INVESTIGATOR'S BROCHURE

Title Page

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Summary of Changes to Investigator's Brochure

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

Section	Summary of Change
1. Summary	Summary information on ODIXa-HIP2 (Study 10944), and ODIXa-KNEE (Study 10945) trials added.
4.2 Pharmacokinetics and drug metabolism in animals	Data on mammary secretion of drug in lactating rats added.
4.2.4.3 Protein binding, blood cell/plasma distribution, and displacement from protein binding sites	Data on displacement from protein binding sites added.
4.2.5 Metabolism	Figure 4-5 (metabolic pathways) updated.
4.2.5.1.4 CYP enzyme induction potential	Text updated.
4.2.7 Discussion including interspecies comparison	Text updated.
4.3 Toxicology	Results of 13-week studies in mice added. Results of 13-week feeding study in rats added Results of 26-week study in rats added.
4.3.7 Local tolerance	Statement on local tolerance added.
4.3.9 Comparison of exposure in animals to human	Data of chronic study in rats added.
5. Effects in humans	Summary information on interaction studies (digoxin, acetylsalicylic acid, naproxen, clopidogrel), QTc study, elderly study, ODIXa-HIP2 (Study 10944), and ODIXa-KNEE (Study 10945) trials added.
5.2 Clinical pharmacology	Update of Table 5-1 "Summary of phase I studies".
5.2.1 Summary	Summary information on interaction studies (digoxin, acetylsalicylic acid, naproxen, clopidogrel) and QTc study added.
5.2.2 Pharmacokinetics	Results of QTc study and study in elderly men and women added.
5.2.4 Safety/tolerability	Results of QTc study added.

Table continued

Section	Summary of Change
5.2.5 Interaction studies	Results of interaction studies (digoxin, acetylsalicylic acid, naproxen, clopidogrel) added.
5.2.6 Special studies	Results of study in elderly men and women added.
5.3 Efficacy and safety	Results of ODIXa-HIP2 (Study 10944), and ODIXa-KNEE (Study 10945) trials added in all subsections.
6. Guidance to investigator	Summary information on ODIXa-HIP2 (Study 10944), and ODIXa-KNEE (Study 10945) trials added.
7. References	Section updated.
8.1.4 Interaction with other medicaments and other forms of interaction	Information on acetylsalicylic acid added.
8.1.6. Undesirable effects	Section updated.
8.1.7. Overdose	Information added on potential use of recombinant factor VIIa (rFVIIa) as a universal antidote.

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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
APTT	Activated partial thromboplastin time
ASAT/SGOT	Aspartate transaminase/serum glutamic-oxaloacetic transaminase
ATIII	Antithrombin III
bid	*bis in die*, twice daily
CI	Confidence interval
DVT	Deep venous thrombosis
EBT	Ear bleeding time
ECG	Electrocardiogram
eg	*exempli gratia*, for example
ETP	Endogenous thrombin potential
FDA	Food and Drug Administration
FXa	Factor Xa
GGT	Gamma-glutamyltransferase
h	Hour(s)
Hb	Hemoglobin
ie	*id est*, that is
INR	International Normalized Ratio (=PT patient/PT normal)
IP	Intraperitoneal(ly)
IV	Intravenous(ly)
LFT	Liver function test
LMWH	Low-molecular-weight heparin
LOQ	Limit of quantification
MI	Myocardial infarction
min	Minute(s)
NA	Not applicable
NC	Not calculated
NOEL	No observed effect level
NS	Difference not statistically significant (P >0.05)
od	*omni die*, once daily
ODIXa-HIP	**O**ral **Di**rect Factor **Xa** inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total **H**ip replacement
ODIXa-KNEE	**O**ral **Di**rect Factor **Xa** inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total **K**nee replacement
PAI-I	Plasminogen activator inhibitor

PE	Pulmonary embolism
PK	Pharmacokinetics
PT	Prothrombin time
R_A	Accumulation ratios: $R_{A1}=\frac{C_{max,\,ss}}{C_{max}}$ $R_{A2}=\frac{C_{min,\,ss}}{C_{min}}$ $R_{A3}=\frac{AUC_{\tau,\,ss}}{AUC_{\tau,\,day0}}$ $R_{A4}=\frac{AUC_{\tau,\,ss}}{AUC}$
RBC	Red Blood Cell
RFU	Relative fluoro units
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SEM	Standard error of the mean
TAT	Antithrombin III/thrombin-complex
TEAE	Treatment-emergent adverse event
tid	*ter in die*, three times daily
THR	Total hip replacement
TKR	Total knee replacement
TFPI	Tissue factor pathway inhibitor
t-PA	Tissue plasminogen activator
UK	United Kingdom
UH	Unfractionated heparin
ULN	Upper limit of normal
uPA	Urinary plasminogen activator
vs	*versus*, as opposed to
VTE	Venous thromboembolism
WBC	White blood cell
w/v	Weight/volume

1. Summary

Key Points:

- BAY 59-7939 is a potent and selective oral direct Factor Xa inhibitor.
- Antithrombotic effects have consistently been demonstrated in different thrombosis in rats and rabbits with ED_{50} of 0.6-5 mg/kg given orally.
- Safety pharmacology showed only a mechanistically driven inhibition of blood coagulation.
- Co-administration of BAY 59-7939 with acetylsalicylic acid, naproxen, diclofenac, clopidogrel, or warfarin showed additive but not potentiating effects on bleeding time prolongation in the tail transection model in rats.
- Antithrombotic effect of enoxaparin and heparin is not diminished by concomitant application of BAY 59-7939.
- Toxicity was low and after subacute to subchronic treatment (4 and 13 weeks). The compound was well tolerated except for changes related to the underlying pharmacological principle of BAY 59-7939.
- 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, in humans renal excretion dominated.
- 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 subjects.
- Multiple dosing with up to 30 mg bid was well tolerated in healthy subjects.
- No drug-related serious adverse events were reported in phase I studies.
- BAY 59-7939 is rapidly absorbed after oral treatment as solution (C_{max} after approximately 30 min) as well as tablet (C_{max} after 2-4 h).
- Elimination of BAY 59-7939 from plasma occurred with terminal half-lives of

4.30 to 5.88 h (Day 1) and 4.86 to 9.15 h (steady state) with no relevant accumulation.

- Steady state after multiple dose application of 30 mg bid was reached approximately after the 2-3 days.
- Administration of BAY 59-7939 with food resulted in an increase of AUC by 25%, a delayed absorption by about 1.5 h 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 men, and 39% higher in elderly women, compared to the young subjects of the same sex.
- Clotting parameters (PT, PTT, HepTest) were affected in a dose-dependent way.
- Factor Xa was inhibited in a dose-dependent way.
- No influence on bleeding time was observed neither after single dose (up to 80 mg) nor multiple dose application (up to 30 mg bid).
- Co-medication of enoxaparin showed an additive effect on pharmacodynamic parameters. Bleeding time was not affected to a clinically relevant degree.
- 3 large dose-ranging studies (ODIXa-HIP, ODIXa-HIP2, and ODIXa-KNEE) have been completed in the indication of VTE prevention in major orthopedic surgery exploring a 12-fold BAY 59-7939 dose range from 2.5 to 30 mg bid.
- BAY 59-7939 prevented total VTE compared with enoxaparin, thus supporting the efficacy of BAY 59-7939 in this indication.
- None of the studies demonstrated a dose trend for BAY 59-7939 regarding the primary efficacy endpoint of total VTE.
- A flat dose response for efficacy and a flat dose response for safety indicate a broad therapeutic window for BAY 59-7939 and thus makes the drug different from other new anticoagulants, which have shown to have less wide therapeutic ranges.
- In the 3 studies, DVT rates were consistent with those observed in other

contemporary trials and even the lower doses of BAY 59-7939 were within the expected ranges of the control drug enoxaparin or even lower.

- There was a dose-response with regard to bleeding events. However, it is important to note that there were neither fatal bleeds or bleeds in critical organs, nor clinically significant bleeds that could not be treated. Most bleeds adjudicated as major were related to the surgical site and no wound healing complications were reported in these patients.

Arterial and venous thromboembolism represents one of the most relevant health problems associated with a high rate of morbidity and mortality. Standard 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 consistent and potent anticoagulation and antithrombotic effects. The endogenously generated FXa in human plasma was inhibited with an IC50 of 21 ± 1 nM. PT and aPTT were increased about 2-fold at concentrations in the submicromolar range. The antithrombotic effect was demonstrated in different thrombosis models at 0.6-10 mg/kg given orally 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 an antithrombotic dose.

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 intravenous (IV) 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 route of excretion contributed considerably in dogs, renal excretion dominated in humans. 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 to subchronic administration (4 and 13 weeks) in dogs and rats BAY 59-7939 was well tolerated. The changes seen in Quick values, increases in PT and aPPT with subsequent spontaneous bleedings at high doses in dogs are related to the underlying pharmacological principle of the compound. There was no evidence for a genotoxic potential based on 2 in vitro and 1 *in vivo* test.

BAY 59-7939 was well tolerated up to 80 mg after single dose in healthy subjects. Multiple dosing with 30 mg 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.

3 studies have been completed in the indication of VTE prevention in major orthopedic surgery.

The open-label proof-of-concept **ODIXa-HIP trial (Study 10942)** tested an 8-day treatment with BAY 59-7939 doses of 2.5, 5, 10, 20, 30 mg bid, and 30 mg od vs enoxaparin 40 mg SC in patients undergoing elective hip replacement. All tested BAY 59-7939 doses including the lowest dose of 2.5 mg bid showed results that were within the confidence limits of enoxaparin and thus indicate a broad therapeutic range. Total daily doses of 20, 30, and 40mg of BAY 59-7939 had lower incidence rates of major VTE than enoxaparin. Major VTE incidence rates occurring with 60 mg BAY 59-7939 (4.3%) and enoxaparin (6.6%) were similar.

The number of bleeding events increased with increasing BAY 59-7939 doses indicating a clear dose-response in this open-label study. The pre-specified number of bleeding events was reached upon completion of the 30 mg bid dose step, thus precluding further dose escalation.

The randomized, double-blind, double-dummy, dose-ranging **ODIXa-HIP2 trial (Study 10944)** tested an 8-day treatment with BAY 59-7939 doses of 2.5, 5, 10, 20, and 30 mg bid vs enoxaparin 40 mg SC in patients undergoing elective hip replacement. BAY 59-7939 prevented total VTE compared with enoxaparin, thus supporting the efficacy of BAY 59-7939 in this indication. VTE incidence rates observed with twice daily administration of 2.5, 5, and 10 mg of BAY 59-7939 were lower than that observed with enoxaparin. The BAY 59-7939 20 mg bid treatment arm had a slightly higher incidence rate than enoxaparin. The results did not demonstrate any dose trend for BAY 59-7939 regarding the primary efficacy endpoint of total VTE.

The randomized, double-blind, double-dummy, dose-ranging **ODIXa-KNEE trial (Study 10945)** tested an 8-day treatment with BAY 59-7939 doses of 2.5, 5, 10, 20, and 30 mg bid vs enoxaparin 30 mg bid SC in patients undergoing elective hip replacement. For all tested BAY 59-7939 doses, lower VTE incidence rates were observed than for enoxaparin. The results did not demonstrate any dose trend for BAY 59-7939 regarding the primary efficacy endpoint.

In any of the studies, there was no indication for any treatment-emergent QTc-prolonging effects of BAY 59-7939.

In surgical patients receiving BAY 59-7939 to prevent VTE transient raises of liver function tests (transaminases, GGT, bilirubin, AP) were seen in a pattern similar to enoxaparin, ie with a peak occurring 1 week after surgery. Lipase and amylase values were found to be increased as well; however, this increase occurs on the first day after surgery and rapidly resolves under continuous treatment.

Once-daily dose regimens appear to be alternative options to twice-daily regimens explored thus far. Total daily doses up to 40 mg have yielded safe and effective study results in the indication of VTE prevention.

A therapeutic INR range for BAY 59-7939 has not yet been determined and therefore the known therapeutic INR range for warfarin cannot automatically be translated. Investigators in double-blind trials using BAY 59-7939 are advised not to measure the INR locally as this would unblind any trial.

2. Introduction

Key Points:

- Thromboembolic disorders are the single largest cause of disease and death in the western world.
- Standard treatments for thrombotic events are antiplatelets and anticoagulants.
- The medical need for oral antithrombotic drugs with an improved risk/benefit ratio is high.

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, eg 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 MI, acute MI, 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.

Therapeutic standard

At present standard therapy for treatment and prevention of thrombotic events are antiplatelet drugs (acetylsalicylic acid, the thienopyridine derivatives ticlopidine 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 coumadin-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 acetylsalicylic acid 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

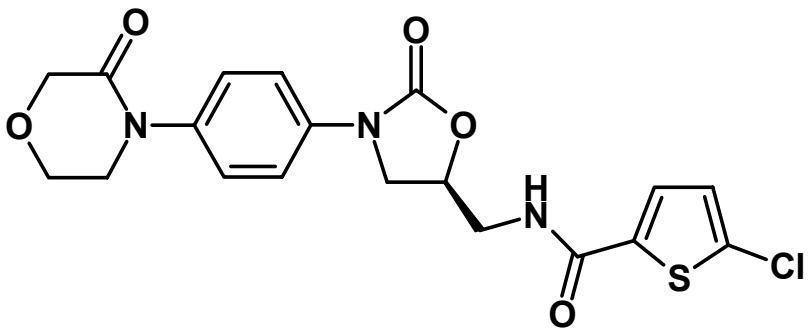
Key Points:

- An oral solution (0.1%) and immediate release tablets (1.25, 5, 10, 20, and 30 mg) have been developed.
- For tablets, no storage restrictions (temperature, humidity, light) apply.

3.1 Investigational Product's Substance Including the Chemical and Structural Formula

Structural formula:

Figure 3-1: Structural formula of BAY 59-7939



Chemical name: 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide

Empirical formula: $C_{19}H_{18}ClN_3O_5S$

Molecular weight: 435.89

3.2 Relevant Physical, Chemical, and Pharmaceutical Properties

BAY 59-7939 is a [redacted] verified by X-ray. NMR data support the BAY 59-7939 structure. [redacted]

The UV absorption maximum was found at [redacted].

BAY 59-7939 solubilities are [redacted].

[redacted]

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 for phase I studies. 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	[redacted] g
Macrogol 400 (PEG 400)	[redacted] g
Polysorbate 20 (Tween 20)	[redacted] g
Peppermint oil	[redacted] g.

Tablets 1.25/5/10/20/30 mg: BAY 59-7939 tablets are available in dose strengths of 1.25, 5, 10, 20, and 30 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 check weighed (density of solution: CCI).

Tablets 1.25/5/10/20/30 mg: BAY 59-7939 tablets are packaged in HDPE bottles, PP blisters, or PVC/PVDC blisters.

For tablets, no storage restrictions (temperature, humidity, light) apply. Storage recommendation: room temperature.

3.5 Known Similar Compounds

No similar compounds are known.

4. Nonclinical Studies

Key Points:

Primary Pharmacology

- BAY 59-7939 is a selective, potent, direct, and competitive inhibitor 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 as expected by the underlying pharmacological mechanism.
- Co-administration of BAY 59-7939 with acetylsalicylic acid, naproxen, diclofenac, clopidogrel, or warfarin showed additive but not potentiating effects on bleeding time prolongation.
- Other safety pharmacological investigations showed no clinically relevant effects.

Pharmacokinetics and Drug Metabolism in Animals

- In rats limited absorption of radioactivity from the gastrointestinal tract (66.8%); almost complete absorption in dogs (92%); bioavailability of 60% in rats and 60-86% in dogs.
- Linear pharmacokinetics in rats and dogs after IV and oral administration.
- No major circulating metabolites in rat, dog, and human plasma.
- Rapid elimination from plasma in rats and dogs.
- Moderate to high concentration- 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.
- Excretion of radioactivity in rats predominantly via biliary/fecal route, renal route contributed considerably in dogs, renal excretion dominated in humans.
- Low radioactive residues, no evidence of irreversible binding or retention of radioactivity in organs and tissues of rats.

Toxicology

- Toxicity was low and after subacute to subchronic treatment (4 and 13 weeks). The compound was well tolerated except for changes related to the underlying pharmacological principle of BAY 59-7939.
- No evidence for genotoxicity.
- No evidence for teratogenicity. Developmental toxicity is mainly characterized by maternal toxicity due to exaggerated pharmacodynamic effects.

4.1 Nonclinical Pharmacology

Key Points:

- BAY 59-7939 is a 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.
- In safety pharmacological studies, BAY 59-7939 showed no clinically relevant adverse effects. There was no evidence for cardiac risk.

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 is a very potent, competitive, selective, and direct FXa inhibitor, as shown by a low K_i (0.4 nM) and a low IC_{50} in the prothrombinase assay (2.1 nM) and in human plasma (21 nM). Its effect on FXa resulted in a prolongation of clotting times *in vitro* and *ex vivo*, and antithrombotic efficacy in rats and rabbits. The antithrombotic effect of BAY 59-7939 was specific for coagulation without impairing platelet function, and was demonstrated in both venous and arterial thrombosis models. In the arterial thrombosis models in rats (AV shunt, chemical damage, mechanical damage), similar ED_{50} values were obtained after oral administration of BAY 59-7939 (2–5 mg/kg). This demonstrates the consistent

effect of BAY 59-7939 in arterial thrombosis. In the rabbit AV shunt, a 14-fold lower concentration of BAY 59-7939 was needed to reduce thrombus formation by 50%, compared with the rat AV shunt. This corresponds to the *in vitro* anti-FXa activity in rabbit and rat plasma, which also differed 14-fold.

The antithrombotic effect of BAY 59-7939 is primarily attributed to its inhibition of FXa, but not of thrombin or other proteins within the coagulation pathway, or to a direct inhibition of platelet aggregation. However, BAY 59-7939 may decrease platelet activation indirectly via inhibition of thrombin generation**.**

Bleeding times in rats and rabbits were unaffected at antithrombotic-effective doses, suggesting a low risk of bleeding.

At antithrombotic-effective doses, BAY 59-7939 did not prolong bleeding times in both rats and rabbits. Since BAY 59-7939 is a reversible inhibitor of FXa, it is conceivable that a minimal amount of thrombin can be produced even when FXa is strongly inhibited. This small amount of thrombin may be sufficient to activate platelets, as thrombin has an approximately 10,000-fold higher affinity for platelets than for fibrinogen.[1, 2] Therefore, treatment with BAY 59-7939 should not compromise primary hemostasis.

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 effects of enoxaparin and heparin in this model were not diminished by BAY 59-7939.

In summary, BAY 59-7939 is an oral, direct FXa inhibitor that inhibited thrombus formation in established rat and rabbit models at doses that did not increase bleeding times. Therefore, based on its potency, selectivity, and efficacy, BAY 59-7939 may offer a safe and effective oral therapy for thromboembolic diseases.

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). By now, scientific evidence supports the concept that the inhibition of FXa represents an attractive approach for clinical intervention in various thrombotic disorders.

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. 1 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

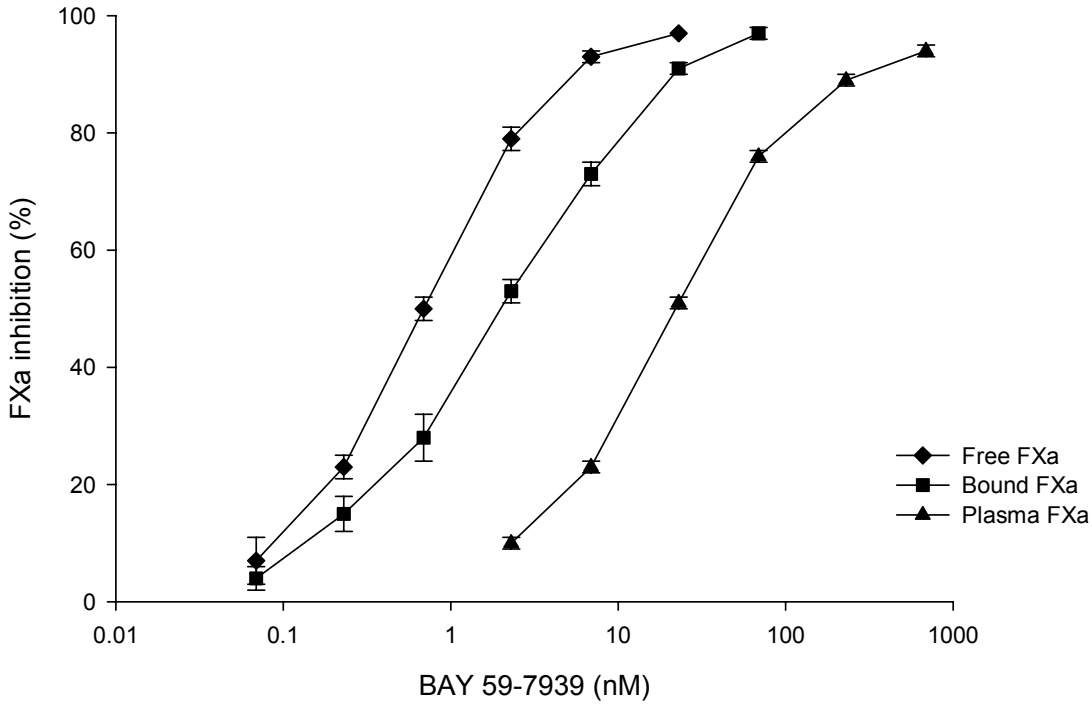
Effect on FXa and related serine proteases

BAY 59-7939 potently inhibited human FXa in a concentration-dependent manner, with an inhibitory constant (K_i) of 0.4 ± 0.02 nM, as demonstrated by an amidolytic assay (Figure 4-1).[3, 4] BAY 59-7939 is a competitive inhibitor of FXa, as demonstrated by Lineweaver–Burk analysis. BAY 59-7939 did not affect related

serine proteases – such as trypsin; thrombin; FVIIa; tissue factor/FVIIa complex; FIXaβ; FXIa; plasmin; urokinase; and activated protein C – at concentrations up to 20 μM. Selectivity was more than 10,000-fold greater for FXa than for these other serine proteases.

In contrast to several other FXa inhibitors, BAY 59-7939 does not inhibit trypsin[5-7] and, therefore, it is not expected to interfere with this digestive enzyme in the gastrointestinal tract.

Figure 4-1: Inhibitory effect of BAY 59-7939 on FXa using a chromogenic substrate of FXa (free FXa), prothrombinase complex activity on platelet surfaces using prothrombin as substrate (bound FXa), and in human plasma after activation of FX to FXa by Russell's viper venom (plasma FXa) (mean ± SEM)



Effect on prothrombinase-bound FXa

BAY 59-7939 inhibited prothrombinase-bound FXa in a concentration-dependent

manner (IC_{50} 2.1 ± 0.4 nM; Figure 4-1), as measured by thrombin generation in a reconstituted prothrombinase complex.[3, 4]

BAY 59-7939 was highly effective in inhibiting FXa bound to the prothrombinase complex. In the prothrombinase complex, the rate of prothrombin conversion is highly accelerated, approximately 280 000-fold.[8] This, in addition to the high concentrations of prothrombin used in our study (almost physiological concentrations), support the high affinity of BAY 59-7939 for prothrombinase-bound FXa.

Anti-FXa activity in human, rabbit, and rat plasma

In human plasma, BAY 59-7939 inhibited endogenous FXa activity in a concentration-dependent manner (Figure 4-1), with an IC_{50} of 21 ± 1 nM.[3, 4] Its anti-FXa activity was comparable in human and rabbit plasma (21 ± 2 nM), but was 14 times lower in rat plasma (290 ± 20 nM) (Table 4-1). These species-dependent differences may be due to the different free plasma fractions of BAY 59-7939 in rabbits (24–27%), humans (5–8%), and rats (1–3%) and to the differences in the activity against human FXa (IC_{50} 0.7nM), rabbit FXa (IC_{50} 0.8 nM) and rat FXa (IC_{50} 3.4 nM).[4]

Table 4-1: Effect of BAY 59-7939 on FXa activity and plasma clotting times in human, rabbit, and rat plasma *in vitro* (mean ± SEM)

Species	Inhibition of FXa IC_{50} (μM)	Concentration of BAY 59-7939 required to double the clotting time (μM)	
		PT	APTT
Human	0.021 ± 0.001	0.23 ± 0.02	0.69 ± 0.09
Rabbit	0.021 ± 0.002	0.12 ± 0.01	1.97 ± 0.49
Rat	0.29 ± 0.02	0.30 ± 0.02	2.09 ± 0.19

Clotting times in human, rabbit, and rat plasma

In human plasma, submicromolar concentrations of BAY 59-7939 prolonged the clotting assays HepTest, PT, and aPTT; this effect was concentration dependent.[3, 4]

The sensitivity of these assays decreased in the following order: HepTest > PT > aPTT (Table 4-2). The anticoagulant effect of BAY 59-7939 was species specific. The concentrations of BAY 59-7939 required to double the PT and aPTT in human and animal plasma are shown in Table 4-2. In the PT assay, anticoagulant activity was greatest in rabbit, followed by human, then rat. In the aPTT assay, the order was: human > rabbit > rat.

Table 4-2: **Effect of BAY 59-7939 on human plasma clotting times *in vitro* (mean ± SEM)**

Clotting assay	Concentration of BAY 59-7939 required to double the clotting time (μM)
HepTest	0.044 ± 0.003
Prothrombin time (PT)	0.230 ± 0.020
Activated partial thromboplastin time (aPTT)	0.690 ± 0.090

Effect on platelet aggregation

BAY 59-7939 did not inhibit collagen-, U46619-, ADP-, or TRAP-6-induced platelet aggregation at concentrations up to 200 μM. In the high micromolar range, BAY 59-7939 had a minor effect on γ-thrombin-mediated platelet aggregation (IC_{50} 81 μM).[3]

4.1.2.2 In vivo

Rat venous stasis model

In a venous thrombosis model employing a combination of stasis and a thrombogenic challenge (thromboplastin), BAY 59-7939 administered by IV bolus before thrombus induction displayed a significant, dose-dependent antithrombotic effect (Figure 4-2 A). The ED_{50} was 0.1 mg/kg. The effect of BAY 59-7939 at its ED_{50} on FXa activity and PT is shown in Table 4-3.[4, 9, 10]

Administration of BAY 59-7939 resulted in a dose-dependent increase in PT and anti-FXa activity in plasma (Figure 4-2 B and C).

Figure 4-2: (A) Effect of BAY 59-7939 on thrombus formation in a venous stasis model in rats. BAY 59-7939 or the appropriate vehicle were given by intravenous bolus injection in a tail vein 15 min before thrombus induction. (B) Prolongation of prothrombin time (PT). (C) Inhibition of endogenous FXa after activation by Russell's viper venom. Blood samples were withdrawn by cardiac puncture immediately after removal of the thrombus. Each value represents the mean±SEM of 10 animals. *P<0.05; **P<0.01; ***P<0.001

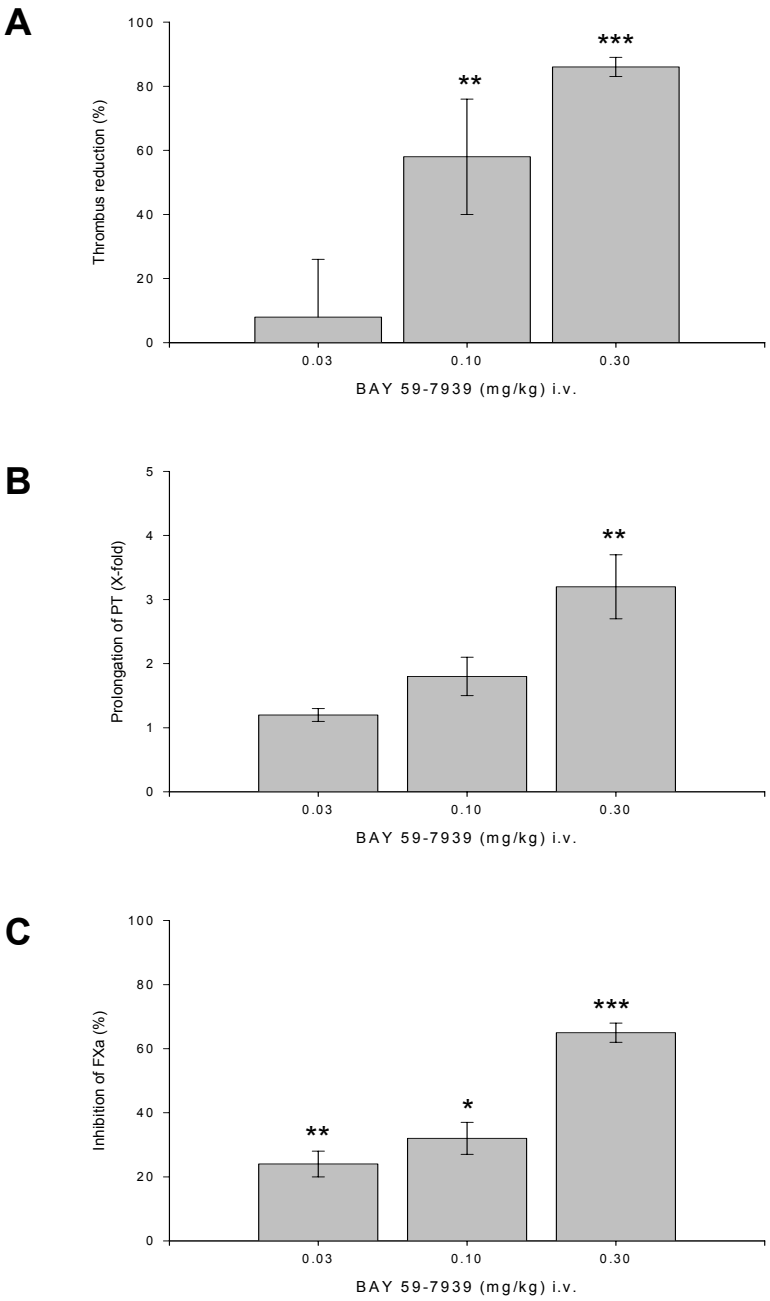


Table 4-3: ED_{50} values of BAY 59-7939 in the rat and rabbit thrombosis models, and estimated plasma concentration of BAY 59-7939, FXa inhibition, and PT prolongation at the ED_{50} (mean ± SEM)

Model	ED_{50} (mg/kg)	BAY 59-7939 (μM)	Inhibition of FXa (%)	Prolongation of PT (X-fold)
Stasis (caval vein), rat	0.1 (IV)	0.10 ± 0.02	32 ± 5	1.8 ± 0.3
AV shunt, rat	5.0 (PO)	1.00 ± 0.03	74 ± 2	3.2 ± 0.3
AV shunt, rabbit	0.6 (PO)	0.07 ± 0.01	92 ± 9	1.3 ± 0.1
Chemical damage, rat	4.0 (PO)	–	–	
Mechanical damage, rat	2.0 (PO)	–	–	

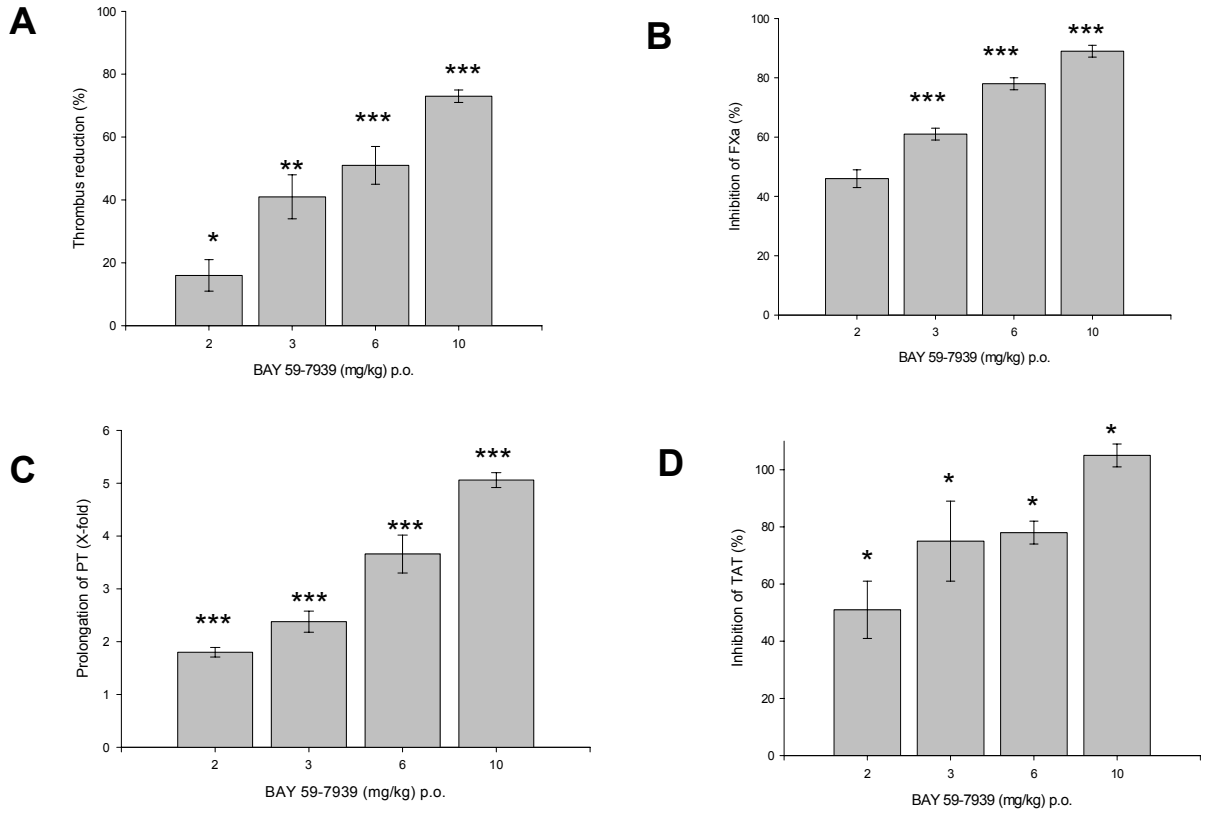
Rat AV-shunt model

Thrombosis was induced by exposure of a thrombogenic surface in an AV shunt.[4, 11] Oral administration of BAY 59-7939 reduced thrombus formation in a dose-dependent manner (Figure 4-3 A), with an ED_{50} of 5.0 mg/kg.

BAY 59-7939 dose-dependently inhibited FXa, prolonged PT, and reduced TAT concentrations in plasma (Figure 4-3 B-D). The effect of BAY 59-7939 at its ED_{50} on FXa activity and PT is shown in Table 4-3.

To reduce thrombus formation by 50%, 10-fold higher concentrations of BAY 59-7939 were required in the AV-shunt model compared with venous thrombosis (venous stasis model). The higher potency of FXa inhibitors in venous vs arterial thrombosis is consistent with the literature.[10, 12, 13]

Figure 4-3: (A) Effect of BAY 59-7939 on thrombus formation in an AV-shunt model in rats. BAY 59-7939 or the vehicle was given orally 90 min before blood was circulated in the shunt model. (B) Inhibition of endogenous FXa after activation by Russell's viper venom. (C) Prolongation of PT. (D) Reduction of thrombin/ antithrombin III complex (TAT). Blood samples were withdrawn from the carotid artery catheter just after removal of the thrombus. Each value represents the mean ± SEM of 6 animals. *P<0.05; **P<0.01; ***P<0.001.



Rat chemical-damage (FeCl3)-induced thrombosis model

Thrombosis was induced by damaging the carotid artery with $FeCl_3$. Oral BAY 59-7939 significantly inhibited thrombus formation with an ED_{50} of approximately 4 mg/kg.[14]

Rat mechanical-damage-induced thrombosis model

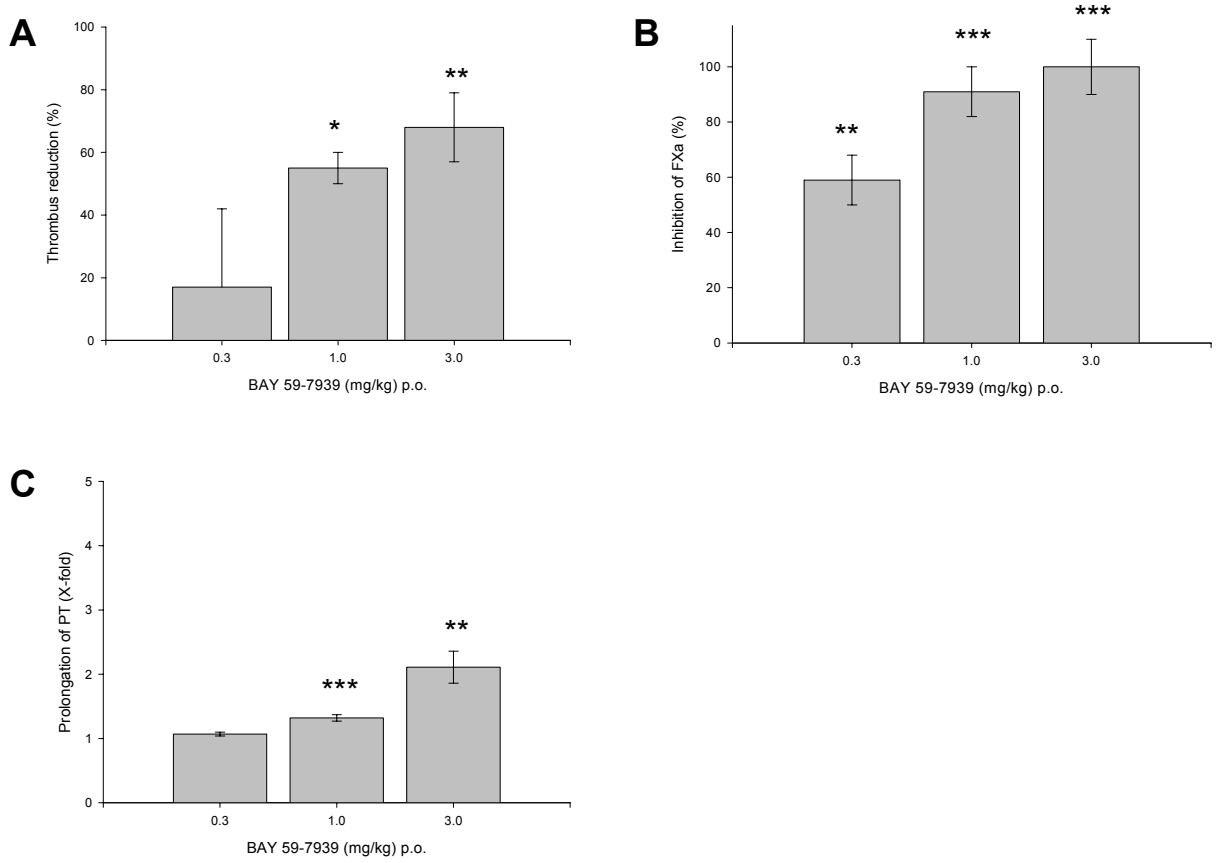
Mechanical damage of the jugular vein caused thrombus formation at the injured

surface. Oral BAY 59-7939 resulted in a significant, dose-dependent inhibition of thrombus formation, with an ED_{50} of 2.0 mg/kg.[15]

Rabbit AV-shunt model

Thrombosis was induced by exposure of a thrombogenic surface in an AV shunt. Oral BAY 59-7939 inhibited thrombus formation significantly and dose dependently (Figure 4-4 A), with an ED_{50} of 0.6 mg/kg.[4, 16] BAY 59-7939 had a dose-dependent effect on FXa activity and PT (Figure 4-4 B and C). At the ED_{50}, FXa activity was reduced almost completely (92 ± 9% inhibition). In contrast, PT was only slightly affected around the ED50 (1.3 ± 0.1-fold increase; Table 4-3). PT values correlated strongly with the plasma concentrations of BAY 59-7939 (r = 0.98).

Figure 4-4: (A) Effect of BAY 59-7939 on thrombus formation in the AV-shunt model in rabbits. The extracorporal circulation was opened 90 min after oral administration of BAY 59-7939 or the appropriate vehicle. (B) Inhibition of endogenous FXa after activation by Russell's viper venom. (C) Prolongation of prothrombin time (PT). Blood samples were withdrawn from the carotid artery catheter just after removal of the thrombus. Each value represents the mean ± SEM of 6 animals. *P<0.05; **P<0.01; ***P<0.001.



Rat bleeding model

Bleeding time was not prolonged after oral administration of 3.0 mg/kg BAY 59-7939, an antithrombotic-effective dose (n = 10), compared with the control group (179 ± 13 sec vs 172 ± 11 sec; P>0.05).[4, 17] After administration of 6.0 mg/kg BAY 59-7939 (n = 10) bleeding time was increased 2.1 ± 0.2-fold, from 185 ± 5 sec

to 381 ± 42 sec (P<0.002), and, after 10.0 mg/kg (n = 10), bleeding time was increased 2.7 ± 0.2-fold, from 171 ± 7 sec to 466 ± 29 sec (P<0.001; Table 4-4).

Table 4-4: Effect of BAY 59-7939 on rat tail-transection bleeding time and rabbit ear-bleeding time (mean ± SEM)

BAY 59-7939 (mg/kg) PO	Prolongation of bleeding time (x-fold)	
	Rat	Rabbit
0.3	-	1.4 ± 0.7
1.0	-	1.7 ± 0.9
3.0	1.0 ± 0.1	1.6 ± 0.8
6.0[a]	2.1 ± 0.2*	-
10.0[a]	2.7 ± 0.2***	-

*P<0.05; ***P<0.001.
[a] At 6.0 and 10 mg/kg, bleeding did not stop within the observation time of 10 min in 2 of 10 rats.

Rabbit bleeding model

At the antithrombotic-effective doses of 1.0 and 3.0 mg/kg, BAY 59-7939 slightly prolonged bleeding times (1.7 ± 0.9-fold and 1.6 ± 0.8-fold, respectively; Table 4-4). However, these effects were not statistically significant (n = 5).[4, 18]

Effect on the antithrombotic activity of enoxaparin or heparin in the arterio-venous shunt model in rats

In order to estimate the interaction potential of BAY 59-7939 with the antithrombotic activity of the LMWH enoxaparin or unfractionated heparin (UFH), the antithrombotic activity of the single compounds was compared to the effects after simultaneous treatment with BAY 59-7939 (given orally) and enoxaparin (given subcutanously) or heparin (given intravenously) in the arteriovenous shunt model in rats.[19]

Oral treatment with 3 mg/kg BAY 59-7939 significantly reduced thrombus formation by 25 ± 4% or 32 ± 9% (Table 4-5 and Table 4-6). Single treatment with 10 or 30 mg/kg enoxaparin given SC 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 4-5). 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 4-6).

Table 4-5: Effects of BAY 59-7939 and enoxaparin (30 mg/kg SC) and their combination on clotting times and FXa activity in the arteriovenous shunt model in rats (mean ± SEM)

Parameter	BAY 59-7939 3 mg/kg PO	Enoxaparin 30 mg/kg SC	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 vs control
*** *P* <0.001 vs control

Table 4-6: Effect of BAY 59-7939 and Enoxaparin (10 mg/kg SC) and their combination on aPTT and FXa activity in the arteriovenous shunt model in rats (mean ± SEM)

Parameter	BAY 59-7939 3 mg/kg PO	Enoxaparin 10 mg/kg SC	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 vs control
** *P* <0.005 vs control
*** *P* <0.001 vs control

15 IE/kg heparin reduced thrombus development by 27 ± 3% (Table 4-7). 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.

Table 4-7: Effect of BAY 59-7939 and heparin and their combinations on clotting times and FXa activity in the arteriovenous shunt model in rats (mean ± SEM)

Parameter	BAY 59-7939 3 mg/kg PO	Heparin 15 IE/kg IV	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 (x-fold prolongation)	1.2 ± 0.1	> 13***	> 14***
Inhibition of FXa (%)	62 ± 3***	96 ± 1***	98 ± 1***

* *P* <0.05 vs control
*** P <0.001 vs control

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.

4.1.3 Safety pharmacology

BAY 59-7939 was studied in a set of acute safety pharmacology assays after single administration (Table 4-8). For PO (rat studies) or intraduodenal (dog study) administration, BAY 59-7939 was prepared as a melt-coprecipitate in demineralized water supplemented with PEG6000 as vehicle. For *in vitro* studies BAY 59-7939 was dissolved in DMSO.

Table 4-8: Safety pharmacological results

Organ system/test item	Animal species, n/group	Route of administration	BAY 59-7939 single dose (mg/kg)	Results	Reference
Behavioral and physiological state					
modified Irwin test	rat 6-8	PO	0,3,10,30	no effect	[20]
Central nervous system					
hypo-/hyperthermic effect (body temperature)	rat 6-8	PO	0,3,10,30	no effect	[20]
psychomotor activity (open field test)	rat 6-8	PO	0,3,10,30	no effect	[20]
nociceptive responsiveness (hot plate test)	rat 6-8	PO	0,3,10,30	nocifensive reactions were dose-dependently delayed with 10 and 30 mg/kg	[21]
anti-/proconvulsive effect (pentylenetetrazole threshold test)	rat 6-8	PO	0,3,10,30	no effect	[21]
anesthesia-potentiating effect (hexobarbital sleeping time test)	rat 6-8	PO	0,3,10,30	no effect	[21]
Cardiovascular and respiratory system					
cardiovascular function, ECG, respiration	anesthetized dog 3	intraduodenal	0,3,10,30	no effect	[22]
hERG mediated potassium channel (*in vitro*)	hERG transfected CHO cells	*in vitro*	0.1-10 μM	no effect	[23]
shape of action potential	Isolated rabbit Purkinje fibers	*in vitro*	0.1-10 μM	no effect	[24]
Metabolism					
blood glucose, triglycerides, cholesterol	rat 6-10	PO	0,3,10,30	no effect	[25, 26]

Table continued

Table 4-8: Safety pharmacological results (continued)

Organ system/test item	Animal species, n/group	Route of administration	BAY 59-7939 single dose (mg/kg)	Results	Reference
Kidneys					
urine volume, electrolyte excretion	rat 10	PO	0,3,10,30	minor natriuretic effect at 10 mg/kg	[25]
Hematology					
erythrocytes, hematocrit, hemoglobin, leucocytes, platelets	rat 10	PO	0,3,10,30	no effect	[25]
thrombin time, thromboplastin time, bleeding time	rat 10	PO	0,3,10,30	coagulation dose-dependently inhibited; thromboplastin time increased; small increase in thrombin time	[25]
Gastrointestinal tract					
barium sulfate transit assay	rat 5	PO	0,3,10,30	no effect	[27]
induction of contractions influence on acetylcholine-, serotonin-, histamine-, barium chloride-induced ileal spasms	guinea pig	isolated ileum	10^{-7}, 10^{-6} g/mL	no effect	[28]

BAY 59-7939 showed no clinically relevant adverse effects. There was no evidence for cardiac risk. As expected from the known pharmacological properties of FXa inhibitors, BAY 59-7939 had the expected effects, ie, dose-dependently inhibition of coagulation with increase of thromboplastin time and small increase of thrombin time (Table 4-9).

Table 4-9: Results of coagulation parameters in rats

Group	Dose (mg/kg) PO	Number of animals	Thrombin time (s)	Thromboplastin time (s)
			(Mean ± SD)	
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 1 sample excluded because of strong coagulation.

BAY 59-7939 plasma concentrations increased dose-dependently up to a mean C_{max} of 3924 µg/L after administration of 30 mg/kg.[22] Key study data and results of kinetics are shown in Table 4-10.

Table 4-10: Summary on exposure in the cardiovascular/respiration study in anesthetized dogs

Parameter	Unit	BAY 59-7939 3 mg/kg		BAY 59-7939 10 mg/kg		BAY 59-7939 30 mg/kg	
		Mean	SD	Mean	SD	Mean	SD
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

Interactions between BAY 59-7939 and other compounds on bleeding time

5 studies assessed the effects of a single oral administration of BAY 59-7939 on the tail transection bleeding time in rats and the potential interactions with acetylsalicylic acid,[29] naproxen,[30] diclofenac,[31] clopidogrel,[32] and warfarin.[33]

The test substances were administered orally at the following doses:

- BAY 59-7939 1, 3, and 10 mg/kg body weight; vehicle: polyethyleneglycol 400 (PEG 400) 100%.

- Clopidogrel (Plavix®) 0.5, 1.5, and 4.5 mg/kg body weight; vehicle: aqueous tylose suspension, 0.5%, w/v.

- Warfarin 0.1, 0.3, and 0.5 mg/kg body weight: vehicle: physiological saline solution, NaCl 0.9%, w/v approximately 24 h before anesthesia and tail transection.

- Diclofenac 1, 3, and 10 mg/kg body weight; vehicle: aqueous hydroxypropyl-methyl-cellulose (HPMC) suspension, 0.2 %, w/v.

- Naproxen 5, 20, and 80 mg/kg body weight; vehicle: aqueous HPMC suspension, 0.2 %, w/v.

- Acetylsalicylic acid 10, 30, and 100 mg/kg body weight; vehicle: ethanol/PEG400/demineralized water, 10:50:40.

Control animals received the appropriate vehicle. Animals were treated with either BAY 59-7939 or the respective other compound alone or by co-administration of both substances. Each treatment group consisted of 12 male rats that were fasted overnight. In the interactions studies of BAY 59-7939 with acetylsalicylic acid, naproxen, diclofenac, and clopidogrel, animals were anesthetized by intraperitoneal injection of pentobarbital-Na (60 mg/kg, Nembutal® or Narcoren®, respectively) approximately 45 min (acetylsalicylic acid, naproxen, diclofenac) and 105 min (clopidogrel) after administration of test substance or vehicle.

In the warfarin interactions study, animals were anesthetized by intraperitoneal injection of pentobarbital-Na (Nembutal®, 60 mg/kg) approximately 45 min after administration of BAY 59-7939 and approximately 24 hours after administration of warfarin or the respective vehicle. Further 15 min later, the distal 2 mm of the animals tails was transected by means of a dorsoventral cut using a razor blade, tails were immersed in physiological saline at 37 °C, and the time to cessation of bleeding was measured. With warfarin only, the tail transection bleeding time was

assessed in 2 independent experiments, ie, in animals that had *ad libitum* access to food (fed rats) and those that were fasted for about 16-20 h before tail transection (fasted rats).

Single administration of BAY 59-7939 and the other 5 substances dose-dependently prolonged the tail transection bleeding time in rats in the dose ranges tested. When co-administered, the bleeding time prolonging effects of BAY 59-7939 and all substances were additive in the dose range tested, which in the case of warfarin was also independent of the animals' feeding state. The additive effects were substantial with naproxen and least prominent with diclofenac.

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 (approximately 92%); bioavailability of 60% in rats and 60 – 86% in dogs.
- Linear pharmacokinetics in rats and dogs after IV and oral administration.
- No major circulating metabolites in rat, dog, and human plasma.
- Rapid elimination from plasma in rats and dogs.
- Moderate tissue affinity of radioactivity in rats, binding to melanin-containing tissues (pigmented skin areas and eyes) to minor extent; only a low amount of the radioactive dose subject to mammary secretion in lactating rats.
- Moderate to high concentration- and species-dependent protein binding.
- Displacement from protein binding sites at therapeutic concentrations in human plasma only by salicylic acid and glibenclamide; no displacement at therapeutic concentrations by 8 other compounds.
- Morpholino moiety as main target of metabolic degradation.
- CYP3A4 decisive enzyme for biotransformation *in vitro.*
- No inhibition or induction of major CYP isoforms.

- 95%, 78%, and 89% of the dose in the excreta attributed to known structures following administration to bile-duct cannulated rats, dogs and humans.
- Excretion of radioactivity in rats predominantly via biliary/fecal route, renal route contributed considerably in dogs, renal excretion dominated in humans.
- 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, displacement from protein binding sites, and drug metabolism in several species including man.

The 2 species used in pharmacokinetic investigations, rat and dog, showed similar pharmacokinetics.

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 (approximately 66.8%) and almost complete in dogs (approximately 92%). 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 IV 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 IV (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 moderate to high, concentration- and species-dependent. The fraction unbound to plasma proteins (fu) was about 1.27% in rats, 10.4% in dogs, and 5.07% in humans, respectively, at the BAY 59-7939 concentration of about 0.1 to 3 mg/L. Albumin was identified as the main binding component in human plasma. Displacement of BAY 59-7939 from protein binding sites occured only by addition of salicylic acid and glibenclamide at therapeutic concentrations in human plasma, resulting in a slight increase of fraction unbound of BAY 59-7939.

The radioactivity was rather heterogeneously distributed to organs and tissues. The distribution patterns after IV and oral administration were similar. There was binding to melanin-containing tissues (pigmented skin areas and eyes) to minor extent in the pigmented rat. [^{14}C]BAY 59-7939 and/or its radiolabeled metabolites showed only a moderate tissue affinity. 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. Hydroxylations lead to metabolites M-2 and M-3, further oxidation and ring opening to M-1 were observed to a minor degree.

In human and rat hepatocytes in sandwich culture, metabolite M-1 was detected as major metabolite. In addition, metabolite M-4, the glycine conjugate of the 5-chloro-2-thiophene-carboxylic acid, was formed in significant amounts. 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 Km 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 may be 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.

The biotransformation of BAY 59-7939 in vivo has been studied in rats, dogs, and humans. Following intraduodenal/oral administration, the unchanged compound was by far the main compound in plasma at all investigated time points, independent of the species. No major circulating metabolites were detected.

The urinary and fecal/biliary radioactivity profiles were qualitatively similar in all three species. The main metabolite M-1 was eliminated via the renal and biliary/fecal routes. Metabolite M-4 was excreted renally.

In total, 95%, 78%, and 89% of the dose administered could be assigned to known structures in rats, dogs and humans.

The radioactivity in the rat was excreted mainly via the biliary/fecal route. Only a low amount of the radioactive dose is subject to mammary excretion in lactating rats. In dogs contributed also the renal route considerably to elimination. In man renal excretion dominated. The residues remaining in the body of rats seven days after administration were low (approximately 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

The pharmacokinetics of [^{14}C]BAY 59-7939-radioactivity was studied after IV bolus administration and after oral administration to male Wistar rats at doses of 3 mg/kg body weight (BW).[34] Additional studies were performed in bile duct-cannulated (BDC) rats with intraduodenal and IV 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 IV 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 4-11).

