1.02 0.75 0.51
Period 2	1d00 00 2d00 00 -1d00 00 Final Examination	0.43 0.41 5.8 0.53

In study 10847 one subject displayed increase liver function tests. A causal relationship to the study drug cannot be excluded. However, all parameters returned to normal without any actions taken. Details are given in the table below (values are given as times of upper limit of normal)

Test	Subject	Screening	-1D	0D	1D	3D	4D	5D	6D	7D	8D	9D	10D	11D	12D	Final Exam	Maximum
30 mg BID																	
SGOT/AST	84								1.31	1.60	1.50	1.61	1.63	1.34	1.18		1.63
SGPT/ALT	84							1.26	2.01	2.62	2.88	3.17	3.33	3.11	2.84	2.07	3.33
GLD	84						1.95	4.07	4.75	5.35	4.68	4.63	4.15	3.25	2.87	1.32	5.35

5.4.2.3. Possible Risks and Adverse Drug Reactions Inferred from Preclinical Data or Related Compounds

Factor Xa is a key factor in the coagulation cascade. Inhibition of factor Xa bears the risk of bleeding complications. From preclinical data it is evident that clotting parameters, such as PT or PTT are prolonged, indicating anticoagulating effects. However, risk of bleeding was not different from LMWH (enoxaparin), which is used as standard in clinical practice.

5.4.2.4. Drug Interactions Encountered in Clinical Trials

No data available

5.4.2.5. Contraindications and Precautions

No data available

5.4.2.6. Countermeasures, Overdose instructions

No data available

5.4.2.7. Effects of Age, Race (including ethnic differences), Sex (Restrictions)

The effect of age and gender on pharmacokinetic was assessed in study Impact 10850. For result see respective paragraphs in section 5.

5.5. Marketing Experience

Not applicable

6. Summary of Data and Guidance for the Investigator

Key Points Preclinical Experience:

- BAY 59-7939 has been characterized as a potent and specific oral factor Xa inhibitor
- BAY 59-7939 was investigated in various preclinical thrombosis models in different species (rat, rabbit). A dose dependent antithrombotic effect was demonstrated across the broad spectrum of experimentally induced arterial and venous thrombosis. Key coagulation parameters were influenced as mechanistically expected; dose dependent prolongation of PT/aPTT and inhibition of factor Xa activity. The potential for an increased risk of bleeding was investigated in several in vitro animal models, showing that the risk for bleeding was not different from the LMWH enoxaparin, used as standard in the prevention and therapy of thrombotic events. Inhibition of factor Xa by BAY 59-7939 did not influence the efficacy of enoxaparin or heparin when used concomitantly.
- The safety pharmacology showed only the mechanistically expected influence on coagulation parameters.
- Bay 59-7939 has a low acute toxicity in rats and mice. After subacute administration (4-weeks) in dogs and rats BAY 59-7939 was well tolerated. The changes seen in Quick values, as well as the increases in PT an aPPT are related to the underlying pharmacological principle. There was no evidence for a genotoxic potential based on two in vitro and one in vivo test.
- The pharmacokinetics in rats and dogs was linear after oral and i.v. administration, with a bioavailability of 60%. Elimination from plasma was rapid and excretion is predominantly via biliary/fecal route (rat), in dogs the renal route contributed significantly. No inhibitory potency or induction potential of BAY 59-7939 on cytochrome P450 isoform was seen.

Guidance to the investigator based on preclinical information

No specific finding in the preclinical pharmacology, toxicology or preclinical pharmacokinetic characterizes a particular risks for the application in humans. BAY 59-7939 shows effects which are inline with the underlying pharmacological mechanism of factor Xa inhibition. The antithrombotic effect and particularly the risk for bleeding are in the range of LMWH, which are used as standard therapy in the prevention and treatment. The effects of LMWH or Heparin is not diminished, which is important, if in clinical trials patients develop a DVT while on BAY 59-7939. These products then still can be used for therapy of DVT.