Table 4-11: Pharmacokinetics of radioactivity in male Wistar rats after single administration of [^{14}C]BAY 59-7939 (geometric means of 3 male animals per time point)

Parameter	Unit	[^{14}C]BAY 59-7939 3 mg/kg IV	[^{14}C]BAY 59-7939 3 mg/kg PO
AUC	[mg-eq·h/L]	8.78	4.20
AUC_{norm}	[kg·h/L]	2.82	1.35
CEQ_{max}	[mg-eq/L]	NC	2.04
$CEQ_{max,norm}$	[kg/L]	NC	0.657
t_{max}	[h]	NC	0.25
$T_{1/2app}$	[h]	1.81	1.46
Interval[a]	[h]	4 – 8	4 - 8
$T_{1/2}$	[h]	18.8	42.1
Interval*	[h]	8 – 48	24 – 72

a Used for regression to determine terminal half-life

4.2.2.1.2 Studies with non-labeled compound

The pharmacokinetics of the unchanged substance was investigated in male Wistar rats after single IV bolus injection of 1 and 3 mg/kg and after oral administration of 1, 3, and 10 mg/kg BW, respectively.[35] The following pharmacokinetic parameters were determined for the unchanged substance (Table 4-12 and Table 4-13, respectively).

Table 4-12: Pharmacokinetics of BAY 59-7939 after IV administration to male Wistar rats (geometric means of 3 animals per time point)

Parameter	Unit	BAY 59-7939 1 mg/kg	BAY 59-7939 3 mg/kg
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[a]	[h]	1-4	4-8

a Used for regression to determine terminal half-life

After single IV 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 1.53 into account,[36] the whole blood clearance is low with 0.6 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/kg BW to male Wistar rats, maximum plasma concentrations were rapidly reached after 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 4-13: Pharmacokinetics of BAY 59-7939 after single oral administration to male Wistar rats (geometric means of 3 animals per time point)

Parameter	Unit	BAY 59-7939 1 mg/kg	BAY 59-7939 3 mg/kg	BAY 59-7939 10 mg/kg
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[a]	[h]	4-8	4-8	2-8
F	[%]	58.2[b]	65.6[b]	57.4[b]

a Used for regression to determine half-life
b Calculated with the mean AUC_{norm} of 2.56 kg·h/L after 1 and 3 mg/kg IV

This half-life roughly approximated that observed after IV 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 approximately 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

The pharmacokinetics of radioactivity was studied in female Beagle dogs after a single IV 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.[37] The following pharmacokinetic parameters (geometric means and deviations) were determined for radioactivity (unchanged substance and metabolites) (Table 4-14).

Table 4-14: Pharmacokinetics of radioactivity after single administration of [^{14}C]BAY 59-7939 to Beagle dogs (geometric means of 3 female animals per time point)

Parameter	Unit	[^{14}C]BAY 59-7939 1 mg/kg IV (T = 0.25 h)	[^{14}C]BAY 59-7939 1 mg/kg PO
AUC	[mg-eq·h/L]	5.55	5.10
AUC_{norm}	[kg·h/L]	5.55	5.10
CEQ_{max}	[mg-eq/L]	2.80	1.67
$CEQ_{max,norm}$	[kg/L]	2.80	1.67
t_{max}	[h]	0.25	0.572
$t_{1/2}$	[h]	111	128
Interval[a]	[h]	48 – 168	48 – 168
f_{abs}[b]	[%]	not calculated	91.9

a Used for regression to determine half-life
b Fraction absorbed
c 1-sec interval ranges from mean/SD to mean SD

The absorption of radioactivity was high after oral administration of [^{14}C]BAY 59-7939 and amounted to 92% of the dose (estimated from a comparison of the AUC_{norm} for the total radioactivity in plasma after oral and IV administration).

4.2.2.2.2 Studies with non-labeled compound

The pharmacokinetics of the unchanged substance was investigated in female Beagle dogs after a single IV 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.[37, 38] Pharmacokinetic parameters

(geometric means and standard deviations) were determined for the unchanged substance (Table 4-15 and Table 4-16).

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 0.34 L/(h·kg) in the dog, taking an *in vitro* plasma to blood ratio of 1.14 into account.[36] The mean volume of distribution (V_{ss}) was moderate, amounting to 0.4 L/kg.

Table 4-15: Pharmacokinetics of BAY 59-7939 after IV infusion (T >0.25 h) to Beagle dogs (geometric means of 3 female animals per time point)

Parameter	Unit	BAY 59-7939 0.3 mg/kg IV	BAY 59-7939 1 mg/kg IV
AUC	[mg·h/L]	1.00	3.18
AUC_{norm}	[kg·h/L]	3.34	3.18
C_{max}	[mg/L]	0.762	2.36
$C_{max,norm}$	[kg/L]	2.54	2.36
t_{max}	[h]	NC	0.250
$t_{1/2}$	[h]	0.952	0.968
Interval[a]	[h]	0.25 - 6	3 – 8
V_{ss}	[L/kg]	0.402	0.398
CL	[L/(h·kg)]	0.300	0.314

a Used for regression to determine terminal half-life

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 IV administration. Generally, the AUC rose also dose-proportionally in the examined dose range.

However, the AUC after oral administration of radiolabeled [^{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%, Table 4-16).

Table 4-16: Pharmacokinetics of BAY 59-7939 after oral administration to Beagle dogs (geometric means of 3 female animals per time point)

Parameter	Unit	BAY 59-7939 0.3 mg/kg PO	BAY 59-7939 1 mg/kg PO	BAY 59-7939 3 mg/kg PO
AUC	[mg·h/L]	0.605	2.72	6.03
AUC_{norm}	[kg·h/L]	2.02	2.72	2.01
C_{max}	[mg/L]	0.254	1.28	2.72
$C_{max,norm}$	[kg/L]	0.848	1.28	0.906
t_{max}	[h]	0.454	0.572	0.500
$t_{1/2}$	[h]	0.876	0.915	0.924
Interval[a]	[h]	2 – 8	1.5 – 10	4 – 8
F	[%]	60.4[b]	85.5[c]	60.2[b]

a Used for regression to determine terminal half-life
b Related to 0.3 mg/kg IV infusion
c Related to 1.0 mg/kg IV infusion

The AUC_{norm} of unchanged BAY 59-7939 covered 57% of the radioactivity AUC_{norm} after IV 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[39, 40] (4 and 13 weeks) and dogs (4 weeks).[41, 42] This is possibly due to differences in absorption between Day 1 and Week 4/Week 13 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). A slightly lower AUC after repeated administration to dogs was observed in the 13 week toxicity study.

4.2.4 Tissue distribution

4.2.4.1 Whole body autoradiography

The qualitative distribution patterns of radioactivity were investigated in rats using whole-body autoradiography.[43]

[^{14}C]BAY 59-7939 was administered at a single oral dose of 3 mg/kg and an IV dose of 1 mg/kg BW 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 1 male pigmented rat (Long Evans). The rats were sacrificed at selected times up to 7 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 min after IV 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).

The distribution of radioactivity during the period of absorption and main elimination is shown in Table 4-17.

Table 4-17: Tissue distribution of radioactivity in male Wistar rats between 2 - 8 h after oral administration of [^{14}C]BAY 59-7939 as determined qualitatively by whole body autoradiography (selected organs after oral administration of [^{14}C]BAY 59-7939)

Highest exposure	Moderate exposure	Low exposure
Gastrointestinal contents	Liver	Blood
Contents of bile-ducts	Kidneys	Heart
Contents of urinary bladder	Skin	Lungs
	Intestinal mucosa	Skeletal muscles
	Coagulation gland	Testes
		Seminal vesicles
		Salivary and lachrymal glands
		Lymphatic system
		Pancreas
		Thyroid
		Adrenals
		Adipose tissues
		Eye wall > (LOD) brain
		Spinal cord
		Bone
		Eye-lens

24 h 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

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 BW.[44]

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

[^{14}C]BAY 59-7939 and/or its radiolabeled metabolites showed moderate tissue affinity with similar radioactivity concentrations in most of the organs and tissues as determined in blood and plasma.

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), esophagus (factor 5.6), 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, adrenal glands, skin, renal fat, aorta, and caval vein showed radioactivity AUCs in the range between blood and plasma. Lower AUCs (<2.0 mg-eq·h/L) were calculated for carcass, eyes, 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) – 11.44 h (brain). 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), spleen ($t_{1/2}$: 6 h) and the body excluding the gastrointestinal tract ($t_{1/2}$: 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, blood cell/plasma distribution, and displacement from protein binding sites

The binding of BAY 59-7939 to proteins was determined by the equilibrium dialysis method *in vitro* in plasma of various animal species and man using radio-labeled [^{14}C]BAY 59-7939 (Table 4-18).[36]

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 5.07% in humans (men) at plasma concentrations of approximately 0.1 to 3 mg-eq/L. The f_u was 6.45% in mouse and thus very similar to humans. At the same concentration level the f_u was lower in rat with only 1.27%. In dog (f) the f_u was about twice as high as in humans amounting to 10.4%. The highest f_u was measured in rabbit with 23.4%.

Albumin was identified as an important binding component in human plasma. Acidic α_1-glycoprotein contributed only marginally to the binding of BAY 59-7939 in human plasma.

Table 4-18: In vitro plasma protein binding of [^{14}C]BAY 59-7939 in different species

Species	Concentration [mg-eq/L]	f_u[a] [%]	C_P/C_B[b]
Human (m, f)	0.104 to 3.09	5.07	1.40
Wistar rat (m, f)	0.0969 to 2.97	1.27	1.53
Dog (f)	0.101 to 2.83	10.4	1.14
Rabbit (f)	0.107 to 3.22	23.4	-
CD-1 mouse (m)	0.108 to 3.03	6.45	-
Rhesus monkey (f)	0.102 to 3.02	18.3	-
Pig (m)	0.100 to 1.41	7.13	-

a Fraction unbound

b Concentration plasma (µg-eq/mL) / concentration blood (µg-eq/mL)

The binding of [^{14}C]BAY 59-7939 to plasma proteins was fully reversible in plasma of rat, dog, and man. The mean ratio C_{plasma}/C_{blood} was between 1.14 and 1.53 for [^{14}C]BAY 59-7939 in the investigated species including rat, dog, and man.

Furthermore, displacement of BAY 59-7939 from plasma protein binding sites by other highly protein bound drugs was investigated.[45] Most of the investigated substances including warfarin, clofibrate, ibuprofen, propranolol, digitoxin, phenytoin, and nifedipine did not exert any influence on the protein binding of BAY 59-7939 neither when added at therapeutic nor at over-therapeutic concentrations. Gemfibrozil slightly increased the fraction unbound of BAY 59-7939 to 9.75%, but only at over-therapeutic concentrations (500 mg/L). Salicylic acid and glibenclamide increased the fraction unbound of BAY 59-7939 slightly to about 11.6% and 9.52%, respectively at therapeutic concentrations of 200 and 100 mg/L, respectively. At over-therapeutic concentrations of 1000 and 500 mg/L f_u increased to 29.0% and 25.9%, respectively.

4.2.5 Metabolism

4.2.5.1 Metabolism in vitro

4.2.5.1.1 Species comparison

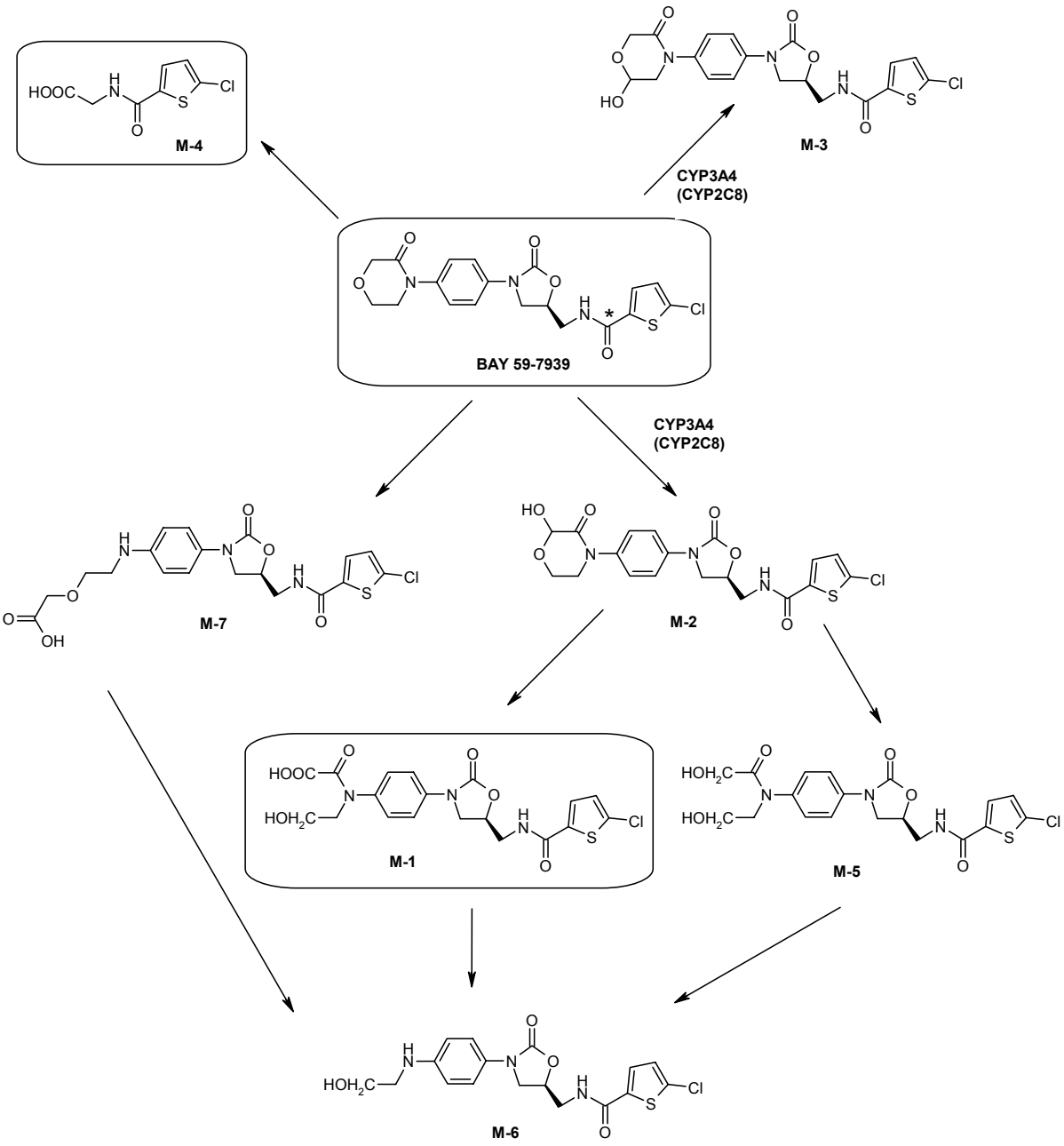
Incubations of [^{14}C]BAY 59-7939 with liver microsomes from man (mix), Rhesus monkey, Beagle dog, New Zealand rabbit, Wistar rat, CD-1 mouse, and NMRI mouse revealed Rhesus monkey and Wistar rat as the most human like animals.[46] Additionally, Beagle dog and NMRI mouse were attributed as human like, 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-3 was only a minor metabolite.[47, 48] 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 4-5: Proposed metabolic pathways observed *in vitro* and *in vivo* (rat, dog, man) studies



*= labeling position

4.2.5.1.2 CYP enzyme involved in metabolism

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.[49] 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

In order to estimate the inhibitory potency of BAY 59-7939 towards 8 human cytochrome P450 enzymes, incubations of standard probes with recombinant CYPs were performed in the absence and presence of the compound.[50] No relevant effects on CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4-catalyzed biotransformation were observed as indicated by K_i 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

The enzyme inducing potential of BAY 59-7939 was investigated in cultured human hepatocytes of 4 different donors.[51] Cells were exposed with 5 ng/mL to

10,000 ng/mL BAY 59-7939 for five days in comparison to the prototypic inducers omeprazole (OME, CYP1A2) and rifampicin (RIF, CYP3A4). No inductive effects of BAY 59-7939 on human CYP1A2 and 3A4 after repeated exposure up to 10,000 ng/mL BAY 59-7939 were observed. This concentration is equivalent to more than 370 times the C_{max} value observed after multiple oral dose applications of 30 mg bid of BAY 59-7939 in volunteers (C_{max} = 451.9 µg/L). Therefore, the risk to observe clinical drug-drug interactions through induction of CYP1A2 and 3A4 is considered to be very low.

4.2.5.1.5 CYP3A4 drug-drug interaction potential with comedications

The potential for drug-drug CYP3A4 interactions between BAY 59-7939 and a number of drugs that may be co-administered clinically was explored in CYP interaction studies *in vitro*.[52]

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, eg, nifedipine 0.09 µM (60 mg PO) or midazolam 0.07 µM (7.5 mg PO); therefore, drug-drug CYP3A4 interactions *in vivo* at therapeutic levels of these drugs are unlikely.

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 PO). 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. Refer to Section 5.2.5 for the results of the clinical interaction studies with CYP3A4 substrates/inhibitors.

4.2.5.2 Metabolism in vivo

4.2.5.2.1 Rat

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.[53, 54] The metabolic pattern is shown in Table 4-19.

Table 4-19: Metabolic pattern of radioactivity [%] in rat plasma (PO, 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

The AUC of unchanged BAY 59-7939 covered 83.3% of the AUC of radioactivity, whereas the most prominent metabolite M-1 (BAY 76-2298) covered only 6.3% of the radioactivity AUC.

1, 2, 4, and 8 h after administration approximately 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 4-20.

Table 4-20: 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	PO	23.6	5.2	9.1	0.7	4.1	3.2
0-48	IV	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	IV (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 (Table 4-21) compared to IV administration, reflecting incomplete absorption from the duodenum.

Approximately 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 IV administration.

The metabolite pattern in rat bile fractions was investigated after intraduodenal and IV administration of 3 mg/kg [^{14}C]BAY 59-7939 to BDC rats. The metabolic pattern is shown in Table 4-21.

Table 4-21: 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	IV	48.4	0.0	44.4	0.0	0.0

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

The metabolite pattern in fecal extracts was investigated after intraduodenal and IV administration of 3 mg/kg [^{14}C]BAY 59-7939. The metabolic pattern is shown in Table 4-22.

Table 4-22: 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	IV	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 IV administration, reflecting incomplete absorption from the duodenum (mainly) in addition to the extrabiliary excretion. About 13% of the dose was recovered in fecal extracts after IV administration, resulting from extrabiliary excretion of BAY 59-7939 related radioactivity.

Approximately 100% of the radioactivity in the 0 - 24 h feces extracts, corresponding to approximately 13% of the dose, could be attributed to known structures after IV administration.

Approximately 87% of the dose could be attributed to known structures in the excreta after IV administration to BDC rats.

4.2.5.2.2 Dog

The biotransformation of BAY 59-7939 was investigated in Beagle dogs following oral and IV administration of 1 mg/kg [^{14}C]BAY 59-7939.[55]

The metabolic pattern in dog plasma is shown in Table 4-23.

Table 4-23: Metabolic pattern [% of radioactivity] in dog plasma (PO, selected metabolites)

Time [h]	BAY 59-7939	M-1	M-2	M-3
0.25	87.7	0.5	0.7	3.8
0.5	86.0	1.1	0.7	3.4
1	72.4	3.5	1.2	4.2
2	69.5	6.8	1.2	2.7
4	68.4	7.3	1.6	2.9
8	43.3	7.8	0.9	1.1
10	30.6	11.1	0.0	0.0

Approximately 42 – 93% of the radioactivity in plasma could be attributed to known structures until 10 h following oral administration. No major circulating metabolites were observed in dog plasma. The drug covered 70.9% and the most prominent metabolite M-1 covered only 5.2% of the radioactivity AUC.

The metabolite pattern in dog urine fractions was investigated after oral and IV administration of 1 mg/kg [^{14}C]BAY 59-7939 to Beagle dogs. The metabolic pattern is shown in Table 4-24

Table 4-24: Metabolic pattern [% of dose] in urine of dogs (selected metabolites)

Time [h]	Route	% of dose excreted	BAY 59-7939	M-1	M-2	M-3	M-4
0 – 120	p.o.	52.0	7.9	8.5	1.9	7.8	15.7
0 – 96	i.v.	50.5	8.6	7.1	1.3	7.4	16.7

Approximately 83% of radioactivity in 0 – 120 h urine fractions, corresponding to 43% of the dose, could be attributed to known structures following oral administration.

The metabolite pattern in dog fecal extracts was investigated after oral and IV administration of 1 mg/kg [^{14}C]BAY 59-7939 to Beagle dogs. The metabolic pattern is shown in Table 4-25.

Table 4-25: Metabolic pattern [% of dose] in feces of dogs (selected metabolites)

Time [d]	Route	% of dose excreted	BAY 59-7939	M-1	M-2	M-3	M-5
0 – 5	PO	42.5	1.1	26.2	0.7	2.8	2.1
0 – 4	IV	40.0	1.3	23.6	0.6	1.6	2.0

Approximately 82% of radioactivity in 0 – 5 day fecal extracts, corresponding to 35% of the dose, could be attributed to known structures following oral administration.

Overall, approximately 78% 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.

4.2.5.2.3 Human

The biotransformation of BAY 59-7939 was investigated in healthy, male subjects following oral administration of approximately 9.5 mg (1.76 MBq) [^{14}C]BAY 59-7939.[56, 57] The metabolic pattern in human plasma is shown in Table 4-26.

Table 4-26: Metabolic pattern [% of radioactivity] in human plasma (PO, selected metabolites)

Time [h]	BAY 59-7939	M-1
0.25	98.2	0.0
0.5	95.9	1.0
1	95.3	2.5
2	93.6	3.9
4	92.2	6.0
8	92.9	5.1
10	100.0	0.0

From 0.25 to 12 h following oral administration, approximately 96 – 100% of the radioactivity in plasma could be attributed to known structures. No major circulating metabolites were observed in human plasma. The drug covered 88.8% and the most prominent metabolite M-1 covered only 3% of the total radioactivity AUC(0-t_n).

The metabolic pattern in human urine is shown in Table 4-27.

Table 4-27: Metabolic pattern [% of dose] in urine of man (selected metabolites)

Time [h]	Route	% of dose excreted	BAY 59-7939	M-1	M-2	M-3	M-4	M-7
0 – 48	PO	65.4	36.2	13.1	2.1	0.7	7.6	3.7

Approximately 99% of radioactivity in 0 – 48 h urine fractions, corresponding to 65% of the dose, could be attributed to known structures.

The metabolic pattern in feces is shown in Table 4-28.

Table 4-28: Metabolic pattern [% of dose] in feces of man (selected metabolites)

Time [d]	Route	% of dose excreted	BAY 59-7939	M-1	M-2	M-3	M-5	M-7
0 – 4	p.o.	26.4	7.3	8.9	1.6	1.1	1.6	2.9

Approximately 92% of radioactivity in 0 – 4 day fecal extracts, corresponding to 24% of the dose, could be attributed to known structures.

Overall, approximately 89% of the dose could be attributed to known structures in the excreta following oral administration to human.

4.2.6 Excretion

[^{14}C]BAY 59-7939 radioactivity was excreted via the biliary/fecal route as well as via the renal route after IV and oral administration to Wistar rats, Beagle dogs, and man (Table 4-29, Table 4-30, and Table 4-31).[34, 37, 55-57]

In ***intact rats***, 65.5% of the radioactivity was found in feces and 28.1% was excreted via urine until Day 7 after IV 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 was excreted within the first day after administration. The recovery amounted to 93.9% (IV) and 91.8% (PO), respectively of the administered radioactive dose.

Bile duct-cannulated rats excreted fairly the whole radioactive dose within 24 h after IV 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 IV administration of [^{14}C]BAY 59-7939 to bile duct-cannulated rats, 30.3% of administered radioactivity was found in urine, 48.4% in bile and 12.9% in feces. In BDC rats with IV 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% (IV) in relation to the administered dose.

The radioactive residues in the animals were low. 24 h after administration, the residues in the animal excluding the gastrointestinal tract were 0.421% (intraduodenal) and 0.755% (IV) 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 4-29: 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[b]	Recovery
IV 7 days	3	28.1	NA	65.5	0.224	93.9
PO 7 days	3	24.7	NA	66.9	0.147	91.8
i.d.[a] 1 day	3	17.1	34.7	46.4	0.421	98.8
IV [a] 1 day	3	30.3	48.4	12.9	0.755	92.7

a Bile duct-cannulated rats (BDC)
b Animal excluding the gastrointestinal tract

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

The extent of radioactivity excretion with milk was investigated in lactating Wistar rats following oral administration of [^{14}C]BAY 59-7939.[58] Only 2.1% of the radioactive dose was secreted into the milk. The milk/plasma ratio for AUC was 2.3. Conclusively, [^{14}C]BAY 59-7939 radioactivity can penetrate from circulating blood into milk. However, due to the rapid biliary and urinary excretion only a low amount of the administered radioactive dose is subject to mammary secretion.

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

Table 4-30: 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
IV 7 days	1	50.7	40.4	1.83	93.0
PO 7 days	1	52.2	42.8	2.03	97.0

In male subjects, 28.0% of the radioactivity was found in feces and 65.7% were excreted via urine until Day 7 after administration. The recovery amounted to 93.7% of the administered radioactive dose.

Table 4-31: Excretion of radioactivity in male human subjects [% of dose] after single administration of [^{14}C]BAY 59-7939

Route / time	Dose [mg]	Urine	Feces	Recovery
PO / 7 days	approximately 9.5	65.7	28.0	93.7

4.2.7 Discussion including interspecies comparison

The 2 animal species showed similar and linear pharmacokinetics within the investigated dose range following IV and oral administration, with a moderate to high bioavailability of 60% in rats and 60 - 86% in dogs. 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 binding of the substance to plasma proteins was moderate to high, concentration- and species-dependent.

BAY 59-7939 exhibited a moderate tissue affinity and did not show evidence of accumulation or irreversible retention in organs and tissues of rats.

Elimination of BAY 59-7939 from plasma was rapid (with no major circulating metabolites detected in plasma of rat, dog and human) and excretion occurred in the investigated animal species and in human via both renal and fecal/biliary routes.

The morpholino moiety of BAY 59-7939 was the main target of oxidative metabolism (CYP3A4) in the animal species and human, leading via ring opening to metabolite M-1, the major metabolite in the excreta of animals and human. The biotransformation pathways of BAY 59-7939 in humans were similar to those in rats and dogs, and were similar to those observed in the *in vitro* metabolism studies.

4.3 Toxicology

Key Points:

- Low acute toxicity in rats and mice.
- In principle well tolerated in rats and dogs after subacute and subchronic (dog, mouse) as well as after chronic administration (rat).
- Except for a slight body weight gain reduction in rats after chronic treatment, compound-related findings in repeat dose toxicity studies (effects on clotting parameters, spontaneous bleeding in dogs with secondary anemia) can be explained by the pharmacological activity of BAY 59-7939.
- No evidence for genotoxicity.
- No evidence for teratogenicity. Developmental toxicity is mainly characterized by maternal toxicity due to exaggerated pharmacodynamic effects.

4.3.1 Summary

BAY 59-7939 has a low acute toxicity in rats and mice, ie, the highest dose that could be technically applied (500 mg/kg PO, 25 mg/kg IV) did not cause any mortality.

BAY 59-7939 was administered to dogs and mice up to treatment duration of 13 weeks and of 26 weeks in rats. BAY 59-7939 was generally well tolerated in all species examined. The changes in the coagulation parameters seen already at low doses were expected and can be explained by the pharmacological activity of the drug.

In dogs, the prolongation of clotting time resulted in an increased bleeding risk after invasive procedures or even spontaneous bleeding with anemia at doses of 150 mg/kg (13-week study). The slight increases in reticulocytes as well as the increase in spleen weights and in spleen extramedullary hematopoiesis are considered as sequels of these hematomas and blood loss, respectively.

In the subchronic feeding study in rats, the increased incidence of pancreatic hemorrhage and bleeding sequels were also considered secondary to the pharmacologic mode of action of the compound.

In the chronic rat study (26-week treatment) and the 13-week rat feeding study body weight gain reduction was seen, which has to be considered as an unspecific toxic effect of the compound. No organ specific toxicity was observed.

In summary, all findings except for a decrease in body weight gain in rats after can be explained as a consequence of the anticoagulant effect of the compound and hence secondary to an enhanced pharmacodynamic effect of BAY 59-7939 under the conditions of the toxicological experiment. However, since the bleeding episodes in dogs resulted in clinically evident and probably life-threatening anemia, the dose of 150 mg/kg clearly exceeds the maximum tolerated dose. The increased incidence of vomitus observed after subacute treatment in dogs was not seen after subchronic treatment in dogs and is therefore most likely considered being an incidental finding. Furthermore, it is not reflected in man.

The genotoxic/mutagenic potential of BAY 59-7939 was assessed in 2 *in vitro* and 1 *in vivo* assays. There was no evidence for a genotoxic potential of BAY 59-7939.

No effect on fertility of male and female rats were seen up to the highest dose tested (200 mg/kg).

Developmental toxicity was characterized by remarkable maternal toxicity (eg vaginal/uterine hemorrhage with subsequent fetal resorption and/or abortion) related to the pharmacological mode of action of the compound. Neither in rats nor in rabbits was a primary teratogenic potential of the compound identified.

In summary and from a toxicological point of view, there are no objections to use BAY 59-7939 in man.

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 PO administration and moderately to non-toxic after IV administration (Table 4-32).[59] Decreased motility, abdominal position, labored breathing, narrowed palpebral fissure, and piloerection were observed in male and female mice after IV administration of BAY 59-7939.

Table 4-32: Summary of acute toxicity studies in mice and rats

Species	Sex	Number of animals	Route of administration	$LD_{50\ mg}$/kg BW
Mouse	male	5	PO	>500[a]
Mouse	female	5	PO	>500[a]
Mouse	male	5	IV	>25[a]
Mouse	female	5	IV	>25[a]
Rat	male	5	PO	>500[a]
Rat	female	5	PO	>500[a]

a Because of technical reasons, higher doses could not be administered

4.3.3 Repeat dose toxicity

BAY 59-7939 was administered in repeat-dose toxicity studies to rats up to a treatment period of 26 weeks and in dogs and mice up to a treatment period of 13 weeks (Table 4-33).[39, 41, 60-65]

After repeated administration up to 26 weeks BAY 59-7939 was generally well tolerated in rats. In the chronic study and the subchronic feeding study a decreased body weight gain without any evidence for organ specific toxicity was seen. The changes in the coagulation time (HQuick) seen at doses ≥12.5 mg/kg were expected and can be explained by the pharmacological activity of the drug.

The same holds true for the increase of PTT and PT in dogs at ≥50 mg/kg. This prolongation of the clotting time resulted in an increased bleeding risk after invasive procedures or even spontaneous bleeding with anemia at doses of 150 mg/kg. The slight increases in reticulocytes as well as the increase in spleen weights and in

spleen extramedullary hematopoiesis are considered as sequels of the hematomas and blood loss, respectively. In summary, all findings except for a slight increased incidence of vomiting after high doses reported in the 4-week and 13-week studies in dogs can be explained as a consequence of the anti-coagulative effect of the compound and hence secondary to an enhanced pharmacodynamic effect of BAY 59-7939. However, since the bleeding episodes resulted in clinically evident and partly life-threatening anemia, the dose of 150 mg/kg clearly exceeds the maximum tolerated dose. Vomiting observed after high doses in dogs is obviously a dog-specific effect and not reflected in man.

Table 4-33: Summary of repeat dose toxicological studies in rats and dogs

Study duration Ref-erence	Species (n)	BAY 59-7939 (mg/kg BW/day)	Findings (at mg/kg/day)	NOAEL (mg/kg/day)
4 weeks [62]	Rat ♂ (10) ♀ (10)	0, 12.5, 50, 200 oral, gavage	Increase in Hquick (♂,♀,≥12.5 mg/kg); Increase in glutathion transferase and epoxide hydrolase in ♂ (50 mg/kg); Decrease in heart weights in ♀ (200 mg/kg); Transient decrease in body weights in ♂ (200 mg/kg)	50 mg/kg (disregarding enhanced pharmaco-dynamic effects of BAY 59-7939)
4 weeks [61]	Dog (Beagle) ♂ (3) ♀ (3)	0, 15, 50, 150 oral, gavage	Increased incidence in hematoma, reticulocytes and hematopoiesis in the spleen in ♂ and ♀ (≥15 mg/kg); Vomiting in ♂ and ♀ (≥50 mg/kg); Increase in PTT and PT in ♂ and ♀ (≥50 mg/kg); Increase in spleen weight in ♂ (≥50 mg/kg); Discolored feces in ♂ and ♀ (150 mg/kg)	15 mg/kg (based on vomiting, disregarding enhanced pharmaco-dynamic effects of BAY 59-7939)
13 weeks [39]	Rat ♂ (10) ♀ (10)	0, 12.5, 50, 200 oral, gavage	Increase in Hquick (≥12.5) mg/kg; Slight transient increase of ALAT in ♂ (≥50 mg/kg); Decrease in LDH in ♂ (≥50 mg/kg) and ♀ (≥12.5 mg/kg); Slight transient increase of calcium and phosphate in ♂ (200 mg/kg); Increased water consumption in ♀ (200 mg/kg); Slight induction of phase II enzymes in ♀ (200 mg/kg)	200 mg/kg (disregarding enhanced pharmaco-dynamic effects of BAY 59-7939)
13 weeks [41]	Dog (Beagle) ♂ (3) ♀ (3)	0, 15, 50, 150 oral, gavage	Episodes of spontaneous bleeding resulting in anemia with respective hematological changes (♂, ♀, 150); Slightly reduced feed intake (♂, ♀, ≥50); Slightly increased vomiting (♂, ♀ 150); Increased PT and aPTT (♂, ♀, ≥15); Focal hemorrhage in several organs (acute or bleeding residues (hemosiderin) (♂ and ♀ (150)	50 mg/kg (based on increased incidence of vomiting disregarding enhanced pharmaco-dynamic effects of BAY 59-7939)

Table continued

Table 4-33: Summary of repeat dose toxicological studies in rats and dogs (continued)

Study duration Ref-erence	Species (n)	BAY 59-7939 (mg/kg BW/day)	Findings (at mg/kg/day)	NOAEL (mg/kg/day)
13 weeks [63]	Rat ♂ (10) ♀ (10	0, 75, 150, 300 oral, dose-adjusted feeding	Increase in HQuick; Decrease of body weights (13-23%) (≥75 mg/kg) Increase in food and water intake (≥75 mg/kg) Increase of total bilirubin up to 1.5-fold (≥150 mg/kg) Pancreas: increased incidence of periinsular/interlobular hemorrhages with subsequent hemosiderosis and fibrosis (♂, 300 mg/kg)	Not established
13 weeks [64]	Mouse ♂ (10) ♀ (10	0, 12.5, 50, 200 oral, gavage	Increase in HQuick (≥12.5 mg/kg);	200 mg/kg (disregarding enhanced pharmaco-dynamic effects of BAY 59-7939)
13 weeks [65]	Mouse ♂ (10) ♀ (10	1250, 2500, 5000 ppm oral, feeding	Increase in HQuick (≥1250 ppm); Increase in food and water increase (≥1250 ppm); Increase of total bilirubin up to 1.5-fold (≥2500 ppm)	1250 ppm (disregarding enhanced pharmaco-dynamic effects of BAY 59-7939)
26 weeks [60]	Rat ♂ (20) ♀ (20)	0, 12.5, 50, 200 oral, gavage	Increase in HQuick (≥12.5 mg/kg); Decrease in terminal body weight (≥50 mg/kg, 8 – 9%), Increased water consumption in ♀ (200 mg/kg)	12.5 mg/kg (disregarding enhanced pharmaco-dynamic effects of BAY 59-7939)

4.3.4 Genotoxicity

BAY 59-7939 was tested in a

- Salmonella/microsome test for point mutations.[66]
- Cytogenetics *in vitro* assay.[67]
- Micronucleus test for clastogenicity.[68]

All tests revealed a negative result. Thus BAY 59-7939 is considered as non-genotoxic.

4.3.5 Reproductive toxicity

BAY 59-7939 was tested in a study on fertility and early embryonic development in rats as well as in studies on embryo-fetal development in rats and rabbits (Table 4-34).[69-71]

In the study on fertility and early embryonic development no effects on reproductive parameters were found up to 200 mg/kg the highest dose tested, whereas systemic tolerability was affected at ≥50 mg/kg by a temporary body weight gain decrease. The NOAEL on fertility and early embryonic development is 200 mg/kg.

In the developmental toxicity study in rats maternal toxicity was found at the highest dose tested (120 mg/kg). Placental alterations were already seen at the lowest dose tested (10 mg/kg). For the 2 cardiovascular malformations found solely at the highest dose group a treatment-relationship at this maternally toxic 120 mg/kg dose level is considered as unlikely due to the comparability with actual and historical control data, possible involvement of the father and/or single appearance.

Furthermore, since these effects were only seen at dose levels demonstrating relevant maternal toxicity there is definitely no evidence for a primary teratogenic potential of BAY 59-7939.

In the developmental toxicity study in rabbits maternal toxicity most likely related to the mode of action (increased bleeding risk due to the anti-coagulative effect of BAY 59-7939) were seen at ≥2.5 mg/kg. A treatment-related increase of common malformations at the levels of ≥40 mg/kg cannot be excluded. However, since this increase was limited to dose levels associated with severe systemic maternal toxicity, a primary teratogenic potential of BAY 59-7939 was not evident.

Table 4-34: Summary of fertility and developmental toxicity studies in rats and rabbits

Study type, species (n), reference	BAY 59-7939 (mg/kg BW/day)	Findings (at mg/kg/day)	NOAEL (mg/kg/day)
Study on fertility and early embryonic development, rat (24) [70]	12.5 - 50 - 200	Temporary body weight decrease in Week 1. No treatment-related effects on organ weights (testes, ovaries), insemination, fertility and gestation index, number of corpora lutea, implantation rate, pre- and post-implantation loss, and the number of viable embryos	Systemic: 12.5 Reproductive parameter: 200
Study on embryo-fetal development, rat (22) [69]	10 - 35 - 120	Maternal toxicity with slightly increased mortality and vaginal/uterine bleeding (120) Slightly reduced mean fetal weight (120) Placental changes (≥12.5) 2 different cardiovascular malformations (120)	Systemic: 35 Placenta: <10 Intrauterine development: 35
Study on embryo-fetal development, rabbit (20) [71, 72]	2.5 - 10 - 40 - 160	Increased mortality (120) Reduced body weight gain (≥10) Reddish vaginal/uterine discharge (≥2.5) Reduced gestation rate (increased abortion and resorption) (≥ 2.5) Placental changes (≥10) Slight increase in common malformations and slightly retarded skeletal ossification (≥40)	Systemic: <2.5 Intrauterine development: <2.5

4.3.6 Carcinogenicity

No data available.

4.3.7 Local tolerance

BAY 59-7939 was administered orally by gavage. To evaluate possible local effect of the test compound or the formulation used, stomach and intestine were thoroughly investigated morphologically. Necropsy as well as histopathological

examination revealed no treatment-related effects. Hence, there is no evidence for any local intolerance of BAY 59-6939.

4.3.8 Special studies

No data available.

4.3.9 Comparison of exposure in animals to human

The available data allow a comparison of systemic exposure in animals and humans. For this purpose, steady-state exposure data after 13-week administration in the 2 species and from the developmental toxicity studies were compared with exposure data in humans after multiple dosing of 30 mg bid, the highest dose currently used in clinical studies (Table 4-35).

Table 4-35: Overview on systemic exposure at steady state and multiples of exposure compared to human exposure

Daily dose [mg/kg/d]	Sex	Systemic exposure: Total exposure C_{max} [mg/L]	MoE	Total exposure $AUC_{(0-24)}$ [mg·h/L]	MoE	Unbound exposure $C_{max, u}$ [mg/L]	MoE	Unbound exposure $AUC_{0-24, u}$ [mg·h/L]	MoE
Chronic toxicity study in rats									
12.5	M	5.4	12	18.0	3	0.07	3	0.23	1
50	M	16.7	37	75.6	14	0.21	9	0.96	3
200	M	25.5	56	137.0	25	0.32	14	1.74	6
12.5	F	10.8	24	32.4	6	0.14	6	0.41	1
50	F	26.3	58	114.0	21	0.33	15	1.45	5
200	F	41.8	92	280.0	51	0.53	23	3.56	13
Subchronic toxicity study in dogs (males and females pooled)									
15		1.9	6	8.6	2	0.20	9	0.89	3
50		3.0	7	16.1	3	0.31	14	1.67	6
150		5.4	12	37.5	7	0.56	24	3.90	14
Developmental toxicity study in rats									
10	F	2.6	6	18.9	4	0.03	1	0.24	1
35	F	6.6	15	77.7	14	0.08	4	0.99	4
160	F	12.9	29	188.0	35	0.16	7	2.39	9
Developmental toxicity study in rabbits									
2.5	F	0.14	0.3	0.7	0.1	0.03	1.4	0.17	0.6
10	F	0.29	0.7	2.8	0.5	0.07	3.0	0.65	2.4
40	F	0.88	1.9	13.1	2.4	0.21	9.0	3.07	11.1
160	F	1.54	3.4	23.9	4.4	0.36	15.7	5.59	20.2
Human exposure[a]									
2 x 30		0.45		5.46		0.023		0.28	

MoE = multiples of exposure (when compared to the human plasma levels)

a Based on a dose of 2 x 30 mg/subject (AUC: 2 x $AUC_{\tau, (168-180)}$)

5. Effects in Humans

Key Points:

- BAY 59-7939 was well tolerated up to 80 mg after single dose application in healthy subjects.
- Multiple dosing 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 studied.
- BAY 59-7939 is rapidly absorbed after oral treatment as solution (C_{max} after approximately 30 min) as well as tablet (C_{max} after 2-4 h).
- Elimination of BAY 59-7939 from plasma occurred with terminal half-lives of 4.30 to 5.88 h (Day 1) and 4.86 to 9.15 h (steady state) 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 (ie 30 mg bid).
- Administration of BAY 59-7939 with food resulted in an increase of AUC by 25%, a delayed absorption by about 1.5 h 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 sex.
- Maximal pharmacodynamic effects were of no relevant difference between old subjects compared to young subjects (men and women).
- Clotting parameters (PT, PTT, HepTest) were affected as mechanistically expected.
- Factor Xa was inhibited in a dose-dependent way.
- No relevant influence on bleeding time was observed neither after single dose nor multiple dose application.

- Co-medication with enoxaparin showed an additive effect on pharmacodynamic parameters. Bleeding time was not affected to a clinically relevant degree.
- The potent cytochrome P450 3A4 inhibitor ketoconazole led to an approximate increase in mean BAY 59-7939 maximum concentration by 50% with concomitant changes in pharmacodynamic parameters.
- There was no relevant interaction between BAY 59-7939 and midazolam (co-substrate of CYP 3A4), the H2 antagonist ranitidine, the antacid aluminum hydroxide / magnesium hydroxide (Maalox®), digoxin, acetylsalicylic acid, and naproxen. There was no PK interaction between BAY 59-7939 and clopidogrel; however, the study results are inconclusive as to a relevant pharmacodynamic interaction exists when clopidogrel and BAY 59-7939 are administered concomitantly.
- No QTc-prolonging effect was observed for BAY 59-7939 after single oral dosing to healthy men and women older than 50 years.
- 3 large dose-ranging studies (ODIXa-HIP, ODIXa-HIP2, and ODIXa-KNEE) have been completed in the indication of VTE prevention in major orthopedic surgery exploring a 12-fold BAY 59-7939 dose range from 2.5 to 30 mg bid.
- BAY 59-7939 prevented total VTE compared with enoxaparin, thus supporting the efficacy of BAY 59-7939 in this indication.
- None of the studies demonstrated a significant dose trend for BAY 59-7939 regarding the primary efficacy endpoint of total VTE.
- A flat dose response for efficacy and a flat dose response for safety indicate a broad therapeutic window for BAY 59-7939 and thus makes the drug different from other new anticoagulants, which have shown to have less wide therapeutic ranges.
- In the 3 studies, DVT rates were consistent with those observed in other contemporary trials and even the lower doses of BAY 59-7939 were within the expected ranges of the control drug enoxaparin or even lower.

- There was a dose-response with regard to bleeding events. However, it is important to note that there were neither fatal bleeds or bleeds in critical organs, nor clinically significant bleeds that could not be treated. Most bleeds adjudicated as major were related to the surgical site and no wound healing complications were reported in these patients.

5.1 Introduction

BAY 59-7939 has been investigated in a number of clinical pharmacological studies in healthy subjects, which included multiple dose administration up to 5 days, an age and gender study, a study in elderly (>60 years of age) subjects, a ^{14}C mass balance study, and several studies addressing potential pharmacokinetic and pharmacodynamic drug interactions. In addition, single and multiple dose studies have been performed in Japanese healthy subjects.

The first clinical proof-of-principle trial (ODIXa-HIP trial) investigating the effects of BAY 59-7939 vs enoxaparin in preventing venous thromboembolism in patients undergoing elective primary total hip replacement has been successfully completed.

5.2 Clinical Pharmacology

Key Points:

- BAY 59-7939 was well tolerated up to 80 mg after single dose application in healthy subjects.
- Multiple dosing 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.
- BAY 59-7939 is rapidly absorbed after oral treatment as solution (C_{max} after approximately 30 min) as well as tablet (C_{max} after 2-4 h).
- Elimination of BAY 59-7939 from plasma occurred with terminal half-lives of 4.30 to 5.88 h (Day 1) and 4.86 to 9.15 h (steady state) 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 (ie 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 h 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 sex.
- Following single dose administration of 30, 40, and 50 mg BAY 59-7939 in elderly men and women (>60 years), mean AUC and C_{max} tended to be higher (approximately 20%) in women than in men.
- Exposure to BAY 59-7939 was higher (approximately 50% in AUC, 12% in C_{max}) in older subjects (>75 years) compared to young subjects following single dose administration of 10 mg BAY 59-7939.
- PT, PTT, and HepTest were prolonged dose-dependently as mechanistically expected.

- Factor Xa inhibition was dose-dependent.
- No relevant influence on bleeding time was observed neither after single dose nor multiple dose application.
- Co-medication with enoxaparin showed an additive effect on pharmacodynamic parameters. Bleeding time was not affected to a clinically relevant degree.
- The potent cytochrome P450 3A4 inhibitor ketoconazole led to an approximate increase in mean BAY 59-7939 maximum concentration by 50% with concomitant changes in pharmacodynamic parameters.
- There was no relevant interaction between BAY 59-7939 and midazolam (co-substrate of CYP 3A4), the H2 antagonist ranitidine, the antacid aluminum hydroxide / magnesium hydroxide (Maalox®), digoxin, acetylsalicylic acid, and naproxen. There was no PK interaction between BAY 59-7939 and clopidogrel; however, the study results are inconclusive as to a relevant pharmacodynamic interaction exists when clopidogrel and BAY 59-7939 are administered concomitantly.
- No QTc-prolonging effect was observed for BAY 59-7939 after single oral dosing to healthy men and women older than 50 years.

5.2.1 Summary

619 healthy subjects were enrolled in phase I trials with BAY 59-7939, 515 of them received active drug, 104 of them received placebo. 429 healthy subjects received BAY 59-7939 as a single dose up to 80 mg, while 86 subjects received multiple dose treatments with doses up to 30 mg bid. 40 healthy Japanese men (32 on active and 8 on placebo) were enrolled a single dose study and 30 (24 on active and 6 on placebo) in a multiple dose study.

BAY 59-7939 has been investigated in several studies with respect to safety, tolerability, pharmacodynamics, and pharmacokinetics:

- Single doses up to 80 mg in Caucasian and 40 mg in Japanese subjects.
- Multiple doses up to 30 mg bid in Caucasian and Japanese subjects.
- Age and gender study.
- Studies in elderly (>60 years, >75 years).
- Food effect study.
- Interaction studies with enoxaparin, ketoconazole (cytochrome P450 3A4 inhibitor), midazolam (co-substrate of CYP 3A4), the H_2 antagonist ranitidine, and the antacid aluminum hydroxide / magnesium hydroxide, digoxin, acetylsalicylic acid, naproxen, and clopidogrel.
- Study to investigate the effects on the QT interval.
- Formulation comparison studies.
- Study to investigate thrombin generation.
- Study to investigate radiolabeled [^{14}C]BAY 59-7939 mass balance and to determine the site of absorption of BAY 59-7939.

Table 5-1 summarizes phase I studies by study number, type, dose, and number of subjects exposed to BAY 59-7939 and placebo.

Table 5-1: Summary of phase I studies

Study no. Reference	Type of study	Dose (mg)	Subjects exposed to BAY 59-7939 (n)	Subjects exposed to placebo (n)
010842[73]	Single dose	1.25, 5, 10, 15, 20, 30, 40, 60, 80	71	32
010846[74]	Food interaction single dose	10	10	0
010847[75]	Multiple dose (5 days)	5 od/bid/tid, 10 bid, 20 bid, 30 bid	43	21
010848[76]	Interaction with enoxaparin 40 mg	10	11	0
010850[77]	Age and gender single dose	10	36	12
010924[78]	Intestinal absorption single dose	10 (tablet), 5 (oral solution)	9	0
010989[79]	Food interaction single dose	4 x 5 vs 1 x 20	11	0
010990[80]	PK food interaction extended release vs immediate release tablet	5 x 5 vs 1 x 25	12	0
010991[57]	[^{14}C] mass balance	10	4	0
010992[81]	Interaction with ketoconazole 200 mg	10	12	0
010993[82]	Interaction with midazolam 7.5 mg	20	12	0
010999[83]	Interaction with digoxin multiple dose	20 bid	19	0
011000[84]	Interaction with ranitidine 150 mg	30	12	0
011001[85]	Interaction with aluminum hydroxide / magnesium hydroxide (Maalox®)	30	11	0
011123[86]	Interaction with acetylsalicylic acid 100 (500) mg	15	14	0
011124[87]	Interaction with naproxen 500 mg	15	13	0
011125[88]	PK food interaction extended release vs immediate release tablet	5 x 5 vs 1 x 25	11	0
011126[89]	Single dose (Japanese subjects)	5, 10, 20, 40	32	8
011127[90]	Multiple dose (Japanese subjects, 6 days)	10 bid, 20 bid, 30 bid	24	6
011140[91]	Thrombin generation	5, 30	8	4
011197[92]	PK food interaction extended release vs immediate release tablet	5 x 5 vs 1 x 25	11	0

Table continued

Table 5-1: Summary of phase I studies (continued)

011275[93]	Effect on QTc duration	15, 45	54	0
011279[94]	Interaction with clopidogrel 75 (300) mg	15	14	0
011529[95]	PD/PK in elderly (>60 years) subjects	30, 40, 50	36	12
011569[96]	PD/PK in elderly (>75 years) subjects	10	25	9
	Total		**515**	**104**

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

Overall, 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 and run in parallel to the pharmacokinetic profile. From the doses tested so far, there are no hints for clinically relevant prolonged bleeding time.

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 in Caucasian as well as in Japanese subjects. The interaction study with enoxaparin showed a moderate increase of the clotting parameters. Investigation of the thrombin generation clearly shows that BAY 59-7939 influences both the intrinsic and extrinsic pathways of coagulation and does not only prolong lag time, but also C_{max} and AUC of thrombin generation as measures of the total effect of the drug.

There was no relevant interaction between BAY 59-7939 and midazolam (co-substrate of CYP 3A4), the H2 antagonist ranitidine, the antacid aluminum

hydroxide / magnesium hydroxide (Maalox®), digoxin, acetylsalicylic acid, and naproxen. There was no PK interaction between BAY 59-7939 and clopidogrel; however, the study results are inconclusive as to a relevant pharmacodynamic interaction exists when clopidogrel and BAY 59-7939 are administered concomitantly.

No QTc-prolonging effect was observed for BAY 59-7939 after single oral dosing to healthy men and women older than 50 years.

5.2.2 Pharmacokinetics (ADME)

Single dose escalation 1.25 to 80 mg (Study 10842):[73] This was a randomized, single-blind, placebo-controlled, group comparison, dose-escalation study in healthy male subjects. The study investigated the safety, tolerability, and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after oral administration of single doses of 1.25, 5, 10, 15, 20, 30, 40, 60, and 80 mg (administered as 5 mg tablets). For pharmacodynamic and safety results, see Section 5.2.3 and Section 5.2.4, respectively.

In addition to testing the tablet formulation, the 5 and 10 mg dose was also tested with solution. After administration of the solution, the plasma concentration time profiles were characterized 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 h. Whilst the dose normalized C_{max} was reduced by approximately 50% after administration of the tablet when compared to the solution, the 2 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). Additional pharmacokinetic parameters are provided in Table 5-2. 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 has 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 5-2, Figure 5-1, and Figure 5-2 summarize the pharmacokinetic study results.

Table 5-2: Pharmacokinetics of BAY 59-7939 after oral administration of selected single doses [geometric mean (geometric SD)]

Para-meter	Unit	5 mg tablet n=6	5 mg solution n=6	10 mg tablet n=8	10 mg solution n=8
AUC	[µg*h/L]	446 (1.26)	461 (1.19)	1020 (1.16)	997 (1.28)
AUC_{norm}	[g*h/L]	7479 (1.24)	7734 (1.21)	8766 (1.20)	8366 (1.41)
AUC/D	[h/L]	0.089 (1.26)	0.092 (1.19)	0.102 (1.16)	0.100 (1.28)
C_{max}	[µg/L]	72.0 (1.22)	119 (1.20)	141 (1.17)	266 (1.28)
$C_{max, norm}$	[g/L]	1208 (1.22)	1991 (1.32)	1211 (1.23)	2231 (1.36)
C_{max}/D	[1/L]	0.014 (1.22)	0.024 (1.20)	0.014 (1.17)	0.027 (1.28)
t_{max}[a]	[h]	1.88 (0.50-4.00)	0.625 (0.50-0.75)	2.00 (0.50-2.50)	0.500 (0.25-1.00)
$t_{1/2}$	[h]	4.27 (1.28)	3.25 (1.09)	9.07 (1.77)	4.16 (1.23)
MRT	[h]	6.84 (1.26)	4.62 (1.08)	11.3 (1.55)	5.06 (1.19)
V_z/f	[L/kg]	0.823 (1.35)	0.605 (1.20)	1.49 (1.83)	0.717(1.21)

Para-meter	Unit	15 mg tablet n=7	20 mg tablet n=7	40 mg tablet n=8	60 mg tablet n=7	80 mg tablet n=7
AUC	[µg*h/L]	1408 (1.32)	1612 (1.42)	2412 (1.22)	3767 (1.61)	3250 (1.37)
AUC_{norm}	[g*h/L]	7446 (1.40)	6369 (1.36)	5128 (1.20)	4328 (1.51)	3238 (1.31)
AUC/D	[h/L]	0.094 (1.32)	0.081 (1.42)	0.060 (1.22)	0.063 (1.61)	0.041 (1.37)
C_{max}	[µg/L]	176 (1.45)	173 (1.41)	234 (1.43)	350 (1.10)	316 (1.48)
$C_{max, norm}$	[g/L]	930 (1.59)	684 (1.38)	499 (1.38)	403 (1.24)	315 (1.36)
C_{max}/D	[1/L]	0.012 (1.45)	0.009 (1.41)	0.006 (1.43)	0.006 (1.10)	0.004 (1.48)
t_{max}[a]	[h]	1.25 (0.75-4.00)	1.50 (0.50-4.00)	1.50 (1.00-4.00)	2.00 (1.00-4.00)	2.00 (0.50-4.00)
$t_{1/2}$	[h]	11.45 (1.51)	7.60 (1.41)	8.88 (1.63)	15.5 (2.51)	16.9 (1.74)
MRT	[h]	12.9 (1.54)	11.2 (1.29)	12.9 (1.36)	18.9 (2.60)	19.6 (1.65)
V_z/f	[L/kg]	2.22 (1.74)	1.72 (1.58)	2.50 (1.53)	5.16 (1.81)	7.55 (1.60)
Ae_{ur}[b]	[%]	NC	NC	19.8 (5.66)	12.6 (2.98)	10.8 (1.56)

a Median

Figure 5-1: Plasma concentration vs time profiles of BAY 59-7939 following oral administration of 5 mg (n=6/group) and 10 mg (n=8/group) BAY 59-7939 either as solution or as tablet (geometric mean/geometric SD)

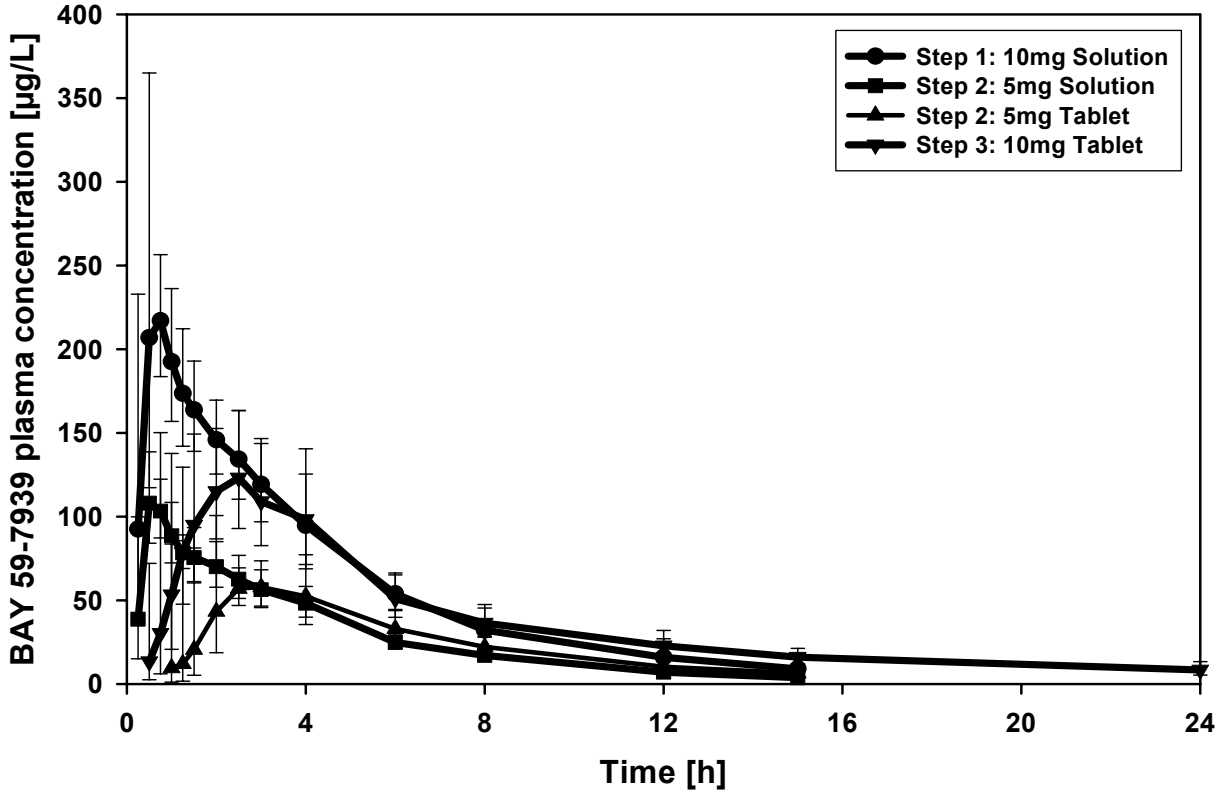
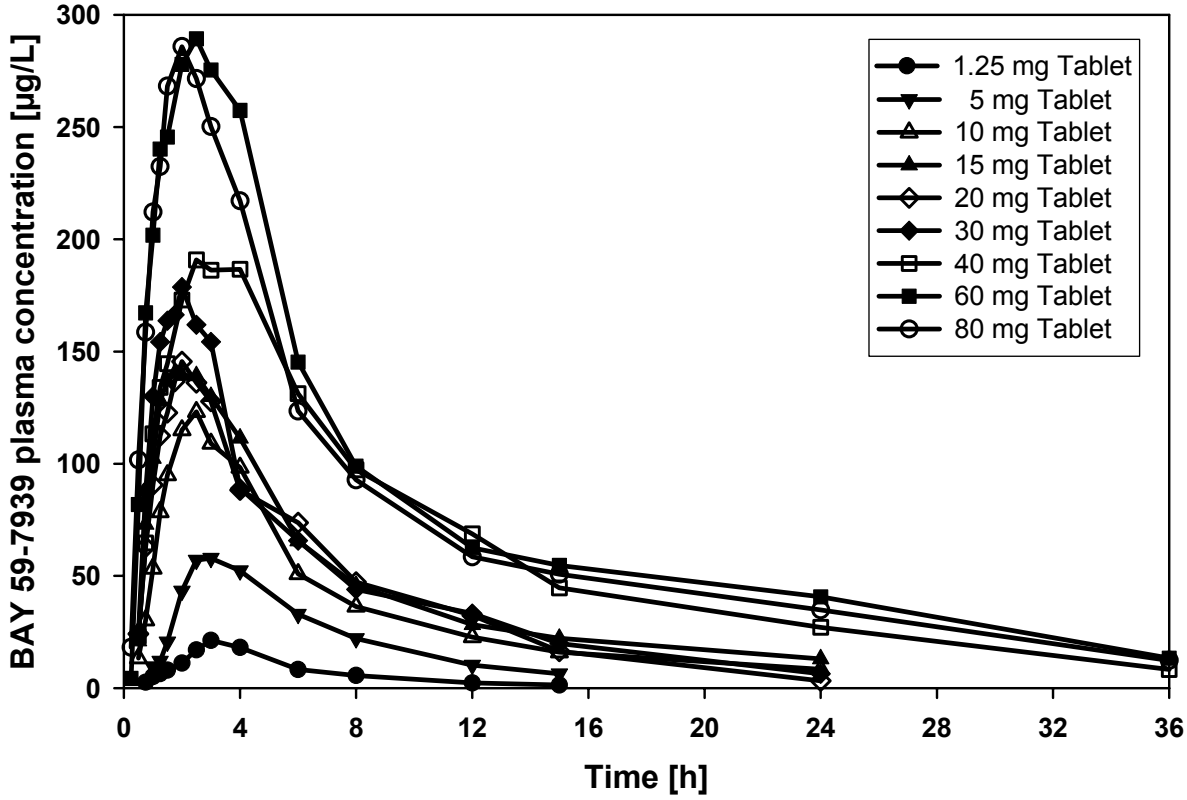


Figure 5-2: Plasma concentration vs time profiles of BAY 59-7939 following administration of 1.25 mg – 80 mg BAY 59-7939 as tablet administrations (linear scale; geometric means, n=6-8/group)



Food effect (Study 10846):[74] This was a randomized, open-label, 2-fold crossover 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 PO as 2 x 5 mg tablets to 12 healthy male subjects. For pharmacodynamic and safety results, see Section 5.2.3 and Section 5.2.4, respectively.

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.

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

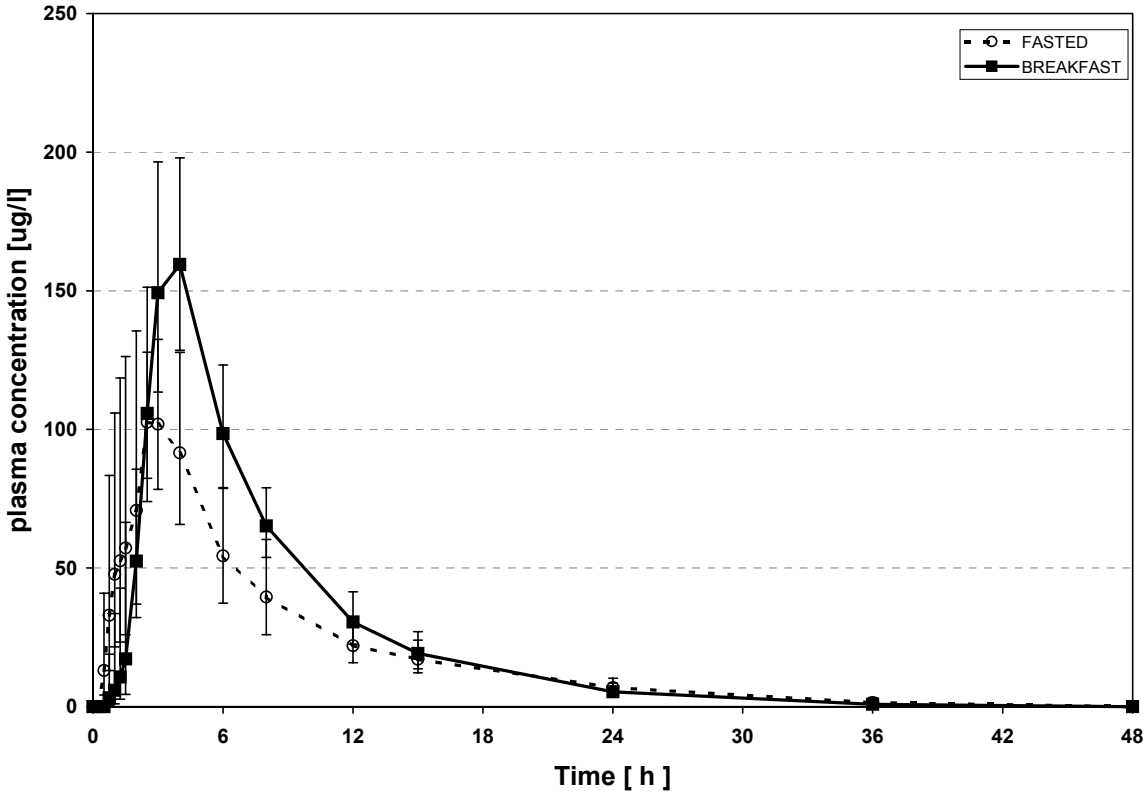
Table 5-3 and Figure 5-3 summarize the pharmacokinetic study results.

Table 5-3: Pharmacokinetics of BAY 59-7939 after oral administration of a single dose of 10 mg with or without administration of a high fat, high calorie meal [geometric means (n=9/group; geometric SD)]

Parameter	Unit	BAY 59-7939 10 mg fasted	BAY 59-7939 10 mg fed
AUC	[µg*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}	[µg/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}[a]	[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)

a Median

Figure 5-3: Plasma concentration vs time profiles of BAY 59-7939 following oral administration with or without a high fat high calorie meal (geometric mean/geometric standard deviation, n=8/group)



Age and gender (Study 10850):[77] This was a 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 given as two 5 mg tablets. For pharmacodynamic and safety results, see Section 5.2.3 and Section 5.2.4, respectively.

Initial estimates of the principal pharmacokinetic parameters for each of the 4 subgroups included in this study are presented in Table 5-4. Pharmacokinetics was similar between males and females. Slight differences in AUC and C_{max} 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.

Exposure to BAY 59-7939 is increased to a clinically relevant degree in elderly subjects. There were no clinically relevant differences in pharmacokinetics between male and female subjects, especially when taking into account common body weight differences.

Table 5-4: Pharmacokinetics of BAY 59-7939 after oral administration of a single dose of 10 mg in young and elderly females and males (n=9/group; geometric means, range)

Parameter	Unit	Young males	Elderly males	Young females	Elderly females
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}[a]	[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

a Median (range)

Elderly men and women (>60 years) (Study 11529):[95] This study investigated the pharmacokinetics of BAY 59-7939 after single dose administration of 30, 40, and 50 mg in subjects >60 years of age. Based on the 30 mg dose step both mean AUC and C_{max} results tended to be higher (approximately 20%) in elderly women than in elderly men which was less pronounced when comparing the groups using respective body weight normalized values (Table 5-5).

Variability in the 50 mg dose group of the elderly PPD was high due to Subject PPD, who demonstrated unusually high plasma concentrations.

While increases in mean exposure (AUC, C_{max}) were still observed when comparing the 30 mg and the 40 mg dose groups, the increases in these parameters from the 40 mg to the 50 mg dose groups were small or even not detectable with nearly complete overlap for the parameter ranges.

Table 5-5: Pharmacokinetic parameters of BAY 59-7939 following single dose administration of 30, 40, and 50 mg BAY 59-7939 in elderly male and female subjects [geometric mean values/geometric CV (range)]

Para-meter	Unit	n	Male subjects 30 mg	n	Female subjects 30 mg	n	Male subjects 40 mg	n	Female subjects 40 mg
AUC	µg*h/L	6	3283/26.10 (2434 – 4479)	6	3798/8.99 (3433 – 4190)	6	3940/21.51 (3220 – 5364)	6	4881/22.95 (3211 – 5903)
AUC_{norm}	g*h/L	6	8796/34.49 (5760 – 12690)	6	9235/14.67 (7794 – 11030)	6	7735/19.78 (6346 – 11000)	6	8776/30.55 (4977 – 11510)
C_{max}	µg/L	6	351.5/23.71 (284.3 – 508.6)	6	436.4/17.75 (345.2 – 565.1)	6	452.2/21.62 (325.3 – 566.4)	6	469.4/12.02 (381.6 – 524.3)
$C_{max,norm}$	g/L	6	941.7/31.34 (703.4 – 1441)	6	1061/23.80 (759.4 – 1488)	6	887.6/15.69 (756.3 – 1125)	6	844.1/18.30 (591.5 – 996.3)
t_{max}[a]	h	6	4 (2 – 4)	6	4 (3 – 4)	6	4 (3 – 4)	6	4 (3 – 6)
$t_{½}$	h	6	7.760/30.33 (5.063 – 10.75)	6	17.72/53.48 (10.07 – 39.72)	6	11.99/14.62 (10.20 – 14.31)	6	14.69/42.76 (8.389 – 22.63)

Para-meter	Unit	n	Male subjects 50 mg	n	Female subjects 50 mg	n	Female subjects 50 mg[b]
AUC	µg*h/L	6	4469/24.33 (3028 – 5825)	6	4524/44.59 (3057 – 9772)	5	3879/22.36 (3057 – 5550)
AUC_{norm}	g*h/L	6	8024/22.62 (5753 – 10370)	6	6409/48.05 (4750 – 14850)	5	5418/22.14 (4750 – 7992)
C_{max}	µg/L	6	426.9/24.70 (313.6 – 616.5)	6	447.7/40.74 (322.6 – 961.4)	5	384.3/13.01 (322.6 – 446.3)
$C_{max,norm}$	g/L	6	766.6/23.06 (608.4 – 1134)	6	634.3/46.17 (445.2 – 1461)	5	536.8/18.23 (445.2 – 648.2)
t_{max}[a]	h	6	4 (3 – 4)	6	4 (2 – 4)	5	4 (2 – 4)
$t_{½}$	h	6	9.717/34.06 (6.643 – 13.87)	6	14.49/52.90 (7.581 – 25.28)	5	14.30/59.95 (7.581 – 25.28)

a Median (range)
b Excluding Subject PPD

Elderly (>75 years) male and female subjects (Study 11569):[96] This study investigated safety, tolerability, pharmacodynamics, and pharmacokinetics of a single oral dose of 10 mg BAY 59-7939 in men and women older than 75 years

compared to young men and women in a randomized, single-blind, placebo-controlled trial.

Table 5-6 summarizes the pharmacokinetic results.

Table 5-6: Pharmacokinetics of BAY 59-7939 [geometric means/geometric coefficient of variation (range)] by sex and age

Parameter	Unit	PPD			
		n=6	n=6	n=7	n=5
AUC	[µg*h/L]	1210/12.69 (1003 – 1368)	1941/16.15 (1600 – 2427)	1462/27.41 (986.2 – 1990)	1950/26.95 (1485 – 2715)
AUC_{norm}	[g*h/L]	8210/13.26 (6933 – 9988)	13221/19.36 (10440 – 17230)	11303/39.28 (6213 – 18900)	15332/31.05 (10540 – 21120)
C_{max}	[µg/L]	209.7/23.95 (153.1 – 276.6)	245.0/18.23 (205.4 – 339.0)	223.7/17.26 (181.4 – 273.2)	234.6/25.73 (177.6 – 327.5)
$C_{max,norm}$	[µg/L]	1423/20.39 (1083 – 1783)	1669/22.39 (1274 – 2169)	1730/27.52 (1183 – 2471)	1845/27.51 (1440 – 2489)
t_{max}[a]	[h]	3.00 (0.50 – 3.05)	4.00 (2.00 – 4.00)	3.00 (2.00 – 4.00)	4.00 (3.00 – 4.00)
$t_{1/2}$	[h]	11.74/81.03 (4.868 – 30.72)	11.97/30.56 (8.941 – 19.04)	7.254/39.01 (4.019 – 10.98)	11.34/36.21 (8.578 – 20.56)
V_Z/f	[L/kg]	2.063/96.58 (0.8021 – 6.392)	1.306/42.25 (0.7542 – 2.631)	0.9258/45.39 (0.5209 – 1.555)	1.067/40.35 (0.5860 – 1.575)
CL/f	[L/h]	8.262/12.69 (7.309 – 9.971)	5.152/16.14 (4.121 – 6.248)	6.842/27.40 (5.026 – 10.14)	5.127/26.95 (3.683 – 6.734)
CL_R	[L/h]	2.873/6.56 (2.630 – 3.091)	1.407/33.29 (0.9827 – 2.382)[b]	2.301/30.82 (1.468 – 3.095)	1.507/26.51 (1.081 – 2.083)

a Median (range)
b n=5

The pharmacokinetic characteristics AUC_{norm}, $C_{max,norm}$, AUC, and C_{max} were analyzed assuming log-normally distributed data. To investigate age and gender effects in a descriptive manner without any assumptions about the nature of the relationship between age and gender and these pharmacokinetic characteristics, an explorative ANOVA including the factors “old/young” and “men/women” as well as their interaction was performed on the log-transformed values of AUC_{norm}, $C_{max,norm}$, AUC, and C_{max}.

With regard to AUC_{norm} a statistically significant age-effect (p=0.0024) and a borderline gender-effect (*P*=0.0509) was found. The statistically significant age-effect was also found for the parameter AUC (*P*=0.0003) with higher values in older subjects. Neither statistically significant interaction effects nor statistically significant differences were found for $C_{max,norm}$, and C_{max}.

Based on these results, the pharmacokinetic characteristics were re-analyzed using an explorative ANOVA including the main effects "old/young" and "men/women". Resulting LS-mean values are shown in Table 5-7.

Table 5-7: Results of main effects ANOVA

Parameter	LS-mean	Value (90% CI)	LS-mean	Value (90% CI)
C_{max}	Women/Men	0.9850 (0.8518 – 1.1390)	Old/Young	1.1078 (0.9575 – 1.2816)
$C_{max,norm}$	Women/Men	0.8591 (0.7263 – 1.0162)	Old/Young	1.1191 (0.9455 – 1.3245)
AUC	Women/Men	0.9008 (0.7739 – 1.0484)	Old/Young	1.4647 (1.2577 – 1.7057)
AUC_{norm}	Women/Men	0.7857 (0.6490 – 0.9512)	Old/Young	1.4798 (1.2215 – 1.7926)

In summary, the group of old subjects exhibited approximately 50% higher AUC (statistically significant; approximately 12% higher C_{max} without statistical significance) than young subjects with only minor differences between men and women, mainly driven by sex-related differences in mean body weight. The old/young difference can be well attributed to reduced total (apparent) body clearance as well as reduced renal clearance in the old subjects.

The overall comparison women/men reveals no difference in C_{max} and an approximately 10% difference in AUC (smaller for women), getting more pronounced when normalized for body weight (14 % lower $C_{max,norm}$ and 21% lower AUC_{norm} in women). When comparing all 4 subgroups, the major differences are thus seen in young women having both the highest total (apparent) body clearance and renal clearance as well as the highest volume of distribution for BAY 59-7939,

leading to the lowest maximum concentration and AUC irrespective of body weight normalization.

Multiple dose escalation 5 mg od to 30 mg bid (Study 10847):[75] This randomized, placebo-controlled, single-blind, parallel-group study investigated the safety, tolerability, pharmacodynamics, and pharmacokinetics of BAY 59-7939 after single and multiple dose applications of BAY 59-7939 as conventional tablets: 5 mg od, 5 mg bid, 5 mg tid, 10 mg bid, 20 mg bid, and 30 mg bid. Subjects received treatment for 1 day followed by 2 days of wash-out and received treatment again for 5 consecutive days. For pharmacodynamic and safety results, see Section 5.2.3 and Section 5.2.4, respectively.

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 4.30 to 5.88 h (Day 1) and 4.86 to 9.15 h (steady state) 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 C_{max} were seen up to the highest dose tested (ie, 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. Table 5-8 and Table 5-9 summarize the pharmacokinetic results.

Table 5-8: Pharmacokinetic parameters in plasma following the first administration of 10 mg, 20 mg, and 30 mg BAY 59-7939 bid on Day 0d [geometric mean values/geometric coefficient of variation (range), all subjects valid for PK, n=7/group]

			BAY 59-7939	
Parameter	Unit	10 mg bid	20 mg bid	30 mg bid
AUC	[µg*h/L]	816.5/22.01 (553.7-993.0)	1875/26.43 (1296-2887)	2472/16.19 (1890-2954)
AUC_{norm}	[g*h/L]	6400/29.34 (4042-9248)	7668/22.49 (5639-9815)	6560/18.31 (5206-8561)
AUC_{τ}(0-12)	[µg*h/L]	639.5/13.61 (503.6-793.2)	1608/26.23 (1154-2524)	1961/13.26 (1550-2216)
$AUC_{\tau,norm}$ (0-12)	[g*h/L]	5013/18.40 (3676-6287)	6577/19.88 (5018-8581)	5203/12.47 (4424-6096)
AUC_{τ}/D	[h/L]	0.06395/13.61 (0.05036-0.07932)	0.08040/26.23 (0.05768-0.1262)	0.06536/13.26 (0.05166-0.07388)
AUC/D	[h/L]	0.08165/22.01 (0.05537-0.09930)	0.09374/26.41 (0.06482-0.1443)	0.08242/16.19 (0.06301-0.09848)
C_{max}	[µg/L]	113.8/15.67 (95.12-142.8)	277.7/24.81 (206.2-427.5)	366.9/13.51 (304.7-428.3)
$C_{max,norm}$	[g/L]	891.9/16.37 (703.9-1086)	1136/18.46 (896.8-1454)	973.3/8.01 (874.8-1097)
C_{max}/D	[1/L]	0.01138/15.67 (0.009512-0.01428)	0.01389/24.82 (0.01031-0.02138)	0.01223/13.51 (0.01016-0.01428)
$t_{½}$	[h]	5.835/13.35 (4.670-6.887)	3.693/20.89 (2.741-5.104)	5.828/19.99 (4.258-7.420)
MRT	[h]	7.856/30.64 (5.024-11.14)	6.734/15.38 (5.844-9.166)	8.004/18.87 (6.691-10.56)
t_{max}[a]	[h]	4.00 (1.00-4.00)	3.00 (2.50-4.00)	3.00 (2.50-4.00)

a Median (range)

Table 5-9: Pharmacokinetic parameters in plasma following the first administration of 10 mg, 20 mg, and 30 mg BAY 59-7939 bid on Day 7d [geometric mean values/geometric coefficient of variation (range), all subjects valid for PK, n=7/group]

			BAY 59-7939	
Parameter	Unit	10 mg bid	20 mg bid	30 mg bid
AUC_{τ}(168-180)	[µg*h/L]	863.8/18.62 (582.7-993.8)	1903/24.47 (1350-2761)	2728/14.58 (2288-3596)
$AUC_{\tau,norm}$ (168-180)	[g*h/L]]	6771/24.51 (4253-9143)	7781/18.76 (5871-9388)	7239/18.35 (5770-9330)
AUC_{τ}/D	[h/L]	0.08638/18.62 (0.05827-0.09938)	0.09512/24.48 (0.06748-0.1381)	0.09095/14.59 (0.07627-0.1199)
C_{max}	[µg/L]	158.0/18.77 (112.5-195.4)	318.1/18.74 (254.4-414.1)	451.9/10.52 (381.2-530.2)
$C_{max,norm}$	[g/L]	1239/23.74 (821.2-1582)	1301/15.98 (989.6-1515)	1199/12.19 (999.2-1482)
C_{max}/D	[1/L]	0.01580/18.77 (0.01125-0.01954)	0.01590/18.75 (0.01272-0.02071)	0.01506/10.51 (0.01271-0.01767)
$t_{½}$	[h]	7.630/26.65 (5.375-10.48)	7.965/40.65 (3.877-12.39)	9.153/64.10 (4.240-24.49)
MRT	[h]	7.102/14.88 (6.158-9.318)	8.474/20.49 (6.629-11.95)	8.943/23.04 (6.647-12.96)
R_{A1}	[%]	138.9/21.01 (105.1-181.4)	114.5/11.42 (96.87-131.2)	123.2/10.32 (108.5-144.5)
R_{A3}	[%]	135.1/13.69 (114.6-164.8)	118.3/12.24 (96.85-137.6)	139.1/19.48 (108.5-197.8)
R_{A4}	[%]	105.8/14.60 (91.55-142.8)	101.5/14.26 (86.94-123.0)	110.3/21.41 (91.48-168.1)
t_{max} [a]	[h]	2.98 (1.50-4.00)	2.50 (0.50-4.00)	3.02 (1.50-4.00)

a Median (range)

For BAY 59-7939 plasma concentrations vs time see Figure 5-4 and Figure 5-5.

Figure 5-4: Plasma concentrations of BAY 59-7939 (µg/L) for each dose step displayed as geometric means from Day 0 to Day 2 – all subjects valid for PK (n=61)

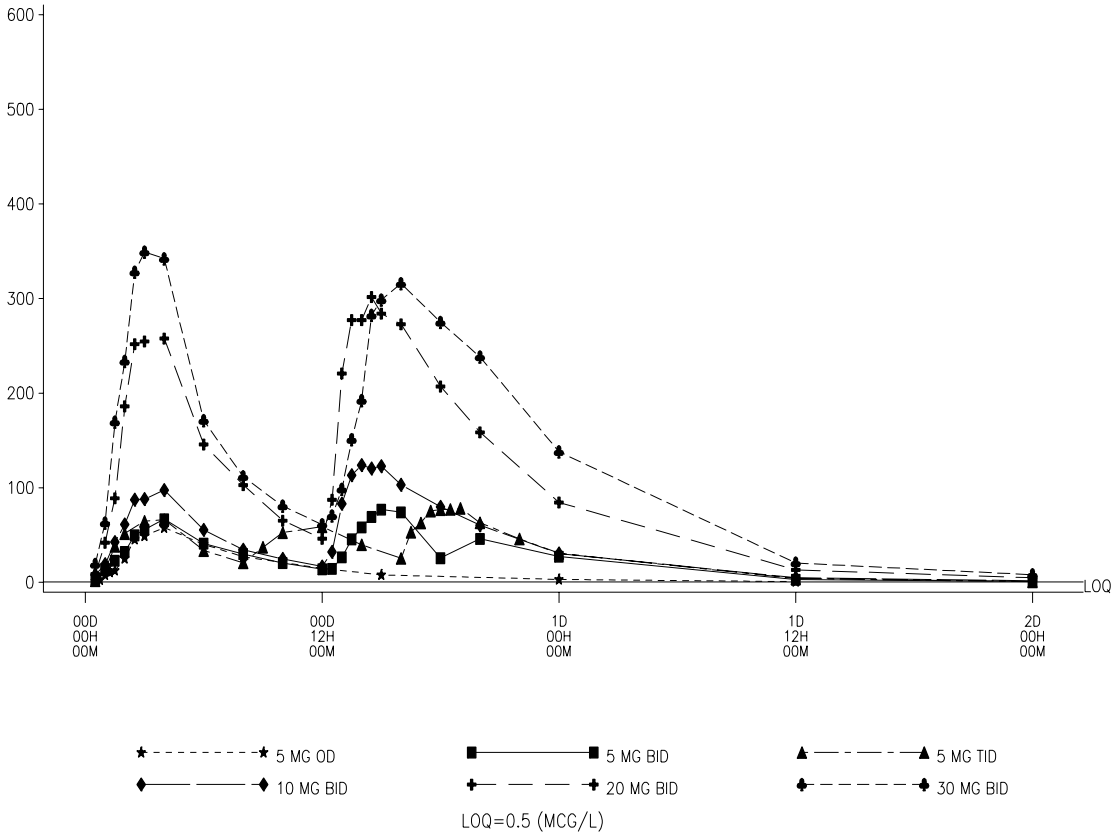
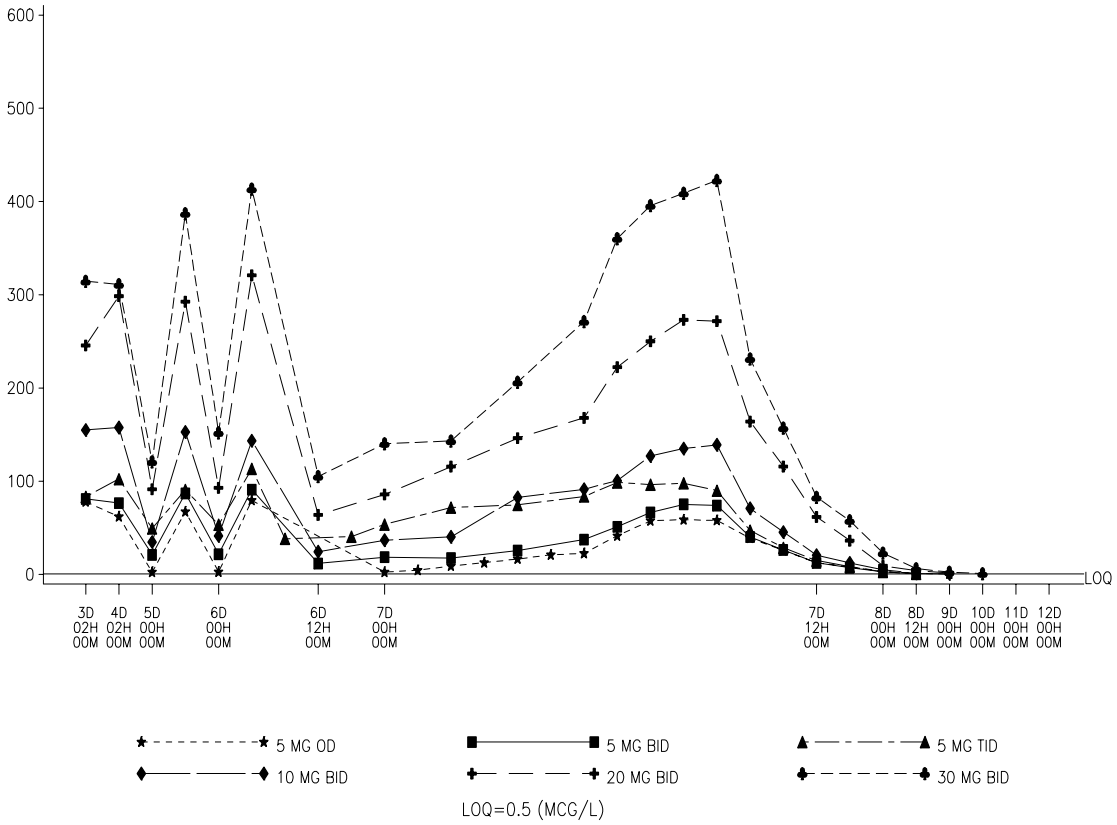


Figure 5-5: Plasma concentrations of BAY 59-7939 (µg/L) for each dose step displayed as geometric means from Day 3 to Day 12 – all subjects valid for PK (n=61)



Formulation comparison of one 20 mg tablet vs four 5 mg tablets (Study 10989):[79] This non-blinded, randomized, non-placebo-controlled crossover study compared the safety, tolerability, pharmacodynamics, and pharmacokinetics of 20 mg BAY 59-7939 given either as 4 tablets of 5 mg or one 20 mg tablet and investigated the effect of a high-fat, high-calorie or high-carbohydrate meal on safety, tolerability, pharmacodynamics, and pharmacokinetics of one 20 mg tablet BAY 59-7939 in healthy, male subjects. For pharmacodynamic and safety results, see Section 5.2.3 and Section 5.2.4, respectively.

With regard to the comparison of the 2 different tablet formulations (4 x 5 mg and 1 x 20 mg) given in fasted state, all pharmacokinetic parameter were very similar and

no apparent differences in pharmacokinetic behavior of the 2 formulations could be detected. Administration after food resulted in significantly higher C_{max} values (approximately 70% increase) and a delay in t_{max}. AUC increased by about 30% in the fed state. Table 5-10 summarizes the pharmacokinetic results.

Table 5-10: Pharmacokinetics of BAY 59-7939 after oral administration of 20 mg either as 4 x 5 mg tablets or 1 x 20 mg tablet both under fasted condition or 1 x 20 mg tablet under fed condition (6 subjects with American breakfast, 4 subjects with continental breakfast) (n=10/group; geometric means/geometric SD, range)

Parameter	Unit	BAY 59-7939 4 × 5 mg	BAY 59-7939 20 mg fasted	BAY 59-7939 20 mg fed
AUC	[µg*h/L]	1678/1.51 (1087-3701)	1629/1.48 (919-3886)	2021/1.39 (1477-4524)
AUC_{norm}	[g*h/L]	7521/1.39 (5463-14250)	7301/1.36 (5192-14960)	9058/1.29 (7227-17420)
C_{max}	[µg/L]	153/1.35 (109-283)	158/1.38 (100-310)	273/1.29 (216-483)
$C_{max,norm}$	[g/L]	684/1.30 (460-1091)	709/1.29 (475-1194)	1226/1.21 (961-1858)
$t_{1/2}$	[h]	9.29/1.74 (5.01-34.0)	9.12/1.68 (4.29-22.7)	7.02/1.34 (3.88-11.2)
MRT	[h]	13.5/1.62 (7.61-44.6)	12.6/1.37 (8.51-23.7)	8.97/1.14 (7.10-10.4)
t_{max}[a]	[h]	1.25 (0.750-4.00)	2.25 (0.750-4.02)	3.50 (1.25-6.00)

a Median

With regard to the comparison of the different kind of meals investigated in this study (continental vs American breakfast), due to the low number of subjects the results can only be seen as exploratory. However, as AUC as well as C_{max} are very well comparable between the 2 different breakfasts, the composition of the meal seems to be without influence on the pharmacokinetic behavior of BAY 59-7939. Both kinds of meal resulted in increased but delayed maximal plasma concentrations of approximately the same magnitude.

Effects of 5 and 30 mg BAY 59-7939 on thrombin generation (Study 11140):[91]
This randomized, open-label, 2-fold crossover pilot study investigated the effect of 5

and 30 mg BAY 59-7939 on the thrombin generation in 12 healthy male subjects. For safety results, see Section 5.2.4.

Overall, BAY 59-7939 pharmacokinetics observed after single doses of either 5 mg or 30 mg, respectively, were similar to the results previously reported (see Study 10842), especially with respect to the less than dose-proportional increase in exposure at higher doses. The mean ratio for AUC/D (30 mg over 5 mg) was about 0.75, thus clearly less than what would have been expected in case of dose-proportionality. Moreover, $C_{max,norm}$ was considerably smaller (by nearly 50%) after the 30 mg dose than after the 5 mg dose. Median t_{max} was 1.5 h for both doses.

Single dose escalation 5 to 40 mg in Japanese subjects (Study 11126):[89] This randomized, single-blind, placebo-controlled, dose-escalation study in healthy Japanese male subjects investigated tolerability, safety, pharmacokinetics, and pharmacodynamic effects of BAY 59-7939 tablet after single PO doses of 5, 10, 20, and 40 mg under fasting conditions. For pharmacodynamic and safety results, see Section 5.2.3 and Section 5.2.4, respectively.

Plasma concentration vs time profiles of BAY 59-7939 reached maximum plasma concentrations at 0.5 to 4 h after administration. As the dose was increased from 5 to 20 mg, C_{max} and AUC increased, while neither C_{max} nor AUC increased after the dose was increased to 40 mg (Table 5-11).

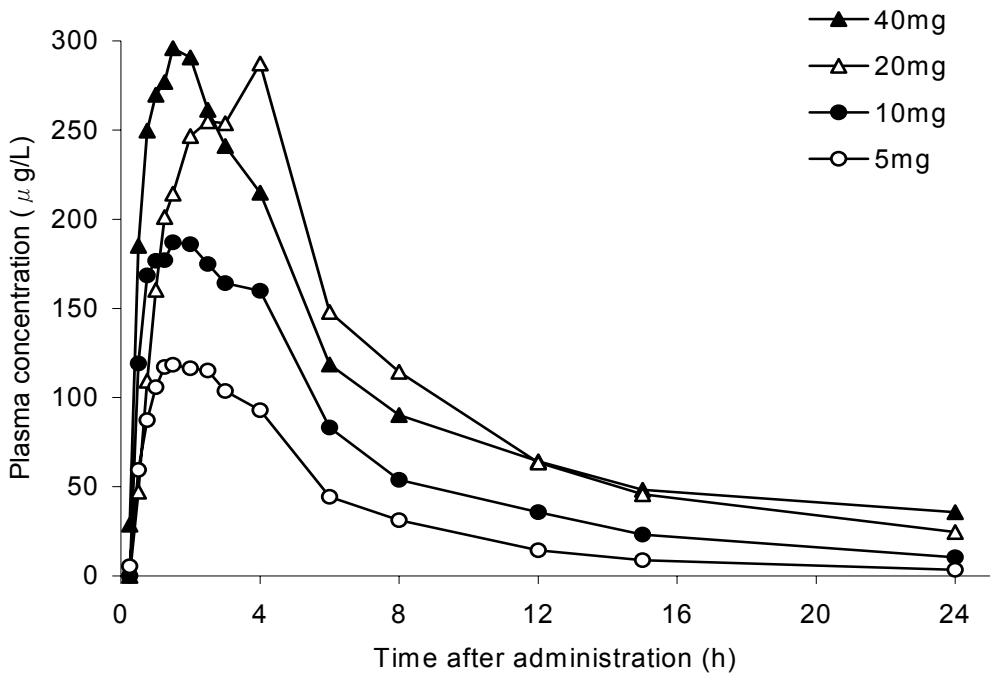
Table 5-11: Pharmacokinetics of BAY 59-7939 after oral administration of a single dose (n=8/group; geometric means, geometric SD)

Parameter	Unit	BAY 59-7939							
		5 mg		10 mg		20 mg		40 mg	
AUC	[µg*h/l]	816	(1.14)	1564	(1.27)	2777	(1.30)	3051	(1.24)
AUC_{norm}	[g*h/L]	9601	(1.12)	9947	(1.27)	8772	(1.30)	4840	(1.29)
AUC/D	[h/L]	0.163	(1.14)	0.156	(1.27)	0.139	(1.30)	0.077	(1.23)
C_{max}	[µg/L]	141	(1.16)	227	(1.20)	342	(1.34)	329	(1.29)
$C_{max, norm}$	[g/L]	1663	(1.08)	1444	(1.29)	1079	(1.35)	523	(1.30)
C_{max}/D	[1/L]	0.028	(1.15)	0.023	(1.20)	0.017	(1.36)	0.008	(1.31)
t_{max}[a]	[h]	1.38	(0.50 – 2.50)	1.38	(0.50 – 4.00)	3.25	(0.50 – 4.00)	1.38	(0.50 – 2.00)
$t_{1/2}$	[h]	5.75	(1.22)	7.08	(1.41)	8.90	(1.62)	12.57	(1.47)
MRT	[h]	6.5	(1.20)	8.7	(1.28)	11.6	(1.41)	15.1	(1.50)
V_z/f	[L/kg]	0.86	(1.18)	1.03	(1.63)	1.46	(1.56)	3.75	(1.49)
Ae_{ur}[b]	[%]	24.1	(5.27)	21.9	(5.34)	17.6	(6.55)	8.1	(2.08)

a Median (range)

b Arithmetic mean ± SD

Figure 5-6: Plasma concentration vs time profiles of BAY 59-7939 following administration of 5 mg – 40 mg BAY 59-7939 as tablet administrations (linear scale; geometric means, n=8/group)



Multiple dose escalation 10 to 30 mg bid in Japanese subjects (Study 11127):[90]
This randomized, single-blind, placebo-controlled, dose-escalation study in healthy Japanese male subjects investigated the tolerability, safety, pharmacokinetics, and pharmacodynamic effects of BAY 59-7939 tablet after multiple oral doses of 10, 20, and 30 mg bid for 6 days (once daily on Day 1 and Day 6). For pharmacodynamic and safety results, see Section 5.2.3 and Section 5.2.4, respectively.

The pharmacokinetic behavior of BAY 59-7939 after multiple dosing did not change and no accumulation was seen compared with Day 1. Dose-proportional increases in AUC and C_{max} at steady state were seen up to the highest dose tested (ie 30 mg bid) by administration of the drug with food. Details on pharmacokinetics are shown in Table 5-12, Table 5-13, and Table 5-14.

Table 5-12: BAY 59-7939 tablet 10 mg bid - pharmacokinetics after oral administration of multiple doses at Day 1 and Day 6 [geometric mean (geometric SD)]

Parameter	Unit	Day 1 (n=8)		Day 6 (n=8)	
AUC	[µg*h/L]	1365	(1.18)	--	--
AUC_{norm}	[g*h/L]	7983	(1.23)	--	--
AUC/D	[h/L]	0.137	(1.18)	--	--
AUC_{tau}	[µg*h/L]	1329	(1.18)	1218	(1.14)
$AUC_{tau,norm}$	[g*h/L]	7772	(1.22)	7126	(1.13)
AUC_{tau}/D	[h/L]	0.133	(1.18)	0.122	(1.14)
C_{max}	[µg/L]	202.5	(1.22)	205.8	(1.09)
$C_{max, norm}$	[g/L]	1185	(1.23)	1204	(1.15)
C_{max}/D	[1/L]	0.020	(1.22)	0.021	(1.09)
t_{max}[a]	[h]	3.50	(2.00-4.00)	2.25	(1.00-4.00)
$t_{1/2}$	[h]	4.30	(1.09)	4.86	(1.28)
MRT	[h]	7.39	(1.19)	6.84	(1.11)
Ra1	[%]	--	--	102	(1.29)
Ra3	[%]	--	--	92	(1.17)
Ra4	[%]	--	--	89.3	(1.17)

a Median (range)

Table 5-13: BAY 59-7939 tablet 20 mg bid - pharmacokinetics after oral administration of multiple doses at Day 1 and Day 6 [geometric mean (geometric SD)]

Parameter	Unit	Day 1 (n=8)		Day 6 (n=8)	
AUC	[µg*h/L]	2471	(1.18)	--	--
AUC_{norm}	[g*h/L]	8080	(1.16)	--	--
AUC/D	[h/L]	0.124	(1.18)	--	--
AUC_{tau}	[µg*h/L]	2379	(1.18)	2480	(1.16)
$AUC_{tau,norm}$	[g*h/L]	7778	(1.15)	8110	(1.15)
AUC_{tau}/D	[h/L]	0.119	(1.18)	0.124	(1.16)
C_{max}	[µg/L]	340.3	(1.14)	400.8	(1.16)
$C_{max, norm}$	[g/L]	1112	(1.11)	1311	(1.11)
C_{max}/D	[1/L]	0.017	(1.14)	0.020	(1.16)
t_{max}[a]	[h]	3.50	(1.00-4.00)	2.50	(1.00-4.00)
$t_{1/2}$	[h]	4.91	(1.15)	6.69	(1.46)
MRT	[h]	7.68	(1.09)	8.05	(1.17)
Ra1	[%]	--	--	118	(1.15)
Ra3	[%]	--	--	104	(1.14)
Ra4	[%]	--	--	100.4	(1.15)

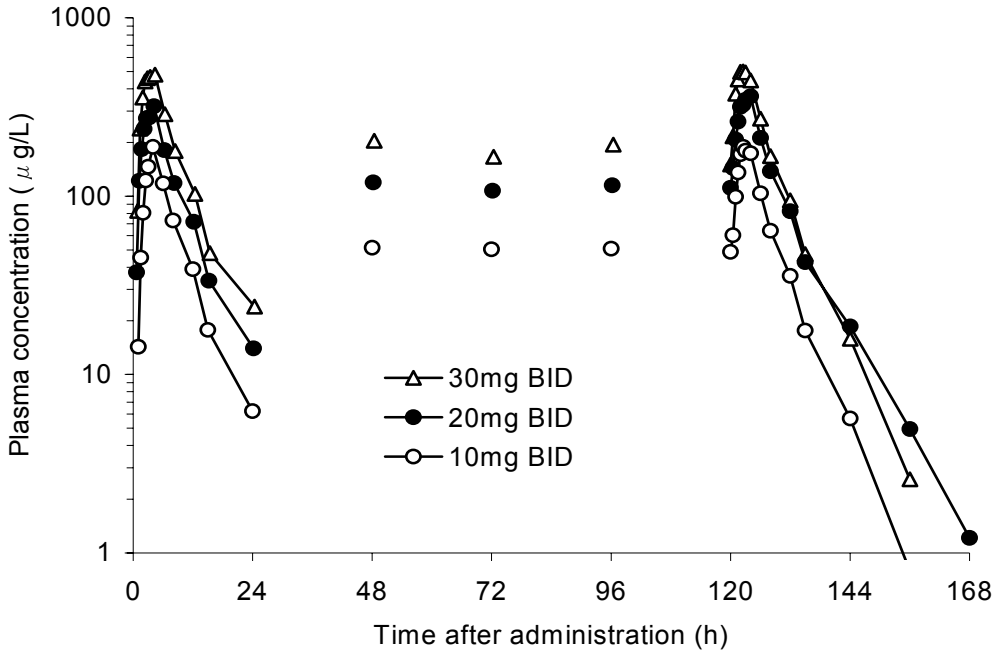
a Median (range)

Table 5-14: BAY 59-7939 tablet 30 mg bid - pharmacokinetics after oral administration of multiple doses at Day 1 and Day 6 [geometric mean (geometric SD)]

Parameter	Unit	Day 1 (N=8)		Day 6 (N=8)	
AUC	[µg*h/L]	3913	(1.22)	--	--
AUC_{norm}	[g*h/L]	7203	(1.23)	--	--
AUC/D	[h/L]	0.130	(1.22)	--	--
AUC_{tau}	[µg*h/L]	3744	(1.21)	3331	(1.24)
$AUC_{tau,norm}$	[g*h/L]	6892	(1.22)	6131	(1.26)
AUC_{tau}/D	[h/L]	0.124	(1.21)	0.111	(1.24)
C_{max}	[µg/L]	537.1	(1.17)	547.0	(1.16)
$C_{max, norm}$	[g/L]	989	(1.17)	1007	(1.17)
C_{max}/D	[1/L]	0.018	(1.17)	0.018	(1.16)
t_{max}[a]	[h]	2.75	(2.00-4.00)	2.50	(1.00-4.00)
$t_{1/2}$	[h]	5.21	(1.18)	5.23	(1.46)
MRT	[h]	7.68	(1.15)	6.92	(1.20)
Ra1	[%]	--	--	102	(1.10)
Ra3	[%]	--	--	89	(1.13)
Ra4	[%]	--	--	85.1	(1.13)

a Median (range)

Figure 5-7: Plasma concentration of BAY 59-7939 for each dose step displayed as geometric means from Day 1 to Day 7 (linear scale; geometric means, n=8/group)



Mass balance (^{14}C) (Study 10991):[57] The primary objectives of the study were the assessment of the cumulative amount of drug-related, radiolabeled material excreted in the urine and feces, the characterization of the metabolic pattern in plasma, urine and feces, and the quantification of plasma total radioactivity and unchanged drug concentrations and the major circulating metabolites in plasma.

Cumulative excretion of total radioactivity is summarized in Table 5-15.

Table 5-15: Cumulative excretion of total radioactivity [%] related to BAY 59-7939 (n=4)

Subject	PPDM	PPDM	PPDM	PPDM	Arithmetic mean
Sample	% of dose excreted (0 - 168 h)				
Urine	67.79	66.32	65.40	63.44	65.74
Feces	27.42	27.08	24.26	33.20	27.99
Total	95.21	93.40	89.66	96.64	93.73

About 94% of the radioactive dose administered was recovered in the excreta. Urinary excretion accounted for 66% and fecal/biliary excretion accounted for 28% of the dose. High amounts of the dose were excreted as unchanged drug.

The oxidative degradation of the morpholino moiety to metabolite M-1 and the hydrolysis of the amide bond with subsequent conjugation of the 5-chloro-2-thiophene-carboxylic acid with glycine to metabolite M-4 were identified as the major sites of biotransformation in humans. Metabolite M-4 is eliminated via renal and fecal/biliary routes, whereas metabolite M-4 is eliminated renally. In total, 89% of the dose administered could be attributed to known structures. Unchanged drug was the main compound in plasma at all investigated time-points and accounted for 89% of AUC(0-t_n) of total radioactivity. No major circulating metabolites were detected in plasma.

Figure 5-8 illustrates the plasma exposure of BAY 59-7939.

Figure 5-8: Plasma concentrations of BAY 59-7939 (µg/L) together with associated radioactivity (µg/L equivalents) displayed as geometric means/geometric SD on a semi-logarithmic scale – all subjects valid for PK (n=4)

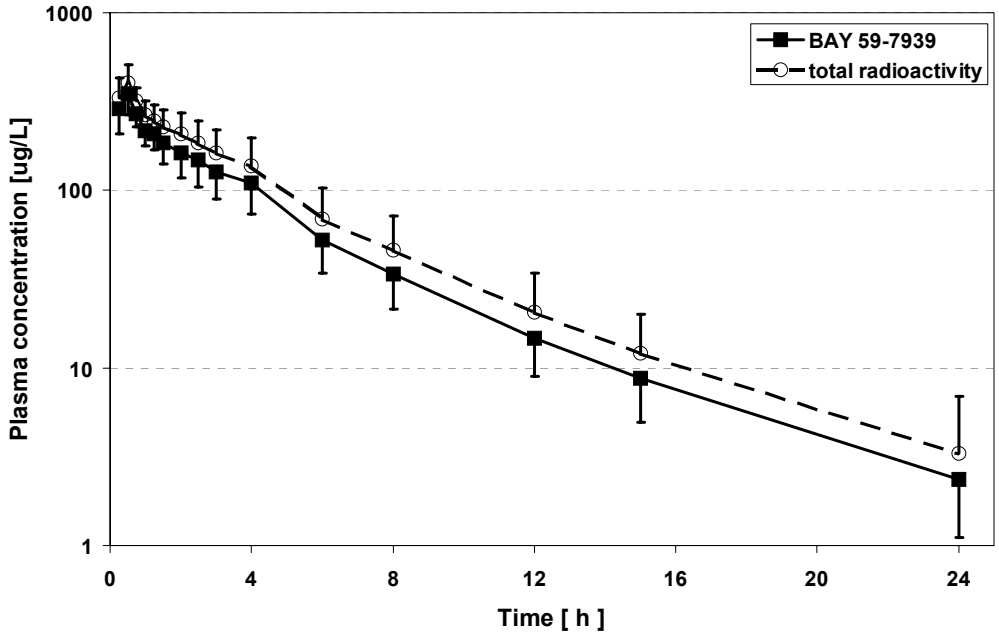


Table 5-16 summarizes the relevant PK parameters for BAY 59-7939 derived total radioactivity and as assessed via a specific HPLC assays.

Table 5-16: BAY 59-7939 pharmacokinetic parameters in plasma following administration of 10 mg [^{14}C]BAY 59-7939 [geometric mean value/geometric coefficient of variation (range), all subjects valid for PK, n=4]

Parameter	n	BAY 59-7939 specific determination	[^{14}C]BAY 59-7939 associated total radioactivity
AUC [(µg*h)/L]	4	1163 / 37.04 (778.7 - 1663)	1448 / 33.96 (965.4 - 2022)
C_{max} [µg/L]	4	347.8 / 27.66 (245.2 - 475.9)	405.2 / 22.54 (307.8 - 529.6)
t_{max} [a] [h]	4	0.5 (0.5 – 0.5)	0.5 (0.5 – 0.5)
$t_{1/2}$ [h]	4	5.523 / 34.29 (3.877 - 8.369)	4.473 / 37.38 (3.341 - 7.560)
CL/f [L/h]	4	8.206 / 37.33 (5.719 - 12.30)	6.590 / 34.28 (4.703 - 9.923)
CLR [L/h]	4	2.417 / 37.47 (1.751 - 4.052)	
Ae_{ur}(0-168) [%][b]	4	29.66 / 15.5 (22.95 - 32.85)	65.7 / 2.76 (63.4 – 67.8)

For BAY 59-7939 associated radioactivity the units µg refer to the corresponding equivalents
a Median (range)
b Arithmetic mean / arithmetic coefficient of variation (range)

In conclusion, the mass balance study and all subsequent metabolic investigations provided all necessary data to adequately describe BAY 59-7939 drug behavior in man with respect to metabolic pathways, routes of elimination and ways and extent of excretion.