Key Points Clinical Experience:

- BAY 59-7939 was well tolerated when administered at single oral doses up to 80 mg and multiple doses of 30 mg bid for 5 days
- Bleeding time was not affected to a relevant degree in these studies
- A dose dependent increase in pharmacodynamic and pharmacokinetic parameters was observed at all doses of BAY 59-7939
- Up to doses of 30 mg bid no relevant accumulation of BAY 59-7939 was observed.
- As PT values run in parallel both to Factor Xa inhibition and pharmacokinetic effects, this parameter may be used on an individual bases to detect extreme responses to BAY 59-7939
- A relevant food effect has been observed after administration of BAY 59-7939 leading to higher peak plasma concentrations (39%) and exposure (25%) after a high fat, high calorie meal
- An increase in peak plasma concentrations and corresponding changes in pharmacodynamic parameters (Factor Xa and PT) were observed in elderly

volunteers (preliminary data).

- Co-medication of Enoxaparin (40 mg SC) showed an additive effect on pharmacodynamic parameters after administration of 10 mg BAY 59-7939. Bleeding time was not prolonged under these circumstances
- BAY 59-7939 is a substrate of the Cytochrome P450 system (3A4). No human data are available to assess the extend of a potential effect if two substrates of 3A4.
-

Guidance to the investigator based on clinical information

Although the experience in humans is currently limited to healthy volunteers the application of BAY 59-7939 was well tolerated. No specific area of risk could identified so far, in particular no hint for increased risk of bleeding or prolongation of bleeding time was observed. The planned doses to be applied in patients within the ODIXaHip trial (phase IIa, dose escalating proof of principle) are 5 to 40 mg BID. In phase I multiple dosing up to 30 mg BID has been investigated and the compound was well tolerated. The decision to escalate doses in ODIXaHip will exclusively remain with the independent steering committee of the ODIXahip trial. Investigators and their responsible IEC/IRB will be informed about the decision of the steering committee.

The use of a LMWH as a rescue medication should be possible on the basis of the decision of the investigator under consideration of the timing of the last dose of BAY 59-7939 and the actual coagulation status of the patient by measurement of PT. The concomitant use of Ketoconazol and BAY 59-7939 is excluded.

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8. Appendices

8.1. Appendix I – Development Core Safety Information (DCSI)

Development Core Safety Information (DCSI)

For reference see 5.2.2.4.1 Adverse Events

8.1.1. Posology and Method Of Administration

Recommended usual dose:

TBD

Range of dose:

TBD

Method and frequency of administration:

TBD

Dose titration, special monitoring advice:

TBD

Elderly (above 65 years):

TBD

Children (from birth to 16 *years*):

NA

Hepatic impairment:

TBD

Renal impairment:

TBD

8.1.2. Contraindications

TBD

8.1.3. Special Warnings And Precautions For Use

TBD

8.1.4. Interaction With Other Medicaments And Other Forms Of Interaction

After concomitant administration of BAY 59-7939 and enoxaparin an additive effect was observed on anti-Xa. Factor Xa, Heptest, PT, and PTT did not demonstrate an additive effect – these tests showed changes which were comparable to those observed after administration of BAY 59-7939 alone.

8.1.5. Pregnancy and Lactation

TBD

8.1.6. Undesirable Effects

The following is based on the current knowledge of the risk profile developed from single case reports reassessed by the company.

The adverse drug reactions (ADRs) mentioned in this appendix are the reference for expectedness used for regulatory purpose. It is not a complete list of adverse events reported in clinical trials. A complete listing of events reported in clinical development are shown in section "5.2.2 4 Adverse Events".

ADR: Headache (21 reports based on 178 volunteers exposed)

ADR: Ecchymoses (2 reports based on 178 volunteers exposed)

No major bleeding reported so far, although bleeding can not be excluded due underlying pharmacological mechanism.

8.1.7. Overdose

TBD

8.1.8. Drug Abuse and Dependence

TBD