Effects of BAY 59-7939 on QTc duration (Study 11275):[93] The pharmacokinetic evaluation of BAY 59-7939 showed adequate dose-dependent drug exposure according to previous study data.

Table 5-17: Pharmacokinetics of BAY 59-7939 [n=50/group; geometric means/geometric SD (range)]

Parameter	Unit	BAY 59-7939 15 mg	BAY 59-7939 45 mg
AUC(0-6)	[µg*h/L]	821.8/27.41 (498.0 – 1780)	1813/31.83 (874.2 – 4890)
AUC(0-tn)	AUC(0-tn)	1692/23.29 (969.8 – 3375)	3953/25.55 (2408 – 9567)
C_{max}	[µg/L]	221.7/28.67 (125.0 – 543.1)	479.7/30.53 (256.3 – 1386)
t_{max}[a]	[h]	4.1 (2.1 – 5.0)	4.1 (0.6 – 5.1)

a Median (range)

5.2.3 Pharmacodynamic effects

Single dose escalation 1.25 to 80 mg (Study 10842):[73] This was a randomized, single-blind, placebo-controlled, group comparison, dose-escalation study in healthy male subjects. The study investigated the safety, tolerability, and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after single PO doses of 1.25, 5, 10, 15, 20, 30, 40, 60, and 80 mg (administered as 5 mg tablets). For pharmacokinetic and safety results, see Section 5.2.2 and Section 5.2.4, respectively.

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. Both clotting tests (PT, PTT, HepTest) and Factor Xa inhibition were influenced by the study medication as expected, however a dose proportional increase was only observed up to doses of 10 mg. At doses above 10 mg the Factor Xa inhibition and the clotting tests were changed less than dose proportional. The dose of 1.25 mg was considered to be the "no effect-dose" in humans. Table 5-18, Table 5-19, Table 5-20, and Table 5-21 summarize the respective results.

Table 5-18: Factor Xa inhibition (%) - maximum mean changes from baseline

Dose/formulation	n	Mean change from baseline/SD	Range
Parallel group studies			
Placebo solution	3	-5.1/6.5	-12 - 1.1
Placebo tablet	25	-2.3/9	-31 - 10
10 mg solution	8	53/7	46 - 65
1.25 mg tablet	8	5.5/5.8	-3 - 15
10 mg (2 x 5 mg tablet)	8	33/7	24 - 43
15 mg (3 x 5 mg tablet)	7	41/9	25 - 53
20 mg (4 x 5 mg tablet)	7	35/10	23 - 48
30 mg (6 x 5 mg tablet)	6	38/9	27 - 50
40 mg (8 x 5 mg tablet)	8	46/13	22 - 60
60 mg (12 x 5 mg tablet)	7	58/6	45 - 63
80 mg (16 x 5 mg tablet)	6	60/11	43 - 75
Crossover studies			
Placebo solution	4	-4.3/2.7	-8.3 - -2.0
Placebo tablet	4	-1.1/4.7	-8.1 - 2.2
5 mg solution	6	30/5	23 - 37
5 mg tablet	6	20/5	14 - 29

Table 5-19: PT (x-fold change) - mean changes from baseline

Dose/formulation	n	Mean change from baseline/SD	Range
Parallel-group studies			
Placebo solution	3	1.0/0.02	1.0 - 1.0
Placebo tablet	25	1.0/0.05	0.9 - 1.1
10 mg solution	8	1.9/0.3	1.3 - 2.5
1,25 mg tablet	8	1.0/0.02	1.1 - 1.1
10 mg (2 x 5 mg tablet)	8	1.3/0.1	1.1 - 1.5
15 m g (3 x 5 mg tablet)	7	1.5/0.17	1.3 - 1.7
20 mg (4 x 5 mg tablet)	7	1.5/0.2	1.3 - 2.0
30 mg (6 x 5 mg tablet)	6	1.7/0.1	1.6 - 2.01
40 mg (8 x 5 mg tablet)	8	1.7/0.2	1.7 - 2.0
60 mg (12 x 5 mg tablet)	7	2.05/0.3	1.5 - 2.4
80 mg (16 x 5 mg tablet)	6	2.08/0.4	1.6 - 2.8
Crossover studies			
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

Table 5-20: PTT (x-fold change) - mean changes from baseline

Dose/formulation	n	Mean change from baseline/SD	Range
Parallel-group studies			
Placebo solution	3	1.0/0.0	1.0 - 1.0
Placebo tablet	25	1.0/0.04	0.9 - 1.1
10 mg solution	8	1.5/0.1	1.2 - 1.7
1,25 mg tablet	8	1.1/0.07	1.0 - 1.2
10 mg (2 x 5 mg tablet)	8	1.3/0.05	1.2 - 1.4
15 mg (3 x 5 mg tablet)	7	1.3/0.06	1.3 - 1.4
20 mg (4 x 5 mg tablet)	7	1.3/0.09	1.3 - 1.5
30 mg (6 x 5 mg tablet)	6	1.74/0.05	1.3 - 1.5
40 mg (8 x 5mg tablet)	8	1.4/0.1	1.2 - 1.5
60 mg (12 x 5 mg tablet)	7	1.5/0.08	1.4 - 1.7
80 mg (16 x 5 mg tablet)	6	1.5/0.1	1.4 - 1.7
Crossover studies			
Placebo solution	4	0.99/0.02	1.0 - 1.0
Placebo tablet	4	1.03/0.02	1.0 - 1.0
5 mg solution	6	1.3/0.04	1.2 - 1.3
5 mg tablet	6	1.2/0.04	1.1 - 1.2

Table 5-21: HepTest (x-fold change) - mean changes from baseline

Dose/formulation	n	Mean change from baseline/SD	Range
Parallel-group studies			
Placebo solution	3	1.0/0.0	1.0 - 1.0
Placebo tablet	25	1.0/0.05	0.9 - 1.1
10 mg solution	8	1.5/0.1	1.2 - 1.7
1,25 mg tablet	8	1.0/0.07	1.0 - 1.2
10 mg (2 x 5 mg tablet)	8	1.3/0.05	1.2 - 1.4
15 mg (3 x 5 mg tablet)	7	1.3/0.06	1.3 - 1.4
20 mg (4 x 5 mg tablet)	7	1.3/0.09	1.3 - 1.5
30 mg (6 x 5 mg tablet)	6	1.7/0.05	1.3 - 1.5
40 mg (8 x 5mg tablet)	8	1.8/0.23	1.6 - 2.2
60 mg (12 x 5 mg tablet)	7	2.3/0.3	1.9 - 2.7
80 mg (16 x 5mg tablet)	6	2.4/0.58	1.9 - 3.4
Crossover studies			
Placebo solution	4	0.99/0.02	1.0 - 1.0
Placebo tablet	4	1.03/0.02	1.0 - 1.0
5 mg solution	6	1.3/0.04	1.2 - 1.3
5 mg tablet	6	1.2/0.04	1.1 - 1.2

Food effect (Study 10846):[74] This was a randomized, open-label, 2-fold crossover 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 PO as 2 x 5 mg tablets to 12 healthy male subjects. For pharmacokinetic and safety results, see Section 5.2.2 and Section 5.2.4, respectively.

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 maximum Factor Xa inhibition as the major pharmacodynamic marker was increased by 27%.

The changes in Factor Xa inhibition were also reflected by the prolongation increases of PT and HepTest. PTT as the least sensitive marker remained unaffected.

Table 5-22: Maximum effects on clotting parameters vs baseline (n=9/group)

Parameter	BAY 59-7939 10 mg fasted Mean (range)		BAY 59-7939 10 mg fed Mean (range)	
Factor Xa inhibition [%]	33.60	(18.3 - 41.8)	42.5	(34.9 - 51.0)
PT prolongation [x fold]	1.44	(1.30 - 1.52)	1.53	(1.37 - 1.72)
PTT prolongation [x fold]	1.31	(1.2 1- 1.38)	1.31	(1.10 - 1.36)
HepTest prolongation [x fold]	1.78	(1.59 - 1.98)	1.91	(1.71 - 2.02)

Age and gender (Study 10850):[77] This was a 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 given as two 5 mg tablets. For pharmacokinetic and safety results, see Section 5.2.2 and Section 5.2.4, respectively.

Changes in the pharmacodynamic parameters Factor Xa inhibition, PT, PTT, and HepTest were consistent with the mechanism of action of BAY 59-7939 and are presented in Table 5-23, Table 5-24, Table 5-25, and Table 5-26.

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.

Table 5-23: Factor Xa inhibition (%) - maximum mean changes from baseline (n=9)

Dose/Formulation	Mean change from baseline	Range
10 mg (2x5 mg tablet) young male	40	29 – 52
10 mg (2x5 mg tablet) elderly male	50	28 – 63
10 mg (2x5 mg tablet) young female	47	35 – 60
10 mg (2x5 mg tablet) elderly female	58	48 – 63

Table 5-24: PT (x-fold change) - mean changes from baseline (n=9)

Dose/Formulation	Mean change from baseline	Range
10 mg (2x5 mg tablet) young male	1.69	1.41 – 1.99
10 mg (2x5 mg tablet) elderly male	1.95	1.51 – 2.48
10 mg (2x5 mg tablet) young female	1.90	1.59 – 2.38
10 mg (2x5 mg tablet) elderly female	2.37	1.79 – 3.00

Table 5-25: PTT (x-fold change) - mean changes from baseline (n=9)

Dose/Formulation	Mean change from baseline/SD	Range
10 mg (2x5 mg tablet) young male	1.39	1.16 – 1.68
10 mg (2x5 mg tablet) elderly male	1.44	1.02 – 1.57
10 mg (2x5 mg tablet) young female	1.40	1.19 – 1.56
10 mg (2x5 mg tablet) elderly female	1.47	1.27 – 1.63

Table 5-26: HepTest (x-fold change) - mean changes from baseline (n=9)

Dose/Formulation	Mean change from baseline/SD	Range
10 mg (2x5 mg tablet) young male	1.80	1.60 – 2.07
10 mg (2x5 mg tablet) elderly male	2.08	1.76 – 2.62
10 mg (2x5 mg tablet) young female	1.84	1.61 – 2.07
10 mg (2x5 mg tablet) elderly female	2.10	1.87 – 2.38

Multiple dose escalation 5 mg od to 30 mg bid (Study 10847):[75] This randomized, placebo-controlled, single-blind, parallel-group study investigated the safety,

tolerability, pharmacodynamics, and pharmacokinetics of BAY 59-7939 after single and multiple dose applications of BAY 59-7939 as conventional tablets: 5 mg od, 5 mg bid, 5 mg tid, 10 mg bid, 20 mg bid, and 30 mg bid. For pharmacokinetic and safety results, see Section 5.2.2 and Section 5.2.4, respectively.

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 were prolonged.

Table 5-27: Factor Xa inhibition (%) - maximum mean changes from baseline

Treatment group, time of assessment	n	Mean change from baseline	Range
5 mg od Day 0	7	20	7 - 25
5 mg od Day 5	7	16	4 - 25
5 mg bid Day 0	7	20	8 - 32
5 mg bid Day 5	7	22	5 - 32
5 mg tid Day 0	7	20	13 - 28
5 mg tid Day 5	6	25	13 - 36
10 mg bid Day 0	7	32	28 - 42
10 mg bid Day 5	7	39	29 - 46
20 mg bid Day 0	7	54	45 - 66
20 mg bid Day 5	7	51	35 - 62
30 mg bid Day 0	8	68	60 - 74
30 mg bid Day 5	7	66	47 - 76

Table 5-28: PT (x-fold change) - mean changes from baseline

Treatment group, time of assessment	n	Mean change from baseline/SD	Range
Placebo	6	1.03/0.04	0.99 - 1.08
Placebo	6	1.01/0.04	0.96 - 1.06
5 mg od Day 0	7	1.18/0.08	1.05 - 1.28
5 mg od Day 5	7	1.22/0.06	1.10 - 1.26
5 mg bid Day 0	7	1.21/0.05	1.12 - 1.27
5 mg bid Day 5	7	1.21/0.09	1.09 - 1.31
5 mg tid Day 0	7	1.24/0.06	1.2 - 1.3
5 mg tid Day 5	6	1.37/0.11	1.2 - 1.5
10 mg bid Day 0	7	1.38/0.09	1.2 - 1.5
10 mg bid Day 5	7	1.55/0.07	1.5 - 1.7
20 mg bid Day 0	7	1.97/0.29	1.7 - 2.6
20 mg bid Day 5	7	2.08/0.33	1.6 - 2.7
30 mg bid Day 0	8	2.37/0.27	2.0 - 2.7
30 mg bid Day 5	7	2.62/0.27	2.4 - 3.1

Table 5-29: PTT (x-fold change) - mean changes from baseline

Treatment group, time of assessment	n	Mean change from baseline/SD	Range
Placebo	6	1.02/0.02	0.99 - 1.04
Placebo	6	1.00/0.04	0.91 - 1.05
5 mg od Day 0	7	1.21/0.06	1.13 - 1.29
5 mg od Day 5	7	1.19/0.05	1.10 - 1.29
5 mg bid Day 0	7	1.15/0.06	1.03 - 1.2
5 mg bid Day 5	7	1.18/0.04	1.11 - 1.24
5 mg tid Day 0	7	1.18/0.05	1.10 - 1.20
5 mg tid Day 5	6	1.22/0.08	1.10 - 1.30
10 mg bid Day 0	7	1.29/0.05	1.20 - 1.40
10 mg bid Day 5	7	1.37/0.07	1.30 - 1.50
20 mg bid Day 0	7	1.67/0.43	1.40 - 2.60
20 mg bid Day 5	7	1.55/0.10	1.40 - 1.70
30 mg bid Day 0	8	1.65/0.08	1.5 - 1.80
30 mg bid Day 5	7	1.70/0.13	1.50 - 1.90

Table 5-30: HepTest (x-fold change) - mean changes from baseline

Treatment group, time of assessment	n	Mean change from baseline/SD	Range
Placebo	6	1.02/0.02	0.99 - 1.04
Placebo	6	1.00/0.04	0.91 - 1.05
5 mg od Day 0	7	1.21/0.06	1.13 - 1.29
5 mg od Day 5	7	1.19/0.05	1.10 - 1.29
5 mg bid Day 0	7	1.15/0.06	1.03 - 1.2
5 mg bid Day 5	7	1.18/0.04	1.11 - 1.24
5 mg tid Day 0	7	1.5/0.1	1.3 - 1.8
5 mg tid Day 5	6	1.7/0.1	1.5 - 1.8
10 mg bid Day 0	7	1.5/0.1	1.3 - 1.7
10 mg bid Day 5	7	1.7/0.1	1.6 - 1.9
20 mg bid Day 0	7	2.2/0.3	1.9 - 2.7
20 mg bid Day 5	7	2.2/0.3	1.8 - 2.8
30 mg bid Day 0	8	2.6/0.1	2.4 - 3.0
30 mg bid Day 5	7	2.7/0.1	2.3 - 2.9

Single dose escalation 5 to 40 mg in Japanese subjects (Study 11126):[89] This randomized, single-blind, placebo-controlled, dose-escalation study in healthy Japanese male subjects investigated tolerability, safety, pharmacokinetics, and pharmacodynamic effects of BAY 59-7939 tablet after single PO doses of 5, 10, 20, and 40 mg under fasting conditions. For pharmacokinetic and safety results, see Section 5.2.2 and Section 5.2.4, respectively.

Clotting parameters PT, PTT, HepTest, and Factor Xa inhibition were assessed as pharmacodynamic surrogate parameters. The Factor Xa inhibition rate increased with dose escalation, and its maximum inhibition rate was 70% after a dose of 40 mg. PT, PTT, and HepTest were prolonged compared with baseline values.

Table 5-31: Factor Xa inhibition (%) - maximum mean changes from baseline (n=8)

Dose/formulation	Mean change from baseline/SD	Range
Placebo tablet	9 / 5	1 - 15
5 mg (1 x 5 mg tablet)	44 / 9	29 - 55
10 mg (2 x 5 mg tablet)	57 / 5	49 - 64
20 mg (4 x 5 mg tablet)	68 / 7	59 - 78
40 mg (8 x 5 mg tablet)	70 / 6	64 - 78

Table 5-32: PT (x-fold change) - mean changes from baseline (n=8)

Dose/formulation	Mean change from baseline/SD	Range
Placebo tablet	1.1 / 0.1	1.0 - 1.2
5 mg (1 x 5 mg tablet)	1.6 / 0.1	1.4 - 1.8
10 mg (2 x 5 mg tablet)	1.9 / 0.2	1.7 - 2.1
20 mg (4 x 5 mg tablet)	2.3 / 0.3	1.9 - 2.7
40 mg (8x 5 mg tablet)	2.5 / 0.4	2.0 - 3.3

Table 5-33: PTT (x-fold change) - mean changes from baseline (n=8)

Dose/formulation	Mean change from baseline/SD	Range
Placebo tablet	1.1 / 0.1	1.0 - 1.2
5 mg (1 x 5 mg tablet)	1.4 / 0.1	1.3 - 1.5
10 mg (2 x 5 mg tablet)	1.5 / 0.1	1.4 - 1.7
20 mg (4 x 5 mg tablet)	1.5 / 0.1	1.3 - 1.7
40 mg (8 x 5 mg tablet)	1.7 / 0.2	1.4 - 1.9

Table 5-34: HepTest (x-fold change) - mean changes from baseline (n=8)

Dose/formulation	Mean change from baseline/SD	Range
Placebo tablet	1.1 / 0.1	1.0 - 1.1
5 mg (1 x 5 mg tablet)	1.7 / 0.1	1.5 - 1.8
10 mg (2 x 5 mg tablet)	2.1 / 0.1	2.0 - 2.3
20 mg (4 x 5 mg tablet)	2.2 / 0.2	2.0 - 2.7
40 mg (8 x 5 mg tablet)	2.4 / 0.3	2.0 - 2.9

Multiple dose escalation 10 to 30 mg bid in Japanese subjects (Study 11127):[90]

This randomized, single-blind, placebo-controlled, dose-escalation study in healthy Japanese male subjects investigated the tolerability, safety, pharmacokinetics, and

pharmacodynamic effects of BAY 59-7939 tablet after multiple oral doses of 10, 20, and 30 mg bid. for 6 days. For pharmacokinetic and safety results, see Section 5.2.2 and Section 5.2.4, respectively.

The pharmacological profile of BAY 59-7939 clotting parameters PT, PTT, HepTest, and Factor Xa inhibition were assessed as pharmacodynamic surrogate parameters. Dose proportional Factor Xa inhibition did not change after multiple dosing. PT, PTT, and Heptest were prolonged dose proportionally at steady state (Table 5-35, Table 5-36, Table 5-37, and Table 5-38).

Table 5-35: Factor Xa inhibition (%) - maximum mean changes from baseline (n=8)

Dose	Mean change from baseline	Range
10 mg bid Day 1	51	45 - 57
10 mg bid Day 6	48	39 - 53
20 mg bid Day 1	63	57 - 66
20 mg bid Day 6	69	58 - 74
30 mg bid Day 1	77	73 - 82
30 mg bid Day 6	77	74 - 81

Table 5-36: PT (x-fold change) - mean changes from baseline (n=8)

Dose	Mean change from baseline/SD	Range
Placebo Day 1	1.12 / 0.03	1.08 - 1.15
Placebo Day 6	1.12 / 0.07	1.06 - 1.22
10 mg bid Day 1	1.74 / 0.14	1.50 - 1.88
10 mg bid Day 6	1.88 / 0.08	1.80 - 2.06
20 mg bid Day 1	2.47 / 0.15	2.25 - 2.73
20 mg bid Day 6	2.80 / 0.40	2.27 - 3.53
30 mg bid Day 1	3.00 / 0.25	2.78 - 3.54
30 mg bid Day 6	3.30 / 0.38	2.89 - 3.98

Table 5-37: PTT (x-fold change) - mean changes from baseline (n=8)

Dose	Mean change from baseline/SD	Range
Placebo Day 1	1.07 / 0.03	1.04 - 1.13
Placebo Day 6	1.14 / 0.06	1.05 - 1.20
10 mg bid Day 1	1.44 / 0.14	1.26 - 1.67
10 mg bid Day 6	1.63 / 0.13	1.49 - 1.91
20 mg bid Day 1	1.63 / 0.07	1.54 - 1.75
20 mg bid Day 6	2.14 / 0.25	1.72 - 2.40
30 mg bid Day 1	1.79 / 0.07	1.65 - 1.86
30 mg bid Day 6	2.01 / 0.09	1.85 - 2.16

Table 5-38: HepTest (x-fold change) - mean changes from baseline (n=8)

Dose	Mean change from baseline/SD	Range
Placebo Day 1	1.00 / 0.01	1.00 - 1.03
Placebo Day 6	1.00 / 0.07	0.88 - 1.07
10 mg bid Day 1	2.04 / 0.28	1.71 - 2.59
10 mg bid Day 6	2.21 / 0.42	1.64 - 3.02
20 mg bid Day 1	2.49 / 0.18	2.17 - 2.72
20 mg bid Day 6	2.64 / 0.18	2.45 - 3.02
30 mg bid Day 1	2.75 / 0.13	2.56 - 2.95
30 mg bid Day 6	2.85 / 0.14	2.62 - 2.99

5.2.4 Safety/tolerability

Single dose escalation 1.25 to 80 mg (Study 10842):[73] This was a randomized, single-blind, placebo-controlled, group comparison, dose-escalation study in healthy male subjects. The study investigated the safety, tolerability, and pharmacodynamic effect as well as the pharmacokinetics of BAY 59-7939 after single PO doses of 1.25, 5, 10, 15, 20, 30, 40, 60, and 80 mg (administered as 5 mg tablets). For pharmacokinetic and pharmacodynamic results, see Section 5.2.2 and Section 5.2.3, respectively.

Of 108 enrolled subjects, 5 dropped out prior to any drug administration and were not included in any analysis. Therefore 103 subjects were analyzed, 10 of them according to crossover design and 93 subjects according to parallel design. 1 adverse event was considered to be medically important and consequently qualified as

"serious "; this subject showed pronounced CK increases, which were considered as not related to the study medication.

39 treatment-emergent adverse events were reported by 29 of 103 healthy subjects. 6 of the 39 adverse events were considered to be possibly related to the study medication: 3 cases of "taste of blood", which occurred after administration of 1.25 mg, 10 mg, and 80 mg BAY 59-7939 without any evidence for bleeding. Additionally both subjects had no unusual prolongation of the clotting parameters or inhibition of Factor Xa. All 3 events resolved without any actions taken after about 30, 45, and 105 min.

1 subject complained of headache. The event resolved after treatment with pain relief medication. 2 episodes of ecchymosis were observed.

There were no clinically relevant changes of vital signs or ECG in any of the dose steps. Bleeding time was not influenced to a clinically meaningful extent. The Rumpel-Leede test was negative at all times. Laboratory tests did not show any clinically relevant changes besides the CK increases mentioned above. In particular, there was no increase in bleeding time.

Food effect (Study 10846):[74] This was a randomized, open-label, 2-fold crossover 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 PO as 2 x 5 mg tablets in healthy male subjects. For pharmacokinetic and pharmacodynamic results, see Section 5.2.2 and Section 5.2.3, respectively.

10 subjects were enrolled in this study, 2 subjects dropped out: 1 withdrew his consent for further participation after the first treatment period; 1 subject was excluded because of high CK values after the wash-out period after 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 drug related adverse events were observed in this study.

Age and gender (Study 10850):[77] This was a 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 given as two 5 mg tablets. For pharmacokinetic and pharmacodynamic results, see Section 5.2.2 and Section 5.2.3, respectively.

48 subjects were enrolled in this study, 36 subjects (9/group) were on active drug, and 12 subjects (3/group) were on placebo.

5 subjects (14%) on active drug and 1 subject (8%) on placebo reported adverse events. 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.

Multiple dose escalation 5 mg od to 30 mg bid (Study 10847):[75] This randomized, placebo-controlled, single-blind, parallel-group study investigated the safety, tolerability, pharmacodynamics, and pharmacokinetics of BAY 59-7939 after single and multiple dose applications of BAY 59-7939 as conventional tablets: 5 mg od, 5 mg bid, 5 mg tid, 10 mg bid, 20 mg bid, and 30 mg bid. For pharmacokinetic and pharmacodynamic results, see Section 5.2.2 and Section 5.2.3, respectively.

68 healthy male subjects were enrolled. 4 subjects were enrolled into the study but not treated with the study drug. They were excluded from the analyses. 3 subjects discontinued participation in the study prematurely: 1 subject was withdrawn because of non-compliance on day 8 of treatment, 1 subject was withdrawn because of pronounced pharmacokinetic response to the drug, and 1 subject was withdrawn

because of invalid essential data. In total, 64 subjects were included in the safety analysis.

There were no serious adverse events or deaths in this study.

102 treatment-emergent adverse events were reported by 44 of 64 healthy subjects. 43 adverse events were considered possibly related to the study medication. The majority of the events were considered to be of mild intensity.

1 subject was found to have relevant increases in liver enzyme tests (GLDH, AST, ALT) on the last day of the administration of 30 mg BAY 59-7939 bid which may have a causal relationship to the study drug. No other laboratory tests showed any clinically relevant changes.

Bleeding times did not appear to be affected neither by single nor by multiple administration of BAY 59-7939 in the dose range from 5 mg od up to 30 mg bid. However, high variability of the data has to be taken into account. Prolongations of bleeding times to values above twice of baseline occurred in subjects with low baseline values and caused no safety concerns. No relevant prolongation of the bleeding time (ie, bleeding time exceeding 2.5 min on an individual basis) occurred after the higher doses.

Increased laboratory values above twice the upper limit of normal (ULN) were observed in 6 of 21 subjects in the placebo group. Elevations of GLDH and ALT were reported. After the 5 mg od treatment, 1 subject showed a more than 2-fold increase of leucine aminopeptidase; after the 5 mg bid treatment 1 subject had a considerable increase of CPK on Day 11. No elevations of laboratory parameters were observed after the 5 mg tid treatment. In the 10 mg bid group, 1 subject presented with a more than 2-fold increase of GLDH starting on Day 3. In the 20 mg bid group, 1 subject experienced an increase of lipase on Day 5, but had also had increased activity at the screening visit. After administration of 30 mg bid, 1 subject

developed increases of ALT and GLDH, which were also reported as adverse events and were considered to be drug related.

Overall incidence rates of increased laboratory values were not higher than in the placebo group. Elevations of liver enzymes were reported in the placebo group as well as after administration of active drug.

BAY 59-7939 did not affect blood pressure and heart rate to a relevant degree. ECGs were rated as normal or not clinically significant at all times during the study.

Details of the drug related adverse events are shown in Table 5-39.

Table 5-39: Study 10847 – drug-related adverse events

Treatment group	Adverse Event	Severity	Relation to Study Drug	Outcome
5 mg od	Feeling of hyperacidity in stomach	Mild	Yes	Resolved
5 mg od	Headache	Moderate	Yes	Resolved
5 mg od	Headache	Mild	Yes	Resolved
5 mg tid	Heartburn	Mild	Yes	Resolved
5 mg tid	Heartburn	Mild	Yes	Resolved
5 mg tid	Heartburn	Mild	Yes	Resolved
5 mg tid	Headache	Mild	Yes	Resolved
5 mg tid	Feeling of exhaustion	Mild	Yes	Resolved
5 mg tid	Diarrhea	Mild	Yes	Resolved
5 mg tid	Headache	Mild	Yes	Worsened
5 mg tid	Feeling of exhaustion	Mild	Yes	Resolved
5 mg tid	Headache	Moderate	Yes	Resolved
Placebo	Feeling of exhaustion	Mild	Yes	Resolved
Placebo	Diarrhea	Mild	Yes	Resolved
Placebo	Flatulence	Mild	Yes	Resolved
Placebo	Feeling of exhaustion	Moderate	Yes	Resolved
Placebo	Exanthema left cubital fossa	Mild	Yes	Resolved
Placebo	Feeling of exhaustion	Mild	Yes	Resolved
Placebo	Feeling of exhaustion	Moderate	Yes	Resolved
Placebo	Diarrhea	Moderate	Yes	Resolved
Placebo	Headache	Mild	Yes	Resolved
5 mg tid	Pressure on left ear	Moderate	Yes	Resolved
5 mg tid	Tinnitus left ear	Mild	Yes	Resolved
Placebo	Feeling of exhaustion	Mild	Yes	Resolved
Placebo	Feeling of exhaustion	Mild	Yes	Resolved
20 mg bid	Headache	Moderate	Yes	Resolved
Placebo	Headache	Mild	Yes	Resolved
20 mg bid	Headache	Mild	Yes	Resolved
20 mg bid	Headache	Mild	Yes	Resolved
Placebo	Headache	Mild	Yes	Resolved
30 mg bid	Heat sensation	Mild	Yes	Resolved
30 mg bid	Salty taste	Mild	Yes	Resolved
30 mg bid	Dizziness	Mild	Yes	Resolved
30 mg bid	Headache	Mild	Yes	Resolved
30 mg bid	Diarrhea	Mild	Yes	Resolved
30 mg bid	Heartburn	Moderate	Yes	Resolved
30 mg bid	Headache	Mild	Yes	Resolved
30 mg bid	Headache	Mild	Yes	Resolved
30 mg bid	Headache	Mild	Yes	Resolved
Placebo	Headache	Mild	Yes	Resolved
30 mg bid	Elevated GLDH	Moderate	Yes	Resolved
30 mg bid	Elevated ALT	Moderate	Yes	Resolved

Intestinal absorption study (Study 10924):[78] This single-center, non-blinded, non-randomized, non-placebo-controlled, crossover study investigated the absorption site in the intestine by administration of either tablet or solution in various parts of the intestine.

There was 1 serious adverse event: A PPD patient experienced a broken PPD index finger. The accident happened in the screening phase prior to the subject receiving any study medication. The investigator assigned the event as having no relationship to study medication.

Formulation comparison of one 20 mg tablet vs four 5 mg tablets (Study 10989):[79] This non-blinded, randomized, non-placebo-controlled crossover study compared the safety, tolerability, pharmacodynamics, and pharmacokinetics of 20 mg BAY 59-7939 given either as 4 tablets of 5 mg or one 20 mg tablet and investigated the effect of a high-fat, high-calorie or high-carbohydrate meal on safety, tolerability, pharmacodynamics, and pharmacokinetics of one 20 mg tablet BAY 59-7939 in healthy, male subjects. For pharmacokinetic results, see Section 5.2.2.

12 subjects were enrolled in this study, 1 dropped out prior to dosing, the other subject was withdrawn after the second study period. 9 of the 11 subjects reported 12 adverse events, of which 4 were considered potentially related to the study drug: 3 cases of headache and 1 “aching of the suprascapular region”. All events resolved completely. No clinically relevant changes of laboratory parameters, vitals signs, bleeding time or ECG which were related to the study drug were observed in this study.

Extended release vs immediate release formulation (Study 10990):[80] This randomized, non-blind, 3-way crossover study assessed the pharmacodynamics, pharmacokinetics, safety, and tolerability of an extended release formulation of

BAY 59-7939 (E 203) with and without food in comparison to the immediate release formulation in healthy male subjects.

12 subjects were enrolled in this study. 2 subjects discontinued treatment prematurely: 1 subject withdrew his consent because he had to leave early for personal reasons, the other subjects was withdrawn because of increased liver enzymes. The increased liver enzymes were 1 of the 2 adverse events that were considered potentially related to study drug. Although there is a timely relation to drug administration it is of note that the subject developed a gastrointestinal infection when the liver enzymes started to decline. Despite the fact that no investigations for liver specific viruses were performed it must be considered that this infection might have been contributed or even caused the increases in liver enzymes in this subject.

The other potentially drug related adverse event was “bleeding of the gums”. This event happened after the subject was brushing his teeth on the evening of the first of three study periods, and on the consecutive morning. Both bleedings stopped without any additional intervention. The subject participated in 2 additional study periods and received the same dose without any additional episodes of gum bleeding. Although the relation to study drug can not be dismissed due to the clear timely relationship to drug administration (but at a time when clotting tests have nearly returned to baseline) it is important to note that the episode could not be observed upon “rechallenge”, although more pronounced changes of clotting tests were present in the second study period.

No other relevant changes of safety parameters were observed in this study. Although slight declines in mean heart rate and blood pressure occurred, these were not accompanied by any clinically relevant signs or symptoms. Likewise no relevant changes were observed on ECG.

Extended release vs immediate release formulation (Study 11125):[88] This randomized, non-blind, 3-way crossover study assessed the pharmacodynamics, pharmacokinetics, safety, and tolerability of an extended release formulation of BAY 59-7939 (E 209) with and without food in comparison to the immediate release formulation in healthy male subjects.

12 subjects were enrolled. 1 subject dropped out prior to receiving any dose of BAY 59-7939. Subsequently 11 subjects were included into the safety analyses. No serious adverse events were observed in this trial. 9 treatment-emergent adverse events were reported by 5 of 11 healthy subjects. 2 of these adverse events (headache) were considered possibly related to the study medication. Both of them were of mild intensity and required no intervention. No clinically relevant changes of laboratory parameters, vital signs, ECG parameters or bleeding time were observed in this study.

Extended release vs immediate release formulation (Study 11197):[92] This randomized, non-blind, 3-way crossover study assessed the pharmacodynamics, pharmacokinetics, safety, and tolerability of an extended release formulation of BAY 59-7939 (E 206) with and without food in comparison to the immediate release formulation in healthy male subjects.

11 subjects were enrolled and completed the trial. No serious adverse events occurred in this trial. 8 treatment-emergent adverse events were reported by 6 of 11 healthy subjects. All events were considered to be of mild intensity. Only 1 adverse event was considered possibly related to the study medication. This “sensation of eye pressure” occurred 1.5 h after administration of the extended release tablet and subsided approximately 14 h later without requiring any intervention. Therefore no further actions were taken.

No clinically meaningful changes of laboratory values, vital signs, bleeding time, or ECG changes were observed in this study.

Effects of 5 and 30 mg BAY 59-7939 on thrombin generation (Study 11140):[91]
This randomized, open-label, 2-fold crossover pilot study investigated the effect of 5 and 30 mg BAY 59-7939 on the thrombin generation in 12 healthy male subjects. For pharmacodynamic results, see Section 5.2.3, respectively.

12 healthy male subjects were enrolled and completed the study. 1 subject reported 1 adverse event, which was a possibly drug-related mild headache. It started about 30 min after administration of the 30 mg dose and had resolved after 8 h.

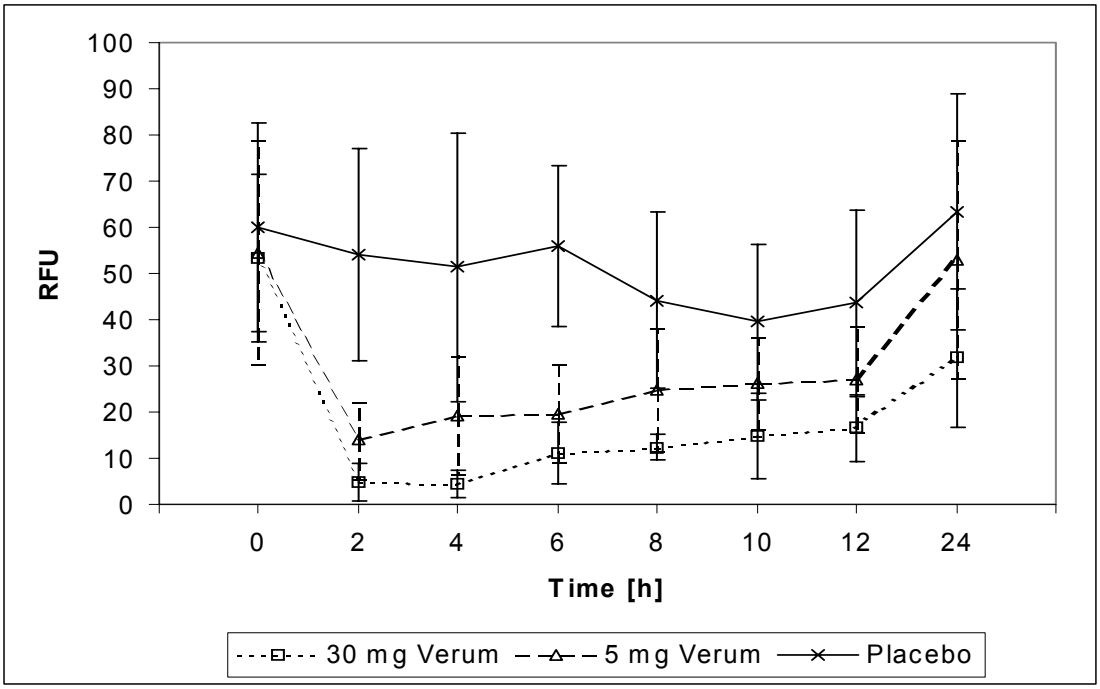
Assessment of laboratory parameters revealed no relevant abnormalities.
BAY 59-7939 did not affect blood pressure, heart rate, and ECG parameters.

BAY 59-7939 inhibited Factor Xa dose dependently, regardless of the method of determination (Factor Xa activity, PICT, anti-Factor Xa). BAY 59-7939 prolonged coagulation tests (PT, aPTT, HepTest) in a dose dependent way.

BAY 59-7939 prolonged the lag time of thrombin generation and decreased both the total amount of thrombin generated as well as the peak of thrombin generation (PITT, ETP AUC, ETP peak). BAY 59-7939 30 mg inhibited thrombin generation for more than 24 h. Plasma thrombin activity and Antithrombin were not affected. Correlation between anti-Factor Xa and plasma concentrations had the highest correlation coefficient, followed by PT with a slightly lower correlation coefficient.

As shown in Figure 5-9, a 30 mg dose of BAY 59-7939 inhibited thrombin generation as assessed by peak endogenous thrombin potential (ETP) for more than 24 h.

Figure 5-9: Thrombin generation inhibition over time (ETP [peak, collagen] measured in relative fluoro units [RFU])



Single dose escalation 5 to 40 mg in Japanese subjects (Study 11126):[89] This randomized, single-blind, placebo-controlled, dose-escalation study in healthy Japanese male subjects investigated tolerability, safety, pharmacokinetics, and pharmacodynamic effects of BAY 59-7939 tablet after single oral doses of 5, 10, 20, and 40 mg under fasting conditions. For pharmacokinetic and pharmacodynamic results, see Section 5.2.2 and Section 5.2.3, respectively.

40 healthy male subjects aged 20 to 45 years were enrolled in this study. 9 treatment-emergent adverse events were reported by 7 of 40 healthy subjects. 4 of the 9 adverse events were considered to be possibly related to the study medication: 3 events of mild bleeding time prolongation were reported at 2 h after administration of 10 mg (2 events) and 20 mg (1 event) in bleeding time examination (Duke method). The maximum bleeding times were 9.5, 9.0, and 5.5 min, respectively.

Bleeding time had returned to the normal range (<5 min) 4 or 8 h after the administration. A decrease in WBC was observed in another subject, however, this resolved without treatment.

Multiple dose escalation 10 to 30 mg bid in Japanese subjects (Study 11127):[90] This randomized, single-blind, placebo-controlled, dose-escalation study in healthy Japanese male subjects investigated the tolerability, safety, pharmacokinetics, and pharmacodynamic effects of BAY 59-7939 tablet after multiple oral doses of 10, 20, and 30 mg bid. for 6 days. For pharmacokinetic and pharmacodynamic results, see Section 5.2.2 and Section 5.2.3, respectively.

30 healthy male Japanese subjects aged 20 to 45 years and body weight 50 to 81 kg were enrolled. 16 treatment-emergent adverse events were reported by 10 of the 30 subjects. 5 of the 16 adverse events were considered possibly related to the study medication: 3 events of mild bleeding time prolongation were reported on Day 1 or Day 6 in the 10 mg dose group (each 1 event) and on Day 6 in the 20 mg dose group (1 event) in bleeding time examination (Duke method). Maximum bleeding times were 5.5, 6.5, and 6.0 min, respectively, and had returned to the normal range (<5 min) 2 h later. An event of mild nosebleed was observed from 05:33 h until 06:00 h on Day 4 in another subject, which resolved without treatment during study drug administration. Mild abdominal pain was reported before drug administration on Day 6 in 1 subject, which resolved without any treatment 2 h after drug administration.

PD/PK in elderly subjects (Study 11529):[95] This was a randomized, single-blind, placebo-controlled, dose-escalation study in healthy elderly (>60 years) male and female subjects to investigate the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 following single-dose administration of 30, 40, and 50 mg BAY 59-7939 given with a standard breakfast.

The drug was well tolerated, with only 7 potentially drug-related adverse events in 48 subjects. All drug-related adverse events were of mild intensity and had resolved by the end of the trial. The only remarkable event was spontaneous gum bleed of short duration in 1 subject with the highest Factor Xa inhibition of about 88%. However due to the short duration and benign course of the event which resolved spontaneously, this event is considered to confirm the broad safety margin of the drug. Laboratory values showed no clinically relevant abnormalities with the exception of 1 subject who had an increase of GLDH to the 2.5 times upper limit of normal after receiving 40 mg of BAY 59-7939. At the same time gamma-GT peaked at 1.4 times the upper limit of normal. No other clinical signs or symptoms related to liver disease were present in this subject.

Factor Xa inhibition, PT, PTT, or HepTest were prolonged as expected. There was no relevant difference in maximal Factor Xa inhibition, PT, PTT, or HepTest prolongation between males and females. Furthermore only a slight increase in inhibition or prolongation was observed between the 30 mg and 40 mg dose step. No further effect in terms of a more pronounced pharmacodynamic response was observed between the 40 mg and 50 mg dose step.

Effects of BAY 59-7939 on QTc duration (Study 11275):[93] This was a randomized, double-blinded, double-dummy, 4-way crossover, placebo- and active-controlled phase-I study to investigate the influence of single doses (15 and 45 mg) of BAY 59-7939 on the QTc interval in healthy male and female subjects. For pharmacokinetic and pharmacodynamic results, see Section 5.2.2 and Section 5.2.3, respectively.

56 treatment-emergent adverse events were reported by 25 of the 54 healthy subjects. 4 were possibly related to the study medication. 46 adverse events of mild and 8 of moderate intensity.

2 serious adverse events unrelated to study drug occurred: 1 olecranon fracture after discharge due to a bicycle accident (6 days after 45 mg BAY 59-7939, severe intensity); 1 case of acute appendicitis (11:35 h after 400 moxifloxacin, severe intensity). 3 subjects dropped out due to adverse events (olecranon fracture, sinusitis, abdominal pain).

No clinically relevant changes of laboratory panel, vital signs were observed. No QTc-prolonging effect was observed for BAY 59-7939.

5.2.5 Drug interaction studies

Enoxaparin interaction (Study 10848):[76] This non-blinded, randomized, non-placebo-controlled, crossover study investigated the influence of 40 mg of SC enoxaparin on the safety, tolerability, pharmacodynamics and pharmacokinetics of 10 mg BAY 59-7939 and vice versa in healthy male subjects.

The LMWH enoxaparin was chosen, because it may be given as a rescue treatment to those patients not responding adequately to BAY 59-7939 treatment.

Plasma concentration time profiles for BAY 59-7939 after PO application of 10 mg BAY 59-7939 either alone or together with 40 mg SC enoxaparin were proven to be virtually identical. Accordingly, no changes in the resulting PK parameter for BAY 59-7939 were detected (Table 5-40). 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. There was no pharmacokinetic interaction between the 2 compounds.

Table 5-40: Pharmacokinetics of BAY 59-7939 after oral application of 10 mg BAY 59-7939 with and without 40 mg enoxaparin SC (geometric means/geometric SD)

Parameter	Unit	BAY 59-7939 alone n=11	BAY 59-7939 plus enoxaparin n=10
AUC	[µg*h/L]	956 (1.33)	957 (1.31)
AUC_{norm}	[g*h/L]	7420 (1.32)	7422 (1.30)
AUC/D	[h/L]	0.096 (1.33)	0.096 (1.31)
C_{max}	[µg/L]	123 (1.22)	119 (1.38)
$C_{max, norm}$	[g/L]	953 (1.22)	923 (1.37)
$C_{max/D}$	[1/L]	0.012 (1.22)	0.012 (1.38)
t_{max}[a]	[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)

a Median

12 subjects were enrolled in this study and 10 completed the trial. 1 subject was withdrawn after the second study period because of non-compliance, the other subject experienced a 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.

In total, 4 of 11 subjects valid for safety analysis experienced 8 treatment-emergent adverse events. 4 subjects reported 4 adverse events after intake of single dose of BAY 59-7939 and 1 subject reported 2 adverse events after administration of enoxaparin and BAY 59-7939 + enoxaparin, respectively. The events, which were at least possibly related to the study medication, were episodes of headache with mild or moderate intensity.

The analysis of laboratory changes did not raise the suspicion of drug-induced changes of laboratory parameters as the changes are not reproducible after re-exposition. Vital signs and ECG were not affected to a clinically relevant extent. Likewise there were no obvious effects on bleeding time. With regard to pharmacodynamic effects, no interactions 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. There were additive effects on parameters like anti-Xa activity, PT, PTT, HepTest, and bleeding time when the 2 compounds were administered concomitantly.

The analysis 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. Anti-Factor Xa activity 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 was longer with BAY 59-7939 treatment than with enoxaparin. The drug combination resulted in slightly prolonged PTT values. Compared with 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.

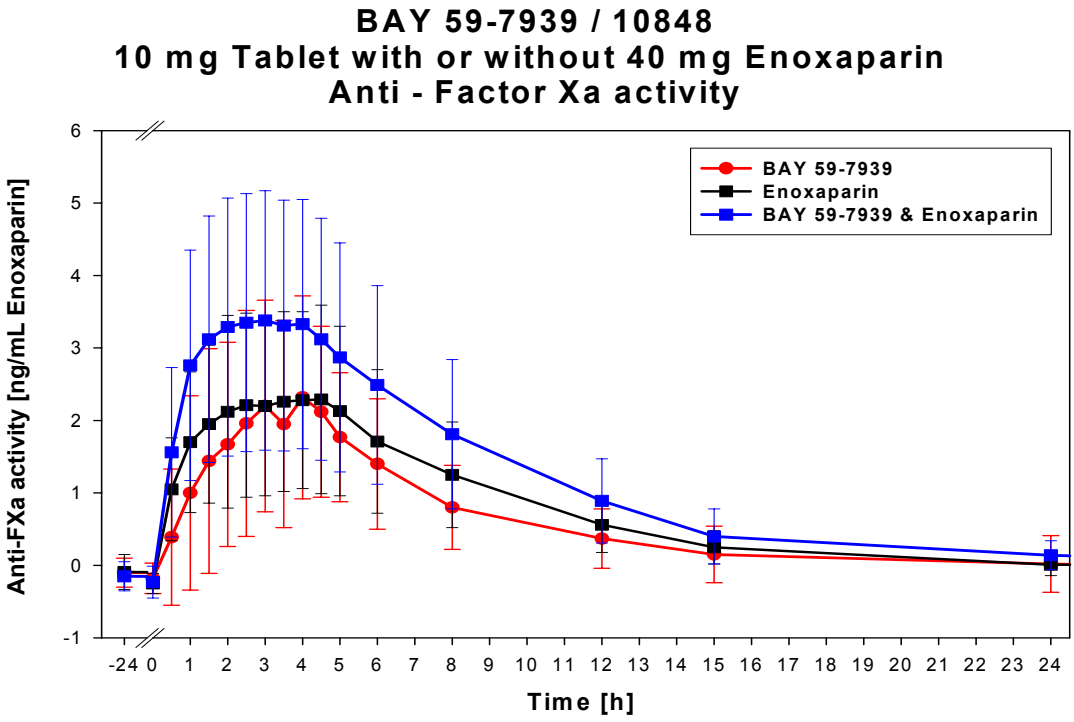
Table 5-41: Treatment effects in different test systems based on maximum observations (ratio; 90% confidence interval)

Parameter	Treatment	Enoxaparin	BAY 59-7939 plus enoxaparin
Factor Xa[a]	BAY 59-7939	1.43 (1.31-1.56)	0.98 (0.90-1.07)
	Enoxaparin	1	0.69 (0.63-0.75)
Anti-Factor Xa activity	BAY 59-7939	1.04 (0.91-1.18)	1.48 (1.30-1.69)
	Enoxaparin	1	1.43 (1.25-1.63)
PT	BAY 59-7939	0.73 (0.70-0.76)	1.01 (0.97-1.05)
	Enoxaparin	1	1.38 (1.33-1.44)
PTT	BAY 59-7939	0.83 (0.71-0.96)	0.97 (0.84-1.13)
	Enoxaparin	1	1.18 (1.01-1.37)
HepTest	BAY 59-7939	2.54 (2.05-3.16)	1.18 (0.95-1.47)
	Enoxaparin	1	0.46 (0.37-0.58)
Bleeding Time	BAY 59-7939	1.23 (1.07-1.43)	1.18 (1.02-1.37)
	Enoxaparin	1	0.96 (0.83-1.11)

a Minimum observations

Anti-FXa activity of BAY 59-7939 and enoxaparin were very similar (Figure 5-10).

Figure 5-10: Anti-FXa activity of BAY 59-7939 10 mg with and without enoxaparin 40 mg up to 24 h post dose



Ketoconazole interaction (Study 10992):[81] This randomized, non-blinded, non-placebo-controlled, 2-fold crossover study investigated the influence of a pre- and co-administration of 200 mg ketoconazole once daily on the safety, tolerability, pharmacodynamics, and pharmacokinetics of a single PO dose of 10 mg BAY 59-7939 in comparison to a single PO dose of 10 mg of BAY 59-7939 alone in 12 healthy male subjects. For safety results, see Section 5.2.4.

The concomitant administration of 200 mg ketoconazole, a known potent cytochrome P450 3A4 inhibitor, led to an approximate increase in mean BAY 59-7939 maximum concentration of 50%. Mean AUC was nearly doubled,

while terminal half-life remained unaffected. Table 5-42 summarizes the pharmacokinetic results.

Table 5-42: Pharmacokinetics of BAY 59-7939 with and without concomitant administration of ketoconazole (n=12/group; geometric means/geometric SD)

Parameter	Unit	BAY 59-7939 10 mg alone	BAY 59-7939 10 mg plus ketoconazole 200 mg
AUC	[µg*h/L]	1088 (1.19)	1980 (1.22)
C_{max}	[µg/L]	149 (1.32)	228 (1.24)
t_{max} [a]	[h]	2.50 (0.75-6.00)	2.25 (0.75-3.00)
$t_{1/2}$	[h]	7.28 (1.61)	5.68 (1.24)
CL/f	[L/h]	9.19 (1.19)	5.05 (1.22)
CL_R [b]	[L/h]	3.21 (1.20)	2.12 (1.35)
Ae_{ur} [b]	[%]	35.5 (6.55)	42.3 (5.67)

a Median (range)
b Arithmetic mean ± SD

12 subjects were enrolled and completed the study. 11 treatment-emergent adverse events were reported by 6 of 12 healthy subjects. 5 of these adverse events were considered possibly related to the study medication. 7 adverse events were considered of mild and 4 events of moderate intensity. 1 serious adverse event occurred in this study (atrial fibrillation), which started 54 days after the last administration of the study drug and was consequently not considered to be drug related. No clinically relevant changes in laboratory parameters, vital signs or ECG were observed in this study.

A considerable influence of the concomitant administration of ketoconazole on the pharmacodynamic parameters was also observed. See Table 5-43 for details.

Table 5-43: Pharmacodynamics of BAY 59-7939 with and without concomitant administration of ketoconazole (n=12/group)

Parameter	Unit	BAY 59-7939 10 mg alone	BAY 59-7939 10 mg plus ketoconazole 200 mg
Factor Xa inhibition	% change from baseline	37.5	51.5
PT	Times of change from baseline	1.4	1.8
PTT	Times of change from baseline	1.3	1.4
HepTest	Times of change from baseline	1.8	2.1

Midazolam interaction (Study 10993):[82] This randomized, non-blinded, non-placebo-controlled, 3-fold crossover study investigated co-administration of 7.5 mg midazolam od and 20 mg BAY 59-7939 on the safety, tolerability, pharmacodynamics, and pharmacokinetics for combination and single administration in 12 healthy male subjects. For pharmacodynamics and safety results, see Section 5.2.3 and Section 5.2.4, respectively.

The pharmacokinetics of midazolam (co-substrate of CYP 3A4), its CYP 3A4-mediated metabolite α-hydroxy-midazolam, and BAY 59-7939 remained unaffected when administered concomitantly compared to their respective mono-treatment arms (Table 5-44, Table 5-45, and Figure 5-11).

Table 5-44: Pharmacokinetics of BAY 59-7939 after oral administration of 20 mg BAY 59-7939 with and without 7.5 mg midazolam (n=12; geometric means/geometric SD)

Parameter	Unit	20 mg BAY 59-7939 alone	20 mg BAY 59-7939 plus 7.5 mg midazolam
AUC	[µg*h/L]	1278 (1.34)	1295 (1.39)
C_{max}	[µg/L]	119 (1.46)	104 (1.59)
t_{max} [a]	[h]	1.50 (1.00-4.00)	4.00 (1.00-6.00)
$t_{1/2}$	[h]	10.7 (1.37)	9.08 (1.49)
Vz/f	[L/kg]	2.98 (1.44)	2.49 (1.70)
CL/f	[L/h]	15.7 (1.34)	15.5 (1.39)
CL_R	[L/h]	3.25 (1.33)	3.43 (1.29)
$Aeur_{0-96}$ [b]	[%]	21.3 (5.81)	22.9 (6.77)

a Median

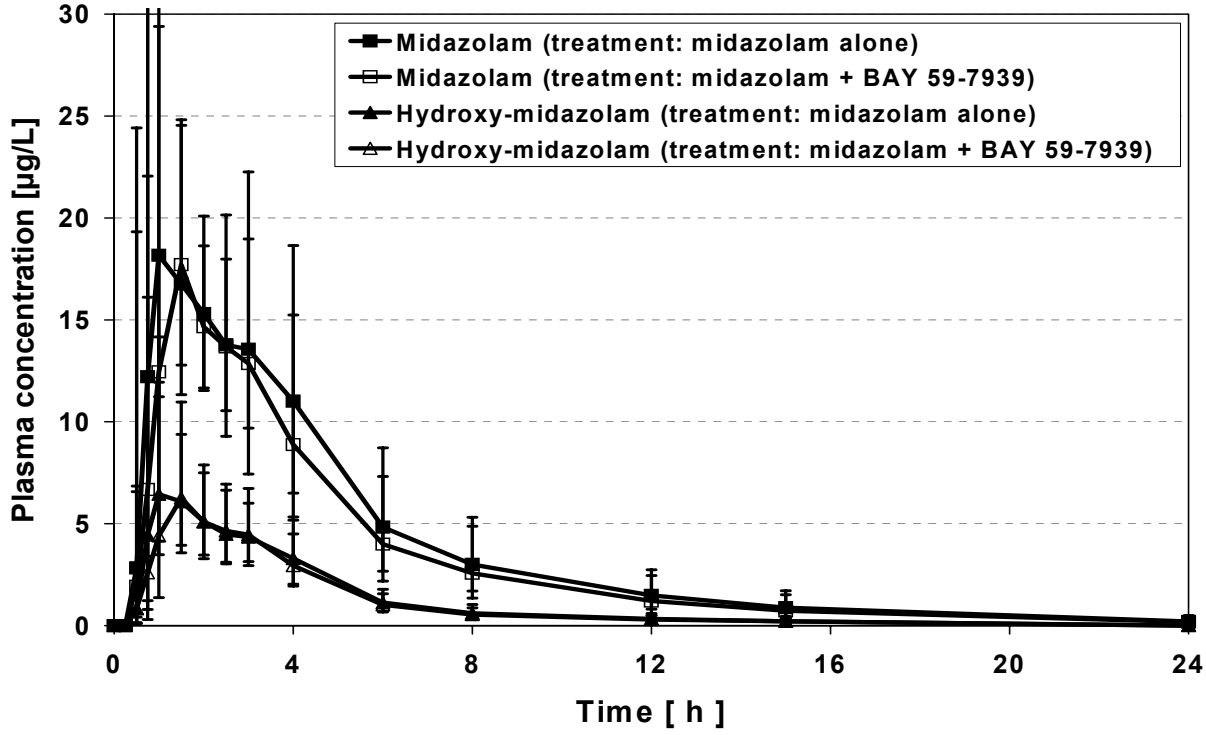
b Arithmetic mean ± SD

Table 5-45: Pharmacokinetics of midazolam and hydroxy-midazolam after oral administration of 7.5 midazolam with and without 20 mg BAY 59-7939 (n=12; geometric means/geometric SD)

		Midazolam		Hydroxy-midazolam	
Parameter	Unit	Midazolam	Midazolam plus 20 mg BAY 59-7939	Midazolam	Midazolam plus 20 mg BAY 59-7939
AUC	[µg*h/L]	97.8 (1.45)	86.9 (1.63)	29.0 (1.40)	28.6 (1.42)
C_{max}	[µg/L]	26.5 (1.49)	26.7 (1.86)	9.08 (1.66)	10.1 (1.99)
t_{max} [a]	[h]	1.50 (0.50-4.00)	1.50 (0.50-3.00)	1.13 (0.50-4.00)	1.00 (0.50-4.00)
$t_{1/2}$	[h]	4.33 (1.29)	4.50 (1.22)	5.06 (1.44)	5.52 (1.60)
CL/f	[L/h]	76.7 (1.45)	86.3 (1.63)	270 (1.40)	274 (1.42)

a Median

Figure 5-11: Plasma concentrations of midazolam and hydroxy-midazolam after administration of midazolam with and without BAY 59-7939 (n=12; geometric means ± geometric SD)



Thus, concomitant administration of the prominent CYP 3A4 substrate midazolam and the CYP 3A4 substrate BAY 59-7939 did not reveal any significant mutual pharmacokinetic drug-drug interaction potential.

12 subjects were enrolled and completed the study. 10 treatment-emergent adverse events were reported by 4 of 12 healthy volunteers. 3 of these adverse events (headaches) were considered possibly related to the study medication. All adverse events were of mild intensity. The 3 potentially drug-related adverse events were evenly distributed between the different treatment regimens. No clinically relevant changes of laboratory parameters, vital signs or ECG were observed in this study.

There was no influence of the concomitant administration of midazolam (co-substrate of CYP 3A4) on the pharmacodynamics of BAY 59-7939. See Table 5-46 for details.

Table 5-46: Pharmacodynamics of BAY 59-7939 with and without concomitant administration of midazolam (n=12/group)

Parameter	Unit	BAY 59-7939 20 mg alone	BAY 59-7939 20 mg plus midazolam 7.5 mg
Factor Xa inhibition	% change from baseline	31.9	29.0
PT	Times of change from baseline	1.41	1.36
PTT	Times of change from baseline	1.28	1.23
HepTest	Times of change from baseline	1.55	1.47

Ranitidine interaction (Study 11000):[84] This was a randomized, non-blinded, non-placebo-controlled, cross-over study to investigate the influence of a 3-day pretreatment with 300 mg ranitidine on the safety, tolerability, pharmacodynamics, and pharmacokinetics of 30 mg BAY 59-7939 single oral dose in healthy male subjects.

The pharmacokinetics of BAY 59-7939 were not altered when co-administered with 150 mg of the H_2-antagonist ranitidine.

Table 5-47: Pharmacokinetics of BAY 59-7939 with and without concomitant administration of ranitidine (n=12/group; geometric means/geometric SD)

Parameter	Unit	BAY 59-7939 30 mg alone	BAY 59-7939 30 mg plus ranitidine 150 mg
AUC	[µg*h/L]	1740 (1.29)	1763 (1.46)
C_{max}	[µg/L]	176 (1.44)	190 (1.52)
t_{max} [a]	[h]	2.0 (1.0-4.0)	2.0 (0.5-6.0)
$t_{1/2}$	[h]	8.39 (1.30)	8.54 (1.43)
CL/f	[L/h]	17.2 (1.29)	18.0 (1.46)
CL_R [b]	[L/h]	2.81 (1.41)	2.59 (1.39)
Ae_{ur} [b]	[%]	17.0 (5.51)	15.5 (3.74)

a Median (range)
b Arithmetic mean ± SD

The drug was well tolerated, with no drug-related adverse events. No clinically relevant changes of laboratory panel, vital signs or on ECG were observed.

The pharmacodynamic response was as expected from previous single dose studies and did not indicate any clinically relevant interaction between BAY 59-7939 and ranitidine.

Aluminum hydroxide / magnesium hydroxide (Maalox®) interaction (Study 11001):[85] This was a randomized, non-blinded, non-placebo-controlled, cross-over study to investigate the influence of a co-administration of 10 mL of aluminum hydroxide/magnesium hydroxide (Maalox®) on the safety, tolerability, pharmacodynamics, and pharmacokinetics of 30 mg BAY 59-7939 single oral dose in healthy male subjects.

The pharmacokinetic evaluation revealed a slightly lower AUC when the drug was given together with aluminum hydroxide / magnesium hydroxide (Maalox®) compared to BAY 59-7939 given alone. In addition, a lower rate of absorption after the combination regimen resulted in a delayed and reduced maximum concentration. Both effects were small and did not represent a relevant difference in the

bioavailability of the 2 drug regimens, leading to the conclusion that pharmacokinetics of BAY 59-7939 were not relevantly altered when it was co-administered with 10 mL aluminum hydroxide / magnesium hydroxide (Maalox®).

Table 5-48: Pharmacokinetics of BAY 59-7939 with and without concomitant administration of aluminum hydroxide / magnesium hydroxide (Maalox®) (n=12/group; geometric means/geometric SD)

Parameter	Unit	BAY 59-7939 30 mg alone	BAY 59-7939 30 mg plus 10 mL Maalox®
AUC	[µg*h/L]	1828 (1.19)	1734 (1.23)
C_{max}	[µg/L]	205 (1.16)	178 (1.37)
t_{max} [a]	[h]	2.0 (1.0-4.0)	2.5 (0.5-4.0)
$t_{1/2}$	[h]	8.56 (1.49)	7.26 (1.43)
CL/f	[L/h]	16.4 (1.19)	17.3 (1.23)
CL_R	[L/h]	2.71 (1.27)	3.02 (1.34)

a Median (range)
b Arithmetic mean ± SD

The drug was well tolerated, with 2 potentially drug- related adverse events: 1 was an episode o loose stool; the other was bleeding at the catheter site the latter requiring only a change of the plaster. Both events did not require any medical intervention (besides changing the plaster), were of mild intensity and subsided spontaneously. No clinically relevant changes of laboratory panel, vital signs or on ECG were observed.

The pharmacodynamic response was as expected from previous single dose studies and did not indicate any clinically relevant interaction between BAY 59-7939 and aluminum hydroxide/magnesium hydroxide (Maalox®).

Digoxin interaction study (Study 10999):[83] This was a randomized, non-blind, non-placebo-controlled, 2-fold cross-over study to investigate the influence of the simultaneous administration of multiple doses of BAY 59-7939 (20 mg bid) and of digoxin (0.375 mg od) on the pharmacokinetics of both drugs and to investigate the safety and tolerability of the combined treatment in 20 healthy male subjects.

Pharmacokinetic results for digoxin and BAY 59-7939 are summarized in Table 5-49, Table 5-50, and Table 5-51.

Table 5-49: Pharmacokinetic parameters of digoxin with and without concomitant administration of BAY 59-7939 [n=17/group; geometric means/geometric SD (range)]

Parameter	Unit	Digoxin 0.375 mg plus BAY 59-7939 20 mg	Digoxin 0.375 mg alone
$AUC_{\tau}(0\text{-}24)$	[µg*h/L]	24.73/19.29 (16.54 – 33.88)	22.93/17.65 (15.31 – 31.91)
C_{max}	[µg/L]	3.119/25.96 (1.41 – 4.20)	3.090/23.99 (1.96 – 4.76)
t_{max} [a]	[h]	1.000 (0.5000 – 2.500)	1.000 (0.5000 – 2.500)
$C_{trough,ss}$ Day 7	[µg/L]	0.699/22.21 (0.40 – 0.89)	0.741/19.63 (0.51 – 1.11)
$C_{trough,ss}$ Day 8	[µg/L]	0.744/28.41 (0.41 – 1.27)	0.729/20.13 (0.48 – 0.97)
$C_{trough,ss}$ Day 9	[µg/L]	0.738/21.38 (0.45 – 0.99)	0.782/19.24 (0.49 – 1.14)
CL_R	[L/h]	9.538/35.25 (4.645 – 14.63)	12.65/29.69 (7.877 – 19.62)
$Ae_{ur}(0\text{-}24)$ [b]	[%]	66.09/20.63 (33.41 – 106.4)	80.03/20.54 (39.27 – 118.8)

a Median (range)
b Arithmetic mean/SD (range)

The primary pharmacokinetic parameters $AUC_{\tau,ss}$ and $C_{trough,ss}$ of digoxin were analyzed using analysis of variance (ANOVA) including a treatment (digoxin / digoxin + BAY 59-7939) and a sequence effect (group A / group B) assuming log-normally distributed data.

Table 5-50: Treatment comparisons of digoxin kinetics based on ANOVA results

Test	Reference	$AUC_{\tau}(t_1\text{-}t_2)$ Ratio (90% CI)	$C_{trough,ss}$ Day 7 Ratio (90% CI)	$C_{trough,ss}$ Day 8 Ratio (90% CI)	$C_{trough,ss}$ Day 9 Ratio (90% CI)
BAY 59-7939 + digoxin	Digoxin	1.0784 (0.9677 – 1.2018)	0.9479 (0.8456 – 1.0624)	1.0254 (0.8961 – 1.1734)	0.9505 (0.8494 – 1.0635)

No statistically significant differences were found and all calculated 90% confidence intervals for $AUC_{\tau,ss}$ and $C_{trough,ss}$ were completely contained in the interval [0.80; 1.25].

Table 5-51: Pharmacokinetics of BAY 59-7939 with and without concomitant administration of digoxin [n=17/group; geometric means/ geometric coefficient of variation (range)]

Parameter	Unit	BAY 59-7939 20 mg alone	BAY 59-7939 20 mg plus digoxin 0.375 mg
AUC	[µg*h/L]	1699/26.49 (1009 – 2600)	1501/17.92 (1086 – 2203)
C_{max}	[µg/L]	183.6/25.46 (115.4 – 310.5)	173.9/21.88 (128.7 – 283.2)
t_{max}[a]	[h]	1.500 (0.667 – 4.000)	2.000 (0.667 – 4.000)
$t_{1/2}$	[h]	9.382/36.07 (4.834 – 17.53)	8.093/32.69 (4.826 – 13.62)
CL_R	[L/h]	2.812/20.63 (1.897 – 4.180)	3.019/31.53 (1.415 – 4.894)[b]
Ae_{ur}(0-24)**	[%]	20.53/18.68 (15.15 – 27.66)	19.69/34.88 (10.12 – 31.96)[b]

a Median (range)
b n=16
c Arithmetic mean/SD (range)

The statistical analysis showed again that the 90% confidence interval for the ratios '20 mg BAY 59-7939 with digoxin / 20 mg BAY 59-7939 alone'of AUC and C_{max} were fully contained in the interval 80% to 125%, which is the conventionally used criterion for bioequivalence. For the other pharmacokinetic parameters of BAY 59-7939 no relevant changes were observed after combined administration of BAY 59-7939 and digoxin.

In conclusion, lack of mutual pharmacokinetic interaction between digoxin and BAY 59-7939 could be demonstrated.

Of 20 enrolled subjects, 1 dropped out before receiving any study medication. Another subject withdrew consent and 1 subject was non-compliant as to intake of

study medication. In total, 17 subjects were valid for PK analysis and 19 subjects for safety analysis.

A total of 93 treatment-emergent adverse events were reported by 19 healthy subjects. 45 adverse events were considered possibly related to study medication. 72 adverse events were of mild, 20 of moderate, and 1 of severe intensity.

Among these events, headache was most common (10 subjects, 2x during digoxin wash-out phase and 8x with digoxin/BAY 59-6939 combination). There was 1 serious adverse event (psychosis 3 days after a 10-day administration of 0.375 mg digoxin) considered unrelated to study drug.

3 increases of CK were observed in 2 subjects: 1 episode of CK 3.17 x ULN was observed in 1 subject receiving digoxin only; 1 episode of CK increase 2.15 x ULN after digoxin administration; 1 epsiode of CK 4.25 x ULN at follow-up. 1 subject had an SGPT/ALT increase by 2.03 x ULN at follow-up. 1 subject had an GLDH increase of 3.03 x ULN during wash-out. These increases were not assessed as related to the administration of study medication. No other laboratory parameters had increases ≥2 x ULN.

No clinically relevant changes of vital signs or ECG were observed.

Administration of 20 mg BAY 59-7939 without digoxin produced pharmacodynamic responses on factor Xa, PT, aPTT, and HepTest comparable to data obtained before. Co-administration of digoxin alone (0.375 mg od for 28 days) did not influence these parameters to a relevant extent. Combined administration led to the same effects as BAY 59-7939, ie, a reduced factor Xa activity and prolongations for PT, aPTT, and HepTest.

Acetylsalicylic acid interaction (Study 11123): This was a randomized, non-blinded, 2-way cross-over study with an acetylsalicylic acid (Aspirin®) run-in period to investigate the influence of 2 doses of 500 mg acetylsalicylic acid once daily on

the safety, tolerability, pharmacodynamics and pharmacokinetics of a single oral dose of 15 mg BAY 59-7939 in 14 healthy male subjects and vice versa.

No serious adverse event was reported and all events were resolved at the end of the trial. Possibly drug related events were headache (1 subject) after BAY 59-7939 alone and after the combination and 3 hematomas of mild intensity. The hematomas were located on the elbows and first seen within 24 h after drug administration. They had resolved within 7 days.

2 subjects presented with elevations of GLDH starting on Day 3 after combined drug administration. Peak activity was measured 3.08 x ULN and 2.48 x ULN. At the final examination GLDH activity was normal. Parallel to GLDH, ALT activity also increased up to 1.53 x ULN and 1.9 x ULN. The drug was well tolerated, with no drug-related adverse events. No relevant changes of vital signs or ECG were observed.

The pharmacodynamic evaluation showed the potential of BAY 59-7939 to inhibit factor Xa with (median) maximum inhibition rates of 34.5% after 15 mg BAY 59-7939 alone. Combination with acetylsalicylic acid did not impair factor Xa inhibition after BAY 59-7939 (33% maximum inhibition). Maximum prolongations for PT exceeded baseline by a median factor of 1.33 /1.34 for BAY 59-7939 alone and the combination respectively. For PTT the factor was 1.31 for both treatment regimens and for HepTest 1.79 / 1.87 for BAY 59-7939 alone and the combination regimen. The effect of the combination treatment was attributable to BAY 59-7939 alone since acetylsalicylic acid alone did not influence factor Xa activity or the clotting tests.

On the other hand acetylsalicylic acid, in contrast to BAY 59-7939, has the potential to inhibit platelet aggregation. Platelet aggregation decreased by almost 100% after acetylsalicylic acid and mildly increased by 19% after BAY 59-7939. The mild increase after BAY 59-7939 alone was clinically not relevant because they are

probably due to technical reasons and furthermore within the known range of variability for platelet aggregation tests.

The difference between acetylsalicylic acid and BAY 59-7939 was statistically significant. Combination of both treatments did not relevantly alter platelet aggregation in comparison to the acetylsalicylic acid run-in period.

Bleeding time 4 h after drug administration as an unspecific parameter was prolonged after acetylsalicylic acid by a median factor of 1.36 over baseline. BAY 59-7939 alone at the dose of 15 mg did not prolong bleeding time. The difference of bleeding times between the 2 mono-treatments was statistically significant as expected. Combination of BAY 59-7939 and acetylsalicylic acid caused a prolongation of bleeding time to values twice as long as the baseline values. The difference between acetylsalicylic acid alone and the combination with BAY 59-7939 was statistically significant but not clinically relevant. Therefore no clinically relevant pharmacodynamic interaction is anticipated between BAY 59-7939 and acetylsalicylic acid at the doses tested in this trial.

The pharmacokinetic evaluation revealed a slightly lower AUC when BAY 59-7939 was given together with acetylsalicylic acid compared to BAY 59-7939 given alone. The effect was small and does not represent a relevant difference in the bioavailability of the 2 drug regimens.

The statistical analysis showed that the 90% confidence interval for the ratio of AUC (81.9% to 100.6%) '15 mg BAY 59-7939 with acetylsalicylic acid / 15 mg BAY 59-7939 alone' was fully contained in the interval 80% to 125%, which is the conventionally used criterion for bioequivalence. The 90% confidence interval for the C_{max} ratio (94.5% to 117.1%) was also in agreement with the bioequivalence conclusion. For the other pharmacokinetic parameters of BAY 59-7939 no relevant changes were observed after combined administration of BAY 59-7939 and acetylsalicylic acid.

Table 5-52: Pharmacokinetics of BAY 59-7939 with and without concomitant administration of acetylsalicylic acid [n=11/group; geometric means/geometric SD (range)]

Parameter	Unit	BAY 59-7939 30 mg alone	BAY 59-7939 15 mg plus acetylsalicylic acid
AUC	[µg*h/L]	1156/30.62 (697.6 – 1847)	1053/22.58 (736.6 – 1483)
C_{max}	[µg/L]	126.3/30.01 (78.53 – 196.1)	133.4/26.44 (85.34 – 195.6)
t_{max} [a]	[h]	1 (1 – 4)	2 (1 – 4)
$t_{1/2}$	[h]	9.310/36.32 (5.939 – 14.80)	8.234/39.32 (5.427 – 22.77)

a Median (range)
b Arithmetic mean ± SD

Naproxen interaction (Study 11124): This was a randomized, non-blinded, 2-way cross-over study with a naproxen run-in period to investigate the influence of 2 doses of 500 mg naproxen once daily on the safety, tolerability, pharmacodynamics, and pharmacokinetics of a single oral dose of 15 mg BAY 59-7939 in 14 healthy male subjects and vice versa.

BAY 59-7939 and naproxen, alone or in combination with each other, were well-tolerated in this study. No adverse events that were assessed as related to the administration of study medication were observed and no serious adverse events occurred. No clinically relevant changes of laboratory panel, vital signs or on ECG were observed.

Administration of 15 mg BAY 59-7939 in combination with naproxen had no relevant additional effect on factor Xa, PT, aPTT, and HepTest. Administration of naproxen alone (500 mg on 2 consecutive days) did not influence these parameters to a relevant extent. Combined administration led to the same effects as BAY 59-7939 alone, ie, a reduced factor Xa activity and prolongations for PT, aPTT, and HepTest.

Bleeding time as an unspecific parameter was prolonged after naproxen whereas BAY 59-7939 alone had no effect. The prolongation of bleeding time after the combination of naproxen with BAY 59-7939 was slightly increased compared to the administration of naproxen alone. Since the overall median degree of the prolongation is small and in a range that is considered to be not clinically relevant. However as one individual showed a more pronounced effect compared to baseline, it can not be excluded that there may be individual patients who may show a more pronounced response to bleeding time. Therefore the bleeding time data may indicate a small pharmacodynamic interaction of questionable clinical relevance.

Platelet aggregation was not affected by BAY 59-7939. It is known that naproxen inhibits platelet function and the observed inhibitory effect on platelet aggregation after combined administration was caused by naproxen. After combined treatment the inhibitory effect on platelet aggregation was not different from that after naproxen alone.

The pharmacokinetic evaluation revealed a slightly higher AUC when BAY 59-7939 was given together with naproxen compared to BAY 59-7939 given alone. Maximum concentration was also higher after combination treatment but was observed slightly later than after BAY 59-7939 alone. The effect was small (approximately 10% increase for both parameters) and does not necessarily represent a relevant difference in the bioavailability of the 2 drug regimens. The statistical analysis showed that the 90% confidence intervals for the ratios of AUC (99.5% to 127.1%) and C_{max} (90.5% to 132.5%) '15 mg BAY 59-7939 with naproxen / 15 mg BAY 59-7939 alone' covered 100% and only slightly exceeded the conventional upper limit for bioequivalence (125%).

Table 5-53: Pharmacokinetics of BAY 59-7939 with and without concomitant administration of naproxen [n=11/group; geometric means/geometric SD (range)]

Parameter	Unit	BAY 59-7939 30 mg alone	BAY 59-7939 15 mg plus naproxen
AUC	[µg*h/L]	1250/28.56 (795.0 – 1987)	1396/26.30 (1067 – 2377)
C_{max}	[µg/L]	152.9/31.51 (87.0 – 235.9)	165.3/27.69 (103.7 – 257.4)
t_{max} [a]	[h]	1.0 (1.0 – 3.0)	2.0 (0.5 – 4.0)
$t_{1/2}$	[h]	8.594/28.99 (5.706 – 13.58)	7.852/24.59 (5.275 – 10.97)

a Median (range)
b Arithmetic mean ± SD

Clopidogrel interaction (Study 11279): This was a randomized, non-blinded, 2-way cross-over study with a clopidogrel run-in period to investigate the influence of 2 doses of clopidogrel once daily (300 mg on the first day and 75 mg on the second day)on the safety, tolerability, pharmacodynamics, and pharmacokinetics of a single oral dose of 15 mg BAY 59-7939 in 14 healthy male subjects and vice versa.

A total of 14 treatment-emergent adverse events were reported by 10 of the 14 healthy volunteers. Among these events, headache was most common (4 subjects, 3x after BAY 59-7939 and 1x after clopidogrel) and was the only event with a possible causal relationship to the administration of study medication (3 subjects, 2x after BAY 59-7939 and 1x after clopidogrel). Intensity of the events was mild in 12 cases and moderate in 3 cases and all events resolved.

There was 1 serious adverse event (radius fracture after a bicycle accident after the clopidogrel run-in period) without any relation to BAY 59-7939 administration.

Increases 2x ULN were observed once with CK after administration of BAY 59-7939 and once with GLDH after combination treatment. These increases were not assessed as related to the administration of study medication. No clinically relevant changes of vital signs or ECG were observed.

No clinically relevant effect on bleeding time was observed after mono-treatment with BAY 59-7939. In contrast a more than 2-fold mean prolongation of bleeding time was observed after clopidogrel alone, which increased to a relevant degree after the combined treatment. However, the analysis clearly showed a statistical significant period effect in the combined treatment group. Since the results of the platelet aggregation did not support the effects on bleeding time, no conclusive results can be drawn from this study. Additional data will be required to conclude on the potential pharmacodynamic interaction between BAY 59-7939 and clopidogrel.

The pharmacokinetic evaluation revealed a slightly higher AUC when BAY 59-7939 was given together with clopidogrel compared to BAY 59-7939 given alone. The effect was small and presumably does not represent a relevant difference in the bioavailability of the 2 drug regimens. The statistical analysis showed that the 90% confidence interval for the ratio of AUC (102.6% to 117.9%) '15 mg BAY 59-7939 with clopidogrel / 15 mg BAY 59-7939 alone' was fully contained in the interval 80% to 125%, which is the conventionally used criterion for bioequivalence. The 90% confidence interval for the C_{max} ratio (85.1% to 119.6%) was also in agreement with the bioequivalence conclusion. For the other pharmacokinetic parameters of BAY 59-7939 no relevant changes were observed after combined administration of BAY 59-7939 and clopidogrel.

Table 5-54: Pharmacokinetics of BAY 59-7939 with and without concomitant administration of clopidogrel [n=11/group; geometric means/geometric SD (range)]

Parameter	Unit	BAY 59-7939 30 mg alone	BAY 59-7939 15 mg plus clopidogrel
AUC	[µg*h/L]	1150/24.77 (756.3 – 1608)	1260/18.75 (964.0 – 1595)
C_{max}	[µg/L]	149.9/41.15 (79.67 – 300.3)	149.8/25.06 (104.1 – 229.2)
t_{max} [a]	[h]	2.0 (0.5 – 4.0)	2.0 (0.5 – 4.0)
$t_{1/2}$	[h]	8.134/26.85 (5.387 – 11.45)	7.528/26.90 (5.303 – 11.25)

a Median (range)
b Arithmetic mean ± SD

5.2.6 Special studies

Age and gender (Study 10850):[77] Exposure to BAY 59-7939 is increased to a clinically relevant degree in elderly subjects. There were no clinically relevant differences in pharmacokinetics between male and female subjects, especially when taking into account common body weight differences. For detailed information see Sections 5.2.2, 5.2.3, and 5.2.4.

Elderly men and women (>60 years) (Study 11529):[95] This study investigated the pharmacokinetics of BAY 59-7939 after single dose administration of 30, 40, and 50 mg in subjects >60 years of age. Based on the 30 mg dose step both mean AUC and C_{max} were higher by approximately 20% in elderly women than in elderly men. This difference was less pronounced when comparing the groups using respective body weight normalized values.

While increases in mean exposure (AUC, C_{max}) were still observed when comparing the 30 mg and the 40 mg dose groups, the increases in these parameters from the 40 mg to the 50 mg dose groups were small or even not detectable with nearly

complete overlap for the parameter ranges. For detailed information see Section 5.2.2.

Elderly men and women (>75 years) (Study 11569):[96] This study investigated safety, tolerability, pharmacodynamics, and pharmacokinetics of a single oral dose of 10 mg BAY 59-7939 in men and women older than 75 years compared to young men and women in a randomized, single-blind, placebo-controlled trial.

For demographic details see Table 5-55.

Table 5-55: Demographics

Parameter		PPD				Total n=34
		n=9	n=8	n=10	n=7	
Age (years)	Mean ± SD	33.9 ± 7.1	77.8 ± 2.7	34.7 ± 7.1	77.1 ± 2.8	53.4 ± 23.6
	Minimum	PPD				18.0
	Median					43.0
	Maximum					83.0
Weight (kg)	Mean ± SD	70.0 ± 6.9	67.4 ± 7.2	79.9 ± 13.7	82.0 ± 10.9	74.8 ± 11.6
	Minimum	PPD				59.0
	Median					74.0
	Maximum					104.0
BMI (kg/m^2)	Mean ± SD	24.6 ± 2.5	26.6 ± 3.0	24.7 ± 3.1	27.4 ± 1.9	25.7 ± 2.8
	Minimum	PPD				20.0
	Median					26.4
	Maximum					31.2

25 subjects were randomized to receive BAY 59-7939 and 9 to receive placebo.

18 treatment-emergent adverse events were reported by 14 subjects (10 active, 4 placebo). 14 adverse events were considered possibly related to study medication. 17 adverse events were of mild and 1 of moderate intensity. Headache was the most common adverse event in 5 subjects receiving BAY 59-7939. No serious adverse events occurred. No clinically relevant changes of vital signs, laboratory parameters or ECG were observed.

As expected , the administration of BAY 59-7939 reduced factor Xa activity and prolonged PT, aPTT, and HepTest. Maximal effects on factor Xa inhibition and PT prolongation were comparable regardless of age and gender in this study. No clinically relevant pharmacodynamic differences of the maximal effects between old subjects compared to young subjects (men and women) were observed.

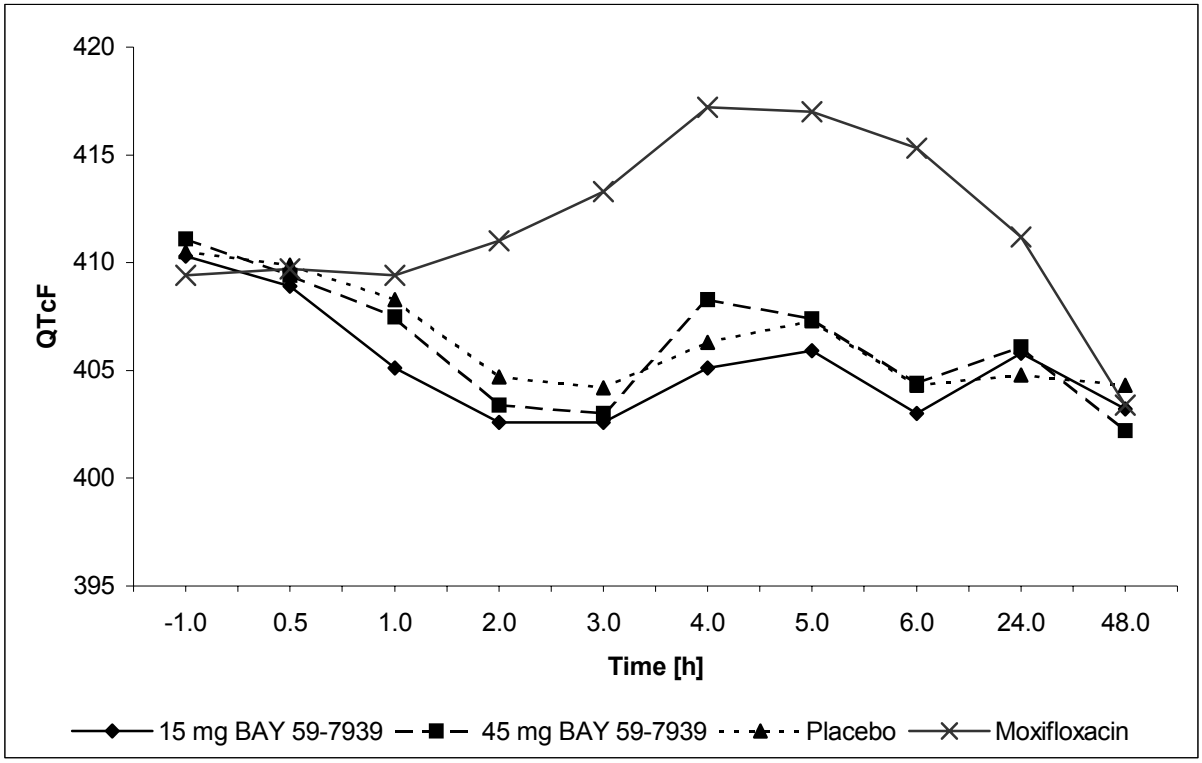
Effects on QTc duration (Study 11275):[93] This study investigated the influence of single doses (15 and 45 mg) of BAY 59-7939 on the QTc interval in healthy male and female subjects comparing BAY 59-7939 with moxifloxacin, a drug known to prolong QTc duration.

The following individual post-dose variables were considered:

- Average QTc measurement after 3 h.
- Average QTc measurement at the actual time of maximum concentration of 45 mg BAY 59-7939.
- Mean of all post-dose QTc measurements.
- Maximum of all post-dose QTc measurements (averaged at each time point).
- Average heart rate at the time where the maximum of all post-dose QTc measurements was observed.

Figure 5-12 displays mean QTc over time for the 4 treatment groups.

Figure 5-12: Mean QTc (ms; Fridericia) over time



No prolongation of mean QTcF or individually corrected mean QTc was observed after 45 mg or 15 mg BAY 59-7939 (placebo subtracted). Neither the mean QTc value (QTcF or individually corrected QTc) nor the confidence interval exceeded 5 ms for any dose of BAY 59-7939 (placebo subtracted). Moxifloxacin proved to be a positive control in this trial with mean QTc prolongations and confidence intervals above 8 ms. The effect of moxifloxacin was in the previously observed range.

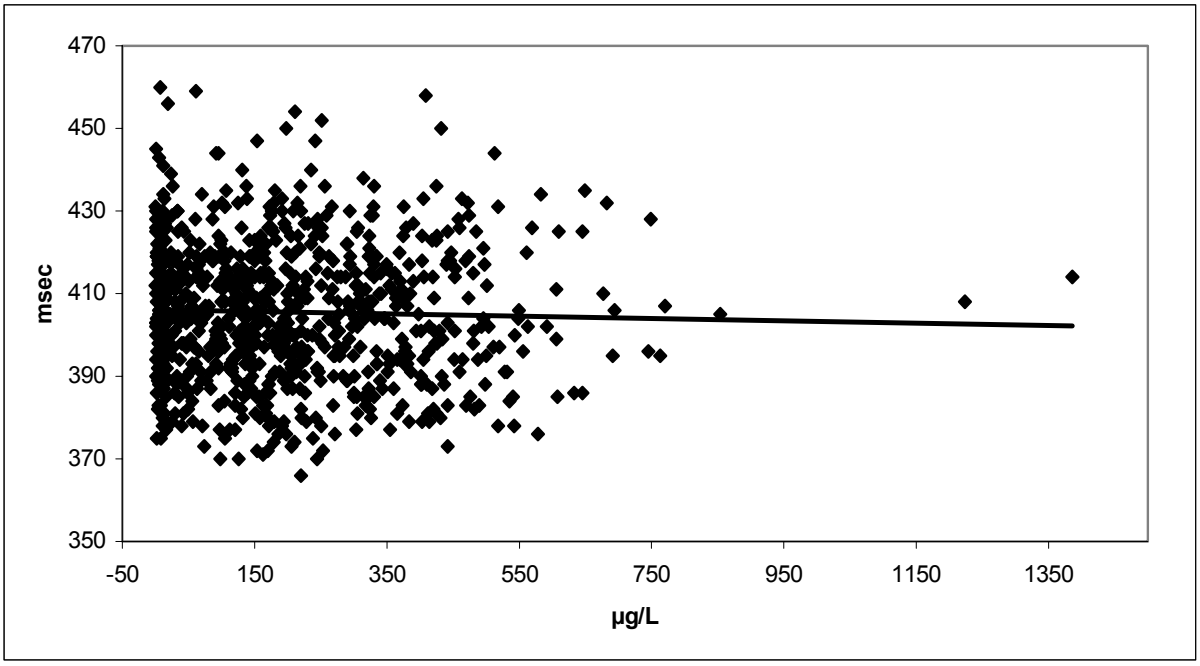
QTcF values of 1 woman were in the range of 450 to 480 ms after all 4 treatments with comparable frequencies and degree of changes after placebo and BAY 59-7939 administration.

No QTcF or QTc individually corrected change from baseline >60 ms was observed in this trial. QTcF or QTc individually corrected change from baseline of 30 to 60

ms occurred only after administration of moxifloxacin. No QTcF or QTc individually corrected change from baseline beyond 30 ms was observed for any dose of BAY 59-7939.

Based on linear regression analysis, the relation between the concentration of BAY 59-7939 and QTcF the slope was statistically not significant different from zero (n=816 observations) (Figure 5-13). The relation between the concentration of moxifloxacin and QTcF an inrease in concentration of 1 mg/L of moxifloxacin implies an increase in QTcF of 4.5 ms (n=370 observations).

Figure 5-13: QTc duration (ms; Fridericia) vs BAY 59-7939 concentrations



5.3 Efficacy and Safety

Key Points:

- 3 studies have been completed in the indication of VTE prevention in major orthopedic surgery.
- The open-label proof-of-concept **ODIXa-HIP trial (Study 10942)** tested an 8-day treatment with BAY 59-7939 doses of 2.5, 5, 10, 20, 30 mg bid, and 30 mg od vs enoxaparin 40 mg SC in patients undergoing elective hip replacement.
- All tested BAY 59-7939 doses including the lowest dose of 2.5 mg bid showed results that were within the confidence limits of enoxaparin and thus indicate a broad therapeutic range.
- Total daily doses of 20, 30, and 40mg of BAY 59-7939 had lower incidence rates of major VTE than enoxaparin. Major VTE incidence rates occurring with 60 mg BAY 59-7939 (4.3%) and enoxaparin (6.6%) were similar.
- The number of bleeding events increased with increasing BAY 59-7939 doses indicating a clear dose-response in this open-label study.
- The pre-specified number of bleeding events was reached upon completion of the 30 mg bid dose step, thus precluding further dose escalation.
- The randomized, double-blind, double-dummy, dose-ranging **ODIXa-HIP2 trial (Study 10944)** tested an 8-day treatment with BAY 59-7939 doses of 2.5, 5, 10, 20, and 30 mg bid vs enoxaparin 40 mg SC in patients undergoing elective hip replacement.
- BAY 59-7939 prevented total VTE compared with enoxaparin, thus supporting the efficacy of BAY 59-7939 in this indication. VTE incidence rates observed with twice daily administration of 2.5, 5, and 10 mg of BAY 59-7939 were lower than that observed with enoxaparin. The BAY 59-7939 20 mg bid treatment arm had a slightly higher incidence rate than enoxaparin. The results

did not demonstrate any dose trend for BAY 59-7939 regarding the primary efficacy endpoint of total VTE.

- The randomized, double-blind, double-dummy, dose-ranging **ODIXa-KNEE trial (Study 10945)** tested an 8-day treatment with BAY 59-7939 doses of 2.5, 5, 10, 20, and 30 mg bid vs enoxaparin 30 mg bid SC in patients undergoing elective hip replacement.
- For all tested BAY 59-7939 doses, lower VTE incidence rates were observed than for enoxaparin. The results did not demonstrate any dose trend for BAY 59-7939 regarding the primary efficacy endpoint.
- In surgical patients receiving BAY 59-7939 to prevent VTE transient raises of liver function tests (transaminases, GGT, bilirubin, AP) were seen in a pattern similar to enoxaparin, ie with a peak occurring 1 week after surgery. Lipase and amylase values were found to be increased as well; however, this increase occurs on the first day after surgery and rapidly resolves under continuous treatment.
- BAY 59-7939 did not reveal any substance-specific effects on laboratory parameters, including liver enzymes, for the treatment duration used in this study when compared with enoxaparin.
- Once-daily dose regimens appear to be alternative options to twice-daily regimens explored thus far. Total daily doses up to 40 mg have yielded safe and effective study results in the indication of VTE prevention.
- A therapeutic INR range for BAY 59-7939 has not yet been determined and therefore the known therapeutic INR range for warfarin cannot automatically be translated. Investigators in double-blind trials using BAY 59-7939 are advised not to measure the INR locally as this would unblind any trial.

5.3.1 Efficacy

5.3.1.1 Oral direct Factor Xa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total hip replacement (ODIXa-HIP trial - Study 10942)

This was a prospective, randomized, open-label, active comparator controlled, multi-center and multi-national trial designed as a proof-of-principle dose finding study in 641 patients undergoing elective primary total hip replacement.[97] The study assessed safety, tolerability, and efficacy of BAY 59-7939 at oral doses of 2.5, 5, 10, 20, and 30 mg bid and 30 mg od compared with subcutaneously administered enoxaparin 40 mg in the prevention of venous thromboembolism.

41 centers in Germany (7), Poland (7), Belgium (4), Denmark (4), Israel (4), Austria (3), France (3), Norway (3), Sweden (3), the Netherlands (2), and the UK (1) participated in the study.

Study drugs were administered for 8 ± 2 days post surgery. Intake of BAY 59-7939 started on the day of surgery 6 to 8 h after wound closure for patients randomized to BAY 59-7939 treatment. Administration of enoxaparin started 12 to 16 h prior to scheduled surgery on the previous day for patients randomized to enoxaparin treatment.

Each BAY 59-7539 treatment arm included between 68 and 88 patients. 162 patients received enoxaparin. The study covered a 12-fold dose range in the use of BAY 59-7939.

The proportion of female patients in the various treatment groups varied between 54.1% and 64.7%; mean age varied between 64.1 and 66.5 years. More than 99% were Caucasians.

Efficacy endpoints: The primary efficacy endpoint was a composite endpoint of any deep venous thrombosis (DVT), non-fatal pulmonary embolism (PE) and death

from all causes done in the PP population. The primary endpoint was evaluated 5 - 9 days after surgery. Secondary efficacy endpoints were the incidence of DVTs, incidence of symptomatic VTEs, the composite endpoint that results from the primary endpoint by using alternative definition of deaths (ie VTE-related death), and the incidence of symptomatic VTEs (total, PE, DVT) within 30 days after stop of treatment with the study drug. Only descriptive and no confirmatory statistical analyses were performed, since this trial served as a proof-of-principle study only.

The analyses of all efficacy endpoints was solely based on the assessments made by the adjudication committees.

Table 5-56 summarizes the major efficacy results.

Table 5-56: ODIXa-HIP trial (Study 10942) - incidence rates (%) of primary and secondary efficacy endpoints (PP population)

Endpoint	BAY 59-7939 2.5 mg bid (N = 63) n (%)	BAY 59-7939 5 mg bid (N = 63) n (%)	BAY 59-7939 10 mg bid (N = 55) n (%)	BAY 59-7939 30 mg od (N = 73) n (%)
Primary efficacy endpoint	14 (22.2%)	15 (23.8%)	11 (20.0%)	11 (15.1%)
Death (any cause)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Pulmonary embolism	2 (3.2%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
DVT, all	13 (20.6%)	15 (23.8%)	11 (20.0%)	9 (12.3%)
VTE subsets				
VTE related death	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT, proximal	6 (9.5%)	5 (7.9%)	2 (3.6%)	0 (0.0%)
DVT, distal	9 (14.3%)	12 (19.0%)	9 (16.4%)	9 (12.3%)
Symptomatic DVT	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)

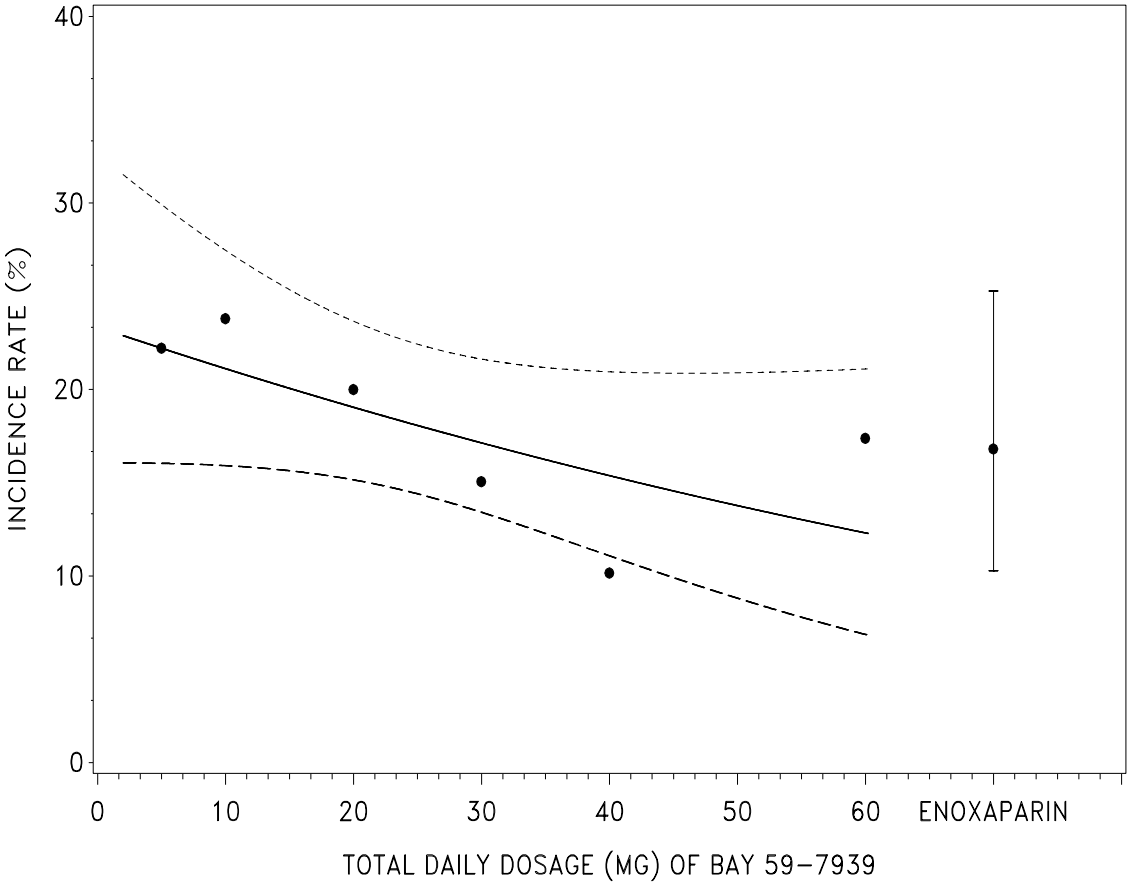
Endpoint	BAY 59-7939 20 mg bid (N = 59) n (%)	BAY 59-7939 30 mg bid (N = 46) n (%)	Enoxaparin 40 mg od (N = 107) n (%)
Primary efficacy endpoint	6 (10.2%)	8 (17.4%)	18 (16.8%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT, all	6 (10.2%)	8 (17.4%)	18 (16.8%)
VTE subsets			
VTE related death	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT, proximal	0 (0.0%)	2 (4.3%)	5 (4.7%)
DVT, distal	6 (10.2%)	7 (15.2%)	18 (16.8%)
Symptomatic DVT	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5-57: ODIXa-HIP trial (Study 10942) – pair-wise comparisons and 2-sided 95% confidence intervals for the primary composite endpoint – differences to enoxaparin by BAY 59-7939 doses (PP population)

	BAY 59-7939 2.5 mg bid (N = 63)	BAY 59-7939 5 mg bid (N = 63)	BAY 59-7939 10 mg bid (N = 55)	BAY 59-7939 30 mg od (N = 73)
Incidence rate				
Point estimate	22.2%	23.8%	20.0%	15.1%
Confidence interval	[12.7%, 34.5%]	[14.0%, 36.2%]	[10.4%, 33.0%]	[7.8%, 25.4%]
Difference vs enoxaparin				
Point estimate	5.4%	7.0%	3.2%	-1.8%
Confidence interval	[-7.1%, 17.9%]	[-5.7%, 19.7%]	[-9.5%, 15.9%]	[-12.6%, 9.1%]

	BAY 59-7939 20 mg bid (N = 59)	BAY 59-7939 30 mg bid (N = 46)	Enoxaparin 40 mg od (N = 107)
Incidence rate			
Point estimate	10.2%	17.4%	16.8%
Confidence interval	[3.8%, 20.8%]	[7.8%, 31.4%]	[10.3%, 25.3%]
Difference vs enoxaparin			
Point estimate	-6.7%	0.6%	N/A
Confidence interval	[-17.1%, 3.8%]	[-12.5%, 13.6%]	N/A

Figure 5-14: ODIXa-HIP trial (Study 10942) – dose-response relationship of BAY 59-7939 with respect to the primary efficacy endpoint (patients valid for PP analysis)



The prevention of VTE (primary composite endpoint) by BAY 59-7939 was dose-dependent in the range from 2.5 to 20 mg bid with incidence rates declining from 22.2% to 10.2% compared with 16.8% in the enoxaparin group. The incidence rate in the 30 mg bid dose group was 17.4%. The 95% confidence intervals were widely overlapping indicating comparable efficacy of all doses with enoxaparin (Table 5-57).

The higher incidence rate of total VTE with the 30 mg dose after a decrease in the incidence rates from 2.5 to 20 mg cannot be explained at this time. Whether the

30 mg or possibly the 20 mg results are chance findings is currently unclear. A 17% VTE incidence rate for enoxaparin is in line with published data.

Subanalyses (not shown here) revealed no obvious differences in efficacy results among various age (<60 years, 60-70 years, >70 years) and body weight groups as well as the types of anesthesia used. Patients with higher body weight (>75 kg) did not have an increase in DVT rates indicating no need for dose adjustments by body weight.

In the PP population, clinical signs of DVT were observed in 1 patient receiving enoxaparin and between 1 to 4 patients in the each of the BAY 59-7939 treatment groups.

Percent changes from baseline for Factor Xa activity and PT in patients receiving BAY 59-7939 are presented in Table 5-58 and Table 5-59.

Table 5-58: ODIXa-HIP trial (Study 10942) - Factor Xa activity - percent change from baseline (PP population)

Visit	BAY 59-7939 2.5 mg bid (N = 63) Mean ± SD	BAY 59-7939 5 mg bid (N = 63) Mean ± SD	BAY 59-7939 10 mg bid (N = 55) Mean ± SD
Day 3 (peak)	-25.2 ± 10.5	-27.1 ± 16.7	-32.0 ± 9.7
Day 5 (peak)	-12.5 ± 12.6	-12.7 ± 24.5	-27.1 ± 12.1
Day 9 (trough)	3.7 ± 13.9	6.5 ± 29.4	-1.5 ± 15.7

Visit	BAY 59-7939 30 mg od (N = 73) Mean ± SD	BAY 59-7939 20 mg bid (N = 59) Mean ± SD	BAY 59-7939 30 mg bid (N = 46) Mean ± SD
Day 3 (peak)	-39.4 ± 11.6	-36.8 ± 12.3	-40.1 ± 10.5
Day 5 (peak)	-32.6 ± 17.1	-30.0 ± 13.7	-37.7 ± 12.7
Day 9 (trough)	5.0 ± 18.4	-7.4 ± 23.7	-9.8 ± 13.4

Note: Only patients on BAY 59-7939 with non-missing baseline as well as post-baseline measurements taken within pre-specified time windows (peak: 2 – 4 h after tablet intake, trough: within 2 h prior to intake) were considered.

Table 5-59: ODIXa-HIP trial (Study 10942) - prothrombin time (PT) - percent change from baseline (PP population)

Visit	BAY 59-7939 2.5 mg bid (N = 63) Mean ± SD	BAY 59-7939 5 mg bid (N = 63) Mean ± SD	BAY 59-7939 10 mg bid (N = 55) Mean ± SD
Day 3 (peak)	9.5 ± 9.3	24.1 ± 50.2	29.2 ± 59.0
Day 5 (peak)	2.1 ± 9.0	6.2 ± 11.3	13.8 ± 11.5
Day 9 (trough)	-0.3 ± 8.4	-0.8 ± 9.9	2.2 ± 10.5

Visit	BAY 59-7939 30 mg od (N = 73) Mean ± SD	BAY 59-7939 20 mg bid (N = 59) Mean ± SD	BAY 59-7939 30 mg bid (N = 46) Mean ± SD
Day 3 (peak)	50.4 ± 39.0	33.1 ± 20.9	44.1 ± 28.7
Day 5 (peak)	29.5 ± 21.0	29.5 ± 20.2	34.8 ± 25.1
Day 9 (trough)	-0.2 ± 8.4	8.4 ± 14.9	6.5 ± 12.4

Note: Only patients on BAY 59-7939 with non-missing baseline as well as post-baseline measurements taken within pre-specified time windows (peak: 2 – 4 h after tablet intake, trough: within 2 h prior to intake) were considered.

Factor Xa activity and PT were measured at peak on Day 3 and Day 5. With increasing doses of BAY 59-7939, there was an increased inhibition of factor Xa and an increased prolongation of PT. For the 30 mg od group a more pronounced prolongation of PT and inhibition of factor Xa activity were seen on Day 3 compared with the 20 mg bid group of BAY 59-7939; peak levels were comparable on Day 5 at steady state. Steady-state trough levels (Day 9) were higher in the 20 mg and 30 mg bid groups compared to all other treatment arms. On Day 3 changes from baseline were more pronounced than on Day 5.

The data confirm the effects of an 8-day treatment with BAY 59-7939 compared with enoxaparin in preventing VTE in adult patients undergoing elective hip replacement, thus confirming the proof-of-principle of BAY 59-7939 in this indication.

5.3.1.2 Oral direct Factor Xa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total hip replacement (ODIXa-HIP2 trial - Study 10944)

This was a prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center, and multi-national trial designed as a dose finding study in 722 patients undergoing elective primary total hip replacement.[98] The study assessed safety, tolerability, and efficacy of BAY 59-7939 at oral doses of 2.5, 5, 10, 20, and 30 mg bid compared with subcutaneously administered enoxaparin 40 mg in the prevention of venous thromboembolism.

47 centers in Germany (7), Poland (6), Italy (5), Spain (4), Israel (4), Sweden (4), Denmark (3), Austria (3), France (3), Norway (3), the Netherlands (3), Belgium (1), and the UK (1) participated in the study.

Study drugs were administered for 8 ± 2 days post surgery. Intake of BAY 59-7939 started on the day of surgery 6 to 8 h after wound closure for patients randomized to BAY 59-7939 treatment. Enoxaparin was administered in the evening prior to surgery according to hospital routine for patients randomized to enoxaparin treatment.

Each BAY 59-7539 treatment arm included between 135 and 139 patients, except for 37 subjects in the 30 mg bid dose group. (The French health authorities raised concerns about the use of the 30 mg bid treatment arm based on the rate of serious adverse events in the previously performed Study 10942; consequently, this dose was discontinued and accounts for the small sample size of this treatment arm). 136 patients received enoxaparin.

The proportion of female patients in the various treatment groups varied between 54% and 64%; mean age varied between 64.1 and 66.8 years. More than 99% were Caucasians.

Efficacy endpoints: identical with those of the ODIXa-HIP trial (Study 010942).

Table 5-60 summarizes the major efficacy results.

Table 5-60: ODIXa-HIP2 trial (Study 10944) - incidence rate of primary efficacy endpoint and its individual components (PP population)

Endpoint	BAY 59-7939 2.5 mg bid (N = 104)	BAY 59-7939 5 mg bid (N = 109)	BAY 59-7939 10 mg bid (N = 101)
Primary efficacy endpoint	16 (15.4%)	15 (13.8%)	12 (11.9%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis	16 (15.4%)	15 (13.8%)	12 (11.9%)
VTE subsets			
VTE-related death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis, proximal	3 (2.9%)	1 (0.9%)	1 (1.0%)
Deep vein thrombosis, distal	14 (13.5%)	14 (12.8%)	12 (11.9%)
Symptomatic deep vein thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)

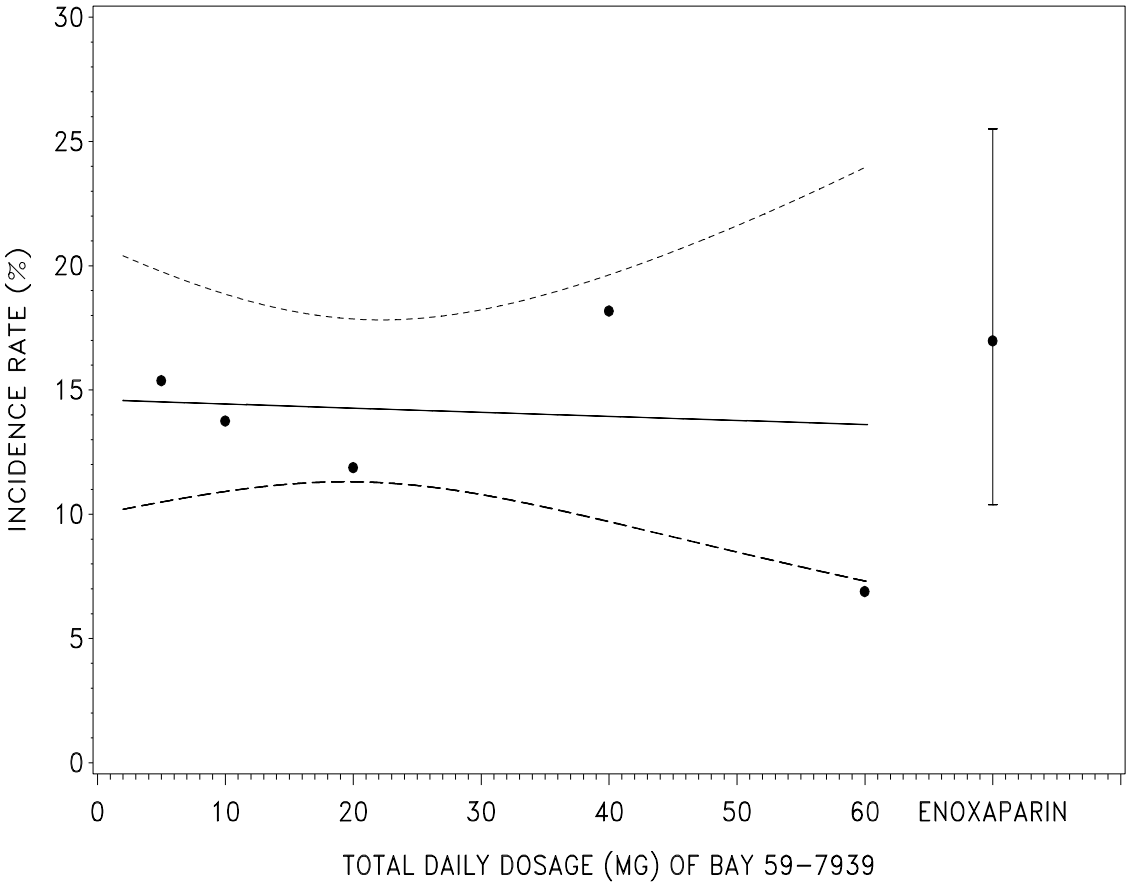
Endpoint	BAY 59-7939 20 mg bid (N = 99)	BAY 59-7939 30 mg bid (N = 29)	Enoxaparin 40 mg od (N = 106)
Primary efficacy endpoint	18 (18.2%)	2 (6.9%)	18 (17.0%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis	18 (18.2%)	2 (6.9%)	18 (17.0%)
VTE subsets			
VTE-related death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis, proximal	3 (3.0%)	1 (3.4%)	5 (4.7%)
Deep vein thrombosis, distal	17 (17.2%)	2 (6.9%)	17 (16.0%)
Symptomatic deep vein thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5-61: ODIXa-HIP2 trial (Study 10944) – pair-wise comparisons and 2-sided 95% confidence intervals for the primary composite endpoint – differences to enoxaparin by BAY 59-7939 doses (PP population)

	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid
Incidence rate			
Point estimate	15.9%	13.5%	11.7%
95% confidence interval	[9.5%, 24.2%]	[7.8%, 21.3%]	[6.2%, 19.5%]
Difference vs enoxaparin			
Point estimate	-0.6%	-3.0%	-4.9%
95% confidence interval	[-10.5%, 9.2%]	[-12.4%, 6.4%]	[-14.2%, 4.5%]

	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 40 mg od
Incidence rate			
Point estimate	17.8%	6.9%	16.5%
95% confidence interval	[10.9%, 26.7%]	[0.8%, 22.8%]	[10.1%, 24.8%]
Difference vs enoxaparin			
Point estimate	1.3%	-9.6%	N/A
95% confidence interval	[-8.9%, 11.5%]	[-21.2%, 1.9%]	N/A

Figure 5-15: ODIXa-HIP2 trial (Study 10944) – dose-response relationship of BAY 59-7939 with respect to the primary efficacy endpoint (patients valid for PP analysis)



The reduction of VTE incidence rates (primary composite endpoint) by BAY 59-7939 was dose-dependent in the range from 2.5 to 10 mg bid with incidence rates declining from 15.4% to 11.9% compared with 17.0% in the enoxaparin group. The incidence rate in the 30 mg bid dose group was 6.9% and that of the 20 mg bid group 18.2%. It must be kept in mind that the number of subjects receiving the 30 mg bid dose was small. Numerically, subjects receiving BAY 59-7939 at doses of 2.5, 5, 10, and 30 mg bid had lower VTE incidence rates (primary composite endpoint) than those receiving enoxaparin. However, the study

failed to detect a trend for BAY 59-7939 in the dose-response relationship regarding the primary efficacy endpoint (*P*=0.9319).

The higher incidence rate of total VTE with the 20 mg bid dose, which was only slightly higher compared with enoxaparin, cannot be explained at this time and may be a chance finding. The 17.0% VTE incidence rate for enoxaparin is in line with other published data as well as with the previously performed Study 10942.

Subanalyses revealed no obvious differences in efficacy results among various age (<60 years, 60-70 years, >70 years) and body weight groups as well as the types of anesthesia used. Subjects with higher body weight (>75 kg) did not have an increase in DVT rates indicating no need for dose adjustments by body weight.

Percent changes from baseline for Factor Xa activity and PT in patients receiving BAY 59-7939 are presented in Table 5-62 and Table 5-63.

Table 5-62: ODIXa-HIP2 trial (Study 10944) – factor Xa activity – percent change from baseline (mean ± SD; PP population)[a]

Visit	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid
Day 3 (peak)	-9.7 ± 11.9 (n=97)	-14.5 ± 12.9 (n=101)	-23.4 ± 17.7 (n=94)
Day 5 (peak)	6.2 ± 16.8 (n=96)	0.3 ± 18.4 (n=97)	-14.2 ± 21.4 (n=93)
Day 9 (trough)[b]	40.2 ± 26.0 (n=82)	29.8 ± 25.0 (n=87)	27.1 ± 35.5 (n=88)
Visit	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 40 mg od
Day 3 (peak)	-28.4 ± 17.2 (n=90)	-44.8 ± 12.4 (n=22)	-1.5 ± 12.6 (n=97)
Day 5 (peak)	-28.8 ± 18.5 (n=89)	-43.7 ± 16.2 (n=27)	21.7 ± 22.6 (n=97)
Day 9 (trough)[b]	16.6 ± 28.1 (n=76)	-8.7 ± 26.6 (n=24)	48.7 ± 31.2 (n=86)

a Only subjects with non-missing baseline as well as post-baseline measurements taken within pre-specified time windows (peak: 2 – 4 h after tablet intake, trough: within 10 – 14 h after previous intake) were considered.
b Samples taken between Day 7 and 11

For the BAY 59-7939 treatment groups a monotonous trend was observed regarding factor Xa inhibition at peak as well as at trough levels with increasing dosage. Factor Xa inhibition was more pronounced in any of the BAY 59-7939 dose groups

compared with the enoxaparin group. Factor Xa inhibition was more pronounced on Day 3 (peak) than on Day 5 (peak).

Table 5-63: ODIXa-HIP2 trial (Study 10944) – prothrombin time (PT) – percent change from baseline (mean ± SD; PP population)[a]

Visit	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid
Day 3 (peak)	12.8 ± 15.5 (n=97)	17.5 ± 16.3 (n=99)	35.4 ± 22.9 (n=93)
Day 5 (peak)	2.5 ± 10.2 (n=96)	8.8 ± 14.7 (n=97)	29.2 ± 21.1 (n=92)
Day 9 (trough)[b]	-6.6 ± 9.9 (n=82)	-1.9 ± 11.7 (n=85)	2.8 ± 12.8 (n=87)
Visit	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 40 mg od
Day 3 (peak)	45.8 ± 32.6 (n=89)	82.3 ± 40.2 (n=22)	1.0 ± 17.7 (n=95)
Day 5 (peak)	50.8 ± 31.8 (n=89)	82.2 ± 37.3 (n=27)	-7.8 ± 15.4 (n=95)
Day 9 (trough)[b]	10.7 ± 23.8 (n=76)	34.0 ± 27.2 (n=24)	-11.3 ± 11.8 (n=83)

a Only subjects with non-missing baseline as well as post-baseline measurements taken within pre-specified time windows (peak: 2 – 4 h after tablet intake, trough: within 10 – 14 h after previous intake) were considered.

There was a monotonous trend in the prolongation of PT with increasing dosage of BAY 59-7939 at peak as well as at trough levels. Slight increases in PT were still detectable at trough on Day 9 in the BAY 59-7939 20 and 30 mg bid dose groups. PT changes in the enoxaparin group were not relevant.

Treatment with BAY 59-7939 prevents total VTE in adult subjects undergoing elective hip replacement compared with enoxaparin, thus supporting the efficacy of BAY 59-7939 in this indication.

5.3.1.3 Oral direct Factor Xa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total knee replacement (ODIXa-KNEE trial - Study 10945)

This was a prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center, and multi-national trial designed as a dose finding study in 621 patients undergoing elective primary total knee replacement.[99] The study assessed safety, tolerability, and efficacy of BAY 59-7939 at oral doses of

2.5, 5, 10, 20, and 30 mg bid compared with subcutaneously administered enoxaparin 30 mg bid in the prevention of venous thromboembolism.

42 centers in Canada (26) and the United States (16) participated in the study.

Study drugs were administered for 8 ± 2 days post surgery. Intake of BAY 59-7939 started on the day of surgery 6 to 8 h after wound closure for patients randomized to BAY 59-7939 treatment. Enoxaparin administration started 12 to 24 h after wound closure for patients randomized to enoxaparin treatment.

Each BAY 59-7539 treatment arm included between 100 and 107 patients. 105 patients received enoxaparin.

The proportion of female patients in the various treatment groups varied between 59% and 68%; mean age varied between 65.8 and 67.8 years. More than 92% were Caucasians.

Efficacy endpoints: identical with those of the ODiXa-HIP trial (Study 010942) and ODiXa-HIP2 trial (Study 010944).

Table 5-64 summarizes the major efficacy results.

Table 5-64: ODIXa-KNEE trial (Study 10945) – incidence rate of primary efficacy endpoint and its individual components (PP population)

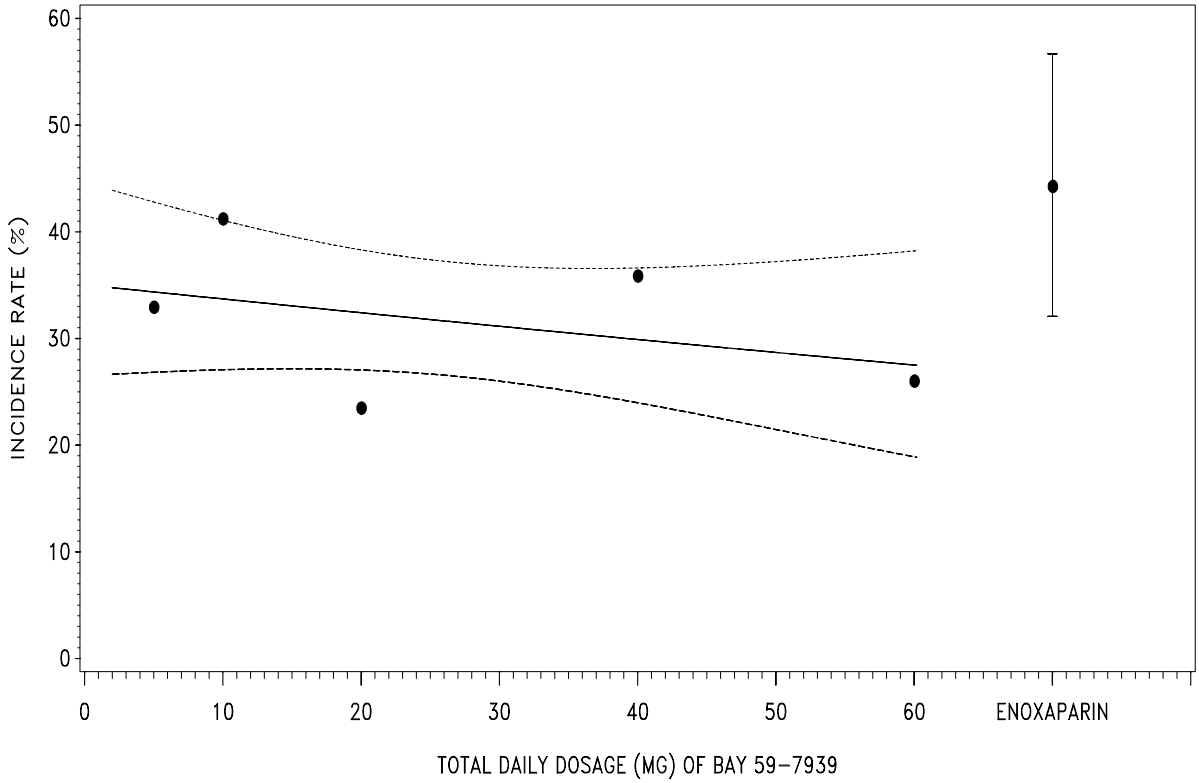
Endpoint	BAY 59-7939 2.5 mg bid (N = 61)	BAY 59-7939 5 mg bid (N = 56)	BAY 59-7939 10 mg bid (N = 60)
Primary efficacy endpoint	20 (32.8%)	23 (41.1%)	14 (23.3%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	2 (3.6%)	0 (0.0%)
Deep vein thrombosis	20 (32.8%)	21 (37.5%)	14 (23.3%)
VTE subsets			
VTE-related death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis, proximal	2 (3.3%)	1 (1.8%)	4 (6.7%)
Deep vein thrombosis, distal	20 (32.8%)	21 (37.5%)	14 (23.3%)
Symptomatic deep vein thrombosis	1 (1.6%)	0 (0.0%)	0 (0.0%)

Endpoint	BAY 59-7939 20 mg bid (N = 56)	BAY 59-7939 30 mg bid (N = 58)	Enoxaparin 30 mg bid (N = 68)
Primary efficacy endpoint	20 (37.5%)	15 (25.9%)	30 (44.1%)
Death (any cause)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis	20 (37.5%)	15 (25.9%	30 (44.1%)
VTE subsets			
VTE-related death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis, proximal	2 (3.6%)	0 (0.0%)	3 (4.4%)
Deep vein thrombosis, distal	19 (33.9%)	15 (25.9%)	29 (42.6%)
Symptomatic deep vein thrombosis	1 (1.8%)	0 (0.0%)	2 (2.9%)

Table 5-65: ODIXa-KNEE trial (Study 10945) – pair-wise comparisons and 2-sided 95% confidence intervals for the primary composite endpoint – differences to enoxaparin by BAY 59-7939 doses (PP population)

	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid
Incidence rate			
Point estimate	32.8%	41.1%	23.3%
95% confidence interval	[21.3%, 46.0%]	[28.1%, 55.0%]	[13.4%, 36.0%]
Difference vs enoxaparin			
Point estimate	-11.3%	-3.0%	-20.8%
95% confidence interval	[-28.0%, 5.3%]	[-20.5%, 14.4%]	[-36.7%, -4.9%]
	P=0.208	*P*=0.855	*P*=0.015
	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 30 mg bid
Incidence rate			
Point estimate	35.7%	26.9%	44.1%
95% confidence interval	[23.4%, 49.6%]	[15.3%, 39.0%]	[32.1%, 56.7%]
Difference vs enoxaparin			
Point estimate	-8.4%	-18.3%	N/A
95% confidence interval	[-25.6%, 8.8%]	[-34.6%, -1.9%]	N/A
	P=0.363	*P*=0.040	

Figure 5-16: ODIXa-KNEE trial (Study 10945) – dose-response relationship of BAY 59-7939 with respect to the primary efficacy endpoint (patients valid for PP analysis)



For all tested BAY 59-7939 doses lower incidence rates of the primary efficacy endpoint were observed (23.3% - 41.1%) than for enoxaparin (44.1%) (Table 5-64). However, a flat dose response was observed for BAY 59-7939 and thus no dose trend could be detected among the BAY 59-7939 dose groups in the confirmative trend test (*P*=0.2488) derived from the logistic regression model. In the exploratory comparisons of each BAY 59-7939 dose group vs enoxaparin, significantly lower incidence rates were detected in the BAY 59-7939 10 mg bid dose group and in the BAY 59-7939 30 mg bid dose group (*P*=0.015 and *P*=0.04, respectively).

The 44.1% VTE incidence rate for enoxaparin is in line with the incidence rates seen in some recent studies where the same Venography Adjudication Committee was used.[100, 101]

All doses of BAY 59-7939 had lower observed incidence rates of *major* VTE than enoxaparin (0.0 – 6.7% vs 7.3%). Major VTE incidence rates were lowest at doses of BAY 59-7939 5 and 30 mg bid.

Percent changes from baseline for factor Xa activity and PT in patients receiving BAY 59-7939 are presented in Table 5-66 and Table 5-67.

Table 5-66: ODIXa-KNEE trial (Study 10945) – factor Xa activity – percent change from baseline (mean ± SD; PP population)

Visit	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid
Day 2 (peak)	-15.6 ± 12.8 (n=54)	-15.4 ± 38.3 (n=51)	-29.8 ± 17.9 (n=52)
Day 5 or 6 (peak)	-1.1 ± 22.2 (n=57)	-4.6 ± 43.3 (n=44)	-34.6 ± 16.8 (n=51)
Day 8 ± 2	18.5 ± 21.4 (n=55)	17.5 ± 58.6 (n=50)	-3.0 ± 22.2 (n=55)
Visit	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 30 mg bid
Day 2 (peak)	-37.5 ± 18.2 (n=52)	-42.2 ± 18.9 (n=51)	-5.7 ± 12.9 (n=62)
Day 5 or 6 (peak)	-42.3 ± 20.2 (n=49)	-52.3 ± 14.7 (n=48)	21.3 ± 34.4 (n=56)
Day 8 ± 2	-19.3 ± 23.8 (n=51)	-36.0 ± 21.5 (n=51)	31.4 ± 24.5 (n=63)

For the BAY 59-7939 treatment groups a monotonous trend was observed regarding factor Xa inhibition with increasing dosage. Factor Xa inhibition was more pronounced in any of the BAY 59-7939 dose groups compared with the enoxaparin group. At BAY 59-7939 doses of 10, 20, and 30 mg bid, factor Xa inhibition was more pronounced on Day 2 (peak) than on Day 5 or 6 (peak).

Table 5-67: ODIXa-KNEE trial (Study 10945) – prothrombin time (PT) – percent change from baseline (mean ± SD; PP population)

Visit	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid
Day 2 (peak)	17.2 ± 14.0 (n=54)	25.6 ± 22.7 (n=51)	44.8 ± 38.9 (n=52)
Day 5 or 6 (peak)	14.4 ± 15.8 (n=57)	27.6 ± 17.6 (n=44)	58.7 ± 31.7 (n=51)
Day 8 ± 2	2.6 ± 9.3 (n=54)	12.0 ± 23.1 (n=50)	22.5 ± 33.7 (n=55)

Visit	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 30 mg bid
Day 2 (peak)	63.1 ± 48.2 (n=51)	73.0 ± 50.5 (n=51)	6.0 ± 11.9 (n=62)
Day 5 or 6 (peak)	90.6 ± 44.8 (n=49)	116.3 ± 54.8 (n=48)	-1.1 ± 14.2 (n=55)
Day 8 ± 2	41.9 ± 41.3 (n=51)	67.5 ± 42.9 (n=51)	-5.8 ± 9.4 (n=62)

There was a monotonous trend in the prolongation of PT with increasing dosage of BAY 59-7939. Increases in PT were still detectable at trough on Day 8 ± 2 at BAY 59-7939 doses of 10, 20, and 30 mg bid dose groups. PT changes in the enoxaparin group were not relevant.

In summary, this study supports evidence for the efficacy of BAY 59-7939 in preventing VTE.

5.3.2 Safety

5.3.2.1 Dosage and administration

All patients should be evaluated for a bleeding disorder before administration of BAY 59-7939.

BAY 59-7939 is administered as oral tablets. The following dosing regimens have been used in phase I and phase II studies:

Phase I studies: Oral single doses of 1.25 mg to 80 mg od for 1 day and oral multiple doses of 5 mg od to 30 mg bid for up to 6 days.

Phase II study (ODiXa-Hip Study 10942): 2.5 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, 30 mg bid and 30 mg od for 8 ± 2 days.

Phase II study (ODIXa-HIP2 Study 10944): 2.5 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, and 30 mg bid for 8 ± 2 days.

Phase II study (ODIXa-KNEE Study 10945): 2.5 mg bid, 5 mg bid, 10 mg bid, and 20 mg bid for 8 ± 2 days.

5.3.2.2 Adverse events

5.3.2.2.1 Oral direct Factor Xa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total hip replacement (ODIXa-HIP trial - Study 10942)

Table 5-68 summarizes the incidence rates of adverse events and serious adverse events.

Table 5-68: ODIXa-HIP trial (Study 10942) – summary of adverse events (safety population)

Adverse event type	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
All adverse events	58 (76.3%)	61 (76.3%)	55 (82.6%)	71 (80.7%)
Treatment-emergent AEs	56 (73.7%)	57 (71.3%)	46 (67.6%)	69 (78.4%)
Drug-related treatment emergent AEs	25 (32.9%)	19 (23.8%)	19 (27.9%)	38 (43.2%)
Discontinuations of study drug due to adverse events	3 (3.9%)	4 (5.0%)	0 (0.0%)	3 (3.4%)
All serious adverse events	9 (11.8%)	15 (18.8%)	10 (14.7%)	13 (14.8%)
Treatment-emergent SAEs	8 (10.5%)	13 (16.3%)	6 (8.8%)	12 (13.6%)
Drug-related treatment emergent SAEs	2 (2.6%)	5 (6.3%)	2 (2.9%)	6 (6.8%)
AEs leading to (prolonged) hospitalization	1 (1.3%)	7 (8.8%)	3 (4.4%)	7 (8.0%)
Deaths	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.1%)

Adverse event type	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
All adverse events	63 (81.8%)	67 (90.5%)	131 (80.9%)
Treatment-emergent AEs	60 (77.9%)	67 (90.5%)	128 (79.0%)
Drug-related treatment emergent AEs	36 (46.8%)	38 (51.4%)	38 (23.5%)
Discontinuations of study drug due to adverse events	5 (6.5%)	13 (17.6%)	4 (2.5%)
All serious adverse events	13 (16.9%)	14 (18.9%)	25 (15.4%)
Treatment-emergent SAEs	12 (15.6%)	14 (18.9%)	22 (13.6%)
Drug-related treatment emergent SAEs	9 (11.7%)	13 (17.6%)	5 (3.1%)
AEs leading to (prolonged) hospitalization	3 (3.9%)	6 (8.1%)	11 (6.8%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)

The overall number of treatment-emergent adverse events was similar in all treatment groups (68 – 79%), except for the 30 mg bid group (91%). There was no clear dose-dependence with regards to the incidence rates of treatment-emergent serious adverse events in the BAY 59-7939 dose groups compared with enoxaparin (9 – 19% vs 14%). Drug-related treatment-emergent serious adverse events were

observed in 3, 6, 3, 7, 12, and 18% of the patients receiving doses of 2.5, 5, 10 mg bid, 30 mg od, and 20 and 30 mg bid of BAY 59-7939, respectively, compared with 3% in the enoxaparin group. Adverse events leading to (prolonged) hospitalization occurred in 1-8% of subjects receiving BAY 59-7939 compared with 7% receiving enoxaparin.

5.3.2.2.2 Oral direct Factor Xa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total hip replacement (ODIXa-HIP2 trial - Study 10944)

Table 5-69 summarizes the incidence rates of adverse events and serious adverse events.

Table 5-69: ODIXa-HIP2 trial (Study 10944) – summary of adverse events (safety population)

Adverse event type	BAY 59-7939 2.5 mg bid (N = 132) n (%)	BAY 59-7939 5 mg bid (N = 136) n (%)	BAY 59-7939 10 mg bid (N = 133) n (%)
All adverse events	100 (75.8%)	101 (74.3%)	102 (76.7%)
Treatment-emergent AEs	98 (74.2%)	99 (72.8%)	98 (73.7%)
Drug-related treatment emergent AEs	30 (22.7%)	36 (26.5%)	36 (27.1%)
Discontinuations of study drug due to adverse events	2 (1.5%)	6 (4.4%)	2 (1.5%)
All serious adverse events	14 (10.6%)	12 (8.8%)	19 (14.3%)
Treatment-emergent SAEs	10 (7.6%)	12 (8.8%)	14 (10.5%)
Drug-related treatment emergent SAEs	5 (3.8%)	7 (5.1%)	4 (3.0%)
AEs leading to (prolonged) hospitalization	7 (5.3%)	7 (5.1%)	11 (8.3%)
Deaths	0 (0.0%)	1 (0.7%)	1 (0.8%)

Adverse event type	BAY 59-7939 20 mg bid (N = 134) n (%)	BAY 59-7939 30 mg bid (N = 37) n (%)	Enoxaparin 40 mg od (N = 132) n (%)
All adverse events	111 (82.8%)	32 (86.5%)	97 (73.5%)
Treatment-emergent AEs	110 (82.1%)	29 (78.4%)	95 (72.0%)
Drug-related treatment emergent AEs	36 (26.9%)	10 (27.0%)	31 (23.5%)
Discontinuations of study drug due to adverse events	7 (5.2%)	2 (5.4%)	2 (1.5%)
All serious adverse events	23 (17.2%)	7 (18.9%)	18 (13.6%)
Treatment-emergent SAEs	20 (14.9%)	6 (16.2%)	15 (11.4%)
Drug-related treatment emergent SAEs	8 (6.0%)	2 (5.4%)	3 (2.3%)
AEs leading to (prolonged) hospitalization	12 (9.0%)	4 (10.8%)	8 (6.1%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)

The incidence rates of treatment-emergent adverse events was similar in the BAY 59-7939 2.5, 5, and 10 mg bid dose groups and the enoxaparin treatment arm (74 – 77%). Incidence rates were 83 and 87% for the 20 and 30 mg bid group. Incidence rates of treatment-emergent serious adverse events increased dose-dependently in the BAY 59-7939 dose groups (8 – 16%) compared with 11% in the

enoxaparin arm. Drug-related treatment-emergent serious adverse events were observed in 4, 5, 3, 6, and 5% of the patients receiving doses of 2.5, 5, 10, 20, and 30 mg bid of BAY 59-7939, respectively, compared with 2% in the enoxaparin group. Adverse events leading to (prolonged) hospitalization occurred in 5-11% of subjects receiving BAY 59-7939 compared with 6% receiving enoxaparin.

5.3.2.2.3 Oral direct Factor Xa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total knee replacement (ODIXa-KNEE trial - Study 10945)

Table 5-70 summarizes the incidence rates of adverse events and serious adverse events.

Table 5-70: ODIXa-KNEE trial (Study 10945) – summary of adverse events (safety population)

Adverse event type	BAY 59-7939 2.5 mg bid (N = 100) n (%)	BAY 59-7939 5 mg bid (N = 102) n (%)	BAY 59-7939 10 mg bid (N = 103) n (%)
All adverse events	86 (86.0%)	92 (90.2%)	95 (92.2%)
Treatment-emergent AEs	84 (84.0%)	87 (85.3%)	92 (89.3%)
Drug-related treatment emergent AEs	18 (18.0%)	24 (23.5%)	25 (24.3%)
Discontinuations of study drug due to adverse events	4 (4.0%)	4 (3.9%)	3 (2.9%)
All serious adverse events	13 (13.0%)	8 (7.8%)	18 (17.5%)
Treatment-emergent SAEs	11 (11.0%)	7 (6.9%)	12 (11.7%)
Drug-related treatment emergent SAEs	0 (0.0%)	1 (1.0%)	4 (3.9%)
AEs leading to (prolonged) hospitalization	11 (11.0%)	6 (5.9%)	14 (13.6%)
Deaths	2 (2.0%)	0 (0.0%)	1 (1.0%)

Adverse event type	BAY 59-7939 20 mg bid (N = 98) n (%)	BAY 59-7939 30 mg bid (N = 106) n (%)	Enoxaparin 40 mg od (N = 104) n (%)
All adverse events	89 (90.8%)	93 (87.7%)	89 (85.6%)
Treatment-emergent AEs	87 (88.8%)	88 (83.0%)	85 (81.7%)
Drug-related treatment emergent AEs	31 (31.6%)	31 (29.2%)	23 (22.1%)
Discontinuations of study drug due to adverse events	7 (7.1%)	8 (7.5%)	2 (1.9%)
All serious adverse events	17 (17.3%)	19 (17.9%)	14 (13.5%)
Treatment-emergent SAEs	14 (14.3%)	13 (12.3%)	12 (11.5%)
Drug-related treatment emergent SAEs	7 (7.1%)	8 (7.5%)	3 (2.9%)
AEs leading to (prolonged) hospitalization	12 (12.2%)	13 (12.3%)	9 (8.7%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)

The incidence rates of treatment-emergent adverse events was similar in all BAY 59-7939 dose groups (84% – 89%) compared with 82% in the enoxaparin treatment arm. Incidence rates of treatment-emergent serious adverse events were lowest in the BAY 59-7939 5 mg dose group (7%) compared with a range of 11% to 14% in the other BAY 59-7939 dose groups and the enoxaparin arm. Drug-related

treatment-emergent serious adverse events increased dose-dependently and were observed in 0, 1, 4, 7, and 8% of the patients receiving doses of 2.5, 5, 10, 20, and 30 mg bid of BAY 59-7939, respectively, compared with 3% in the enoxaparin group. Adverse events leading to (prolonged) hospitalization occurred in 6% – 14% of subjects receiving BAY 59-7939 compared with 9% receiving enoxaparin.

5.3.2.2.4 Adverse Events (Tabular summaries for all clinical trials)

5.3.2.2.4.1 ODIXa-HIP (Study 10942) - treatment-emergent and drug-related treatment-emergent adverse events

Table 5-71 summarizes the most frequent treatment-emergent adverse events with incidence rates ≥5% in at least 1 of the 7 treatment groups.

Table 5-71: ODIXa-HIP (Study 10942) - incidence rates (≥5% in any treatment group) of treatment-emergent adverse events by MedDRA preferred term (safety population)

MedDRA system organ class / preferred term	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any event	56 (73.7%)	57 (71.3%)	46 (67.6%)	69 (78.4%)
Blood and lymphatic system disorders				
Any event	3 (3.9%)	9 (11.3%)	7 (10.3%)	3 (3.4%)
Anemia	2 (2.6%)	6 (7.5%)	5 (7.4%)	3 (3.4%)
Gastrointestinal disorders				
Any event	25 (32.9%)	25 (31.3%)	18 (26.5%)	25 (28.4%)
Constipation	8 (10.5%)	11 (13.8%)	8 (11.8%)	2 (2.3%)
Diarrhea	1 (1.3%)	2 (2.5%)	2 (2.9%)	4 (4.5%)
Nausea	11 (14.5%)	9 (11.3%)	7 (10.3%)	10 (11.4%)
Vomiting	7 (9.2%)	7 (8.8%)	4 (5.9%)	6 (6.8%)
General disorders and administration site conditions				
Any event	11 (14.5%)	19 (23.8%)	13 (19.1%)	11 (12.5%)
Pyrexia	7 (9.2%)	12 (15.0%)	10 (14.7%)	6 (6.8%)
Infections and infestations				
Any event	4 (5.3%)	3 (3.8%)	1 (1.5%)	4 (4.5%)
Urinary tract infection	3 (3.9%)	1 (1.3%)	0 (0.0%)	2 (2.3%)
Injury, poisoning, and procedural complications				
Any event	9 (11.8%)	5 (6.3%)	7 (10.3%)	20 (22.7%)
Operative hemorrhage	1 (1.3%)	2 (2.5%)	0 (0.0%)	4 (4.5%)
Post-procedural hemorrhage	4 (5.3%)	2 (2.5%)	1 (1.5%)	2 (2.3%)
Wound secretion	3 (3.9%)	0 (0.0%)	1 (1.5%)	8 (9.1%)
Investigations				
Any event	13 (17.1%)	16 (20.0%)	16 (23.5%)	23 (26.1%)
aPTT prolonged	2 (2.6%)	2 (2.5%)	4 (5.9%)	5 (5.7%)
Body temperature increased	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.1%)
GGT increased	2 (2.6%)	0 (0.0%)	3 (4.4%)	2 (2.3%)
Hemoglobin decreased	1 (1.3%)	4 (5.0%)	2 (2.9%)	7 (8.0%)
INR increased	2 (2.6%)	0 (0.0%)	4 (5.9%)	4 (4.5%)
Metabolism and nutrition disorders				
Any event	1 (1.3%)	6 (7.5%)	4 (5.9%)	4 (4.5%)
Hypokalemia	1 (1.3%)	4 (5.0%)	0 (0.0%)	0 (0.0%)

Table continued

Table 5-71: ODIXa-HIP (Study 10942) - incidence rates (≥5% in any treatment group) of treatment-emergent adverse events by MedDRA preferred term (safety population) (continued)

MedDRA system organ class / preferred term	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Psychiatric disorders				
Any event	8 (10.5%)	15 (18.8%)	13 (19.1%)	6 (6.8%)
Insomnia	5 (6.6%)	9 (11.3%)	11 (16.2%)	3 (3.4%)
Renal and urinary disorders				
Any event	7 (9.2%)	3 (3.8%)	0 (0.0%)	8 (9.1%)
Urinary retention	4 (5.3%)	2 (2.5%)	0 (0.0%)	1 (1.1%)
Vascular disorders				
Any event	8 (10.5%)	18 (22.5%)	13 (19.1%)	18 (20.5%)
Deep vein thrombosis	4 (5.3%)	7 (8.8%)	3 (4.4%)	4 (4.5%)
Hematoma	1 (1.3%)	5 (6.3%)	4 (5.9%)	8 (9.1%)

Table continued

Table 5-71: ODIXa-HIP (Study 10942) - incidence rates (≥5% in any treatment group) of treatment-emergent adverse events by MedDRA preferred term (safety population) (continued)

MedDRA system organ class / preferred term	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Any event	60 (77.9%)	67 (90.5%)	128 (79.0%)
Blood and lymphatic system disorders			
Any event	6 (7.8%)	10 (13.5%)	9 (5.6%)
Anemia	5 (6.5%)	9 (12.2%)	9 (5.6%)
Gastrointestinal disorders			
Any event	26 (33.8%)	19 (25.7%)	55 (34.0%)
Constipation	8 (10.4%)	8 (10.8%)	16 (9.9%)
Diarrhea	1 (1.3%)	0 (0.0%)	11 (6.8%)
Nausea	17 (22.1%)	7 (9.5%)	33 (20.4%)
Vomiting	5 (6.5%)	6 (8.1%)	15 (9.3%)
General disorders and administration site conditions			
Any event	9 (11.7%)	12 (16.2%)	25 (15.4%)
Pyrexia	3 (3.9%)	7 (9.5%)	13 (8.0%)
Infections and infestations			
Any event	4 (5.2%)	5 (6.8%)	13 (8.0%)
Urinary tract infection	4 (5.2%)	1 (1.4%)	4 (2.5%)
Injury, poisoning, and procedural complications			
Any event	18 (23.4%)	15 (20.3%)	20 (12.3%)
Operative hemorrhage	3 (3.9%)	5 (6.8%)	3 (1.9%)
Post-procedural hemorrhage	3 (3.9%)	4 (5.4%)	5 (3.1%)
Wound secretion	4 (5.2%)	2 (2.7%)	5 (3.1%)
Investigations			
Any event	14 (18.2%)	24 (32.4%)	37 (22.8%)
aPTT prolonged	4 (5.2%)	4 (5.4%)	0 (0.0%)
Body temperature increased	1 (1.3%)	4 (5.4%)	9 (5.6%)
GGT increased	1 (1.3%)	4 (5.4%)	6 (3.7%)
Hemoglobin decreased	3 (3.9%)	7 (9.5%)	9 (5.6%)
INR increased	4 (5.2%)	9 (12.2%)	0 (0.0%)
Metabolism and nutrition disorders			
Any event	3 (3.9%)	4 (5.4%)	10 (6.2%)
Hypokalemia	0 (0.0%)	2 (2.7%)	7 (4.3%)

Table continued

Table 5-71: ODIXa-HIP (Study 10942) - incidence rates (≥5% in any treatment group) of treatment-emergent adverse events by MedDRA preferred term (safety population) (continued)

MedDRA system organ class / preferred term	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Psychiatric disorders			
Any event	10 (13.0%)	7 (9.5%)	28 (17.3%)
Insomnia	10 (13.0%)	5 (6.8%)	21 (13.0%)
Renal and urinary disorders			
Any event	2 (2.6%)	6 (8.1%)	8 (4.9%)
Urinary retention	0 (0.0%)	1 (1.4%)	3 (1.9%)
Vascular disorders			
Any event	12 (15.6%)	14 (18.9%)	30 (18.5%)
Deep vein thrombosis	3 (3.9%)	4 (5.4%)	15 (9.3%)
Hematoma	4 (5.2%)	8 (10.8%)	4 (2.5%)

The most common gastrointestinal adverse events were nausea and vomiting. Other common adverse events were insomnia and pyrexia.

With regards to drug-related treatment-emergent adverse events, the rate was lowest in the enoxaparin group (23.5%) and highest in the BAY 59-7939 30 mg bid group (51.4%) (Table 5-72).

Table 5-72: ODIXa-HIP (Study 10942) - incidence rates (≥3% in any treatment group) of drug-related treatment-emergent adverse events by MedDRA preferred term (safety population)

MedDRA system organ class / preferred term	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any event	25 (32.9%)	19 (23.8%)	19 (27.9%)	38 (43.2%)
Blood and lymphatic system disorders				
Any event	0 (0.0%)	2 (2.5%)	0 (0.0%)	0 (0.0%)
Anemia	0 (0.0%)	2 (2.5%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders				
Any event	8 (10.5%)	9 (11.3%)	4 (5.9%)	10 (11.4%)
Constipation	1 (1.3%)	3 (3.8%)	2 (2.9%)	0 (0.0%)
Gingival bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	2 (2.6%)	4 (5.0%)	1 (1.5%)	4 (4.5%)
Vomiting	3 (3.9%)	3 (3.8%)	0 (0.0%)	1 (1.1%)
Injury, poisoning and procedural complications				
Any event	5 (6.6%)	3 (3.8%)	3 (4.4%)	13 (14.8%)
Operative hemorrhage	1 (1.3%)	1 (1.3%)	0 (0.0%)	3 (3.4%)
Post-procedural hemorrhage	2 (2.6%)	2 (2.5%)	0 (0.0%)	1 (1.1%)
Wound secretion	1 (1.3%)	0 (0.0%)	1 (1.5%)	7 (8.0%)
Investigations				
Any event	5 (6.6%)	5 (6.3%)	10 (14.7%)	12 (13.6%)
aPTT prolonged	2 (2.6%)	2 (2.5%)	4 (5.9%)	5 (5.7%)
Hemoglobin decreased	1 (1.3%)	2 (2.5%)	0 (0.0%)	5 (5.7%)
Hepatic enzyme increased	0 (0.0%)	0 (0.0%)	2 (2.9%)	0 (0.0%)
INR increased	2 (2.6%)	0 (0.0%)	3 (4.4%)	4 (4.5%)
Psychiatric disorders				
Any event	4 (5.3%)	5 (6.3%)	1 (1.5%)	0 (0.0%)
Insomnia	3 (3.9%)	4 (5.0%)	1 (1.5%)	0 (0.0%)
Renal and urinary disorders				
Any event	3 (3.9%)	1 (1.3%)	0 (0.0%)	2 (2.3%)
Urinary retention	3 (3.9%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Vascular disorders				
Any event	3 (3.9%)	8 (10.0%)	5 (7.4%)	11 (12.5%)
Deep vein thrombosis	1 (1.3%)	3 (3.8%)	1 (1.5%)	2 (2.3%)
Hematoma	0 (0.0%)	4 (5.0%)	4 (5.9%)	7 (8.0%)

Table continued

Table 5-72: ODIXa-HIP (Study 10942) - incidence rates (≥3% in any treatment group) of drug-related treatment-emergent adverse events by MedDRA preferred term (safety population) (continued)

MedDRA system organ class / preferred term	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Any event	36 (46.8%)	38 (51.4%)	38 (23.5%)
Blood and lymphatic system disorders			
Any event	0 (0.0%)	6 (8.1%)	1 (0.6%)
Anemia	0 (0.0%)	5 (6.8%)	1 (0.6%)
Gastrointestinal disorders			
Any event	11 (14.3%)	4 (5.4%)	13 (8.0%)
Constipation	1 (1.3%)	0 (0.0%)	2 (1.2%)
Gingival bleeding	0 (0.0%)	3 (4.1%)	0 (0.0%)
Nausea	6 (7.8%)	0 (0.0%)	7 (4.3%)
Vomiting	0 (0.0%)	1 (1.4%)	1 (0.6%)
Injury, poisoning and procedural complications			
Any event	10 (13.0%)	11 (14.9%)	7 (4.3%)
Operative hemorrhage	3 (3.9%)	5 (6.8%)	1 (0.6%)
Post-procedural hemorrhage	2 (2.6%)	4 (5.4%)	4 (2.5%)
Wound secretion	2 (2.6%)	1 (1.4%)	1 (0.6%)
Investigations			
Any event	13 (16.9%)	17 (23.0%)	17 (10.5%)
aPTT prolonged	3 (3.9%)	4 (5.4%)	0 (0.0%)
Hemoglobin decreased	2 (2.6%)	3 (4.1%)	4 (2.5%)
Hepatic enzyme increased	2 (2.6%)	0 (0.0%)	5 (3.1%)
INR increased	4 (5.2%)	9 (12.2%)	0 (0.0%)
Psychiatric disorders			
Any event	4 (5.2%)	2 (2.7%)	6 (3.7%)
Insomnia	4 (5.2%)	2 (2.7%)	6 (3.7%)
Renal and urinary disorders			
Any event	0 (0.0%)	1 (1.4%)	0 (0.0%)
Urinary retention	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders			
Any event	10 (13.0%)	12 (16.2%)	7 (4.3%)
Deep vein thrombosis	3 (3.9%)	3 (4.1%)	2 (1.2%)
Hematoma	4 (5.2%)	8 (10.8%)	4 (2.5%)

Bleeding events

All bleeding adverse events were reported to the bleeding event adjudication committee that performed a blinded assessment according to the categories pre-specified for bleeding events.

According to the protocol, bleeding events were classified into 3 categories: major bleeding events, clinically relevant non major bleeding events, and minor bleeding events.

According to the EMEA guidelines major bleeding events were defined as follows:

- Fatal bleeding.
- Clinically overt bleeding associated with ≥2 g/dL fall in hemoglobin.
- Clinically overt bleeding leading to transfusion of ≥2 units blood.
- Retroperitoneal, intracranial, intraocular or intraspinal bleeding.
- Bleeding warranting treatment cessation.
- Bleeding leading to re-operation.

Clinically relevant non major bleeding events were any of the bleeding events considered as clinically relevant by the investigator which did not meet the criteria of major bleeding events, eg:

- Multiple source bleeding.
- Spontaneous hematoma >25 cm^2.
- Excessive wound hematoma.
- Spontaneous nose bleeding >5 min.

- Macroscopic hematuria (spontaneous or lasting >24 h if associated with an intervention).
- Spontaneous rectal bleeding (more than spot on toilet paper).
- Gingival bleeding >5 min.
- Coughing blood.
- Hematemesis.
- Prolonged bleeding after venipuncture >5 min.

All other bleeding events which did not fulfill the criteria of major bleeding event or clinically relevant non major bleeding event were classified as minor bleeding events. The analysis of bleeding events was solely based on the assessment provided by the bleeding event committee.

The incidence rates of all bleeding events are tabulated in Table 5-73 by the 3 main categories defined for bleeding events.

Table 5-73: ODIXa-HIP (Study 10942) - Incidence rates of all bleeding events (safety population)

Bleeding classification	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any bleeding event	9 (11.8%)	9 (11.3%)	13 (19.1%)	19 (21.6%)
Any major bleeding event	1 (1.3%)	2 (2.5%)	5 (7.4%)	4 (4.5%)
Any non-major bleeding	8 (10.5%)	8 (10.0%)	8 (11.8%)	15 (17.0%)
Clinically relevant bleeding	2 (2.6%)	1 (1.3%)	4 (5.9%)	6 (6.8%)
Minor bleeding	6 (7.9%)	7 (8.8%)	4 (5.9%)	9 (10.2%)

Bleeding classification	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Any bleeding event	15 (19.5%)	18 (24.3%)	12 (7.4%)
Any major bleeding event	5 (6.5%)	9 (12.2%)	0 (0.0%)
Any non-major bleeding	12 (15.6%)	13 (17.6%)	12 (7.4%)
Clinically relevant bleeding	5 (6.5%)	7 (9.5%)	4 (2.5%)
Minor bleeding	7 (9.1%)	8 (10.8%)	9 (5.6%)

Note: Bleeding events starting more than 2 days after last study medication intake not considered.

With increasing doses of BAY 59-7939 bleeding events tended to increase. The incidence rates seen in the lower dose groups of BAY 59-7939 were slightly higher than those seen in the enoxaparin group.

The primary focus was on post-operative bleeding events. Any bleeding that started ≥4 h after the end of surgery (or after the first post-operative study medication intake, whatever occurred first) but not >2 days after last administration of study medication was classified as ‘post-operative’ bleeding.

Table 5-74 summarizes post-operative bleeding events focusing on main categories and on the corresponding sub-categories which had been defined for bleeding events.

Table 5-74: ODIXa-HIP (Study 10942) - incidence rates of post-operative bleeding events (safety population)

Bleeding classification	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any bleeding event	7 (9.2%)	7 (8.8%)	7 (10.3%)	19 (21.6%)
Any major bleeding event	0 (0.0%)	2 (2.5%)	2 (2.9%)	4 (4.5%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retroperitoneal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraspinal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraocular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding associated with fall in Hb	0 (0.0%)	2 (2.5%)	1 (1.5%)	4 (4.5%)
Clinically overt bleeding leading to blood transfusion	0 (0.0%)	2 (2.5%)	2 (2.9%)	3 (3.4%)
Bleeding leading to re-operation	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Bleeding warranting treatment cessation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-major bleeding	7 (9.2%)	5 (6.3%)	5 (7.4%)	15 (17.0%)
Clinically relevant bleeding	2 (2.6%)	1 (1.3%)	3 (4.4%)	6 (6.8%)
Multiple source bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unexpected hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Excessive wound hematoma	1 (1.3%)	0 (0.0%)	2 (2.9%)	3 (3.4%)
Nose bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Gingival bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Macroscopic hematuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Rectal bleeding	1 (1.3%)	1 (1.3%)	0 (0.0%)	1 (1.1%)
Coughing blood	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematemesis	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)
Prolonged bleeding after venipuncture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Minor bleeding	5 (6.6%)	4 (5.0%)	2 (2.9%)	9 (10.2%)

Table continued

Table 5-74: ODIXa-HIP (Study 10942) - incidence rates of post-operative bleeding events (safety population) (continued)

Bleeding classification	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Any bleeding event	14 (18.2%)	18 (24.3%)	11 (6.8%)
Any major bleeding event	5 (6.5%)	8 (10.8%)	0 (0.0%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retroperitoneal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraspinal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraocular	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding associated with fall in Hb	3 (3.9%)	7 (9.5%)	0 (0.0%)
Clinically overt bleeding leading to blood transfusion	0 (0.0%)	6 (8.1%)	0 (0.0%)
Bleeding leading to re-operation	0 (0.0%)	1 (1.4%)	0 (0.0%)
Bleeding warranting treatment cessation	2 (2.6%)	3 (4.1%)	0 (0.0%)
Non-major bleeding	11 (14.3%)	13 (17.6%)	11 (6.8%)
Clinically relevant bleeding	4 (5.2%)	7 (9.5%)	3 (1.9%)
Multiple source bleeding	1 (1.3%)	1 (1.4%)	0 (0.0%)
Unexpected hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)
Excessive wound hematoma	1 (1.3%)	5 (6.8%)	3 (1.9%)
Nose bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gingival bleeding	0 (0.0%)	2 (2.7%)	0 (0.0%)
Macroscopic hematuria	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rectal bleeding	1 (1.3%)	0 (0.0%)	0 (0.0%)
Coughing blood	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematemesis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prolonged bleeding after venipuncture	1 (1.3%)	0 (0.0%)	0 (0.0%)
Other	1 (1.3%)	0 (0.0%)	0 (0.0%)
Minor bleeding	7 (9.1%)	8 (10.8%)	8 (4.9%)

Note: Bleeding events starting more than 2 days after last study medication intake not considered.

As for bleeding in general, a tendency towards an increased incidence rate with increasing dosage of BAY 59-7939 can be seen for post-operative bleeding. No fatal bleedings or bleedings into critical organs were reported.

No fatal bleedings or bleedings into critical organs were reported.

More than 76% of first post-operative bleeding events occurred on the day of surgery or within 3 days after surgery. 5% of first post-operative bleeding events occurred 7 or more days after surgery.

Incidence rates of post-operative bleeding were stratified by potential risk factors. The risk factors were identical as those considered in the context of the primary endpoint. The only exception are blood transfusions that are more likely a consequence of bleeding rather than a risk factor as such. When using the variable selection process based on logistic regression as already applied for the primary efficacy endpoint, country, total daily dosage of BAY 59-7939 and age were identified to be potential risk factors. Increasing age and increasing total daily dosage were associated with an increased bleeding risk.

The pre-specified number of bleeding events was reached upon completion of the 30 mg bid dose step, thus precluding further dose escalation.

Post-operative major bleeding events

Table 5-75 summarizes post-operative major bleeding events by treatment group. A graphical presentation of the incidence rates of post-operative major bleeding events by individual treatment groups is given in Figure 5-17.

Table 5-75: ODIXa-HIP trial (Study 10942) - incidence rates of post-operative major bleeding events (safety population)

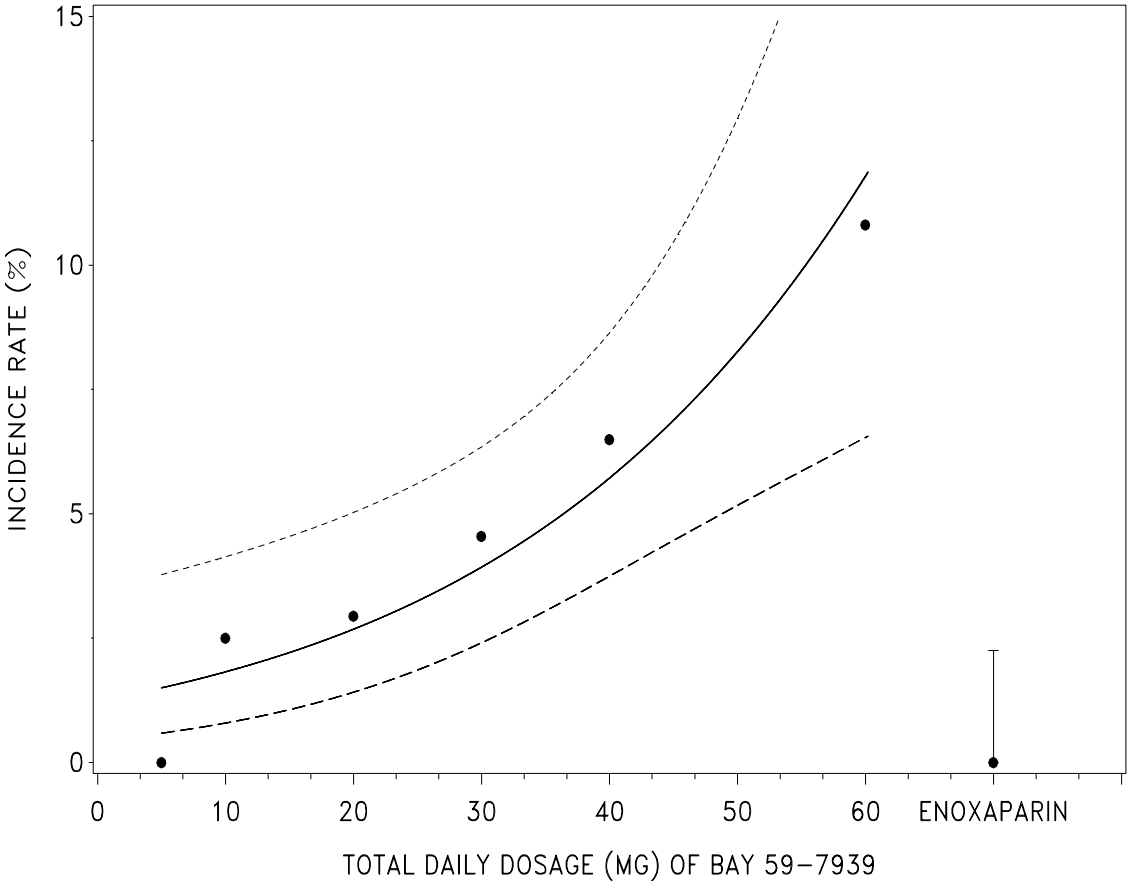
Bleeding classification	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any event	0 (0.0%)	2 (2.5%)	2 (2.9%)	4 (4.5%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Critical bleeding	0 (0.0%)	0 (0.0%)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

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

No fatal or critical post-operative bleedings occurred during the study. 2 post-operative major bleedings led to re-operation. Other post-operative major bleedings were classified as major bleeding because they resulted in treatment cessation or

were clinically overt bleeding associated with a fall in hemoglobin and/or blood transfusion of 2 units or more.

Figure 5-17: ODIXa-HIP trial (Study 10942) - dose relationship of BAY 59-7939 with respect to post-operative major bleeding (patients valid for safety analysis)



Note: The solid line represents the dose-response curve estimated by logistic regression. The dotted lines represent the point wise lower and upper 95% confidence limits. Dots represent observed frequencies. The applied logistic regression model includes dosage as a covariate.

There is a clear tendency towards higher incidences of post-operative major bleeding with increasing dosage of BAY 59-7939. No post-operative major bleeding events were observed in the enoxaparin group.

A trend test performed in a logistic regression model including the total daily dose of BAY 59-7939 as a covariate resulted in a *P* value of *P*=0.0008 providing strong evidence for a trend in the dose relationship of BAY 59-7939 with respect to post-operative major bleeding events.

Table 5-76: ODIXa-HIP trial (Study 10942) – pair-wise comparisons of BAY 59-7939 vs enoxaparin with respect to post-operative major bleeding events (safety population)

	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Incidence rate				
Point estimate	0.0%	2.5%	2.9%	4.5%
Confidence interval	[0.0%, 4.7%]	[0.3%, 8.7%]	[0.4%, 10.2%]	[1.3%, 11.2%]
Difference to enoxaparin				
Point estimate		2.5%	2.9%	4.5%
Confidence interval		[-0.9%, 5.9%]	[-1.1%, 7.0%]	[0.2%, 8.9%]
P value		0.108	0.086	0.014

	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Incidence rate			
Point estimate	6.5%	10.8%	0.0%
Confidence interval	[2.1%, 14.5%]	[4.8%, 20.2%]	[0.0%, 2.3%]
Difference to enoxaparin			
Point estimate	6.5%	10.8%	N.A.
Confidence interval	[1.0%, 12.0%]	[3.7%, 17.9%]	N.A.
P value	0.003	< 0.001	N.A.

Note: No comparison between BAY 79-5939 and enoxaparin was performed as no event was observed in either group.

Table 5-76 presents the pair-wise comparisons of each individual dose group of BAY 59-7939 vs enoxaparin. Differences between BAY 59-7939 and enoxaparin were nominally significant in the dose range of BAY 59-7939 30 mg od up to BAY 59-7939 30 mg bid.

More than 90% of first post-operative major bleeding events occurred on the day of surgery or within 3 days after surgery and less than 10% of post-operative major bleeding events started 4 or 5 days after surgery.

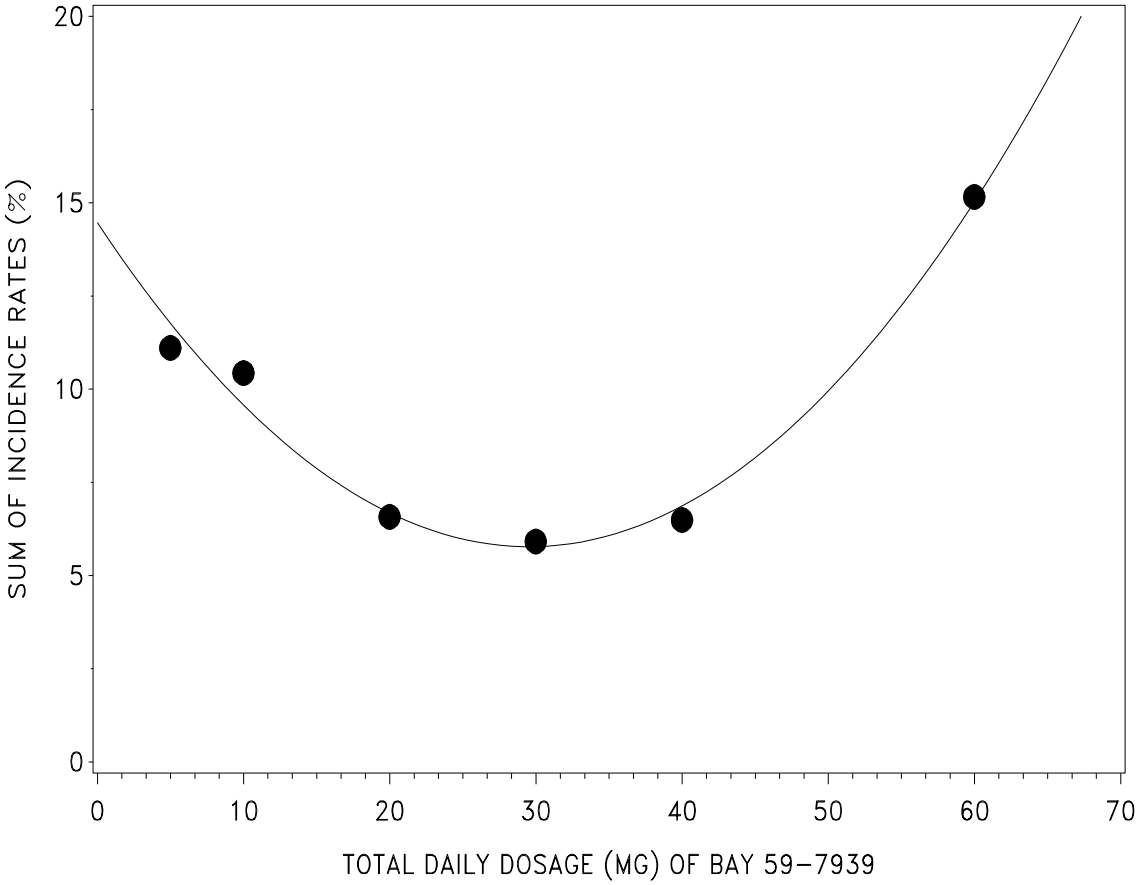
Incidence rates of post-operative major bleeding were stratified by potential risk factors. The risk factors were identical as those considered in the context of the primary endpoint. The only exception are blood transfusions that are more likely a consequence of bleeding rather than a risk factor as such.

When using the variable selection process as already applied for the primary efficacy endpoint, age, use of therapeutic adjuncts, and total daily dosage of BAY 59-7939 were selected. Increasing age, increasing total daily dosage, and the use of therapeutic adjuncts were associated with an increased risk for post-operative major bleeding.

Dose-response relationship major venous thromboembolism and post-operative major bleeding

Figure 5-18 demonstrates the dose-response relationship of BAY 59-7939 with respect to the sum of the incidence rate of major venous thromboembolism (PP population) and the incidence rate of post-operative major bleeding (safety population).

Figure 5-18: Dose-response relationship of BAY 59-7939 with respect to the sum of the incidence rate of major venous thromboembolism (PP population) and the incidence rate of post-operative major bleeding (safety population)

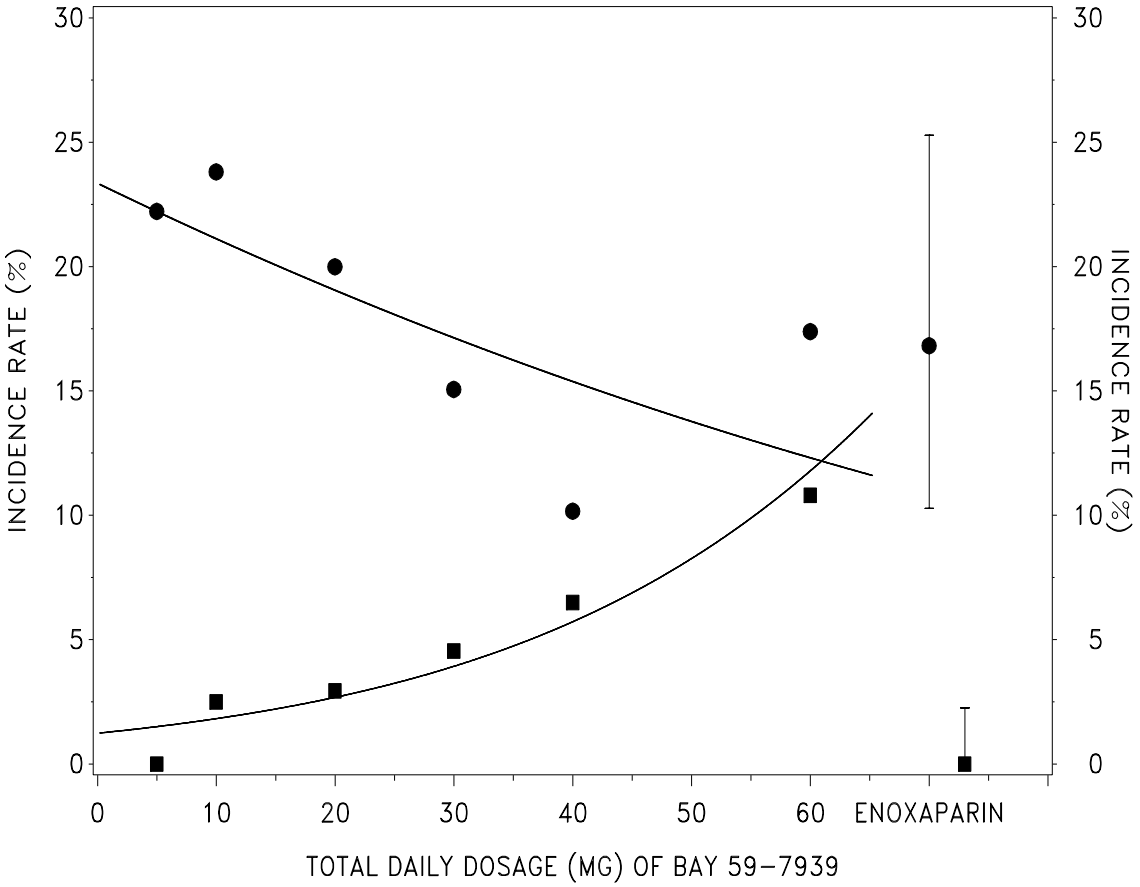


Dots represent the sum of the two incidence rates considered here. The solid line represents the dose-response curve of BAY 59-7939 estimated by simple quadratic regression.

The data presented in Figure 5-18 indicate that the optimum total daily dosage of BAY 59-7939 with respect to this criterion, ie the sum of the incidence rate of major VTE and the incidence rate of post-operative major bleeding, is in the range from 20 to 40 mg, close to 30 mg. Please note that deliberately the sum of the two incidence rates rather than the incidence rate of the composite endpoint (ie major VTE and/or post-operative bleeding) was calculated. If the latter was calculated, patients with

both, major VTE and post-operative major bleeding, would contribute only once rather than twice to the incidence rate what was assumed to be inappropriate.

Figure 5-19: Dose-response relationship of BAY 59-7939 with respect to the primary efficacy endpoint (PP population) and post-operative major bleeding (safety population)



Note: Dots represent the incidence of VTE, squares the incidence of post-operative major bleeding. The solid lines represent the dose-response curve of BAY 59-7939 estimated by logistic regression for VTE and post-operative major bleeding, respectively. The applied logistic regression model includes dosage as a covariate.

5.3.2.2.4.2 ODIXa-HIP2 (Study 10944) - treatment-emergent and drug-related treatment-emergent adverse events

Table 5-77 summarizes the most frequent treatment-emergent adverse events with incidence rates ≥5% in at least 1 of the 6 treatment groups.

Table 5-77: ODIXa-HIP2 trial (Study 10944) - incidence rates (≥5% in any treatment group) of treatment-emergent adverse events by MedDRA preferred term (safety population)[a]

MedDRA System Organ Class/ Preferred Term	BAY 59-7939 2.5 mg bid (N=132)	BAY 59-7939 5 mg bid (N=136)	BAY 59-7939 10 mg bid (N=133)
Any event	98 (74%)	99 (73%)	98 (74%)
Blood and lymphatic system disorders	9 (7%)	12 (9%)	8 (6%)
Anemia	9 (7%)	12 (9%)	8 (6%)
Cardiac disorders	8 (6%)	6 (4%)	4 (3%)
Gastrointestinal disorders	48 (36%)	43 (32%)	47 (35%)
Constipation	7 (5%)	7 (5%)	13 (10%)
Diarrhea	2 (2%)	5 (4%)	0 (0%)
Dyspepsia	1 (1%)	0 (0%)	2 (2%)
Nausea	36 (27%)	25 (18%)	32 (24%)
Vomiting	18 (14%)	13 (10%)	19 (14%)
General disorders and administration site conditions	29 (22%)	23 (17%)	21 (16%)
Malaise	1 (1%)	1 (1%)	1 (1%)
Edema peripheral	6 (5%)	6 (4%)	3 (2%)
Pain	4 (3%)	6 (4%)	3 (2%)
Pyrexia	16 (12%)	6 (4%)	12 (9%)
Infections and infestations	6 (5%)	10 (7%)	7 (5%)
Injury, poisoning and procedural complications	24 (18%)	20 (15%)	30 (23%)
Anemia postoperative	2 (2%)	3 (2%)	4 (3%)
Wound secretion	11 (8%)	7 (5%)	14 (11%)
Investigations	18 (14%)	14 (10%)	19 (14%)
Alanine aminotransferase increased	2 (2%)	4 (3%)	2 (2%)
Aspartate aminotransferase increased	2 (2%)	5 (4%)	2 (2%)
Blood pressure decreased	2 (2%)	3 (2%)	4 (3%)
Body temperature increased	0 (0%)	1 (1%)	0 (0%)
Gamma-glutamyltransferase increased	2 (2%)	5 (4%)	3 (2%)
Metabolism and nutrition disorders	7 (5%)	3 (2%)	4 (3%)
Hypokalemia	5 (4%)	1 (1%)	3 (2%)
Musculoskeletal and connective tissue disorders	12 (9%)	13 (10%)	11 (8%)
Nervous system disorders	9 (7%)	11 (8%)	13 (10%)
Dizziness	5 (4%)	3 (2%)	7 (5%)
Syncope	1 (1%)	4 (3%)	2 (2%)
Psychiatric disorders	12 (9%)	12 (9%)	11 (8%)
Insomnia	11 (8%)	8 (6%)	5 (4%)
Renal and urinary disorders	6 (5%)	10 (7%)	3 (2%)
Hematuria	0 (0%)	1 (1%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	4 (3%)	9 (7%)	3 (2%)
Skin and subcutaneous tissue disorders	7 (5%)	4 (3%)	10 (8%)
Vascular disorders	25 (19%)	21 (15%)	26 (20%)
Deep vein thrombosis	10 (8%)	5 (4%)	6 (5%)
Hematoma	6 (5%)	11 (8%)	9 (7%)
Hypotension	5 (4%)	1 (1%)	4 (3%)

Table continued

Table 5-77: ODIXa-HIP2 trial (Study 10944) - incidence rates (≥5% in any treatment group) of treatment-emergent adverse events by MedDRA preferred term (safety population)a (continued)

MedDRA System Organ Class/ Preferred Term	BAY 59-7939 20 mg bid (N=134)	BAY 59-7939 30 mg bid (N=37)	Enoxaparin 40 mg od (N=132)
Any event	110 (82%)	29 (78%)	95 (72%)
Blood and lymphatic system disorders	15 (11%)	4 (11%)	13 (10%)
Anemia	14 (10%)	3 (8%)	11 (8%)
Cardiac disorders	8 (6%)	1 (3%)	6 (5%)
Gastrointestinal disorders	56 (42%)	16 (43%)	51 (39%)
Constipation	11 (8%)	2 (5%)	9 (7%)
Diarrhea	7 (5%)	1 (3%)	4 (3%)
Dyspepsia	7 (5%)	0 (0%)	2 (2%)
Nausea	34 (25%)	9 (24%)	32 (24%)
Vomiting	24 (18%)	6 (16%)	22 (17%)
General disorders and administration site conditions	30 (22%)	6 (16%)	16 (12%)
Malaise	1 (1%)	2 (5%)	1 (1%)
Edema peripheral	10 (7%)	0 (0%)	4 (3%)
Pain	7 (5%)	1 (3%)	3 (2%)
Pyrexia	11 (8%)	3 (8%)	8 (6%)
Infections and infestations	12 (9%)	1 (3%)	6 (5%)
Injury, poisoning and procedural complications	29 (22%)	7 (19%)	19 (14%)
Anemia postoperative	7 (5%)	1 (3%)	1 (1%)
Wound secretion	15 (11%)	2 (5%)	6 (5%)
Investigations	19 (14%)	10 (27%)	18 (14%)
Alanine aminotransferase increased	1 (1%)	3 (8%)	8 (6%)
Aspartate aminotransferase increased	1 (1%)	3 (8%)	7 (5%)
Blood pressure decreased	2 (1%)	2 (5%)	3 (2%)
Body temperature increased	4 (3%)	2 (5%)	0 (0%)
Gamma-glutamyltransferase increased	3 (2%)	3 (8%)	6 (5%)
Metabolism and nutrition disorders	7 (5%)	0 (0%)	8 (6%)
Hypokalemia	6 (4%)	0 (0%)	6 (5%)
Musculoskeletal and connective tissue disorders	11 (8%)	2 (5%)	9 (7%)
Nervous system disorders	17 (13%)	5 (14%)	15 (11%)
Dizziness	7 (5%)	3 (8%)	7 (5%)
Syncope	0 (0%)	2 (5%)	1 (1%)
Psychiatric disorders	17 (13%)	4 (11%)	9 (7%)
Insomnia	14 (10%)	1 (3%)	6 (5%)
Renal and urinary disorders	15 (11%)	5 (14%)	13 (10%)
Hematuria	4 (3%)	2 (5%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	4 (3%)	0 (0%)	6 (5%)
Skin and subcutaneous tissue disorders	10 (7%)	2 (5%)	5 (4%)
Vascular disorders	35 (26%)	6 (16%)	26 (20%)
Deep vein thrombosis	8 (6%)	2 (5%)	12 (9%)
Hematoma	18 (13%)	2 (5%)	5 (4%)
Hypotension	1 (1%)	0 (0%)	7 (5%)

a Only treatment-emergent adverse events which occurred up to 7 days after the last dose of study medication were included.

The incidence of DVT reported by the respective investigators was highest in the enoxaparin group (9%) and varied between 4% and 8% in the BAY 59-7939 treatment groups. These DVT incidence rates were lower compared with those detected by the AC/V; the latter were used in the evaluation of efficacy.

Table 5-78: ODIXa-HIP2 trial (Study 10944) - incidence rates (≥3% in any treatment group) of drug-related treatment-emergent adverse events by MedDRA preferred term (safety population)[a]

MedDRA System Organ Class/ Preferred Term	BAY 59-7939 2.5 mg bid (N=132)	BAY 59-7939 5 mg bid (N=136)	BAY 59-7939 10 mg bid (N=133)
Any event	30 (23%)	36 (26%)	36 (27%)
Gastrointestinal disorders	9 (7%)	7 (5%)	9 (7%)
Abdominal distension	0 (0%)	0 (0%)	0 (0%)
Constipation	0 (0%)	0 (0%)	2 (2%)
Gastric hemorrhage	0 (0%)	0 (0%)	0 (0%)
Nausea	8 (6%)	5 (4%)	5 (4%)
Vomiting	4 (3%)	2 (1%)	2 (2%)
Injury, poisoning and procedural complications	7 (5%)	9 (7%)	12 (9%)
Wound secretion	5 (4%)	5 (4%)	5 (4%)
Investigations	8 (6%)	10 (7%)	7 (5%)
Alanine aminotransferase increased	2 (2%)	4 (3%)	1 (1%)
Aspartate aminotransferase increased	1 (1%)	5 (4%)	1 (1%)
Blood alkaline phosphatase increased	0 (0%)	0 (0%)	1 (1%)
Blood bilirubin increased	1 (1%)	0 (0%)	0 (0%)
Blood creatinine increased	0 (0%)	1 (1%)	1 (1%)
Blood lactate dehydrogenase increased	0 (0%)	1 (1%)	0 (0%)
Gamma-glutamyltransferase increased	1 (1%)	5 (4%)	2 (2%)
Urine output decreased	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders	0 (0%)	2 (1%)	2 (2%)
Syncope	0 (0%)	1 (1%)	1 (1%)
Renal and urinary disorders	1 (1%)	3 (2%)	0 (0%)
Hematuria	0 (0%)	1 (1%)	0 (0%)
Micturition disorder	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	11 (8%)	11 (8%)	12 (9%)
Hematoma	6 (5%)	9 (7%)	8 (6%)

Table continued

Table 5-78: ODIXa-HIP2 trial (Study 10944) - incidence rates (≥3% in any treatment group) of drug-related treatment-emergent adverse events by MedDRA preferred term (safety population)a (continued)

MedDRA System Organ Class/ Preferred Term	BAY 59-7939 20 mg bid (N=134)	BAY 59-7939 30 mg bid (N=37)	Enoxaparin 40 mg od (N=132)
Any event	36 (27%)	10 (27%)	31 (23%)
Gastrointestinal disorders	13 (10%)	4 (11%)	12 (9%)
Abdominal distension	0 (0%)	1 (3%)	0 (0%)
Constipation	1 (1%)	1 (3%)	0 (0%)
Gastric hemorrhage	0 (0%)	1 (3%)	0 (0%)
Nausea	7 (5%)	2 (5%)	8 (6%)
Vomiting	3 (2%)	2 (5%)	4 (3%)
Injury, poisoning and procedural complications	9 (7%)	1 (3%)	6 (5%)
Wound secretion	8 (6%)	1 (3%)	4 (3%)
Investigations	8 (6%)	5 (14%)	10 (8%)
Alanine aminotransferase increased	1 (1%)	3 (8%)	5 (4%)
Aspartate aminotransferase increased	1 (1%)	3 (8%)	6 (5%)
Blood alkaline phosphatase increased	0 (0%)	1 (3%)	2 (2%)
Blood bilirubin increased	2 (1%)	1 (3%)	0 (0%)
Blood creatinine increased	0 (0%)	1 (3%)	0 (0%)
Blood lactate dehydrogenase increased	0 (0%)	1 (3%)	1 (1%)
Gamma-glutamyltransferase increased	1 (1%)	3 (8%)	6 (5%)
Urine output decreased	0 (0%)	1 (3%)	0 (0%)
Nervous system disorders	2 (1%)	1 (3%)	3 (2%)
Syncope	0 (0%)	1 (3%)	0 (0%)
Renal and urinary disorders	4 (3%)	2 (5%)	1 (1%)
Hematuria	2 (1%)	1 (3%)	0 (0%)
Micturition disorder	0 (0%)	1 (3%)	0 (0%)
Vascular disorders	16 (12%)	2 (5%)	7 (5%)
Hematoma	11 (8%)	2 (5%)	4 (3%)

a Only treatment-emergent adverse events which occurred up to 7 days after the last dose of study medication were included.

The most frequent drug-related treatment-emergent events were hematoma, nausea, and wound secretion with incidence rates between 3% and 8% in any of the treatment groups. Hematoma were slightly less frequent in subjects receiving enoxaparin (3% vs 5 – 8% with BAY 59-7939). Incidence rates were not dose related regarding BAY 59-7939. These adverse events were typical sequelae to the surgical and anesthesiological interventions.

Compared with enoxaparin, higher incidence rates of hematoma were observed in all dose group of BAY 59-7939. No relevant differences between any of the BAY 59-7939 treatments groups and the enoxaparin group were observed with regard to other bleeding events.

Bleeding events

The incidence rates of all bleeding events are tabulated in Table 5-79.

Table 5-79: ODIXa-HIP2 trial (Study 10944) - incidence rates of all bleeding events (safety population)[a]

Bleeding event	BAY 59-7939 2.5 mg bid (N=132)	BAY 59-7939 5 mg bid (N=136)	BAY 59-7939 10 mg bid (N=133)
Any event	7 (5.3%)	15 (11.0%)	17 (12.8%)
Major bleeding	1 (0.8%)	3 (2.2%)	3 (2.3%)
Non-major bleeding	6 (4.5%)	13 (9.6%)	14 (10.5%)
Any clinically relevant non-major bleeding	2 (1.5%)	8 (5.9%)	4 (3.0%)
Any minor bleeding	4 (3.0%)	6 (4.4%)	11 (8.3%)

Bleeding event	BAY 59-7939 20 mg bid (N=134)	BAY 59-7939 30 mg bid (N=37)	Enoxaparin 40 mg od (N=132)
Any event	25 (18.7%)	4 (10.8%)	8 (6.1%)
Major bleeding	6 (4.5%)	2 (5.4%)	2 (1.5%)
Non-major bleeding	20 (14.9%)	2 (5.4%)	6 (4.5%)
Any clinically relevant non-major bleeding	6 (4.5%)	1 (2.7%)	0 (0.0%)
Any minor bleeding	14 (10.4%)	1 (2.7%)	6 (4.5%)

a Bleeding events starting more than 2 days after last study medication intake were not considered.

With increasing doses of BAY 59-7939 bleeding events tended to increase as well. The incidence rates observed with BAY 59-7939 2.5 mg bid (5.3%) was slightly lower than those seen in the enoxaparin group (6.1%); those observed with the other BAY 59-7939 groups ranged between 10.8% and 18.7%.

The primary focus was on post-operative bleeding events. Any bleeding that started ≥6 h after the end of surgery (or after the first post-operative study medication intake, whatever occurred first) but not >2 days after last administration of study medication was classified as ‘post-operative’ bleeding. Table 5-80 summarizes post-

operative bleeding events focusing on main categories and on the corresponding sub-categories, which had been defined for bleeding events.

Table 5-80: Incidence rates of post-operative bleeding events (safety population)[a]

Bleeding event	BAY 59-7939 2.5 mg bid (N=132)	BAY 59-7939 5 mg bid (N=136)	BAY 59-7939 10 mg bid (N=133)
Any event	7 (5.3%)	15 (11.0%)	16 (12.0%)
Major bleeding	1 (0.8%)	3 (2.2%)	3 (2.3%)
Clinically overt bleeding associated with fall in Hb[b]	0 (0.0%)	1 (0.7%)	1 (0.8%)
Clinically overt bleeding leading to blood transfusion[c]	1 (0.8%)	1 (0.7%)	1 (0.8%)
Bleeding leading to re-operation	0 (0.0%)	2 (1.5%)	2 (1.5%)
Clinically overt bleeding warranting treatment cessation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-major bleeding	6 (4.5%)	13 (9.6%)	13 (9.8%)
Any clinically relevant non-major bleeding	2 (1.5%)	8 (5.9%)	3 (2.3%)
Multiple source bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unexpected hematoma (>25 cm^2)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Excessive wound hematoma	2 (1.5%)	3 (2.2%)	2 (1.5%)
Nose bleeding (>5 min)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Macroscopic hematuria[d]	0 (0.0%)	1 (0.7%)	0 (0.0%)
Hematemesis	0 (0.0%)	1 (0.7%)	0 (0.0%)
Prolonged bleeding after venipuncture (>5 min)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Prolongation of hospitalization	0 (0.0%)	1 (0.7%)	1 (0.8%)
Any minor bleeding	4 (3.0%)	6 (4.4%)	11 (8.3%)

Bleeding event	BAY 59-7939 20 mg bid (N=134)	BAY 59-7939 30 mg bid (N=37)	Enoxaparin 40 mg od (N=132)
Any event	25 (18.7%)	4 (10.8%)	8 (6.1%)
Major bleeding	6 (4.5%)	2 (5.4%)	2 (1.5%)
Clinically overt bleeding associated with fall in Hb[b]	3 (2.2%)	1 (2.7%)	2 (1.5%)
Clinically overt bleeding leading to blood transfusion[c]	4 (3.0%)	2 (5.4%)	2 (1.5%)
Bleeding leading to re-operation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding warranting treatment cessation	1 (0.7%)	1 (2.7%)	1 (0.8%)
Non-major bleeding	20 (14.9%)	2 (5.4%)	6 (4.5%)
Any clinically relevant non-major bleeding	6 (4.5%)	1 (2.7%)	0 (0.0%)
Multiple source bleeding	1 (0.7%)	1 (2.7%)	0 (0.0%)
Unexpected hematoma (>25 cm^2)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Excessive wound hematoma	3 (2.2%)	0 (0.0%)	0 (0.0%)
Nose bleeding (>5 min)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Macroscopic hematuria[d]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematemesis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Prolonged bleeding after venipuncture (>5 min)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prolongation of hospitalization	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any minor bleeding	14 (10.4%)	1 (2.7%)	6 (4.5%)

a Bleeding events starting more than 2 days after last study medication intake were not considered.
b Associated with a fall in Hb of ≥2g/dL within 24 h from first post-operative day.
c Leading to transfusion of ≥2 units of blood.
d Either spontaneous or lasting >24 h if associated with an intervention.

The incidence rates of bleeding events in general were identical with those classified as postoperative bleeding events. The most frequent clinically relevant non-major bleeding event was excessive wound hematoma with an incidence of 1.5% to 2.2% in the BAY 59-7939 2.5, 5, 10, and 20 mg bid dose groups. No excessive wound hematoma was reported for subjects receiving BAY 59-7939 30 mg bid and enoxaparin.

Post-operative major bleeding events

Table 5-81 summarizes post-operative *major* bleeding events by treatment group. A graphical presentation of the incidence rates of post-operative *major* bleeding events by individual treatment groups is given in Figure 5-20.

Table 5-81: ODIXa-HIP2 trial (Study 10944) - incidence rates of post-operative major bleeding events (safety population)

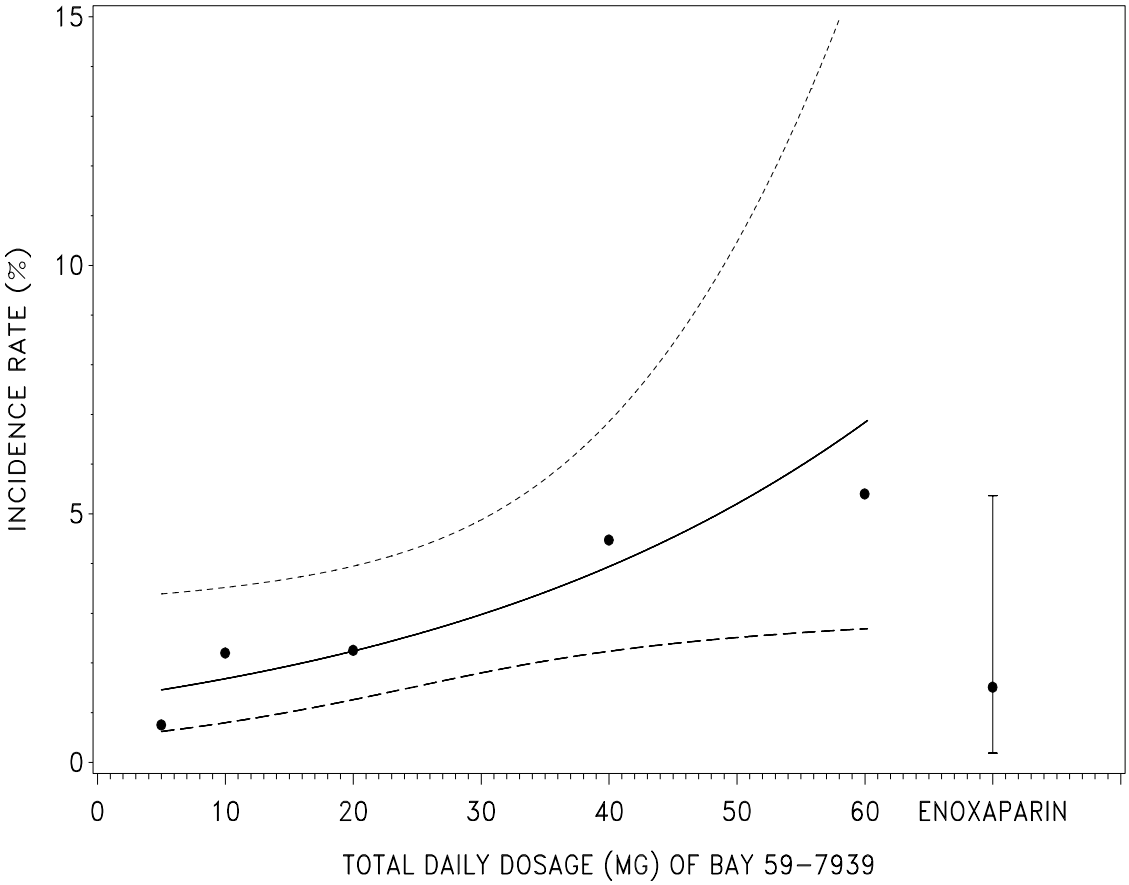
Bleeding classification	BAY 59-7939 2.5 mg bid (N = 132) n (%)	BAY 59-7939 5 mg bid (N = 136) n (%)	BAY 59-7939 10 mg bid (N = 133) n (%)
Any event	1 (0.8%)	3 (2.2%)	3 (2.3%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retroperitoneal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraspinal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraocular	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding associated with fall in Hb	0 (0.0%)	1 (0.7%)	1 (0.8%)
Clinically overt bleeding leading to blood transfusion	1 (0.8%)	1 (0.7%)	1 (0.8%)
Bleeding leading to re-operation	0 (0.0%)	2 (1.5%)	2 (1.5%)
Clinically overt bleeding warranting treatment cessation	0 (0.0%)	0 (0.0%)	0 (0.0%)

Bleeding classification	BAY 59-7939 20 mg bid (N = 134) n (%)	BAY 59-7939 30 mg bid (N = 37) n (%)	Enoxaparin 40 mg od (N = 132) n (%)
Any event	6 (4.5%)	2 (5.4%)	2 (1.5%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retroperitoneal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraspinal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraocular	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding associated with fall in Hb	3 (2.2%)	1 (2.7%)	2 (1.5%)
Clinically overt bleeding leading to blood transfusion	4 (3.0%)	2 (5.4%)	2 (1.5%)
Bleeding leading to re-operation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding warranting treatment cessation	1 (0.7%)	1 (2.7%)	1 (0.8%)

No fatal bleeds or bleeds into critical organs occurred during the study. 4 post-operative major bleeds led to re-operation, ie, 2 each in the BAY 59-7939 5 mg bid and 10 mg bid treatment groups. Most bleeding events were related to the surgical

site. Other post-operative major bleeds were classified as major bleeding because they resulted in treatment cessation or were clinically overt bleeding associated with a fall in hemoglobin and/or blood transfusion of ≥2 units.

Figure 5-20: ODIXa-HIP2 trial (Study 10944) - dose relationship of BAY 59-7939 with respect to post-operative major bleeding (patients valid for safety analysis)



There is a clear tendency towards higher incidences of post-operative major bleeding events with increasing dosage of BAY 59-7939. Only minor differences in the incidence of post-operative major bleeding events were observed between the BAY 59-7939 groups of 2.5, 5, and 10 mg bid and the enoxaparin group.

69.4% of first post-operative bleeding events occurred on the day of surgery or within 3 days after surgery. 12% of first post-operative bleeding events occurred 6 or more days after surgery, all of them in subjects receiving BAY 59-7939.

As expected, the number of major bleeding events occurred primarily at sites related to surgery. Since subjects randomized to BAY 59-7939 treatment received study medication only after surgery had been performed, the relevant numbers of bleeding events are found in the post-operative (up to 2 days after last intake of study medication), where surgical-site bleeds increased dose-dependently. Only 2 subjects experienced late post-operative major bleeding events (BAY 59-7939 2.5 mg bid and 20 mg bid).

2 subjects receiving 20 mg bid of BAY 59-7939 and 1 subject receiving enoxaparin experienced extra-surgical-site bleeding events (urogenital bleed; skin/tracheal/ urogenital bleed; gastrointestinal bleed).

Table 5-82 presents the pair-wise comparisons of each individual dose group of BAY 59-7939 vs enoxaparin with regard to post-operative major bleeding events. Differences between any of the BAY 59-7939 dose groups and enoxaparin were not statistically significant.

Table 5-82: ODIXa-HIP2 trial (Study 10944) - pair-wise comparisons of BAY 59-7939 vs enoxaparin with respect to post-operative major bleeding events (safety population)

	BAY 59-7939 2.5 mg bid (N = 132)	BAY 59-7939 5 mg bid (N = 136)	BAY 59-7939 10 mg bid (N = 133)
Incidence rate			
Point estimate	0.8%	2.2%	2.3%
95% confidence interval	[0.0%, 4.1%]	[0.5%, 6.3%]	[0.5%, 6.5%]
Difference to enoxaparin			
Point estimate	-0.8%	0.7%	0.7%
95% confidence interval	[-3.3%, 1.8%]	[-2.5%, 3.9%]	[-2.5%, 4.0%]
P value	1.000	1.000	1.000

	BAY 59-7939 20 mg bid (N = 134)	BAY 59-7939 30 mg bid (N = 37)	Enoxaparin 40 mg od (N = 132)
Incidence rate			
Point estimate	4.5%	5.4%	1.5%
95% confidence interval	[1.7%, 9.5%]	[0.7%, 18.2%]	[0.2%, 5.4%]
Difference to enoxaparin			
Point estimate	3.0%	3.9%	N/A
95% confidence interval	[-1.1%, 7.0%]	[-3.7%, 11.5%]	N/A
P value	0.281	0.208	N/A

5.3.2.2.4.3 ODIXa-KNEE (Study 10945) - treatment-emergent and drug-related treatment-emergent adverse events

Table 5-83 summarizes the most frequent treatment-emergent adverse events with incidence rates ≥5% in at least 1 of the 6 treatment groups.

Table 5-83: ODIXa-KNEE trial (Study 10945) - incidence rates (≥5% in any treatment group) of treatment-emergent adverse events by MedDRA preferred term (safety population)[a]

MedDRA System Organ Class/ Preferred Term	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Any event	84 (84%)	87 (85%)	92 (89%)
Cardiac disorders	6 (6%)	7 (7%)	8 (8%)
Tachycardia	3 (3%)	4 (4%)	4 (4%)
Gastrointestinal disorders	33 (33%)	46 (45%)	39 (38%)
Constipation	17 (17%)	18 (18%)	17 (17%)
Dyspepsia	2 (2%)	7 (7%)	3 (3%)
Nausea	18 (18%)	20 (20%)	18 (18%)
Vomiting	4 (4%)	8 (8%)	7 (7%)
General disorders and administration site conditions	25 (25%)	29 (28%)	30 (29%)
Edema peripheral	8 (8%)	7 (7%)	12 (12%)
Pyrexia	14 (14%)	16 (16%)	16 (16%)
Infections and infestations	9 (9%)	7 (7%)	5 (5%)
Injury, poisoning and procedural complications	22 (22%)	19 (19%)	23 (23%)
Blister	7 (7%)	6 (6%)	6 (6%)
Post-procedural pain	3 (3%)	5 (5%)	6 (6%)
Investigations	23 (23%)	32 (31%)	39 (38%)
Alanine aminotransferase increased	1 (1%)	3 (3%)	5 (5%)
Aspartate aminotransferase increased	1 (1%)	2 (2%)	5 (5%)
Blood pressure decreased	2 (2%)	3 (2%)	4 (3%)
Body temperature increased	0 (0%)	1 (1%)	0 (0%)
Gamma-glutamyltransferase increased	2 (2%)	5 (4%)	3 (2%)
Hemoglobin decreased	3 (3%)	7 (7%)	14 (14%)
Oxygen saturation decreased	2 (2%)	3 (3%)	6 (6%)
Metabolism and nutrition disorders	4 (4%)	8 (8%)	14 (14%)
Hypokalemia	3 (3%)	5 (5%)	8 (8%)
Musculoskeletal and connective tissue disorders	14 (14%)	4 (4%)	10 (10%)
Pain in extremity	5 (5%)	0 (0%)	3 (3%)
Nervous system disorders	18 (18%)	11 (11%)	11 (11%)
Dizziness	6 (6%)	7 (7%)	6 (6%)
Psychiatric disorders	15 (15%)	10 (10%)	20 (19%)
Confusional state	7 (7%)	2 (2%)	9 (9%)
Insomnia	7 (7%)	7 (7%)	8 (8%)
Renal and urinary disorders	9 (9%)	5 (5%)	11 (11%)
Hematuria	2 (2%)	2 (2%)	1 (1%)
Urinary retention	5 (5%)	3 (3%)	5 (5%)
Respiratory, thoracic and mediastinal disorders	8 (8%)	12 (12%)	7 (7%)
Skin and subcutaneous tissue disorders	18 (18%)	16 (16%)	16 (16%)
Erythema	8 (8%)	1 (1%)	3 (3%)
Pruritus	6 (6%)	10 (10%)	4 (4%)
Vascular disorders	22 (22%)	24 (24%)	19 (18%)
Deep vein thrombosis	20 (20%)	16 (16%)	14 (14%)

Table continued

Table 5-83: ODIXa-KNEE trial (Study 10945) - incidence rates (≥5% in any treatment group) of treatment-emergent adverse events by MedDRA preferred term (safety population)a (continued)

MedDRA System Organ Class/ Preferred Term	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 30 mg bid (N=106)	Enoxaparin 30 mg bid (N=104)
Any event	87 (89%)	88 (83%)	85 (82%)
Cardiac disorders	9 (9%)	10 (9%)	10 (10%)
Tachycardia	5 (5%)	5 (5%)	6 (6%)
Gastrointestinal disorders	33 (34%)	39 (37%)	33 (32%)
Constipation	21 (21%)	20 (19%)	18 (17%)
Dyspepsia	2 (2%)	1 (1%)	4 (4%)
Nausea	16 (16%)	13 (12%)	12 (12%)
Vomiting	7 (7%)	7 (7%)	7 (7%)
General disorders and administration site conditions	27 (27%)	34 (32%)	26 (25%)
Edema peripheral	10 (10%)	12 (11%)	12 (12%)
Pyrexia	12 (12%)	15 (14%)	9 (9%)
Infections and infestations	10 (10%)	7 (7%)	5 (5%)
Injury, poisoning and procedural complications	32 (33%)	26 (25%)	24 (23%)
Blister	4 (4%)	4 (4%)	4 (4%)
Investigations	37 (38%)	30 (28%)	32 (31%)
Alanine aminotransferase increased	4 (4%)	5 (5%)	6 (6%)
Aspartate aminotransferase increased	3 (3%)	6 (6%)	7 (5%)
Blood urine present	5(5%)	2 (2%)	1 (1%)
Body temperature increased	10 (10%)	8 (8%)	11 (11%)
Gamma-glutamyltransferase increased	7 (7%)	4 (4%)	8 (8%)
Hemoglobin decreased	9 (9%)	8 (8%)	5 (5%)
Oxygen saturation decreased	2 (2%)	2 (2%)	3 (3%)
Metabolism and nutrition disorders	9 (9%)	12 (11%)	7 (7%)
Hypokalemia	5 (5%)	6 (6%)	2 (2%)
Musculoskeletal and connective tissue disorders	11 (11%)	10 (9%)	10 (10%)
Pain in extremity	7 (5%)	5 (5%)	1 (1%)
Nervous system disorders	17 (13%)	15 (14%)	15 (14%)
Dizziness	6 (6%)	6 (6%)	4 (4%)
Psychiatric disorders	16 (16%)	12 (12%)	12 (12%)
Confusional state	5 (5%)	5 (5%)	3 (3%)
Insomnia	7 (7%)	2 (2%)	4 (4%)
Renal and urinary disorders	9 (9%)	14 (13%)	5 (5%)
Hematuria	1 (1%)	7 (7%)	1 (1%)
Urinary retention	5 (5%)	4 (4%)	2 (2%)
Respiratory, thoracic and mediastinal disorders	13 (13%)	12 (11%)	7 (7%)
Skin and subcutaneous tissue disorders	19 (19%)	23 (22%)	15 (14%)
Erythema	3 (3%)	2 (2%)	1 (1%)
Pruritus	9 (9%)	13 (12%)	1 (1%)
Vascular disorders	28 (29%)	19 (18%)	36 (35%)
Deep vein thrombosis	19 (19%)	11 (10%)	29 (27.9%)

a Only treatment-emergent adverse events which occurred up to 7 days after the last dose of study medication were included.

The incidence of DVT reported by the respective investigators was highest in the enoxaparin group (28%) and varied between 10% and 20% in the BAY 59-7939 treatment groups. These DVT incidence rates were lower compared with those detected by the Adjudication Committee/Venography; the latter were used in the evaluation of efficacy.

Table 5-84: ODIXa-KNEE trial (Study 10945) - incidence rates (≥3% in any treatment group) of drug-related treatment-emergent adverse events by MedDRA preferred term (safety population)[a]

MedDRA System Organ Class/ Preferred Term	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Any event	18 (18%)	24 (24%)	25 (24%)
Gastrointestinal disorders	3 (3%)	2 (2%)	2 (2%)
Nausea	3 (3%)	1 (1%)	1 (1%)
General disorders and administration site conditions	2 (1%)	1 (1%)	0 (0%)
Injury, poisoning and procedural complications	3 (3%)	4 (4%)	4 (4%)
Operative hemorrhage	2 (2%)	3 (3%)	1 (1%)
Investigations	9 (9%)	7 (7%)	15 (15%)
Alanine aminotransferase increased	1 (1%)	2 (2%)	3 (3%)
Blood lactate dehydrogenase increased	2 (2%)	1 (1%)	3 (3%)
Blood urine present	4 (4%)	1 (1%)	0 (0%)
Gamma-glutamyltransferase increased	1 (1%)	1 (1%)	4 (4%)
Hemoglobin decreased	1 (1%)	1 (1%)	6 (6%)
Psychiatric disorders	1 (1%)	2 (2%)	0 (0%)
Renal and urinary disorders	1 (1%)	1 (1%)	1 (1%)
Respiratory, thoracic, and mediastinal disorders	1 (1%)	4 (4%)	1 (1%)
Vascular disorders	4 (4%)	5 (5%)	4 (4%)
Deep vein thrombosis	2 (2%)	4 (4%)	4 (4%)

Table continued

Table 5-84: ODIXa-KNEE trial (Study 10945) - incidence rates (≥3% in any treatment group) of drug-related treatment-emergent adverse events by MedDRA preferred term (safety population)a (continued)

MedDRA System Organ Class/ Preferred Term	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 30 mg bid (N=106)	Enoxaparin 30 mg bid (N=104)
Any event	31 (32%)	31 (29%)	23 (22%)
Gastrointestinal disorders	5 (5%)	8 (8%)	3 (3%)
Nausea	2 (2%)	1 (1%)	0 (0%)
General disorders and administration site conditions	3 (3%)	2 (2%)	2 (2%)
Injury, poisoning and procedural complications	7 (7%)	8 (8%)	2 (2%)
Operative hemorrhage	4 (4%)	4 (4%)	2 (2%)
Investigations	16 (16%)	14 (13%)	12 (12%)
Alanine aminotransferase increased	2 (2%)	2 (2%)	4 (4%)
Blood lactate dehydrogenase increased	3 (3%)	2 (2%)	1 (1%)
Blood urine present	3 (3%)	2 (2%)	2 (2%)
Gamma-glutamyltransferase increased	4 (4%)	3 (3%)	6 (6%)
Hemoglobin decreased	5 (5%)	5 (5%)	2 (2%)
Psychiatric disorders	3 (3%)	1 (1%)	1 (1%)
Renal and urinary disorders	2 (2%)	4 (4%)	0 (0%)
Respiratory, thoracic, and mediastinal disorders	1 (1%)	5 (5%)	0 (0%)
Vascular disorders	8 (8%)	3 (3%)	5 (5%)
Deep vein thrombosis	4 (4%)	1 (1%)	2 (2%)

a Only treatment-emergent adverse events which occurred up to 7 days after the last dose of study medication were included.

The most frequent drug-related treatment-emergent events were decreased hemoglobin, operative hemorrhage (ie, surgical site bleed), nausea, increases in ALAT, LDH, and GGT, and presence of blood in urine. The incidence rates of these events were between 0% and 6% in any of the treatment groups. Incidence rates were not clearly dose related regarding BAY 59-7939. Most adverse events were typical sequelae to the surgical and anesthesiological interventions.

Compared with enoxaparin, higher incidence rates of decreased hemoglobin were observed in the BAY 59-7939 10, 20, and 30 mg bid (5% - 6% vs 2%). No relevant differences were observed between any of the BAY 59-7939 treatments groups and the enoxaparin group with regard to other bleeding events.

Bleeding events

The incidence rates of all bleeding events are tabulated in Table 5-85.

Table 5-85: ODIXa-KNEE trial (Study 10945) - incidence rates of all bleeding events (safety population)[a]

Bleeding event	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Any event	8 (8.0%)	8 (7.8%)	7 (6.8%)
Major bleeding	1 (1.0%)	0 (0.0%)	2 (1.9%)
Non-major bleeding	8 (8.0%)	8 (7.8%)	6 (5.8%)
Any clinically relevant non-major bleeding	2 (2.0%)	3 (2.9%)	1 (1.0%)
Any minor bleeding	6 (6.0%)	6 (5.9%)	6 (5.8%)

Bleeding event	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 30 mg bid (N=106)	Enoxaparin 30 mg bid (N=104)
Any event	20 (20.4%)	23 (21.7%)	9 (8.7%)
Major bleeding	4 (4.1%)	8 (7.1%)	2 (1.9%)
Non-major bleeding	16 (16.3%)	18 (17.0%)	7 (6.7%)
Any clinically relevant non-major bleeding	6 (6.1%)	7 (6.6%)	4 (3.8%)
Any minor bleeding	11 (11.2%)	12 (11.3%)	3 (2.9%)

a Bleeding events starting more than 2 days after last study medication intake were not considered.

With increasing doses of BAY 59-7939 bleeding events tended to increase as well. The incidence rates observed with BAY 59-7939 2.5, 5, and 10 mg bid (6.8% - 8.0%) were slightly lower than those seen in the enoxaparin group (8.7%); those observed in the BAY 59-7939 20 and 30 mg bid groups ranged between 20.4% and 21.7%.

The primary focus was on post-operative bleeding events. Any bleeding that started ≥6 h after the end of surgery (or after the first post-operative study medication intake, whatever occurred first) but not >2 days after last administration of study medication was classified as ‘post-operative’ bleeding. Table 5-86 summarizes post-operative bleeding events focusing on main categories and on the corresponding sub-categories, which had been defined for bleeding events.

Table 5-86: Incidence rates of post-operative bleeding events (safety population)[a]

Bleeding event	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Any event	8 (8.0%)	8 (7.8%)	7 (6.8%)
Major bleeding	1 (1.0%)	0 (0.0%)	2 (1.9%)
Clinically overt bleeding associated with fall in Hb[b]	1 (1.0%)	0 (0.0%)	1 (1.0%)
Clinically overt bleeding leading to blood transfusion[c]	1 (1.0%)	0 (0.0%)	2 (1.9%)
Bleeding leading to re-operation	0 (0.0%)	0 (0.0%)	1 (1.0%)
Clinically overt bleeding warranting treatment cessation	0 (0.0%)	0 (0.0%)	1 (1.0%)
Non-major bleeding	8 (8.0%)	8 (7.8%)	6 (5.8%)
Any clinically relevant non-major bleeding	2 (2.0%)	3 (2.9%)	1 (1.0%)
Multiple source bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unexpected hematoma (>25 cm^2)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Excessive wound hematoma	0 (0.0%)	1 (1.0%)	0 (0.0%)
Nose bleeding (>5 min)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Macroscopic hematuria[d]	1 (1.0%)	1 (1.0%)	0 (0.0%)
Rectal bleeding	0 (0.0%)	0 (0.0%)	1 (1.0%)
Coughing blood	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematemesis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other bleeding considered clinically relevant by the investigator	0 (0.0%)	1 (1.0%)	0 (0.0%)
Any minor bleeding	6 (6.0%)	6 (5.9%)	6 (5.8%)

Table continued

Table 5-86: Incidence rates of post-operative bleeding events (safety population)a (continued)

Bleeding event	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 30 mg bid (N=106)	Enoxaparin 30 mg bid (N=104)
Any event	17 (17.3%)	23 (21.7%)	8 (7.7%)
Major bleeding	3 (3.1%)	8 (7.5%)	2 (1.9%)
Clinically overt bleeding associated with fall in Hb[b]	1 (1.0%)	8 (7.5%)	2 (1.9%)
Clinically overt bleeding leading to blood transfusion[c]	3 (3.1%)	7 (6.6%)	2 (1.9%)
Bleeding leading to re-operation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinically overt bleeding warranting treatment cessation	1 (1.0%)	2 (1.9%)	0 (0.0%)
Non-major bleeding	14 (14.3%)	18 (17.0%)	6 (5.8%)
Any clinically relevant non-major bleeding	6 (6.1%)	7 (6.6%)	4 (3.8%)
Multiple source bleeding	0 (0.0%)	2 (1.9%)	0 (0.0%)
Unexpected hematoma (>25 cm^2)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Excessive wound hematoma	0 (0.0%)	0 (0.0%)	2 (1.9%)
Nose bleeding (>5 min)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Macroscopic hematuria[d]	0 (0.0%)	2 (1.9%)	0 (0.0%)
Rectal bleeding	0 (0.0%)	1 (0.9%)	1 (1.0%)
Coughing blood	0 (0.0%)	1 (0.9%)	0 (0.0%)
Hematemesis	0 (0.0%)	1 (0.9%)	1 (1.0%)
Other bleeding considered clinically relevant by the investigator	4 (4.1%)	3 (2.8%)	0 (0.0%)
Any minor bleeding	10 (10.2%)	12 (11.3%)	3 (2.9%)

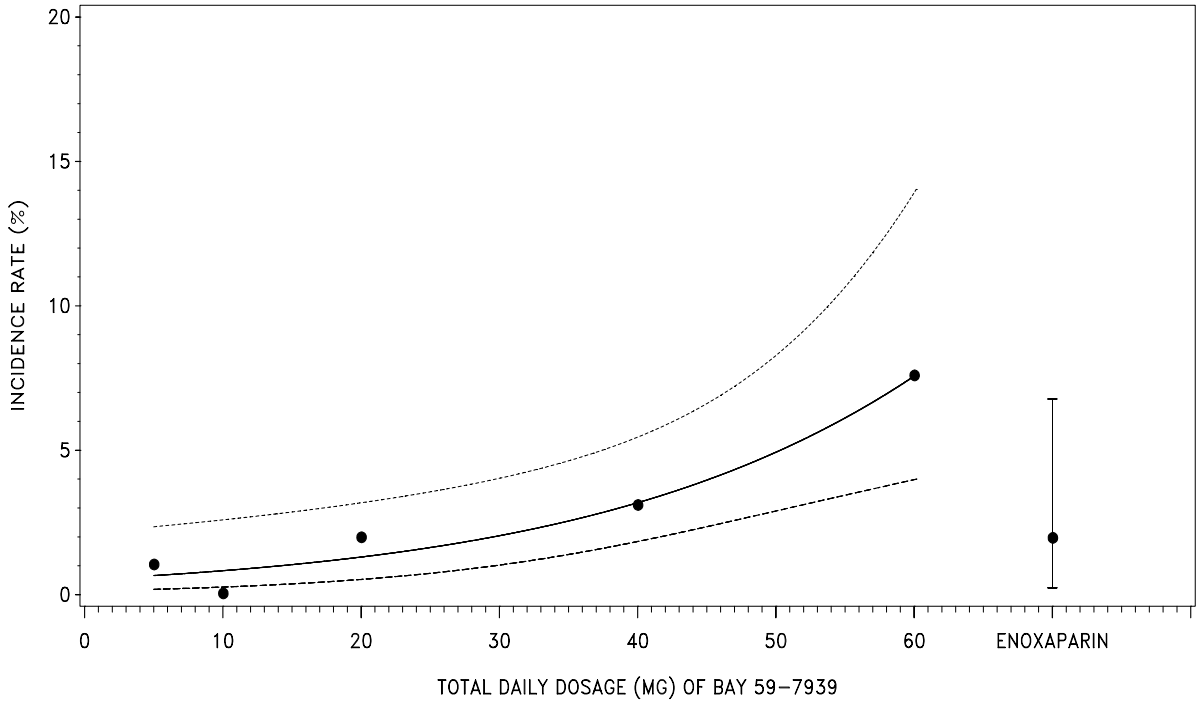
a Bleeding events starting more than 2 days after last study medication intake were not considered.
b Associated with a fall in Hb of ≥2g/dL within 24 h from first post-operative day.
c Leading to transfusion of ≥2 units of blood.
d Either spontaneous or lasting >24 h if associated with an intervention.

Incidence rates of major post-operative bleeding events were 1.0%, 0.0%, 1.0%, 3.1%, and 6.6% for the BAY 59-7939 doses of 2.5, 5, 10, 20, and 30 mg bid, respectively compared with 1.9% in the enoxaparin group. The dose trend observed with BAY 59-7939 doses was statistically significant (*P*=0.0007).

No fatal bleeds or bleeds into critical organs occurred during the study. 1 post-operative major bleeds led to re-operation in 1 subject receiving BAY 59-7939 10 mg bid. Most bleeding events were related to the surgical site. Other post-operative major bleeds were classified as major bleeding because they resulted in

treatment cessation or were clinically overt bleeding associated with a fall in hemoglobin and/or blood transfusion of ≥2 units.

Figure 5-21: ODIXa-KNEE trial (Study 10945) - dose relationship of BAY 59-7939 with respect to post-operative major bleeding (patients valid for safety analysis)



There is a clear tendency towards higher incidences of post-operative major bleeding events with increasing dosage of BAY 59-7939. The number of postoperative bleeding events increased with the BAY 59-7939 20 and 30 mg bid doses (17.3% and 21.7%) indicating a dose-response compared with the 2.5, 5, and 10 mg bid treatment arms. The event rates of the latter dose groups were similar to that seen with enoxaparin (6.8% - 8.0% vs 7.7%).

The percentages of *major* bleeding events increased with increasing BAY 59-7939 doses indicating a dose-response. Percentages of post-operative major bleeds were similar for BAY 59-7939 at doses of 2.5 to 20 mg bid and enoxaparin (0.0% - 3.1%

vs 1.9%). Major bleeds (all overt bleeds with fall in hemoglobin) occurred in 7.5% of subjects receiving BAY 59-7939 30 mg bid. It is important to note that there were neither fatal bleeds or bleeds in critical organs, nor clinically significant bleeds that could not be treated. Most bleeds adjudicated as major were related to the surgical site and no wound healing complications were reported in these subjects. Differences between enoxaparin and any of the BAY 59-7939 dose groups with regard to the number of post-operative major bleeding events were not statistically significant.

About 80% of first post-operative bleeding events occurred on the day of surgery or within 3 days after surgery and 7% of first post-operative bleeding events occurred 6 or more days after surgery.

Table 5-87 presents the pair-wise comparisons of each individual dose group of BAY 59-7939 vs enoxaparin with regard to post-operative major bleeding events. Differences between any of the BAY 59-7939 dose groups and enoxaparin were not statistically significant.

Table 5-87: ODIXa-KNEE trial (Study 10945) - pair-wise comparisons of BAY 59-7939 vs enoxaparin with respect to post-operative major bleeding events (safety population)

	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Incidence rate			
Point estimate	1.0%	0.0%	1.9%
95% confidence interval	[0.0%, 5.4%]	[0.0%, 3.6%]	[0.2%, 6.8%]
Difference to enoxaparin			
Point estimate	-0.9%	-1.9%	0.0%
95% confidence interval	[-4.2%, 2.4%]	[-4.6%, 0.7%]	[-3.7%, 3.8%]
P value	1.000	0.497	1.000

	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 30 mg bid (N=106)	Enoxaparin 30 mg bid (N=104)
Incidence rate			
Point estimate	3.1%	7.5%	1.9%
95% confidence interval	[0.6%, 8.7%]	[3.3%, 14.3%]	[0.2%, 6.8%]
Difference to enoxaparin			
Point estimate	1.1%	5.6%	N/A
95% confidence interval	[-3.2%, 5.5%]	[-0.1%, 11.3%]	N/A
P value	0.675	0.101	N/A

5.3.2.2.5 Adverse event discontinuations

5.3.2.2.5.1 ODIXa-HIP2 (Study 10942)

The incidence rates of discontinuation due to adverse events are tabulated in Table 5-88.

Table 5-88: ODIXa-HIP trial (Study 10942) - discontinuations due to adverse events (safety population)

	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Discontinuation due to AE	3 (3.9%)	4 (5.0%)	0 (0.0%)	3 (3.4%)

	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Discontinuation due to AE	5 (6.5%)	13 (17.6%)	4 (2.5%)

The percentage of discontinuations due to adverse events was highest in the BAY 59-7939 30 mg bid group (17.6%). The frequency of discontinuations due to adverse events was similar in the enoxaparin group (2.5%) and in the BAY 59-7939 dose groups up to 20 mg bid (0.0% - 6.5%).

5.3.2.2.5.2 ODIXa-HIP2 (Study 10944)

The incidence rates of discontinuation due to adverse events are tabulated in Table 5-89.

Table 5-89: ODIXa-HIP2 trial (Study 10944) - discontinuations due to adverse events (safety population)

	BAY 59-7939 2.5 mg bid (N = 132)	BAY 59-7939 5 mg bid (N = 136)	BAY 59-7939 10 mg bid (N = 133)
Discontinuation due to AE	2 (1.5%)	6 (4.4%)	2 (1.5%)

	BAY 59-7939 20 mg bid (N = 134)	BAY 59-7939 30 mg bid (N = 37)	Enoxaparin 40 mg od (N = 132)
Discontinuation due to AE	7 (5.2%)	2 (5.4%)	2 (1.5%)

The percentage of discontinuations due to adverse events was the same in the enoxaparin group and the BAY 59-7939 2.5 and 10 mg bid groups (1.5%). The percentages ranged between 4.4% and 5.4% in the BAY 59-7939 5, 20, and 30 mg bid dose groups.

5.3.2.2.5.3 ODIXa-KNEE (Study 10945)

The incidence rates of discontinuation due to adverse events are tabulated in Table 5-90.

Table 5-90: ODIXa-KNEE trial (Study 10945) - discontinuations due to adverse events (safety population)

	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Discontinuation due to AE	4 (4.0%)	4 (3.9%)	3 (2.9%)
	BAY 59-7939 20 mg bid (N=98)	**BAY 59-7939 30 mg bid (N=106)**	**Enoxaparin 30 mg bid (N=104)**
Discontinuation due to AE	7 (7.1%)	8 (7.5%)	2 (1.9%)

The percentage of discontinuations due to adverse events was lowest in the enoxaparin group (1.9%) and ranged between 2.9% and 4.0% in the BAY 59-7939 2.5, 5, and 10 mg bid dose groups. The percentages ranged between 7.1% and 7.5% in the BAY 59-7939 20 and 30 mg bid dose groups.

5.3.2.2.6 Serious adverse events

In the phase I single dose escalation study (10842),[73] 1 subject was found to have an increased CK value 7 days after administration of the study drug. As there is a clear alternate explanation for this event, it was judged to be serious but not drug related.

In the phase I enoxaparin interaction study (10848),[76] 1 subject experienced a myocardial infarction after screening but prior to admission to the first study period,

ie, prior to the administration of any study drug. This event was judged to be serious but not drug related.

In the phase I gastrointestinal absorption study (10924),[78] 1 subject broke an index finger prior to intake of any study medication. This event was serious but not drug related.

In the phase I ketoconazole interaction study (10992),[81] 1 subject experienced atrial fibrillation 54 days after the last administration of the study drug, which converted to sinus rhythm within 1 day. This event was judged to be serious but not drug related.

In the phase I digoxin interaction study (10999),[83] a serious adverse event was reported in a subject, who developed a psychosis 3 days after a 10-day administration of digoxin 0.375 mg. This serious adverse event was considered unrelated to study drug.

In the study assessing the influence on the QT interval (11275),[93] 2 serious adverse events unrelated to study drug occurred: 1 olecranon fracture after discharge due to a bicycle accident (6 days after 45 mg BAY 59-7939, severe intensity); 1 case of acute appendicitis (11:35 h after 400 mg moxifloxacin, severe intensity).

In the clopidogrel interaction study (11279),[94] 1 subject experienced a serious adverse event (radius fracture after a bicycle accident after the clopidogrel run-in period) without any relation to BAY 59-7939 administration.

5.3.2.2.6.1 ODIXa-HIP (Study 10942)

There were 86 serious adverse events of which 50 were associated with BAY 59-7939 intake. Table 5-91 summarizes the most common serious adverse events by study drugs.

Table 5-91: ODIXa-HIP trial (Study 10942) - incidence rates (≥2% in any treatment group) of treatment-emergent serious adverse events by MedDRA preferred term (safety population)

MedDRA system organ class / preferred term	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any event	8 (10.5%)	13 (16.3%)	6 (8.8%)	12 (13.6%)
Injury, poisoning, and procedural complications				
Any event	1 (1.3%)	2 (2.5%)	1 (1.5%)	2 (2.3%)
Operative hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Post-procedural hemorrhage	0 (0.0%)	2 (2.5%)	1 (1.5%)	1 (1.1%)
Investigations				
Any event	0 (0.0%)	4 (5.0%)	0 (0.0%)	0 (0.0%)
Hemoglobin decreased	0 (0.0%)	2 (2.5%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders				
Any event	2 (2.6%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Pulmonary embolism	2 (2.6%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Vascular disorders				
Any event	4 (5.3%)	8 (10.0%)	4 (5.9%)	4 (4.5%)
Deep vein thrombosis	4 (5.3%)	7 (8.8%)	3 (4.4%)	4 (4.5%)
Hematoma	0 (0.0%)	1 (1.3%)	1 (1.5%)	0 (0.0%)

MedDRA system organ class / preferred term	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Any event	12 (15.6%)	14 (18.9%)	22 (13.6%)
Injury, poisoning, and procedural complications			
Any event	4 (5.2%)	7 (9.5%)	0 (0.0%)
Operative hemorrhage	2 (2.6%)	5 (6.8%)	0 (0.0%)
Post-procedural hemorrhage	1 (1.3%)	1 (1.4%)	0 (0.0%)
Investigations			
Any event	1 (1.3%)	3 (4.1%)	2 (1.2%)
Hemoglobin decreased	1 (1.3%)	2 (2.7%)	2 (1.2%)
Respiratory, thoracic, and mediastinal disorders			
Any event	1 (1.3%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders			
Any event	5 (6.5%)	6 (8.1%)	16 (9.9%)
Deep vein thrombosis	3 (3.9%)	4 (5.4%)	15 (9.3%)
Hematoma	1 (1.3%)	2 (2.7%)	1 (0.6%)

The overall incidence rate of serious TEAEs was highest the 30 mg bid group (18.9%) of BAY 59-7939 and ranged from 8.8% to 16.3% in the other dose groups. In the enoxaparin group the incidence rate was 13.6%.

Table 5-92 summarizes drug-related TEAEs.

Table 5-92: ODIXa-HIP (Study 10942) - incidence rates (≥2% in any treatment group) of drug-related treatment-emergent serious adverse events by MedDRA preferred term (safety population)

MedDRA system organ class / preferred term	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Any event	2 (2.6%)	5 (6.3%)	2 (2.9%)	6 (6.8%)
Injury, poisoning and procedural complications				
Any event	0 (0.0%)	2 (2.5%)	0 (0.0%)	2 (2.3%)
Operative hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Post-procedural hemorrhage	0 (0.0%)	2 (2.5%)	0 (0.0%)	1 (1.1%)
Investigations				
Any event	0 (0.0%)	2 (2.5%)	0 (0.0%)	0 (0.0%)
Hemoglobin decreased	0 (0.0%)	2 (2.5%)	0 (0.0%)	0 (0.0%)
Vascular disorders				
Any event	1 (1.3%)	4 (5.0%)	2 (2.9%)	2 (2.3%)
Deep vein thrombosis	1 (1.3%)	3 (3.8%)	1 (1.5%)	2 (2.3%)
Hematoma	0 (0.0%)	1 (1.3%)	1 (1.5%)	0 (0.0%)

MedDRA system organ class / preferred term	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Any event	9 (11.7%)	13 (17.6%)	5 (3.1%)
Injury, poisoning and procedural complications			
Any event	3 (3.9%)	7 (9.5%)	0 (0.0%)
Operative hemorrhage	2 (2.6%)	5 (6.8%)	0 (0.0%)
Post-procedural hemorrhage	1 (1.3%)	1 (1.4%)	0 (0.0%)
Investigations			
Any event	1 (1.3%)	3 (4.1%)	1 (0.6%)
Hemoglobin decreased	1 (1.3%)	2 (2.7%)	1 (0.6%)
Vascular disorders			
Any event	5 (6.5%)	5 (6.8%)	3 (1.9%)
Deep vein thrombosis	3 (3.9%)	3 (4.1%)	2 (1.2%)
Hematoma	1 (1.3%)	2 (2.7%)	1 (0.6%)

Drug-related serious TEAEs were most frequent in the BAY 59-7939 30 mg bid group (17.6%) and 20 mg bid group (11.7%). The incidence rates observed in the 2.5 mg bid group (2.6%) and 10 mg bid group (2.9%) were below the incidence rate seen in the enoxaparin group (3.1%).

The incidence rates of adverse events resulting in (prolonged) hospitalization are tabulated in Table 5-93.

Table 5-93: ODIXa-HIP (Study 10942) - incidence of (prolonged) hospitalization due to adverse events (safety population)

	BAY 59-7939 2.5 mg bid (N = 76) n (%)	BAY 59-7939 5 mg bid (N = 80) n (%)	BAY 59-7939 10 mg bid (N = 68) n (%)	BAY 59-7939 30 mg od (N = 88) n (%)
Incidence rate	1 (1.3%)	7 (8.8%)	3 (4.4%)	7 (8.0%)

	BAY 59-7939 20 mg bid (N = 77) n (%)	BAY 59-7939 30 mg bid (N = 74) n (%)	Enoxaparin 40 mg od (N = 162) n (%)
Incidence rate	3 (3.9%)	6 (8.1%)	11 (6.8%)

The highest incidence rate of (prolonged) hospitalization was seen in the BAY 59-7939 5 mg bid group (8.8%), while the lowest rate was seen in the 2.5 mg bid group (1.3%) of BAY 59-7939.

5.3.2.2.6.2 ODIXa-HIP2 (Study 10944)

There were 77 serious adverse events, of which 62 were associated with BAY 59-7939 intake. Table 5-94 summarizes the most common serious adverse events by study drugs.

Table 5-94: ODIXa-HIP2 trial (Study 10944) - incidence rates (≥2% in any treatment group) of treatment-emergent serious adverse events by MedDRA preferred term (safety population)

MedDRA system organ class/ preferred term	BAY 59-7939 2.5 mg bid (N = 132)	BAY 59-7939 5 mg bid (N = 136)	BAY 59-7939 10 mg bid (N = 133)
Any event	10 (8%)	12 (9%)	14 (11%)
Blood and lymphatic system disorders	0 (0%)	0 (0%)	1 (1%)
Iron deficiency anemia	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal disorders	0 (0%)	2 (1%)	0 (0%)
Gastric hemorrhage	0 (0%)	0 (0%)	0 (0%)
Infections and infestations	0 (0%)	1 (1%)	1 (1%)
Diarrhea infectious	0 (0%)	0 (0%)	0 (0%)
Injury, poisoning and procedural complications	2 (2%)	3 (2%)	2 (2%)
Post procedural hemorrhage	0 (0%)	1 (1%)	0 (0%)
Wound secretion	0 (0%)	0 (0%)	2 (2%)
Investigations	1 (1%)	2 (1%)	0 (0%)
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	0 (0%)
Dermatitis bullous	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	8 (6%)	4 (3%)	8 (6%)
Deep vein thrombosis	5 (4%)	3 (2%)	4 (3%)
Hematoma	2 (2%)	1 (1%)	2 (2%)

MedDRA system organ class/ preferred term	BAY 59-7939 20 mg bid (N=134)	BAY 59-7939 30 mg bid (N=37)	Enoxaparin 40 mg od (N=132)
Any event	20 (15%)	6 (16%)	15 (11%)
Blood and lymphatic system disorders	2 (1%)	1 (3%)	0 (0%)
Iron deficiency anemia	0 (0%)	1 (3%)	0 (0%)
Gastrointestinal disorders	1 (1%)	1 (3%)	1 (1%)
Gastric hemorrhage	0 (0%)	1 (3%)	0 (0%)
Infections and infestations	1 (1%)	1 (3%)	2 (2%)
Diarrhea infectious	0 (0%)	1 (3%)	0 (0%)
Injury, poisoning and procedural complications	2 (1%)	1 (3%)	2 (2%)
Post procedural hemorrhage	0 (0%)	1 (3%)	0 (0%)
Wound secretion	1 (1%)	0 (0%)	0 (0%)
Investigations	0 (0%)	0 (0%)	2 (2%)
Skin and subcutaneous tissue disorders	1 (1%)	1 (3%)	0 (0%)
Dermatitis bullous	0 (0%)	1 (3%)	0 (0%)
Vascular disorders	11 (8%)	2 (5%)	9 (7%)
Deep vein thrombosis	5 (4%)	1 (3%)	9 (7%)
Hematoma	4 (3%)	1 (3%)	0 (0%)

The incidence rate of serious TEAEs increased dose-dependently from 8% in the BAY 59-7939 2.5 mg bid group to 16% in the 30 mg bid group. In the enoxaparin

group the incidence rate was 11% (Table 5-94). DVT and hematoma were the most frequent serious TEAEs. No hematoma were reported for subjects receiving enoxaparin; however, the percentage of DVTs was highest (7%) in this treatment arm.

Table 5-95: ODIXa-HIP2 trial (Study 10944) - incidence rates (≥2% in any treatment group) of drug-related treatment-emergent serious adverse events by MedDRA preferred term (safety population)

MedDRA system organ class/ preferred term	BAY 59-7939 2.5 mg bid (N = 132)	BAY 59-7939 5 mg bid (N = 136)	BAY 59-7939 10 mg bid (N = 133)
Any event	5 (4%)	7 (5%)	4 (3%)
Gastrointestinal disorders	0 (0%)	1 (1%)	0 (0%)
Gastric hemorrhage	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	4 (3%)	1 (1%)	4 (3%)
Hematoma	2 (2%)	1 (1%)	2 (2%)

MedDRA system organ class/ preferred term	BAY 59-7939 20 mg bid (N = 134)	BAY 59-7939 30 mg bid (N = 37)	Enoxaparin 40 mg od (N = 132)
Any event	8 (6%)	2 (5%)	3 (2%)
Gastrointestinal disorders	0 (0%)	1 (3%)	0 (0%)
Gastric hemorrhage	0 (0%)	1 (3%)	0 (0%)
Vascular disorders	6 (4%)	1 (3%)	1 (1%)
Hematoma	4 (3%)	1 (3%)	0 (0%)

Drug-related serious TEAEs were most frequent in the BAY 59-7939 20 mg bid group (6%) (Table 5-95). The incidence rates observed in the other BAY 59-7939 dose groups ranged between 3% and 5%, with 2% observed with enoxaparin.

Adverse events resulting in (prolonged) hospitalization: The incidence rates of adverse events resulting in (prolonged) hospitalization are tabulated in Table 5-96.

Table 5-96: ODIXa-HIP2 trial (Study 10944) - incidence of (prolonged) hospitalization due to adverse events (safety population)

	BAY 59-7939 2.5 mg bid (N = 132)	BAY 59-7939 5 mg bid (N = 136)	BAY 59-7939 10 mg bid (N = 133)
Incidence rate	7 (5.3%)	7 (5.1%)	11 (8.3%)
	BAY 59-7939 20 mg bid (N = 134)	**BAY 59-7939 30 mg bid (N = 37)**	**Enoxaparin 40 mg od (N = 132)**
Incidence rate	12 (9.0%)	4 (10.8%)	8 (6.1%)

Incidence rates of (prolonged) hospitalization increased dose-dependently from 5% to 11%. The incidence rate in subjects receiving enoxaparin was 6.1%.

None of the major post-operative bleeding events resulted in (prolonged) hospitalization.

5.3.2.2.6.3 ODIXa-KNEE (Study 10945)

There were 69 serious adverse events, of which 57 were associated with BAY 59-7939 intake. Table 5-97 summarizes the most common serious adverse events by study drugs.

Table 5-97: ODIXa-KNEE trial (Study 10945) - incidence rates (≥2% in any treatment group) of treatment-emergent serious adverse events by MedDRA preferred term (safety population)

MedDRA system organ class/ preferred term	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Any event	11 (11%)	7 (7%)	12 (12%)
Cardiac disorders	3 (3%)	2 (2%)	2 (2%)
General disorders and administration site conditions	0 (0%)	0 (0%)	3 (3%)
Injury, poisoning and procedural complications	1 (1%)	0 (0%)	2 (2%)
Operative hemorrhage	0 (0%)	0 (0%)	0 (0%)
Investigations	0 (0%)	1 (1%)	3 (3%)
Respiratory, thoracic, and mediastinal disorders	2 (2%)	2 (2%)	2 (2%)
Vascular disorders	3 (3%)	1 (1%)	1 (1%)
Deep vein thrombosis	3 (3%)	1 (1%)	0 (0%)

MedDRA system organ class/ preferred term	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 30 mg bid (N=106)	Enoxaparin 30 mg bid (N=104)
Any event	14 (14%)	13 (12%)	12 (12%)
Cardiac disorders	1 (1%)	2 (2%)	0 (0%)
General disorders and administration site conditions	1 (1%)	2 (2%)	0 (0%)
Injury, poisoning and procedural complications	4 (4%)	8 (8%)	0 (0%)
Operative hemorrhage	3 (3%)	3 (3%)	0 (0%)
Investigations	2 (2%)	1 (1%)	1 (1%)
Respiratory, thoracic, and mediastinal disorders	0 (0%)	1 (1%)	1 (1%)
Vascular disorders	4 (4%)	1 (1%)	7 (7%)
Deep vein thrombosis	4 (4%)	1 (1%)	6 (6%)

The incidence rates of serious TEAEs varied between 7% and 14% in the BAY 59-7939 treatment groups and were not dose dependent. In the enoxaparin group the incidence rate was 12%. DVT was the most frequent serious TEAEs and highest in the enoxaparin treatment arm (6%).

Table 5-98 summarizes incidence rates of drug-related treatment-emergent serious adverse events.

Table 5-98: ODIXa-HIP2 trial (Study 10944) - incidence rates (≥2% in any treatment group) of drug-related treatment-emergent serious adverse events by MedDRA preferred term (safety population)

MedDRA system organ class/ preferred term	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Any event	0 (0%)	1 (1%)	4 (4%)
Injury, poisoning, and procedural complications	0 (0%)	0 (0%)	1 (1%)
Operative hemorrhage	0 (0%)	0 (0%)	0 (0%)
Investigations	0 (0%)	0 (0%)	3 (3%)
Vascular disorders	0 (0%)	0 (0%)	0 (0%)

MedDRA system organ class/ preferred term	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 30 mg bid (N=106)	Enoxaparin 30 mg bid (N=104)
Any event	7 (7%)	8 (8%)	3 (3%)
Injury, poisoning, and procedural complications	3 (3%)	6 (6%)	0 (0%)
Operative hemorrhage	2 (2%)	3 (3%)	0 (0%)
Investigations	1 (1%)	0 (0%)	1 (1%)
Vascular disorders	2 (2%)	0 (0%)	2 (2%)

Drug-related serious TEAEs increased dose-dependently and were most frequent in the BAY 59-7939 30 mg bid group (8%). The incidence rate observed with enoxaparin was 3%.

Adverse events resulting in (prolonged) hospitalization: The incidence rates of adverse events resulting in (prolonged) hospitalization are tabulated in Table 5-99.

Table 5-99: ODIXa-HIP2 trial (Study 10944) - incidence of (prolonged) hospitalization due to adverse events (safety population)

	BAY 59-7939 2.5 mg bid (N=100)	BAY 59-7939 5 mg bid (N=102)	BAY 59-7939 10 mg bid (N=103)
Incidence rate	11 (11.0%)	6 (5.9%)	14 (13.6%)

	BAY 59-7939 20 mg bid (N=98)	BAY 59-7939 30 mg bid (N=106)	Enoxaparin 30 mg bid (N=104)
Incidence rate	12 (12.2%)	13 (12.3%)	9 (8.7%)

Incidence rates of (prolonged) hospitalization ranged between 6% and 14% for BAY 59-7939 with no apparent dose dependency. The incidence rate in subjects receiving enoxaparin was 9%.

5.3.2.2.7 Deaths

5.3.2.2.7.1 ODIXa-HIP trial (Study 10942)

2 deaths were reported: 1 occurred in the BAY 59-7939 2.5 mg bid group and 1 in the BAY 59-7939 30 mg od group. Table 5-100 summarizes deaths per country for subjects valid for safety analysis.

Table 5-100: ODIXa-HIP trial (Study 10942) - deaths during study period (safety population)

Treatment/ country	Subject identifier	Adverse event	Day of onset	Duration of event (days)
BAY 59-7939 2.5 mg bid PPD	010942-PPD	Sudden death, cardiac arrest, pulmonary embolism	4	<1
BAY 59-7939 30 mg od PPD	010942-PPD	Cardiorespiratory arrest	6	<1

5.3.2.2.7.2 ODIXa-HIP2 trial (Study 10944)

2 deaths were reported: 1 occurred in the BAY 59-7939 5 mg bid group (Subject 010944-PPD and 1 in the BAY 59-7939 10 mg bid group (Subject 010944 PPD PPD Table 5-101 summarizes information on the deaths that occurred during the study.

Table 5-101: ODIXa-HIP2 trial (Study 10944) - deaths during study period (safety population)

Treatment/ country	Subject identifier	Adverse event	Day of onset	Duration of event (days)
BAY 59-7939 5 mg bid	010944 PPD	Sepsis, pneumonia	5	38
BAY 59-7939 10 mg bid	010944 PPD	Broncho-pneumonia	27	5

5.3.2.2.7.3 ODIXa-KNEE trial (Study 10945)

3 deaths were reported: 2 occurred in the BAY 59-7939 2.5 mg bid group (Subject 010945-PPD and Subject 010945 PPD and 1 in the BAY 59-7939 10 mg bid group (Subject 010945-PPD Table 5-102 summarizes information on the deaths that occurred during the study.

Table 5-102: ODIXa-KNEE trial (Study 10945) - deaths during study period (safety population)

Treatment/ country	Subject identifier	Adverse event	Day of onset	Duration of event (days)
BAY 59-7939 2.5 mg bid	010945-PPD	Pulmonary embolism	3	1
BAY 59-7939 2.5 mg bid	010945-	Respiratory failure	15	10
BAY 59-7939 10 mg bid	010945-	Pulmonary embolism	36	5

5.3.2.2.8 Laboratory abnormalities

5.3.2.2.8.1 ODIXa-HIP (Study 10942)

Table 5-103 summarizes the incidence rates of pre-specified lab abnormalities regarding platelets, SGOT/AST, and SGPT/ALT.

For lab abnormalities of SGOT/AST and SGPT/ALT >3x ULN, the highest incidence rate was observed in the BAY 59-7939 30 mg od group (7.0%) for SGPT/AST.

Table 5-103: ODIXa-HIP (Study 10942) - incidence rates of pre-specified treatment-emergent lab abnormalities up to 7 days after end of treatment (safety population)

Laboratory parameter	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid	BAY 59-7939 30 mg od
Platelets				
Thrombocytopenia[a]	1/76 (1.3%)	0/16 (0.0%)	1/60 (1.7%)	0/86 (0.0%)
SGOT/AST				
>1xULN	28/71 (39.4%)	24/72 (33.3%)	22/62 (35.5%)	37/78 (47.4%)
>3xULN	1/75 (1.3%)	2/78 (2.6%)	1/65 (1.5%)	2/83 (2.4%)
>5xULN	0/75 (0.0%)	1/78 (1.3%)	0/65 (0.0%)	0/83 (0.0%)
>10xULN	0/75 (0.0%)	1/78 (1.3%)	0/65 (0.0%)	0/83 (0.0%)
SGPT/ALT				
>1xULN	19/70 (27.1%)	20/68 (29.4%)	21/60 (35.0%)	24/79 (30.4%)
>3xULN	4/76 (5.3%)	3/78 (3.8%)	1/66 (1.5%)	6/86 (7.0%)
>5xULN	1/76 (1.3%)	1/78 (1.3%)	1/66 (1.5%)	1/86 (1.2%)
>10xULN	0/76 (0.0%)	1/78 (1.3%)	0/66 (0.0%)	0/86 (0.0%)

Laboratory parameter	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 40 mg od
Platelets			
Thrombocytopenia[a]	0/76 (0.0%)	0/74 (0.0%)	3/133 (2.3%)
SGOT/AST			
>1xULN	31/69 (44.9%)	16/67 (23.9%)	65/141 (46.1%)
>3xULN	0/71 (0.0%)	3/71 (4.2%)	3/150 (2.0%)
>5xULN	0/71 (0.0%)	0/71 (0.0%)	2/150 (1.3%)
>10xULN	0/71 (0.0%)	0/71 (0.0%)	0/150 (0.0%)
SGPT/ALT			
>1xULN	22/70 (31.4%)	15/66 (22.7%)	60/138 (43.5%)
>3xULN	1/75 (1.3%)	3/72 (4.2%)	7/152 (4.6%)
>5xULN	0/75 (0.0%)	1/72 (1.4%)	4/152 (2.6%)
>10xULN	0/75 (0.0%)	0/72 (0.0%)	1/152 (0.7%)

a Platelets <100,000/mm^3 or <50% compared with baseline

1 case of increased liver function tests (LFT) was reported as a serious adverse event.

5.3.2.2.8.2 ODIXa-HIP2 (Study 10944)

Table 5-104 summarizes the incidence rates of pre-specified lab abnormalities regarding platelets, SGOT/AST, and SGPT/ALT.

Table 5-104: ODIXa-HIP2 trial (Study 10944) - incidence rates of pre-specified treatment-emergent lab abnormalities up to 7 days after end of treatment (safety population)

Laboratory parameter	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid
Platelets			
Thrombocytopenia[a]	5/130 (3.8%)	3/130 (2.3%)	5/127 (3.9%)
SGPT/ALT >3xULN / bilirubin >2xULN	0/128 (0.0%)	0/125 (0.0%)	0/127 (0.0%)
SGOT/AST			
>1xULN	57/119 (47.9%)	54/118 (45.8%)	51/122 (41.8%)
>3xULN	6/128 (4.7%)	6/125 (4.8%)	6/127 (4.7%)
>5xULN	2/128 (1.6%)	3/125 (2.4%)	1/127 (0.8%)
>8xULN	1/128 (0.8%)	1/125 (0.8%)	0/127 (0.0%)
>10xULN	1/128 (0.8%)	0/125 (0.0%)	0/127 (0.0%)
SGPT/ALT			
>1xULN	37/117 (31.6%)	39/111 (35.1%)	25/118 (21.2%)
>3xULN	7/128 (5.5%)	8/125 (6.4%)	5/128 (3.9%)
>5xULN	2/128 (1.6%)	3/125 (2.4%)	1/128 (0.8%)
>8xULN	1/128 (0.8%)	0/125 (0.0%)	1/128 (0.8%)
>10xULN	1/128 (0.8%)	0/125 (0.0%)	0/128 (0.0%)

Laboratory parameter	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 40 mg od
Platelets			
Thrombocytopenia[a]	5/128 (3.9%)	1/35 (2.9%)	6/125 (4.8%)
SGPT/ALT >3xULN / bilirubin >2xULN	0/119 (0.0%)	0/35 (0.0%)	2/125 (1.6%)
SGOT/AST			
>1xULN	55/112 (49.1%)	18/35 (51.4%)	66/117 (56.4%)
>3xULN	4/121 (3.3%)	3/36 (8.3%)	11/125 (8.8%)
>5xULN	1/121 (0.8%)	1/36 (2.8%)	3/125 (2.4%)
>8xULN	0/121 (0.0%)	1/36 (2.8%)	2/125 (1.6%)
>10xULN	0/121 (0.0%)	1/36 (2.8%)	1/125 (0.8%)
SGPT/ALT			
>1xULN	43/109 (39.4%)	18/35 (51.4%)	66/109 (60.6%)
>3xULN	7/122 (5.7%)	2/36 (5.6%)	14/125 (11.2%)
>5xULN	0/122 (0.0%)	2/36 (5.6%)	3/125 (2.4%)
>8xULN	0/122 (0.0%)	1/36 (2.8%)	1/125 (0.8%)
>10xULN	0/122 (0.0%)	1/36 (2.8%)	1/125 (0.8%)

a Platelets <100,000/mm^3 or <50% compared with baseline.

Thrombocytopenia was reported more frequently with enoxaparin (5.6%) than with BAY 59-7939 treatment groups (range 2.3% to 3.9%).

For lab abnormalities of SGOT/AST and SGPT/ALT >3x ULN, the highest incidence rates were observed in the enoxaparin group (8.8% SGOT/AST, 11.2% SGPT/ALT). Corresponding percentages ranged between 3.3% and 8.3% (SGOT/AST) and 3.9% and 5.7% (SGPT/ALT) in the BAY 59-7939 treatment groups.

2 subjects receiving enoxaparin experienced increases of SGPT/ALT >3xULN and bilirubin >2xULN. This lab abnormality was not observed in any subject receiving any of the BAY 59-7939 treatments.

1 subject each experienced SGOT/AST >10xULN as well as SGPT/ALT >10xULN in the enoxaparin and BAY 59-7939 2.5 and 30 mg bid treatment arms.

4 cases of increased LFTs were reported as serious adverse events: 2 with BAY 59-7939 and 2 with enoxaparin treatment.

The following case of liver enzyme elevations occurred after the end of follow-up as defined in the study protocol and is considered an off-protocol serious adverse event: Subject 010944 PPD was a PPD with a history of cholecystolithiasis, who received BAY 59-7939 10 mg bid for 8 days. Bilirubin and liver enzymes were normal during the study period. 39 days after the last intake of study medication and an uneventful recovery, PPD developed jaundice (bilirubin 18.3 mg/dL, SGPT/ALT 190, SGOT/AST 504, GGT 566 U/L). Ultrasound sonography and endoscopic retrograde cholangio-pancreatography (ERCP) revealed no other abnormality than cholecystolithiasis. Repeat examinations over the following weeks showed pancreatitis (transient following ERCP), peptic ulcer, phlegmonic cholecystitis, cholangitis, and bronchopneumonia. Lab examinations 80 days after last intake of study medication: bilirubin 33.7 mg/dL, SGPT/ALT 639, SGOT/AST

550, GGT 1987, AP 2764 U/L. The patient died 118 days after last intake of study medication. Autopsy revealed septic-cholemic cardiovascular insufficiency with bronchopneumonia, acute cholecystitis, and acute necrotizing pancreatitis. Liver histology showed autolytic hepatocytes, no increased portal area, and no intrahepatic signs of cholestasis. (See Section 14.3.3 for details.)

5.3.2.2.8.3 ODIXa-KNEE (Study 10945)

Table 5-105 summarizes the incidence rates of pre-specified lab abnormalities regarding platelets, SGOT/AST, and SGPT/ALT.

Table 5-105: ODIXa-KNEE trial (Study 10945) - incidence rates of pre-specified treatment-emergent lab abnormalities up to 7 days after end of treatment (safety population)

Laboratory parameter	BAY 59-7939 2.5 mg bid	BAY 59-7939 5 mg bid	BAY 59-7939 10 mg bid
Platelets			
Thrombocytopenia[a]	5/100 (5.0%)	1/102 (1.0%)	2/102 (2.0%)
SGPT/ALT >3xULN / bilirubin >2xULN	0/99 (0.0%)	0/101 (0.0%)	1/102 (1.0%)
SGOT/AST			
>1xULN	29/78 (37.2%)	31/85 (36.5%)	36/81 (44.4%)
>3xULN	3/96 (3.1%)	7/98 (7.1%)	5/96 (5.2%)
>5xULN	0/98 (0.0%)	1/98 (1.0%)	2/101 (2.0%)
>8xULN	0/98 (0.0%)	0/99 (0.0%)	2/101 (2.0%)
>10xULN	0/98 (0.0%)	0/99 (0.0%)	3/102 (2.9%)
SGPT/ALT			
>1xULN	17/86 (19.8%)	26/86 (30.2%)	20/82 (24.4%)
>3xULN	2/98 (2.0%)	4/98 (4.1%)	4/100 (4.0%)
>5xULN	0/98 (0.0%)	0/98 (0.0%)	3/101 (2.9%)
>8xULN	0/98 (0.0%)	0/100 (0.0%)	1/102 (1.0%)
>10xULN	0/98 (0.0%)	1/101 (1.0%)	0/102 (0.0%)

Laboratory parameter	BAY 59-7939 20 mg bid	BAY 59-7939 30 mg bid	Enoxaparin 30 mg bid
Platelets			
Thrombocytopenia[a]	3/98 (3.1%)	2/105 (1.9%)	3/103 (2.9%)
SGPT/ALT >3xULN / bilirubin >2xULN	1/97 (1.0%)	0/105 (0.0%)	0/103 (0.0%)
SGOT/AST			
>1xULN	28/73 (38.4%)	33/84 (39.3%)	47/81 (58.0%)
>3xULN	6/91 (6.6%)	8/99 (8.1%)	6/100 (6.0%)
>5xULN	7/94 (7.4%)	2/101 (2.0%)	1/102 (1.0%)
>8xULN	5/95 (5.3%)	1/103 (1.0%)	1/102 (1.0%)
>10xULN	4/95 (4.2%)	1/104 (1.0%)	1/102 (1.0%)
SGPT/ALT			
>1xULN	22/76 (28.9%)	25/89 (28.1%)	32/83 (38.6%)
>3xULN	8/94 (8.5%)	3/102 (2.9%)	5/102 (4.9%)
>5xULN	6/96 (6.3%)	2/104 (1.9%)	2/102 (2.0%)
>8xULN	6/97 (6.2%)	1/104 (1.0%)	0/103 (0.0%)
>10xULN	3/97 (3.1%)	0/105 (0.0%)	0/103 (0.0%)

a Platelets <100,000/mm^3 or <50% compared with baseline.

Thrombocytopenia was reported more frequent with the BAY 59-7939 2.5 mg bid dose (5.0%) than in any of the other treatment groups (range 1.0% to 3.1%).

For abnormalities of SGOT/AST and SGPT/ALT >3x ULN, the highest incidence rates were observed in the BAY 59-7939 30 mg bid group (8.1% for SGOT/AST) and the BAY 59-7939 20 mg bid group (8.5% SGPT/ALT). Corresponding percentages ranged between 3.1% and 6.6% (SGOT/AST) and 2.0% and 4.9% (SGPT/ALT) in the remaining treatment groups.

9 subjects experienced SGOT/AST >10xULN and 4 subjects SGPT/ALT >10xULN, the majority of them received BAY 59-7939.

4 cases of increased LFTs were reported as serious adverse events, which all occurred in patients treated with BAY 59-7939.

5.3.2.3 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 anticoagulant effects. However, risk of bleeding was not different from the LMWH enoxaparin, which is used as standard in clinical practice.

5.3.2.4 Drug interactions encountered in clinical trials

Not applicable.

For formal interaction studies, see Section 5.2.5.

5.3.2.5 Contraindications and precautions

Contraindications: BAY 59-7939 is contraindicated in patients with active major bleeding and hypersensitivity to BAY 59-7939 or any excipient of the tablet or solution. BAY 59-7939 must not be used in pregnant women.

Precautions: BAY 59-7939 should be used in women of childbearing potential only with reliable contraception. BAY 59-7939 should be used with caution in nursing mothers and children, because it has not been studied in these populations.

BAY 59-7939 should be used with care in patients receiving concomitant treatment with drugs, which are strong inhibitors of CYP3A4, eg ketoconazole. Such drugs may increase BAY 59-7939 plasma concentrations to a clinically relevant degree. PT measurements are recommended for monitoring in such cases.

BAY 59-7939 should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. There is no experience with BAY 59-7939 in patients with renal or hepatic impairment.

If thromboembolic events occur despite BAY 59-7939 prophylaxis, appropriate therapy should be initiated, eg with a low molecular weight heparin (LMWH).

BAY 59-7939 should be administered with extreme caution in patients with

- *Hemorrhage:* BAY 59-7939, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

- *Spinal/epidural hematomas during neuraxial anesthesia:* When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated with BAY 59-7939 for prevention of thromboembolic complications may be at risk of developing an epidural or spinal hematoma

which can result in long-term or permanent paralysis. Anticoagulation with BAY 59-7939 should commence not earlier than 6 h after spinal puncture or withdrawal of the epidural catheter.

The risk of these events may be increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit vs risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

5.3.2.6 Countermeasures, overdose instructions

No cases of accidental or deliberate overdosage with BAY 59-7939 are known. Overdosage following administration of BAY 59-7939 may lead to hemorrhagic complications due to the pharmacodynamic properties of the compound.

Bleeding complications should be treated with fresh frozen plasma and as clinically indicated.

5.3.2.7 Effects of age, race (including ethnic differences), sex (restrictions)

Age and gender: Exposure (AUC and C_{max}) to BAY 59-7939 is increased to a clinically relevant degree in elderly subjects. There were no clinically relevant differences in pharmacokinetics between male and female subjects, especially when taking into account common body weight differences (see Section 5.2.2).

Japanese subjects: Exposure (AUC and Cmax) to BAY 59-7939 is higher by about 50% (1.3 - 2.0 times) after fasting single administration and 20-40 % at steady state after multiple administration in Japanese subjects compared with Caucasians. Likewise, pharmacodynamic parameters like Factor Xa inhibition are slightly affected accordingly (see Section 5.2.2 and Section 5.2.3). This higher exposure can be explained by differences in body weight rather than by true ethnic differences.

5.4 Marketing Experience

Not applicable.

6. Summary of Data and Guidance for the Investigator

Key Points:

Preclinical data

- BAY 59-7939 has been characterized as a potent and specific oral direct 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.
- Co-administration of BAY 59-7939 with acetylsalicylic acid, naproxen, diclofenac, clopidogrel, or warfarin showed additive but not potentiating effects on bleeding time prolongation in the rat tail model.
- BAY 59-7939 has a low acute toxicity in rats and mice. After repeated dose administration (4 and 13 weeks) in dogs and rats BAY 59-7939 was well tolerated. The changes seen in Quick values, increases in PT and aPTT with subsequent spontaneous bleeding at high doses are related to the underlying pharmacological principle of the compound.

- In the developmental toxicity study in rats maternal toxicity was found at the highest dose tested. Placental alterations were already seen at the lowest dose tested.
- There was no evidence for a genotoxic potential based on 2 *in vitro* and 1 *in vivo* test.
- The pharmacokinetics in rats and dogs was linear after oral and IV 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 data

- 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 in line 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.
- BAY 59-7939 is contraindicated in pregnant women because of exaggerated pharmacodynamic effects on both the maternal and fetal sites. BAY 59-7939 is also contraindicated in patients with active major bleeding and hypersensitivity to BAY 59-7939.

Clinical data

- 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 basis to detect extreme responses to BAY 59-7939. However, clinical experience does not yet allow to recommend target ranges or cut-off values.
- 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.
- 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.
- Concomitant administration of the potent CYP 3A4 inhibitor ketoconazole increases the exposure to BAY 59-7939 by about 50% with increases in its pharmacodynamic effects. Therefore, BAY 59-7939 should be used with care in patients receiving concomitant treatment with drugs, which are strong inhibitors of CYP3A4. PT measurements are recommended for monitoring.
- 3 large dose-ranging studies have been completed in the indication of VTE prevention in major orthopedic surgery exploring a 12-fold BAY 59-7939dose range from 2.5 to 30 mg bid.BAY 59-7939 prevented total VTE compared with enoxaparin, thus supporting the efficacy of BAY 59-7939 in this indication.

- None of the studies demonstrated a significant dose trend for BAY 59-7939 regarding the primary efficacy endpoint of total VTE.
- A flat dose response for efficacy and a flat dose response for safety indicate a broad therapeutic window for BAY 59-7939 and thus makes the drug different from other new anticoagulants, which have shown to have less wide therapeutic ranges.
- In the 3 studies, DVT rates were consistent with those observed in other contemporary trials and even the lower doses of BAY 59-7939 were within the expected ranges of the control drug enoxaparin or even lower.
- There was a dose-response with regard to bleeding events. However, it is important to note that there were neither fatal bleeds or bleeds in critical organs, nor clinically significant bleeds that could not be treated. Most bleeds adjudicated as major were related to the surgical site and no wound healing complications were reported in these patients.
- Higher BAY 59-7939 doses than 30 mg bid are not recommended in surgical patients because the net clinical benefit would disappear.
- In any of the studies, there was no indication for any treatment-emergent QTc-prolonging effects of BAY 59-7939.
- When used in surgical patients to prevent VTE both patient groups treated with BAY 59-7939 as well as with the comparator drug enoxaparin had transient increases of liver enzymes, in a similar temporal pattern and to a comparable extent. Surgical patients treated with BAY 59-7939 had a higher incidence of increased lipase and amylase values. These parameters peaked on the first day after surgery and resolved rapidly under continuous treatment.
- Once-daily dose regimens appear to be alternative options to twice-daily regimens explored thus far. Total daily doses up to 40 mg have yielded safe and effective study results in the indication of VTE prevention.

Guidance to the investigator based on clinical data

- BAY 59-7939 is contraindicated in pregnant women, in patients with active major bleeding, and in patients with a hypersensitivity to BAY 59-7939.
- Due to the pharmacological action of BAY 59-7939 as a Factor Xa inhibitor, prolongation of coagulation parameters (eg bleeding time, PT, aPTT, HepTest) occurs regularly.
- A therapeutic INR range for BAY 59-7939 has not yet been determined and therefore the known therapeutic INR range for warfarin cannot automatically be translated. Investigators in double-blind trials using BAY 59-7939 are advised not to measure the INR locally as this would unblind the trial.
- With regard to serious adverse events, there is an increased dose-dependent risk for hemorrhage for the same reason. This may include overt or occult bleeding resulting in hematoma or anemia.
- BAY 59-7939 has been well tolerated with most data derived from a large clinical study in patients undergoing elective hip replacement; however, bleeding events may occur with an increased incidence at BAY 59-7939 doses of 30 mg bid and beyond. Therefore, doses up to 30 mg bid can be studied in double-blind phase IIb trials, given that an independent Safety Committee will monitor online all safety-relevant aspects.
- If thromboembolic events occur despite BAY 59-7939 prophylaxis, appropriate therapy should be initiated, eg with low molecular weight heparins.
- Bleeding complications should be treated with fresh frozen plasma and as clinically indicated.
- BAY 59-7939 should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. There is no experience with BAY 59-7939 in patients with renal or hepatic impairment.

- During neuraxial anesthesia indwelling catheters must be avoided. Anticoagulation with BAY 59-7939 should commence not earlier than 6 h after spinal puncture or withdrawal of the epidural catheter.
- BAY 59-7939 should be used with caution in woman of childbearing potential without reliable contraception, nursing mothers, and children, because it has not been studied in these populations.
- BAY 59-7939 should be used with care in patients receiving concomitant treatment with drugs, which are strong inhibitors of CYP3A4, eg ketoconazole. Such drugs may increase BAY 59-7939 plasma concentrations to a clinically relevant degree. PT measurements are recommended for monitoring in such cases.

7. References

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8. Appendices

8.1 Appendix I – Development Core Safety Information (DCSI)

Development Core Safety Information (DCSI)

Effective Date: 04 Feb 2005
Replaces last version: 09 Jul 2004

8.1.1 Posology and method of administration

Recommended usual dose:

A usual dose cannot be recommended at this stage of the clinical development.

Range of dose:

Twice daily doses of 2.5, 5, 10, 20, and 30 mg and once-daily doses of 30 mg have been administered to patients for the prevention of VTE following elective primary hip or knee replacement.

Method and frequency of administration:

In clinical studies, BAY 59-7939 has been administered orally as tablets once or twice daily.

Dose titration, special monitoring advice:

Not applicable at this stage of the clinical development.

Elderly (above 65 years):

Patients up to the age of 89 years have been included in clinical studies.

Children (from birth to 16 *years*):

No experience.

Hepatic impairment:

No experience.

Renal impairment:

No experience.

8.1.2 Contraindications

BAY 59-7939 is contraindicated in patients with active major bleeding and hypersensitivity to BAY 59-7939 or any excipient of the tablet or solution.
BAY 59-7939 must not be used in pregnant women.

8.1.3 Special warnings and precautions for use

BAY 59-7939 should be used in women of childbearing potential only with reliable contraception. BAY 59-7939 should be used with caution in nursing mothers and children, because it has not been studied in these populations.

BAY 59-7939 should be used with care in patients receiving concomitant treatment with drugs, which are strong inhibitors of CYP3A4, eg ketoconazole. Such drugs may increase BAY 59-7939 plasma concentrations to a clinically relevant degree. PT measurements are recommended for monitoring in such cases.

BAY 59-7939 should be used with extreme caution in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. There is no experience with BAY 59-7939 in patients with renal or hepatic impairment.

If thromboembolic events occur despite BAY 59-7939 prophylaxis, appropriate therapy should be initiated, eg with low molecular weight heparins.

BAY 59-7939 should be administered with extreme caution in patients with

- *Hemorrhage:* BAY 59-7939, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

- *Spinal/epidural hematomas during neuraxial anesthesia:* When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated with BAY 59-7939 for prevention of thromboembolic complications may be at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis. Anticoagulation with BAY 59-7939 should commence not earlier than 6 h after spinal puncture or withdrawal of the epidural catheter.

The risk of these events may be increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk may also be increased by traumatic or repeated epidural or spinal puncture. During neuraxial anesthesia indwelling catheters must be avoided. BAY 59-7939 should be used with caution in patients receiving neuroaxial anaesthesia not before 6 h after spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary. The physician should consider the potential benefit vs risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

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.

Concomitant administration of the potent CYP 3A4 inhibitor ketoconazole increases the plasma concentration (AUC, C_{max}) of BAY 59-7939 by about 50% and 80%, respectively, with increases in its pharmacodynamic effects.

BAY 59-7939 can be used with caution concomitantly with acetylsalicylic acid (at doses up to 500 mg a day).

8.1.5 Pregnancy and lactation

No experience.

8.1.6 Undesirable effects

Due to the pharmacological action of BAY 59-7939 as a Factor Xa inhibitor, prolongation of coagulation parameters (eg bleeding time, PT, INR, PTT, HepTest) occurs regularly. A therapeutic INR range for BAY 59-7939 has not yet been determined and therefore the known therapeutic INR range for warfarin cannot automatically be translated.

With regard to serious adverse events, there is an increased dose-dependent risk for hemorrhage for the same reason. This may include overt or occult bleeding resulting in hematoma or anemia.

In surgical patients receiving BAY 59-7939 to prevent VTE transient raises of liver function tests (transaminases, GGT, bilirubin, AP) were seen in a pattern similar to enoxaparin, ie with a peak occurring 1 week after surgery. In single cases,

ALT>8xULN have been observed both in patients receiving BAY 59-7939 and enoxaparin. Lipase and amylase values were found to be increased as well; however, this increase occurs on the first day after surgery and rapidly resolves under continuous treatment.

8.1.7 Overdose

No cases of accidental or deliberate overdosage with BAY 59-7939 are known. Overdosage following administration of BAY 59-7939 may lead to hemorrhagic complications due to the pharmacodynamic properties of the compound.

Bleeding complications should be treated with fresh frozen plasma and as clinically indicated. There is increasing published evidence that recombinant factor VIIa (rFVIIa) may be of use as a universal antidote in patients with over-anticoagulation. However, no data are available so far on the use of rFVIIa in patients receiving BAY 59-7939.

8.1.8 Drug abuse and dependence

Not applicable.